ALKALOSIS AND DIGOXIN EFFECTS ON PLASMA POTASSIUM, IONIC HOMEOSTASIS AND EXERCISE PERFORMANCE IN HEALTHY HUMANS

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ABSTRACT

Muscle contractions induce cellular potassium (K^+) efflux which may contribute to impaired muscle cell membrane excitability and fatigue. The magnitude of K^+ changes are dependent on the size of contracting muscle mass, duration and intensity of exercise, and health and fitness status of participants. Activation of the sarcolemmal and t-tubular bound sodium-potassium adenosine 5' triphosphatase enzyme (Na^+,K^+ATPase, NKA) mediates muscle cell K^+ and Na^+ active exchange, and is instrumental in the maintenance of muscle cellular and plasma K^+ homeostasis during exercise. Therefore modulations of NKA function might enhance or impair exercise induced K^+ disturbances, and theoretically can have a profound effect on muscle excitability and exercise performance. This thesis examined the effects of two interventions designed to induce acute or short term upregulation and downregulation of NKA activity on K^+ homeostasis and exercise performance in healthy humans. Study 1 investigated the effects of metabolically induced alkalosis on plasma K^+ regulation during submaximal finger flexion (small muscle mass) contractions and fatigue in healthy humans. Study 2 investigated the effects of a clinically relevant dose of digoxin administration on K^+ regulation, during intermittent supramaximal finger flexion contractions (small muscle mass) and fatigue in healthy humans. Study 3 investigated the effects of digoxin on K^+ regulation during progressive increasing intensity submaximal leg cycling exercise (large muscle mass) and fatigue in the same healthy participants as in study 2. A secondary focus of this thesis was to examine the ionic, metabolic and acid-base disturbances during small and large muscle mass exercise and in recovery. This included the regulatory role of NKA in active (study 1 and 2) and inactive tissue (study 3), during small (study 1 and 2) and large (study 3) muscle mass exercise.

Study 1 Alkalosis enhances human exercise performance, and reduces K^+ loss in contracting rat muscle. We investigated alkalosis effects on K^+ regulation, ionic regulation and fatigue during intense exercise in nine untrained volunteers. Concentric finger flexions were conducted at 75% peak workrate (~3 W) until fatigue, under alkalosis (ALK, $NaHCO_3$, $0.3g.kg^{-1}$) and control (CON, $CaCO_3$) conditions, 1 month apart in a randomised, double-blind, crossover design. Deep antecubital venous (v) and radial arterial (a) blood was drawn at rest, during exercise and recovery, to determine arteriovenous differences for electrolytes, fluid shifts, acid-base and gas exchange. Finger flexion exercise barely perturbed arterial plasma ions and acid-base status, but induced marked arterio-venous changes. ALK elevated [HCO_3^-] and PCO_2, and lowered [H^+] ($P<0.05$). Time to fatigue increased substantially during ALK (25±8%, $P<0.05$), whilst both $[K^+]_a$ and $[K^+]_v$ were reduced ($P<0.01$) and $[K^+]_{a-v}$ during exercise

tended to be greater (P=0.056, n=8). Muscle K^+ efflux at fatigue was greater in ALK (21.2±7.6 μmol.min^{-1}, 32±7%, P<0.05, n=6), but peak K^+ uptake rate was elevated during recovery (15±7%, P<0.05) suggesting increased muscle Na^+,K^+ATPase activity. ALK induced greater $[Na^+]_a$, $[Cl^-]_v$, muscle Cl^- influx and muscle $[Lac^-]$ efflux during exercise and recovery (P<0.05). The lower circulating $[K^+]$ and greater muscle K^+ uptake, Na^+ delivery and Cl^- uptake with ALK, are all consistent with preservation of membrane excitability during exercise. This suggests that lesser exercise-induced membrane depolarisation may be an important mechanism underlying enhanced exercise performance with ALK. Thus ALK was associated with improved regulation of K^+, Na^+, Cl^- and Lac^-.

Study 2 During intense exercise, cellular potassium (K^+) loss is attenuated by increased Na^+K^+ATPase (NKA) activity above rest, and both excessive K^+ loss and impaired NKA activity have been linked to skeletal muscle fatigue. We hypothesised that digoxin, a specific NKA inhibitor, would impair K^+ homeostasis and increase peripheral muscle fatigability. Ten healthy volunteers (9 male, 1 female) performed high intensity, intermittent finger flexion exercise following oral digoxin (0.25mg; DIG) or placebo (CON) for 14 days using a crossover, double-blind, randomised, counterbalanced design. Exercise comprised three 1 min bouts at 105% peak finger flexion work rate, followed by a fourth bout to fatigue. Forearm blood flow (FBF) and simultaneous arterial and deep antecubital venous blood samples were measured pre, during and post-exercise for electrolytes, acid-base, gas exchange and fluid shifts. In DIG, serum digoxin concentration was 0.8±0.1 nM. Fatigue time during exercise at a mean power output of 5.4±0.5W was unaffected by DIG. Forearm blood flow during exercise increased 12-fold from rest to fatigue (P<0.001), and plasma volume decreased by 6% at fatigue (P<0.001), but with no DIG treatment effects. Arterial $[K^+]$ increased slightly (P<0.001) and venous $[K^+]$ increased dramatically with each bout of exercise (P<0.001). During CON, $[K^+]_{a-v}$ decreased by the first exercise bout (-1.32±0.11 mM, P<0.05) and K^+ efflux from contracting muscle increased dramatically from -1.9±1.6 μM.min^{-1} at rest to 167±60 μM.min^{-1} at fatigue (P<0.001). However, no digoxin treatment effect was found for any K^+ measures. Arterial $[HCO_3^-]$ and C_aCO_2 did not change during exercise, whilst venous PCO_2 and $[H^+]$ increased from rest during exercise (P<0.001). Arterial PCO_2 decreased from rest to fatigue (P<0.001) and plasma $[Lac^-]_{a-v}$ decreased from rest during exercise and recovery (P<0.01). During digoxin trials, arterial $[HCO_3^-]$, P_aCO_2, C_aCO_2 and $[Lac^-]_{a-v}$ were lower during exercise and recovery (P<0.01) and venous $[H^+]$ was lower at fatigue (P<0.05). In conclusion, 14 d oral intake of DIG did not impair K^+ homeostasis or muscle function during small

muscle mass exercise. This might reflect either inadequate digitalisation or compensatory NKA upregulation. Acid-base disturbances during exercise were reduced by digoxin, possibly associated with a decreased muscle glycolysis , although this was not associated with any apparent decrease in NKA activity.

Study 3 Exercise involving large muscle mass invokes a substantial rise in K^+ efflux which may contribute to a decline in cell membrane excitability and ultimately fatigue. Exercise induced K^+ increase are regulated by increased NKA activity in active and inactive muscle, in order to minimise cardiovascular risks and preserve muscle cell excitability and function. It was hypothesised that digoxin binding to NKA would inhibit K^+ uptake by active and inactive muscle, thereby contributing to a greater systemic hyperkalemia, and also to impaired muscle function. Ten healthy volunteers (9 male, 1 female) took oral digoxin (0.25 mg; DIG) or placebo (CON) for 14 days in a crossover, double blind, randomised, counterbalanced design. Participants cycled for 10 min at both 33% and 67% $\dot{V}O_{2peak}$, and then to fatigue at 90% $\dot{V}O_{2peak}$. Arterial and antecubital venous blood samples were drawn simultaneously at rest, during and after exercise, and analysed for electrolytes, acid-base, gas exchange and fluid shifts. The forearm was positioned to minimise any active contractions during leg cycling exercise. Serum digoxin concentration in DIG was 0.8±0.1 nM. The exercise $\dot{V}O_2$ and time to fatigue (262±156 s and 254±125 s for DIG and CON respectively) were unaffected by DIG. Plasma volume shifts from rest and across the inactive forearm were unaffected by DIG. Arterial $[K^+]$, venous $[K^+]$ and the arterio-venous $[K^+]$ difference across the inactive forearm were to ~6.5, ~5.0 and ~1.25 mM at fatigue, respectively ($P<0.001$). None of the $[K^+]_a$, $[K^+]_v$ or $[K^+]_{a-v}$ were affected by DIG. Plasma $[Lac^-]_a$ tended to be lower during DIG at 67% $\dot{V}O_{2peak}$ ($P=0.07$), and plasma $[Lac^-]_v$ was lower during DIG at 33% $\dot{V}O_{2peak}$ ($P<0.05$) but did not affect $[H^+]_a$. Plasma $[Cl^-]_a$ tended to be greater in DIG at rest to 67% $\dot{V}O_{2peak}$ ($P=0.11$, $d = 0.25$). Thus digoxin did not impair K^+ homeostasis during exercise involving large muscle mass and DIG did not affect exercise performance. A companion study investigating DIG effects on skeletal muscle NKA function (see appendix) in the same participants found that DIG induced 7% occupancy of muscle NKA, but NKA activity was unchanged. DIG effects on glycolysis during large muscle mass exercise were minor, and were not associated with any apparent altered NKA. Therefore the lack of DIG effect on plasma K^+ homeostasis during exercise in likely due to an adaptive compensatory NKA upregulation with DIG in healthy humans. These findings also demonstrate remarkable self-preservation in otherwise healthy muscle to

maintain K^+ homeostasis and subsequent muscle function. Inactive muscle also plays an important role in the regulation of strong ions during submaximal cycling exercise.

Conclusions

Submaximal and supramaximal exercise with a small muscle mass barely perturbed systemic ionic, acid-base and metabolic status; however a substantial increase in blood flow and ionic exchanges across contracting muscle was observed. Rapid forearm muscle K^+ uptake in recovery demonstrated the important regulatory role of previously active muscle in re-establishing K^+ homeostasis. Leg cycling exercise induced significant systemic ionic, acid-base and metabolic disturbances, and uptake of K^+ into inactive muscle during exercise demonstrates that inactive tissue is also critical in alleviating exercise induced hyperkalemia.

Finger flexion exercise performance was substantially improved with alkalosis, which was linked to changes in K^+, Na^+, Cl^- and Lac^- ions. Systematically lower $[K^+]_a$ and $[K^+]_v$ also suggest that alkalosis may have preserved the intracellular to extracellular $[K^+]$ gradient, whilst greater K^+ re-uptake during recovery point to increased muscle NKA activity with alkalosis. Greater Na^+ delivery and Cl^- uptake with alkalosis are also consistent with enhanced stabilization of cell membranes in contracting muscle.

Unexpectedly, K^+ homeostasis did not change at a clinically relevant digoxin serum concentration during exercise with either a small or large contracting muscle mass. Indeed, consistency of the K^+ responses to exercise in DIG vs CON was remarkable. Measures of muscle NKA content and DIG inhibition conducted by others (appendix 7) is consistent with the lack of DIG effect on K^+ homeostasis during exercise, which indicate this is likely due to an adaptive compensatory NKA upregulation to DIG. This phenomenon highlights remarkable self-preservation in otherwise healthy muscle tissue to maintain K^+ homeostasis, regardless of the contracting muscle mass size. A decrease in glycolysis was observed at numerous time points during exercise with both small and large muscle mass, but is not due to any apparent digoxin induced NKA inhibition.

DECLARATION

"I, Simon M Sostaric, declare that the PhD thesis entitled *Alkalosis and digoxin effects on plasma potassium, ionic homeostasis and exercise performance in healthy humans* are no more than 100 000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work"

Signature Date 30/03/12

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ABBREVIATIONS

Subscripts		Units
i	intracellular	
e	extracellular	
I	interstitial	
E_m	Muscle membrane potential	
a	Arterial	
v	Venous	
a-v	Arteriovenous difference	
Electrolytes		
K^+	Potassium ion	mM
Na^+	Sodium ion	mM
Cl^-	Chloride ion	mM
Lac^-	Lactate ion	mM
Ca^{2+}	Calcium ion	mM
Mg^{2+}	Magnesium ion	mM
SID	Strong ion difference	mM
Haematology & Fluid Shifts		
Hb	Haemoglobin	$g.dl^{-1}$
Hct	Haematocrit	%
ΔPV	Change in plasma volume	%
ΔBV	Change in blood volume	%
Acid-Base & Metabolism		
pH_m	Muscle pH	
H^+	Hydrogen ion	nM
HCO_3^-	Bicarbonate ion	mM
$BLac^-$	Whole blood lactate ion	mM
C_{CO2}	Blood carbon dioxide content	$ml.l^{-1}$
C_{O2}	Blood oxygen content	$ml.l^{-1}$
$\dot{V}_{mO2}$	Muscle oxygen consumption	$ml.min^{-1}$
$\dot{V}_{m,CO2}$	Muscle carbon dioxide production	$ml.min^{-1}$
RER_m	Muscle respiratory exchange ratio	
A_{tot}	Plasma protein weak acids	
Cardiovascular & Blood Gases		
PCO_2	Partial pressure of carbon dioxide	mmHg

PO_2	Partial pressure of oxygen	mmHg
HR	Heart rate	beats.min^{-1}
$\dot{V}O_2$	Oxygen consumption	l.min^{-1}
$\dot{V}O_{2peak}$	Peak oxygen consumption	l.min^{-1}
$\dot{V}CO_2$	carbon dioxide output	l.min^{-1}
BP	Blood pressure	mmHg
FBF	Forearm blood flow	ml.min^{-1}
Muscle		
Na^+,K^+-ATPase	Sodium-potassium adenosine 5' triphosphatase	
NKA	Sodium-potassium adenosine 5' triphosphatase	
NKCC	$Na^+,K^+,2Cl^-$ cotransporter	
ATP	Adenosine 5' triphosphate	
ADP	Adenosine diphosphate	
PCr	Phosphocreatine	
Cr	Creatine	
t-tubules	Transverse tubules	
Work & Power		
WR_{peak}	Work rate peak	
PO	Power output	
W	Watts	
Experimental interventions		
CON	Control (placebo)	
$NaHCO_3$	Sodium bicarbonate	
ALK	Sodium-bicarbonate induced alkalosis	
DIG	Digoxin therapy	
Other		
[ ]	Concentration	
Δ	Delta (change)	
CV	Coefficient of variation	

LIST OF PUBLICATIONS AND PRESENTATIONS

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Simon M. Sostaric, Sandford L. Skinner, Malcolm J. Brown, Termboon Sangkabutra, Ivan Medved, Tanya Medley, Steve E. Selig, Ian Fairweather, Danny Rutar and Michael J.McKenna.

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"Effects of digoxin therapy on K^+ release and fatigue during small muscle mass exercise in healthy humans".

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"Digoxin and exercise effects on Na^+,K^+-pump activity, content, isoform gene and protein expression in human skeletal muscle".
Australian Physiological Society, Canberra, September 2005.

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CHAPTER 1: INTRODUCTION

Potassium (K^+) is an inorganic cation that plays a substantial role in facilitating muscle and nerve cell excitability and subsequent muscle function (Sejersted & Sjøgaard, 2000). During muscle contractions, K^+ is released at a high rate, which is predominantly due to electrical activity at the sarcolemmal and t-tubular membranes during action potential repolarisation (Sejersted & Sjøgaard, 2000). However, the continued release of K^+ during ongoing muscle contractions may also contribute to fatigue (McKenna, 1995).

Fatigue has been defined as "a condition where there is a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load which is reversible at rest" (NHLBI, 1990). The cause of muscle fatigue is not a consequence of one single isolated factor. However, one site of exercise-induced muscle fatigue is suggested to be the muscle membrane, including the sarcolemma and t-tubules (Sjøgaard 1990). Firstly, a sufficient increase in extracellular ($[K^+]_e$) and decrease in intracellular ($[K^+]_i$) can depolarise cell membranes, impairing membrane excitability (Hodgkin & Horowicz, 1959; Yensen et al, 2002). Secondly, a strong link exists between interstitial H^+ and K^+ accumulation (Juel 2007). A decrease in intracellular ($[K^+]_i$) during intense muscle contractions contributes to an increase in intracellular hydrogen ion concentration ($[H^+]_i$) (Lindinger and Heigenhauser, 1991), and leg K^+ release during moderate intensity exercise was increased in the presence of lower leg pH compared to control (Bangsbo et al, 1996). A study by Street et al (2005) demonstrated that citrate induced alkalosis decreased interstitial pH with a concomitant decrease in interstitial $[K^+]$ compared to control. However the direct H^+ effect on fatigue during exercise in humans is currently equivocal (Bangsbo & Juel, 2006). A decline in intracellular strong ion difference will directly increase $[H^+]_I$ (Lindinger and Heigenhauser, 1988). This decline in strong ion difference is primarily a result of increases in intracellular lactate ($[Lac^-]_i$) and chloride ($[Cl^-]_i$); decrease in $[K^+]_i$; and counteracted by an increase in sodium $[Na^+]_i$. (Stewart 1981,1983; Lindinger et al 1987; Lindinger and Heigenhauser 1988, 1990, 1991; Lindinger et al. 1995). It has been proposed that mechanisms involved in the regulation of K^+ in contracting skeletal muscle play an important role in maintaining contractile function (Lindinger et al 1995).

Alkalosis (Alk) induced by sodium-bicarbonate ($NaHCO_3$) ingestion has long been used as an ergogenic aid and demonstrated to enhance short term intense exercise performance (Katz et al, 1984; Kinderman et al, 1977; George et al, 1988; Linderman and Fahey, 1991; Sutton et al, 1981; Verbitsky et al, 1997). One study has also demonstrated an improvement in endurance exercise with alkalosis (Potteiger et al, 1996).

Alkalosis has also been shown to enhance glycolytic adenosine 5' triphosphate (ATP) production and muscle Lac^- release during intense exercise (Brooks, 1991). Research investigating the effects of alkalosis on muscle and plasma pH during intense exercise has been extensive, but little has been done to investigate the effects of alkalosis on K^+ regulation, despite the strong links demonstrated between changes in H^+ and K^+ during exercise (Lindinger and Heigenhauser, 1991; Bangsbo et al, 1996; Street et al, 2005; Juel 2007). In electrically stimulated rat muscle, K^+ release was decreased and contractile force increased following increased perfusate [$NaHCO_3$] (Lindinger et al 1990). Thus it is plausible that performance enhancement in humans due to alkalosis may also be at least partially attributed to reduced K^+ release during intense exercise and improved K^+ regulation, with subsequent preservation of membrane excitability. Also, very little is understood about the effects of alkalosis on K^+ regulation in small muscles eliciting a small absolute work rate. Thus Study 1 investigated the effects of acute $NaHCO_3$ ingestion on plasma K^+, ionic and acid-base regulation during high intensity forearm exercise.

Large increases in arterial [K^+] during intense exercise have been observed in healthy individuals (Sejersted & Sjøgaard, 2000; McKenna et al, 2008). In some clinical cases, such as renal failure and heart failure patients, only a small to moderate workrate is necessary to elevate plasma [K^+] to alarmingly high levels (McMahon et al, 1999). It has become established in recent times that the NKA content and activity are important modulators of K^+ release and uptake in active and inactive skeletal muscle (Clausen 2003). NKA function may be altered by changes in physical activity, intracellular electrolytes and endocrine status. Digoxin (DIG) is a specific inhibitor of NKA and commonly administered to patients suffering congestive heart failure due to its inotropic effect on the myocardium (Goldberg et al, 2007). Only ~3% of total body DIG binds to cardiac muscle, whilst ~50% binds to skeletal muscle NKA (Doherty et al, 1967; Steiness 1978; Joreteg 1986; Schmidt et al, 1991) following therapeutic digitization, which may exacerbate K^+ loss from contracting skeletal muscle or uptake by inactive skeletal muscle (Schmidt et al, 1995; Norgaard et al, 1991). However, the independent effect of DIG on K^+ regulation and skeletal muscle function in patients is equivocal, due to concomitant effects of other medications and potentially of chronic inactivity. DIG binding to NKA in healthy skeletal muscle has been found to increase during exercise (Joretag & Jogestrand, 1983). However, little is understood about the consequent effects on K^+ regulation and exercise performance following chronic DIG therapy in healthy humans. Thus, Study 2 and 3 focus on the effects of acute functional down regulation of NKA, via partial inhibition by chronic DIG therapy on K^+ regulation and exercising muscle performance in healthy humans. This is studied during forearm and

leg cycling exercise; representing small and large muscle mass respectively. Studies 2 and 3 were designed to shed further light on the specific role of NKA in the aetiology of K^+ regulation and muscle fatigue. These studies will also be the first examining altered NKA function and K^+ regulation through alkalosis and digoxin on peripheral and whole body exercise in humans.

This dissertation comprises a brief literature review, three experimental studies, general discussion, conclusions, future perspectives, references and appendices.

CHAPTER 2: LITERATURE REVIEW

The first section of this literature review is focused on K^+ fluxes from contracting muscle, and subsequent effects on muscle function and exercise performance. Concomitant changes in other strong ions and acid-base status will also be described, as will numerous mechanisms and interventions deemed significant regulators of plasma potassium, especially including NKA. The second section describes the effects of acutely altered acid-base status, via ingestion of a $NaHCO_3$ dose, and the effects of chronic DIG therapy, via its partial inhibition of NKA, on K^+ regulation and performance in healthy humans. The final section outlines the specific study aims and hypotheses. This literature review prioritises studies exploring these factors in human skeletal muscle or during exercise, although data from other tissue or species is described where appropriate.

2.1 Potassium regulation in resting muscle

2.1.1 Resting membrane potential

Skeletal muscle cells have a potential difference across their plasma membrane, being negatively charged on the inside with respect to the outside of the cell. At rest the membrane potential of human skeletal muscle is ~ -90mV (Fitts et al 1996; Sjøgaard et al 1985). The magnitude of the membrane potential is primarily determined by; difference in ion concentrations of intracellular and extracellular fluids; and the permeability of the plasma membranes to other types of ions (Hodgkin & Horowitz, 1959). The key ions responsible for generating resting membrane (E_m) potential are K^+, Na^+ and Cl^- (Sejersted et al 2000; Cunningham et al 1971). The trans-membrane difference in $[Na^+]$ and $[K^+]$ is due to the plasma membrane active transport system which pumps Na^+ and K^+ out of and into the cell, respectively; and low permeability to Na^+ (Sjøgaard, 1990). The membrane potential electrical force of an ion is equal in magnitude but opposite in direction to the concentration force of the ion is known as the equilibrium potential, which for K^+ is equivalent to ~-100mV; Na^+ ~+55mV; and ~Cl^- -86mV, in a variety of species including rats, frogs and guinea pigs (for extensive review see Sejersted & Sjøgaard, 2000). At the equilibrium potential there is no net movement of the respective ion due to balanced opposing forces (Sejersted & Sjøgaard, 2000). The K^+ equilibrium potential can be calculated using the Nernst Equation (Appendix 1). Resting E_m is not equal to K^+ equilibrium potential, due to numerous open Na^+ channels allowing continual cell diffusion of Na^+. Likewise, diffusion of K^+ ions out of the cell balances the electrogenic effect of Na^+ influx. However, the resting membrane is significantly more permeable to K^+ than Na^+ (Sejersted & Sjøgaard, 2000). Thus resting membrane potential is closer to the K^+ equilibrium potential than that of Na^+ (Hodgkin & Horowitz, 1959). As predicted by the Goldman Equation (Appendix 2), changes in

$[Na^+]_e$ have little effect in altering membrane potential, whereas a decrease in $[K^+]_e$ will decrease the membrane potential. Intracellular and extracellular Na^+ and K^+ concentrations at rest are largely regulated by the activity of the Na^+K^+ATPase (NKA), which will be discussed further in this literature review (2.1.4).

2.1.2 Ion changes and action potentials

Action potential initiation requires a cell membrane potential of ~ -80mV (Sjøgaard, 1990). During an action potential, the membrane permeability to K^+ and Na^+ ions are markedly altered. As voltage sensitive Na^+ channels open, an influx of Na^+ ions into the cell follows, culminating in the depolarization phase of an action potential (Sejersted & Sjøgaard, 2000). The membrane is rapidly repolarised by closure of the Na^+ channels, opening of K^+ channels and continuous NKA activity. Hodgkin & Katz (1949) demonstrated that reduced $[Na^+]_e$ decreases the action potential magnitude, but only has a negligible effect on the resting membrane potential. Under circumstances of rapid depolarization, opening of Na^+ channels overcomes repolarisation forces (Hodgkin & Huxley, 1952). Conversely, depolarisation produced slowly cannot initiate an action potential, as the opening of the K^+ channels balances the gradual opening of Na^+ channels. Disturbances in intracellular and extracellular $[K^+]$ and $[Na^+]$ are proposed to be associated with muscle fatigue (Sjøgaard et al 1995; Lindinger and Heigenhauser, 1988; Gonzales-Serratis et al, 1978; Hnik et al, 1986). A decrease in extracellular $[K^+]$ will cause gradual depolarisation of the membrane and changes in the shape of the action potential (Westerblad and Lännergren, 1986; Metzer and Fitts, 1986). A decrease of more than 20mV will inactivate the membrane to action potential transmission (Hodgkin and Huxley, 1952).

Membrane permeability to Na^+ changes with alteration in E_m. Depolarization increases Na^+ permeability and hyperpolarization decreases Na^+ permeability, predominantly due to Na^+ channel inactivation (Adrian et al 1970; Hodgkin & Huxley 1952; Ruff 1999). An action potential only occurs when there is enough Na^+ influx due to the opening of Na^+ channels exceeding K^+ efflux. Most skeletal muscle cells have a increase in E_m by ~10-15mV at contractile induced fatigue (Balog et al 1994; Renaud & Mainwood 1985), although continuous stimulation of single muscle fibres have been found to elicit depolarisations greater than 25mV (Westerblad & Lännergren, 1986). As muscle contractions continue, cellular K^+ efflux occurs with each action potential, substantially elevating extracellular $[K^+]$, which subsequently contributes to E_m depolarization (McKenna et al, 2008). The K^+ efflux effect on depressing E_m is attenuated by activation of NKA (Clausen 2003) and Cl^- redistribution across the muscle membrane (Cairns et al, 2004). The amplitude of change in E_m, action potentials and ionic gradients, is likely to be greater in the t-tubular system compared to the sarcolemma (Overgaard et al

1999; Fitts et al 1996). Therefore, there is resultant increased interstitial [K^+] and intracellular [Na^+]; decreased intracellular [K^+] and membrane potential; decreased action potential amplitude (McKenna et al, 2008).

2.1.3 ATP - sensitive K^+ channels

ATP-sensitive K^+ channels ($K^+_{(ATP)}$) are abundant on the sarcolemma (Spruce et al, 1985; Nielsen et al, 2003) and at lower density in the T-system (Nielsen et al, 2003). Until recently, there was no evidence to suggest that $K^+_{(ATP)}$ open in resting or unfatigued skeletal muscle. Renaud et al (1996) found that $K^+_{(ATP)}$ are voltage insensitive in frogs, open in the absence of ATP or increased ADP and AMP, and significantly contribute to the K^+ efflux induced effects on action potential duration. However, Nielsen et al (2003) demonstrated that $K^+_{(ATP)}$ are active at rest in human muscle, therefore suggesting $K^+_{(ATP)}$ contribute substantially to resting muscle membrane permeability. During exhaustive muscle contractions, opening $K^+_{(ATP)}$ are largely the result of a significant decrease in [ATP], potentiated by a reduction in pH_m (Davies et al 1992) resulting in outwardly rectifying K^+ current. Discrepancies in $K^+_{(ATP)}$ characteristics may be a species effect, or that $K^+_{(ATP)}$ are inactive under in vitro conditions, but active under in vivo conditions (Nielsen et al, 2003). The $K^+_{(ATP)}$ inhibitor glibenclamide had no effect on increasing interstitial [K^+] during exercise in humans (Nielsen et al, 2003), thus $K^+_{(ATP)}$ do not appear to contribute to increased K^+ release in human contracting muscle.

2.1.4 Skeletal muscle Na^+K^+ATPase

The Na^+K^+ATPase enzyme (NKA) is a transmembranous protein present in all cells and in skeletal muscle is located in the sarcolemma, t-tubules, and possibly at specific isoform specific intracellular sites (Clausen 2003). The majority of NKA are located in the t-tubule (Clausen 2003); however location specifics are largely unknown in humans. NKA is both an antiport protein and electrogenic pump, as it transports 3 K^+ and 2 Na^+ ions against their concentration gradients, and against the electrical gradient in the case of Na^+ (Skou 1998) and also functions to regulate fluids and solutes (Blanco & Mercer, 1998). The carrier moves three Na^+ ions out of the cell and two K^+ in for each molecule of ATP that is hydrolyzed (Post & Jolly, 1957). The pumping activity is responsible for maintenance of a high $[K^+]_i$ and low $[Na^+]_i$, and consequent establishment and preservation of intracellular to extracellular [Na^+] and [K^+] gradients in skeletal muscle. As NKA regulates Na^+ and K^+ fluxes across the cell membrane, it therefore has the capacity to substantially influence membrane potential, excitation and contractile function in skeletal muscle (Clausen, 2011; Clausen, 2003; Blanco & Mercer, 1998b).

The NKA is made up of α, β and γ subunits (Crambert et al, 2003). The catalytic α subunit has an affinity for Na^+, K^+, Mg^{2+}, ATP and for the cardiac glycosides ouabain and digoxin (Jorgensen 1982; Lingrel el al, 1994). The β subunit regulates the α subunit and NKA movement to the plasma membrane (Geering 1991). NKA subunits are expressed in 7 isoforms in mammalian cells (Blanco & Mercer 1998b), with their four α (α_1, α_2, α_3, α_4) and three β subunits (β_1, β_2, β_3). With the exception of α4, each of these is expressed in human skeletal muscle (Murphy et al, 2006b; Murphy et al, 2004). The α_1 and α_2 isoforms appear to have specific distribution to muscle fibre type, although inconsistencies prevail. An equal distribution of isoforms has been observed in type 1 and type 2 muscle fibres in rats (Hundal et al, 1993, Thompson et al, 1996a). However, Fowles et al (2004) found a greater abundance of α_1, α_2 isoforms in type 1 compared to type 2 muscle fibres. Inconsistencies have been reported for the abundance of β isoforms in rat skeletal muscle. β_1 abundance was significantly greater in type 1 compared to type 2 muscle fibres (Fowles *et al.* 2004, Hundal *et al.* 1993), whereas β_2 was greater in type 2 compared to type 1 rat muscle fibres (Fowles et al, 2004; Hundal et al, 1993).

Human skeletal muscle NKA content is most commonly measured by vandate-facilitated [^{3}H]ouabain binding site content (Norgaard et al, 1983; Norgaard 1986), which ranges between 223 - 425 pmol.(g wet weight)$^{-1}$ in healthy muscle (Kjeldsen et al, 1984b; Schmidt et al, 1994; Medbo et al, 2001; Nordsborg et al, 2005a; Aughey et al, 2006). No sex differences in NKA content have been found (Green et al, 2001; Murphy et al, 2007), with exception of 18% greater NKA content in male compared to female endurance athletes (Evertsen et al, 1997). A correlation for [^{3}H]ouabain binding sites to type 2 muscle fibres has been observed in human muscle (McKenna et al, 2003a), however numerous studies have not found relationships between NKA content and muscle fibre type in human muscle (Benders et al, 1992; Madsen et al, 1994; Fraser et al, 2002). In young rat muscle, [^{3}H]ouabain binding was ~20% greater in EDL (type 2) compared to soleus (type 1) (Clausen et al, 2004). In contrast, Chin and Green (1993) found that [^{3}H]ouabain binding was greater in type 1 compared to type 2 muscle fibres in mature rats.

At rest, NKA activity is low in skeletal muscle, but increases rapidly during muscle contractions, by up to 22-fold in isolated, stimulated rat soleus muscle (Nielsen & Clausen, 2000; Everts & Clausen, 1994). NKA activity in healthy human skeletal muscle, measured via maximal in-vitro 3-O-methylfluoroscein phosphate (3-O-MFPase), typically ranges between ~180 and ~300 (nmol.min^{-1}.(g wet weight)$^{-1}$) (Fraser et al, 2002; Nordsborg et al, 2005a; McKenna et al, 2006; Murphy et al, 2006).

No sex differences in NKA activity have been found (Murphy et al, 2007), and the effects of fibre types in human skeletal muscle is currently unknown. NKA activity is tightly controlled at rest, operating at a very low percentage (~5-10%) of theoretical capacity (Clausen et al, 1987a). Acute effects of catecholamines, insulin, β_2-agonists, calcitonin gene-related peptide (CGRP) and thyroid hormones (Clausen 2003) induce activation of NKA and resultant therapeutic hypokalemia. Numerous studies examining chronic physical training have also increased NKA content in human vastus lateralis muscle, including sprint (McKenna et al 1993) endurance (Madsen et al 1994) and strength training (Fraser et al 2002). Conversely, physical inactivity is strongly associated with downregulation of NKA in healthy individuals (Leivseth & Reikeras, 1994) and CHF patients (Norgaard et al, 1990). Six weeks of swimming training increased the total content of [^{3}H]ouabain binding sites by ~46% in rat hindlimb muscle compared to control, whereas 1 week of immobilization down regulated content of [^{3}H]ouabain binding sites by ~22% in rat hindlimb (Kjeldsen et al, 1986). Similarly, immobilization caused ~25% downregulation of [^{3}H]ouabain binding sites in guinea pig hindlimb muscle (Kjeldsen et al, 1986).

2.2 Intracellular and extracellular K^+, Na^+ and Cl^- regulation during exercise

The electrolyte concentration of muscles are altered with exercise and closely linked to the multifactorial processes that contribute to muscle fatigue (McKenna, et al 2008). The rate and magnitude of many of these changes is dependant on intensity and duration of muscle contractions.

2.2.1 Potassium regulation during exercise

Intracellular and extracellular potassium concentration ([K^+]) in skeletal muscle is an important contributor to the highly complex regulation of cardiovascular, respiratory, and skeletal muscle function. Following cellular K^+ release, increased interstitial [K^+] stimulates muscle chemoreceptors and this may play a role in to stimulating increases in heart rate, cardiac output and ventilation. Peripheral vasodilation will increase blood flow to exercising muscles, and assist delivery of metabolic substrates and removal of end products. In addition, increased arterial plasma [K^+] may stimulate carotid body chemoreceptors, thus contributing to the rise in exercise ventilation under some exercise conditions (Paterson, 1992).

The membrane potential of the t-tubule and sarcolemma is raised (ie less negative) by increased $[K^+]_e$ and decreased $[K^+]_i$ during exercise (Sejersted & Sjøgaard, 2000; McKenna et al, 2008). Depolarization of the membrane will follow a decrease in the K^+ gradient, significantly reducing the action potential (Hodgkin and Horowicz, 1959; Hodgkin and Huxley, 1952; Baker et al, 1962a,b). Consequently K^+ within intracellular and extracellular compartments requires precise regulation for effective muscle

function to prevail. With short-term high intensity exercise, maintenance of membrane potential and contractile function require rapid removal of K^+ from the interstitium; this occurs via activation of sarcolemmal NKA, increase in muscle blood flow, and K^+ uptake by non-contracting muscles and other tissues (Heigenhauser et al, 1988; Clausen 2008). Although both high and low intensity exercise result in K^+ efflux from contracting muscle and subsequent K^+ influx into plasma, peak values of K^+ influx into plasma are reached during short-term high intensity exercise (McKenna et al, 1997a; Medbø and Sejersted, 1990).

A decrease in $[K^+]_i$ is an important contributor to depolarization of the cell membrane (Lindinger and Heigenhauser, 1990). Thus the recovery of $[K^+]_i$ is important for action potential propagation and effective muscle function. Muscle $[K^+]_i$ has been calculated to decrease by ~35mM from 165mM at rest during intense exercise (Sjøgaard et al, 1985), and is not fully restored until after 10 minutes following a single bout of high intensity exercise (Lindinger et al, 1995), possibly due to delayed activity of NKA during exercise.

Accumulation of K^+_e is in part due to slower and incomplete activation of NKA compared to muscle efflux of K^+ via outward rectifier channels. The increase in $[K^+]_e$ is the major contributor to cellular depolarization (Lindinger et al, 1995). It has been proposed that an increase in $[K^+]_e$ contributes to the onset of fatigue due to action potential failure (Bigland-Ritchie et al, 1979) and impaired membrane excitability (Fitts, 1994). An increase in $[K^+]_e$ to ~10 mM was measured by microelectrodes inserted in human forearm muscle during isometric contraction (Vyskocil, 1983), and by microdialysis up to 13 mM during leg extension exercise (Green et al 1999; Nordsborg et al, 2003; Nielsen et al 2004; Street et al, 2005). As $[K^+]_e$ increases, K^+ diffuses into the plasma and is also taken up into red blood cells. K^+ is then distributed to non-contracting tissue which helps regulate cellular and whole body K^+ homeostasis (Heigenhauser et al, 1988; Sejersted & Sjøgaard, 2000).

As K^+ is lost from exercising muscle, muscle force is reduced (Verberg et al, 1999; Juel et al, 2000c). The size of the contracting muscle mass appears to be important in determining the magnitude of muscle K^+ loss. During cycling exercise, the arterio-venous $[K^+]$ difference ($[K^+]_{a-v}$) across contracting muscle typically declines to zero before the end of exercise (Putman et al 2003; Wasserman et al 1997; Vøllestad et al 1994), whereas during knee extensions, the $[K^+]_{a-v}$ remained negative (Bangsbo et al 1992; Bangsbo et al 1996; Rollet et al 1990). These differences may be associated with a larger reduction in muscle K^+ during smaller muscle mass exercise (Sejersted and Sjøgaard 2000). Small increases in $[K^+]_v$ of ~1mM have been observed during dynamic handgrip exercise at low work rates (MacDonald et al 2001) and also during

incremental wrist flexion exercise (Raymer et al 2004), which are in contrast to a 4-fold greater magnitude of change observed during large muscle mass exercise (McKenna et al, 1997a). Arterial and venous plasma [K^+] have been measured during maximal exercise at 7 and 8 mM respectively (Kowalchuk et al, 1988; Medbø and Sejersted, 1985, 1990; Vøllestad et al, 1994; McKenna et al, 1997a; Verberg et al, 1999; Sejersted & Sjøgaard, 2000; Table 2.1).

At the completion of cycling exercise to exhaustion, Van Beaumont et al (1973) showed that as much as two-thirds of a 24% rise in venous plasma [K^+] was due to haemoconcentration and one-third due to release of K^+ from contracting muscle and erythrocytes. The decrease in blood volume is due to a shift of water from the plasma compartment into the interstitial and intracellular compartments of contracting muscle (Lindinger and Heigenhauser, 1988; Sjøgaard and Saltin, 1982). Thus interpretation of [K^+] changes with exercise also requires evaluation of fluid shifts.

2.2.2 Sodium and chloride regulation during exercise

A substantial decrease in $[Cl^-]_e$ from 128 to 10 mM accelerated fatigue during prolonged and intermittent tetanic stimulation in the isolated mouse soleus and EDL muscles (Cairns et al, 2004). In non-fatigued mouse soleus muscle exposed to high $[K^+]_e$ of 9 mM and low $[Cl^-]_e$, a greater depression in force and accompanied depolarization was observed, compared to normal $[Cl^-]_e$ (Cairns et al, 2003). In electrically stimulated mouse soleus muscle exposed to low $[Na^+]_e$ (30-120 mM), the rate of fatigue was accelerated, whereas there was only negligible change observed in non-fatigued muscle (Cairns et al, 2003). Therefore normal extracellular [Na^+] and [Cl^-] maintenance influence cell membrane potential and fatigue, providing protective effects on skeletal muscle function, at least in isolated skeletal muscle preparations in mice. Increased extracellular [Na^+] and [Cl^-] during exercise can also alter muscle [H^+] via the strong ion difference ([SID]) (Lindinger et al,1990).

In human skeletal muscle, $[Na^+]_i$ increases substantially during intense exercise, from 6-24 mM (Sjøgaard et al, 1985). Increases in plasma $[Na^+]_a$ and $[Na^+]_v$ by ~3-6 mM and ~5-15 mM respectively during sub-maximal and sprint exercise (Putman et al, 2004; McKenna et al, 1997a). Na^+ fluxes during exercise and at fatigue in humans is inconsistent, with several studies demonstrating no net muscle Na^+ uptake during moderate intensity arm cranking exercise (Volianitis and Secher, 2002), and moderate intensity cycling (Wasserman et al 1997). In contrast, net Na^+ uptake by red blood cells was observed during sprint cycling exercise (McKenna et al 1997a).

Table 2.1: Peak $[K^+]$ in arterial and venous plasma during exercise

Reference	n	Mode	Time (min)	Intensity	$[K^+]_a$ (mM)	Femoral $[K^+]_v$ (mM)	Arm $[K^+]_v$ (mM)
(Maassen, et al, 1998)	10	Handgrip	2	Exhaustive			7
(Janssen et al, 2009)	11	Handgrip	3	30% MVC			4.6
(Volianitis et al, 2002)	10	Armcrank	6	80% WR_{peak}; 122W	4.5		6.1
(Bangsbo et al, 1996)	7	Leg ext	5	Exhaustive; 61W	5.5	6.5	
(Juel et al, 1999)	7	Leg ext	30	Submax, 36W	4.3	4.4	
(Verburg et al, 1999)	9	Leg Ext	60	30% MVC	4.7	5.1	
(Nielsen et al, 2003)	6	Leg ext	30	Submax; 30W	4	4.8	
(Nielsen et al, 2003)	6	Leg ext	12	Step-wise; 90W peak	5.4	6.1	
(Lindinger et al, 1990)	11	Cycle	4x0.5	Exhaustive; 4min rest	6	5.5	
(Vøllestad et al, 1994)	4	Cycle	4	110% VO_{2peak}; 440W	8	8.2	
(Hallén et al, 1994)	6	Cycle	22	Step-wise; 200W peak	6.4	6.8	
(McKenna et al, 1997a)	6	Cycle	0.5	Exhaustive; 951W av	7	8.2	
Wasserman et al, 1997	5	Cycle	6	85% VO_{2peak}	6.6	6.5	
(Kowalchuk et al, 1998)	9	Cycle	0.5	Exhaustive	7	8	
(Putman et al, 2003)	6	Cycle	3x15	30% VO_{2peak} 65% VO_{2peak} 75% VO_{2peak}	4.6 5.2 5.5	4.6 5.2 5.6	
(Medbo & Sejersted, 1990)	20	Running	1	Exhaustive	8.2	8.3	

*Values taken from Figures and therefore approximate

Intracellular $[Cl^-]$ ($[Cl^-]_i$) was unaltered during cycling exercise in humans (Kowalchuk et al, 1988), and little is otherwise known about changes in $[Cl^-]_i$ during exercise in humans. $[Cl^-]_i$ was unchanged during electrical stimulation in isolated rat muscle preparations (Lindinger et al, 1987). Another study demonstrated that $[Cl^-]_i$ changes are

dependent on muscle types, whereby $[Cl^-]_i$ increased in perfused rat hindlimb from 12-23mM in plantaris, but no changes were found in soleus or gastrocnemius (Lindinger & Heigenhauser, 1988). In humans there is also little change in plasma $[Cl^-]$ during exercise, primarily due to concomitant Cl^- and fluid loss from plasma (McKenna et al, 2008; Kowalchuk et al, 1988). Both arterial (a) $[Cl^-]_a$ and femoral venous (v) $[Cl^-]_v$ increased during sub-maximal and sprint cycling exercise, by ~3-7 mM and ~2-6 mM, respectively (Putman et al, 2004; McKenna et al, 1997a).

Net Cl^- efflux from plasma occurs throughout exercise, and is consistent with muscle Cl^- uptake during sprint cycling exercise (McKenna et al 1997a). Some increases in $[Cl^-]$ may also occur in the interstitial and intracellular spaces (Sjøgaard et al 1985), whilst red blood cell uptake of Cl^- may also occur (Prange et al 2001).

2.3 Effects of training, hormones, age & gender on K^+ regulation

2.3.1 Training and K^+ regulation

Endurance and sprint training results in a blunting of the exercise- induced hyperkalemia when respective workrate and duration are identical, or when changes in $[K^+]$ are corrected for work done (Green et al, 1993; Nielsen et al, 2004; Harmer et al, 2006). This is possibly due to a contribution of reduced loss of K^+ from the contracting muscle, increased uptake of K^+ by contracting & non-contracting muscle, and increased total content of NKA in skeletal muscle (McKenna, 1995; Lindinger and Sjøgaard, 1991; Lindinger, 1995; McKenna et al, 1993; Harmer et al, 1994). Following sprint training, McKenna et al (1997a) observed an increase in net K^+ uptake across exercising muscle. In arterialised venous plasma, the $\Delta[K^+]$ (~19%) and the ratio of $\Delta[K^+]$ $work^{-1}$ (~27%) were both lower during maximal exercise bouts after sprint training (McKenna et al, 1993). During peak incremental exercise, plasma $[K^+]$ was reduced following endurance training (Kjeldsen et al, 1990; Green et al, 1993). During single leg extension exercise following intense intermittent training, there was less accumulation of interstitial $[K^+]$, and time to fatigue increased by 28% (Nielsen et al, 2003). In the same study skeletal muscle NKA α_1 and α_2 subunit abundance increased by ~29% and 15% respectively. Increased activation of NKA during exercise after training may improve K^+ regulation, however an improvement in work performance was not correlated to NKA content following endurance (Madsen et al, 1994) or sprint training (McKenna et al, 1993).

2.3.2 Catecholamine and insulin regulation of K^+ flux during exercise

During whole body exercise, plasma epinephrine, norepinephrine, and insulin concentrations increase substantially and induce NKA activation (Galbo et al, 1975;

Nielson et al, 1984; Clausen, 1986). As a consequence of NKA activation via β_2-adrenoceptors in skeletal muscle, plasma [K^+] during exercise is reduced. Catecholamines released from the sympathetic nervous system are important modulators of K^+ shifts during exercise (Williams et al, 1985). Exercise induced increases in plasma catecholamines are principally responsible for increased K^+ uptake by non-contracting tissues, with an increase in arterial plasma [K^+] playing only a minor role (Lindinger et al, 1995). An increased $[Na^+]_i$ associated with muscle contraction may eventually be attenuated by an increase in circulating catecholamines due to increased NKA activity (Sejersted and Hallén, 1987).

Insulin stimulates NKA, and subsequently increases K^+ uptake in human forearm muscle (Zierler & Rabinowitz, 1964; Ferrannini et al, 1988). Calcitonin gene-related peptide (Nielsen et al, 1998) and the thyroid hormone triiodothyronine (Asano et al, 1996; Ismail-Beigi & Edelman) stimulate NKA in rats, but their effects on plasma K^+ regulation during muscle contractions in humans are unknown. The influence of these hormones on NKA activation is presented in Figure 2.1.

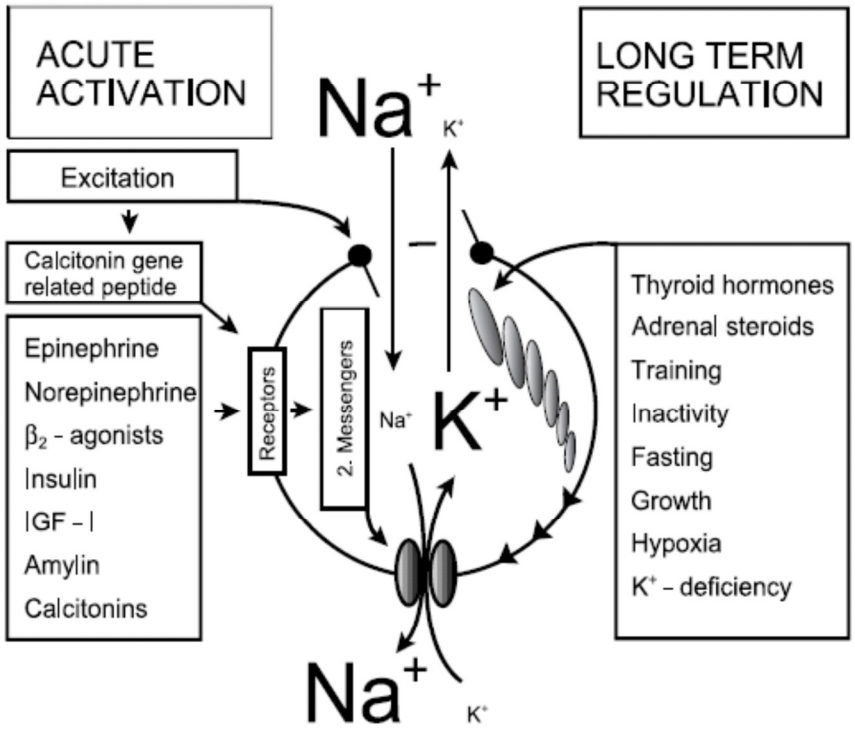

Figure 2.1 Regulatory factors controlling activity and contents of NKA in skeletal muscle. The left side panel includes factors eliciting acute stimulation of NKA via second messengers. The right side panel includes factors influencing NKA content by modifying their synthesis or degradation. From (Clausen, 2003).

2.3.3 Effects of age and sex on K^+ regulation

The difference in muscle water and electrolyte contents due to age is generally insignificant. Forsburg et al (1991) found that $[Na^+]_i$ and $[K^+]_i$ were stable and showed no variation with age and sex. No sex differences have been previously found in skeletal muscle [^{3}H]ouabain binding site content (Murphy et al, 2006a; 2007; Green et al, 2001), nor NKA activity (Murphy et al, 2007).

NKA content in human skeletal muscle remains similar from birth to old age (Kjeldsen and Gron, 1989; Nørgaard et al, 1994), although some have found a decrease with age (Dorup et al, 1988; Klitgaard and Clausen, 1989). The density of NKA may change due to age, muscle activity, and K^+ availability in rodent skeletal muscle (Kjeldsen et al, 1984, 1985, 1986). The [^{3}H]ouabain binding sites per unit weight increased by ~ 5-fold in rat skeletal muscle from birth to ~22 weeks of age. Similar observations were made in mice, although reaching a plateau by ~4 weeks of age. However the NKA content decreased by ~60% from birth to maturity in guinea pigs (Kjeldsen et al, 1984). Compared to untrained, a 32-40% increase in ouabain binding site concentration has been found in trained elderly humans (Klitgaard and Clausen, 1989).

2.4 NKA changes during exercise, following training & in disease

2.4.1 Role of skeletal muscle Na^+,K^+-ATPase on exercise induced fatigue

During muscle contractions, NKA facilitate K^+ reuptake by both active and inactive skeletal muscle. While NKA are rapidly activated, and reach theoretical maximal activity in isolated rat muscle stimulated at 100Hz, (Clausen, 1998), this level of activation does not occur during exercise in human muscle (Sejersted and Sjøgaard, 2000). Failure of the NKA to reach theoretical maximal activity in humans may in part be due to the low stimulation frequency elicited during motor unit activation (McKenna, 1998). Changes in electrolyte, endocrine and physical activity status are associated with long term regulation of NKA in skeletal muscle. Upregulation of NKA is demonstrated following training (McKenna, et al. 1993; Evertson et al 1997; Green et al, 1992) and glucocorticoid administration (Clausen, 1998); see figure 2.1. Conversely, downregulation of NKA occurs through hypothyroidism, cardiac insufficiency, myotonic dystrophy, McArdle's disease (Clausen 1998) and limb immobilisation (Leivseth et al, 1992; Kjeldsen et al, 1986). Fraser et al (2002) found that intense knee extension exercise reduces the maximal NKA activity by ~17% when measured by in-vitro 3-O-MFPase activity. Numerous other exercise studies using the same technique have also demonstrated decreased NKA activity by ~11-21% following repeated knee extensions (Petersen et al, 2005), 30-72 min sub maximal cycling (Sandiford et al, 2004; Leppik et al, 2004; Murphy et al, 2006b), and following incremental cycling (Aughey et al, 2005). Depressed maximal invitro NKA activity maybe explained by partial muscle glycogen

depletion, effects of free radicals, increased cytosolic [Ca^{2+}] and α subunit phosphorylation (Fraser et al, 2002; Kourie et al, 1998; Cheng et al, 1997; Matsuda et al, 1991b). This might suggest that muscle K^+ release could be exacerbated with fatigue, consistent with studies reporting a widening of the arterio-venous [K^+] difference across contracting muscle during fatiguing exercise (Verburg et al. 1999; Sahlin and Broberg 1989). However, most studies examining arterio-venous [K^+] during muscle contractions in humans report a progressive decline (reduced net K^+ release) soon after the early stages of exercise (Gullestad et al 1995; Hallen et al 1994; Vøllestad et al 1994). It is well recognised that factors such as mode, intensity and duration of exercise, muscle mass, training or pharmacological intervention will influence the rate of K^+ release and uptake.

2.4.2 Physical activity and disease affect skeletal muscle NKA content and maximal in-vitro NKA activity

Physical training increases the muscle NKA content and reduces the plasma arterialised venous [K^+] during exercise, but no relationship has yet been found between these variables (McKenna et al. 1993, McKenna 1995; Madsen et al 1994; Evertson et al, 1997). Following 7 weeks of intense intermittent single leg knee extension training, time taken to fatigue was ~28% longer in the trained leg compared to control during a progressive incremental knee extension test to exhaustion (Nielsen et al, 2003). In the same study, NKA α_1 and α_2 subunits were ~29 and 15% higher in the trained leg, whilst there was no difference in abundance of β_1 subunits or K_{ATP}. Interstitial [K^+] ([K^+]$_I$) increased more rapidly in the control leg at submaximal work rates, however there was no difference in [K^+]$_I$ at fatigue. These findings demonstrate that a reduced accumulation of [K^+]$_I$ contributed to a delay in exercise fatigue following 7 weeks of training.

Chronic inactivity is characteristic of patients with major organ failure, who also demonstrate abnormal K^+ regulation. Heart failure patients have reduced muscle NKA content by up to 25% (Nørgaard et al. 1990), and also demonstrate an excessive rise in arterial [K^+] during exercise (Barlow et al. 1995). However, Green et al (1998) found that downregulated NKA in skeletal muscle is not associated with chronic heart failure. Haemodialysis (HD) and renal transplant (RTx) patients exhibit a 31 and 28% reduction in vastus medialis maximal in-vitro NKA activity compared to control, although no differences were found for NKA content. Plasma [K^+] increased more substantially during knee extension exercise in HD compared to RTx and control. These patients also exhibited concomitantly reduced VO_{2peak} by ~35% compared to control, and exacerbated muscle fatigability by ~25% compared to control (Petersen, 2007). In

uremic rats, maximal in vitro NKA activity was decreased by 30-50% compared to control (Bonilla et al, 1991; Druml et al, 1988; Goecke et al, 1991).

Downregulation of NKA content was found in immobilized rat and guinea pig skeletal muscles, followed by restoration and eventual upregulation (Kjeldsen et al 1986; Leivseth et al 1992). Similar observations have been found in humans with chronically inactive deltoid muscle, where NKA content was downregulated by ~27% (Leivseth and Reikeras, 1994).

2.5 Effects of altered acid-base status on plasma K^+ during exercise

2.5.1 Metabolic and acid-base changes during exercise & effects on fatigue

During muscle contractions adenosine 5' triphosphatase (ATP) energy demands are high in order to sustain cross-bridge cycling, sarcoplasmic reticulum (SR) calcium adenosine 5' triphosphatase (Ca^{2+}ATPase) activity and NKA activity. The source of ATP energy supply varies depending on the muscle contractile demands, and includes high energy phosphates, glycolysis, and oxidative phosphorylation. Reductions in ATP during contractions are accompanied by increases in numerous metabolic by-products, including adenosine monophosphate (AMP), adenosine diphosphate (ADP), inosine monophosphate (IMP), inorganic phosphate (P_i) and hydrogen (H^+) ions (Fitts, 1994). Accumulation of P_i contributes to impaired myofibrillar Ca^{2+} sensitivity and Ca^{2+} binding and sequestration within the SR with consequent decreased tetanic $[Ca^{2+}]_i$ which may be significant in the aetiology of late stage muscle fatigue (Allen et al, 2008).

During intense muscle contractions, significant accumulation of Lac^- and H^+ ions occurs (Fitts, 1994) and these coexist with reductions in muscle force. The notion of a causal relationship between increased acidosis and reduced muscle function has been a topic of great interest for decades, particularly in relation to enhanced muscle performance in the presence of training and alkalosis-induced improvements in pH regulation (Juel, 2008; Linderman and Gosselink, 1994). However, even markedly increased $[Lac^-]_i$ (~30mM) and $[H^+]_i$ do not appear to be major factors contributing to muscle fatigue (Allen et al, 2008). The relationship between elevated lactate and fatigue is weak (Karlsson et al, 1978) and Lac^- per se does not appear to impair muscle force (Posterino et al 2001). In fact intracellular acidosis may even exert a protective effect on muscle function, mediated via lower muscle Cl^- conductance (Nielsen et al 2001; Pedersen et al 2004; Pedersen et al. 2005). Non-physiological $[Lac^-]$ of up to 50mM did not impair force production or Ca^{2+} sensitivity in isolated muscle fibres (Andrews et al, 1996; Posterino et al, 2001). Muscle fatigue also occurs in humans with only small increases in $[H^+]_i$, thus demonstrating that the role of increased H^+ may not be significant (Allen et al, 2008). Whilst the relationship between an increase in Lac^- and H^+ accumulation on muscle fatigue in humans during exercise is currently equivocal,

acid-base changes are considered as there may be indirect effects of H^+ on K^+ homeostasis (Juel, 2008). Numerous studies have demonstrated that metabolically induced alkalosis improves exercise performance (Bishop et al, 2004; Raymer et al, 2004; Verbitsky et al, 1997). These studies have taken a traditionally focussed approach to investigating concomitant changes in extracellular buffering, intracellular acidification and non-oxidative glycolysis links between alkalosis and improved exercise performance. However changes in K^+ homeostasis during exercise with alkalosis might shed light on understanding other mechanisms associated with alkalosis induced improvements in exercise performance, and will be described further in section 2.5.2.

Acid-base regulation can be described via mechanisms that are dependent on compartments and membrane transport systems (Juel, 2008). The origin of acidosis in skeletal muscle and plasma can also be determined via independent variables determining $[H^+]$, which include PCO_2, the strong ion difference $(Na^+ + K^+) – (Lac^- + Cl^-)$ concentration ([SID]) and weak acids and bases ($[A_{TOT}]$) (Stewart, 1983; Johnson et al. 1996), commonly known as the physicochemical approach. This approach assumes that H^+ and HCO_3^- are dependent variables, and in context with changes in K^+ and other strong ions will be described further in section 2.5.2.

2.5.2 Alkalosis and K^+ regulation

Sodium bicarbonate ($NaHCO_3$) ingestion can enhance muscle performance, which has been traditionally thought to be attributed to enhanced muscle proton buffering capacity (Street et al, 2005; Raymer et al, 2005; Lindinger et al, 1999; Costill et al, 1984) and increasing muscle efflux of Lac^- and H^+ (Linderman and Fahey, 1991). Since maximal exercise is dependent upon glycolysis to sustain power output, a decrease in glycolytic activity may contribute to a decline in exercise performance (Allen et al, 2008). As a result of a drop in muscle pH from 7.0 to 6.5 during intense exercise, an increase in $[H^+]$ may allosterically inhibit glycolytic flux (phosphorylase) and rate limiting (phosphofructokinase) enzyme activity (Hollidge-Horvat et al, 2000; Chasiotis et al, 1983; Danforth, 1965; Trivedi and Danforth, 1966). However Donaldson et al (1978) suggest a reduction in force associated with an increased intramuscular $[H^+]$ may be primarily due to reduced excitation coupling of contractile proteins rather than a reduced glycolytic flux per se. Costill et al (1984) found that HCO_3 ingestion resulted in a slightly higher pH_m (6.87) compared to placebo (6.72) following intense intermittent exercise. Resting pH_m was found to be unchanged following $NaHCO_3$ ingestion (Costill et al, 1984; Greenhaff et al, 1989). Furthermore it appears ATP levels in heavy exercise are not limiting (Spriet et al, 1989).

An increase in muscle [Lac^-] following repeated high intensity sprint cycle exercise with alkalosis may be a result of enhanced non-oxidative glycolysis (Bishop et al, 2004). These authors did not measure arterio-venous [Lac^-] difference or blood flow across active or inactive muscle, therefore the observed increase in muscle lactate following exercise with alkalosis may also be due to increased Lac^- efflux from exercising muscle and/or reduced uptake of Lac^- by other inactive muscle. Bouissou et al (1988) found greater Lac^- accumulation in muscle with alkalosis (32 $mmol.kg^{-1}$ wet wt) compared to control (17 $mmol.kg^{-1}$ wet wt) at 125% VO_{2max}, which was associated with a ~30% reduced catecholamine responses during exercise with alkalosis. At 95% VO_{2max} Sutton et al (1981) also found greater muscle Lac^- with alkalosis (17.1 $mmol.kg^{-1}$ wet wt) compared to control (14.7 $mmol.kg^{-1}$ wet wt). This study also found that plasma [Lac^-] was lower in control during exercise, possibly due to a combined effect of lower muscle glycogen and decreased Lac^- efflux from exercising muscle (Sutton et al, 1981). An increase in muscle Lac^- efflux during alkalosis in both animal and human studies might be due to direct effects of [H^+] on transport mechanisms, as an increase in [H^+] inhibits anionic channels and anionic monocarboxylate carrier mechanisms (Mason and Thomas, 1988; Hutter and Warner, 1967).

The acid-base relationship following induced alkalosis has dominated previous research into fatigue. However, development of fatigue due to exercise induced K^+ disturbances could be attenuated by inducing muscular alkalosis, since interactions between muscle pH and K^+ accumulation during exercise are well known (Juel, 2007). Bangsbo et al (1996) demonstrated that muscle K^+ release was greater during high intensity leg extension exercise when vastus medialis muscle [Lac^-] was higher and pH lower than in control. These altered muscle pH and [Lac^-] conditions during leg exercise were achieved via preceding high intensity arm exercise. Subsequently it was concluded that increased muscle acidosis did not impair muscle glycogenolysis or glycolysis, and that interstitial accumulation of K^+ during exercise is a major contributor to muscle fatigue (Bangsbo et al, 1996). An isolated rat muscle preparation electrically stimulated at a high frequency for 5 min also demonstrated that a tight relationship exists between a decrease in $[K^+]_i$ and an increase in $[H^+]_i$ (Lindinger and Heigenhauser, 1991).

Numerous studies have investigated the [H^+] and [K^+] relationship more directly by inducing alkalosis prior to commencing muscle contractions. During 5 min intense intermittent tetanic stimulation of isolated perfused rat hindlimb, K^+ efflux was reduced with metabolic (MALK) and respiratory (RALK) alkalosis compared to control (Lindinger et al, 1990). In the same study, MALK and RALK also contributed to an increase in muscle Lac^- efflux, and reduced Na^+, Cl^- and water influx into muscle. However

alkalosis induced ionic changes did not affect muscle performance (Lindinger et al, 1990). In a study investigating the time course of change in plasma electrolytes with alkalosis in humans at rest, $[K^+]_a$ and $[K^+]_v$ decreased with alkalosis, coupled with a decrease in $[H^+]_a$ and $[H^+]_v$ (Lindinger et al, 1999). It was suggested that the mild hypokalemia observed in this study is likely due to increased intracellular $[Na^+]$, via Na^+-H^+ antiporter exchange of intracellular H^+ for extracellular Na^+ (Lindinger et al, 1999). Consequently it is likely that increased $[Na^+]_i$ stimulates NKA activity to reduce extracellular $[K^+]$, with a resultant hypokalemia. Furthermore, when acid-base status was manipulated with sodium citrate induced alkalosis in humans, interstitial $[K^+]$ and $[H^+]$ were significantly reduced during single leg extension exercise compared to control (Street et al, 2005). However, there was no change in exercise performance with alkalosis. Alkalosis effects on $[K^+]_v$ are inconsistent, where no changes were found during knee extension or cycling exercise (Street et al, 2005; Stephens et al, 2002), although $[K^+]_v$ decreased during wrist flexion exercise (Raymer et al, 2004).

Lindinger et al (1999) investigated the origin of alkalosis induced change in plasma $[H^+]$ at rest in humans, and found that an increase in arterial [SID] was the primary determinant for the decrease in arterial $[H^+]$. The increased arterial [SID] with alkalosis was equally due to an increase in plasma $[Na^+]$ and decrease in plasma $[Cl^-]$. However the relative ionic contribution to the [SID] will vary considerably during exercise compared to rest, due in part to increasing metabolic demands by contracting muscle. Lac^- efflux from muscle during exercise is also accompanied by a large efflux of K^+ and small influx of Na^+, Cl^-, and water (Hermansen et al, 1984; Kowalchuk et al, 1988; Lindinger et al, 1987; Lindinger and Heigenhauser, 1988; Sjøgaard et al, 1985; Sjøgaard, 1986; Sjøgaard and Saltin, 1982; Streter, 1963). As such, the effect of altered Lac^- and K^+ shifts with alkalosis on plasma [SID] during exercise in humans is unknown. No previous studies have simultaneously examined alkalosis effects on $[K^+]_a$, $[K^+]_v$, $[K^+]_{a-v}$ or K^+ efflux from exercising muscle in humans, therefore the net effect of alkalosis on K^+ regulation during exercise is yet to be determined.

2.6 Effects of digitalis on K^+ regulation in heart failure and in healthy humans

2.6.1 Overview

Digitalis purpurea, commonly known as “digitalis” or “cardiac glycosides”, has played a prominent role in the treatment of congestive heart failure for over 200 years. During the 1990’s, digoxin was the most commonly prescribed cardiac drug, eliciting positive inotropic effects for the relief of systolic ventricular dysfunction (Hauptman & Kelly, 1999). The following section will examine the specific digoxin inhibitory effects on skeletal muscle NKA and subsequent plasma K^+ disturbances during exercise.

2.6.2 Mechanisms of Digoxin Therapy

2.6.2.1 Inotropic, NKA and plasma K^+ responses to digoxin therapy

Congestive heart failure patients (CHF = all patients with left ventricle ejection fraction less than 40%; O'Connor et al, 1998) administered DIG have responded to treatment with positive inotropic, electrophysiological and neurally mediated effects (Mason et al 1964; Edner and Jogestrand 1994; Schmidt et al 1995; McMahon et al 1996; O'Connor et al 1998; Clausen 1998; Hauptman & Kelly, 1999; Demers et al 1999). The molecular target for digoxin is inhibition of the NKA α-subunit (Lichtstein, 1995). Consequently, increased $[Na^+]_i$ activates the Na^+/Ca^{2+} exchange mechanism (see Fig 2.1, Clausen 1998), leading to increased $Ca^{2+}{}_i$ via Ca^{2+} entry and/or reduced Ca^{2+} efflux (Hauptman & Kelly, 1999; O'Connor et al 1998; Clausen 1998). Elevated sarcoplasmic reticulum Ca^{2+} stores allow an increase in Ca^{2+} which mediates activation of contractile filaments and atrial excitation (Levi et al 1995; Clausen 1998). Consequently, positive inotropic and arrhythmogenic actions augment ventricular function, and typically respond by increasing; myocardial excitability; vagal tone; systolic force of ventricular contraction; ventricular emptying, cardiac output, peripheral circulation, oxygen consumption, renal function, and by decreasing; ventricle end diastolic pressure, myocardial enlargement, and venous pressure. While digoxin provides inotropic relief for many congestive heart failure symptoms, the electrogenic effect of cardiac (Smith, 1988) and skeletal muscle (Schmidt 1995) NKA function is significantly reduced, given that 50% of the total amount of digoxin in the body is bound to skeletal muscle, whilst only ~3% of digoxin is bound to cardiac muscle (Steiness, 1978). Digoxin NKA occupancy in skeletal muscle ranges from 9% (Schmidt et al, 1995) to 35% in heart failure patients (Green et al, 2001), and exercise increases digoxin binding to muscle whilst decreasing serum digoxin concentration in healthy humans (Joretag & Jogestrand 1983). Consequently, a therapeutic dose of digoxin will induce K^+ loss from the myocardium at rest (Brennan et al, 1972, cited in Clausen 1998) and from skeletal muscle during exercise (Schmidt et at, 1995). Edner and colleagues (1993) found that venous plasma K^+ increased by 0.19mM at rest, following 10 days of digoxin therapy at 0.37-0.5mg.d^{-1}. There was no arterial K^+ or serum digoxin concentration data reported, therefore the effects of apparent partial NKA inhibition on contracting muscle function was unknown in this study. No changes in serum $[K^+]$ were found in healthy humans after digoxin administration (Ericsson et al, 1981), however muscle $[K^+]$ content and whole body K^+ decreased by 5% and 9% respectively.

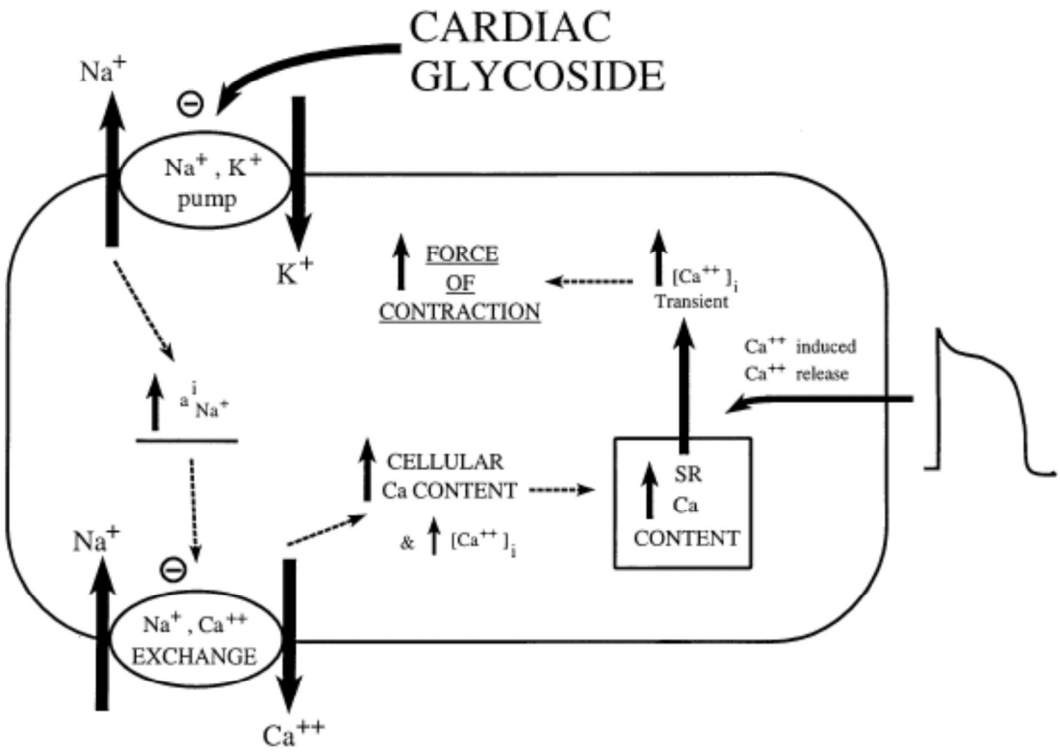

Fig 2.2 NKA inhibition hypothesis for digoxin in heart muscle cells. Digoxin binds and inhibits NKA, reduces Na^+ extrusion from cell, leading to a rise in intracellular [Na^+] (Na^+_i shown as the activity of Na^+_I (a^i_{Na}). This reduces Ca^{2+} extrusion from (or increases Ca^{2+} entry into) the cell via the Na^+-Ca^{2+} exchanger, and causes a rise of Ca^{2+}_i and cellular Ca^{2+} content. By increasing SR Ca^{2+} release and generating a larger Ca^{2+}_i transient, this results in an increase of the force of contraction of cardiac muscle. From Levi et al, 1995 – cited in Clausen 1998.

2.6.2.2 Neural Effects

The neural resonses to DIG include altered sympathetic nervous activity. Mason and Braunwald (1964) examined acute effects of intravenously infused ouabain (8.5 μg.kg^{-1}) on various autonomic nervous system responses in healthy and diseased individuals. Following 10 min ouabain infusion, cardiac patients elicited a decline in resting forearm vascular resistance; decline in resting venous tone; and an increase in resting forearm blood flow from 1.7 to 2.2 ml.100g^{-1}.min^{-1}; with no change in mean arterial pressure. Conversely, healthy individuals elicited an increase in forearm vascular resistance; increase in vascular tone; decrease in forearm blood flow from 3.6 to 2.9 ml.100g^{-1}.min^{-1}; and increased mean arterial pressure from 83 to 92 mmHg. Heart rate decreased with DIG infusion in both healthy (69 to 63 beats.min^{-1}) and CHF (108 to 87 beats.min^{-1}). The changes observed in cardiac patients might be due to baroreflex mediated sympathetic activity decline (Mason and Braunwald, 1964). In healthy individuals the

authors suggested cardiac output remained stable and systemic arterial pressure increased, whilst ouabain probably acted directly on peripheral vascular tone (Mason and Braunwald, 1964). Interestingly, Grossman et al (1998) suggested chronic digoxin exposure in healthy normotensive subjects elicited similar sympathetic activity changes seen in CHF patients. In healthy normotensive subjects treated with 0.25 $mg.day^{-1}$ digoxin, heart rate decreased significantly by 8 and 7 beats per minute at day 4 and 10, and diastolic blood pressure decreased by 7 and 5 mmHg respectively. Hauptman & Kelly (1999) also suggested that digoxin-induced decrease in sympathetic and increase in parasympathetic activity may also occur in individuals administered a dose lower than that normally necessary to elicit an inotropic effect.

2.6.2.3 Effects of digoxin on exercise

Several studies have previously demonstrated inhibition of skeletal muscle NKA activity associated with digoxin therapy in heart failure patients (Schmidt et al, 1995) and in healthy humans (Joretag & Jogestrand, 1983). Schmidt et al (1995) found that K^+ regulation was impaired during exercise in congestive heart failure patients undergoing chronic digoxin therapy. The $[K^+]_{a-v}$ across the exercising leg was increased by 50-100% during exercise, and ~9% of NKA were blocked, thus ouabain increased muscle K^+ release. However there was no exercise or muscle performance data reported in that study. Their findings suggest digoxin therapy and exercise training have opposing effects on plasma K^+ during exercise, mediated via either NKA down-or up-regulation, respectively (see Fig 2.2 from McKenna, 1998).

Patients in atrial fibrillation show higher digoxin binding in the right atrium than patients in sinus rhythm, possibly due to a higher activation rate of atrial myocardium, and thus also of NKA in that condition. This has similarly been found in skeletal muscle. Joreteg and Jogestrand (1983) demonstrated that during exercise in healthy volunteers, uptake of digoxin into skeletal muscle was increased and serum digoxin concentration was decreased compared to rest. This effect was also positively related to exercise intensity. During these studies, 10 healthy young adults ingested 0.5 mg digoxin for 2 weeks and performed two exercise tests at 70-90W and at 140-180W, both 24hr after the preceding dose, at 2-7 day interval.

During the lower exercise intensity, skeletal muscle digoxin content increased by 9%, with mean serum digoxin decreasing 26%. Similar, although more pronounced trends, followed during heavier exercise, with increased skeletal muscle digoxin (20%) and decreased serum digoxin (40%). Unfortunately, changes in exercise performance or in plasma or muscle $[K^+]$ were not quantified in this study. Schmidt et al (1995) reported digoxin did not change arterial or venous pH following various bouts of exercise in cardiac patients pre and post digoxin therapy. No effect of two weeks digoxin therapy

at 0.5mg.d^{-1} in healthy humans was found on $\dot{V}O_{2peak}$ (Sundqvist et al 1982). However, NKA content and activity were not measured in this study.

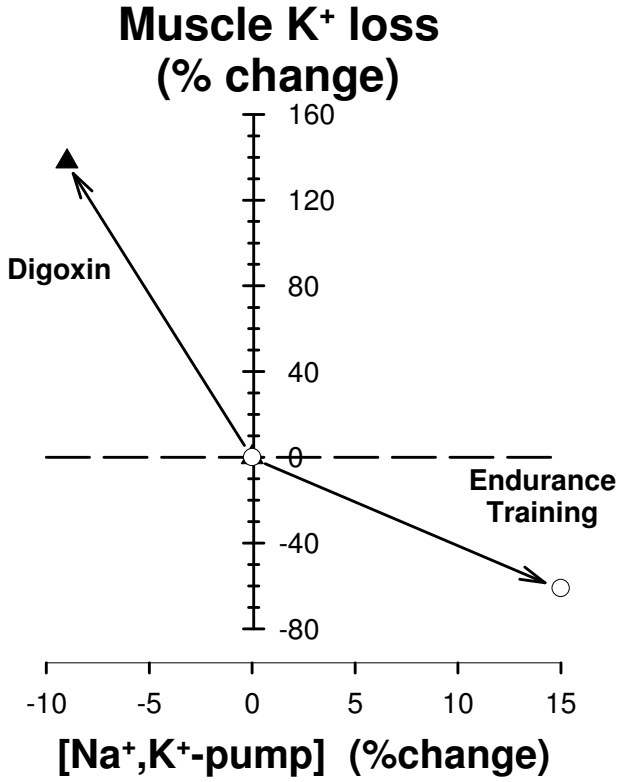

Fig 2.3 Effects of altered NKA concentration in human muscles; K^+ loss during exercise. Percent change in muscle K^+ loss shown for digoxin therapy (Schmidt et al, 1995) and for endurance training (Kiens and Saltin 1986). From McKenna (1998).

2.6.2.4 Digoxin Dosing and Toxicology

Numerous studies have investigated pharmacokinetics of acute digoxin therapy (dose range: 0.25 to 2.0 mg.day^{-1}) in healthy humans without adverse incident (Lyon et al, 1995; Hornestam et al, 1999; Grossman et al, 1998; Edner and Jogestrand, 1994; Morisco et al, 1996; Cauffield et al, 1997; Mason and Braunwald, 1964). See Appendix 3 for more information on digoxin characteristics, including; composition, description, distribution, elimination, dosing and toxicity.

2.6.2.5 Digoxin-induced compensatory NKA upregulation

The effects of chronic digoxin on adaptive compensatory NKA upregulation in humans are unclear. Digoxin induced compensatory NKA upregulation has been observed in

human and pig erythrocytes (Ford et al, 1979; Whittaker et al, 1983), but not in skeletal muscle in cardiac patient (Schmidt et al, 1993; 1995; Green et al, 2001).

2.7 Aims and hypotheses

Alkalosis is known to enhance exercise performance in humans, and has been found to decrease interstitial [K^+] in humans during leg extension exercise, and reduce K^+ loss in electrically stimulated isolated rat muscle. Numerous studies have investigated metabolic and cardiovascular responses to isometric muscle contractions of the forearm (Hamann et al 2004; Binzoni et al 2002; Van Beekvelt et al 2001). However, there are no known studies that have investigated the effects of alkalosis on K^+ homeostasis utilising small muscle mass in humans. Therefore the aims of study 1 were to determine the influence of exercise and alkalosis on K^+, ionic, acid-base, metabolic and cardiovascular responses to sub-maximal finger flexor muscle contractions in healthy humans. An important part of this study also required the development of a novel custom-designed integrated finger flexion ergometer to quantify workloads with precision.

It is well established that muscle K^+ loss and hyperkalemia occur during intense exercise and is attenuated by increased NKA activity; and that impaired NKA function contributes to skeletal muscle fatigue. Digoxin therapy provides myocardial inotropic benefits in heart failure patients due to partial inhibition of myocardial NKA. However NKA is ubiquitously expressed in all tissues, and therefore digoxin also binds to NKA in non-targeted skeletal muscle. The consequences of NKA inhibition on K^+ regulation in heart failure patients are inconclusive due to the coexistence of medications and inactivity that may also affect NKA function. The effects of NKA inhibition on K^+ regulation and exercise performance in healthy skeletal muscle are largely unknown. Therefore this study aims to investigate the effects of a standard clinical oral dose of digoxin on K^+ regulation in blood, and consequent muscle function during, and following supramaximal forearm muscle contractions in healthy young participants. The aim in study 2 was to investigate digoxin effects on ionic shifts across small exercising muscle with a small absolute cardiovascular demand.

Inactive muscle tissue is an important regulator of K^+ and other strong ions that are released from contracting skeletal muscle (Lindinger et al 1990). Little is known about the effect of digoxin therapy on ionic, metabolic and acid-base disturbances in healthy humans during large muscle mass exercise. Thus the purpose of study 3 was to investigate the role of inactive tissue in regulating ionic disturbances following digoxin therapy in healthy humans during cycling exercise.

2.7.1 Study 1

This study investigated three hypotheses;

(1) sodium bicarbonate induced alkalosis would delay fatigue during intense, dynamic, concentric finger flexion exercise in humans.

(2) alkalosis would enhance K^+ handling, as measured by reductions during finger flexion exercise in each of arterial [K^+], venous [K^+] and the arterio-venous [K^+] difference, as well as muscle K^+ efflux at fatigue.

(3) alkalosis would elevate plasma [Cl^-] and [Na^+] and augment muscle Cl^- and Na^+ uptake during exercise.

2.7.2 Study 2

It was hypothesised that 14 days of digoxin therapy in healthy young adults would;

(1) increase forearm muscle K^+ release and arterial K^+ concentration during exercise at the same absolute work rates

(2) inhibit post-exercise muscle K^+ re-uptake, reflecting NKA inhibition

(3) decrease glycolytic energy demands due to partial NKA inhibition

(4) impair peripheral muscle function leading to accelerated fatigue

2.7.3 Study 3

It was hypothesised that digoxin therapy would;

(1) augment the increase arterial plasma [K^+] during progressive bouts of submaximal cycling

(2) decrease K^+ uptake into non active muscle during exercise and in recovery

(3) decrease glycolytic energy demands due to partial NKA inhibition

(4) impair large muscle mass exercise performance leading to accelerated fatigue.

CHAPTER 3 ALKALOSIS INCREASES MUSCLE K^+ RELEASE, BUT LOWERS PLASMA [K^+] AND DELAYS FATIGUE DURING DYNAMIC FOREARM EXERCISE

3.1 INTRODUCTION

Marked ionic disturbances occur within contracting skeletal muscle cells and the surrounding interstitium, and these most likely contribute to the complex, multifactorial phenomenon known as muscle fatigue. Muscle excitation elicits cellular potassium (K^+) efflux, sodium (Na^+) influx (for review, see Sejersted and Sjøgaard 2000) and to counter these ion fluxes, a rapid and dramatic activation of the Na^+-K^+-ATPase enzyme (Clausen, 2003). However, the maximal Na^+-K^+-ATPase activity in muscle is acutely depressed during fatiguing exercise (Leppik et al 2004; Fraser et al 2002) and during intense muscle contractions is insufficient to match excitation-induced Na^+/K^+ fluxes (Clausen 2003, Sejersted and Sjøgaard 2000). Subsequently, depressed Na^+-K^+-ATPase activity results in at least a doubling of muscle extracellular [K^+] (Juel et al 2000, Nielsen et al 2004, Street et al 2005) and of intracellular [Na^+] (Juel et al 1986, Balog and Fitts, 1996; Sjøgaard et al 1985), and up to a 20% decline in intracellular [K^+] (Sjøgaard et al 1985; Lindinger et al 1991). These changes may impair cell membrane excitability and thereby contribute to muscle fatigue (Fitts 1994, Sejersted and Sjøgaard, 2000). Furthermore, muscle K^+ efflux during intense muscle contractions is considerable, with arterial and venous potassium concentrations ([K^+]) increasing to as much as 7 and 8 mM, respectively (Sejersted and Sjøgaard, 2000).

Whilst intense muscle contractions increase intracellular lactate ([Lac^-]) and hydrogen ion concentrations ([H^+]) (Fitts, 1994), these do not appear to be major factors contributing to muscle fatigue. Elevated lactate per se does not impair muscle force (Posterino et al 2001) and intracellular acidosis may even exert a protective effect on muscle function, via lower muscle chloride (Cl^-) conductance (Nielsen et al 2001; Pedersen et al 2004; Pedersen et al. 2005). Furthermore, maintenance of normal extracellular [Na^+] and [Cl^-], each counter the effects of elevated extracellular [K^+] on membrane potential and fatigue and thereby also confer protective effects on skeletal muscle function (Cairns et al 2004). Maintenance of muscle extracellular [Na^+] is vital since a decline in extracellular [Na^+] exacerbates the K^+-induced decline in force (Bouclin et al, 1995).

In apparent contrast to recent studies in isolated rat muscles, which indicate that acidosis may benefit muscle performance (Nielsen et al 2001, Pedersen et al 2004, Pedersen et al 2005), metabolic alkalosis in humans typically enhances whole body

exercise performance, including during short-term intense (Siegler et al, 2010; Verbitski et al 1997; Sutton et al 1981) and endurance exercise (Potteiger et al 1996). The suggested beneficial effects of alkalosis include an increase in extracellular proton buffer capacity (Lindinger et al 1999; Kesl and Engen 1998; Bouissou et al 1988; Costill et al 1984; Street et al 2005), increased muscle phosphorylase, phosphofructokinase and pyruvate dehydrogenase activities (Hollidge-Harvat et al 2000) and enhanced muscle Lac^- and H^+ release (Linderman and Fahey 1991). Far less is known about possible effects of alkalosis on muscle K^+, Na^+ and Cl^- fluxes, their regulation in blood, and whether improved regulation of these ions exerts any beneficial effects on human muscle performance.

Both respiratory and metabolic alkalosis increased muscle Lac^- efflux, decreased K^+ efflux, and reduced Na^+, Cl^- and water influx during stimulation of isolated rat hind limb muscle, but force output was unchanged (Lindinger et al, 1990). In resting humans, metabolic alkalosis decreased arterial and venous $[K^+]$, and increased the arterial plasma strong ion difference ([SID]); however exercise effects with this lowered extracellular $[K^+]$ were not determined (Lindinger et al 1999). The effects of alkalosis on venous $[K^+]$ ($[K^+]_v$) during exercise are unclear, with reports of no change during knee extension or cycling exercise (Stephens et al. 2002, Street et al 2005), but a reduction in $[K^+]_v$ during wrist flexion exercise (Raymer et al 2004). Interestingly, the decreased $[K^+]_v$ occurred together with improved exercise performance (Raymer et al 2004). However, since none of arterial $[K^+]$, arteriovenous $[K^+]$ differences, muscle K^+ efflux, or $[K^+]$ recovery data were reported in these studies, it is not possible to determine the overall effects of alkalosis on K^+ regulation, or whether these changes were important in enhanced muscle performance. Recently, alkalosis was found to lower muscle interstitial $[K^+]$ during knee extensor contractions, but $[K^+]_v$ was unchanged and muscle performance was not significantly improved (Street et al 2005). Therefore studies investigating K^+ regulation across contracting muscle and in plasma are required to determine the effects of alkalosis on K^+ regulation and explore the role of improved K^+ homeostasis in enhanced exercise performance in humans. No previous studies have investigated the effects of alkalosis on Na^+, or Cl^- exchange across muscle during fatiguing exercise in humans. The importance of such investigation is evident since Na^+ and Cl^- can each affect muscle function (Renaud et al 1996, Cairns et al 2004) and can also modulate muscle $[H^+]$ via the [SID] (Lindinger et al, 1990). Investigation of Na^+, or Cl^- regulation in plasma and their exchange across muscle are clearly required to understand alkalosis effects on human muscle function.

The contracting muscle mass may be important in determining alkalosis effects on muscle function. During whole body exercise, the arterio-venous $[K^+]$ difference ($[K^+]_{a-v}$)

across contracting muscle typically declines to zero before the end of exercise (Putman et al 2003; Wasserman et al 1997; Vøllestad et al 1994), whereas during knee extensions, the $[K^+]_{a-v}$ remained negative (Bangsbo et al 1992; Bangsbo et al 1996; Rollet et al 1990). These differences may reflect a larger reduction in muscle K^+ during smaller muscle mass exercise (Sejersted and Sjogaard 2000). Consequently, the effects of alkalosis on muscle K^+ efflux, plasma K^+, recovery K^+ uptake and exercise performance, may be more readily determined during exercise with a smaller muscle mass. Hence the effects of alkalosis on regulation of K^+ and other strong ions were investigated during and following exercise performed by a small muscle group, the forearm finger flexors, which also allowed measurement of arteriovenous ion differences.

Finally, although numerous studies have investigated metabolic and cardiovascular responses to isometric muscle contractions of the forearm (Hamann et al 2004; Binzoni et al 2002; Van Beekvelt et al 2001) very little is known about the effects of dynamic, concentric exercise in small muscle mass exercise. It is known that very high blood flows occur during small muscle mass exercise, with the potential for greater ion exchange across muscle. We therefore also determined the influence of both exercise and alkalosis on ionic, acid-base, metabolic and cardiovascular responses to finger flexor muscle contractions. This utilised a novel custom-designed ergometer which enabled dynamic, concentric contractions of the forearm finger flexor muscles.

This study investigated three hypotheses. First, that sodium bicarbonate induced alkalosis would delay fatigue during intense, dynamic, concentric finger flexion exercise in humans. Second, that alkalosis would enhance muscle K^+ handling, as measured by reductions during finger flexion exercise in each of arterial $[K^+]$, venous $[K^+]$ and the arterio-venous $[K^+]$ difference, as well as muscle K^+ efflux at fatigue. Third, that alkalosis would elevate plasma $[Cl^-]$ and $[Na^+]$ and augment muscle Cl^- and Na^+ uptake during exercise.

3.2 METHODS

3.2.1 Subjects

Nine healthy untrained volunteers, comprising five males and four females, signed informed consent (Appendix 4A) and participated in the study. Ethical clearance was obtained from the Victoria University of Technology Human Research Ethics Committee, and conforms to the Declaration of Helsinki. Physical characteristics of the subjects were (mean ±SD) age 22.7 ± 1.4 years, body mass 70.6 ± 2.3 kg, and height 172.8± 3.4 cm. In the 24 h prior to each visit, subjects refrained from vigorous activity and ingestion of caffeine and alcohol.

3.2.2 Overview of Test Procedures

Subjects attended the laboratory on five separate occasions. During their initial laboratory visit, anthropometric measurements of forearm length and circumferences were made in triplicate (CV range, 1.5-4.4%) to determine forearm volume. Total forearm muscle mass was estimated at 414±35 g based on published MRI models (Jahn et al 1999). Subjects were familiarised with finger flexion contractions, which was followed by an incremental finger flexion test. Incremental rhythmic finger flexion contractions were performed at a rate of 30 min^{-1}, commencing at 2.64 ± 0.22W. Resistance and thus power output were increased at the end of each min, with power increased by an average of ~0.17 W each min. Contractions continued until volitional fatigue, to allow determination of their peak work rate (WR_{peak}). This allowed calculation of work rates at an intensity of 75% WR_{peak}, used in all subsequent finger flexion trials. Following a 30 min rest, subjects were familiarised with this experimental protocol.

To classify their general training status, subjects then underwent an incremental cycling test on an electrically braked ergometer (Excalibur Lode, Groningen, Netherlands) to determine peak oxygen uptake ($\dot{V}O_{2peak}$). All methods, equipment and procedures for the $\dot{V}O_{2peak}$ test were as previously described (Li et al, 2002). On all subsequent laboratory visits, subjects performed a finger flexion trial at 75% WR_{peak} continued to fatigue. The second and third pre-experimental trials determined intra-subject variability in finger flexion power output and time to fatigue. During two final visits, subjects performed finger flexion exercise to fatigue trials under randomised, cross-over, counterbalanced double-blind conditions of both alkalosis (ALK) and control (CON). These were conducted one month apart, and included arterial and venous blood sampling and measurements of forearm blood flow.

3.2.3 Finger Flexion Exercise Tests

3.2.3.1 Finger Flexion Dynamometer

Subjects performed isotonic finger flexor contractions between pre-defined extension and flexion limits at a rate of 30 contractions min^{-1} on a custom-made finger flexion ergometer (Figure 3.1). The unique ergometer design allowed concentric muscle contractions with negligible eccentric load, to minimise any eccentric-induced effects on muscle, including soreness or damage. The forearm of the non-dominant arm was used, with the principal muscles involved being the flexor digitorum profundus and flexor digitorum superficialis.

3.2.3.2 Mode of Operation

Subjects lay supine on a couch with the arm extended placed perpendicular to the body in a frontal plane and elevated at an angle of ~130° from the shoulder (Figure 3.1). The arm was elevated above the heart, and also fully supported. Subjects flexed the fingers in an arc from the distal 3rd row phalanges, to the proximal end of the metacarpals, ensuring the finger tips made contact with the palm of the hand. The torso was secured to the couch by velcro straps to minimise lateral body movement, and involvement of other muscle groups. A handgrip was secured to the subject's fingers at the distal third row phalanges (exclusive of thumb) by adjusting a cushioned bar securely against the fingers. The handgrip was connected by a multistrand stainless steel cable (19 Gauge, 90 lb breaking strain) to a pneumatic piston (Bimba Manufacturing, Melbourne, Australia), with an intervening pulley, ensuring that the piston was lifted vertically. A load cell (Xtran 200N, Applied Measurement, Sydney, Australia) and a precision potentiometer (RS Components, Sydney, Australia) were fitted to the piston and to the pulley, to record force and displacement respectively, thus enabling calculation of power output during finger flexion contractions. The load cell and potentiometer were calibrated prior to, and at the completion of each test by hanging precision weights from the pulley hand piece and by displacing the piston through a series of precise distances, respectively, using custom software (Labview 3.1, National Instruments 1995, Austin USA). Subjects viewed a continuous real-time visual display of contraction rate and finger displacement on an elevated computer monitor. A personal computer fitted with an analogue to digital converter card (Computer Boards multi-channel DAS16), enabled simultaneous acquisition of contraction force, piston displacement, as well as extensometer strain gauge displacement (blood flow) and arterial and venous blood pressure data.

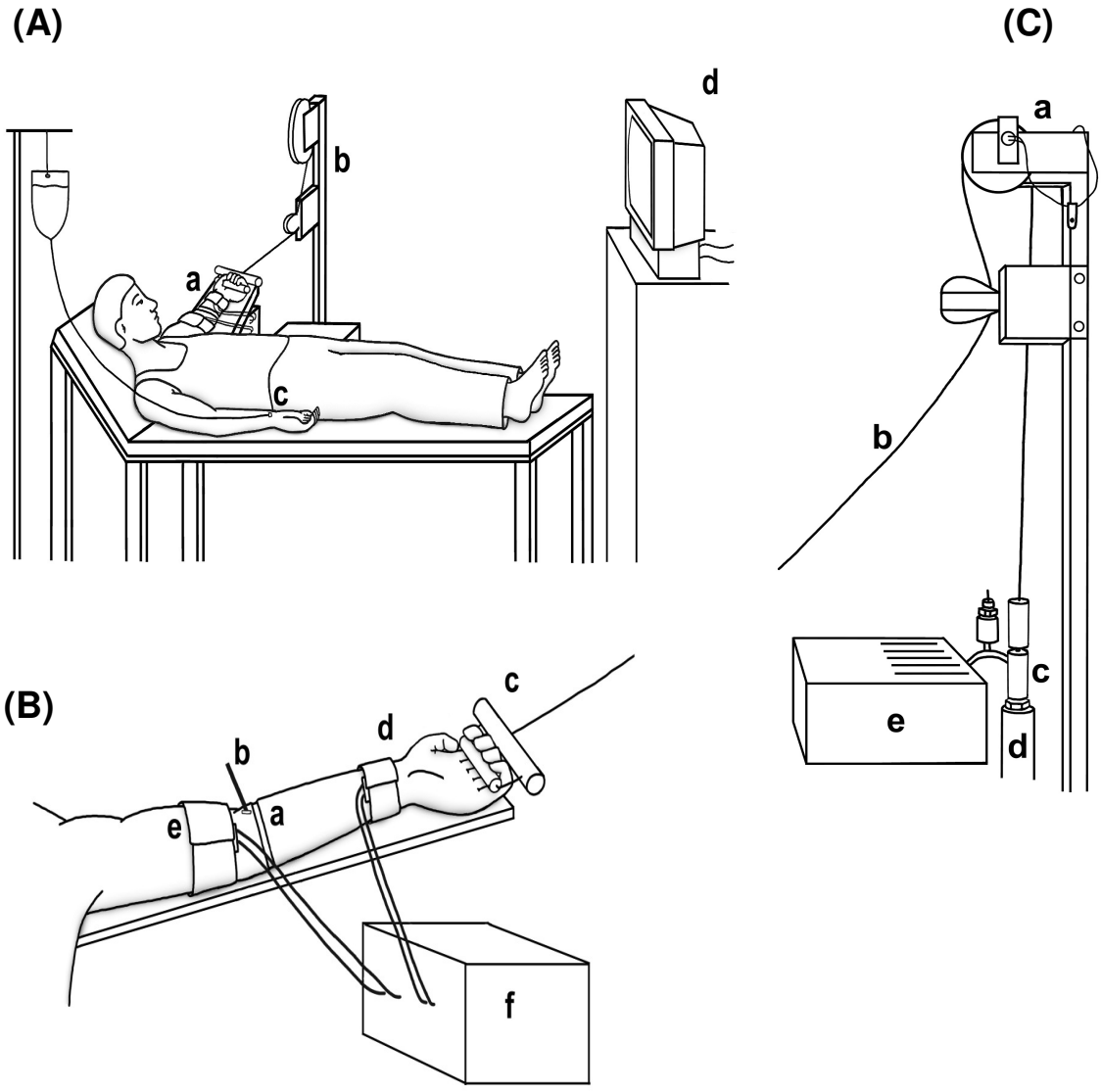

Figure 3.1. Detail of Finger Flexion Ergometer and Subject Experimental Setup

(A) Detail of subject position during finger flexion exercise. (a) Subjects lying supine with non-dominant exercising forearm elevated at an angle of ~130° from the shoulder; (b) finger flexion exercise ergometer; (c) radial artery cannulae; (d) continuous real-time visual display of contraction rate and finger displacement on an elevated computer monitor.

(B) Detail of forearm. (a) Extensometer strain gauge; (b) antecubital venous cannulae (retrograde); (c) handgrip secured to fingers and connected to a multistrand stainless steel cable; (d) high pressure arterial occluding cuff; (e) low pressure venous occluding cuff; (f) plethysmograph

(C) Detail of finger flexion dynamometer. (a) precision potentiometer fitted to pulley; (b) multistrand stainless steel cable; (c) external plumbing; (d) pneumatic piston; (e) ergometer electronic controls

3.2.4 Forearm Blood Flow

Forearm blood flow (FBF) was measured using venous occlusion plethysmography. Laboratory environmental conditions were maintained constant to minimise fluctuations in skin blood flow between visits. A venous occlusion cuff was placed just proximal to the olecranon process of the exercising forearm and periodically inflated to 55 mmHg, to occlude venous outflow. An extensometer strain gauge (Brimacombe et al, 1991) was placed around the widest circumference of the forearm to detect circumference changes. The extensometer dimensions were 4 mm diameter, 120 mm flaccid length, with resolution noise-limited to 0.1 μm. The extensometer was calibrated prior to each test by manually stretching the extensometer through a range of precise distances (Linear Tools digital caliper) via custom-made software (Labview 3.1, National Instruments 1995, Austin USA). The hand circulation was occluded during all FBF measurements using a wrist cuff inflated to 200 mmHg. Deep antecubital venous blood pressure measurements were recorded simultaneously with forearm circumference measurements using a pressure transducer (Abbott Critical Care Systems, Chicago, USA) attached to the catheter via a saline filled extension set. Pressure transducers were calibrated following each test against a range of pressures measured by a mercury sphygmomanometer. Three consecutive FBF measurements were taken in rapid succession at each time point and data averaged. The duration of venous occlusion depended on the rate of flow on each occasion, being 10-20 s for low flows under resting conditions, but only 1-3 s for high flows immediately after contractions (Figure 3.2). FBF measurements were terminated when venous pressure exceeded 55 mmHg. FBF were calculated as a change in forearm circumference (mm s^{-1}), then corrected for any change in forearm baseline due to the forearm swelling effects of finger flexion contractions, and substituted with the subject's forearm anthropometric data. A double truncated cone forearm geometric model (Appendix 5) was used to determine forearm volume changes and express FBF in ml min^{1}.

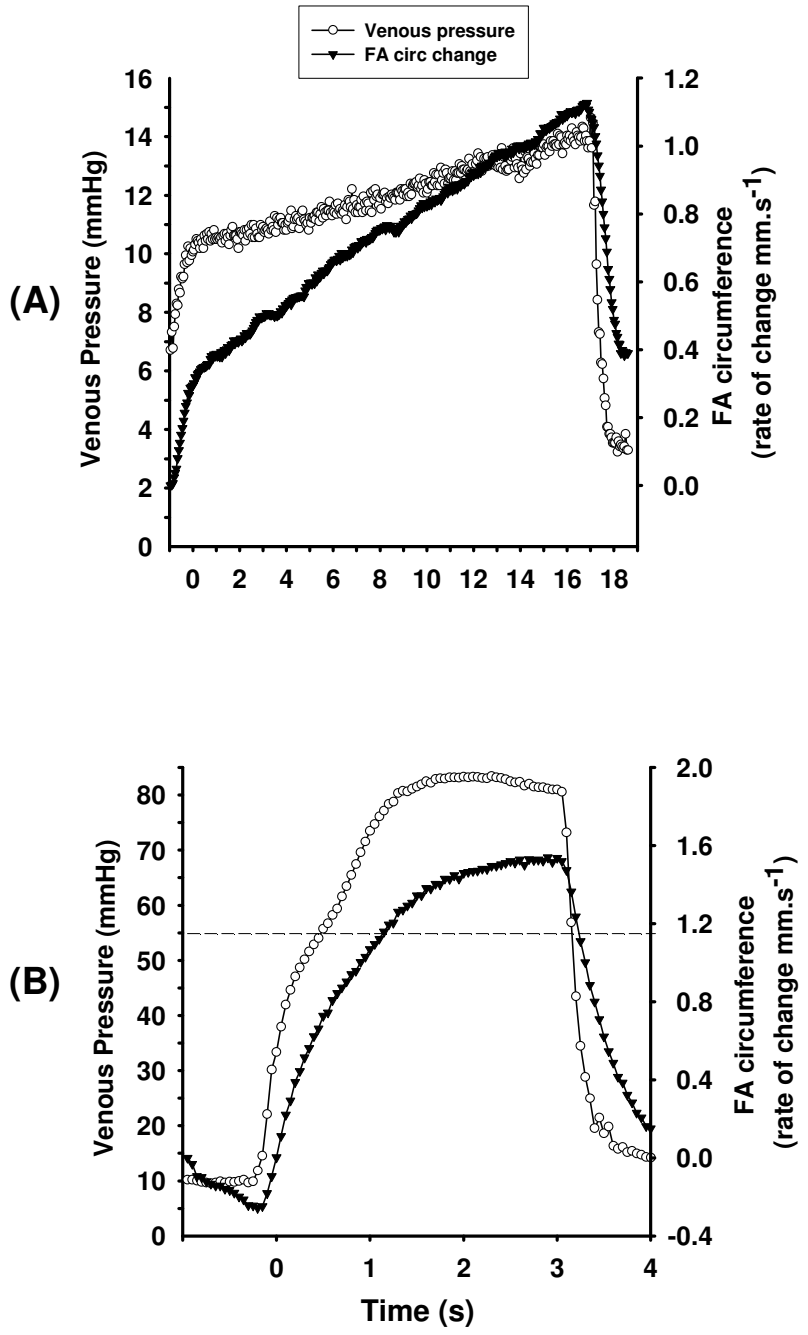

Figure 3.2. Typical Forearm Circumference Change and Venous Pressure.
Venous blood pressure (○ primary *y* axis) and simultaneous rate of change in forearm (FA) circumference (▼secondary *y* axis), used to calculated forearm blood flow at rest (A) and at fatigue (B). Dashed line represents the venous cut off pressure of 55 mmHg, at which point the flow measurement was discontinued. Note plateau effects above 55 mmHg.

3.2.5 Experimental Trials

All subjects completed one trial under $NaHCO_3$ (ALK) and CON (CON) conditions, one month apart. Subjects reported to the laboratory after consuming 0.3 $g^{-1}kg^{-1}$ of either encapsulated $NaHCO_3$ or $CaCO_3$ (AnalaR BDH, England) together with 1 l of water, in five equal doses at 15 min intervals, starting 3 h prior to exercise. Heart rate and rhythm were monitored by electrocardiogram (Mortara, Boston, USA). Catheters (20 or 22G Jelco) were inserted retrograde into the deep antecubital vein (v) of the contracting forearm and anterograde in the radial artery (a) of the non-contracting arm, under local anaesthesia (2% lignocaine injection). Subjects then rested for ~30 min prior to the commencement of each trial. Intra-arterial and intra-venous pressures were continually monitored (Marquette 710, Wisconsin, USA) by electronic pressure transducers (Abbott Critical care Systems, Chicago Illinois, USA) connected to saline filled cannulae via an extension line. Blood pressure signals were then interfaced with the finger flexion exercise computer system, enabling continual integration between power output, forearm circumference and blood pressure data. Arterial lines were kept patent by a slow, sterile, isotonic saline infusion under pressure. Subjects then performed finger flexion contractions at 75% WR_{peak} at a rate of 30 contractions min^{-1} and continued until fatigue. Fatigue for all trials was defined as a failure to maintain power output and/or cadence for eight consecutive contractions. Arterial and venous blood samples (each 5 ml) were taken simultaneously at rest, during 1 min intervals until fatigue, and at 1, 2, 5 and 10 min post exercise. Hand blood flow was occluded for 10 s prior to and during venous blood sampling by a high pressure wrist cuff. Forearm circumference measurements were made for FBF calculations immediately following blood sampling at rest, fatigue, 1, 2, 5, and 10 min-post exercise.

3.2.6 Blood Sampling and Analyses

Blood samples were immediately analysed in duplicate for plasma electrolytes (K^+, Na^+, Cl^-), acid-base status (HCO_3^-, pH), gas tensions (PO_2 and PCO_2), O_2 saturation (SO_2), haemoglobin (Hb) and haematocrit (Hct), using automated blood gas and haematology analysers and plasma and whole blood lactate concentration ($[Lac^-]$) spectrophotometrically, as previously described in detail (Sangkabutra et al 2003; Fraser et al 2002). All analysers were calibrated immediately before, during and after measurements with precision standards in the range of the measurements. Analytical precision for plasma $[K^+]$ was 0.03±0.05 mM. Plasma $[A_{TOT}]$ was not measured due to freezer failure and loss of plasma samples. An additional 5 ml of blood was taken at rest and at fatigue for plasma catecholamine analyses using the following method. Blood was immediately placed in lithium heparin tubes (125 IU) and 0.1M sodium metabisulphite (125 μl), mixed and centrifuged at 4000 rpm for 10 min at 4°C (3K 15

refrigerated centrifuge Sigma, Laborzentrifugen, Germany). Plasma was stored at -80°C until assayed for adrenaline ([Adr]) and noradrenaline ([Nor]) concentrations by high performance liquid chromatography with electrochemical detection (Sangkabutra et al 2003).

3.2.7 Calculations

Plasma hydrogen concentration ($[H^+]$ nmol l^{-1}) was derived from measured pH. Changes from resting levels in plasma volume (ΔPV_a) and blood volume (ΔBV_a) and changes in venous compared to arterial plasma (ΔPV_{a-v}) and blood volume (ΔBV_{a-v}) across the forearm were calculated during and following exercise, from changes in [Hb] and Hct, as previously described (McKenna et al, 1997). These calculations enabled corrections to be made for effects of fluid shifts on ion concentrations in plasma and blood during and following exercise. Plasma and blood ion efflux data were corrected for fluid shifts. Plasma $[ion]_{a-v}$ (mmol l^{-1}) were corrected for ΔPV_{a-v} using the equation: $[ion]_{a-v} = ([ion]_a / (1+ \Delta PV_{a-v})) - [ion]_v$ (McKenna et al, 1997a). Net ion fluxes across the forearm were calculated as the product of corrected $[ion]_{a-v}$ and plasma blood flow, and expressed in µmol min^{-1}. A similar correction was made for whole blood $[ion]_{a-v}$ but using ΔBV_{a-v}. Plasma strong ion difference ([SID], mmol l^{-1}) was calculated as $([K^+] + [Na^+]) - ([Lac^-] + [Cl^-])$ (McKenna et al 1997a) and calculations of whole blood CO_2 and O_2 content, muscle $\dot{V}CO_2$, $\dot{V}O_2$ and RER were as previously described (McKenna et al 1997b). Plasma flow was calculated as FBF x Hct (expressed as a fraction).

3.2.8 Statistical Analysis

Results are expressed as mean ± standard error (mean ± SEM) unless otherwise stated. A two-way ANOVA with repeated measures was employed for all blood variables to assess treatment (ALK, CON) or time (rest, exercise, recovery) main effects. Treatment x time interactions were not significant unless stated. Post-hoc analyses used the least significant difference test. Time to fatigue was analysed using a paired student t-test. Statistical significance was accepted at $P < 0.05$. Calculated effect size using Cohen's d are presented when a variable was close to significantly different between treatments.

3.3 RESULTS

3.3.1 Exercise Tests

3.3.1.1 Pre-Experiment Peak Exercise Performance Tests

Leg cycling incremental exercise $\dot{V}O_{2peak}$ was 3.52 ± 0.30 l min^{-1} (49.9 ± 4.2 ml kg^{-1} min^{-1}), and peak workrate was 269 ± 25 W. In contrast, incremental finger flexion exercise test peak workrate (WR_{peak}) was only 4.06 ± 0.34 W, and the peak force was 19.22 ± 1.27 N. During incremental tests, the average finger power output and force production at each workrate were each linear over time (both R^2 = 0.99). Mean force, power output and time to fatigue during finger flexion were each highly reproducible during variability trials, with a CV ≤3.3% (Table 3.1).

3.3.1.2 Alkalosis enhanced finger flexion exercise performance

Time to fatigue at 75% WR_{peak} was increased by 25.4 ± 8.1% during ALK compared to CON ($P<0.05$). This was not due to differences between trials in mean power output or force as these were well matched, with no differences between ALK and CON (Table 3.1). No trial order effects were found.

Table 3.1: Performance characteristics during finger flexion exercise at 75% work rate peak to fatigue for control (CON, $CaCO_3$, 0.3 $g.kg^{-1}$) and alkalosis (ALK, $NaHCO_3$, 0.3 $g.kg^{-1}$).

Trial	Mean Force (N)	Mean Power Output (W)	Fatigue Time (min)
Variability 1	16.6 ± 0.9	2.86 ± 0.16	10.1 ± 0.8
Variability 2	16.9 ± 0.8	2.89 ± 0.14	10.2 ± 0.8
CV(%)	3.3 ± 0.6	3.1 ± 0.6	2.1 ± 0.5
CON	16.5 ± 0.9	2.95 ± 0.12	10.2 ± 0.8
ALK	16.8 ± 0.8	2.98 ± 0.16	12.7 ± 1.2 †

† ALK greater than CON ($p<0.05$). Mean ± SEM n=9 for CON and ALK, and for pre-experiment variability trials, n=12. Coefficient of variation was calculated from variability trials 1 and 2.

3.3.2 Cardiovascular changes during finger flexion exercise

3.3.2.1 Forearm blood flow.

Exercise. FBF increased ~20-fold from rest to immediately post- exercise ($P<0.001$), then decreased by ~50% within the first min of recovery, and remained ~3.5-fold higher than rest at 10 min post-exercise ($P< 0.05$, Table 3.2).

Alkalosis. No significant differences were found in FBF between CON and ALK (Table 3.2).

3.3.2.2 Heart rate.

Heart rate increased above rest (CON, 55±3; ALK, 67±4 bpm) to fatigue during finger flexion exercise (CON, 81±5; ALK, 82±7 bpm), and then fell to below rest by 10 min recovery (CON, 54±2; ALK, 60±5 bpm; $P<0.01$). Although the pre-exercise heart rate was lower in CON ($P<0.01$), there were no differences in heart rate during exercise or recovery between CON and ALK.

3.3.3 Plasma Catecholamines

Exercise. Arterial plasma noradrenaline increased from rest to fatigue for CON (0.72 ± 0.12, 1.24 ± 0.2 nmol l^{-1}, respectively, $P<0.01$), whilst arterial plasma adrenaline tended to increase at fatigue for CON (0.49 ± 0.08, 0.74 ± 0.15 nmol l^{-1}, respectively, $P=0.08$, Cohen $d = 0.36$).

Alkalosis. Arterial plasma noradrenaline increased from rest to fatigue also for ALK (0.78 ± 0.09, 1.20 ± 0.3 nmol l^{-1}, respectively, $P<0.01$). Arterial plasma adrenaline similarly tended to increase at fatigue in ALK (0.37 ± 0.06, 0.58 ± 0.08 nmol l^{-1}). However, no significant effects were found between trials for noradrenaline or adrenaline.

Table 3.2: Rate of forearm blood flow (ml min^{-1}) measured at rest, immediately post-fatigue, and during recovery, under CON and ALK conditions.

	Rest	Fatigue	Recovery (min)			
			+1	+2	+5	+10
CON	7.6±1.0	162.4±30.9 **	83.8±5.1 *	55.9±9.5 *	34.3±5.3 *	25.7±2.8 *
ALK	8.5±0.9	162.2±32.4 **	82.4±14.7*	61.5±13.1 *	37.6±8.3 *	30.5±6.2 *

* Greater than rest ($P < 0.001$), ** greater than all other time points ($P < 0.001$). Mean ± SEM, *n = 6*

3.3.4 Acid-base balance and metabolism during finger flexion exercise

3.3.4.1 Plasma [H^+]

Exercise. Arterial plasma [H^+] ($[H^+]_a$) did not differ from rest during exercise or recovery (Figure 3.3A). In contrast, antecubital venous plasma [H^+] ($[H^+]_v$) increased rapidly to a plateau during the first 3 min of exercise ($P<0.05$), then decreased rapidly throughout recovery ($P<0.05$), not differing from rest by 5 min (Figure 3.3B). The plasma $[H^+]_{a-v}$ became increasingly negative during the first 4 min of exercise ($P<0.05$) and increased throughout recovery, but remained negative at 10 min recovery ($P<0.05$, Figure 3.3C). Muscle H^+ efflux (plasma $[H^+]_{a-v}$ x plasma flow) increased from rest to fatigue by ~58-fold (CON) and 64-fold (ALK), decreased by ~50% at 1 min recovery, and continued to decline until 10 min recovery ($P<0.001$, Table 3.3).

Alkalosis. Both $[H^+]_a$ and $[H^+]_v$ were lower in ALK ($P<0.05$), whereas $[H^+]_{a-v}$ (Figure 3.3C) and H^+ efflux (Table 3.3) were unchanged by ALK. Resting plasma $[H^+]_a$ and $[H^+]_v$ were 2.9 ± 0.2 and 3.5 ± 0.4 nmol l^{-1} lower during ALK than CON, respectively, whilst the peak rise in $[H^+]_a$ or $[H^+]_v$ above rest did not differ between trials.

3.3.4.2 Plasma [HCO_3^-]

Exercise. Plasma $[HCO_3^-]_a$ was unchanged during exercise or recovery (Figure 3.4A), whereas $[HCO_3^-]_v$ increased with exercise and then fell below resting levels during recovery ($P<0.05$, Figure 3.4B). Plasma $[HCO_3^-]_{a-v}$ remained negative throughout exercise and recovery (except at 5 min recovery in ALK), indicating a net gain in plasma HCO_3^- across forearm muscles ($P<0.05$, Figure 3.4C). Muscle HCO_3^- "apparent efflux" increased from rest to fatigue by ~43-fold (CON), decreasing substantially by 1 min recovery, continued to decline for the remainder of recovery, but remained ~3-fold greater at 10 min post exercise than at rest ($P<0.001$, Table 3.3).

Alkalosis. Both $[HCO_3^-]_a$ and $[HCO_3^-]_v$ were greater during ALK than CON ($P<0.05$), and plasma $[HCO_3^-]_{a-v}$ was less negative during ALK than CON ($P<0.05$, Figure 3.4C). There was no difference in muscle HCO_3^- efflux between ALK and CON (Table 3.3).

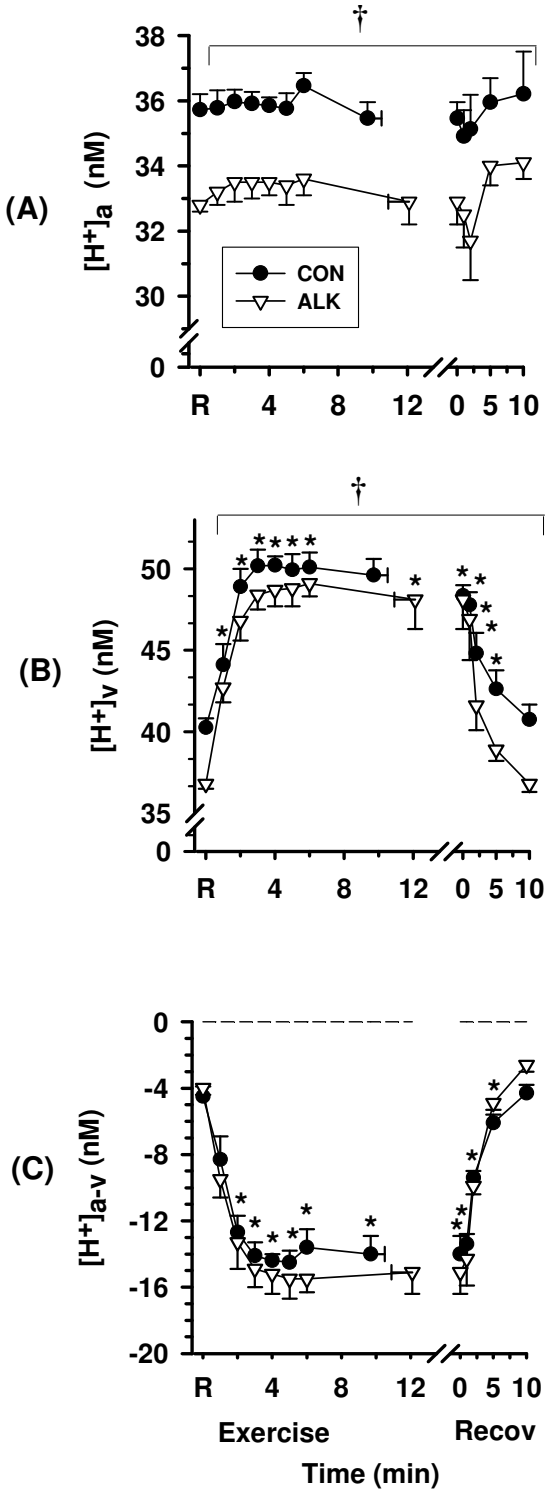

Figure 3.3. Effects of alkalosis on plasma [H^+] at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [H^+] differences, under CON (●) and ALK (▽) conditions. *Different from rest ($P<0.01$, time main effect). † CON > ALK ($P<0.05$, treatment main effect). Data expressed as Mean ± SEM, n = 8. The fatigue point during exercise has been replotted as time zero in recovery. Dashed line represents zero arteriovenous difference.

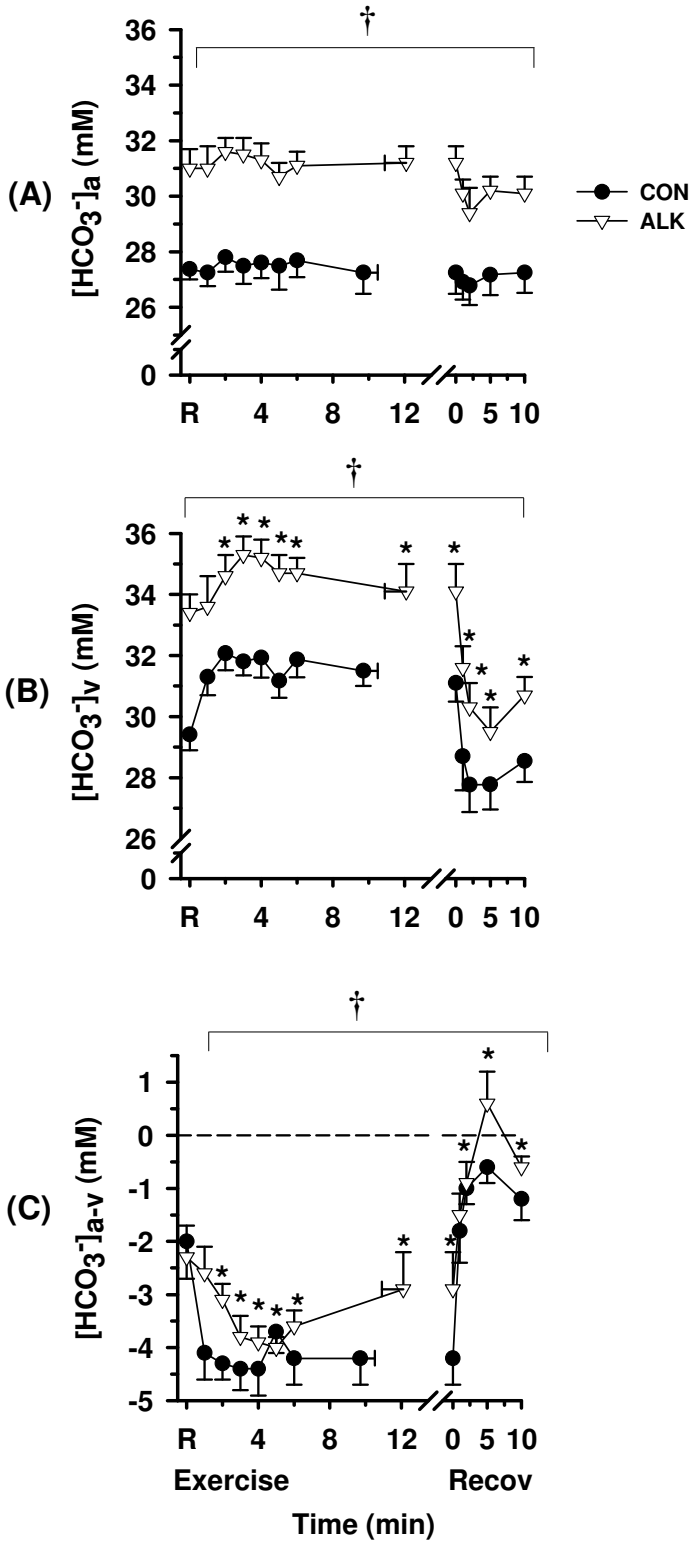

Figure 3.4. Effects of alkalosis on plasma [HCO_3^-] at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [HCO_3^-] differences, under CON (●) and ALK (▽) conditions. * Different from rest ($P<0.05$ time main effect). † ALK different to CON ($P<0.05$, treatment main effect). Sample size and data presentation as in Fig 3.

Table 3.3: Net ion fluxes into or out of plasma across the forearm musculature measured at rest, immediately post-fatigue, and during recovery, under CON and ALK conditions. All units are µmol min^{-1}, except for H^+ which is pmol min^{-1}.

	Rest	Fatigue	Recovery (min)			
			+1	+2	+5	+10
CON						
H^+_{efflux}	-21±4	-1233±181*	-628±61*	-320±41*	-144±6*	-77±13*
$HCO_3^-{}_{efflux}$	-10.3±4.2	-456.3±131*	-101.8±43.5*	-40.8±7.3*	-26.6±8.4	-31.2±9.7*
K^+_{fluxes}	0.1±0.3	-42.5±10.7*	30.9±7.8*	20.1±7.5*	10.3±4.2*	7.0±2.8*
Na^+_{fluxes}	-7.7±5.7	-276.1±190.8*	-47.5±152*	25.6±65.3	-69.1±27.3*	-68.7±31.5*
Cl^-_{fluxes}	2.6±3.9	407.1±101.9*	204.2±28.5	46.2±47.2	-48.3±30.5	-59±19.0
Lac^-_{efflux}	-0.3±0.5	-148.8±37.8*	-111.5±30.3*	-78.6±24.2*	-37.2±11.4*	-10.6±3.3*
ALK						
H^+_{efflux}	-21±1	-1364±248*	-754±174*	-394±82*	-135±22*	-69±20*
$HCO_3^-{}_{efflux}$	-13.9±3.2	-459±94.9*	-99.0±39.3*	-44.4±19.7*	-12.9±20.1	-32.5±8.9*
K^+_{fluxes} †	0.5±0.5	-63.7±13.5*	22.4±6.3*	22.8±10.7*	12.6±3.5	7.3±1.7
Na^+_{fluxes}	18.1±8.0	-78.6±121.3*	-114.6±73.9*	-2.3±34.5	-87.1±26.1*	-75.9±36.1*
Cl^-_{fluxes} †	2.4±5.2	558.2±162.8*	8.9±72.1	194.1±132.2	-24±21.6	-61.8±22.4
Lac^-_{efflux} †	-0.3±0.6	-295.5±62*	-173.4±45.4*	-124.7±35.5*	-39.3±7.6*	-15.5±3*

Mean ± SEM, *n = 6*; * Different to rest (P<0.001). † ALK > CON (P<0.05). A negative value denotes net ion flux into plasma across forearm musculature, and positive values denote net flux from plasma across musculature. Fluxes calculated from (a-v [ion] difference) x Forearm plasma Flow). Fluxes for K^+, Na^+, Cl^- and Lac^- corrected for arterio-venous ΔPV.

3.3.4.3 Plasma pCO_2

Exercise. Plasma P_aCO_2 did not differ from rest during exercise or recovery (Figure 3.5A). In contrast, plasma P_vCO_2 increased sharply during the first three min of exercise, then plateaued, and fell rapidly in recovery ($P<0.05$, Figure 3.5A).

Alkalosis. P_vCO_2 was greater at rest and throughout exercise during ALK ($P<0.01$), with a similar trend in P_aCO_2 ($P=0.068$, Cohen d =0.4). No difference was evident between treatments in recovery for either P_vCO_2 or P_aCO_2.

3.3.4.4 Plasma pO_2

Exercise. P_aO_2 was not significantly changed during exercise and recovery (Figure 3.5B). P_vO_2 was unchanged during exercise, but rose sharply during the first two min of recovery and remained above rest ($P<0.05$, Figure 3.5B).

Alkalosis. No effect of ALK was found on either arterial or venous pO_2.

3.3.5 Blood CO_2 content (C_{CO2}) and forearm $\dot{V}CO_2$ ($\dot{V}_mCO_2$)

Exercise. C_{aCO2} did not vary from rest during exercise or recovery (Fig 3.6A), whilst C_{vCO2} increased during early exercise ($P<0.01$) and decreased rapidly during the first two min of recovery ($P<0.01$, Figure 3.6B). $C_{a\text{-}vCO2}$ decreased during exercise ($P<0.01$) and except for 5 min recovery in ALK, remained negative throughout recovery (Figure 3.6C). Forearm muscle CO_2 output ($\dot{V}_mCO_2$) increased 35-fold from rest to fatigue ($P<0.001$, Table 3.4), before declining to near pre-exercise resting values by 1 min recovery.

Alkalosis. C_{aCO2} and C_{vCO2} were higher during ALK, by 85.5±6.2 ml l^{-1} and 115±13.2 ml l^{-1} ($P<0.05$) respectively, whereas no differences were found between trials for $C_{a\text{-}vCO2}$ (Figure 6) or $\dot{V}_mCO_2$ (Table 3.4).

3.3.6 Blood O_2 content (C_{O2}) and forearm muscle $\dot{V}O_2$ ($\dot{V}_mO_2$)

Exercise. C_{aO2} did not change significantly from rest during exercise or recovery (Figure 3.7A), whereas C_{vO2} decreased during exercise ($P<0.01$), and increased rapidly during recovery ($P<0.01$, Figure 3.7B). $C_{a\text{-}vO2}$ increased rapidly during exercise ($P<0.01$), and decreased rapidly during recovery ($P<0.01$, Figure 3.7C). Forearm muscle O_2 uptake ($\dot{V}_mO_2$) increased rapidly from rest to fatigue by 37-fold ($P<0.001$, Table 3.4), before decreasing towards pre-exercise values by 1 min recovery.

Alkalosis. There was no effect of ALK on C_{aO2}, C_{vO2}, $C_{a\text{-}vO2}$, or $\dot{V}_mO_2$.

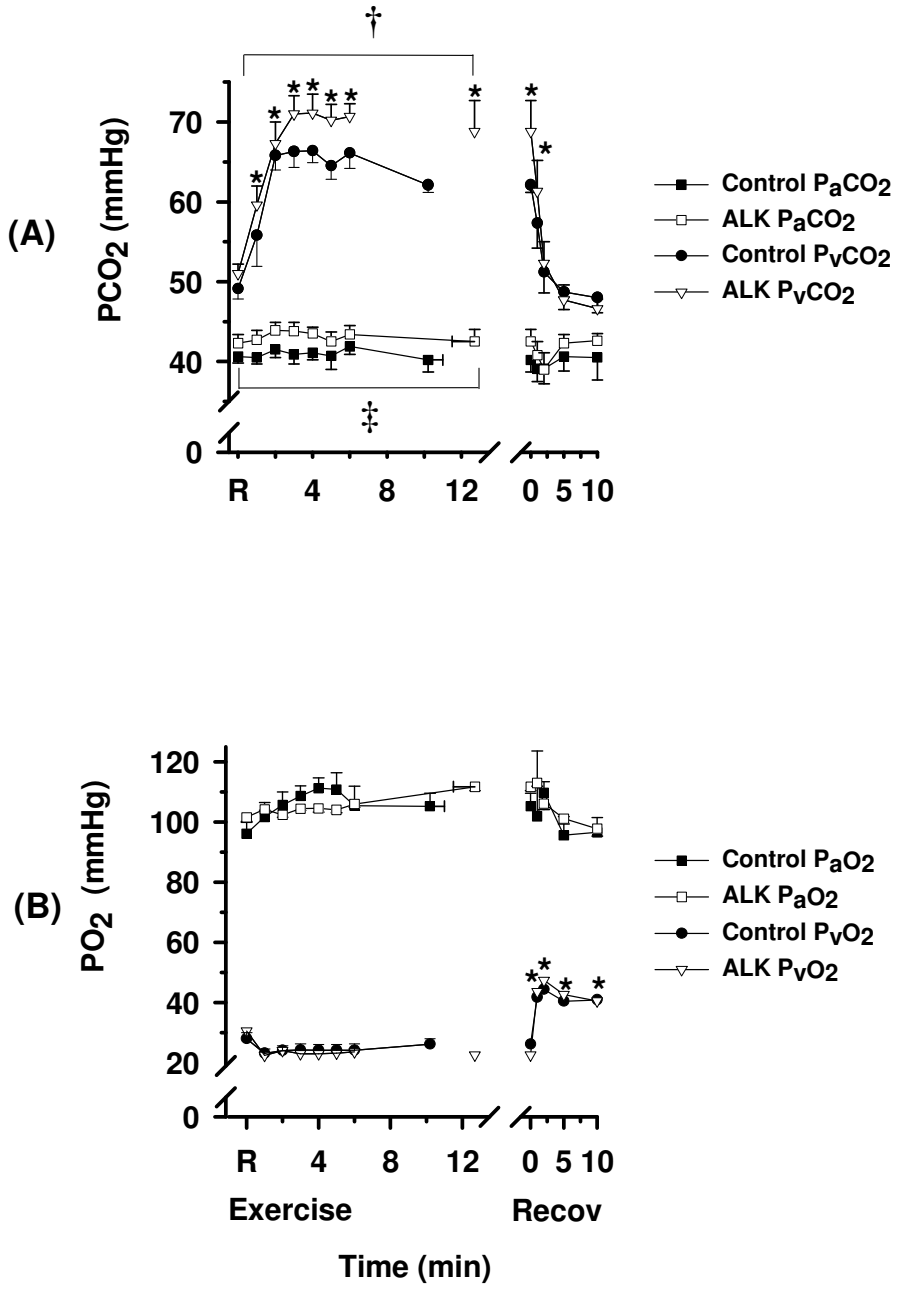

Figure 3.5. Effects of alkalosis on plasma PCO_2 and PO_2 at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial CON (■), ALK (□) and venous CON (●), ALK (▽) PCO_2 (B) arterial CON (■), ALK (□) and venous CON (●), ALK (▽) PO_2. * Different from rest ($P<0.05$, main effect for time). † treatment main effect for P_vCO_2 during exercise ($P<0.05$). ‡ Treatment effect for P_aCO_2 during exercise ($P = 0.068$, Cohen $d = 0.4$). Sample size and data presentation as in Fig 3.

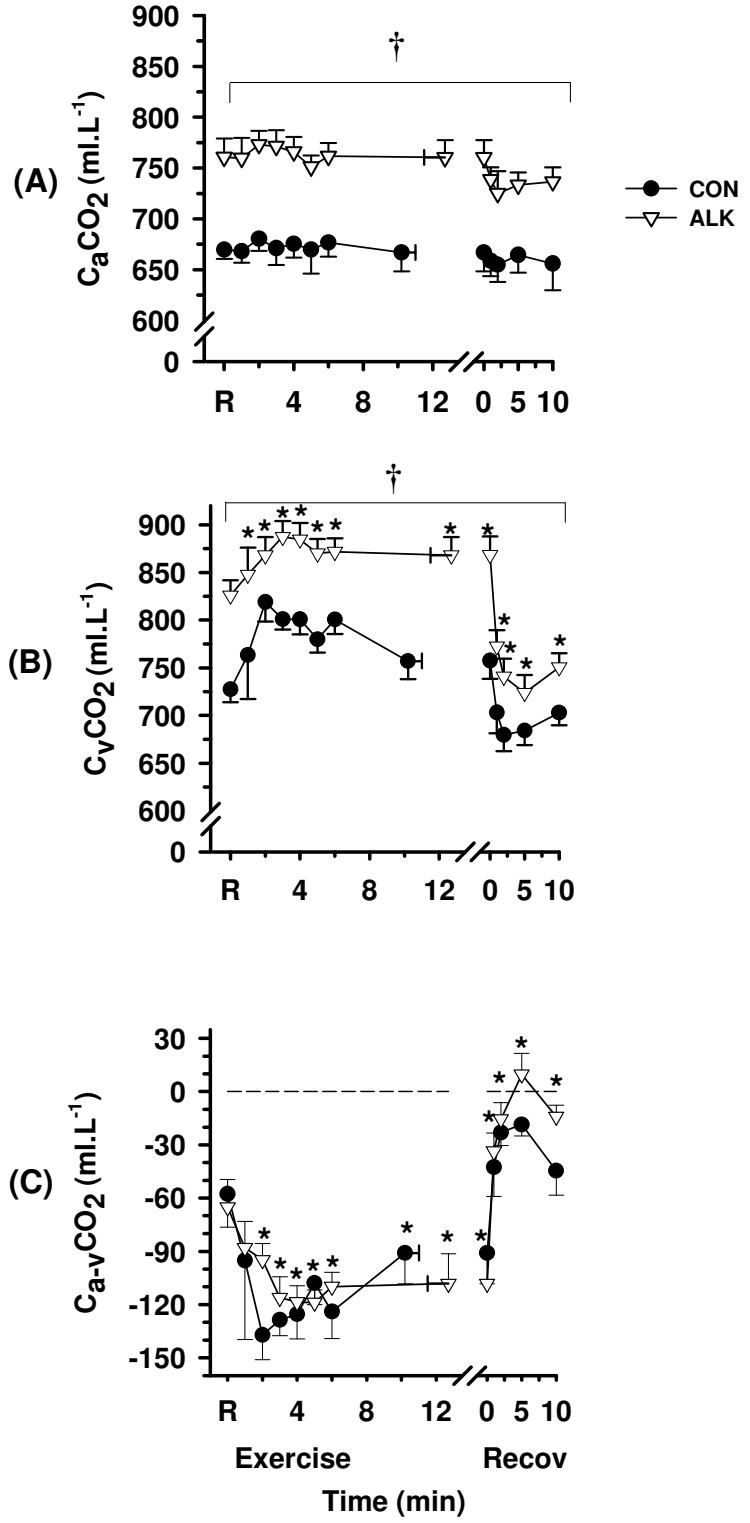

Figure 3.6. Effects of alkalosis on CO_2 content at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous CO_2 content differences, under CON (●) and ALK (▽) conditions. * Different from rest ($P<0.01$, time main effect). † ALK > CON ($P<0.05$, treatment main effect). Sample size and data presentation as in Fig 3.

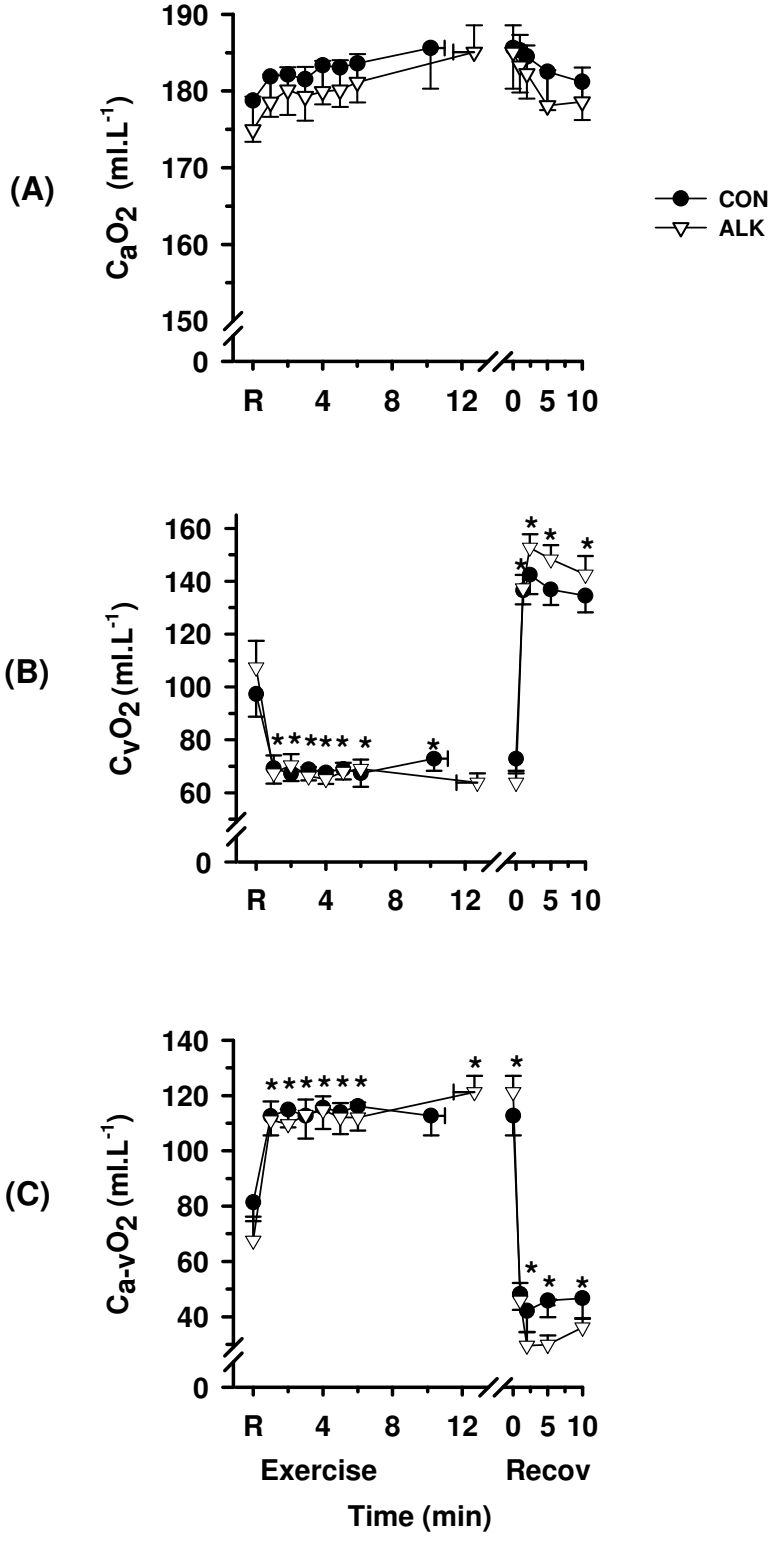

Figure 3.7. Effects of alkalosis on O_2 content at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial (B) venous and (C) calculated arteriovenous O_2 content differences, under CON (●) and ALK (▽) conditions. * Different from rest ($P<0.01$, time main effect). Sample size and data presentation as in Fig 3.

Table 3.4: Forearm muscle lactate efflux, $\dot{V}O_2$, $\dot{V}CO_2$ and RER at rest, immediately post-fatigue and during recovery, under CON and ALK conditions. Net Lac^- flux expressed in µmol min^{-1} and $\dot{V}O_2$, $\dot{V}CO_2$ in ml min^{-1}.

	Rest	Fatigue	Recovery (min)			
			+1	+2	+5	+10
CON						
$Lac^-_{m\ efflux}$	-0.2±0.6	-182.3±50.8*	-134.8±36.4*	-88.0±24.8*	-46.8±14.2*	-18.3±6.2*
$\dot{V}_mO_2$	0.6±0.1	22.2±4.0*	4.5±0.5	1.8±0.2	1.3±0.1	1.0±0.1
$\dot{V}_mCO_2$	0.5±0.2	17.7±7.3*	4.9±1.5	1.1±0.3	0.8±0.2	1.0±0.3
RER_m	0.71±0.2	0.98±0.06*	0.86±0.19*	0.59±0.08*	0.56±0.09*	0.56±0.25*
ALK						
$Lac^-_{m\ efflux}$‡	-1.0±1.4	-353.7±110.4*	-159.0±45.9*	-144.9±52.7*	-57.6±21.0*	-24.8±11.6*
$\dot{V}_mO_2$	0.6±0.1	20.4±4.1*	4.4±1.1	2.1±0.5	1.1±0.2	1.0±0.2
$\dot{V}_mCO_2$	1.6±0.9	18.1±4.3*	9.9±3.2	7.7±3.3	4.8±2.1	3.8±1.3
RER_m	0.94±0.2	0.90±0.08*	0.92±0.17*	0.70±0.57*	0.60±0.46*	0.54±0.08*

Mean ± SEM, *n = 6;* * Different from rest (P<0.001). ‡ ALK > CON during recovery (P<0.05). A negative value denotes net efflux from contracting musculature, and positive values denote net influx. Muscle lactate efflux calculated from $[BLac^-]_{a\text{-}v}$ x Forearm Blood Flow), with $[BLac^-]_{a\text{-}v}$ corrected for arterio-venous ΔBV.

3.3.7 Forearm muscle RER

Exercise. Forearm respiratory exchange ratio (RER_m) increased at fatigue from rest, and fell to below rest in recovery ($P<0.05$; Table 3.4).

Alkalosis. There were no effects of ALK on RER_m.

3.3.8 Blood [Lac^-]

Exercise. Whole blood $[Lac^-]_a$ was unchanged, whilst $[Lac^-]_v$ increased above rest during exercise and decreased during recovery ($P<0.05$, Figure 3.8). Blood $[Lac^-]_{a-v}$ decreased during exercise and increased in recovery, but remained negative throughout, reflecting a continued net release of lactate from muscle into blood across the forearm musculature ($P<0.05$, Figure 3.8C). Muscle lactate efflux increased from rest to fatigue by ~900-fold in CON ($P<0.01$, Table 3.4).

Alkalosis. Blood $[Lac^-]_a$ and $[Lac^-]_v$ were not significantly different between CON and ALK. Blood $[Lac^-]_{a-v}$ was more negative in ALK during exercise ($P<0.05$), with the greatest difference at fatigue (CON, -1.62±0.36; ALK, -2.19±0.22 mmol l^{-1}, $P<0.05$). Muscle lactate efflux increased from rest to fatigue by ~ 350 fold in ALK ($P<0.01$, Table 3.4) and was ~ 2 fold greater at fatigue during ALK compared to CON ($P<0.05$).

3.3.9 Haematology and Fluid Shifts

3.3.9.1 Haemoglobin and haematocrit

Exercise. Arterial and venous [Hb] increased from rest (CON, 13.6±0.4; ALK, 13.4±0.4 g dl^{-1}) to fatigue (CON, 14.1±0.4; ALK, 14.0±0.4 g dl^{-1}; $P<0.001$). Arterial and venous Hct also increased from rest (CON, 38.5±1.5; ALK, 37.6±0.9 %) to fatigue (CON, 39.9±1.5; ALK, 38.9±1.1 %; $P<0.001$).

Alkalosis. There were no differences between CON and ALK for either [Hb] or Hct.

3.3.9.2 Plasma and blood volume changes

Exercise. Plasma volume (PV) declined from rest during exercise when calculated for both arterial and venous blood, by ~5% at fatigue ($P<0.05$, data not shown). Whilst ΔPV_a remained negative throughout recovery, ΔPV_v increased above rest at 10 min recovery ($P<0.05$). A negative ΔPV_{a-v} indicating a small net loss in PV occurred across the exercising forearm ($P<0.05$), which was reversed to a net PV gain in recovery ($P<0.05$, data not shown). Similar exercise effects were found for ΔBV_a and for ΔBV_v (data not shown).

Alkalosis. There was no effect of ALK on ΔPV_a, ΔPV_v or ΔPV_{a-v}. The nadir ΔPV_a (CON, -4.8 ± 0.9 vs ALK, -6.6 ± 1.1%) and ΔPV_v (CON, -6.4 ± 1.9 vs ALK, –7.0 ± 0.8 %) were not significantly different between treatments. No ALK main effects were found on BV_a, BV_v or BV_{a-v} (data not shown).

3.3.10 Plasma Electrolytes

3.3.10.1 Plasma [K^+]

Exercise. Plasma $[K^+]_a$ increased above rest by 1 min exercise, continued to increase throughout exercise, decreased slowly in recovery, but remained above rest at 10 min ($P<0.01$; Figure 3.9A. In contrast, $[K^+]_v$ rose sharply by 1 min of exercise, plateaued until fatigue and then declined rapidly during recovery ($P<0.01$, Figure 3.9B). The $[K^+]_{a-v}$ decreased by 1 min of exercise (-0.90±0.10 mmol l^{-1} during CON), representing net K^+ entry into plasma traversing forearm muscle. An immediate reversal of $\Delta[K^+]_{a-v}$ to positive values occurred within the first 1 min of recovery, reflecting K^+ loss from plasma ($P<0.01$, Figure 3.9C). K^+ efflux from muscle into plasma increased dramatically from 0.1±0.3 µmol min^{-1} at rest, to 42.5±10.7 µmol min^{-1} at fatigue ($P<0.001$, Table 3.3), with net K^+ removal from plasma evident throughout recovery (Table 3.3).

Alkalosis. Both $[K^+]_a$ and $[K^+]_v$ were less in ALK than in CON ($P<0.01$), being lower at rest by 0.49 ± 0.08 and 0.41 ± 0.08 mmol l^{-1}, respectively ($P<0.05$). The peak rise in $[K^+]_a$ during exercise ($\Delta[K^+]_a$ 0.46±0.02 and 0.46±0.01 mmol l^{-1}) and in $\Delta[K^+]_v$ (1.02±0.04 and 1.13±0.01 mmol l^{-1}) were similar during CON and ALK, respectively. Similar to CON, $[K^+]_{a-v}$ decreased rapidly by 1 min of exercise (-1.04±0.14 mmol l^{-1}) and a tendency was observed for a wider (more negative) $[K^+]_{a-v}$ during exercise in ALK ($P=0.056$; Cohen d = 0.44, Figure 3.9C). At fatigue, muscle K^+ efflux was greater during ALK by 21.2 ± 7.6 µmol min^{-1} (32±7%, $P<0.05$, Table 3.3). In contrast, the subsequent K^+ uptake from fatigue to 10 min recovery was greater during ALK, with the estimated peak at 86±19 compared to 73±14 µmol min^{-1} in CON (15±7%, $P<0.05$). This likely reflects greater Na^+,K^+ATPase-mediated K^+ uptake into forearm muscle with ALK.

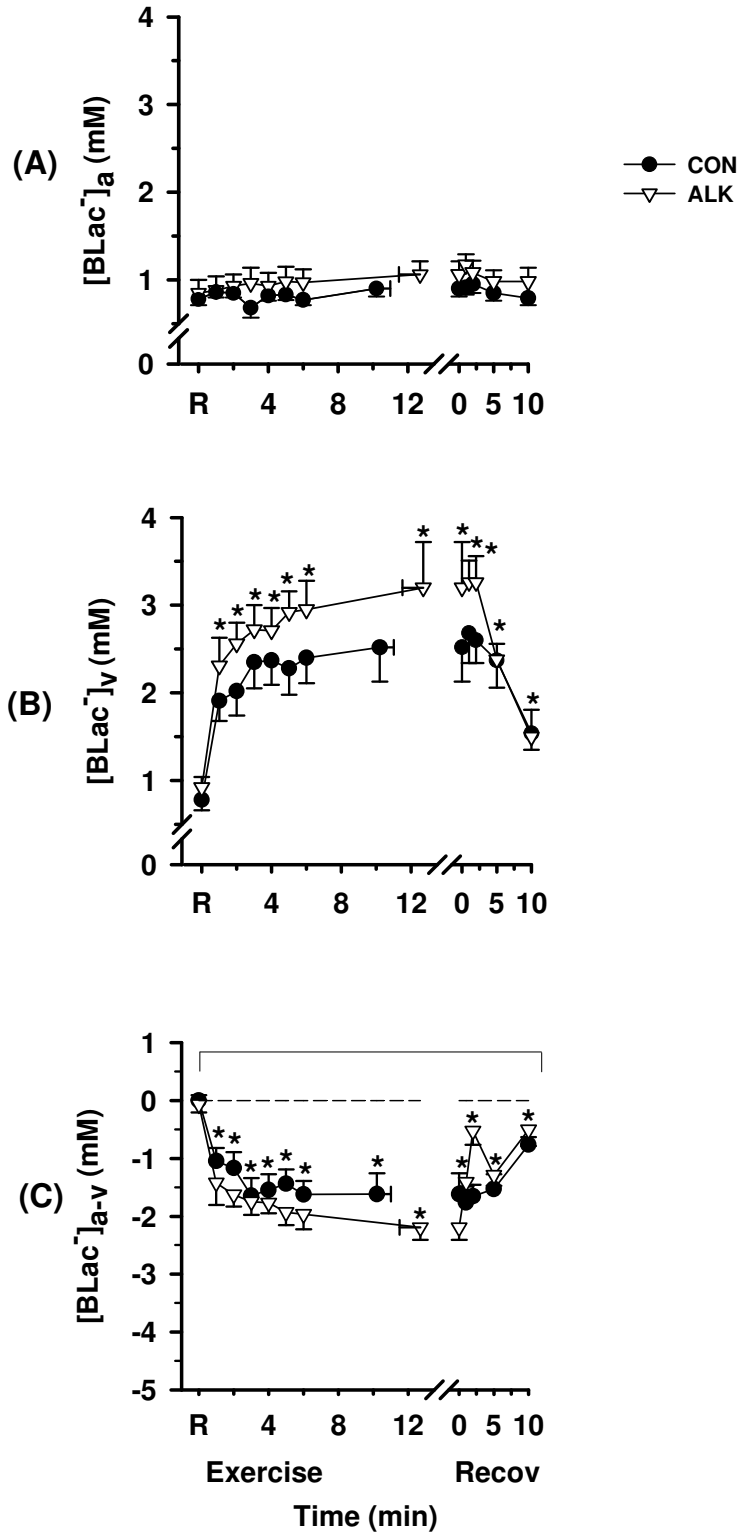

Figure 3.8. Effects of alkalosis on whole blood [Lac$^-$] at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous whole blood [Lac$^-$] differences, under CON (●) and ALK (▽) conditions. * Different from rest (P<0.05, time main effect). † ALK > CON (P<0.05, treatment main effect). Data and presentation as in Fig 3.3. Arteriovenous WB [Lac$^-$] differences are corrected for the a-v decline in blood volume.

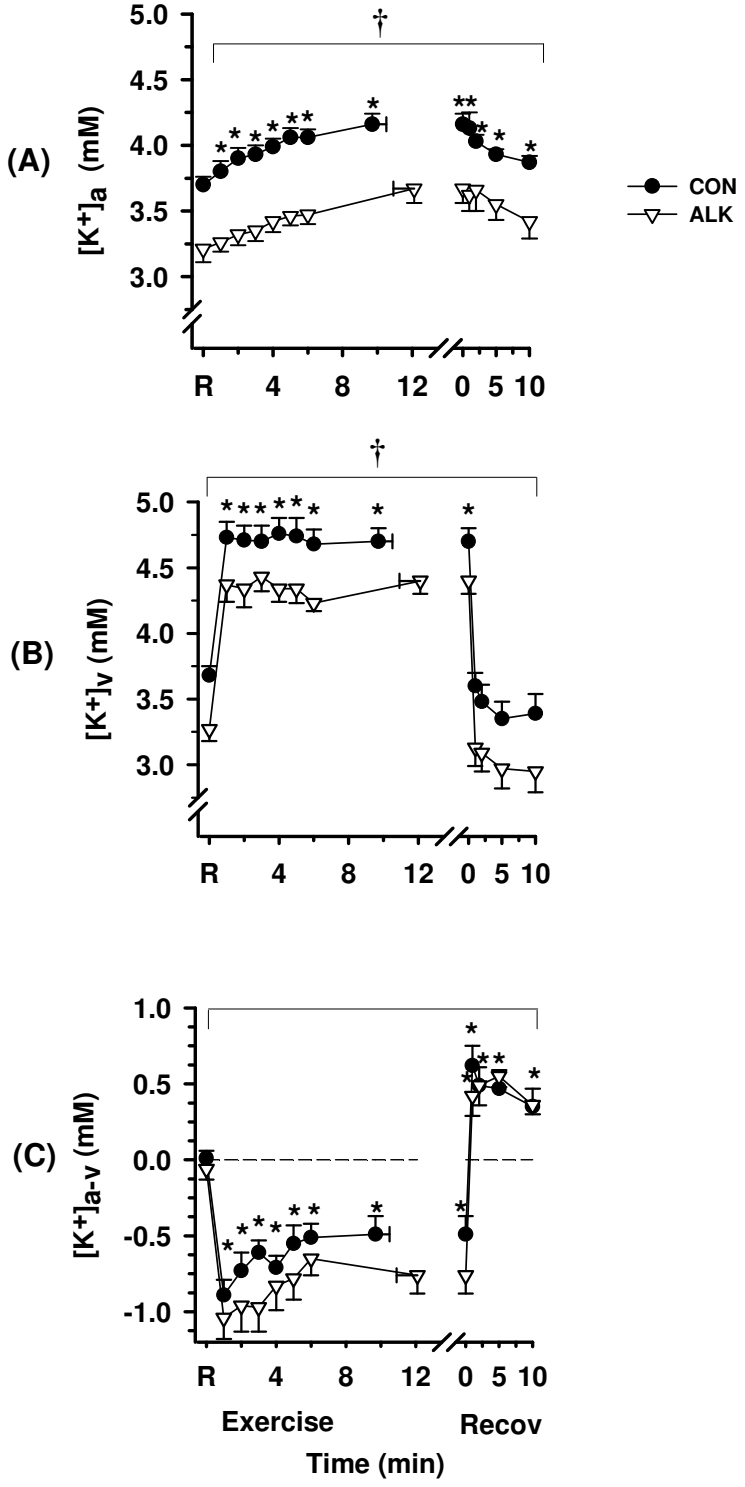

Figure 3.9. Effects of alkalosis on plasma [K^+] at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [K^+] differences, under CON (●) and ALK (▽) conditions. * Different from rest ($P<0.01$, time main effect). † ALK < CON ($P<0.05$, treatment main effect). ‡ ALK > CON ($P=0.056$, $d=0.44$, treatment main effect). Sample size and data presentation as in Fig 3.3. Arteriovenous [K^+] differences are corrected for the a-v decline in plasma volume.

3.3.10.2 Plasma [Na^+]

Exercise. Plasma $[Na^+]_a$ did differ significantly from rest during exercise or recovery (Figure 3.10A), whilst $[Na^+]_v$ increased during exercise ($P<0.05$, Figure 3.10B) and declined to rest levels during recovery. Plasma $[Na^+]_{a-v}$ fluctuated considerably and did not differ significantly from rest during exercise or in recovery. Despite considerable variability, during CON, an apparent muscle Na^+ flux was greater at fatigue than rest, and decreased in recovery ($P<0.05$, Table 3.3).

Alkalosis. $[Na^+]_a$ was greater ($P<0.05$) and $[Na^+]_v$ tended to be greater during ALK ($P=0.066$, Cohen d=0.46). There was no effect of ALK on $[Na^+]_{a-v}$ and there were no treatment main effects detected for muscle Na^+ flux.

3.3.10.3 Plasma [Cl^-]

Exercise. Both $[Cl^-]_a$ and $[Cl^-]_v$ decreased slightly from rest during exercise ($P<0.05$, Figure 3.11A, 3.11B). Plasma $[Cl^-]_{a-v}$ was positive throughout rest, exercise, and up to 5 min recovery during CON, reflecting net Cl^- movement out of plasma traversing the forearm ($P<0.01$; FIG 3.11C). By 10 min recovery, the $[Cl^-]_{a-v}$ was negative, indicating a reversal to a net Cl^- movement from muscle into plasma. Influx of Cl^- from plasma to muscle from rest to fatigue increased substantially during CON ($P<0.001$, Table 3.3).

Alkalosis. ALK did not significantly affect plasma $[Cl^-]_a$ or $[Cl^-]_{a-v}$, but $[Cl^-]_v$ was greater during ALK ($P<0.05$). However, Cl^- flux was 27% greater during ALK (151.1±178.0 μmol min^{-1}, $P<0.05$, Table 3.3), indicating greater Cl^- flux from plasma across the forearm muscles.

3.3.10.4 Plasma [Lac^-]

Exercise. Plasma $[Lac^-]_a$ did not differ from rest during exercise or recovery. Plasma $[Lac^-]_v$ increased during exercise ($P<0.05$), peaked at 5 min exercise, and decreased after 2 min recovery ($P<0.05$, Figure 3.12B). Plasma $[Lac^-]_{a-v}$ decreased from rest during exercise to a nadir of -2.3±0.5 mmol l^{-1} during CON, reflecting net lactate release into plasma across the contracting forearm muscles. Following ~2 min of recovery, $[Lac^-]_{a-v}$ increased ($P<0.05$) but remained negative at 10 min recovery (Figure 3.12C). Lac^- flux into plasma increased from 0.3±0.5 μmol min^{-1} at rest, to 148.8±37.8 μmol min^{-1} at fatigue , and decreased during recovery to remain elevated at 10.6±6.6 μmol min^{-1} by 10 min recovery, during CON trials ($P<0.001$, Table 3.3).

Alkalosis. Plasma $[Lac^-]_a$, $[Lac^-]_v$ and $[Lac^-]_{a-v}$ did not differ significantly between ALK and CON. However, at fatigue, lactate flux at fatigue was 50% greater during ALK, and remained greater throughout recovery ($P<0.01$, Table 3.3).

3.3.10.5 Strong ion difference ([SID])

Exercise. Plasma $[SID]_a$ increased above rest during exercise ($P<0.01$) and remained slightly elevated during recovery ($P<0.01$, Figure 3.13A). Plasma $[SID]_v$ also increased

during exercise, but in contrast, decreased rapidly during recovery ($P<0.001$; Figure 3.13B). Plasma $[SID]_{a-v}$ was negative throughout exercise, and became positive after 1 min recovery (Figure 13B).

Alkalosis. Plasma $[SID]_a$ did not differ significantly between trials, whilst $[SID]_v$ was lower in ALK than in CON during exercise and recovery ($P<0.05$). Plasma $[SID]_{a-v}$ was less negative at fatigue during ALK than CON ($P<0.05$, Figure 3.13C).

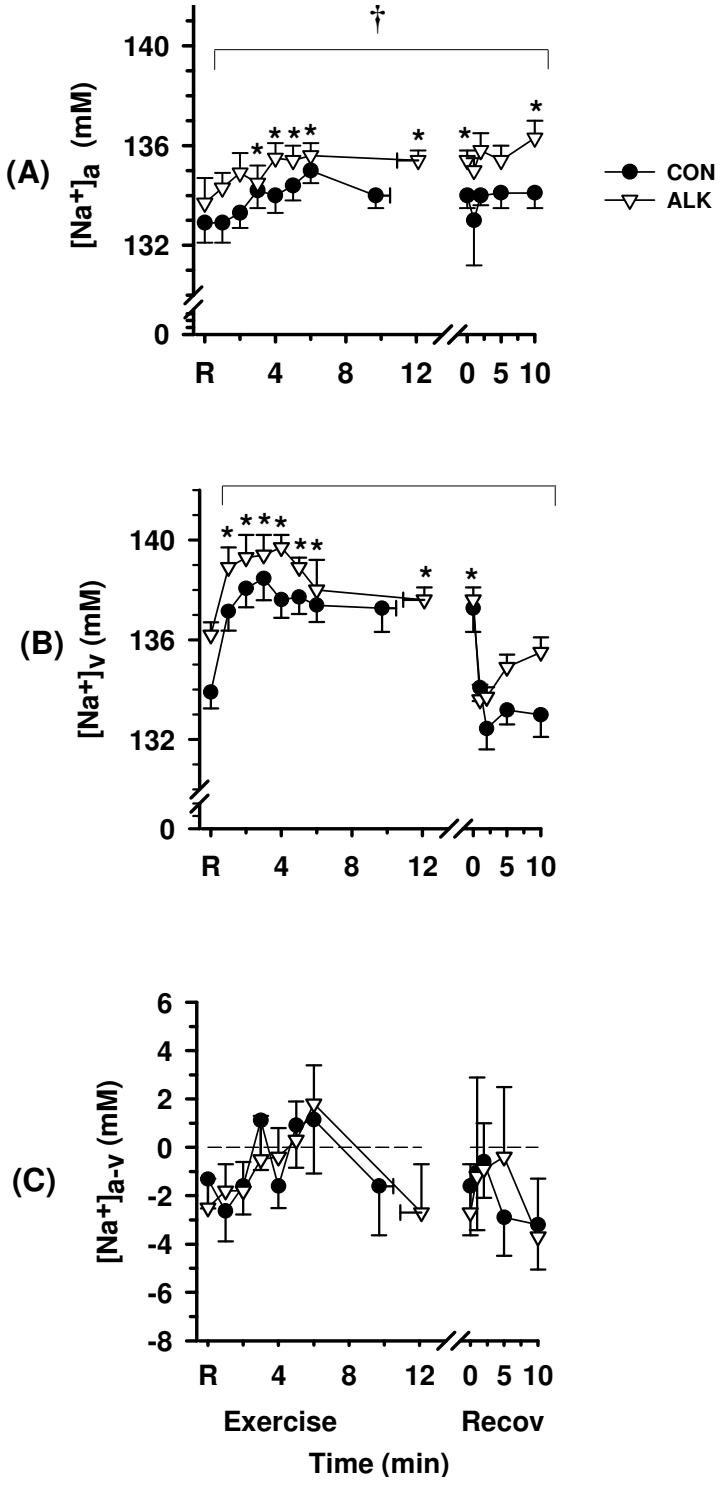

Figure 3.10. Effects of alkalosis on plasma [Na^+] at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [Na^+] differences, under CON (●) and ALK (▽) conditions. * Different from rest ($P<0.05$, time main effect). † ALK > CON ($P<0.05$, treatment main effect). ‡ ALK tended to be > CON ($P=0.066$, d = 0.46, treatment main effect). Sample size and data presentation as in Fig 3.3. Arteriovenous [Na^+] differences are corrected for the a-v decline in plasma volume.

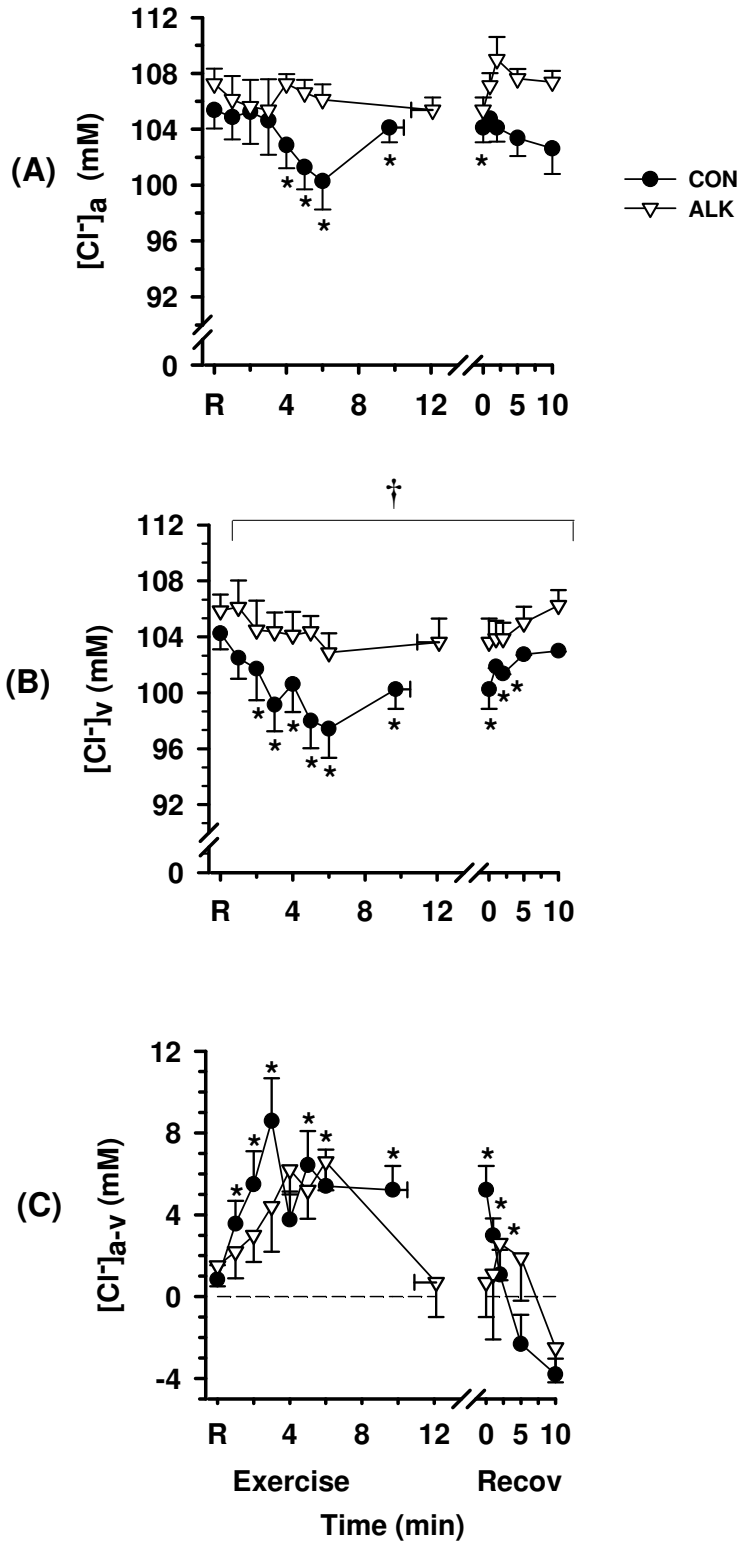

Figure 3.11. Effects of alkalosis on plasma [Cl^-] at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [Cl^-] differences, under CON (●) and ALK (▽) conditions. * Different from rest ($P<0.01$, time main effect). † ALK > CON ($P<0.05$, treatment main effect). Sample size and data presentation as in Fig 3.3. Arteriovenous [Cl^-] differences are corrected for the a-v decline in plasma volume.

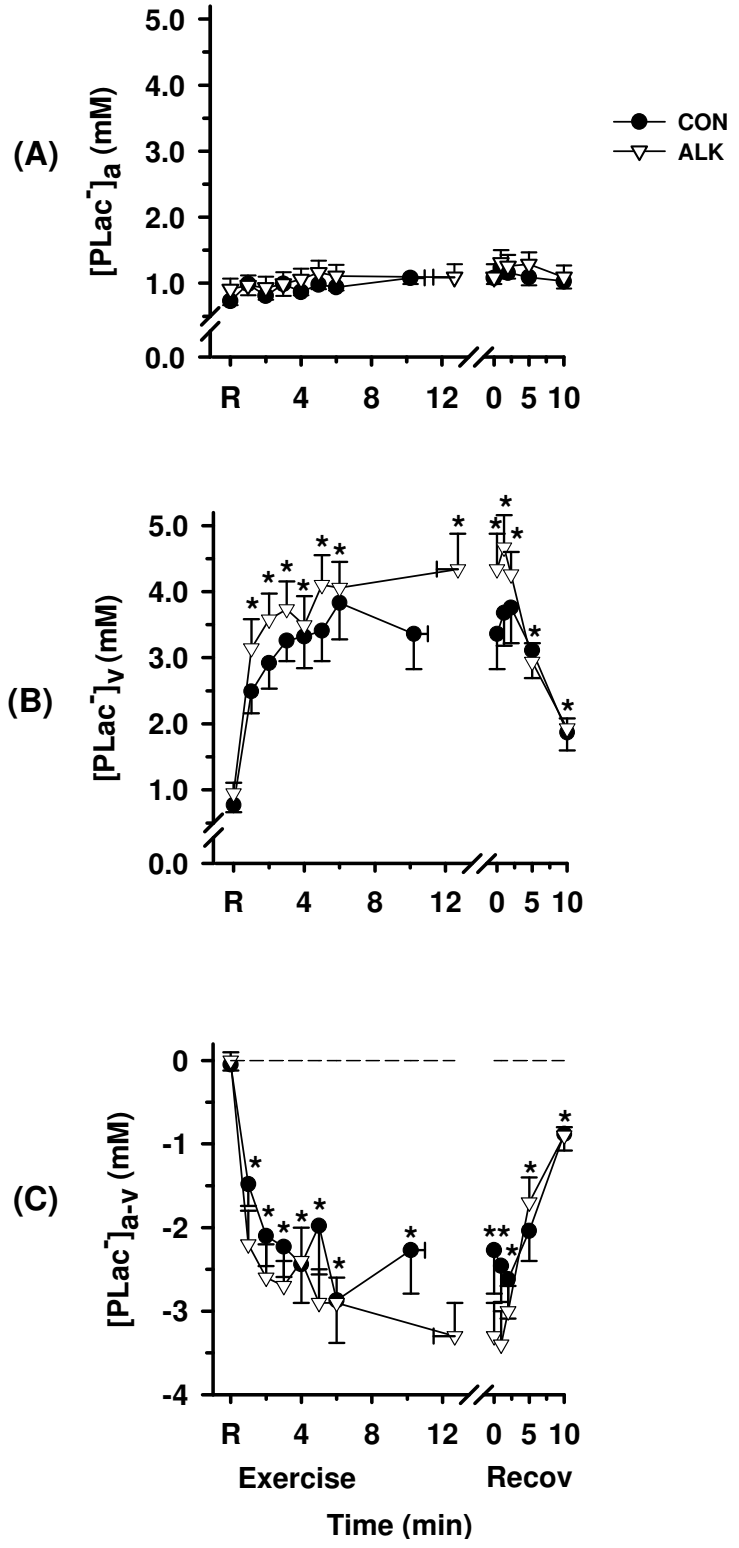

Figure 3.12. Effects of alkalosis on plasma [Lac$^-$] at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [Lac$^-$] differences, under CON (●) and ALK (▽) conditions. * Different from rest ($P<0.001$, time main effect). Data and presentation as in Fig 3.3. Arteriovenous [Lac$^-$] differences are corrected for the a-v decline in plasma volume.

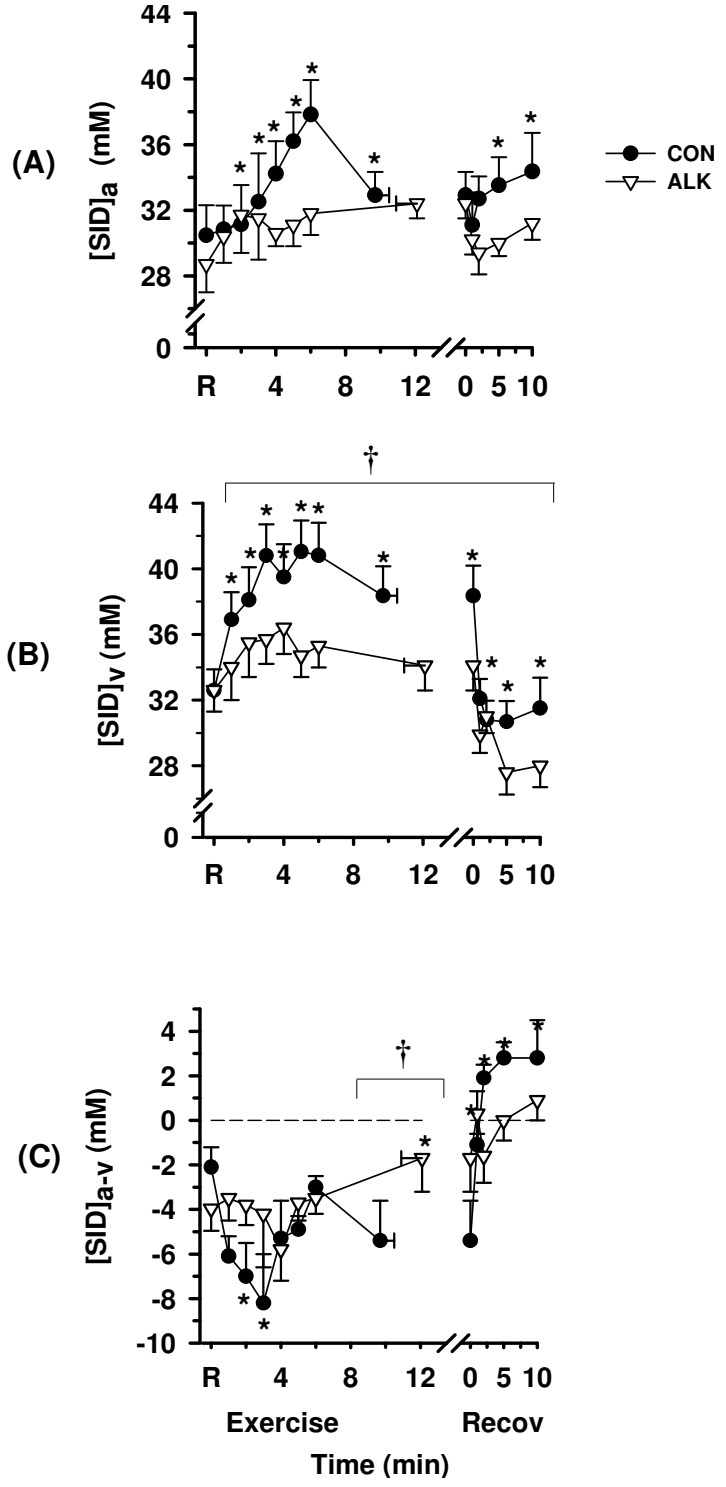

Figure 3.13. Effects of alkalosis on plasma [SID] at rest, during finger flexion exercise at 75% WR_{peak} continued to fatigue, and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [SID] differences, under CON (●) and ALK (▽) conditions. * Different from rest (P<0.001, main effect for time). § time main effect where post hoc analysis could not detect the location of differences (p<0.01). CON > ALK (P<0.05, treatment main effect). Data and presentation as in Fig 3.3. Dashed line represents zero arteriovenous difference.

3.4 DISCUSSION

This study examined the effects of alkalosis during and following exercise on ionic and acid-base status, metabolism and blood flow during fatiguing contractions of the finger flexor muscles performed using a unique custom-designed ergometer. The acute effects of exercise on these variables were firstly comprehensively described, since little is known about these during dynamic, concentric exercise with such a small muscle mass. Furthermore, this is important to allow understanding of the responses to alkalosis. Despite fatiguing exercise barely perturbing arterial plasma ionic and acid-base variables, large arterio-venous differences across the contracting forearm muscles occurred. These, together with a dramatic increase in blood flow, indicated substantial ionic fluxes and acid-base disturbances with small muscle mass exercise.

Sodium bicarbonate induced alkalosis markedly affected these muscle ionic exchanges and enhanced muscle performance, with a ~25% increase in time to fatigue during finger flexion exercise. The major findings were that whilst ALK lowered arterial and venous plasma [K^+] compared to CON, K^+ efflux into plasma at fatigue was greater, indicating greater muscle K^+ release during fatiguing exercise. Conversely, a greater muscle K^+ uptake was found in recovery with ALK, which indicates increased muscle Na^+,K^+ATPase activity and possible increased Na^+-K^+-2Cl^--cotransporter (NKCC) activity. These together suggest that ALK increased muscle K^+ loss during exercise despite increased muscle Na^+,K^+ATPase activity. We also demonstrate for the first time that arterial [Na^+] was higher and Cl^- influx into muscle greater in ALK; which together with lower [K^+] and increased muscle Na^+,K^+ATPase activity, may have contributed to muscle performance enhancement via a membrane stabilising effect. We confirm in this exercising model that muscle Lac^- efflux was greater during alkalosis, indicating enhanced Lac^- transport from the muscle and most likely, an increased glycolytic rate. Finally, ALK had no effect on fluid shifts, forearm blood flow, muscle $\dot{V}O_2$ or RER during exercise or recovery.

3.4.1 Physiological responses to dynamic exercise of the finger flexor muscles

To understand alkalosis effects in the contractile model used, it was first essential to determine the ionic, acid-base, metabolic and cardiovascular responses during and after dynamic exercise of the finger flexor muscles. Although numerous studies have investigated metabolic and cardiovascular responses to isometric muscle contractions of the forearm (Hamann et al 2004; Van Beekvelt et al 2001), relatively little is known about these effects using such a small muscle mass performing dynamic, concentric exercise. This investigation firstly necessitated development of a unique ergometer capable of enabling dynamic forearm flexor contractions, with precise measures of

muscle power and work, but which also restricted exercise to concentric contractions, to avoid eccentric contraction induced muscle soreness and damage. The “eccentric unloading” of the ergometer during the relaxation part of the duty cycle of this model means it is highly likely that the forearm extensor muscles would contribute very little to contractions, in contrast to what would occur in handgrip or wrist flexion exercise models.

The extremely low peak power output of ~ 3 W represented only ~1.5% of that achieved during two legged incremental cycling exercise and verifies the small magnitude of contracting muscle mass that was utilised. Consequently, disturbances in arterial plasma ionic and acid-base status were minimal or absent, as expected. No changes were found with exercise in any of arterial plasma [H^+], [HCO_3^-], PCO_2, PO_2, [Lac^-] or [Na^+], with only a small increase in arterial plasma [K^+] (~0.5 mmol l^{-1}) and small declines in plasma volume (~5%), [Cl^-] (~5 mmol l^{-1}) and [SID] (~7 mmol l^{-1}). Additionally, only small increases in heart rate, blood pressure and adrenaline were observed, which are all in keeping with activation of only a small muscle mass. In contrast, dramatic increases were observed in forearm blood flow, O_2 uptake and CO_2 output during dynamic exercise to fatigue, by ~20-, 35- and 37-fold, respectively. Furthermore, relatively large ionic and acid-base changes were observed in blood draining the active muscles, with increases in deep antecubital venous plasma [H^+] (~10 nmol l^{-1}), [HCO_3^-] (~3 mmol l^{-1}), PCO_2 (~17 mmHg), [Lac^-] (~3 mmol l^{-1}), [Na^+] (~4 mmol l^{-1}), [K^+] (~1 mmol l^{-1}) and [SID] (~8 mmol l^{-1}), and with declines in plasma volume (~5%) and [Cl^-] (~7 mmol l^{-1}). These changes are much more dramatic when considered in the context of the large increase observed in forearm blood flows, indicating large ionic and metabolic fluxes across the forearm muscles.

3.4.2 Forearm blood flow

Whilst venous occlusion plethysmography is a well-established non-invasive method of estimating forearm blood flow, there are important limitations. This includes an inability to collect measurements during forearm exercise due to movement artefacts, resulting in a time lag of ~2-5 s between the end of exercise and the initiation of blood flow measurements. Therefore, absolute blood flow measurements at fatigue could be slightly underestimated due to a possible immediate decrement in blood flow. Consequently ionic and metabolic fluxes across the forearm muscles would also be slightly underestimated. However, since FBF timing was consistent between trials and FBF was unaffected by ALK, this is therefore not a major limitation. Furthermore, the peak blood flow measured here was ~162 ml min^{-1}, very similar to the ~175 ml min^{-1} measured by Doppler ultrasound after 5 min dynamic handgrip exercise (Perrey et al

2001). No recovery flow data was provided in that study, which would also have utilised a higher muscle mass (Perrey et al 2001). In this study, increases in blood flow with exercise are assumed to primarily reflect skeletal muscle blood flow, as arterial inflow to and venous outflow from the hand was occluded ~10 s prior to blood sampling, which immediately preceded forearm circumference measures. Also, the contribution of forearm skin blood flow is assumed minimal and constant between trials, due to a constant cool laboratory temperature of 21°C. Finally, it is likely that blood flow was at ~steady-state for the majority of exercise (between ~2-6 min), since each of $C_{a-v}O_2$, $C_{a-v}CO_2$, $[Blac^-]_{a-v}$ and $[K^+]_v$ were relatively unchanged after the first minute during exercise, and each of these would be sensitive to altered blood flow. Furthermore tight coupling also exists between power output, blood flow, contracting musculature and peripheral $\dot{V}_mO_2$ (Saltin et al 1998) and power output was maintained constant during the exercise protocol. At fatigue $\dot{V}_mO_2$ was ~21 ml min^{-1} and both FBF and $\dot{V}_mO_2$ decreased rapidly within the first minute of recovery, similar to other reports (Perrey et al, 2001; MacDonald et al 2001).

3.4.3 Marked ion fluxes during finger flexion exercise

To our knowledge, no previous studies have published fluid shifts during dynamic forearm exercise. Interestingly, the arterio-venous fluid loss during exercise for ΔPV_{a-v} was only ~3% and for ΔBV_{a-v} ~2%. These were minor compared to the corresponding ~14% and ~9% losses during high intensity sprint cycling exercise (McKenna et al. 1997a), reflecting the far smaller size of contracting muscle and also the high blood flow observed. Consequently, dynamic finger flexor exercise invoked considerable fluxes of strong ions across the contracting finger flexor muscles, with dramatic increases at fatigue in plasma fluxes of, K^+ and Lac^-, and decline in plasma Cl^- flux, together with large increases in arterio-venous H^+ and HCO_3^- differences. Thus, despite the small contracting muscle mass, dramatic increases in ionic exchanges were observed.

The small peak rise in $[K^+]_v$ during finger flexion exercise (~1 mmol l^{-1}) was similar to that observed during 5 min of dynamic handgrip exercise at a similar relative work rate (MacDonald et al 2001) and also during incremental wrist flexion exercise (Raymer et al 2004). However, these $[K^+]_v$ increases were small compared to 30 s sprint exercise with a large muscle mass, where the peak increases in plasma $[K^+]_a$ and of $[K^+]_v$ were ~2.6 and 3.8 mmol l^{-1}, respectively, at a far higher power output (McKenna et al 1997a). An undershoot of $[K^+]_v$ below initial resting values was observed during recovery, consistent with observations in most other forms of exercise, most likely due to the

concomitantly decreased muscle interstitial [K^+] (Sejersted and Sjøgaard 2000). Due to the movement of K^+ and water in opposite directions across the contracting muscle membrane, the $[K^+]_{a-v}$ and K^+ fluxes were corrected for ΔPV_{a-v} (McKenna et al 1997). An important finding was that no widening of the $[K^+]_{a-v}$ was apparent at fatigue in the control trial, which contrasts previous reports during isometric quadriceps contractions (Verburg et al 1999) and cycling (Sahlin and Broberg 1989). This suggests that under these conditions there was not a sudden rise in muscle K^+ loss that precipitated muscle fatigue.

3.4.4 Loss of Cl^- but not Na^+ from plasma during finger flexion exercise

There was a clear net Cl^- efflux from plasma throughout exercise, with a 156-fold increase in efflux observed from rest to fatigue. This is consistent with muscle Cl^- uptake during intense large muscle mass exercise (McKenna et al 1997a). Presumably most of this Cl^- entered the forearm muscle with increases in both the interstitial and intracellular spaces (Sjøgaard et al 1985), although some Cl^- shift into the red blood cells may also have occurred (Prange et al 2001). In isolated rat muscle, low extracellular [Cl^-] reduced force and high Cl^- conductance may counter, in part, a hyperkalemic-induced reduction in membrane potential (Cairns et al 2004). Thus it is possible that muscle Cl^- influx during exercise in human muscle contractions may similarly act to preserve muscle function and delay fatigue.

The Na^+ fluxes during exercise and at fatigue were inconsistent and differed to large muscle mass exercise. Whilst the fatigue data indicate an apparent Na^+ influx into plasma, suggesting Na^+ release by the contracting muscles, this is quite unlikely. First, the arterio-venous Na^+ difference fluctuated throughout exercise, without a clear direction of net Na^+ movement. Second, there was considerable between-subject variability in the calculated muscle Na^+ fluxes during exercise and early recovery (note high SEM for $[Na^+]_{a-v}$). The lack of consistent Na^+ fluxes observed also match with reports of no net muscle Na^+ uptake during moderate intensity arm cranking exercise (Volianitis and Secher, 2002), or during low and moderate intensity cycling (Wasserman et al 1997). The lack of net Na^+ exit from plasma appears consistent with the very small arterio-venous fluid shifts observed during finger flexion exercise, in contrast to a clear Na^+ loss from the circulating plasma across the muscle seen in high intensity cycling exercise (McKenna et al 1997a).

3.4.5 Acid-base changes with forearm exercise

The small contracting muscle mass was insufficient to perturb arterial acid-base status, whereas an ~20% increase in venous [H^+] during exercise was observed. The origin of

this venous acidosis can be ascertained through analysis of the independent variables determining $[H^+]$, namely PCO_2, [SID] and $[A_{TOT}]$ (Johnson et al. 1996). The rise in venous $[H^+]$ is consistent with the sharp increase in PCO_2, similar to observations made during intense leg cycling exercise (Kowalchuk et al. 1988, McKenna et al. 1997), being attenuated by the corresponding ~8 mmol l^{-1} rise in venous [SID] during exercise in the control trial. The increased $[SID]_v$ was mainly influenced by an ~7 mmol l^{-1} decrease in $[Cl^-]_v$ with similar, opposing increases in $[Na^+]$ and $[Lac^-]$; and a ~1 mmol l^{-1} rise in $[K^+]$. The direction and magnitude of venous strong ion and [SID] changes in the circulation was similar to those described during handgrip exercise (Raymer et al 2004) and during low intensity cycling exercise (Miller et al 2005), but clearly differ from the decreased plasma SID observed at the end of high intensity cycling exercise (McKenna et al 1997a). In recovery, whilst [SID] declined, the sharp decline in PCO_2 allowed a decline in $[H^+]_v$. Increased plasma $[HCO_3^-]_v$ and thus a more negative $[HCO_3^-]_{a-v}$ during exercise are consistent with the effects of increases in P_vCO_2 and $[SID]_v$ (Johnson et al. 1996). Whilst plasma $[A_{Tot}]$ was not assessed in this study, this reflects plasma protein concentration, which was probably slightly increased with exercise due to the small decline in plasma volume. The resultant increase in $[A_{Tot}]$ would therefore tend to increase $[H^+]_v$ during finger flexion exercise.

3.4.6 Alkalosis enhanced finger flexion exercise performance

An important finding was that ALK clearly enhanced performance during small muscle group contractions, with time to fatigue delayed by 25%. Our exercise findings are in broad agreement with numerous human exercise studies utilising a large muscle mass, that demonstrated 19-49% increases in performance with alkalosis (Sutton et al 1981, Costill et al 1984, Iwaoka et al 1989). This study advances a previous finding of performance enhancement in a small exercising muscle mass with ALK (Raymer et al 2004), through analysis of arterio-venous ion fluxes across contracting muscle.

3.4.7 Alkalosis effects on K^+ during exercise

Following alkalosis, subjects were mildly hypokalemic at rest, consistent with previous findings in humans (Lindinger et al 1999, Raymer et al 2004) and in dogs (Suzuki et al 1990). A possible mechanism is Na^+-H^+ antiporter mediated Na^+/H^+ exchange, with consequent increased intracellular $[Na^+]$ (Lindinger et al 1990), driving increased Na^+,K^+-ATPase activity (Sabatini 1996; Weinman and Shenolikar 1993) and lowering extracellular $[K^+]$. With alkalosis, both $[K^+]_a$ and $[K^+]_v$ remained systematically lower throughout exercise and recovery. Although we did not measure muscle interstitial $[K^+]$, it is likely that this was also lower during ALK (Street et al. 2005). Muscle force is substantially depressed by a reduced intracellular-to-extracellular $[K^+]$ ratio (Cairns et al 1995; Nielsen et al 1998). It is therefore conceivable that reduced plasma $[K^+]$

contributes to lower muscle extracellular [K^+] with ALK, maintaining a high intracellular-to-extracellular [K^+] ratio and thus muscle membrane excitability during exercise, thereby contributing to the observed improvement in muscle performance.

We hypothesised that ALK would reduce peak muscle K^+ release, based on findings in isolated contracting rat muscles (Lindinger et al. 1990). In contrast, muscle K^+ release at fatigue was actually 49% greater in ALK compared to CON (~64 vs ~43 µmol min^{-1}, respectively). This magnitude of K^+ release was similar to that observed (~69 µmol min^{-1}) across the gastrocnemius muscle during 3 min of plantar flexion, at a similar low workrate of 2.6 W (Green et al 2000). The greater K^+ release was not influenced by differences in fluid shifts, as the arterio-venous decline in plasma volume was small and unchanged by ALK. The increased K^+ release at fatigue with ALK must be considered in the context of the ~17% greater K^+ uptake rates into previously contracting muscles during recovery in ALK. Greater muscle K^+ re-uptake most likely reflects an increased muscle Na^+,K^+-ATPase activity and possibly Na^+-K^+-$2Cl^-$-cotransporter activity (Gosmanov et al 2003). This was unlikely to be mediated by catecholamines as these were barely elevated and did not differ between trials. Thus increased K^+ release at fatigue in ALK likely occurred in the face of augmented muscle Na^+,K^+-ATPase activity, suggesting increased opening of some K^+ channels. It is unlikely that this greater K^+ leak occurred via K^+_{ATP} channels as numerous studies show that intracellular [H^+] is reduced with ALK at rest and/or during exercise (Raymer et al 2004, Neilsen et al. 2002, Stephens et al. 2002). It is possible that voltage sensitive K^+ channels are responsible for the majority of K^+ leak across the sarcolemma during ALK. Increased Na^+,K^+-ATPase activity would likely exert a greater electrogenic effect, which together with lower extracellular fluid [K^+], would act to preserve muscle membrane potential and excitability with ALK. This suggests that maintenance of a [K^+] gradient for dissipation during exercise is important for muscle performance (Lindinger et al. 1995).

3.4.8 Alkalosis affects plasma Na^+ and Cl^- regulation

Arterial plasma [Na^+] was higher and $[Na^+]_v$ tended to be higher with ALK, consistent with previous reports of increased $[Na^+]_v$ (Lindinger et al 1999, Street et al 2004; Raymer et al 2004) and $[Na^+]_a$ with oral $NaHCO_3$ intake (Lindinger et al 1999). ALK did not modulate either the arterio-venous Na^+ difference or the calculated muscle Na^+ fluxes during exercise and early recovery and these measures were quite variable. However, elevated systemic [Na^+] and thus Na^+ delivery to muscles may be important in enhancing muscle function with ALK by providing a higher plasma-interstitium-intracellular gradient and thereby preserving t-tubular [Na^+]. Similarly, ALK effects on

Cl^- may also be important to delayed muscle fatigue. Both $[Cl^-]_v$ and muscle Cl^- fluxes during exercise were higher with ALK, which together with elevated muscle Cl^- conductance may stabilise the cell membrane during contractions, as demonstrated under non-physiological conditions in mice muscles (Cairns et al 2004).

3.4.9 Alkalosis interpreted via a physicochemical approach

Alkalosis increased venous PCO_2 (~5 mmHg), arterial CO_2 content (~ 90 ml l^{-1}), venous CO_2 content (~70 ml l^{-1}), and decreased venous [SID] (~7 mmol l^{-1}). No difference was found between trials for arterial PCO_2 and [SID]. Few studies have examined the effects of alkalosis during exercise using the Stewart physico-chemical approach to acid-base balance. The lower $[SID]_v$ with ALK was the result of systematic ionic changes during exercise, predominantly contributed to by a greater $[Cl^-]$ (~80% of lower [SID] in ALK) and $[Lac^-]$ (~1%) and by a decrease in $[K^+]$ (~3%), partially countered by a greater $[Na^+]$ (~16%). These findings differ from estimates of a greater increase in $[SID]_v$ during alkalosis, where $[Lac^-]_v$ and $[Cl^-]_v$ were less than in the control trial (Raymer et al 2004). The lower $[SID]_v$ during recovery in ALK was mainly due to the higher $[Lac^-]_v$. The small increments in $[Na^+]_v$ of ~2-3 mmol l^{-1}in control and ALK trials were balanced by ~2-3 mmol l^{-1}increments in $[Lac^-]_v$, which is almost identical to the changes observed in stimulated rat muscle following alkalosis (Lindinger et al 1990). The effects of ALK on increasing arterial and venous $[HCO_3^-]$ can be mainly attributed to the increased PCO_2, although the lesser decline in $[HCO_3^-]_{a-v}$ during exercise in ALK may be attributed to a smaller rise in $[SID]_v$. The lower $[H^+]$ with ALK cannot be explained by either [SID] which was lower, or the PCO_2, which was higher with ALK.

During ALK, Lac^- flux into plasma was greater at fatigue, probably reflecting both enhanced glycolytic ATP production and augmented Lac^- transport from exercising muscle (Sutton et al 1981, Juel 1997). However, it is unlikely that lactate played a significant fatiguing role in the present study (Posterino et al. 2001). Increased acidosis was found to have little effect on glycolysis or fatigue in humans (Bangsbo et al 1996) or in isolated muscle preparations (Westerblad and Lännergren 1988). Indeed, in isolated rat muscle preparations, intracellular acidosis had a protective effect on excitability, and performance (Pedersen et al 2004; Nielsen et al 2000), although this has been recently challenged (Kristensen et al. 2004). Interestingly, a number of *in situ* and *in vivo* ^{31}P-MRS studies have demonstrated a strong correlation between a decline in intracellular pH and force production (Raymer et al 2004; Wilson et al 1988; Miller et al 1988). Greater blood lactate during alkalosis may in addition have been due to reduced uptake by non-contracting tissue (Hollidge-Horvat et al 2000).

3.5 Summary

Dynamic, concentric contractions of the finger flexor muscles barely perturbed systemic acid-base and ionic status but induced marked ionic exchanges across the contracting muscle, along with a dramatic increase in blood flow and metabolism. Muscle function was substantially improved with alkalosis. Responses of each of the strong ions K^+, Na^+, Cl^- and Lac^- during exercise were modified by alkalosis and their combined effects likely contributed to the improvement in muscle performance. Whilst increased muscle K^+ efflux was observed at fatigue in alkalosis, the lower arterial and venous [K^+], and presumably lower interstitial [K^+], suggests preservation of the intracellular-to-extracellular [K^+] gradient with alkalosis. Furthermore, the greater K^+ reuptake in recovery suggests an increase in muscle Na^+,K^+-ATPase activity. The higher Na^+ delivery to muscle and enhanced Cl^- uptake by muscle would likely act in concert to further stabilise the muscle membrane in the face of exercise-induced hyperkalemia. Together these suggest preservation of membrane excitability with alkalosis. Finally, enhanced Lac^- release with alkalosis would act to reduce intracellular [H^+], but whether this affects cellular excitability is unclear. Thus a major beneficial effect of alkalosis on muscle performance might be consequent to the integrated effects on K^+, Na^+, Cl^- and Lac^- homeostasis.

CHAPTER 4 EFFECTS OF DIGOXIN ON POTASSIUM HOMEOSTASIS AND MUSCLE FATIGUE DURING INTENSE INTERMITTENT MUSCLE CONTRACTIONS IN HEALTHY HUMANS

4.1 INTRODUCTION

Intracellular and extracellular ionic regulation during muscle contractions, mediated via multitude processes, is critical for the maintenance of cell membrane excitability and muscle contractile function (Allen et al, 2008; McKenna et al, 2008). Of particular importance is the sarcolemmal and t-tubular sodium-potassium adenosine 5' triphosphatase (NKA), which regulates Na^+/K^+ transport and is energized via ATP hydrolysis. At the onset of muscle contractions, NKA activity increases as much as 22-fold to minimise both muscle K^+ loss and Na^+ gain (Nielsen and Clausen 2000). Despite this however, the transport capacity of NKA is not reached, with consequent elevated muscle interstitial [K^+], and intracellular [Na^+], and reduced intracellular [K^+] (Sejersted & Sjøgaard, 2000). Furthermore there is evidence that the maximal NKA activity is depressed during exercise by 12-21% in humans (Fraser et al 2002; Leppik et al 2004; Sandiford et al 2004; Aughey et al 2005; Murphy et al 2006b). Together these are implicated as potential contributory factors to muscle fatigue (Sejersted and Sjøgaard, 2000; McKenna et al, 2008).

Interventions that increase the NKA content in muscle, such as physical training and dexamethasone, also lower circulating [K^+] and are associated with increased muscle performance (McKenna et al, 1993; Green et al, 1993; Nordsborg et al, 2005, 2008). Furthermore, increased NKA activity and lowered plasma [K^+] induced by alkalosis was also associated with enhanced muscle function (Nielsen et al, 2004; Chapter 3 of this thesis). However these interventions are non-specific to the NKA and most likely alter multiple cellular processes. A specific inhibitor of NKA is digoxin, which binds selectively to the NKA α-subunit and which is routinely administered to patients suffering from congestive heart failure (CHF) (Goldberg et al, 2007). In cardiac muscle, digoxin increases Na^+/Ca^{2+} exchange (Clausen 1998), increasing intracellular $Ca^{2+}{}_i$ (Hauptman & Kelly, 1999; O'Connor et al 1998; Clausen 1998), elevating Ca^{2+} in the sarcoplasmic reticulum (Clausen 1998; Levi et al 1995), ultimately eliciting a positive inotropic action in cardiac muscle (Hauptman & Kelly, 1999). However ~4% is bound to NKA in the myocardium whilst 50% of total in-vivo digoxin is bound to NKA in skeletal muscle (Steiness, 1978). Digoxin inhibits skeletal muscle NKA (Schmidt et al 1991), with occupancy of NKA ranging from 13% (Schmidt et al, 1991) to 35% in heart failure patients (Green et al, 2001). Therefore it could be anticipated that selective inhibition of a small fraction of NKA in skeletal muscle will lead to a more pronounced hyperkalemia

during exercise, and therefore facilitate premature fatigue. An early study reported a digoxin induced increase in serum K^+ with exercise in atrial fibrillation patients (Norgaard et al, 1991).

Following digoxin therapy in healthy humans (Edner & Jogestrand 1993), resting serum K^+ was elevated at rest by ~0.19 mM, consistent with a partial inhibition of skeletal muscle NKA. An increased affinity of digoxin to muscle during exercise and subsequent decrease in serum digoxin concentration has also been demonstrated in healthy humans (Jogestrand & Sundquist 1981; Joretag & Jogestrand 1983). Thus the impact of digoxin on skeletal muscle NKA during exercise is likely to be exacerbated (Green et al, 2007). Therefore the effects of digoxin on K^+ homeostasis and skeletal muscle function were investigated in the present study.

A recent study in septic shock patients found that ouabain infusion reduced production of lactate and pyruvate (Levy et al 2005). Thus a partial Inhibition of NKA by digoxin could also reduce muscle glycolysis during rest and exercise, and consequently also modulate acid-base status. Janssen et al (2009) intravenously infused digoxin at 0.01mg.kg^{-1} in healthy adults and did not find any change in venous K^+ and Lac^- during 3 min of sub-maximal dynamic handgrip exercise. However serum digoxin concentration was not reported and thus it is difficult to predict likely occupation of NKA. Furthermore, both $[K^+]_v$ and $[Lac^-]_v$ was low, and the timing of samples was not clear. Finally it is not clear how the site of venous sampling affected results in their study, suggesting a failure to detect exercise $[K^+]$. The regulation of Cl^- and Na^+ is important for maintaining cell membrane potential and muscle function (Pedersen et al, 2004, 2005; Cairns et al 2004). T-tubular and sarcolemmal membranes are more permeable to Cl^- than K^+ (Allen and Lamb, 2008), however the effects of digoxin on plasma Cl^- and Na^+ are currently unknown.

The previous experiment utilized a forearm finger flexion exercise model which invoked large ionic, metabolic and acid-base disturbances across forearm muscle (Chapter 3). A similar exercise model was chosen here and provided opportunity to study arterio-venous fluxes during exercise and in recovery. Therefore the effects of digoxin on ionic, metabolic and acid-base changes across healthy contracting musculature were explored also here. In addition to digoxin effects in response to exercising small muscle mass, we also evaluated the ionic, metabolic and acid-base responses to intermittent supra-maximal finger flexion exercise.

This experiment therefore investigated the effects of a standard clinical oral dose of digoxin on plasma ionic, metabolic and acid-base regulation in blood, and arterio-venous differences across muscle during and following intense fatiguing forearm muscle contractions, in healthy young participants.

It was hypothesised that digoxin would; (i) increase muscle potassium release and arterial potassium concentration during exercise and inhibit post-exercise muscle potassium re-uptake; (ii) decrease glycolytic and acid-base disturbances during exercise; and (iii) impair peripheral muscle function.

4.2 METHODS

4.2.1 Subjects

Ten healthy untrained volunteers, comprising nine males and one female, signed informed consent (Appendix 4B) and participated in the study. Ethical clearance was obtained from Victoria University Human Research Ethics Committee and the Alfred Hospital Ethics Committee, conforming to the Declaration of Helsinki. Physical characteristics of the volunteers were (mean ±SD) age 26.1 ± 6 years, body mass 75.7 ± 11.3 kg, and height 178.4 ± 9.2 cm. In the 72 h prior to each experimental trial, volunteers consumed pre-packaged iso-energetic meals and beverages (Appendix 6). In the 24 h prior to each visit, volunteers refrained from vigorous activity and ingestion of caffeine and alcohol.

4.2.2 Overview of Test Procedures

Participants underwent an initial medical history screening and physical examination. An antecubital venous blood sample was assessed to verify normal plasma electrolytes and kidney function. Volunteers were screened for a history of adverse cardiovascular events, and a resting electrocardiogram (ECG) was taken and evaluated to ensure normal heart rate and rhythm. Volunteers then attended the laboratory on five separate occasions. During their initial visit, anthropometric measurements of forearm length and circumferences were made in triplicate for estimation of forearm volume, and subjects were familiarised with finger flexion contractions, followed by an incremental finger flexion test on a custom designed dynamometer (Chapter 3). Incremental rhythmic finger flexion contractions were performed at a rate of 30 min^{-1}, commencing at mean power output of 3.37 ± 0.19 W. Resistance and thus power output were increased at the end of each min, such that power output increased by 0.16 ± 0.03 W each min. Contractions continued until volitional fatigue, to allow determination of their peak work rate (WR_{peak}), and subsequent intensity required in all experimental finger flexion trials (105% WR_{peak}). Fatigue for all trials was defined as a failure to maintain power output and/or cadence for eight consecutive contractions (Chapter 3). Following a 30 min rest, volunteers were familiarised with this experimental protocol. Comprehensive details on the custom made finger flexion dynamometer and plethysmographic method of blood flow have been previously described in detail (Chapter 3).

Volunteers also completed an incremental leg cycling test, completing 4min at each of 60, 90, 120 & 150W, then 25W increments per minute until volitional fatigue to determine $\dot{V}O_{2peak,}$ on an electrically braked ergometer (Excalibur Lode, Groningen, Netherlands) with all methods, equipment and procedures as previously described (Li et al, 2002). On each subsequent laboratory visits, subjects performed a finger flexion

trial comprising three one minute exercise bouts (EB1-3) separated by 1min recovery, followed by a fourth bout continued to fatigue. During the second and third laboratory visits, trials were undertaken to determine the intra-subject variability in power output and time to fatigue during the finger flexion exercise. During two final visits, volunteers performed finger flexion exercise to fatigue trials under randomised, cross-over, counterbalanced and double-blind conditions of both digoxin (DIG) and control (CON) treatment. Volunteers were administered either oral digoxin 0.25 $mg.d^{-1}$ (Lanoxin, Glaxo Smith Kline) taken at the end of each day, to replicate a typical clinical oral dose, or a placebo for 14 days. A four week washout period was given between treatments. Thus after DIG trials, the 4 week washout 2 weeks placebo enabled a DIG clearance of 6 weeks. This easily allows for DIG clearance, as the half-time clearance from serum after DIG injection was ~45 h (range 32-131 h) (Kramer *et al*., 1974) and from skeletal muscle after oral DIG was ~2.2 d (Jogestrand & Sundqvist, 1981). The attending medical physician was not blinded for ethical reasons. Repeated arterial and venous blood samples, and measurements of forearm blood flow were also made during the DIG and CON experimental trials.

4.2.3 Finger flexion experimental trials

Heart rate and rhythm were monitored by 12-lead electrocardiogram (Mortara, Boston, USA). Catheters (20 or 22G Jelco) were inserted anterograde in the radial artery (a) of the non-contracting arm, under local anaesthesia (2% lignocaine injection) and retrograde into the deep antecubital vein (v) of the contracting forearm. Subjects then rested for ~30 min prior to the commencement of each DIG and CON trials. Intra-arterial and intra-venous pressures were continually monitored (Marquette 710, Wisconsin, USA) by electronic pressure transducers (Abbott Critical care Systems, Chicago Illinois, USA) connected to saline filled cannulae via an extension line. Blood pressure signals were then interfaced with the finger flexion exercise computer system, enabling continual integration between power output, forearm circumference changes and blood pressure data. Arterial lines were kept patent by a slow, sterile, isotonic saline infusion under pressure. Subjects then performed three one minute exercise bouts (EB1-3) separated by 1min recovery, followed by a fourth bout continued to fatigue, at a work rate corresponding to 105% WR_{peak} at 30 contractions min^{-1}. Arterial and venous blood samples (each 5 ml) were taken simultaneously at rest in the final 10s of each 1min exercise bout; immediately prior to the start of the next exercise bout; during the final contractions at fatigue; and at 1, 2, 5, 10 and 30 min post exercise. Hand blood flow was occluded for 10 s prior to and during venous blood sampling by a high-pressure wrist cuff. Forearm circumference measurements were made for FBF

calculations immediately following blood sampling at rest, during exercise, and in recovery (Chapter 3).

An additional blood sample (8 ml) was taken to measure serum [DIG] on days 7, 13 and 14 of the treatment period. Blood samples were allowed to clot and then centrifuged at 4000 rpm for 10 min at 4°C (3K 15 refrigerated centrifuge Sigma, Laborzentrifugen, Germany). Serum was subsequently removed and stored at -20°C until assayed for serum digoxin by Multigent™ (Abbot Laboratories, Inc; IL USA) homogenous particle-enhanced turbidimetric immunoassay. Blood samples were also immediately analysed in duplicate for plasma electrolyte concentrations (K^+, Na^+, Cl^-), acid-base status (HCO_3^-, pH), gas tensions (PO_2 and PCO_2), O_2 saturation (SO_2), haemoglobin (Hb) and haematocrit (Hct), using automated blood gas and haematology analysers; plasma and whole blood lactate concentrations ($[Lac^-]$) were determined spectrophotometrically (not measured at rest periods during exercise or during the first min of the final bout of exercise). All measurements and analysers were calibrated immediately before, during and after measurements with precision standards in the range of the measurements, as previously detailed (Sangkabutra et al 2003; Fraser et al 2002).

4.2.4 Calculations

Plasma hydrogen concentration ($[H^+]$ nmol l^{-1}) was derived from measured pH. Changes from resting levels in plasma volume (ΔPV_a) and blood volume (ΔBV_a) and changes in venous compared to arterial plasma (ΔPV_{a-v}) and blood volume (ΔBV_{a-v}) across the forearm were calculated during and following exercise, from changes in [Hb] and Hct, as previously described (McKenna et al, 1997). These calculations enabled corrections to be made for effects of fluid shifts on ion concentrations in plasma and blood during and following exercise. Plasma and blood ion efflux data were corrected for fluid shifts. Plasma $[ion]_{a-v}$ (mmol l^{-1}) were corrected for ΔPV_{a-v} using the equation: $[ion]_{a-v} = ([ion]_a / (1+ \Delta PV_{a-v})) - [ion]_v$ (McKenna et al, 1997a). Net ion fluxes across the forearm were calculated as the product of corrected $[ion]_{a-v}$ and plasma blood flow, and expressed in µmol min^{-1}. A similar correction was made for whole blood $[ion]_{a-v}$ but using ΔBV_{a-v}. Plasma strong ion difference ([SID], mmol l^{-1}) was calculated as $([K^+] + [Na^+]) - ([Lac^-] + [Cl^-])$ (McKenna et al 1997a) and calculations of whole blood CO_2 and O_2 content, muscle $\dot{V}CO_2$, $\dot{V}O_2$ and RER were as previously described (McKenna et al 1997b). Plasma flow was calculated as FBF x Hct (expressed as a fraction; Chapter 3).

4.2.5 Statistical Analysis

Results are expressed as mean ± standard error (mean ± SEM) unless otherwise stated. A two-way ANOVA with repeated measures was employed for all blood variables to assess main effects of treatment (DIG, CON) or time (rest, exercise, recovery). Treatment by time interactions was not significant unless stated. Post-hoc analyses used the least significant difference test. Exercise time to fatigue was analysed using a paired student t-test. Statistical significance was accepted at $P < 0.05$. Effect size (Cohen's *d*) is reported when a variable was close to significantly different between treatments. Cohen's conventions for effect size were adopted for interpretations, where 0, 0.2, 0.5, and 0.8 are considered trivial, small, moderate and large, respectively (Cohen, 1988). Moderate to large effect size signify a functional effect of an intervention.

4.3 RESULTS

4.3.1 Serum digoxin concentration

Subjects undergoing digoxin therapy were compliant for the required 2 weeks, and no DIG mediated adverse events were reported. During DIG, SDC was 0.7±0.2 nM on day 7 and 0.8±0.2 nM on day 14. During CON, SDC was below the detection limit of <0.4 nM. One subject was reported at the lower detection limit of 0.4 nM for SDC in CON, whilst their corresponding SDC in the DIG trial was 0.9-1.0 nM. For all others in CON, no digoxin was detected.

4.3.2 Exercise tests performance

4.3.2.1 Pre-experiment peak exercise and performance variability tests

Leg cycling incremental exercise $\dot{V}O_{2peak}$ and WR_{peak} were 3.67±0.42 l min^{-1} and 298±23W, respectively. In contrast the WR_{peak} during incremental finger flexion exercise test was only 5.10±0.43 W. During finger flexion incremental tests, the average finger flexion power output at each work rate was linear over time (R^2 = 0.986). Mean power output during finger flexion variability trials were highly reproducible, with a CV of 1.0% (Table 4.1). The time to fatigue during variability trials was more variable, with a CV of 12.4%.

4.3.2.2 Finger flexion exercise performance

The mean force and power output were well matched between trials, with no differences between DIG and CON (Table 4.1). Time to fatigue at 105% WR_{peak} was not different between trials (Table 4.1). No trial order effects were found.

4.3.3 Forearm blood flow during finger flexion exercise

Exercise. FBF increased ~12-fold from rest to fatigue (P<0.001), decreased by ~60% within the first 1 min of recovery, and returned to resting values at 30 min post-exercise (Table 4.2).

Digoxin. No significant differences were found in FBF between CON and DIG (Table 4.2).

4.3.4 Haematology and Fluid Shifts

4.3.4.1 Haemoglobin and haematocrit

Exercise. Arterial and venous [Hb] and Hct increased from rest to fatigue and early recovery (P<0.001; Table 4.3).

Digoxin. There were no differences between CON and DIG for either [Hb] or Hct.

4.3.4.2 Plasma and blood volume changes

Exercise. Plasma volume (PV) declined from rest during exercise when calculated for both arterial and venous blood, by ~4 and 8% at fatigue respectively ($P<0.001$, Table 4.4). Whilst ΔPV_a remained negative for the first 5 min of recovery, ΔPV_v increased above rest at 10 min recovery ($P<0.001$). A negative $\Delta PV_{a\text{-}v,}$ indicating a small net loss in PV occurred across the exercising forearm ($P<0.05$, Table 4.4). Similar exercise effects were found for ΔBV_a and for ΔBV_v, although at a lesser magnitude ($P<0.05$, Table 4.4).

Digoxin. There were no effects of DIG on ΔPV_a, ΔPV_v or $\Delta PV_{a\text{-}v}$ or on BV_a, BV_v or $BV_{a\text{-}v}$ (Table 4.4).

Table 4.1. Performance characteristics during finger flexion exercise

Trial	*n*	Mean Force (N)	Mean Power Output (W)	Fatigue Time (min)
Variability 1	10	35.99 ± 3.32	5.33 ± 0.34	4.86 ± 0.8
Variability 2	10	36.02 ± 3.25	5.29 ± 0.35	4.89 ± 0.8
CV(%)	10	3.5 ± 0.7	1.0 ± 0.3	12.4 ± 3.3
CON	9	36.23 ± 3.5	5.36 ± 0.5	3.94 ± 1.1
DIG	9	37.37 ± 3.5	5.44 ± 0.5	2.62 ± 0.7

Exercise was at WR corresponding to 105% $WR_{peak,}$ with three 1 min bouts separated by 1min recovery, and a final bout continued to fatigue. Values are Mean ± SEM for control (CON) and digoxin (DIG, 0.25 mg). Coefficient of variation (CV) was calculated from variability trial 1 and 2.

Table 4.2: Rate of forearm blood flow (ml min^{-1}) measured at rest, immediately after each exercise bout and subsequent recovery periods, at fatigue, and during recovery, under CON and DIG conditions.

		Exercise							Recovery (min)				
	Rest	**EB1**	**Pre EB2**	**EB2**	**Pre EB3**	**EB3**	**Pre EB4**	**F**	**+1**	**+2**	**+5**	**+10**	**+30**
CON													
Blood flow	22.8	159.4*	79.9*	193.7*	119.1*	230.2*	131.6*	279.1*	125.6*	85.9*	62.1	33.9	24.1
SEM	3.5	22.7	20.1	40.8	42.1	53.0	52.1	54.0	33.9	29.7	20.7	10.0	5.6
DIG													
Blood flow	20.9	152.3*	80.1*	180.3*	111.8*	221.6*	107.5*	256.4*	92.3*	61.8*	45.6	30.8	21.3
SEM	2.7	24.4	17.9	26.1	25.7	30.3	35.5	37.8	18.3	13.5	15.9	8.6	4.7

* Greater than rest ($P < 0.001$). Mean ± SEM, *n =10*

Exercise bout (EB), Fatigue (F), 1 min to 30 min recovery (+1 to +30)

Table 4.3: Effects of digoxin on haemoglobin ([Hb]) and hematocrit (Hct) at rest, during intermittent finger flexion exercise to fatigue, and recovery. Units are g dl^{-1} haemoglobin and % for Hct.

	Exercise									Recovery (min)				
	Rest	EB1	Pre EB2	EB2	Pre EB3	EB3	Pre EB4	EB4(1min)	F	+1	+2	+5	+10	+30
CON														
$[Hb]_a$	14.2	14.2	14.3*	14.3*	14.3*	14.3*	14.4*	14.4*	14.5*	14.5*	14.4*	14.3*	14.2	14.1
SEM	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
$[Hb]_v$	14.0	14.4*	14.2	14.4*	14.2	14.4*	14.2	14.4*	14.7*	14.3*	14.2*	14.1	13.9	13.9
SEM	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Hct_a	39.7	40.2*	40.2*	40.1*	40.3*	40.3*	40.5*	40.5*	40.9*	40.9*	40.9*	40.5*	40.1*	39.8
SEM	0.6	0.7	0.6	0.6	0.7	0.6	0.6	0.7	0.7	0.6	0.6	0.6	0.6	0.6
Hct_v	39.5	40.9*	40.3	40.8*	40.2*	41.0*	40.4	41.2*	41.7*	40.6*	40.5*	40.1*	39.3	39.2
SEM	0.8	0.7	0.7	0.7	0.7	0.8	0.8	0.8	0.8	0.8	0.8	0.7	0.8	0.7
DIG														
$[Hb]_a$	14.1	14.4*	14.2*	14.3*	14.3*	14.4*	14.4*	14.5*	14.8*	14.7*	14.7*	14.6*	14.4	14.4
SEM	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3
$[Hb]_v$	13.9	14.3*	14.0	14.2*	13.9	14.3*	14.0	14.3*	14.3*	14.2*	14.0*	13.9	13.7	13.9
SEM	0.4	0.4	0.4	0.5	0.4	0.4	0.4	0.4	0.5	0.4	0.5	0.4	0.4	0.5
Hct_a	39.3	40.4*	39.9*	40.1*	40.0*	40.4*	40.3*	41.0*	41.4*	41.3*	41.5*	41.2*	40.6*	40.3
SEM	0.7	0.6	0.7	0.8	0.8	0.8	0.7	0.5	0.6	0.5	0.6	0.6	0.6	0.6
Hct_v	39.3	40.6*	39.6	40.3*	40.0*	40.5*	39.5	40.5*	40.8*	40.3*	40.1*	39.5*	39.1	39.5
SEM	0.8	0.9	0.9	1.0	0.9	0.8	0.8	0.9	1.0	0.9	1.0	0.9	0.9	1.0

Mean ± SEM, *n = 9* for CON Hb_a, Hct_a *n = 8* for DIG, *n = 7* for Hb_v, Hct_v.* Greater than rest (P<0.001). Exercise bout (EB), Fatigue (F), 1 min to 30 min recovery (+1 to +30)

Table 4.4: Changes from resting levels in plasma volume (ΔPV_a) and blood volume (ΔBV_a) and changes in venous compared to arterial plasma (ΔPV_{a-v}) and blood volume (ΔBV_{a-v}) across the forearm calculated at rest, during intermittent finger flexion exercise to fatigue, and recovery, under CON and DIG conditions, from changes in [Hb] and Hct. Units are percent change for ΔPV_a, ΔBV_a, ΔPV_{a-v}, ΔBV_{a-v}.

		Exercise								Recovery (min)				
	Rest	EB1	Pre EB2	EB2	Pre EB3	EB3	Pre EB4	EB4(1min)	F	+1	+2	+5	+10	+30
CON														
ΔPV_a		-1.3	-1.7*	-1.6*	-2.1*	-2.7*	-3.5*	-3.0*	-4.1*	-4.2*	-3.6*	-2.5*	0.5	2.0
SEM		1.0	0.7	0.5	0.8	0.9	0.8	1.5	1.2	0.9	1.3	0.7	0.6	0.6
ΔPV_v		-5.4*	-3.0	-5.0*	-2.6	-5.7*	-4.0	-7.3*	-8.0*	-4.1*	-3.3*	-2.1	6.3*	4.5*
SEM		1.2	1.0	1.3	1.3	1.6	1.6	1.9	1.7	1.5	1.3	1.1	1.7	1.0
ΔPV_{a-v}	0.9	-3.2*	-0.8	-3.0*	-0.4	-2.9*	-0.1	-3.6*	-4.2*	-0.5	-0.6	0.3*	0.7*	0.1
SEM	0.7	1.4	1.2	0.8	0.5	0.7	0.5	0.8	0.6	0.4	1.0	0.7	0.4	1.2
ΔBV_a		-0.6	-0.9*	-1.0*	-1.1*	-1.5*	-1.9*	-1.6*	-2.3*	-2.3*	-1.8*	-1.3*	0.3	1.2
SEM		0.6	0.4	0.3	0.5	0.5	0.5	0.8	0.7	0.5	0.7	0.4	0.4	0.4
ΔBV_v		-3.1*	-1.7	-2.9*	-1.5	-3.2*	-2.2	-3.8*	-4.6*	-2.3*	-1.7*	-1.2	3.5*	2.6
SEM		0.7	0.8	0.9	0.8	0.9	0.9	1.2	1.0	0.8	0.8	0.6	0.7	0.7
ΔBV_{a-v}	-0.9	-1.3	-1.1	-1.2*	-1.0	-1.2*	-1.0	-1.2	-1.3	-1.0	-1.1	-0.9	-0.9	-1.0
SEM	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.1

	Exercise								Recovery (min)					
	Rest	**EB1**	**Pre EB2**	**EB2**	**Pre EB3**	**EB3**	**Pre EB4**	**EB4(1min)**	**F**	**+1**	**+2**	**+5**	**+10**	**+30**
DIG														
ΔPV_a		-2.3	-1.8*	-3.1*	-2.5*	-3.7*	-4.1*	-3.9*	-5.4*	-5.7*	-5.9*	-4.9*	-0.3	0.1
SEM		0.9	0.7	0.8	1.0	0.9	0.9	0.7	1.0	1.0	1.0	0.8	0.9	0.9
ΔPV_v		-4.6*	-0.9	-3.7*	-0.9	-5.0*	-1.7	-3.4*	-6.0*	-3.5*	-2.2*	-0.5	6.4*	0.8*
SEM		1.7	1.7	2.0	2.3	1.1	2.0	1.2	0.8	0.8	0.8	1.2	1.9	1.9
ΔPV_{a-v}	0.1	-5.0*	-1.1	-3.0*	-1.0	-2.6*	1.1	-1.1*	-2.4*	0.6	2.7	3.1*	2.3*	0.5
SEM	0.7	0.4	0.6	0.5	0.4	0.8	0.7	1.0	0.7	1.1	0.6	1.5	0.4	0.8
ΔBV_a		-1.1	-0.7*	-1.7*	-1.4*	-2.0*	-2.1*	-1.1*	-3.0*	-3.1*	-3.1*	-2.5*	0.0	-0.1
SEM		0.6	0.4	0.5	0.6	0.5	0.6	1.0	0.6	0.6	0.6	0.5	0.4	0.5
ΔBV_v		-2.5*	-0.4	-2.1*	0.3	-2.9*	-0.8	-1.5*	-3.5*	-1.8*	-0.9*	-0.2	3.8*	0.6
SEM		1.1	1.0	1.2	2.1	0.7	1.3	0.6	0.4	0.4	0.4	0.7	1.1	1.1
ΔBV_{a-v}	-1.0	-1.4	-1.1	-1.2*	-1.0	-1.2*	-0.9	-1.1	-1.2	-0.9	-0.7	-0.7	-0.8	-0.9
SEM	0.1	0.0	0.1	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Mean ± SEM, *n = 9* for CON ΔPV_a, ΔBV_a, *n = 8* for DIG; *n = 7* for ΔPV_v, ΔBV_v; *n = 6* for CON ΔPV_{a-v}, ΔBV_{a-v}, *n = 5* for DIG.* Different to rest (P<0.001). A negative value denotes a decline, and a positive value denotes a gain in plasma or blood volume across the forearm, respectively. These calculations enabled corrections to be made for effects of fluid shifts on ion concentrations in plasma and blood during and following exercise

4.3.5 Electrolytes

4.3.5.1 Plasma [K^+]

Exercise. Plasma $[K^+]_a$ increased above rest during intermittent finger flexion exercise at EB2, EB3 and EB4, peaking at fatigue, and then gradually decreased to rest values by 30 min recovery ($P<0.01$; Figure 4.1A). Plasma $[K^+]_v$ rose dramatically at EB1, decreased rapidly during the rest period, and subsequently followed this pattern throughout the remainder of the trial to fatigue. Plasma $[K^+]_v$ decreased rapidly in the first minute of recovery to below the resting value, and remained low throughout the remainder of recovery ($P<0.01$, Figure 4.1B). $[K^+]_{a-v}$ decreased at EB1, representing net K^+ entry into plasma traversing forearm muscle. An immediate reversal of $[K^+]_{a-v}$ to resting values occurred during the first pre-exercise bout, and $[K^+]_{a-v}$ subsequently continued to follow this trend of net K^+ loss to plasma during EB2, EB3 and fatigue ($P<0.01$, Figure 4.1C). Net K^+ loss from plasma (positive $[K^+]_{a-v}$) occurred at pre EB3, pre EB4, +1 min and +2 min recovery ($P<0.01$). K^+ efflux into plasma (plasma $[K^+]_{a-v}$ x plasma flow) increased dramatically by ~70-fold at fatigue ($P<0.001$, Table 4.5), with net K^+ removal from plasma evident throughout recovery (Table 4.5).

Digoxin. There was no treatment effect of DIG on $[K^+]_a$, $[K^+]_v$, $[K^+]_{a-v}$ and K^+ efflux (Figure 4.1, Table 4.5).

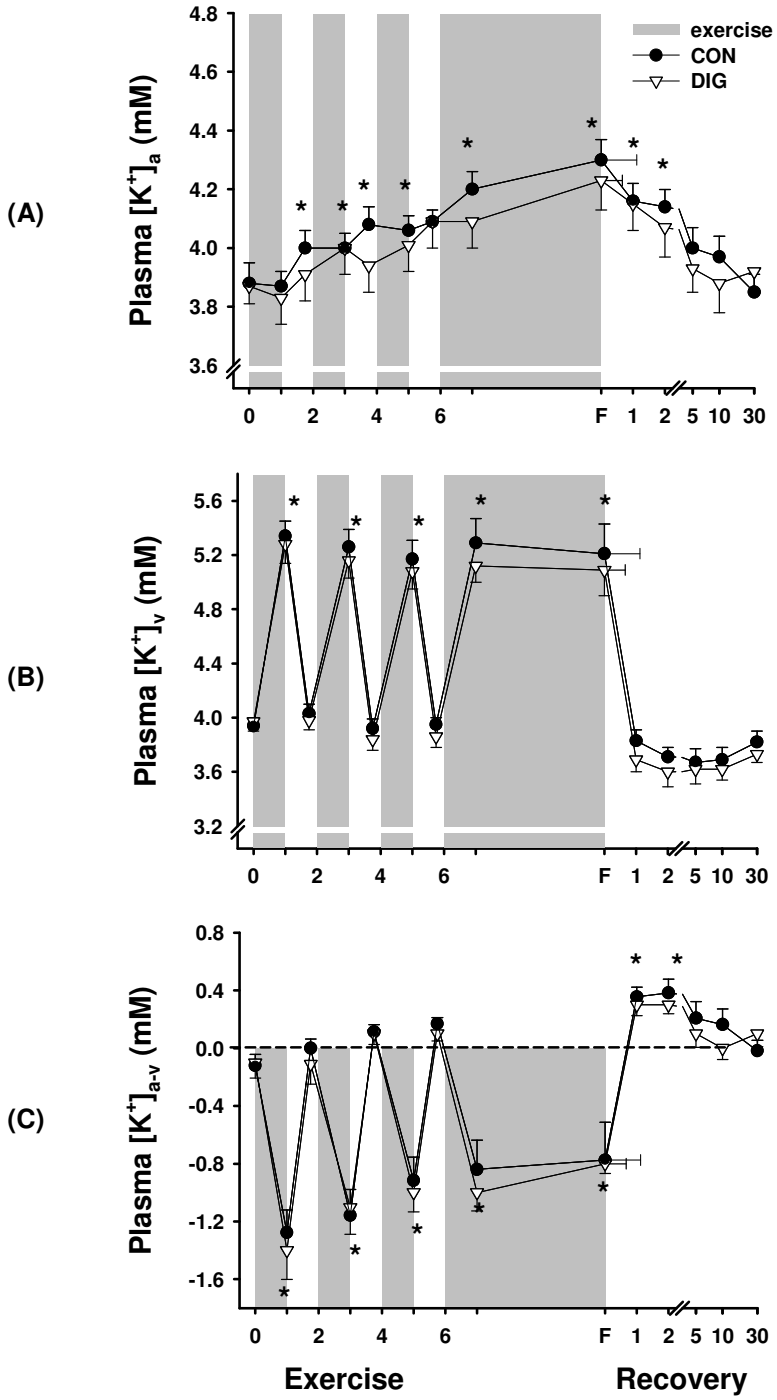

Figure 4.1. Effects of digoxin on plasma [K^+] at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous (a-v) plasma [K^+] differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.01$, time main effect). Data expressed as Mean ± SEM, $n = 10$ for CON $[K^+]_a$, $n = 9$ for DIG; $n = 8$ for $[K^+]_v$; $n = 6$ for CON $[K^+]_{a-v}$, $n = 5$ for DIG. Arteriovenous [K^+] differences are corrected for the a-v decline in plasma volume.

Table 4.5: Net ion fluxes into or out of plasma across the forearm musculature measured at rest, immediately after each exercise bout (EB) and subsequent recovery periods, at fatigue, and during recovery, under CON and DIG conditions. Ion flux calculated by (FBF x $[ion]_{a-v}$). Flux into plasma indicated by negative value and out of plasma by positive value. All units are µmol min^{-1}, except for H^+ which is pmol min^{-1}.

	Exercise								Recovery (min)				
	Rest	**EB1**	**Pre EB2**	**EB2**	**Pre EB3**	**EB3**	**Pre EB4**	**F**	**+1**	**+2**	**+5**	**+10**	**+30**
CON													
H^+	-88.2	-918.3*	-1106.4*	-1464.1*	-1840.2*	-2119.9*	-2079.1*	-3507.5*	-1717.7*	-917.3*	-516.9	-182.4	-70.6
SEM	21.0	108.4	388.7	379.9	936.7	654.7	1165.8	594.8	519.2	447.1	224.8	62.8	16.5
HCO_3^-	-64.9	-430.2	-390.8	-634.5	-320.4	-800.0	-700.2	-1220.8*	-278.3	-112.1	-135.9	-66.5	-59.6
SEM	13.3	152.0	157.4	256.0	50.7	325.5	402.4	312.7	152.5	93.8	89.1	25.5	36.2
K^+	-1.9	-149.0*	-1.1	-173.4*	5.9*	-164.4*	12.3*	-167.5*	27.1*	20.9*	1.1	1.1	-1.6
SEM	1.6	32.5	3.6	46.8	2.6	49.1	4.2	60.8	5.3	7.5	6.9	3.5	2.1
Na^+	-32.8	142.6	-175.2	39.7	-201.6	91.2	-215.8	704.7*	-213.7	-214.6	4.9	-4.0	16.3
SEM	20.3	326.8	125.4	156.0	130.3	158.4	140.1	225.0	131.6	261.9	61.0	19.8	24.9
Cl^-	4.0	413.3*	151.4	699.7*	85.9*	781.6*	271.9*	1257.4*	186.2*	239.4*	155.6	78.3	45.7
SEM	13.7	197.5	93.3	253.6	76.2	257.9	101.5	375.2	68.0	84.2	81.8	39.8	35.7
Lac^-	-3.6	-390.2*		-649.9*		-574.3*		-539.0*	-401.3*	-350.4	-148.0	-81.9	-131.0
SEM	2.4	114.9		274.5		232.0		171.7	175.4	223.6	59.1	37.6	100.6

	Exercise								Recovery (min)				
	Rest	**EB1**	**Pre EB2**	**EB2**	**Pre EB3**	**EB3**	**Pre EB4**	**F**	**+1**	**+2**	**+5**	**+10**	**+30**
DIG													
H^+	-69.5	-1331.8*	-1321.0*	-1839.5*	-1788.1*	-1786.3*	-1548.5*	-2752.8*	-1149.4*	-831.0*	-460.1	-160.9	-78.9
SEM	5.6	390.6	441.8	462.3	513.2	397.2	724.6	397.0	337.0	176.9	159.3	52.9	32.8
HCO_3^-	-50.6	-474.1	-325.7	-533.9	-485.3	-680.9	-509.8	-1073.0*	-239.5	-109.8	-100.1	-71.4	-48.4
SEM	12.1	133.3	148.0	154.5	198.3	123.6	272.1	186.4	32.2	35.0	45.3	39.6	26.5
K^+	-1.2	-171.9*	-4.1	-152.3*	17.4*	-146.3*	8.3*	-168.3*	24.4*	14.1*	1.2	-2.9	0.8
SEM	1.4	37.7	5.8	37.9	7.5	26.6	3.0	27.1	7.3	4.1	3.6	3.7	1.2
Na^+	-12.2	248.9	-248.2	-75.4	-152.9	-95.3	-279.0	203.3*	-227.8	-223.4	-136.8	-75.2	-12.5
SEM	21.4	174.1	110.8	118.4	82.6	121.9	102.6	191.3	91.5	77.1	42.2	23.7	20.0
Cl^-	15.6	740.9*	97.9	616.1*	322.4*	709.2*	157.8*	889.8*	141.9*	22.4*	23.4	13.6	48.0
SEM	13.3	150.3	63.9	113.2	89.7	132.7	126.0	214.6	96.3	41.5	20.2	26.7	18.4
Lac^-	-3.7	-375.5*		-423.5*		-510.7*		-772.3*	-148.3*	-137.7	-126.2	-25.1	-6.5
SEM	5.6	102.1		144.5		228.7		259.1	130.4	89.8	52.1	13.9	5.2

Mean ± SEM, *n= 6* for CON H^+, K^+, Na^+, Cl^- flux; *n = 6* for DIG H^+ flux; *n = 5* for DIG K^+, Na^+, Cl^- flux; *n = 5* for CON Lac^- flux, *n = 4* for DIG; *n = 4* for HCO_3^- flux. * Different to rest (P<0.001) except Na^+ flux, (P<0.05). A negative value denotes net ion influx into plasma across forearm musculature, and positive values denote net efflux from plasma across musculature. Fluxes calculated from (a-v [ion] difference) x Forearm plasma Flow). Fluxes for K^+, Na^+, Cl^- and Lac^- have been corrected for the arterio-venous ΔPV, whereas for H^+ and HCO_3^- no corrections were made.

4.3.5.2 Plasma [Na^+]

Exercise. Plasma $[Na^+]_a$ was unchanged from rest throughout exercise and recovery (Figure 4.2A). Plasma $[Na^+]_v$ increased during exercise and decreased to below rest during recovery, except for +1 min ($P<0.001$, Figure 4.2B). Plasma $[Na^+]_{a-v}$ changes during exercise and recovery were small, and did not differ from rest, but was positive at fatigue (Figure 4.2C). Muscle Na^+ flux was variable but was 16-fold greater at fatigue than at rest ($P<0.05$, Table 4.5). For positive Na^+ efflux values, Na^+ is exiting plasma across the contracting forearm muscle.

Digoxin. There was no treatment effect of DIG on $[Na^+]_a$, $[Na^+]_v$, $[Na^+]_{a-v}$, (figure 4.2) except for Na^+ efflux ($P<0.05$, Table 4.5) .

4.3.5.3 Plasma [Cl^-]

Exercise. Plasma $[Cl^-]_a$ increased above rest at EB1 ($P<0.01$, Figure 4.3A). Plasma $[Cl^-]_v$ declined at pre EB4 and at fatigue and in recovery ($P<0.01$, Figure 4.3B). Plasma $[Cl^-]_{a-v}$ was positive throughout exercise and recovery, reflecting net Cl^- movement out of plasma traversing the forearm ($P<0.01$; Figure 4.3C). Efflux of Cl^- from plasma increased substantially from rest to fatigue ($P<0.001$, Table 4.5).

Digoxin. Plasma $[Cl^-]_a$, $[Cl^-]_v$, $[Cl^-]_{a-v}$ and Cl^- flux were not affected significantly by DIG (Figure 4.3, Table 4.5).

4.3.5.4 Plasma [Lac^-]

Exercise. Plasma $[Lac^-]_a$ increased above rest during exercise and recovery ($P<0.001$, Figure 4.4A). Plasma $[Lac^-]_v$ increased during EB1 and each subsequent bout of exercise to ~5 mM and increased further during recovery ($P<0.001$, Figure 4.4B). Plasma $[Lac^-]_{a-v}$ decreased from rest throughout exercise and recovery until +30 min recovery ($P<0.001$, Figure 4.4B). Lac^- flux into plasma increased ~157-fold from rest to fatigue, and decreased during recovery to remain elevated by ~29-fold at 30 min recovery ($P<0.01$, Table 4.5).

Digoxin. Plasma $[Lac^-]_a$ did not differ between trials (Figure 4.4A). Plasma $[Lac^-]_v$ was lower during the DIG trial (Figure 4.4B, $P<0.01$) and $[Lac^-]_{a-v}$ was greater in DIG during exercise bouts, but lower during recovery in DIG (Figure 4.4C, $P<0.01$). Lactate flux from muscle to plasma was not affected by DIG (Table 4.5).

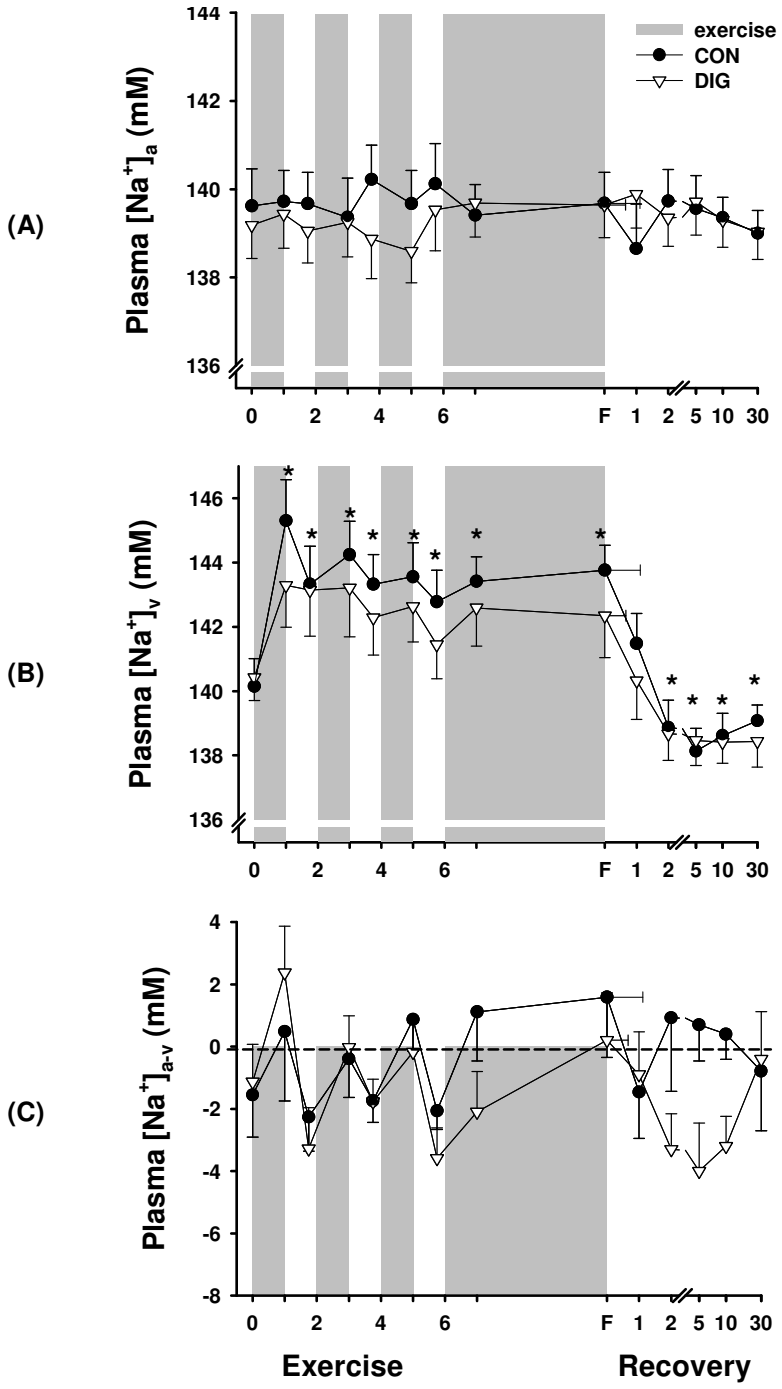

Figure 4.2. Effects of digoxin on plasma [Na^+] at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous (a-v) plasma [Na^+] differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.01$, time main effect). Data expressed as Mean ± SEM, $n = 10$ for CON $[Na^+]_a$, $n = 9$ for DIG; $n = 9$ for $[Na^+]_v$; $n = 6$ for CON $[Na^+]_{a\text{-}v}$, $n = 5$ for DIG. Arteriovenous [Na^+] differences are corrected for the a-v decline in plasma volume.

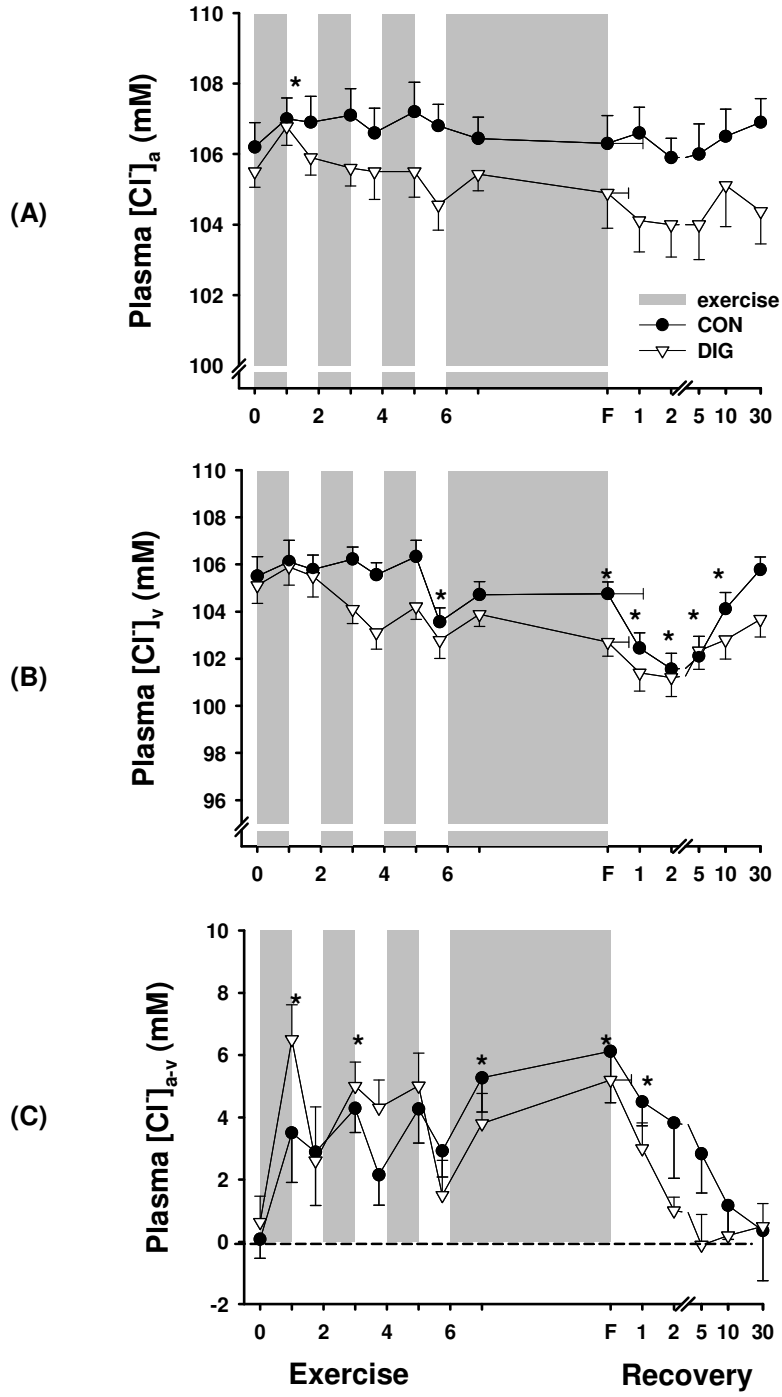

Figure 4.3. Effects of digoxin on plasma [Cl^-] at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous (a-v) plasma [Cl^-] differences, under CON (●) and DIG (▽) conditions. *Different from rest ($P<0.01$, time main effect). Data expressed as Mean ± SEM, n = 10 for CON $[Cl^-]_a$, $n = 9$ for DIG; $n = 9$ for $[Cl^-]_v$; $n = 6$ for CON $[Cl^-]_{a\text{-}v}$, $n = 5$ for DIG. Arteriovenous [Cl^-] differences are corrected for the a-v decline in plasma volume.

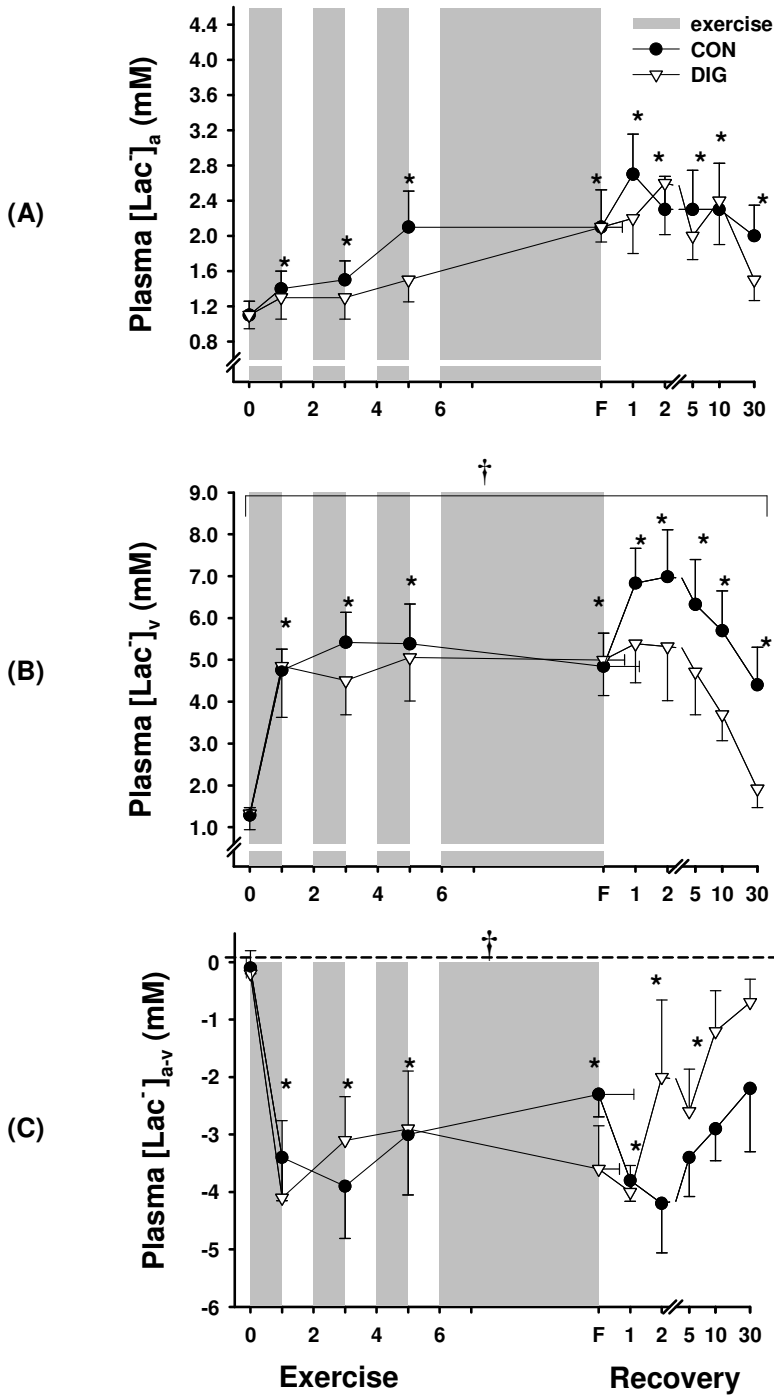

Figure 4.4 Effects of digoxin on plasma [Lac$^-$] at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous (a-v) plasma [Lac$^-$] differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.001$, time main effect; $P<0.05$ for $[Lac^-]_{av}$). † DIG < CON for $[Lac^-]_v$ and $[Lac^-]_{a-v}$ ($P<0.01$, treatment main effect).

Data expressed as Mean ± SEM, $n = 9$ for CON $[Lac^-]_a$, $n = 8$ for DIG; $n = 8$ for $[Lac^-]_v$; $n = 5$ for CON $[Lac^-]_{a-v}$, $n = 4$ for DIG. Arteriovenous [Lac$^-$] differences are corrected for the a-v decline in plasma volume.

4.3.5.5 Strong ion difference ([SID])

Exercise. Plasma $[SID]_a$ did not change during exercise or recovery, apart from a small decline in EB1 ($P<0.05$, Figure 4.5A). Plasma $[SID]_v$ did not change during exercise, but declined during recovery ($P<0.001$; Figure 4.5B). Plasma $[SID]_{a-v}$ was negative throughout exercise and 1 min recovery, and became positive during late stages of recovery ($P<0.01$; Figure 4.5C).

Digoxin. Plasma $[SID]_a$ was not affected by DIG, whereas $[SID]_v$ tended to be greater throughout exercise and in recovery in DIG ($P=0.072$, $d=0.44$, Figure 4.5B). $[SID]_{a-v}$ was not affected by DIG (Figure 4.5C) .

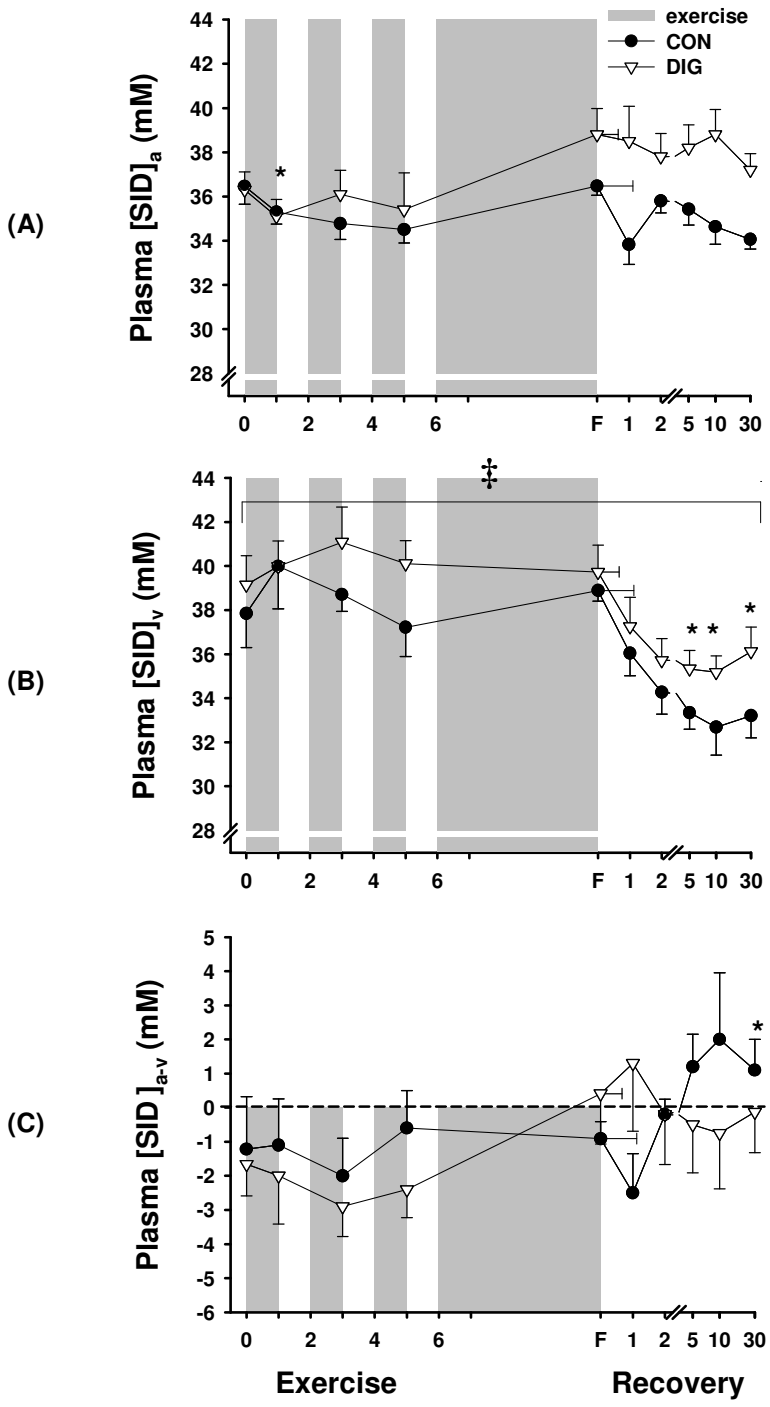

Figure 4.5. Effects of digoxin on plasma [SID] at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous (a-v) plasma [SID] differences, under CON (●) and DIG (▽) conditions. *Different from rest (P<0.05, main effect for time). ‡ DIG > CON for $[SID]_v$ (P = 0.07; *d* = 0.45, treatment main effect). Data expressed as Mean ± SEM, *n* = 9 for CON $[SID]_a$, *n = 8* for DIG; *n = 7* for $[SID]_v$; *n = 5* for CON $[SID]_{a-v}$, *n = 4* for DIG.

4.3.6 Metabolism

4.3.6.1 Blood CO_2 content (C_{CO2}) and forearm muscle $\dot{V}CO_2$ ($\dot{V}_mCO_2$)

Exercise. C_{aCO2} did not change significantly from rest during exercise or recovery (Figure 4.6A). C_{vCO2} increased above rest during EB1, pre-EB2 and EB2 ($P<0.001$, Figure 4.6B) and C_{vCO2} decreased below rest during recovery except for +1 ($P<0.01$, Figure 4.6B). $C_{a\text{-}vCO2}$ declined below rest during exercise and subsequent 1min recovery bouts indicating net muscle CO_2 output, but then was increased from fatigue throughout recovery ($P<0.001$, Figure 6C). Forearm muscle CO_2 output ($\dot{V}_mCO_2$) increased 24-fold from rest to fatigue ($P<0.001$, Table 4.6), before declining to near pre-exercise resting values by 5 min into recovery.

Digoxin. C_{aCO2} had a tendency to be systematically lower in DIG from the final bout of exercise to 2 min recovery ($P=0.059$, $d=0.48$) whereas C_{vCO2}, $C_{a\text{-}vCO2}$ and $\dot{V}_mCO_2$ did not different between CON and DIG (Figure 4.6, Table 4.6).

4.3.6.2 Blood O_2 content (C_{O2}) and forearm muscle $\dot{V}O_2$ ($\dot{V}_mO_2$)

Exercise. C_{aO2} did not increase significantly above rest during exercise or in recovery (Figure 4.7A). C_{vO2} decreased from rest during exercise, and rose rapidly during recovery to exceed rest levels from 5 to 30 min recovery ($P<0.001$, Figure 4.7B). The $C_{a\text{-}vO2}$ was positive throughout, indicating net O_2 uptake; increased during exercise, decreased rapidly during recovery, and was lower than rest at 10 min recovery ($P<0.001$, Figure 4.7C). Forearm muscle O_2 uptake ($\dot{V}_mO_2$) increased 21-fold from rest to fatigue ($P<0.001$, Table 4.6), before decreasing towards pre-exercise values by 10 min recovery.

Digoxin. There was no effect of DIG on C_{aO2}, C_{vO2}, $C_{a\text{-}vO2}$, or $\dot{V}_mO_2$ (Figure 4.7, Table 4.6).

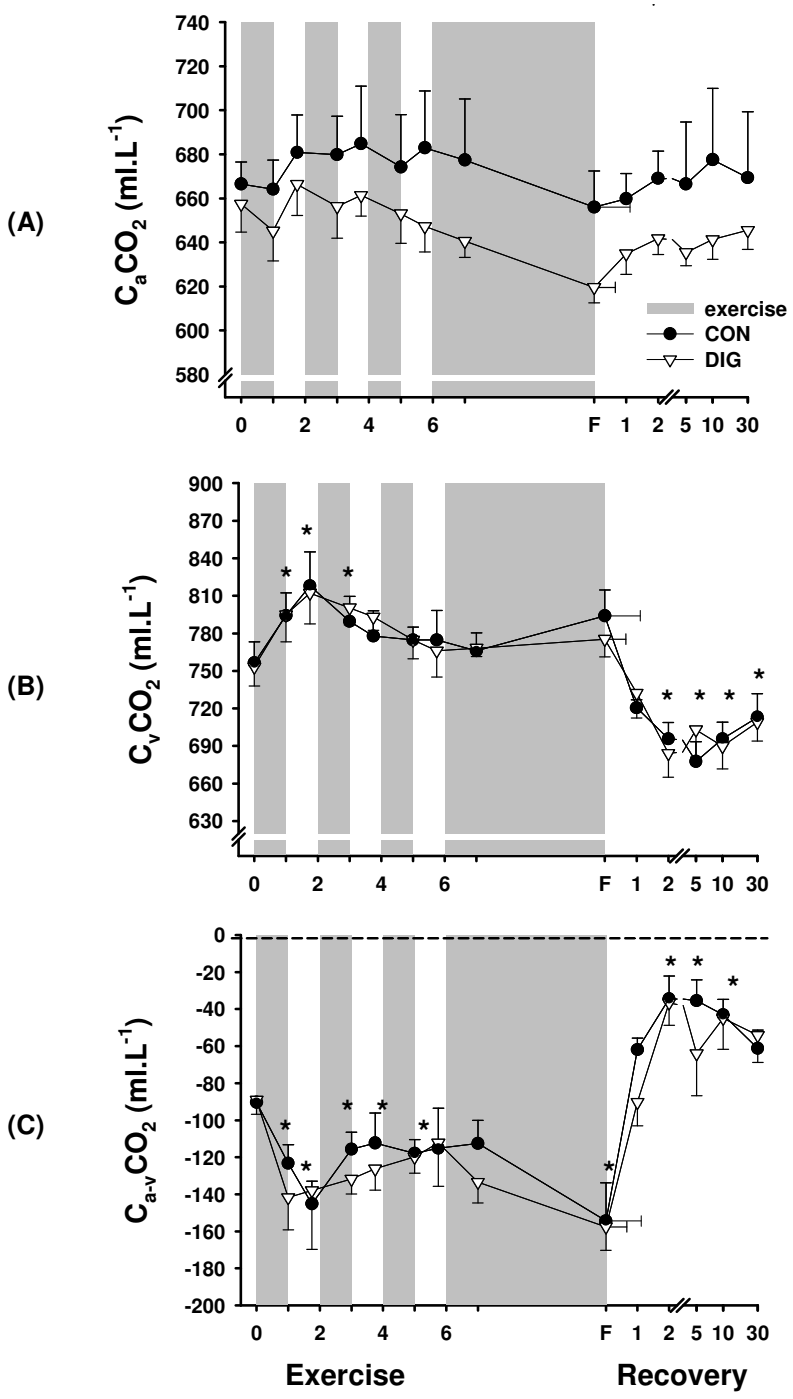

Figure 4.6. Effects of digoxin on blood CO_2 content at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous (a-v) CO_2 content differences, under CON (●) and DIG (▽) conditions.* Different from rest ($P<0.001$, time main effect), for C_vCO_2; $C_{a-v}CO_2$.
Data expressed as Mean ± SEM, $n = 7$ (C_aCO_2); $n = 5$ (C_vCO_2; $C_{a-v}CO_2$).

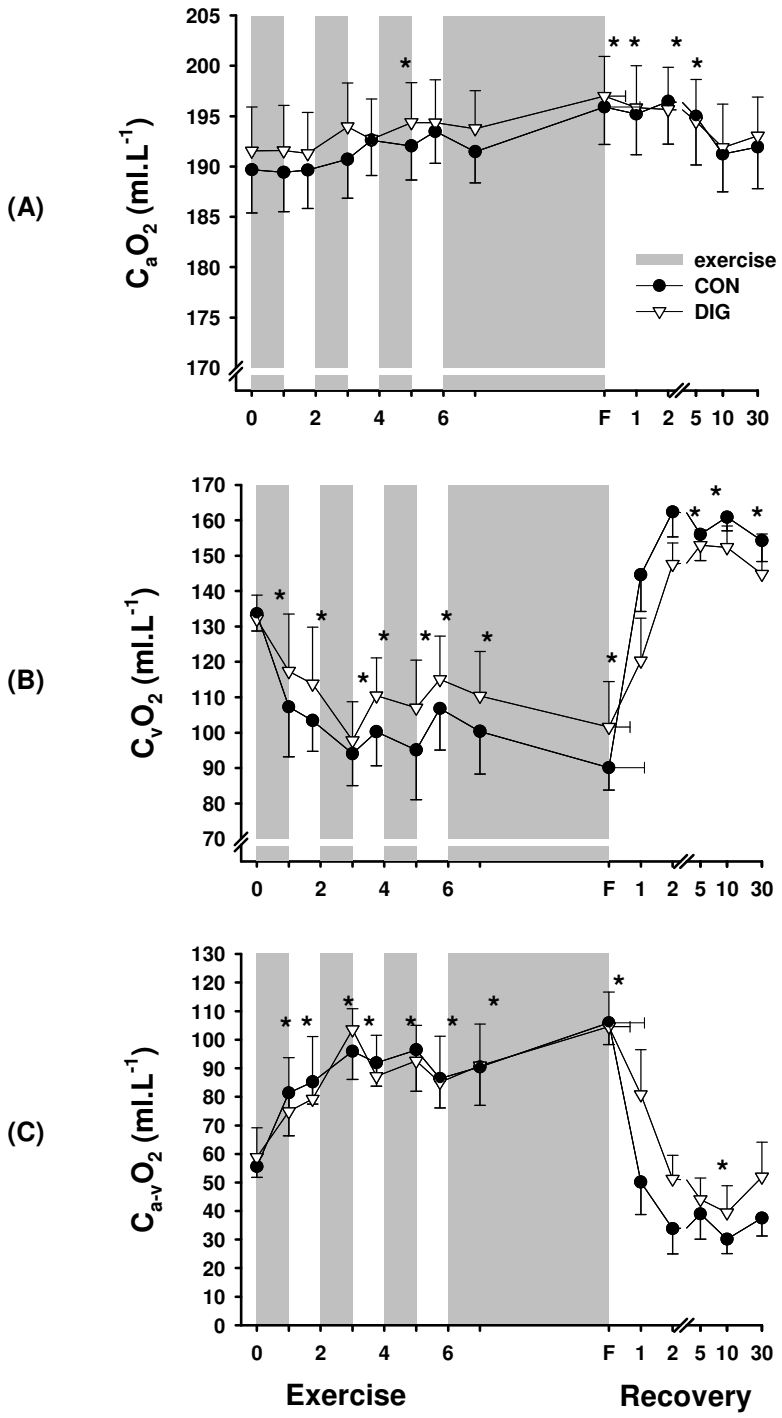

Figure 4.7. Effects of digoxin on blood O_2 content at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial (B) venous and (C) calculated arteriovenous (a-v) O_2 content differences, under CON (●) and DIG (▽) conditions. * Different from rest (P<0.001, time main effect).

Data expressed as Mean ± SEM, *n = 7* for C_aO_2; *n = 6* for C_vO_2; *n = 5* for $C_{a-v}O_2$.

Table 4.6: Forearm muscle lactate fluxes, $\dot{V}O_2$, $\dot{V}CO_2$ at rest, during intermittent finger flexion exercise to fatigue, and recovery, under CON and DIG conditions. Net Lac^- flux expressed in µmol min^{-1} and $\dot{V}O_2$, $\dot{V}CO_2$ in ml min^{-1}.

		Exercise								Recovery (min)				
	Rest	EB1	Pre EB2	EB2	Pre EB3	EB3	Pre EB4	EB4(1min)	F	+1	+2	+5	+10	+30
CON														
$Blac^-$flux	-2.4	-418.8*		-451.1*		-677.2*			-1002.6*	-575.8*	-212.6*	-141.4*	-35.8*	-21.9
SEM	3.7	94.3		147.03		246.9			475.3	236.7	88.3	52.5	19.8	12.2
V_mO_2	1.4	12.2*	10.6	20.0*	16.7*	24.9*	20.1*	28.8*	36.6*	7.1*	3.7*	3.3	1.4	1.6
SEM	0.2	3.0	3.4	6.1	8.1	7.7	10.2	5.6	7.7	1.7	1.1	1.1	0.3	0.3
V_mCO_2	2.4	22.8*	16.5	29.5*	15.4*	36.4*	26.9*	44.3*	57.5*	10.7*	4.5	4.5	2.2	2.3
SEM	0.5	6.4	5.4	12.1	4.3	13.3	14.4	14.7	14.6	4.5	3.0	3.1	0.9	1.2
DIG														
$Blac^-$flux	0.1	-315.9*		-430.3*		-623.3*			-938.7*	-442.1*	-232.4*	-158.3*	-55.4*	-4.7
SEM	2.7	143.7		150.3		218.1			403.7	139.1	64.7	59.2	36.2	35.0
V_mO_2	1.4	13.7*	6.7	20.4*	11.6*	24.4*	10.9*	26.2*	32.3*	7.6*	4.1*	2.0	1.5	1.5
SEM	0.4	5.4	2.3	4.6	2.3	5.5	3.3	3.2	5.1	1.1	0.9	0.6	0.3	0.6
V_mCO_2	2.2	21.1*	13.4	24.3*	14.7*	32.1*	20.0*	35.7*	47.9*	6.8*	2.8	3.3	2.0	2.0
SEM	0.3	6.5	4.8	7.4	2.3	7.0	10.0	7.5	8.4	1.9	1.1	2.3	0.7	1.0

Mean ± SEM, *n = 6* for DIG V_mO_2 and V_mCO_2, *n = 5* for CON; *n = 4* for $Blac^-$ flux. * Different from rest (P<0.001); P<0.01 for $Blac^-$ flux. A negative value denotes net efflux from contracting musculature, and positive values denote net influx. Muscle lactate efflux calculated from $[BLac^-]_{a-v}$ x Forearm Blood Flow), with $[BLac^-]_{a-v}$ corrected for arterio-venous ΔBV.

4.3.6.3 Blood [Lac^-]

Exercise. Whole blood $[Lac^-]_a$ and $[Lac^-]_v$ increased above rest during exercise and throughout recovery ($P<0.001$, Figure 4.8A, 4.8B). Blood $[Lac^-]_{a-v}$ decreased during exercise and returned towards rest level in late recovery, but remained negative throughout, reflecting a continued net release of lactate from muscle into whole blood across the forearm musculature ($P<0.001$, Figure 4.8C). Muscle lactate efflux increased from rest to fatigue by ~400-fold in CON ($P<0.001$, Table 4.6).

Digoxin. Blood $[Lac^-]_a$, $[Lac^-]_v$, $[Lac^-]_{a-v}$ and muscle lactate efflux were not significantly different between CON and DIG (Figure 4.8, Table 4.6).

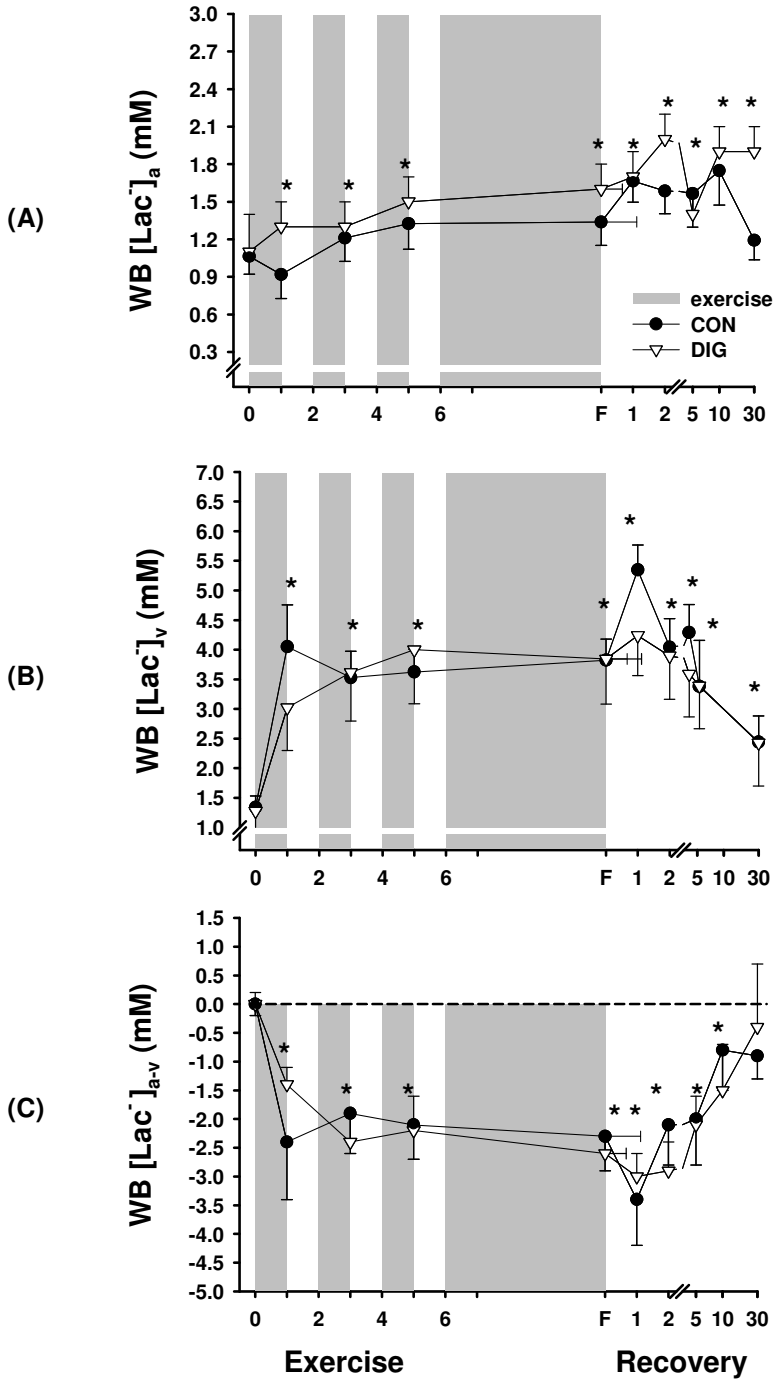

Figure 4.8. Effects of digoxin on blood [Lac$^-$] at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous (a-v) blood [Lac$^-$] differences, under CON (●) and DIG (▽) conditions. * Different from rest (P<0.001, time main effect); P<0.01 for $[BLac^-]_{a-v}$. Data expressed as Mean ± SEM, *n* = 9 for CON $[BLac^-]_a$, *n = 8* for DIG; *n = 7* for $[BLac^-]_v$; *n = 5* for $[BLac^-]_{a-v}$. Arteriovenous WB [Lac$^-$] differences are corrected for the a-v decline in blood volume.

4.3.7 Acid-base balance

4.3.7.1 Plasma [H^+]

Exercise. $[H^+]_a$ fell slightly at fatigue ($P<0.01$, Figure 4.9A), before returning to the pre-exercise values after 5 min recovery. $[H^+]_v$ increased during the EB1 and reached ~15 nM above rest during Pre EB2 and oscillated thereafter during the remaining bouts of exercise ($P<0.001$, Figure 4.9B). $[H^+]$ decreased throughout recovery ($P<0.001$), until reaching rest level by 10 min (Figure 4.9B). Plasma $[H^+]_{a-v}$ was negative throughout exercise and recovery, indicating a net increase in $[H^+]$ in plasma traversing muscle ($P<0.001$, Figure 4.9C). H^+ influx into plasma increased 40-fold from rest to fatigue, and then declined progressively throughout recovery ($P<0.001$, Table 4.5).

Digoxin. No systematic digoxin effects were found for $[H^+]_a$, $[H^+]_v$, $[H^+]_{a-v}$ and H^+ efflux (Figure 4.9, table 4.5), except at fatigue, where $[H^+]_v$ was lower and $[H^+]_{a-v}$ less negative during DIG ($P<0.05$).

4.3.7.2 Plasma [HCO_3^-]

Exercise. Plasma $[HCO_3^-]_a$ was unchanged during exercise and recovery (Figure 4.10A). Conversely, $[HCO_3^-]_v$ increased by ~3 mM during the first 2 min, pre EB3 and at fatigue, declining to below rest at 10 min recovery ($P<0.001$, Figure 4.10B). Plasma $[HCO_3^-]_{a-v}$ remained negative throughout exercise and recovery, indicating a net gain in plasma HCO_3^- across the forearm muscle ($P<0.001$, Figure 4.10C). Muscle HCO_3^- "apparent efflux" increased 15-fold (CON) from rest to fatigue, decreasing rapidly by 1 min recovery, continued to decline for the remainder of recovery, returning to resting value 30 min post exercise. ($P<0.001$, Table 4.5).

Digoxin. $[HCO_3^-]_a$ was lower than CON (Figure 4.10A). No DIG effects were found for $[HCO_3^-]_v$, $[HCO_3^-]_{a-v}$ and HCO_3^- efflux (Figure 4.10, Table 4.5).

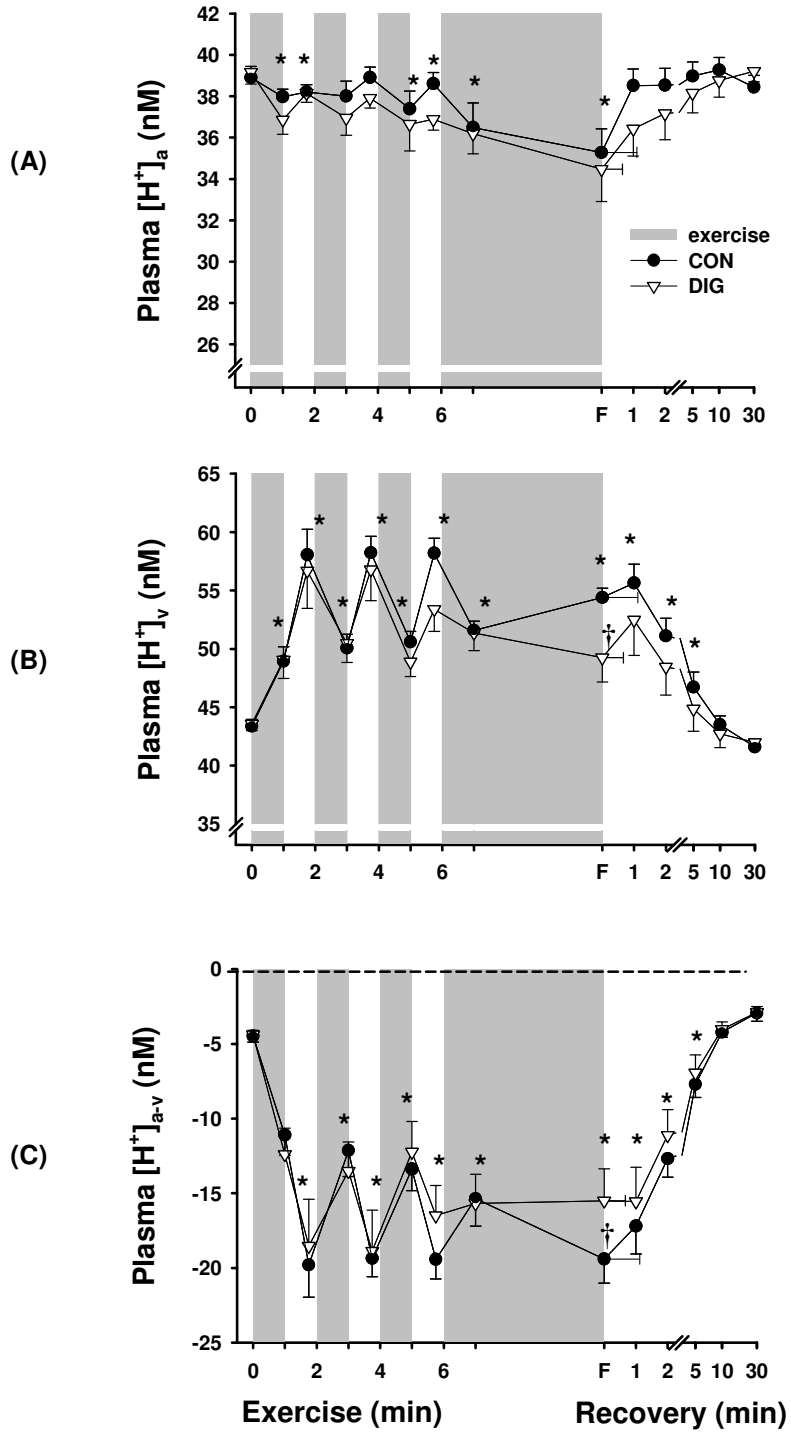

Figure 4.9. Effects of digoxin on plasma [H^+] at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous (a-v) plasma [H^+] differences, under CON (●) and DIG (▽) conditions. *Different from rest ($P<0.001$, time main effect). † DIG < CON at fatigue for $[H^+]_v$ and $[H^+]_{a-v}$ ($P<0.05$, treatment main effect). Data expressed as Mean ± SEM, *n* = 10 for CON $[H^+]_a$, *n = 9* for DIG; *n = 9* for $[H^+]_v$; *n = 9* for CON $[H^+]_{a-v}$, *n = 8* for DIG.

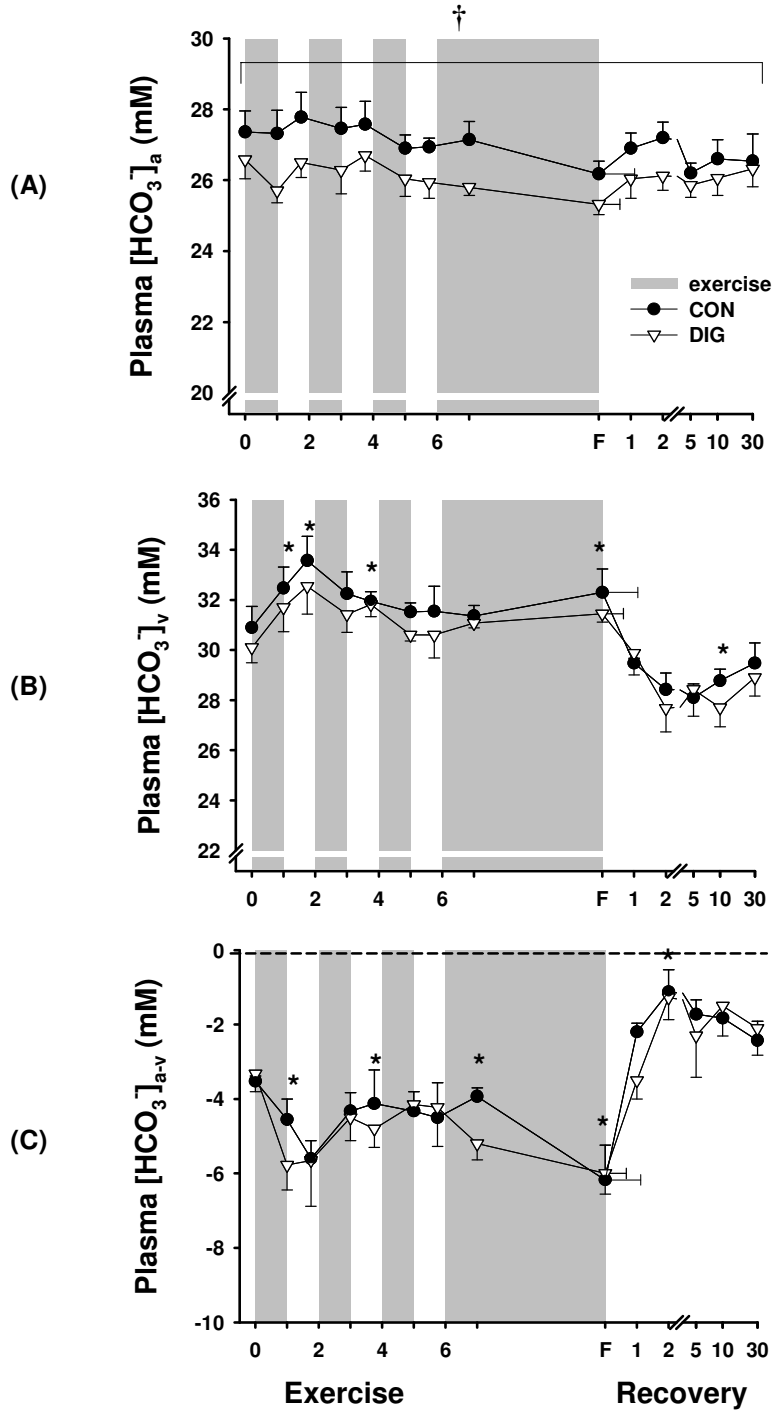

Figure 4.10. Effects of digoxin on plasma [HCO_3^-] at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous (a-v) plasma [HCO_3^-] differences, under CON (●) and DIG (▽) conditions. *Different from rest ($P<0.05$, time main effect). † DIG < CON for $[HCO_3^-]_a$ ($P<0.01$, treatment main effect).

Data expressed as Mean ± SEM, $n = 5$ for $[HCO_3^-]_a$, $n = 4$ for $[HCO_3^-]_v$ and $[HCO_3^-]_{a-v}$.

4.3.7.3 *Plasma pCO_2*

Exercise. Arterial plasma PCO_2 (P_aCO_2) decreased below rest at fatigue ($P<0.001$), then increased again during recovery (Figure 4.11A). Venous plasma PCO_2 (P_vCO_2) was increased throughout the exercise period, and decreased to rest levels during the recovery period ($P<0.001$, Figure 4.11B).

Digoxin. P_aCO_2 was systematically higher at rest, and lower throughout exercise and recovery during DIG ($P<0.001$, Figure 4.11A). P_vCO_2 was lower at fatigue during DIG ($P<0.01$, 4.11B).

4.3.7.4 *Plasma pO_2*

Exercise. Arterial plasma PO_2 (P_aO_2) was increased above rest during EB1, EB2 and EB4 ($P<0.001$), before decreasing to rest levels in recovery ($P<0.01$; Figure 4.12A). P_vO_2 decreased from rest during each exercise bout, increased during pre-exercise bouts, decreased at fatigue, and increased in recovery above rest ($P<0.001$, Figure 4.12B).

Digoxin. No effect of DIG was found on either arterial or venous PO_2 (Figure 4.12).

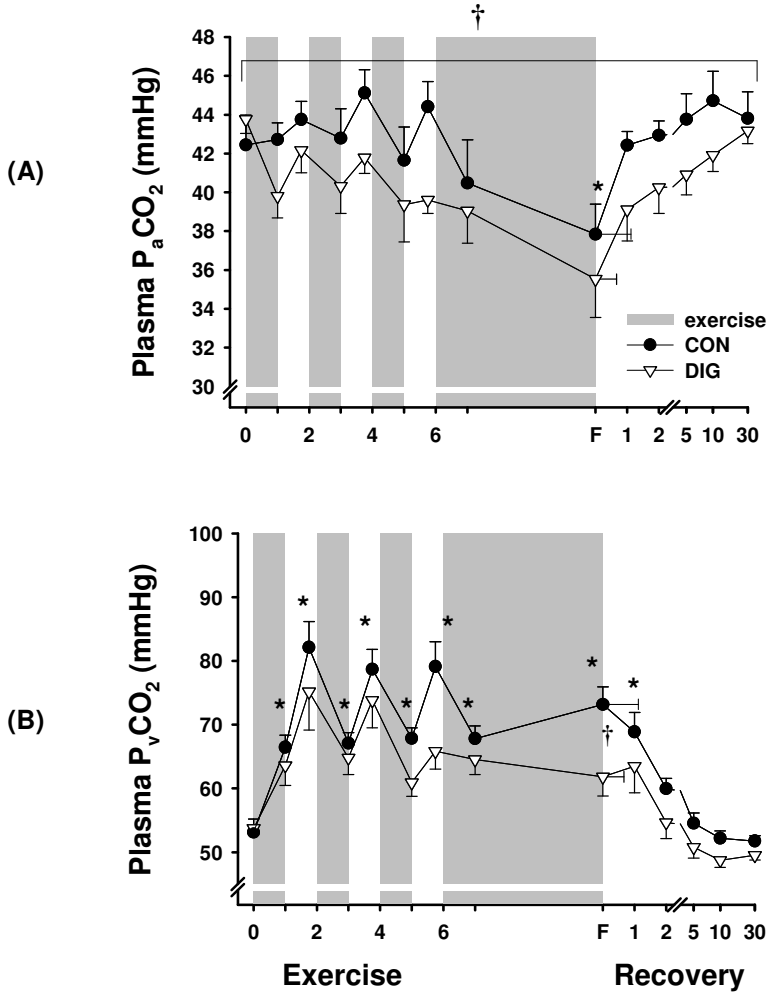

Figure 4.11. Effects of digoxin on plasma PCO_2 at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial and (B) venous PCO_2 under CON (●) and DIG (▽) conditions.

*Different from rest (P<0.001, main effect for time). † DIG < CON, treatment main effect for P_aCO_2 (P<0.001). † DIG < CON, treatment main effect for P_vCO_2 at fatigue (P<0.05).

Data expressed as Mean ± SEM, *n* = 9 (P_aCO_2); *n = 10* for DIG P_vCO_2; *n = 8* for CON P_vCO_2.

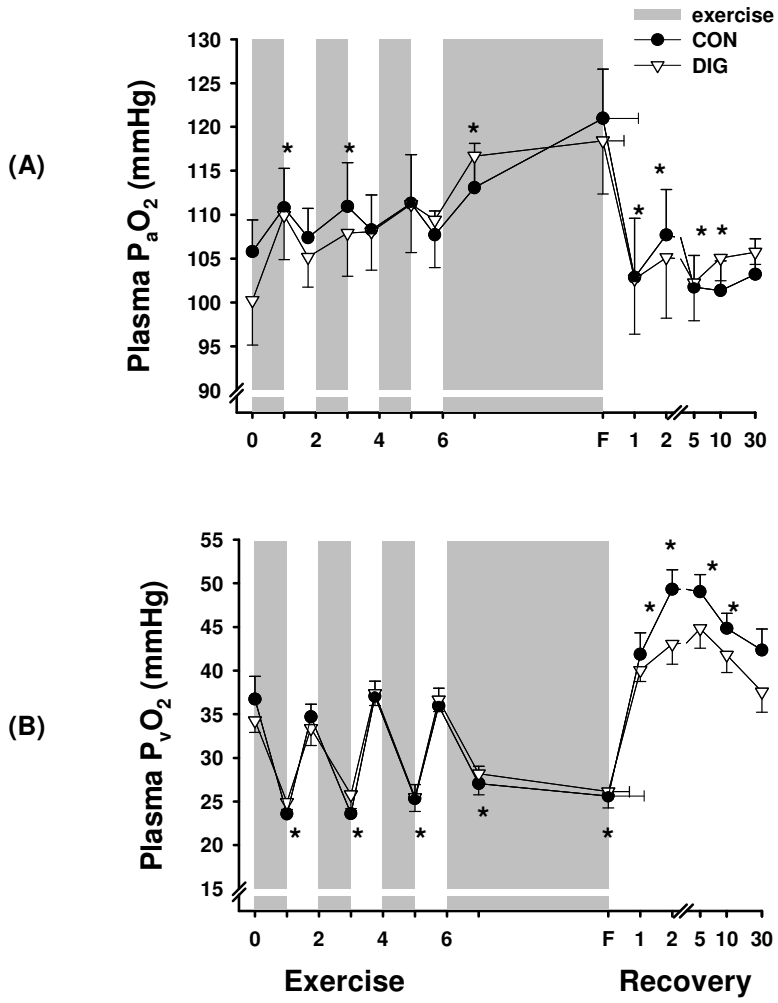

Figure 4.12. Effects of digoxin on plasma PO_2 at rest, during intermittent finger flexion exercise (shaded bars) to fatigue (F), and recovery. (A) arterial and (B) venous plasma PO_2 under CON (●) and DIG (▽) conditions.

* Different from rest (P<0.001, main effect for time). Data expressed as Mean ± SEM, *n* = 10 for CON P_aO_2, *n = 9* for DIG; *n = 9 for* P_vO_2.

4.4 DISCUSSION

This study comprehensively investigated the effects of 14 days of digoxin therapy on ionic and acid-base disturbances, metabolism, forearm blood flow and muscle fatigue during intermittent supramaximal bouts of forearm finger flexor exercise in healthy humans. The treatment achieved the anticipated result with serum digoxin concentration of 0.8 nM (~0.62 $ng.ml^{-1}$) in the DIG trial, which is within the optimal therapeutic range of 0.65-1.15 nM (Ahmed et al 2006). Supramaximal intermittent exercise intervals were utilised here to maximise K^+, ionic and acid-base disturbances and metabolic demands during contractions; and to investigate possible impacts of digoxin on K^+ re-uptake across the active forearm muscles during rest intervals. The main findings of the study were that digoxin did not impair K^+ homeostasis or exacerbate fatigue during exercise. However, digoxin therapy induced numerous novel changes in metabolism during exercise. Ionic, metabolic and acid-base responses to intermittent supramaximal finger flexion exercise were more pronounced than during submaximal finger flexion exercise (Chapter 3).

4.4.1 Clinically relevant serum digoxin concentration

The mean serum digoxin concentration (SDC) was 0.8 nM, or ~0.62 $ng.ml^{-1}$ following 14 days of digoxin administration at 0.25$mg.day^{-1}$. Similar SDC of 0.9 nM was reported following the same dose in healthy males (Schenck-Gustafsson et al 1987). Higher SDC have been reported (~1 nM) following 14 days of digoxin at 0.5 $mg.day^{-1}$ in healthy humans (Sundqvist et al 1983). The resultant SDC observed in the current study satisfies the preferred therapeutic range of ~0.65-1.15 nM or ~0.5-0.9 $ng.ml^{-1}$ which has previously demonstrated reduced hospitalisation and mortality rates, and alleviation of numerous clinical symptoms in heart failure patients (Ahmed et al 2006; Wang & Song 2005). Whilst higher SDC can be attained however, SDC greater than 1.2 nM in heart failure patients has been associated with increased mortality (Rathore et al 2003). Therefore the dosage administered within the present study, and subsequent SDC, is clinically relevant.

4.4.2 Chronic digoxin therapy does not impair K^+ homeostasis during exercise

Muscle contractions increase muscle interstitial [K^+] and this can potentially impair force development, but this effect is countered primarily by NKA activation (Sejersted & Sjøgaard, 2000). Digoxin binds to and partially inhibits skeletal muscle NKA. Furthermore this binding in skeletal muscle increases with exercise (Joretag & Jogestrand, 1983), consistent with increased ouabain binding found during muscle stimulation in rat muscle (McKenna et al, 2003). On the basis of expected DIG binding in resting muscle, an increase in digoxin binding to skeletal muscle NKA during

exercise was also expected. Subsequently an exacerbation of plasma [K^+] elevation during exercise was hypothesised with DIG in healthy humans.

The elevated SDC indicates that some inhibition of NKA in skeletal muscle should have occurred. Contrary to our hypothesis, and surprisingly, 14 days of chronic digoxin therapy did not increase any of the $[K^+]_a$, $[K^+]_v$, $[K^+]_{a-v}$ or the calculated muscle K^+ efflux, whether at rest, during exercise or in recovery. During muscle contractions, the rise in plasma [K^+] is dependent on the rates of K^+ entry and removal from plasma (Sejersted and Sjøgaard, 2000), with entry via contracting muscle K^+ release. Numerous studies have found K^+ uptake into red blood cells during high intensity cycling exercise (Lindinger et al, 1992; McKelvie et al, 1991, 1992), therefore it is possible that some K^+ entered plasma during contractions via K^+ release from red blood cells. However these findings are in contrast to others, whereby red blood cells did not take up K^+ during intense forearm exercise (Maassen et al, 1998) or during submaximal knee extension exercise (Juel et al, 1999). Therefore increases in red blood cell [K^+] during exercise might be due to a decrease in red cell volume (Juel et al, 1999; Maassen et al, 1998). Thus the contribution of red cell K^+ release to the increase in plasma [K^+] during intense contractions in the present study is likely to be negligible, though inconclusive. Clearance of K^+ accumulation in plasma is subsequently facilitated via NKA in contracting (Verberg et al, 1999; Sahlin and Broberg, 1989; Chapter 3) and non-contracting muscle (Kowalchuk et al, 1988; Lindinger et al, 1990; Chapter 5). K^+ uptake by contracting muscle was not impaired by digoxin during intermittent exercise or recovery in the present study. Although $[K^+]_{a-v}$ across inactive muscle was not assessed, there was no DIG effect on $[K^+]_{a-v}$ found across inactive muscle in the same participants during cycling exercise (Chapter 5), therefore a DIG effect on K^+ uptake across inactive muscle would be unlikely during forearm contractions. There was only a very small rise in arterial [K^+] during small muscle mass contractions, which also highlights that the predominantly large volume of inactive muscle has a substantial capacity for K^+ clearance. In fact there was remarkable consistency of K^+ data between the DIG and CON trials. The lack of change in $[K^+]_{a-v}$ or K^+ fluxes were not due to differences in forearm blood flow, which was not affected by digoxin. This is consistent with Glover et al (1967), who found no effects on forearm or hand blood flow and venous tone following intravenous ouabain infusion (0.05 $mg.min^{-1}$, 10 min) in healthy males. Furthermore, altered fluid shifts cannot explain the unchanged [K^+] with digoxin, as there were no digoxin effects on ΔPV or ΔBV during exercise.

The effects of digoxin-induced NKA inhibition and subsequent K^+ homeostasis in healthy humans undertaking whole body exercise is largely unknown, and was

investigated in detail in Chapter 5. During three submaximal bouts of incremental cycling exercise (10 min each at 33%, 67% $\dot{V}O_{2peak}$, and the final bout of 90% $\dot{V}O_{2peak}$ to fatigue), K^+ homeostasis was not impaired by digoxin, nor was there an effect on muscle fatigue, which is consistent with the present forearm exercise study. Digoxin occupancy of NKA was not analysed for the forearm muscle, therefore the fraction of digoxin binding specific to the contracting musculature is unknown. However, digoxin binding to vastus lateralis muscle NKA was measured in the same volunteers on the same days (appendix 7). These muscle analyses revealed no change in NKA content (measured by [^{3}H]ouabain binding site content) or in NKA activity (measured by 3-O-MFPase activity) at rest after digoxin. Importantly, they indicated 7% digoxin occupancy following Digibind® antibody removal of bound digoxin (appendix 7). It is highly likely that similar digoxin occupancy occurred in forearm muscle. Thus the most likely interpretation is that an upregulation of NKA occurred in skeletal muscle after 14 d DIG in healthy humans. The net result was that NKA content and maximal NKA activity was therefore unchanged, and this fits with the highly consistent [K^+] data between DIG and CON trials. The small exercising muscle mass in the present study does not provide a rationale to explain the lack of DIG effect on K^+ homeostasis. Whilst $[K^+]_a$ changes are small in absolute terms, marked changes in $[K^+]_v$ during exercise were observed, and the $[K^+]_{a-v}$ demonstrates a large net influx of K^+ into plasma during exercise as blood traversed the exercising forearm muscle. Blood flow was high across the forearm, consequently K^+ efflux was pronounced, but there was no DIG effect observed. During cycling exercise in the companion study (Chapter 5) where exercising muscle mass was considerably greater than the forearm, and $[K^+]_a$ was substantially higher, there was still no digoxin effect observed. The rationale for insufficient forearm muscle NKA activation to explain a lack of DIG effect is not valid, as there was a complete reversal of K^+ release into plasma to K^+ from plasma during the recovery transition between each intermittent exercise bout, therefore in-vivo NKA activity was high.

No studies have thoroughly investigated K^+ homeostasis during arm exercise in digitalized humans. Janssen et al (2009) recently reported that venous [K^+] during handgrip exercise was not different between digoxin and control in healthy individuals. However, the rise in $[K^+]_v$ was surprisingly small, suggesting either post-exercise blood sampling, with a consequent lower $[K^+]_v$, or an inappropriate exercise model. Furthermore the digoxin uptake by muscle was not quantified, nor was blood flow evaluated, thus making their results difficult to interpret.

It is possible that the elevated plasma [K^+] found during cycling exercise with DIG in cardiac patients (Norgaard et al, 1991; Schmidt et al, 1995) might be greater due to the

reduced skeletal muscle NKA content in these patients due to the concomitant effects of heart disease, inactivity, as well as the specific inhibitory digoxin effects on NKA. Whilst digoxin occupancy in skeletal muscle NKA was ~9% after 3 d treatment (Schmidt et al, 1995) and ~13% in muscle post-mortem (Schmidt et al, 1993), there was no evidence of compensatory upregulation of NKA content. The absence of upregulated NKA content has also been confirmed by Green et al (2001) in digitalised chronic heart failure patients.

Serum digoxin concentration was within the therapeutic range; therefore it appears likely that the unchanged K^+ at rest, during exercise and in recovery with DIG was associated with a compensatory up-regulation of NKA in healthy human skeletal muscle. This finding is consistent with K^+ being a tightly regulated physiological variable. However, the lack of change in $[K^+]$ with digoxin makes it not possible to conclude on the importance of K^+ regulation to muscle fatigue.

4.4.3 Digoxin does not impair forearm muscle performance

It was hypothesised that digoxin would increase $[K^+]$ and accelerate muscle fatigue during finger flexion exercise. However, very similar K^+ dynamics were seen after DIG, possibly due to limited adverse effects of digitalisation when NKA function is normal in healthy humans, probably reflecting compensatory NKA upregulation to digoxin (Appendix 7). Therefore it is not surprising that no performance effect was seen with DIG. Similarly, digoxin did not affect time to fatigue during incremental submaximal cycling exercise (Chapter 5) or during repeated isokinetic leg extension contractions (Gong et al, 2005) in the same participants in this study. These findings are consistent with Sundqvist et al (1983), whereby digoxin did not affect isokinetic muscle strength in healthy humans. In contrast to our exercise performance findings, Bruce et al (1968) found that treadmill running time was reduced following DIG in healthy individuals. Conflicting effects of DIG on exercise performance cannot be explained by dosage alone as both the Bruce et al (1968) and Russell & Reeves (1963) studies used short term high dose digoxin administration.Exercise capacity increased in heart failure patients medicated with digoxin, with an accompanying increase in $\dot{V}O_2$ (Sullivan et al, 1989). However, we did not find any digoxin affects on $\dot{V}_mO_2$ during finger flexion contractions in the present study, nor was there any change in $\dot{V}O_2$ during incremental sub-maximal cycling exercise (Chapter 5). Consistent with our findings, $\dot{V}O_2$ during exercise was also unaffected by digoxin in healthy humans (Sundqvist et al, 1983; Russell & Reeves 1963).

4.4.4 Lower plasma [Lac$^-$] from exercising muscle with digoxin is not due to reduced NKA activity

In skeletal muscle, NKA has a preference for ATP via glycolysis (Clausen 2003), therefore increased NKA activation is associated with increased lactate production (James et al, 1999; Bundgaard et al, 2002), and inhibition of NKA by ouabain is associated with reduced lactate production (James et al, 1999). It was hypothesized that digoxin inhibition of NKA activity would reduce NKA related glycolysis and consequently reduce lactate production in contracting skeletal muscle and lower plasma [Lac$^-$]. Plasma $[Lac^-]_v$ and $[Lac^-]_{a-v}$ were in fact lower in DIG, but this was probably not due to reduced NKA activity. It also seems unlikely to be due to increased DIG binding to skeletal muscle during exercise, as there were no DIG effects on [K^+] during exercise which would otherwise be expected.

Digoxin inhibits NKA in all tissues, and ~50% of total body digoxin is bound to skeletal muscle (Schmidt et al 1991). Digoxin binds to NKA in both type 1 and 2 muscle fibers. In healthy humans at rest, digoxin binding was ~33% greater in type 1 compared to type 2 muscle fibers; during moderate intensity cycling exercise digoxin binding increased by 28% in type 1 fibers whilst remaining unchanged in type 2 fibers (Joretag, 1986). The principle muscles involved during contractions in the present study include flexor digitorum profundus and superficialis, which generally contain a similar proportion of type 1 and 2 muscle fiber types (Johnson et al 1973). It would be expected that both type 1 and 2 muscle fibers are recruited during high intensity forearm contractions, particularly at fatigue, which is unlikely to be affected by DIG. Lactate production and peak workload are lower in CHF patients taking DIG compared to controls during exercise (Okita et al, 1998; Näveri et al, 1997). However, the specific effects of DIG on skeletal muscle NKA inhibition and consequent decreased lactate production per se is unknown in CHF patients, due to the concomitant effects of additional medications, muscle atrophy and muscle hypoperfusion. However, several studies have also demonstrated in the absence of disease that lactate production is reduced when NKA is inhibited. Firstly, Clausen (1965; 1966) illustrated that a relationship exists between glycolysis and NKA activity, when rat diaphragm lactate production was reduced by ouabain or incubation in K^+-free medium. In recent times, James et al (1999) confirmed the tight glycolysis/NKA relationship in resting rat skeletal muscle, whereby epinephrine and amylin stimulated NKA activity with subsequent increased lactate production; and ouabain inhibited NKA with subsequent inhibited glycolysis and reduced lactate production. This relationship is also highlighted in resting skeletal muscle in healthy human volunteers, when endotoxemia induced a decrease in plasma [K^+] with concomitant rise in plasma [Lac$^-$] (Bundgaard et al, 2002).

Whilst NKA activity was not analysed, it is assumed that the decrease in plasma [K^+] was mediated by increased NKA activity, based on an increase in NKA activity observed in endotoxic rats (O'Brien et al, 1996). The glycolysis/NKA relationship described by Bundgaard et al (2002) was not associated with hypoperfusion or hypoxia.

The effects of inhibited NKA activity on glycolysis have not been explored in healthy human skeletal muscle during exercise. Since exercise increases DIG binding to skeletal muscle (Joretag and Jogestrand, 1983), it is plausible that the glycolysis/NKA relationship observed in resting human skeletal muscle (Bundgaard et al, 2002) and in rat muscle (James et al, 1999) would be exacerbated during exercise. However, lower lactate efflux from working muscle observed in the present study was probably not due to a decrease in NKA activity (appendix 7) and is not consistent with K^+ homeostasis being unchanged during rest, exercise and recovery with DIG. There was also no DIG effect on $\dot{V}_mO_{2,}$ or perfusion to exercising muscle. Contrary to our findings, Janssen et al (2009) found no changes in $[Lac^-]_v$ with DIG in healthy humans performing hand grip exercise. However, the rise in $[Lac^-]_v$ was very small. Thus reduced plasma [Lac^-] in DIG from working muscle may be due to either or all of; decreased lactate production, decreased lactate release or increased lactate clearance.

4.4.5 Digoxin decreases acidosis during exercise

This is the first known study to consider acid-base balance during exercise following digoxin therapy. The Stewart physico-chemical approach was utilised, given the ionic and metabolic perturbations expected as a result of NKA inhibition. Plasma $[H^+]_a$ did not change with DIG, however both $[H^+]_v$ and $[H^+]_{a-v}$ were lower at fatigue in DIG. P_aCO_2 was systematically lower throughout DIG which contributed to a lower $[HCO_3^-]_a$. A decrease in P_aCO_2 can be due to an increase in ventilation, but this was not measured during forearm exercise. Substantial CO_2 is produced in the presence of increased glycolysis within contracting skeletal muscle (McCartney et al, 1986; Jones, 1980). Systematically lower arterial CO_2 content through exercise and recovery may also be caused by a decrease in glycolysis and accompanied lower lactate production as previously described. Plasma $[SID]_v$ was greater in DIG, which was primarily due to lower plasma [Lac^-] during DIG, since K^+, Na^+ and Cl^- were not different from CON. Contrary to our findings, arterial and venous pH during progressive intensity cycling exercise was unchanged in digitised heart failure patients compared to controls (Schmidt et al, 1995). However leg blood flow also increased with digoxin treatment, therefore the mechanisms for acid-base changes in these patients is difficult to determine.

The DIG induced decrease in $[H^+]_v$ and $[H^+]_{a-v}$ at fatigue were associated with a decreased P_vCO_2 and an increased [SID]. These acid-base changes were not associated with improved performance, as time to fatigue during the final bout of exercise was not different between DIG and CON. Although muscle $[H^+]$ was not measured, these findings are consistent with the understanding that muscle fatigue is associated with factors other than acidosis (Allen and Westerblad, 2008).

4.4.6 Physiological responses to supramaximal intermittent finger flexion exercise

In Chapter 3 it was demonstrated that submaximal finger flexion exercise provoked a dramatic increase in blood flow and substantial ionic fluxes and acid-base disturbances across contracting forearm muscles, even despite small contracting muscle mass exercise. This study investigated supramaximal intermittent finger flexion exercise to maximise ionic and acid-base disturbances and these findings are assessed here.

K^+ fluxes were found to be remarkably sensitive to very small absolute workloads (~5W) and tightly regulated, as previously also observed during submaximal forearm exercise (Chapter 3). There were small changes compared to rest in ionic and metabolic variables measured in arterial plasma, and as expected, larger changes in blood flow, venous plasma and arterio-venous differences across contracting muscle. Plasma P_aO_2 increased ~5 mmHg above rest during several exercise bouts, and the peak decline in arterial plasma volume was ~6%.

Changes in deep antecubital venous plasma acid–base, ionic and metabolic variables were considerably more pronounced than in arterial plasma. Peak increases above rest in venous plasma during exercise comprised; $[H^+]$ (~18 nM), $[HCO_3^-]$ (~3 mM), PCO_2 (~30 mmHg), CO_2 content (~60 $ml.min^{-1}$), [WB Lac^-] (~2.3 mM), $[K^+]$ (~1.5 mM), $[Na^+]$ (~5 mM), and $[Lac^-]$ (~4.3 mM). Significant declines below rest were observed during exercise for; plasma volume (~8%), PO_2 (~13 mmHg), and O_2 content (~38 $ml.min^{-1}$). As expected, venous plasma changes using supramaximal intensity exercise are also greater than reported during submaximal exercise recruiting the same musculature (Chapter 3). However, absolute power output and blood flow were both ~42% greater in the present study. Interestingly, the absolute changes were greater in $[H^+]_v$, P_vCO_2 and ΔPV_v, compared to the same variables examined in Sostaric et al (2006), by ~44%, ~43%, and ~37% respectively; which suggests that comparatively, these changes were almost entirely attributed to the increase in power output and associated increase in blood flow.

4.4.6.1 Plasma K^+

Plasma $[K^+]_v$ increase during exercise in this study was ~33% greater than corresponding data in Chapter 3. Also, the undershoot of $[K^+]_v$ below that previously

established at rest, is consistent with sub maximal forearm exercise (Chapter 3) and other forms of exercise (McKenna et al 1997a; Nielsen et al 2003; Juel et al 1990 Vøllestad et al 1994) which is likely due to a decreased interstitial $[K^+]$. As expected, $[K^+]_{a-v}$ decreased (became more negative) during each bout of exercise, with the peak change (widest $[K^+]_{a-v}$) occurring during the first minute of exercise, which has also been reported during the first minute of submaximal forearm exercise (Chapter 3). During recovery the $[K^+]_{a-v}$ was rapidly reversed, due to high muscle NKA activity. The $[K^+]_{a-v}$ did not get wider at fatigue, which appears to be a characteristic that is unique to single limb exercise (Chapter 3; Bangsbo et al 1992; Bangsbo et al 1996; Rollet et al 1990) and in contrast to high intensity cycling exercise, where $[K^+]_{a-v}$ across contracting muscle typically declines to zero before the end of exercise (Putman et al 2003; Wasserman et al 1997; Vøllestad et al 1994). Therefore the size of the contracting muscle mass appears to be important in determining the magnitude of muscle K^+ loss.

4.4.6.2 Plasma Cl^- and Na^+

Significant Cl^- loss from plasma was apparent throughout exercise and recovery, which is consistent with submaximal forearm exercise (Chapter 3) and supra maximal whole body exercise (McKenna et al 1997a). Peak Cl^- efflux from plasma occurred at fatigue which was ~300-fold greater than at rest; this was ~2 times greater than that observed during submaximal forearm exercise (Chapter 3) at a work rate and blood flow that was approximately half of that observed in the present study. Also, consistent with observations made in Chapter 3, Cl^- efflux and consequent increased Cl^- conductance during exercise, may contribute to maintenance of muscle cell membrane potential (Cairns et al 2004). There was no significant Na^+ efflux or influx from rest during exercise or recovery, which is consistent with observations made in Chapter 3 during submaximal forearm exercise, and in contrast to net Na^+ flux from plasma to muscle during supramaximal whole body exercise (McKenna et al 1997a).

4.4.6.3 Acid-base changes during supra maximal forearm contractions

There was little change in arterial H^+ during exercise and recovery, although venous H^+ increased substantially during exercise and decreased in recovery. Subsequently, there was net H^+ flux from muscle or red blood cells to plasma during exercise and recovery. The contribution of independent variables PCO_2, [SID] and $[A_{tot}]$ that determine H^+ (Johnson et al 1996) will be considered here.

$[H^+]_v$ changes throughout exercise and recovery were consistent with changes in PCO_{2v}, and consistent with findings in Chapter 3 and during and supramaximal cycling exercise (McKenna et al 1997a). There was no change in $[SID]_v$ during exercise, therefore unlikely to have contributed to $[H^+]_v$, with exception to recovery. In contrast to the present study, $[SID]_v$ increased during submaximal forearm exercise (Chapter 3),

which was predominantly affected by a decrease in $[Cl^-]_v$ and not observed in the present study. Plasma $[K^+]_v$ and $[Na^+]_v$ increased during exercise but were counterbalanced by an increase of the same amplitude in $[Lac^-]_v$. Venous [SID] and PCO_2 declined in recovery, and this declined $[H^+]_v$ and $[HCO_3^-]_v$ in recovery. Plasma $[HCO_3^-]_v$ also increased above rest during exercise, which is consistent with observations made during sub maximal forearm exercise (Chapter 3), and coupled with net flux of HCO_3^- from muscle to plasma during exercise. $[A_{tot}]$ was not assessed, though probably increased slightly due to a small decline in plasma volume.

4.4.6.4 Cardiovascular responses

The venous occlusion plethysmography method was used to estimate changes in forearm blood flow at rest, at the end of each bout of exercise and preceding each subsequent interval, and during recovery. Principles and limitations of plethysmography were described in detail in the previous chapter. Following each exercise bout and recovery period, blood flow progressively increased, ultimately increasing ~12 fold from rest to fatigue. Blood flow decreased rapidly following each bout of exercise, and consistently remained above initial resting values during bouts of recovery, which highlights a mild hyperaemic response. Blood flow is closely associated with changes in power output, even when the absolute work rates are very small (Saltin et al, 1998). Peak blood flow of ~280 $ml.min^{-1}$ was required to sustain an average work rate of ~5 W at fatigue, which equates to ~55 $ml.min^{-1}watt^{-1}$. These relative blood flow requirements are identical to the results presented in Chapter 3, where peak blood flow of ~162 $ml.min^{-1}$ was required to sustain an average power output of ~3 W at fatigue; which also equates to ~55 $ml.min^{-1}watt^{-1}$. The $\dot{V}_mO_2$ increased ~21-fold from rest to fatigue, which further demonstrates tight coupling between contracting musculature, workload and vascular responses (Chapter 3; Saltin et al 1998).

4.5 CONCLUSIONS

Despite therapeutic serum digoxin concentration being achieved, 14 d oral digoxin had no effect on plasma K^+ during exercise or recovery. This is likely due to compensatory up regulation of NKA. The decreased glycolytic energy demands in DIG were not due to any apparent decrease in NKA activity. The reduced acidosis in blood draining from exercising muscle at fatigue during DIG was primarily contributed to by a reduction in lactate accumulation, and was not associated with altered exercise performance. Interestingly, tightly regulated K^+ homeostasis is consistent with maintained muscle contractile function and exercise performance. Secondary to these findings, ionic disturbances during intermittent supra maximal finger flexion contractions were more pronounced than previously observed in small muscle mass, and K^+ changes in

particular, were tightly coupled to changes in power output, blood flow, acid-base balance and metabolism. To avoid the compensatory adaptive NKA up-regulation evidenced here in healthy humans during chronic digoxin therapy, future investigations examining the detailed effects of acute digoxin induced NKA inhibition on K^+ homeostasis in healthy tissue are warranted.

CHAPTER 5 EFFECTS OF DIGOXIN & INACTIVE MUSCLE ON PLASMA IONS AND FATIGUE DURING CYCLING EXERCISE IN HEALTHY HUMANS

5.1 INTRODUCTION

Exercise induces considerable K^+ efflux from muscle cells during repeated muscle contractions, which accumulates in the extracellular spaces, depressing cell excitability and contributing to fatigue (McKenna et al, 2008). The magnitude of K^+ accumulation is dependent on exercise mode, intensity, duration, and the size of contracting muscle mass. Substantial K^+ loss occurs from well-perfused large muscles during high intensity exercise, where interstitial $[K^+]$ increases by up to ~9 mM (Sejersted and Sjøgaard, 2000). Sub-maximal cycling exercise also invokes considerable K^+ loss from muscle during leg cycling at 80% $\dot{V}O_{2peak}$; with $[K^+]$ rising to ~6.5 mM in arterial and ~7.7 mM femoral venous plasma, and ~-1.2 mM for the $[K^+]_{a-v}$ (Wasserman et al, 1997). K^+ uptake across inactive forearm muscle has also been previously observed, with $[K^+]_{a-v}$ of ~1.3 mM across inactive forearm muscles during sprint cycling exercise (Kowalchuk et al, 1990).

Skeletal muscle Na^+K^+ATPase (NKA) activity is the primary mechanism for regulating exercise-induced K^+ disturbances, and NKA is pivotal for maintenance and restoration of muscle membrane excitability.

The previous chapter details the consequences of up-regulation and down-regulation of NKA on muscle contractile function, fatigue and thus on exercise performance. Digoxin inhibition of NKA provides myocardial inotropic relief in heart failure patients – but will also indiscriminately bind to and inhibit NKA in other tissue, including skeletal muscle; consequently causing a greater rise in plasma $[K^+]$ during exercise (Schmidt et al 1995; Nørgaard et al 1991). However K^+ disturbances during exercise in CHF patients are difficult to interpret due to pre-existing myopathies and deconditioning.

Numerous studies have investigated a range of physiological responses to digoxin therapy in healthy humans, but little is understood about K^+ disturbances. Edner et al (1993) found that venous plasma $[K^+]$ increased by 0.19 mM at rest following 10 days of oral digoxin therapy at 0.37-0.5 $mg.d^{-1}$. There was no arterial $[K^+]$ or serum [digoxin] data reported and consequent effects of apparent partial NKA inhibition on contracting muscle function is unknown. Venous $[K^+]$ did not change with DIG during handgrip exercise (Janssen et al, 2009), nor was K^+ regulation perturbed during supra-maximal forearm exercise in healthy humans (Chapter 4). However it is conceivable that K^+ disturbances in digitalised healthy humans will be more pronounced during cycling exercise compared to forearm exercise. Only 3-4% of a digoxin dose binds to NKA in targeted myocardium, whilst ~50% binds to non-targeted NKA in skeletal muscle

(Steiness, 1978). Cycling exercise increases digoxin binding to muscle whilst decreasing serum [digoxin] in healthy humans (Joretag & Jogestrand 1983). Various modes of large muscle mass exercise depresses NKA activity, when measured by maximal in-vitro 3-O-MFPase activity (Aughey et al 2006, 2005; Murphy et al 2006a; Petersen et al 2005; Leppik et al 2004; Fraser et al 2002). Therefore leg cycling exercise induced depression of NKA activity might be further exacerbated by NKA inhibition by digoxin, theoretically increasing K^+ loss from contracting muscle and accelerating fatigue due to the effects on the excitation-contraction coupling processes. The important role of non-active muscle (Lindinger et al 1990; Kowalchuk et al 1988) and active muscle in the regulation of exercise induced K^+ and other ionic disturbances is well established (Chapter 3; Putman et al 2003; McKenna et al 1997a; Lindinger et al 1991 & 1995; Vøllestad et al 1994; Juel et al 1990). However the effects of digoxin on NKA function and K^+ regulation in non-contracting tissue during cycling exercise is yet to be investigated.

Skeletal muscle trans-membranous transport of K^+ and Na^+ ions by NKA has a preference for ATP via glycolysis (Clausen 2003). Therefore increased NKA activation is associated with increased lactate production (James et al, 1999; Bundgaard et al, 2002), whereas inhibition of NKA by ouabain is associated with reduced lactate production (James et al, 1999). Lactate accumulation at various time points during exercise was lower with DIG during forearm contractions in healthy humans (Chapter 4). Furthermore, when considering the Stewart (1983) physicochemical approach to acid-base balance, the changes expected with DIG on K^+ and Lac^- during cycling exercise would also affect the strong ion difference, and thus acid-base disturbances, which has not been previously investigated in healthy humans administered with DIG.

Thus this study investigated the effects of 14 days digoxin therapy on K^+ regulation, metabolism, acid-base balance and fatigue during a series of sub-maximal bouts of cycling exercise in healthy humans. The study also investigated the regulatory role of inactive tissue on electrolyte, metabolic and acid base responses to cycling exercise.

It was hypothesised that digoxin would (i) exacerbate the increase in arterial plasma $[K^+]$ during sub-maximal and intense cycling exercise (ii) decrease net K^+ uptake into non-active muscle (iii) decrease glycolysis, and (iv) diminish intense cycling exercise performance.

5.2 METHODS

5.2.1 Preliminary statement

All participant details, screening procedures, digoxin therapy details, arterial/venous cannulae and subsequent blood analyses, familiarisation testing procedures, calculations and statistical analyses were as described in the previous chapter and are therefore not repeated here. Only methods specific to this chapter are reported here.

5.2.2 Leg cycling exercise tests

Following $\dot{V}O_{2peak}$ tests, volunteers returned to the laboratory on 2 further occasions to undertake cycling (70-80 rpm) variability trials at work rates corresponding to 10 min at 33% $\dot{V}O_{2peak,}$ 10 min at 67% $\dot{V}O_{2peak}$ and at 90% $\dot{V}O_{2peak}$ continued to fatigue. The first two cycling bouts were separated by a 2 min rest period with the subject remaining on the cycle ergometer. During two final visits, volunteers completed the 3 bouts of cycling to fatigue trials under randomised, cross-over, counterbalanced and double-blind conditions of both digoxin (DIG) and control (CON) treatment. Fatigue for all trials was defined as a failure to maintain pedal cadence above 55 rpm for ten consecutive seconds. Arterial and venous blood samples (each 5 ml) were taken simultaneously at rest, at the completion of each cycling bout; immediately prior to the start of the proceeding cycling bout; at fatigue; and at 1, 2, 5, 10 and 30 min post exercise. Blood analyses were as previously described (Chapter 3). During these experiments, we carefully considered methods to ensure that the forearm draining venous blood was representative of inactive tissue. Firstly, we used a modified semi recumbent cycling position to remove the need to support arms on handlebars. Secondly, the sampled forearm was elevated and secured by support straps to ensure that there was no movement or contraction of the arm during rest, exercise or recovery. The trunk of each volunteer was also secured to minimise inadvertent forearm contractions.

This study was part of a larger project. Volunteers underwent intense forearm muscle contractions 3 hrs prior to the commencement of these leg cycling experiments (detailed in Chapter 4). Arterial and venous [K^+] was analysed prior to the start of these trials to ensure resting values had been re-established. Also, as part of the larger study, a muscle biopsy was taken at rest, immediately following bouts of cycling at 67% $\dot{V}O_{2peak,}$ 90% $\dot{V}O_{2peak}$ to fatigue, and at 3 hrs recovery. Muscle samples were analysed for maximal in-vitro NKA activity (3-O-MFPase), NKA content ([^{3}H]ouabain binding site) and digoxin binding; which are reported in Appendix 7.

5.3 RESULTS

5.3.1 Serum digoxin concentration

Subjects undergoing digoxin therapy were compliant for the required 2 weeks, and no DIG mediated adverse events were reported. During DIG, SDC was 0.7±0.2 nM on day 7 and 0.8±0.2 nM on day 14. During CON, SDC was below the detection limit of <0.4 nM. One subject was reported at the lower detection limit of 0.4 nM for SDC in CON, whilst their corresponding SDC in the DIG trial was 0.9-1.0 nM. For all others in CON, no digoxin was detected.

5.3.2 Leg Cycling Exercise Tests

The initial leg cycling incremental exercise $\dot{V}O_{2peak}$ was 3.67±0.42 l min^{-1}. During initial leg cycling variability trials, the time to fatigue at 90% $\dot{V}O_{2peak}$ was reproducible (CV 5.9%). The $\dot{V}O_2$ during exercise increased with each work rate (P<0.001) but did not differ between DIG and CON at 33% (1.21±0.20 vs 1.19±0.21 $l.min^{-1}$, CV=2.2%); 67% (2.63±0.51 vs 2.68±0.54 $l.min^{-1}$, CV=1.9%); or 90% $\dot{V}O_{2peak}$ (3.61±0.28 vs 3.55±0.67 $l.min^{-1}$, CV=4.4%), respectively. The time to fatigue during the final bout of cycling exercise at 90% $\dot{V}O_{2peak}$ (262±156 vs 254±125 sec) did not differ between DIG and CON, respectively. Whilst heart rate increased from rest to fatigue and remained elevated at 30 min recovery (P<0.05), heart rate was not altered by DIG compared to CON at rest (80±4 vs 77±5 $beats.min^{-1}$), fatigue (193±5 vs 191±6 min^{-1}) or at 30 min recovery (94±7 vs 93±5 $beats.min^{-1}$), respectively.

5.3.3 Haematology and Fluid Shifts

5.3.3.1 Haemoglobin and haematocrit

Exercise. Arterial and venous [Hb] as well as Hct increased from rest and peaked at fatigue (P<0.01; Table 5.1).

Digoxin. There were no differences between CON and DIG for either [Hb] or Hct.

5.3.3.2 Plasma and blood volume changes

Exercise. Plasma volume (PV) declined from rest during exercise when calculated for both arterial and venous blood, by ~18% at fatigue (P<0.01, Table 5.2). Both ΔPV_a and ΔPV_v remained negative throughout recovery, until a small expansion above rest at 30 min recovery for ΔPV_a (P<0.01). A small net loss in PV across the inactive forearm was apparent (negative ΔPV_{a-v}) at several points during the late stages of exercise and in recovery (P<0.01, Table 2). Similar exercise effects were found for ΔBV_a and for ΔBV_v, although the magnitude was halved (P<0.01, Table 5.2).

Digoxin. There were no effects of DIG on ΔPV_a, ΔPV_v or $\Delta PV_{a\text{-}v,}$ or on BV_a, BV_v or $BV_{a\text{-}v}$ (Table 5.2).

5.3.4 Plasma Electrolytes

5.3.4.1 Plasma [K^+]

Exercise. Plasma $[K^+]_a$ increased above rest during each bout of cycling, peaking at fatigue at ~6.5 mM ($P<0.001$, Figure 5.1A). $[K^+]_a$ decreased rapidly to resting value after the 2 min recovery following each of the exercise bouts. $[K^+]_a$ decreased further to below rest values at 5 and 10 min recovery ($P<0.001$; Fig 1A). Plasma $[K^+]_v$ increased above rest during the final two cycling bouts with a peak at only ~5 mM, and the first 2 min recovery before returning to rest levels ($P<0.001$, Figure 5.1B). $[K^+]_{a\text{-}v}$ increased above rest (more positive) after 1 min at 67% $\dot{V}O_{2peak}$ and peaked at fatigue at ~1.5 mM ($P<0.001$, Fig 5.1C), representing net K^+ uptake into inactive forearm muscle. An immediate reversal of $[K^+]_{a\text{-}v}$ to resting values occurred at 1 min recovery, and decreased to below rest between 2 and 10 min recovery ($P<0.001$, Figure 5.1C), representing a net release of K^+ from inactive forearm muscle during this period.

Digoxin. There was no treatment effect of DIG on $[K^+]_{a,}$ $[K^+]_v$ and $[K^+]_{a\text{-}v.}$

Table 5.1: Changes from resting levels in haemoglobin ([Hb]) and hematocrit (Hct) across the non-exercising forearm were calculated at rest, during the first 1 min (a) and at the end of each exercise bout (b) and immediately before (pre) each subsequent bout cycling exercise for 10 min at 30%, 67% $\dot{V}O_{2peak}$ and 90% $\dot{V}O_{2peak}$ to fatigue (F), and in recovery, under CON and DIG conditions. Units are % for Hct, and g dl^{-1} for [Hb].

		Exercise								Recovery				
	Rest	**33%a**	**33%b**	**Pre-67%**	**67%a**	**67%b**	**Pre-90%**	**90%a**	**F**	**+1**	**+2**	**+5**	**+10**	**+30**
CON														
$[Hb]_a$	14.7	14.8	14.9*	14.7	15.1	15.7*	15.5*	15.8*	16.3*	16.3*	15.9*	15.5*	15.2*	14.4
SEM	0.3	0.2	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.3	0.4	0.4	0.3	0.3
$[Hb]_v$	14.4	14.4	14.6	15.0	14.8	15.4*	15.6*	15.6*	15.9*	15.8*	15.5*	15.4*	15.3*	14.4
SEM	0.4	0.3	0.4	0.5	0.6	0.5	0.5	0.5	0.5	0.5	0.6	0.4	0.5	0.7
Hct_a	41.0	41.6	41.6	41.2	42.2	44.2*	43.5*	44.4*	46.5*	46.6*	45.7*	44.8*	43.9*	40.1
SEM	0.5	0.5	0.5	0.5	0.6	0.7	0.8	0.8	0.9	0.7	0.9	1.0	0.9	1.0
Hct_v	39.9	40.3	41.0	42.1	42.4	43.6*	43.8*	44.3*	45.2*	45.3*	44.2*	44.1*	44.0*	40.6
SEM	0.6	0.5	0.6	1.2	1.3	0.9	1.1	1.1	1.0	1.1	1.5	1.0	1.1	1.0
DIG														
$[Hb]_a$	14.6	14.9	14.9*	14.9	15.0	15.7*	15.5*	16.3*	16.6*	16.3*	16.2*	15.6*	15.5*	14.6
SEM	0.4	0.5	0.4	0.4	0.4	0.5	0.6	0.4	0.4	0.3	0.5	0.5	0.3	0.3
$[Hb]_v$	14.2	14.2	14.4	14.4	14.3	15.4*	15.4*	15.2*	15.6*	15.8*	15.5*	15.4*	15.4*	14.7
SEM	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.5	0.6	0.4	0.4
Hct_a	41.8	41.7	41.9	41.7	42.4	44.5*	43.9*	46.1*	47.3*	46.8*	46.1*	44.7*	44.0*	41.4
SEM	1.4	1.1	0.9	0.9	1.0	1.1	1.3	0.8	0.7	0.6	0.8	1.0	0.8	0.6
Hct_v	40.1	40.4	40.6	40.7	40.7	43.7*	43.5*	44.2*	44.5*	44.7*	44.0*	44.0*	42.9*	41.5
SEM	0.9	0.9	0.9	0.9	0.9	1.3	1.3	0.9	1.1	1.3	1.1	1.3	1.2	0.7

Mean ± SEM, *n* = 10 for CON arterial, *n = 9* for DIG; *n* = 8 for CON venous, *n = 7* for DIG * Greater than rest (P<0.01).

Table 5.2: Changes from resting levels in plasma volume (ΔPV_a) and blood volume (ΔBV_a) and changes in venous compared to arterial plasma (ΔPV_{a-v}) and blood volume (ΔBV_{a-v}) across the non-exercising forearm were calculated at rest, during the first 1 min (a) and at the end of each exercise bout (b) and immediately before (pre) each subsequent bout cycling exercise for 10 min at 30%, 67% $\dot{V}O_{2peak}$ and 90% $\dot{V}O_{2peak}$ to fatigue (F), and in recovery, under CON and DIG conditions, from changes in haemoglobin ([Hb]) and hematocrit (Hct). Units are % for ΔPV_a, ΔBV_a, ΔPV_{a-v}, ΔBV_{a-v}.

		Exercise							**Recovery**					
	Rest	**33%a**	**33%b**	**Pre-67%**	**67%a**	**67%b**	**Pre-90%**	**90%a**	**F**	**+1**	**+2**	**+5**	**+10**	**+30**
CON														
ΔPV_a		-2.4	-1.7	-0.7	-4.9	-11.7*	-8.9*	-12.3*	-18.3*	-17.0*	-15.1*	-11.5*	-8.5*	3.3*
SEM		0.7	0.8	0.6	0.8	1.2	1.5	1.5	1.3	0.9	1.6	1.8	1.5	1.3
ΔPV_v		-0.6	-3.3*	-7.0	-6.5	-12.1*	-13.6*	-14.3*	-17.2*	-17.3*	-13.3*	-12.9*	-12.4*	-1.0
SEM		0.9	1.5	3.5	3.3	1.3	1.6	1.6	2.0	1.7	3.8	1.1	1.5	2.4
ΔBV_a		-1.4	-0.7*	-0.4	-2.9	-6.7*	-5.0*	-6.9*	-9.9*	-8.7*	-7.8*	-5.3*	-3.7*	1.9
SEM		0.4	0.6	0.4	0.5	0.6	0.7	0.9	0.7	0.4	0.8	0.9	0.9	0.6
ΔBV_v		0.0	-1.7*	-3.8*	-2.8*	-6.4*	-7.6*	-7.6*	-9.4*	-9.1*	-6.9*	-6.5*	-6.1*	0.0
SEM		0.6	0.7	1.9	1.5	0.4	0.8	0.6	1.2	0.8	2.0	0.5	0.6	1.1
ΔPV_{a-v}	3.3	5.2	1.2	-1.1	2.5	1.8	-2.8*	-0.1	3.4	0.6*	4.1	0.4	-2.3*	-2.5*
SEM	1.3	0.7	1.4	1.7	1.8	1.2	1.7	1.2	1.9	1.2	3.0	2.2	2.1	1.4
ΔBV_{a-v}	-0.8	-0.5	-0.9	-1.3	-0.8	-0.7	-1.3*	-0.9	-0.7	-0.1	-0.7	-1.0	-1.2*	-1.1
SEM	0.1	0.1	0.1	0.3	0.2	0.1	0.1	0.1	0.2	0.1	0.2	0.2	0.2	0.2

		Exercise							Recovery					
	Rest	**33%a**	**33%b**	**Pre-67%**	**67%a**	**67%b**	**Pre-90%**	**90%a**	**F**	**+1**	**+2**	**+5**	**+10**	**+30**
DIG														
ΔPV_a		-1.2	-1.9	-1.0	-3.4	-10.8*	-8.4*	-13.9*	-17.5*	-15.3*	-13.5*	-10.7*	-6.3*	3.9*
SEM		2.1	2.6	2.7	2.5	2.3	3.1	2.8	2.0	2.0	2.0	2.0	2.4	2.0
ΔPV_v		-1.8	-3.7*	-3.9	-2.2	-13.6*	-12.8*	-13.1*	-16.8*	-17.9*	-15.6*	-13.7*	-12.3*	-2.6
SEM		0.7	1.0	0.8	0.7	1.7	1.6	2.1	1.4	1.6	1.2	1.7	1.2	1.3
ΔBV_a		-1.7	-2.2*	-1.7	-2.8	-6.9*	-5.5*	-8.3*	-10.4*	-8.9*	-8.1*	-6.3*	-4.1*	1.5
SEM		0.9	0.8	0.9	0.8	0.8	1.4	1.0	0.7	0.5	0.8	0.8	0.8	0.7
ΔBV_v		-0.9	-2.5*	-2.5*	-1.2*	-8.1*	-7.6*	-7.3*	-9.3*	-10.6*	-9.3*	-7.7*	-6.9*	-1.5
SEM		0.4	0.8	0.6	0.5	0.8	0.8	1.2	0.9	1.1	0.8	1.0	0.9	0.8
ΔPV_{a-v}	2.5	2.4	1.5	0.7	4.7	0.6	-1.8*	3.5	1.9	-0.3*	0.9	1.4	-1.9*	-1.5*
SEM	0.7	1.3	1.5	1.4	1.8	0.9	1.4	1.6	1.1	2.6	1.6	1.0	1.8	0.8
ΔBV_{a-v}	-0.8	-0.7	-0.9	-0.9	-0.6	-1.0	-1.2*	-0.7	-0.9	-1.2	-1.0	-0.9	-1.1*	-1.1
SEM	0.1	0.1	0.2	0.1	0.2	0.1	0.1	0.2	0.1	0.2	0.3	0.1	0.2	0.1

Mean ± SEM, *n = 10* for CON arterial, *n = 9* for DIG; *n* = 8 for CON venous, *n = 7* for DIG; *n = 8* for CON arteriovenous differences, *n = 7* for DIG * Greater than rest (P<0.01). A negative value denotes a decline, and a positive value denotes a gain in plasma or blood volume across the forearm, respectively. These calculations enabled corrections to be made for effects of fluid shifts on ion concentrations in plasma and blood during and following exercise.

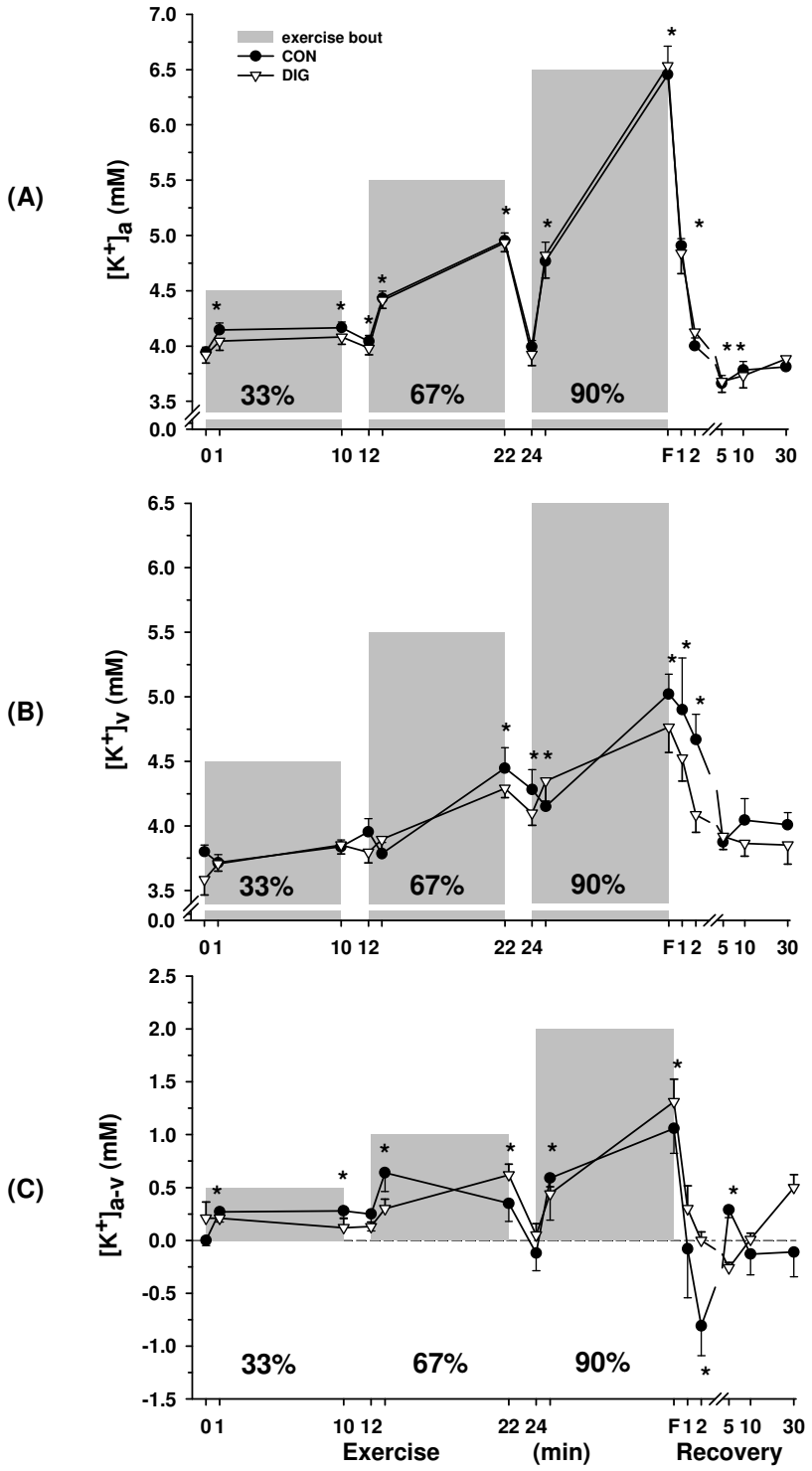

Figure 5.1. Effects of digoxin on plasma [K^+] at rest, during cycling exercise (shaded bars) to fatigue (F) and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [K^+] differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.001$, time main effect). Data expressed as Mean ± SEM, *n* = 10 for CON arterial, *n = 9* for DIG; *n* = 8 for CON venous and arteriovenous differences, *n = 7* for DIG. The $[K^+]_{a-v}$ was corrected for the a-v decline in plasma volume.

5.3.4.2 Plasma [Na^+]

Exercise. Plasma $[Na^+]_a$ increased during each of the 3 bouts of cycling, peaking at fatigue at ~148 mM ($P<0.001$, Figure 5.2A). Plasma $[Na^+]_a$ decreased throughout recovery, and returned to rest levels at 5 min recovery ($P<0.001$). Plasma $[Na^+]_v$ increased above rest during the final 2 bouts of cycling ($P<0.001$, Figure 5.2B), showing similar directional changes during recovery as for $[Na^+]_a$, although at a lesser magnitude ($P<0.001$, Figure 5.2B). Plasma $[Na^+]_{a-v}$ increased above rest at the end of the final two bouts of cycling ($P<0.01$, Figure 5.2C), with a positive $[Na^+]_{a-v}$ prior to the start of 90% $\dot{V}O_{2peak}$, fatigue, 1 and 30 min recovery, which indicates a net Na^+ uptake at these times by inactive forearm muscle.

Digoxin. There was no treatment effect of DIG on $[Na^+]_a$, $[Na^+]_v$ or $[Na^+]_{a-v}$.

5.3.4.3 Plasma [Cl^-]

Exercise. Plasma $[Cl^-]_a$ increased above rest during 33% $\dot{V}O_{2peak}$, after 1 min at 67% $\dot{V}O_{2peak}$ and at fatigue, and decreased to below rest during recovery ($P<0.001$, Figure 5.3A). Plasma $[Cl^-]_v$ did not differ from rest during exercise and recovery (Figure 5.3B). Plasma $[Cl^-]_{a-v}$ differed from rest during exercise and recovery ($P<0.05$, Figure 5.3C). A significant time main effect was found for plasma $[Cl^-]_{a-v}$ but no differences could be detected with post-hoc analyses.

Digoxin. Plasma $[Cl^-]_a$ tended to be greater in DIG from rest to 67% $\dot{V}O_{2peak}$ ($P=0.11$, $d = 0.25$). There was no treatment effect in plasma $[Cl^-]_v$ or $[Cl^-]_{a-v}$.

5.3.4.4 Plasma [Lac^-]

Exercise. Plasma $[Lac^-]_a$ increased above rest during each cycling bout, reaching ~17 mM at fatigue, further increasing during 2 min recovery ($P<0.001$, Figure 5.4A), before declining progressively but remaining above rest at 30 min recovery ($P<0.001$, Fig 5.4A). Plasma $[Lac^-]_v$ changes during exercise and recovery were similar to $[Lac^-]_a$ ($P<0.001$. Figure 5.4B), although at a lesser magnitude, and with no significant increase in $[Lac^-]_v$ above rest at 33% $\dot{V}O_{2peak}$. Plasma $[Lac^-]_{a-v}$ increased to positive values during the final two bouts of cycling, and the first 5 min of recovery ($P<0.001$, Figure 5.4C), with a positive $[Lac^-]_{a-v}$ reflecting net lactate loss from plasma.

Digoxin. Plasma $[Lac^-]_a$ tended to be lower at 67% $\dot{V}O_{2peak}$ ($P=0.07$). Plasma $[Lac^-]_v$ was lower in DIG at 33% $\dot{V}O_{2peak}$ ($P<0.05$) and there was no treatment effect in $[Lac^-]_{a-v}$.

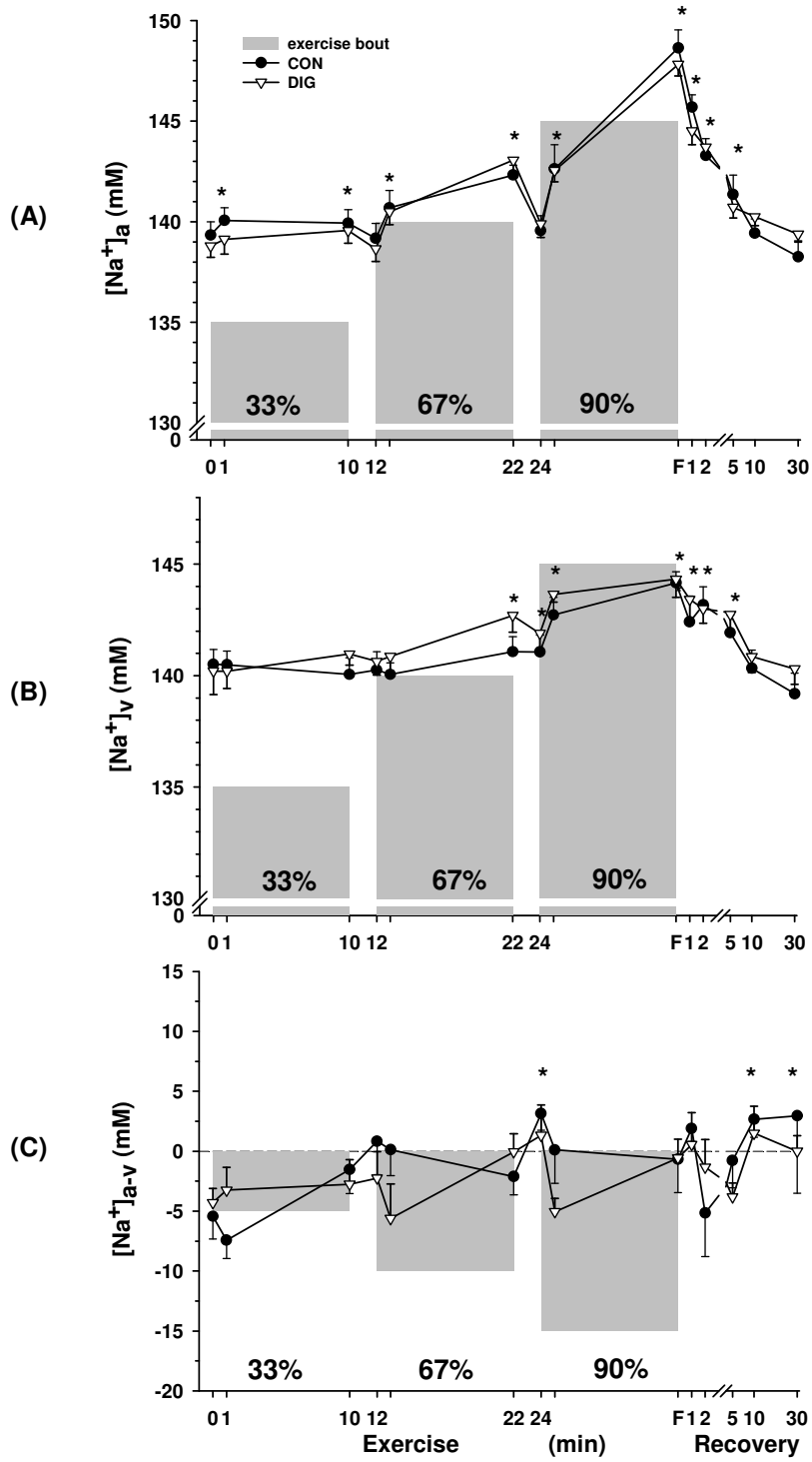

Figure 5.2. Effects of digoxin on plasma [Na^+] at rest, during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [Na^+] differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.001$, for arterial and venous; $P<0.05$ for arteriovenous time main effect). Data expressed as Mean ± SEM, *n* = 10 for CON arterial, *n = 9* for DIG; *n* = 8 for CON venous and arteriovenous differences, *n = 7* for DIG. The $[Na^+]_{a-v}$ was corrected for the a-v decline in plasma volume.

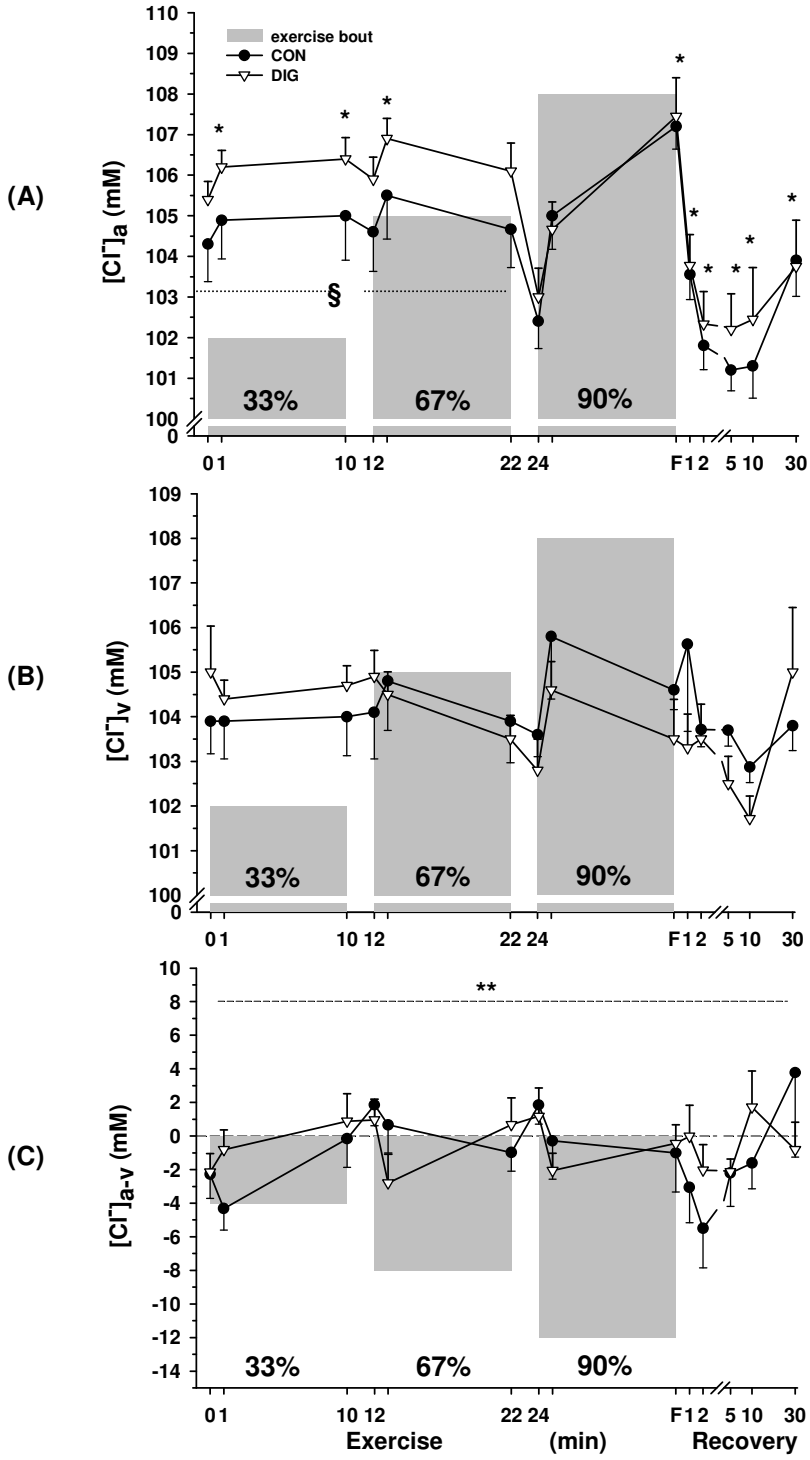

Figure 5.3. Effects of digoxin on plasma [Cl^-] at rest, during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [Cl^-] differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.001$, time main effect). ** Time main effect ($P<0.05$), post hoc analyses could not detect the location of differences. § DIG > CON ($P=0.11$, $d = 0.25$). Data expressed as Mean ± SEM, $n = 10$ for CON arterial, $n = 9$ for DIG; $n = 8$ for CON venous and arteriovenous differences, $n = 7$ for DIG. The $[Cl^-]_{a-v}$ was corrected for the a-v decline in plasma volume.

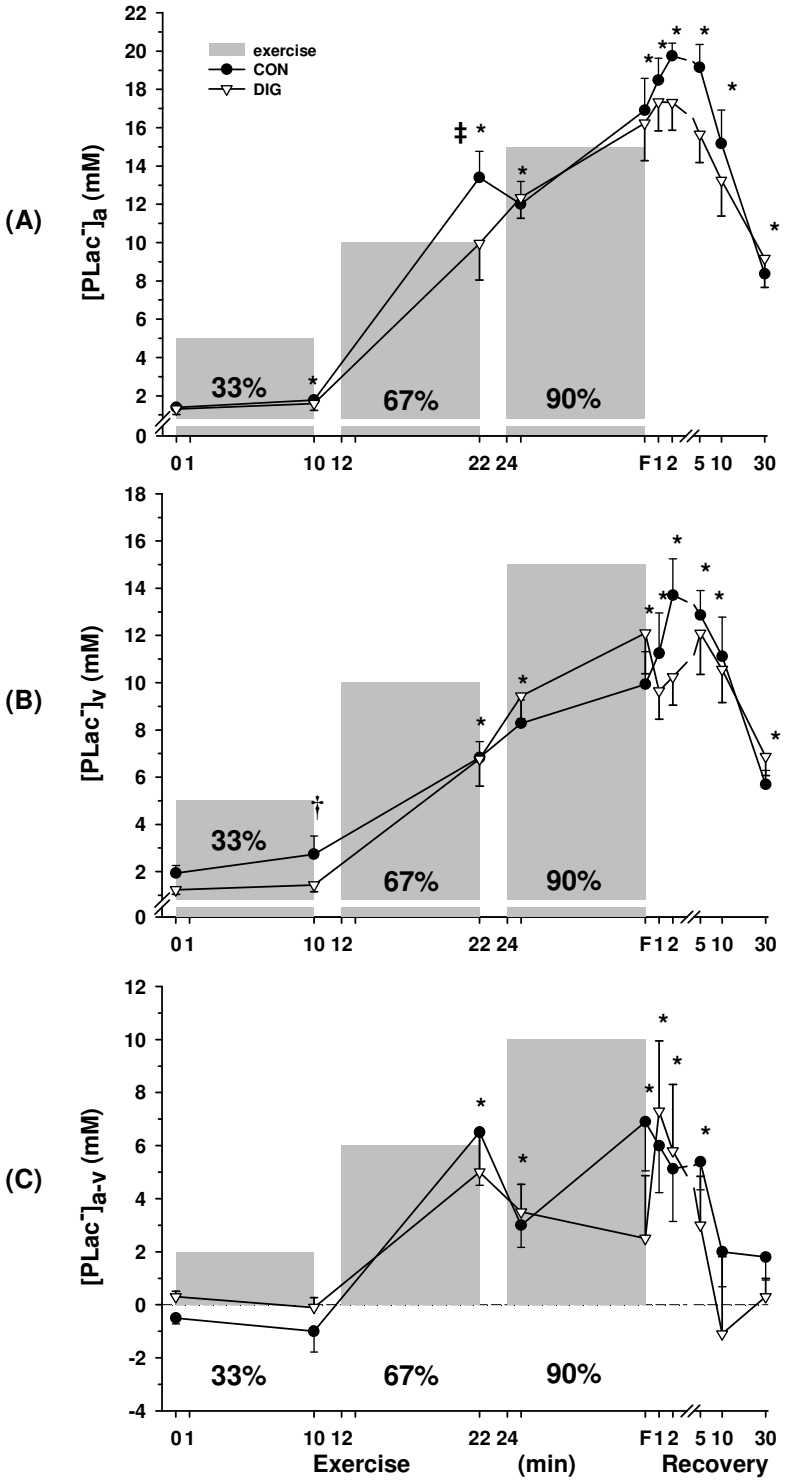

Figure 5.4. Effects of digoxin on plasma [Lac⁻] at rest, during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [Lac⁻] differences, under CON (●) and DIG (▽) conditions. * Different from rest (P<0.001, time main effect). †DIG < CON (P<0.05). ‡DIG < CON (P=0.07). Data expressed as Mean ± SEM, *n* = 8 for CON arterial, *n = 7* for DIG; *n* = 6 for venous; *n = 6* for CON arteriovenous differences, *n = 5* for DIG. The $[Lac^-]_{a-v}$ was corrected for the a-v decline in plasma volume.

5.3.4.5 Strong ion difference ([SID])

Exercise. Plasma $[SID]_a$ decreased below rest during the final two bouts of exercise and in recovery and remained below rest at 30 min recovery ($P<0.001$, Figure 5.5A). Plasma $[SID]_v$ changes from rest were similar to $[SID]_a$ ($P<0.001$; Figure 5.5B). Plasma $[SID]_{a-v}$ was negative throughout exercise and recovery, but did not significantly different from rest (Figure 5.5C).

Digoxin. Plasma $[SID]_a$ was lower in DIG at rest and 33% $\dot{V}O_{2peak}$ ($P<0.05$), whereas $[SID]_v$ and $[SID]_{a-v}$ were not affected by DIG.

5.3.5 Metabolism

5.3.5.1 Blood CO_2 content (C_{CO2})

Exercise. C_{aCO2} and C_{vCO2} decreased substantially from 67% $\dot{V}O_{2peak}$ to early recovery, but remained below rest at 30 min ($P<0.001$, Figure 5.6A, 5.6B). C_{a-vCO2} remained negative throughout exercise and recovery, indicating net CO2 release from forearm muscles, and significantly lower than rest at fatigue until 10 min recovery ($P<0.001$, Figure 5.6C).

Digoxin. $C_{aCO2,}$ C_{vCO2} and C_{a-vCO2} were not different between trials.

5.3.5.2 Blood O_2 content (C_{O2})

Exercise. C_{aO2} increased during exercise at 67% $\dot{V}O_{2peak}$ and 90% $\dot{V}O_{2peak}$, before decreasing after 2 min recovery, until lower at 30 min recovery than at rest ($P<0.05$, Figure 5.7A). C_{vO2} was greater than rest only after 1 min at 90% $\dot{V}O_{2peak}$ ($P<0.05$, Figure 5.7B). C_{a-vO2} remained positive throughout rest, exercise and recovery, indicating forearm muscle net O_2 uptake, but did not differ significantly from rest at any time (Figure 5.7C).

Digoxin. There was no DIG effect on C_{aO2}, C_{vO2} or C_{a-vO2}.

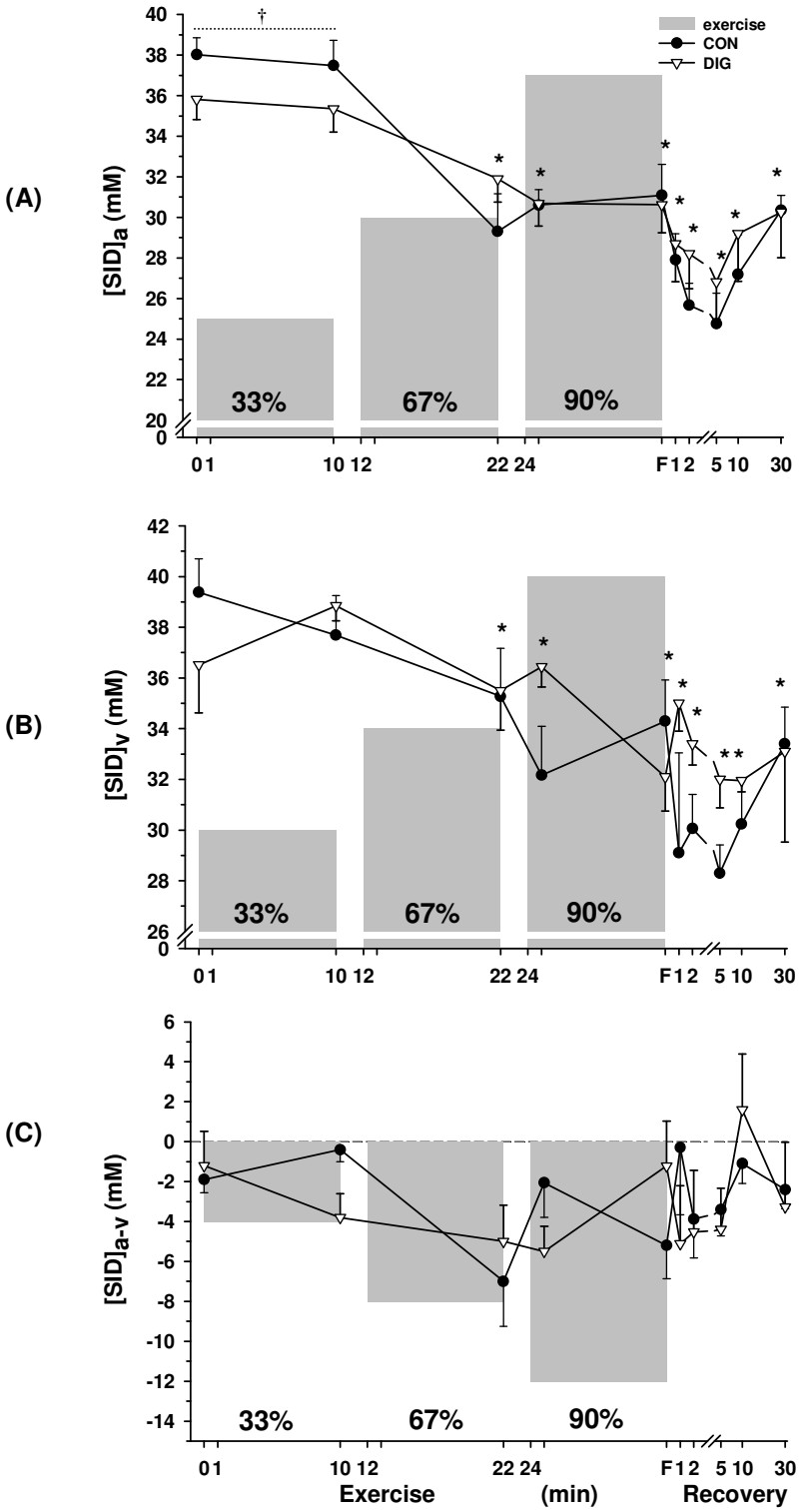

Figure 5.5. Effects of digoxin on plasma [SID] at rest, during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [SID] differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.001$, main effect for time). † DIG different to CON ($P<0.05$). Data expressed as Mean ± SEM, *n* = 8 for CON arterial, *n = 7* for DIG; *n* = 6 for CON venous, *n = 5* for DIG; *n = 6* for CON arteriovenous differences, *n = 5* for DIG. The $[SID]_{a-v}$ was corrected for the a-v decline in plasma volume.

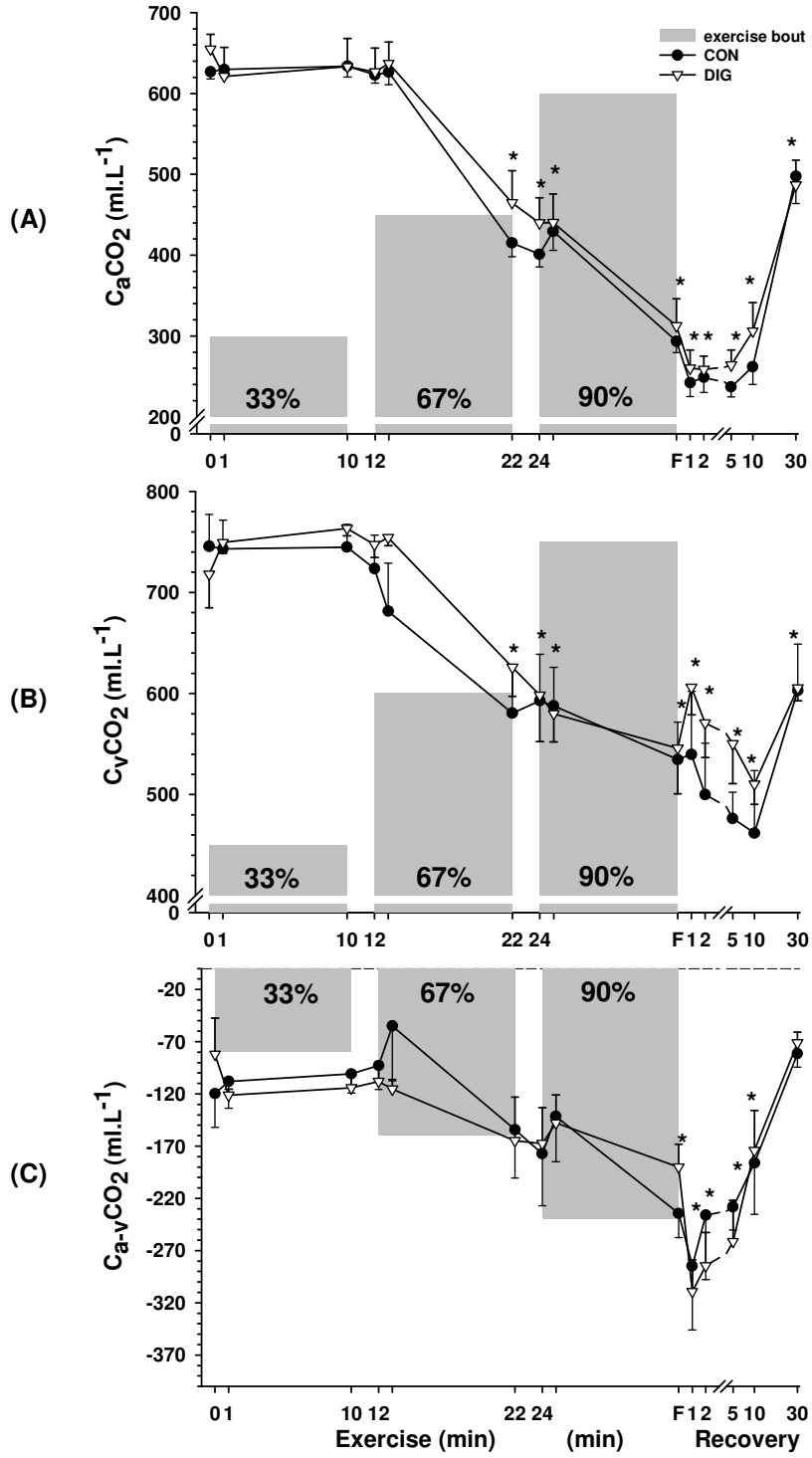

Figure 5.6. Effects of digoxin on CO_2 content at rest, during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous CO_2 content differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.001$, time main effect). Data expressed as Mean ± SEM, *n = 7* for arterial; *n = 5* for CON venous and arteriovenous differences, *n = 4* for DIG.

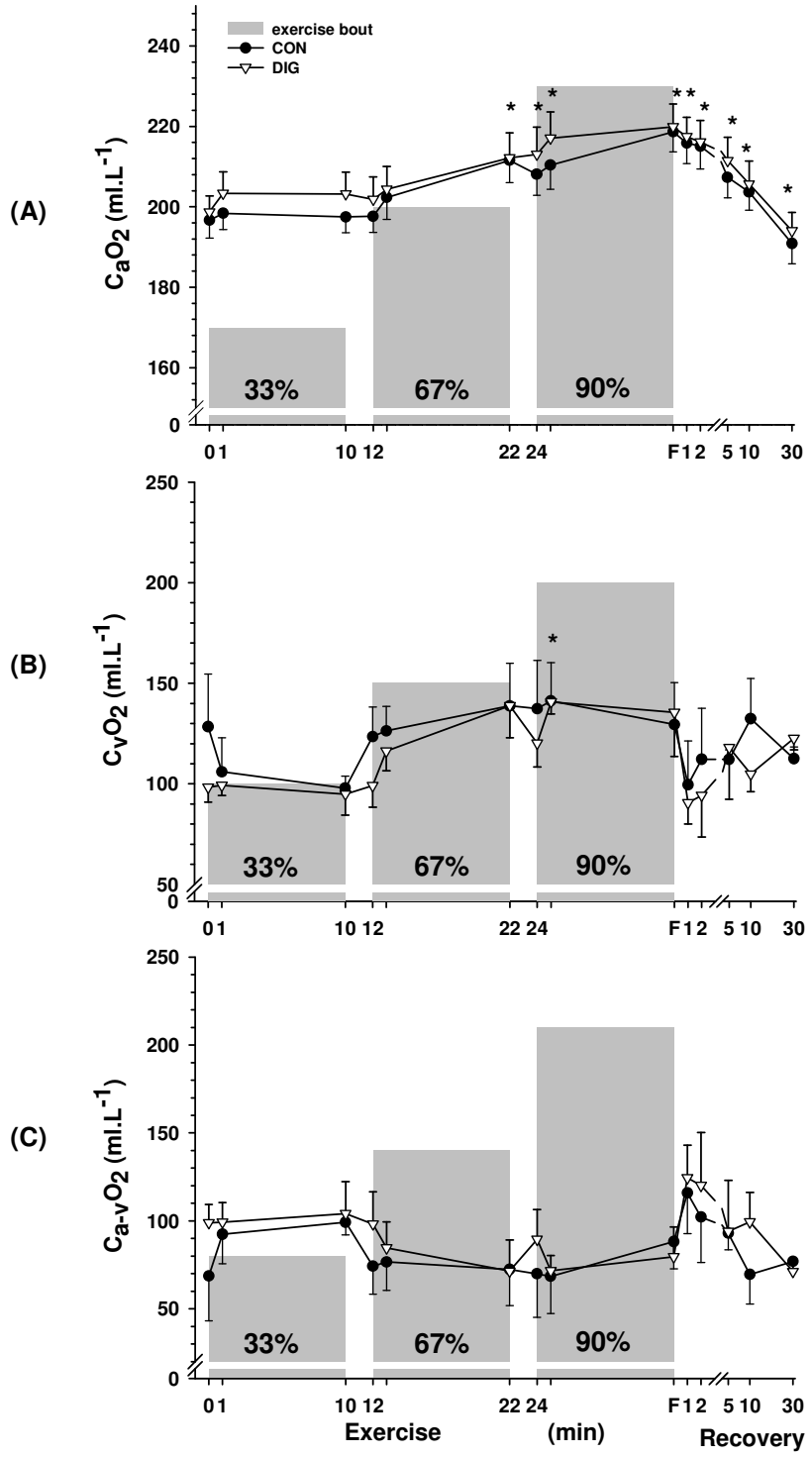

Figure 5.7. Effects of digoxin on O_2 content at rest, during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial (B) venous and (C) calculated arteriovenous O_2 content differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.05$, time main effect). Data expressed as Mean ± SEM, *n* = 7 for arterial; *n* = 5 for CON venous and arteriovenous differences, *n = 4* for DIG.

5.3.5.3 Blood [Lac$^-$]

Exercise. Whole blood $[Lac^-]_a$ increased above rest during each cycling bout to ~15mM at fatigue, rising another 1 mM at 1-2 min recovery, then decreasing thereafter ($P<0.001$, Figure 5.8A). Whole blood $[Lac^-]_v$ increased above rest during 67% and 90% $\dot{V}O_{2peak}$ and remained throughout recovery ($P<0.001$, Figure 5.8B). Blood $[Lac^-]_{a-v}$ increased (became positive) above rest during 90% $\dot{V}O_{2peak}$ and recovery until 10 min, reflecting a net uptake of lactate from blood by the inactive forearm musculature ($P<0.001$, Figure 5.8C).

Digoxin. Blood $[Lac^-]_{a,}$ $[Lac^-]_v$ and $[Lac^-]_{a-v}$ were not changed by DIG.

5.3.6 Acid-base balance

5.3.6.1 Plasma [H$^+$]

Exercise. Arterial plasma $[H^+]_a$ was increased above rest during exercise at 67% and 90% $\dot{V}O_{2peak}$ ($P<0.001$, Figure 5.9A). $[H^+]_a$ peaked at ~66 nM at 5 min recovery, and decreased rapidly thereafter, although remaining higher than at 30 min recovery ($P<0.001$, Figure 5.9A). Plasma $[H^+]_v$ was similarly increased during 67% $\dot{V}O_{2peak}$ and 90% $\dot{V}O_{2peak}$, and peaking at 5 min recovery ($P<0.001$, Figure 5.9B), decreased thereafter, and similar to rest by 30 min recovery. Plasma $[H^+]_{a-v}$ became more negative prior to and during the first minute of exercise at 67% $\dot{V}O_{2peak}$ ($P<0.001$). The $[H^+]_{a-v}$ were reversed, becoming more positive than rest at fatigue, and during the first 10 min of recovery ($P<0.001$, Figure 5.9C), thus representing net H^+ increase in plasma across non-contracting muscle.

Digoxin. Plasma $[H^+]_a$, and $[H^+]_v$ were unchanged by DIG. Plasma $[H^+]_{a-v}$ was greater in DIG ($P<0.01$, Figure 5.9C), thus less H^+ uptake into plasma across non-contracting muscle.

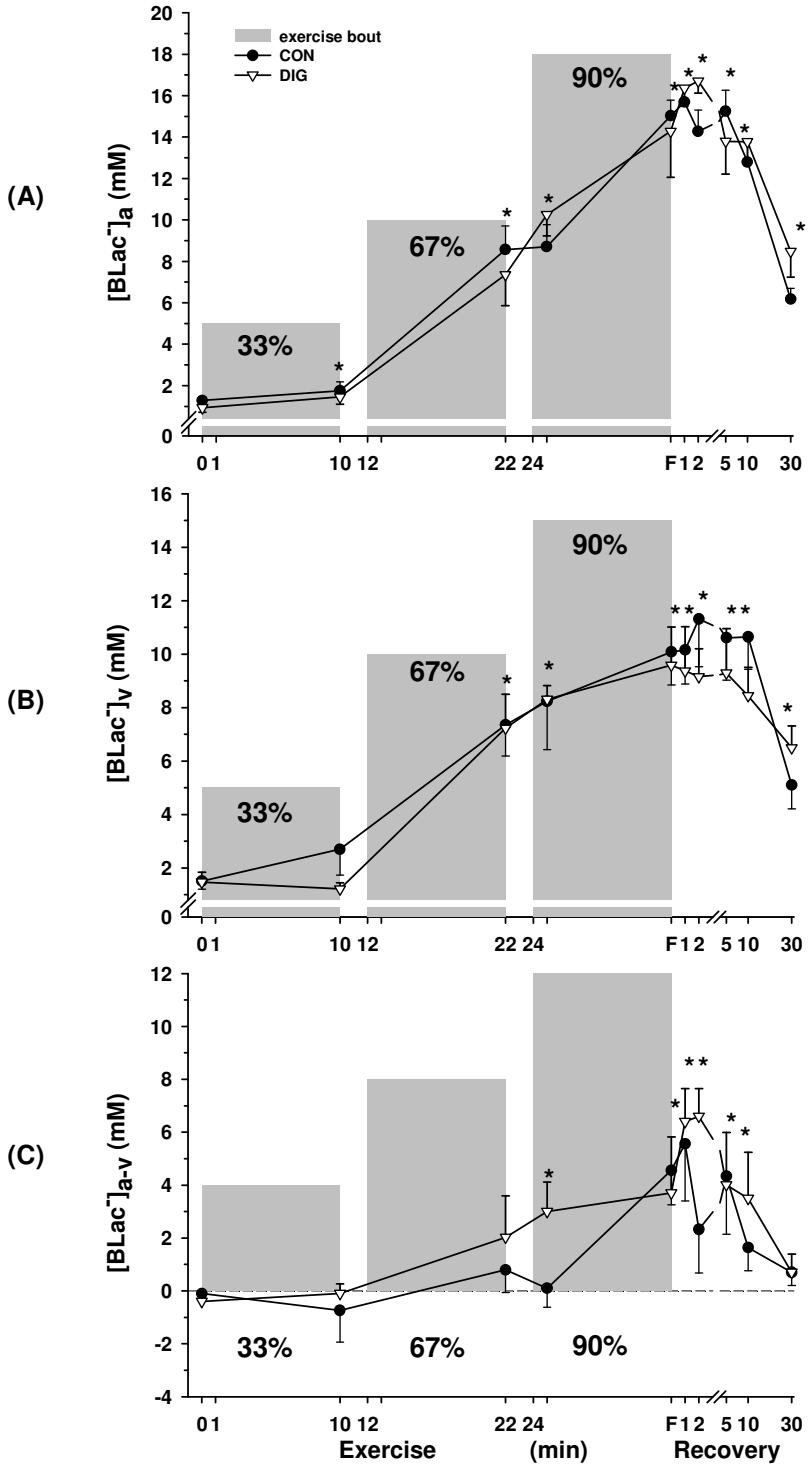

Figure 5.8. Effects of digoxin on whole blood [Lac^-] at rest during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous whole blood [Lac^-] differences, under CON (●) and DIG (▽) conditions. *Different from rest ($P<0.001$, time main effect). Data expressed as Mean ± SEM, *n* = 8 for CON arterial, *n = 7* for DIG; *n* = 6 for venous; *n = 6* for CON arteriovenous differences, *n = 5* for DIG. The WB $[Lac^-]_{a-v}$ was corrected for the a-v decline in blood volume.

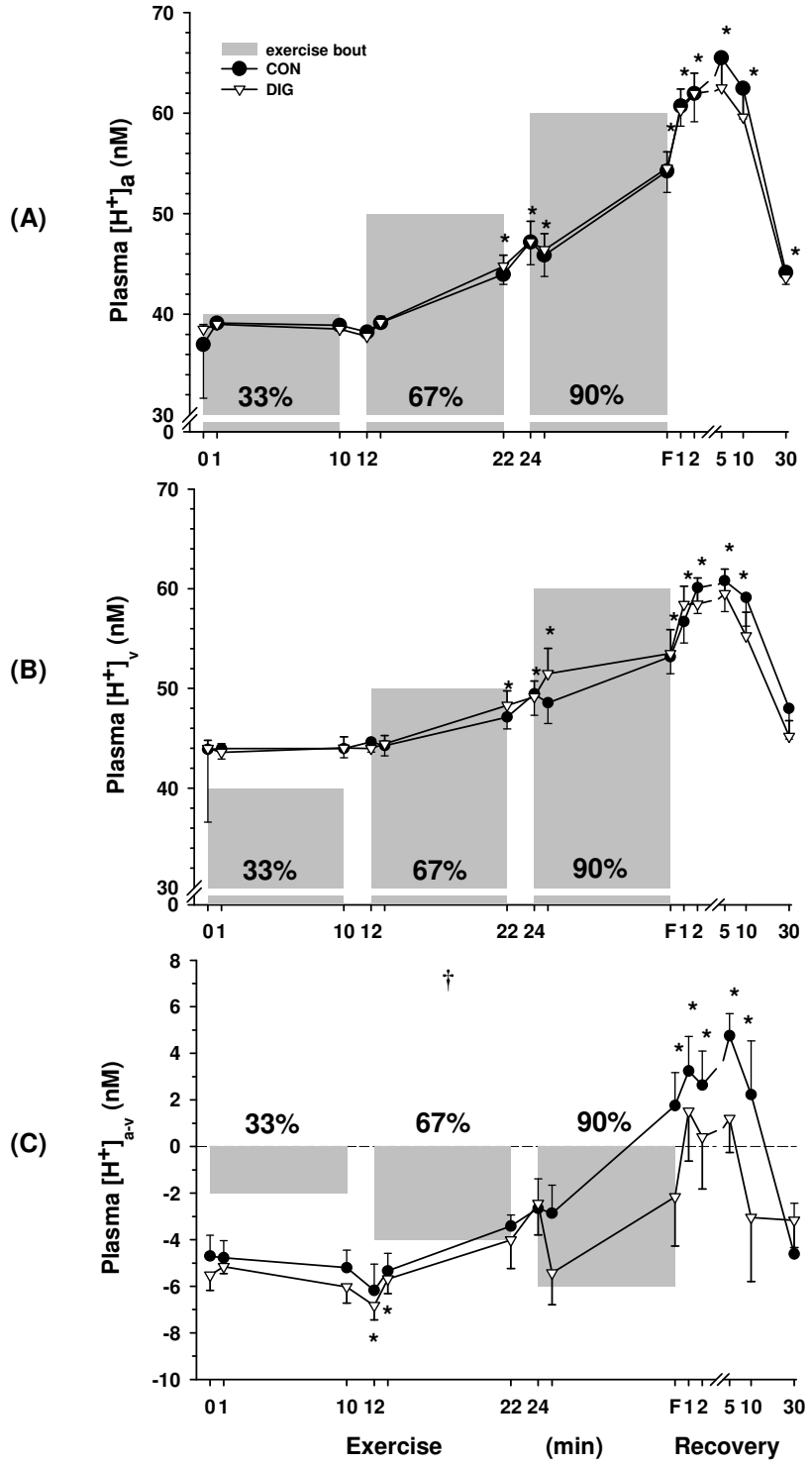

Figure 5.9. Effects of digoxin on plasma [H^+] at rest, during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [H^+] differences, under CON (●) and DIG (▽) conditions. † DIG > CON ($P<0.01$, treatment main effect). *Different from rest ($P<0.001$, time main effect). Data expressed as Mean ± SEM, *n* = 10 for CON arterial, *n = 9* for DIG; *n = 8* for venous; *n = 8* for CON arteriovenous differences, *n = 7* for DIG.

5.3.6.2 Plasma [HCO_3^-]

Exercise. Plasma $[HCO_3^-]_a$ declined at the end of 67% $\dot{V}O_{2peak}$ ($P<0.001$, Figure 5.10A). Plasma $[HCO_3^-]_a$ continued to decrease during 90% $\dot{V}O_{2peak}$ and remained low for the first 5 min of recovery, reaching values ~15mM less than rest before increasing after 5 min recovery, but remaining less than rest at 30 min recovery ($P<0.001$, Figure 5.10A). The trend for plasma $[HCO_3^-]_v$ during exercise and recovery was similar ($P<0.001$, Figure 5.10B), but with lesser magnitude of change, with the peak decline ~10 mM at 10 min recovery. Plasma $[HCO_3^-]_{a-v}$ remained negative throughout exercise and recovery, indicating a net $[HCO_3^-]$ gain in plasma across the inactive forearm muscles. From 67% $\dot{V}O_{2peak}$ to 5 min recovery, the $[HCO_3^-]_{a-v}$ widened to ~11 mM at 1 min recovery before returning to rest at 10 min ($P<0.001$, Figure 5.10C).

Digoxin. There was no treatment main effect for plasma $[HCO_3^-]_a$, $[HCO_3^-]_v$ and $[HCO_3^-]_{a-v}$.

5.3.6.3 *Plasma pCO_2*

Exercise. Plasma P_aCO_2 declined during 67% $\dot{V}O_{2peak}$, 90% $\dot{V}O_{2peak}$ and recovery ($P<0.001$, Figure 5.11A). Plasma P_vCO_2 declined at 67% $\dot{V}O_{2peak}$ and from 10 to 30 min recovery ($P<0.001$, Figure 5.11B).

Digoxin. P_aCO_2 and P_vCO_2 were not changed by DIG.

5.3.6.4 *Plasma pO_2*

Exercise. Plasma P_aO_2 was lower in the first minute at 33% $\dot{V}O_{2peak}$ and increased above rest at 67% $\dot{V}O_{2peak}$, 90% $\dot{V}O_{2peak}$ and during the first 10 min recovery ($P<0.001$, Figure 5.12A). P_vO_2 increased from rest during the final two bouts of cycling, and remained greater than rest until 10 min recovery ($P<0.001$, Figure 5.12B).

Digoxin. Plasma P_aO_2 and P_vO_2 were not changed by DIG.

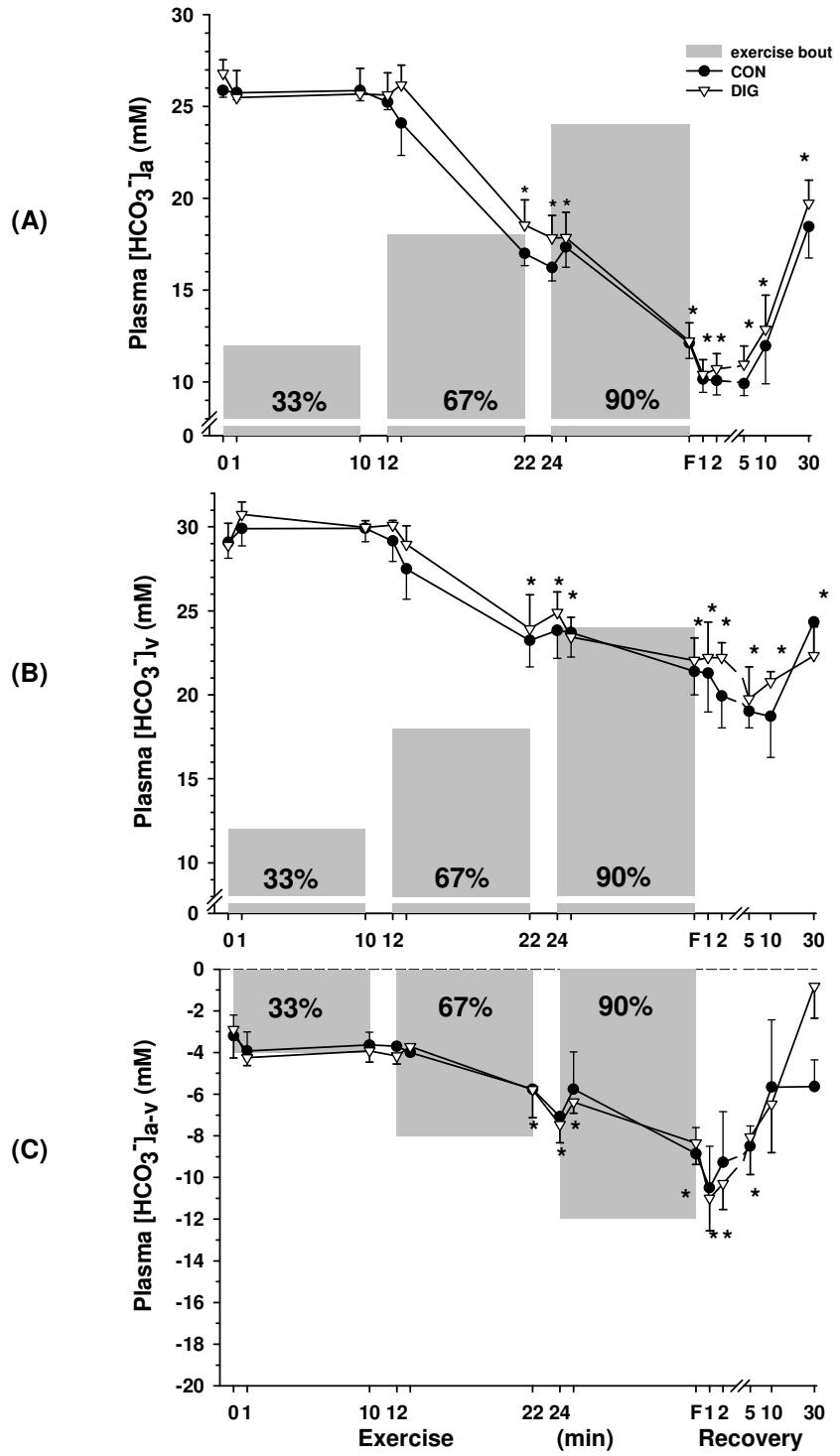

Figure 5.10. Effects of digoxin on plasma [HCO_3^-] at rest, during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial, (B) venous, and (C) calculated arteriovenous plasma [HCO_3^-] differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.001$ time main effect). Data expressed as Mean ± SEM, n = 7 for arterial; n = 5 for CON venous and arteriovenous differences, $n = 4$ for DIG.

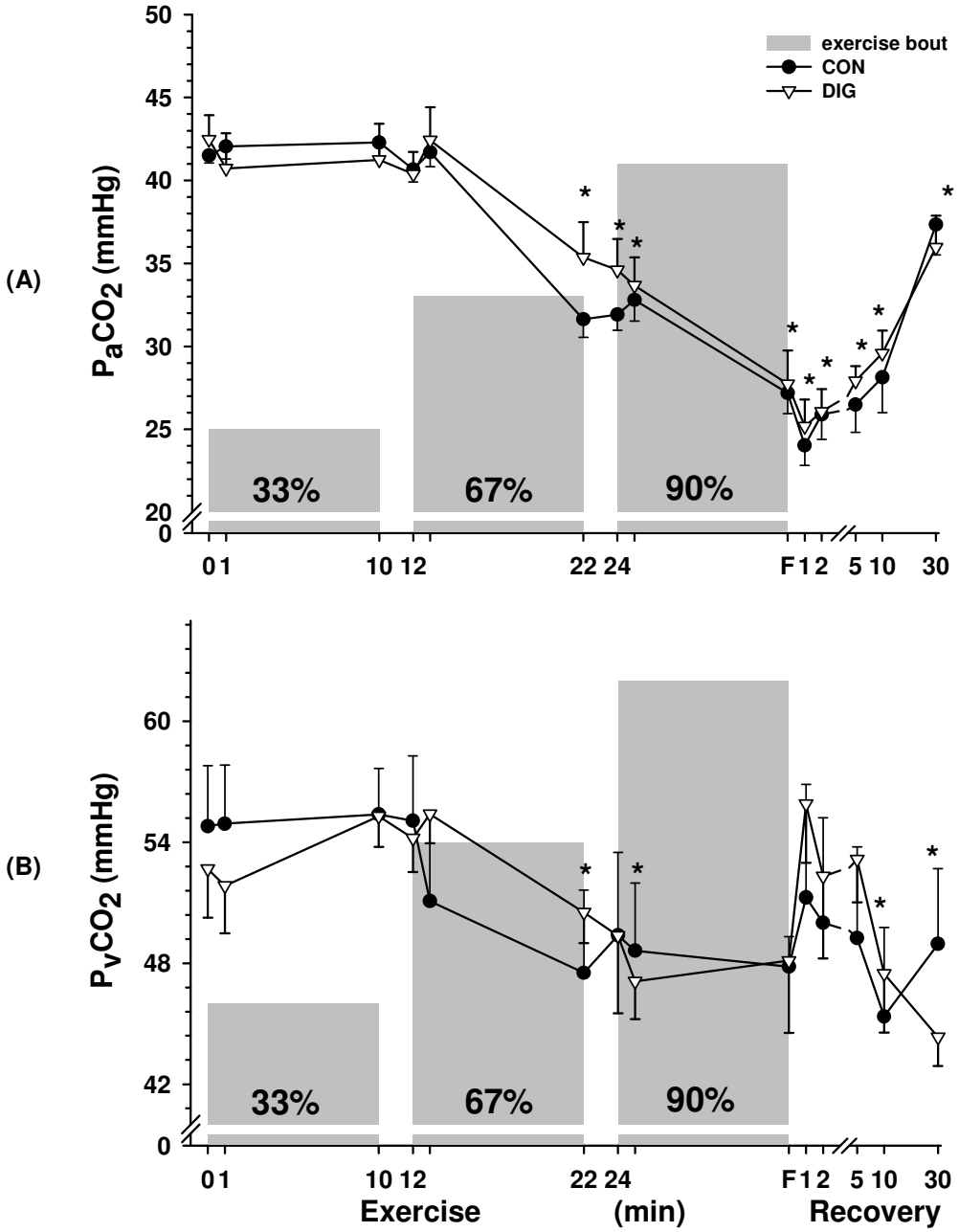

Figure 5.11. Effects of digoxin on plasma PCO_2 at rest, during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial, and (B) venous plasma [PCO_2] differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.001$, main effect for time). Data expressed as Mean ± SEM, $n = 7$ for arterial, $n = 5$ for venous.

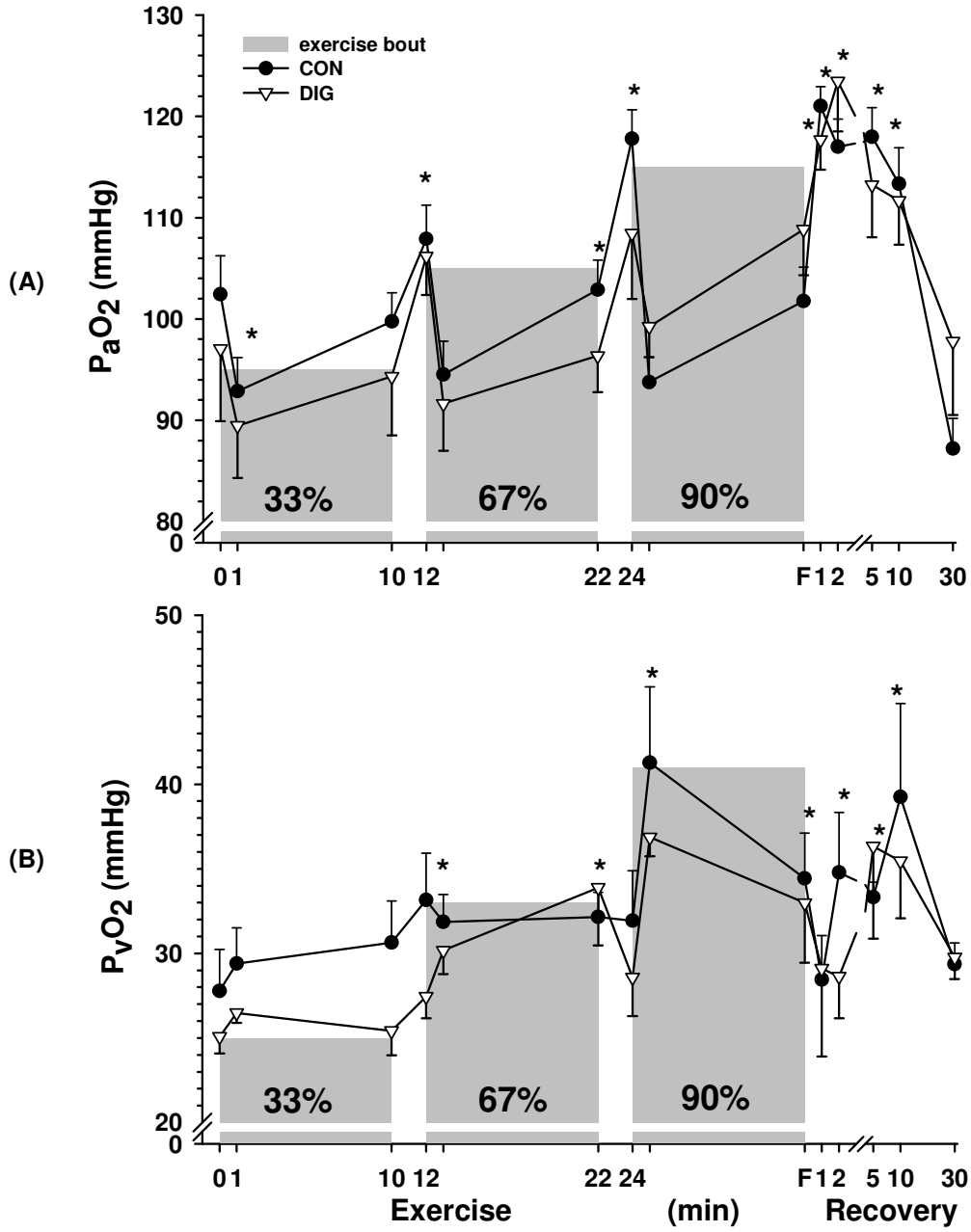

Figure 5.12. Effects of digoxin on plasma PO_2 at rest, during cycling exercise (shaded bars), to fatigue (F) and recovery. (A) arterial and (B) venous plasma [PO_2] differences, under CON (●) and DIG (▽) conditions. * Different from rest ($P<0.001$, main effect for time). Data expressed as Mean ± SEM, *n* = 10 for CON arterial, *n = 9* for DIG; *n = 7* for venous.

5.4 DISCUSSION

This study examined the effects of 14 days digoxin therapy on ionic, metabolic, and acid-base changes in arterial blood and the impacts of inactive forearm muscle on these in healthy humans at rest, during and bouts of cycling exercise at progressively increasing intensity. The first key findings were that circulating plasma [K^+] and exercise performance at 90% $\dot{V}O_{2peak}$ were not affected by DIG, despite serum digoxin concentration being within the optimal therapeutic range. Secondly, DIG did not have a major impact on metabolism and acid-base balance during exercise or recovery during large muscle mass exercise.

5.4.1 Digoxin effects on strong ions, metabolism, acid-base balance and performance

5.4.1.1 Serum digoxin concentration

Following 14 days of digoxin administration at 0.25 mg.day^{-1}, the mean serum digoxin concentration (SDC) was 0.8nM, or ~0.62 ng.ml^{-1}, within the optimal therapeutic range of ~0.65-1.15 nM or ~0.5-0.9 ng.ml^{-1}. See Chapter 4 for additional detail.

5.4.1.2 Digoxin does not impair plasma K^+ homeostasis during submaximal cycling exercise

This is the first study to comprehensively investigate the effects of DIG on plasma K^+ homeostasis during exercise with a large muscle mass in healthy humans. Despite therapeutic serum digoxin concentration being achieved, there was no change in plasma $[K^+]_a$, $[K^+]_v$ in blood draining inactive forearm muscles, or the corresponding $[K^+]_{a-v}$ at rest, during sub-maximal cycling exercise or in recovery. Similar to observations made in the previous chapter, [K^+] changes were remarkably consistent between DIG and CON. Forearm blood flow was not reported during leg cycling exercise and therefore K^+ influx/efflux from plasma traversing forearm muscle could not be calculated. However, it is unlikely that blood flow was affected by DIG as forearm blood flow did not change with DIG during forearm contractions in the same participants (Chapter 4). Blood flow to the inactive arm during cycling exercise may have increased above rest by ~2-fold (Ahlborg et al, 1975; Bevegaard et al, 1966), which would contribute to attenuation of arterial plasma K^+ and other electrolyte disturbances, and thus not limit transmembranous ion exchanges (Lindinger et al, 1990). Hence it is unlikely that inactive muscle K^+ influx/efflux was altered by DIG, consistent with the previous chapter. The lack of DIG effect on K^+ homeostasis was not affected by fluid shifts, as there was also no change in PV or BV, which is also consistent with findings during small muscle mass contractions (Chapter 4). A large $[K^+]_{a-v}$ was observed during exercise, which progressively widened with each bout of

increasing intensity, indicating net disappearance of K^+ from plasma across the forearm muscle. This most likely reflects muscular K^+ uptake, thus highlighting that NKA was significantly challenged and activated. Therefore the exercise model employed during these experiments was sufficient to exacerbate active muscle K^+ loss in the face of theoretical NKA inhibition by DIG.

Plasma [K^+] increased by ~0.2 to 0.3 mM with DIG in cardiac patients during cycling exercise (Norgaard et al 1991; Schmidt et al, 1995), with a total K^+ loss from the leg increasing by ~138% in DIG (Schmidt et al, 1995). Numerous concomitant factors such as decreased muscle mass (Strassburg et al, 2005), reduced muscle NKA content (Norgaard et al, 1990) and other morphological changes associated with inactivity are likely to have been already prominent in these patients; therefore the isolated effects of DIG on plasma [K^+] changes are complicated and subsequently difficult to compare to the present study. Digoxin administered to healthy participants in the present study is likely to have dispersed across a substantially greater area of skeletal muscle, thus minimising DIG binding effects to NKA compared to cardiac patients. Skeletal muscle [DIG] was not measured in this study; however SDC was lower than the previously reported range of 1.2 – 2.3 nM in these cardiac patients (Schmidt et al, 1995; Schmidt et al, 1993a; Norgaard et al, 1991). Thus it cannot be excluded that a higher DIG dose could have impaired K^+ homeostasis even in healthy individual. There is no current data that has previously demonstrated compensatory skeletal muscle NKA upregulation in digitised patients (Clausen 2003).

As part of a companion study, vastus lateralis muscle biopsies were extracted from the same participants at rest, during cycling exercise including fatigue, 3 hr recovery, and comprehensively analysed for DIG occupancy, NKA content and maximal in-vitro NKA activity. NKA content ([^{3}H] ouabain binding) and activity (3-O-MFPase) were not affected by DIG at rest; however digoxin removal with Digibind® antibodies revealed increased NKA content, with 7% digoxin occupancy. Protein abundance of NKA isoforms with DIG did not change, however α_2 and β subunits tended to increase with DIG (appendix 7). Therefore an adaptive compensatory upregulation of NKA in skeletal muscle appears to have been instrumental in preserving NKA functional capacity with chronic DIG in healthy humans. This also highlights remarkable self-preservation in otherwise healthy muscle to maintain K^+ homeostasis and subsequent muscle function (McKenna et al, 2008; Clausen 2003; Sejersted and Sjøgaard 2000).

5.4.1.3 Digoxin does not impair cycling exercise performance

It was hypothesised that DIG binding to NKA in skeletal muscle would exacerbate exercise induced K^+ loss, increasing muscle extracellular [K^+], which would impair contractile function and exercise performance. Despite achieving a therapeutically

relevant SDC, there was no effect on time to fatigue at 90% $\dot{V}O_{2peak}$. The same subjects also participated in additional experiments not reported in this chapter, whereby there was also no digoxin effect on quadriceps muscle strength and fatigability, or respiratory muscle function (Appendix 7). Muscle NKA content and maximal in-vitro activity were also unaffected by digoxin therapy in the same subjects (appendix 7), and in keeping with this, arterial [K^+] was not different between conditions. Therefore the hypothesis that DIG impairs cycling performance in healthy individuals under the conditions of this experiment is rejected. Consistent with our unchanged $\dot{V}O_2$ during each work rate and muscle function findings, Sundqvist and colleagues (1983) did not find any effects from 14 days DIG therapy on $\dot{V}O_{2max}$ or isokinetic muscle strength in well-trained humans. Nor was $\dot{V}O_{2max}$ changed in healthy untrained men (Russell & Reeves 1963), or muscle fatigue during 30% MVC sustained isometric forearm contractions (Bruce et al 1968). However, in contrast, Bruce and colleagues (1968) found impaired incremental treadmill running time following 7 days DIG in healthy individuals. Conflicting effects of DIG on exercise performance cannot be explained by dosage alone, as short term – high dose DIG administration was consistent between the Bruce et al (1968) and Russell & Reeves (1963) studies. None of these studies measured muscle NKA or DIG occupancy at rest or during exercise. Whilst DIG induced 7% occupancy of muscle NKA in participants of this study, it appears that compensatory upregulation of NKA in healthy individuals may have preserved skeletal muscle function, thus in effect countering DIG occupancy in these individuals. This could then account for a lack of effect on [K^+] and on performance.

5.4.1.4 Digoxin affects glycolysis and arteriovenous [H^+] difference.

Ouabain inhibition of skeletal muscle NKA in rats is associated with decreased lactate production (James et al, 1999) whist the reverse is evident with increased skeletal muscle NKA activation in rats (James et al, 1999) and in humans (Bundgaard et al, 2002). This is in keeping with skeletal muscle NKA preference for ATP via glycolysis (Clausen 2003). Therefore it was hypothesized that digoxin inhibition of NKA activity would reduce glycolysis associated with NKA energy demands and subsequently reduce lactate accumulation during large muscle mass exercise of increasing sub-maximal intensity.

Plasma Lac^- was lower during DIG in arterial plasma at 67% and in venous plasma at 33% $\dot{V}O_{2peak}$. These reflect either reduced Lac^- production or release from muscle via other glycolysis mediated events; or increased oxidation or clearance from muscle or

plasma. However, no other effects of DIG on plasma lactate were seen; although post exercise $[Lac^-]_a$ and $[Lac^-]_v$ appear lower during recovery, these were not significant. Furthermore no effects of DIG were observed for whole blood lactate. Thus the impacts of DIG on Lac^- during leg cycling exercise were small. Blood flow was not measured to the exercising legs or to the inactive forearm musculature, but there was no DIG effect on blood flow across exercising forearm muscle in Chapter 4. Therefore it is likely that blood flow changes with DIG did not affect the rate of Lac^- release or clearance from exercising muscle or uptake into inactive forearm muscle. It is unlikely that DIG caused mitochondrial changes, as there was no change in $\dot{V}O_2$ or respiratory exchange ratio (data not reported in results) at each sub-maximal bout of cycling exercise.

These results are largely consistent with Sundqvist et al (1983), who found no DIG effect on cubital venous serum lactate at rest, during exercise and recovery in well trained humans. They induced a serum digoxin concentration of 1.0 nM; however serum $[K^+]$ was unchanged at rest and no muscle NKA analyses were provided. This might suggest that a lack of DIG effect on NKA provides a rationale of unchanged serum lactate; however forearm contractions during cycling will release lactate into cubital veins, and the training status of participants and subsequent effects on muscle metabolic adaptations renders such conclusions difficult. Lactate production during large muscle mass exercise is lower in CHF patients taking DIG compared to controls (Okita et al, 1998; Näveri et al, 1997). However, this is likely to be exacerbated by concomitant effects of muscle atrophy and reduced muscle perfusion. That the digoxin effects on plasma lactate were only minor during cycling exercise is not surprising given the relatively small 7% DIG occupancy of NKA in skeletal muscle and compensatory NKA upregulation observed in this study (appendix 7).

The contribution of independent variables PCO_2 and [SID] that determine H^+ (Johnson et al 1996) are also considered here, given the effects that changes in lactate has on PCO_2, and the combined effects of lactate and other strong ions has on plasma [SID]. Plasma $[H^+]_a$ and $[H^+]_v$ were not affected by DIG, however $[H^+]_{a-v}$ was greater (more negative) during exercise and in recovery, suggesting less H^+ increase in plasma across the non-contracting forearm. Plasma PCO_2 was unchanged with DIG, thus the contribution of PCO_2 to the $[H^+]_{a-v}$ change with DIG is not substantial. Plasma $[SID]_a$ was lower in DIG at rest and 33% $\dot{V}O_{2peak}$, although not systemically so throughout exercise and recovery. The origin of the initial DIG effect on $[SID]_a$ was not caused by changes in Lac^-, rather by changes in Cl^-. As cycling exercise intensity increased, the decrease in plasma $[SID]_a$ was predominantly accounted for by a rise in plasma $[Lac^-]$ and $[Cl^-]$. As $[SID]_v$ decreased during exercise, $[Cl^-]_v$ did not change, but the rise in $[Lac^-$

$]_v$ exceeded the combined increases of $[K^+]$ and $[Na^+]$. Whilst the effects of DIG on plasma [SID] were only very minor, Lac^- contributes significantly to changes in arterial and venous [SID] during exercise and recovery, which might be an important determinant of the greater $[H^+]_{a-v}$ found across the non-contracting forearm during exercise and recovery with DIG. Plasma proteins and weak electrolytes were not assessed in this study, however exercise induced changes would be expected (Kowalchuk et al, 1988; Friesinger et al, 1987; Rossing et al, 1986). The effects of exercise induced changes in $[A_{tot}]$ on plasma H^+ would be presumably small (Kowalchuk et al, 1988). DIG effects on $[A_{tot}]$ is unlikely, given there was no effect of DIG on fluid shifts.

5.4.1.5 Plasma $[Cl^-]_a$ changes with digoxin during submaximal cycling

An interesting observation was the tendency for $[Cl^-]_a$ to be higher in DIG at rest and during the first two sub-maximal bouts of exercise. This is the first known report of Cl^- tending to change with DIG therapy in healthy humans. It is possible that a tendency for elevated $[Cl^-]_a$ with DIG may provide a stabilising effect on $E_{m,}$ however the mechanism of DIG effects on Cl^- is unknown and needs to be investigated further in a larger sample size. Putman and colleagues (2003) demonstrated a similar rise in arterial and venous plasma $[Cl^-]$ following 7 days of cycling training, which was also accompanied by a systematic decrease in arterial and venous plasma Lac^-. We also found that arterial and venous plasma Lac^- was reduced in DIG at a number of time points. Therefore it is plausible that changes in Cl^- during DIG accompanied changes in Lac^-, via a non-specific anion exchanger that has an affinity for Lac^-; or via alterations in other ion exchangers (Putman et al 2003). A compensatory upregulation of NKA was apparent (appendix 7). Similarly, corresponding compensatory upregulation of Na^+-K^+-$2Cl^-$ co-transporter (NKCC) might also be possible.

5.4.2 Effects of exercise and inactive forearm muscle on ionic and acid-base disturbances during leg cycling exercise.

Development of skeletal muscle fatigue during moderate to heavy exercise occurs in the presence of marked ionic and acid-base disturbances. It is also well known that inactive tissue is an important regulator of ionic homeostasis during exercise and recovery (Kowalchuk et al 1988; Lindinger et al 1990; Rolett et al 1990; Lindinger et al 1995; Bangsbo et al 1995). Exercise induced acidosis has historically been considered deleterious to muscle contractile properties and metabolism (see review by Jones 2008). However, the contribution of acidosis to fatigue is debatable, as numerous studies have shown that muscle fatigue occurs in humans whilst intracellular $[H^+]$ remains low (Hogan et al 1999; Bangsbo et al 1996), and that in rodent muscle, intracellular acidosis may actually have a protective effect on muscle function via

higher muscle Cl^- conductance (Nielsen et al 2001; Pedersen et al 2004, 2005). This thesis considers the physicochemical variables that contribute to acidosis, which includes the influence of strong ions, acting as the strong ion difference (Stewart 1985; Johnson et al, 1996).

5.4.2.1 Plasma K^+

As expected, plasma [K^+] increased progressively with each bout of cycling exercise, where arterial, venous [K^+] and arteriovenous [K^+] difference peaked during exercise at 90% $\dot{V}O_{2peak}$, at ~6.5, 5.0 and 1.2 mM respectively. These [K^+] were similar to those found by Wasserman and colleagues (1997) during leg cycling at 80% $\dot{V}O_{2peak,}$ where arterial [K^+] and veno-arterial [K^+] peaked at ~6.5 and 1.2 mM respectively. However their venous K^+ was considerably greater than in the present study, due to blood sampling from the femoral vein, which drained exercising leg muscles (Wasserman et al 1997). A lower [K^+] is expected in antecubital venous blood, which drains inactive forearm muscle, reflecting K^+ uptake by inactive muscle. Similar plasma [K^+] results have also been presented by Vøllestad et al (1994), where $[K^+]_a$ increased to ~6 mM during cycling exercise at 85% $\dot{V}O_{2peak.}$ Higher intensity bouts of sprint cycling exercise may elicit greater increases in $[K^+]_a$ to ~ 7 mM (McKenna et al, 1997a; Kowalchuk et al; 1990). K^+ uptake across inactive forearm was apparent at the end of 30 s sprint cycling exercise, evidenced by an $[K^+]_{a-v}$ of ~1.3 mM (Kowalchuk et al 1990). This was similar to the present study, which demonstrates that K^+ regulation during exercise is not just dependent on work rate. As expected, $[K^+]_a$ decreased rapidly in recovery, such that participants were hypokalemic by 5 min recovery. This arterial [K^+] "undershoot" is consistent with other forms of exercise and is probably due to increased NKA activation and concomitantly decreased muscle interstitial [K^+] (Sejersted & Sjøgaard 2000). During recovery the $[K^+]_{a-v}$ across the inactive forearm reversed from positive to negative values indicating a shift from net uptake by muscle to net release to the circulation. This effect compensates for and minimises the post-exercise arterial hypokalemia. We did not measure $[K^+]_{a-v}$ across the exercising leg muscle in this study, but it can be assumed that K^+ is also taken up by active muscle during recovery, as previously demonstrated following high intensity cycling exercise (McKenna et al, 1997a; Medbo et al, 2000; Bangsbo et al, 1995) and forearm muscle contractions (Chapters 3 and 4). Red blood cells may also contribute to K^+ regulation during exercise submaximal cycling exercise, however, as discussed in Chapter 4, conflicting results have been observed. Numerous studies have reported K^+ uptake into red blood cells during high intensity cycling exercise (Lindinger et al, 1992; McKelvie et al, 1991,

1992). In contrast, red blood cells did not take up K^+ during intense forearm exercise (Maassen et al, 1998), during submaximal knee extension exercise (Juel et al, 1999) or in venous blood during incremental cycling exercise (Bodemann et al, 1987; Juel et al, 1990). Juel et al (1999) suggested that metholological differences may account for these conflicting findings, and that obtaining red blood cell [K^+] directly from a fixed volume of sedimented cells is required to account for [K^+] fluctuations due to cell volume changes and transmembrane K^+ fluxes.

5.4.2.2 Plasma Na^+

Arterial plasma [Na^+] increased in the late stages of cycling exercise, and peaked at fatigue, ~9mM above rest. Venous plasma [Na^+] also increased progressively, although by a smaller magnitude, and changes in [Na^+] oscillated between apparent small net Na^+ uptake and release from inactive forearm. These changes were consistent with plasma Na^+ shifts found during cycling exercise of similar relative intensity (Putman et al 2003; Wasserman et al 1997). A similar increase in $[Na^+]_a$ has also been demonstrated following sprint cycling exercise (McKenna et al 1997a; Kowalchuk et al 1988). The rise in plasma [Na^+] was less than the decline in PV, thus indicating a net loss of Na^+ from the circulation into contracting muscle. The magnitude of plasma [Na^+] increase in the antecubital vein in the present study was consistent with observations made at the completion of sprint cycling exercise (Kowalchuk et al 1988). Na^+ fluxes across the inactive forearm during exercise and recovery were inconsistent, with no clear direction of net movement, which is in keeping with observations made during forearm exercise in Chapters 3 and 4 of this thesis; and also consistent with findings following moderate cycling exercise (Wasserman et al 1997) and moderate intensity arm cranking (Volianitis & Secher 2002). When stimulation of resting skeletal muscle is not particularly high, intracellular [Na^+] changes are minimal, due to; (i) low Na^+ influx with relatively few action potentials, (ii) likely increased NKA activation with circulating catecholamines and insulin, and (iii) restriction to the intracellular space in proximity to sarcolemmal membrane (Semb and Sejersted 1995). Na^+ influx into erythrocytes (Putman et al 2003) and exercising muscle has also been demonstrated during moderate intensity cycling (Putman et al 2003; Lindinger et al 1994) and sprint cycling (McKenna et al 1997a), and as such may provide an additional regulatory role in attenuating the decrease in [SID] within erythrocyte and plasma compartments.

5.4.2.3 Plasma Cl^-

Arterial plasma [Cl^-] changes were minor during the first two bouts of cycling exercise, with a small increase of ~3 mM occurring at fatigue, which is consistent with changes found during cycling exercise at 75% $\dot{V}O_{2peak}$ (Putman et al 2003) but lower than the

increase of ~6-7 mM following 30s sprint cycling exercise (Kowalchuk et al 1988; McKenna et al, 1997a). The $[Cl^-]_a$ decreased to below previous resting values during recovery, which was also consistent with $[Cl^-]_a$ recovery data reported by Kowalchuk and co-workers (1988) by a similar magnitude. There was no net change in $[Cl^-]_v$ across inactive forearm muscle, which is also consistent with Kowalchuk et al (1988).

Small increases in $[Cl^-]_v$ were found following immediately following 75% $\dot{V}O_{2peak}$ (Putman et al 2003) and 30s sprint cycling exercise (McKenna et al 1997a), however $[Cl^-]$ in the femoral veins draining exercising muscle during these two studies are expected to differ from forearm veins draining inactive tissue. We also did not find any exercise effects on $[Cl^-]_{a-v}$ across the forearm, whereas Kowalchuk and colleagues (1988) reported a net Cl^- uptake across forearm muscle immediately after exercise and during recovery. Whilst plasma $[Cl^-]$ changes are relatively minor during exercise, large changes in erythrocyte $[Cl^-]$ have been demonstrated during moderate intensity cycling exercise (Putman et al 2003). The erythrocyte membrane contains a non specific anion exchanger that has a strong affinity for Lac^- ions, therefore possibly also contributing to Lac^- uptake into erythrocytes (Deuticke et al 1982). Thus movement of Cl^-, coupled with Lac^- into erythrocytes, contributes to attenuating large increases in H^+ during heavy exercise (Putman et al 2003). Cl^- uptake into exercising muscle of differing mass has been previously observed (McKenna et al 1997a; Chapters 3 and 4), which is likely in the present study, and may also play an intrinsic role in preserving muscle function.

5.4.2.4 Plasma Lac^-

Arterial plasma $[Lac^-]$ increased substantially throughout exercise and peaked at 5 min recovery, before decreasing, and remaining ~7 mM greater than rest by 30 min recovery. Except for the first bout of mild-intensity exercise, a positive $[Lac^-]_{a-v}$ was found throughout exercise and recovery across inactive forearm muscle. The fate of this Lac^- taken up by inactive tissue is unknown, but assumed to have been predominantly oxidised (Brooks & Gaesser 1980), rather than converted to glycogen. Some suggest inactive muscle is more effective than other tissue to metabolise Lac^- (Ahlborg et al 1975, 1976). A rapid rise in $[Lac^-]_a$ and subsequent uptake across inactive forearm muscle was also found following sprint cycling exercise (Kowalchuk et al 1988), which highlights the importance of inactive tissue as a regulator of Lac^- from the arterial circulation. Historical perspectives previously suggested accumulation of lactate in muscle as a major contributor to fatigue (see review by Fitts 1994). However, recent findings refute these arguments, as elegantly demonstrated by skinned fiber preparations exposed to very high $[Lac^-]$, but at constant ionic strength, maintaining force production and Ca^{2+} integrity (Posterino et al 2001; Dutka & Lamb 2000). It is

unlikely that Lac^- played a significant fatiguing role during exercise in the current study. Whole blood [Lac^-] changes were consistent with plasma [Lac^-] observations, although at a lesser magnitude, which is expected given the additional time required for Lac^- released from muscle to diffuse into erythrocytes.

5.4.2.5 Acid-base balance

The independent variables PCO_2, [SID] and [A_{tot}] collectively determine [H^+] and [HCO_3^-] (Johnson et al 1996). PCO_2 and [SID] were also unchanged in arterial and venous plasma at 33% $\dot{V}O_{2peak}$, hence there was no change in $[H^+]_a$ from rest during 33% $\dot{V}O_{2peak}$. Arterial [H^+] increased by ~7 nM at 67% $\dot{V}O_{2peak}$, and by ~17 nM at 90% $\dot{V}O_{2peak}$, and the peak $[H^+]_a$ of ~66 nM occurred at 5 min recovery. This is consistent with $[H^+]_a$ observations made during 30s sprint cycling (McKenna et al, 1997a), and $[H^+]_a$ at 67% $\dot{V}O_{2peak}$ was similar to cycling at 75% $\dot{V}O_{2peak}$ (Putman et al, 2003). The $[H^+]_v$ was greater than $[H^+]_a$ at rest, and systematically higher throughout exercise, with exception to the final bout to fatigue, where arterial [H^+] was greater. $[H^+]_v$ continued to rise and peaked at 5 min recovery. These changes were consistent with those found in the inactive forearm immediately following sprint cycling (Kowalchuk et al 1988), however, contrary to our findings, $[H^+]_v$ remained greater than $[H^+]_a$ throughout recovery. Plasma $[H^+]_{a-v}$ was negative during the first 2 bouts of exercise, which signifies net gain of H^+ from plasma across inactive forearm muscle. However, there was net H^+ uptake into plasma across inactive forearm at fatigue and during recovery, except for 30 min recovery; indicating that inactive muscle is an important regulator minimising H^+ perturbations following high intensity exercise.

Arterial PCO_2 decreased rapidly throughout the remainder of exercise bouts and continuing for the first ~5 min recovery, before a directional change occurred. These changes reflected the reverse in observed H^+ movement in arterial plasma, and are consistent with observations made during steady state cycling (Putman et al 2003) and sprint cycling (McKenna et al 1997a; Kowalchuk et al 1988). As the exercise intensity increased during the present study, so did glycolytic energy demands, with subsequent increase in blood lactate accumulation. Therefore the decline in P_aCO_2 would have constrained any rise in $[H^+]_a$ changes in this study, similar to observations made by Putman et al (2003) during steady state cycling exercise. The increase in $[H^+]_v$ in the current study was not associated with CO_2 output per se from inactive forearm tissue, as P_vCO_2 decreased during exercise. Contrary to these findings, P_vCO_2 increased immediately following 30s sprint cycling exercise which indicates at least partial increase in CO_2 output from inactive forearm tissue. This is likely due to a decrease in

intracellular [SID] leading to a decrease in intracellular PCO_2, and subsequent increase in P_vCO_2. Also, a large oxygen deficit associated with supramaximal exercise is accompanied by a very large CO_2 output via the lungs (Kowalchuk et al 1988). Whilst measures were made to preserve forearm inactivity during their sprint trials (Kowalchuk et al 1988), some small inadvertent isometric and or concentric contractions by the forearms may have also occurred whilst supporting the upper body, thus potentially providing another source of CO_2 output by the forearm. During this study the forearm was secured to minimize movement. The integrity of inactive muscle status is subsequently supported by a lack of change during exercise in $C_{a-v}O_2$, and trivial changes in P_vCO_2, $[H^+]_v$ and $[K^+]_v$. In contrast, substantial increases in these respective indices were observed during forearm exercise in Chapter 4. Therefore the P_vCO_2 contribution to changes in H^+ would be considered negligible in the current study. The decrease in $[HCO_3^-]_a$ during exercise and into recovery can be attributed to the concurrent decrease in P_aCO_2.

The magnitude of decrease in $[SID]_a$ during exercise in this study is similar to changes in $[SID]_a$ following sprint cycling (McKenna et al 1997a; Kowalchuk et al 1988), steady state cycling (Putman et al 2003). The decline in $[SID]_a$ at 67% $\dot{V}O_{2peak}$ is predominantly due to the rise in $[Lac^-]_a$, whereas SID changes found at fatigue were counterbalanced by a significant increase in $[Na^+]_a$, therefore $[SID]_a$ did not change significantly from the previous bout of exercise. $[SID]_a$ decreased further during 90% $\dot{V}O_{2peak}$ which was mainly due to the decrease in $[Cl^-]_a$ and $[Lac^-]_a$, but attenuated by significant re-uptake of Na^+ and K^+. A similar trend prevailed for $[SID]_v$ across the inactive forearm during exercise and in recovery. However, Lac^- was also the major contributor to $[SID]_v$ changes found at fatigue.

Plasma proteins ($[A_{tot}]$) were not assessed in this study, although changes may have only been negligible or possibly only increased slightly due to a small net loss in plasma volume. $[A_{tot}]$ previously estimated from plasma [protein] increased by ~2 and ~3 mM in arterial and femoral venous plasma following 30s sprint cycling exercise (McKenna et al 1997a), where peak $[H^+]_a$ was similar to the present study, however, the changes in $[H^+]_v$ (draining exercising muscle) were far greater in McKenna et al (1997a) as were subsequent fluid shifts.

Therefore the large increase in $[H^+]_a$ and $[H^+]_v$ found during exercise and in recovery were predominantly due to the decline in [SID]; and $[Lac^-]$ contributed significantly to declines in SID in both the arterial and venous compartments. This is consistent with observations made following steady state cycling (Putman et al 2003), and also supports findings in arterial compartments following sprint cycling (McKenna et al

1997a; Kowalchuk et al 1988). Contrary to our findings, McKenna et al (1997a) found that changes in P_vCO_2 dominated changes in $[SID]_v$ following sprint cycling, although those observations were made from the femoral vein draining active muscle. Data from the present study also support the notion that the relative contribution of PCO_2, [SID] and $[A_{tot}]$ to changes found in H^+ vary considerably, depending on the mode, duration and intensity of exercise; and on the recovery time period reported. Also, that strong ions in addition to Lac^- contribute to exercise induced acidosis (McKenna and colleagues 1997a).

5.5 CONCLUSIONS

Plasma K^+ dynamics were unperturbed by digoxin during and in recovery from leg cycling exercise in healthy humans after 14 days DIG administration, despite achieving optimal serum digoxin concentration. These findings are consistent with unchanged K^+ dynamics during DIG in the same healthy humans undertaking small muscle mass exercise. As described in Chapter 4, this lack of change is likely due to compensatory up regulation of NKA. Tightly regulated K^+ homeostasis is consistent with K+ being a critical factor in maintaining contractile muscle function, and with exercise performance not being affected by DIG. Decreased glycolytic energy contributions in DIG were minor and limited to sub-maximal exercise. Plasma acid-base status was altered with DIG, which included a decrease in $[H^+]_{a-v}$. However consequent effects on cellular excitability are unknown, although altered acid-base status did not affect fatigue. A tendency to elevated plasma $[Cl^-]$ in DIG at sub-maximal workloads was observed, which may have contributed to stabilization of contracting muscle membrane potential. Systemic K^+ changes during progressive intensity sub-maximal cycling exercise, coupled with K^+ changes across inactive muscle and a wide $[K^+]_{a-v}$, suggest that NKA function was substantially challenged, therefore the exercise model was not a limiting factor contributing to a lack of DIG effect on K^+ homeostasis. Furthermore, the progressive widening of the $[K^+]_{a-v}$ during each bout of exercise also demonstrate the important regulatory role of inactive muscle, and not likely due to a decrease in forearm blood flow. These results suggest that exercising large muscle mass behaves in a similar way to exercising small muscle mass when DIG inhibits NKA in healthy humans.

CHAPTER 6 GENERAL DISCUSSION, CONCLUSIONS, & FUTURE PERSPECTIVES

7.1 GENERAL DISCUSSION

This thesis examined the effects of acutely altered acid-base status and digoxin on K^+ homeostasis, NKA function and fatigue during exercise with a small and large contracting muscle mass, in healthy humans. Acute ionic, metabolic and acid-base disturbances in response to exercise were also investigated due to their important regulatory roles in muscle function. These studies highlighted the importance of regulation of K^+ and of other electrolytes in maintaining skeletal muscle contractile function in healthy humans. The important regulatory role of active and inactive muscle in constraining the exercise-induced hyperkalemia was also demonstrated during small and large muscle mass contractions.

7.1.1 Modifying plasma K^+ homeostasis with alkalosis and digoxin – implications for exercise performance and fatigue

The consistent theme addressed in this thesis was that altered K^+ homeostasis would affect exercise induced muscle fatigue. In study 1, acute oral sodium bicarbonate ingestion induced alkalosis, which systematically lowered $[K^+]_a$ and $[K^+]_v$. This likely also contributed to a high intracellular-to-extracellular $[K^+]$ ratio and subsequent maintenance of membrane excitability within the myocytes. Consequently, finger flexion exercise performance was enhanced by ~25%. It was hypothesized that $[K^+]$ release would be reduced with alkalosis, based on findings in stimulated isolated rat muscle (Lindinger et al, 1990). However muscle K^+ release was in fact 49% greater at fatigue with alkalosis, which must be considered in the context of ~17% greater K^+ uptake rates into previously contracting muscle immediately after exercise. Greater K^+ reuptake with alkalosis most likely reflects greater forearm muscle NKA activity and possibly Na^+-K^+-$2Cl^-$ co-transporter activity (Gosmanov et al, 2003). Alkalosis decreases interstitial $[K^+]$ during larger muscle mass exercise (Street et al, 2005), however, NKA muscle analyses were not provided, nor have they been examined in previous alkalosis studies, therefore the mechanisms of altered $[K^+]_i$ during exercise in large muscle during exercise are also equivocal. Muscle contractions are also associated with increases in $[H^+]_i$ and $[H^+]_e$ (Street et al, 2001; Juel 2008), thus the contribution of H^+ to muscle fatigue should also considered via indirect effects of H^+ on K^+ homeostasis (Juel 2008). But also balanced against this are protective effects of acidosis on muscle contractile function (Nielsen et al, 2001; Pedersen et al, 2004, 2005). In study 2 and 3, it was hypothesized that chronic oral digoxin administration in healthy humans would block a significant fraction of NKA in skeletal muscle and

thereby would impair NKA function during exercise, exacerbate K^+ loss from contracting muscle and subsequently accelerate exercise-induced muscle fatigue. To the contrary, despite achieving a clinically relevant serum digoxin concentration of 0.8 nM, plasma [K^+] during exercise and recovery was unchanged, and exercise performance was not affected by digoxin in either study. Vastus lateralis muscle biopsies were extracted from the same participants in a companion study (appendix 7) and subsequently analysed for NKA content (^{3}H-ouabain binding) and activity (3-O-MFPase). Without digoxin antibody fragments (F_{ab}, Digibind®, GlaxoSmithKline, Melbourne, Australia) resting muscle [^{3}H]ouabain binding site content did not change (DIG, 352±54 vs CON, 353±42 pmol.g wet weight^{-1}). Resting skeletal muscle total protein content was also unaltered by DIG, thus [^{3}H]ouabain binding site content did not change when expressed relative to muscle total protein (DIG, 1789±367, vs CON, 1831±378 pmol.g protein^{-1}). However skeletal muscle [^{3}H]ouabain binding site content was 8.2% higher in DIG when measured with F_{ab} ($F_{ab,}$ 381±53 vs without F_{ab}, 352±54 pmol.g wet weight^{-1} P<0.05), signifying digoxin occupancy of 7% in DIG. Maximal in-vitro NKA activity in resting muscle was not affected by DIG when expressed relative to muscle wet weight (DIG, 300±53 vs. CON, 297±79 nmol.min^{-1}.g wet weight^{-1}), or protein content (DIG, 1533±372 vs. CON, 1514±369 pmol.min^{-1}.g protein^{-1}). These muscle observations are in keeping with the lack of plasma [K^+] changes presented in studies 1 and 2, therefore suggesting adaptive compensatory NKA upregulation.

The K^+ data in all 3 studies in this thesis was consistent with K^+ being a highly regulated variable during rest, exercise, and recovery, with K^+ shifts being strongly influenced by the size of contracting muscle mass and intensity of exercise. Whilst K^+ status is strongly linked to exercise performance outcomes in all 3 studies, and changes in K^+ were consistent with reduced fatigue, the data presented in studies 2 and 3 does not provide conclusive evidence that unchanged K^+ status and unchanged performance were exclusively linked.

Increased exercise performance with alkalosis in study 1 is consistent with 19-49% increases in performance previously demonstrated with alkalosis (Sutton et al, 1981; Costill et al 1984; Iwaoka et al, 1989). In study 1 there were also accompanying changes in acid-base balance (ie more alkaline), greater muscle Lac^- efflux, [Na^+], [Cl^-]$_v$ and Cl^- fluxes that likely contributed to an improvement in muscle performance. Interestingly, there were also numerous accompanying metabolic, acid-base and ionic changes during digoxin in studies 2 and 3, but these were without a discernable effect on small and large muscle mass exercise performance. An interesting observation was that in these studies with healthy young adults, plasma [K^+] homeostasis and muscle performance during exercise in studies 1 and 2 are at odds with previous observations

in rat muscle and in human cardiac patients. Partial inhibition of NKA by ouabain in isolated rat muscles in high K^+ solution accelerated the rate of force decline by up to 3-fold (Nielsen & Clausen, 1996; Clausen 2003), and K^+ regulation during exercise is impaired with digoxin in cardiac patients (Norgaard et al, 1991; Schmidt et al, 1995). However, it is difficult to extrapolate these findings to intact healthy human skeletal muscle, due to the concomitant muscle morphological challenges coexisting in cardiac patients, and the non-physiological status of isolated rodent muscle preparations. It cannot validly be argued that the small muscle mass exercise model is inappropriate to detect digoxin effects on K^+ homeostasis. This is evident given that substantial K^+ loss during exercise was apparent (via negative $[K^+]_{a-v}$ and forearm blood flow), and NKA activity was considerable, which was demonstrated via net K^+ uptake across active muscle during recovery in study 2. The experiments in studies 1 and 2 comprehensively examine the effects of digoxin administration on K^+ homeostasis and exercise performance in healthy humans. The lack of K^+ changes with DIG during exercise are novel, and inadvertently demonstrate that healthy tissue is remarkably adaptive and resilient to acute NKA inhibitory changes that would otherwise be expected to perturb NKA function in healthy skeletal muscle (McKenna et al, 2008; Clausen 2003; Sejersted and Sjøgaard 2000). Future studies may consider acute digitalisation in order to prevent compensatory NKA upregulation, and thus shed light on whether inhibited NKA in healthy human skeletal muscle perturbs K^+ homeostasis and exercise performance.

7.1.2 Plasma $[K^+]$ responses to small and large muscle mass exercise

In order to more fully understand the effects of alkalosis and digoxin on K^+ regulation and fatigue, it was essential to determine other ionic, acid-base, metabolic and cardiovascular responses to exercise. In study 1, submaximal concentric contractions of the finger flexor muscles barely perturbed systemic ionic, acid-base and metabolic states, but substantial increases in blood flow and ionic exchanges across contracting muscle were observed. These observations were consistent in study 2 during intermittent supramaximal finger flexion contractions. Rapid forearm muscle K^+ uptake during recovery following exercise demonstrated the important regulatory role of previously active muscle tissue in re-establishing K^+ homeostasis in both studies 1 and 2. As expected, the magnitude of blood flow, ionic, metabolic and acid-base disturbances were greater during intermittent supramaximal concentric contractions of the finger flexors in study 2 compared to study 1. Leg cycling exercise induced substantial systemic ionic, acid-base and metabolic disturbances, and uptake of K^+ into inactive muscle during exercise; demonstrating that inactive muscle is also critical in alleviating exercise- induced hyperkalemia.

The magnitude of plasma [K^+] disturbances varied between exercise mode, relative intensity and absolute work rate during control conditions. A mean work rate of ~3W was elicited in study 1, whereby peak exercise [K^+] rise above rest corresponded to ~0.45, ~1.0 and ~0.9 mM for $[K^+]_a$, $[K^+]_v$ and $[K^+]_{a-v}$ respectively. Venous [K^+] was measured across active muscle for studies 1 and 2, and across inactive muscle for study 3. A mean work rate of ~5W was elicited in study 2, with peak [K^+] rise above rest corresponding to ~0.35, ~1.3, and ~1.3 mM in $[K^+]_a$, $[K^+]_v$ and $[K^+]_{a-v}$ respectively. Muscle K^+ efflux at fatigue were -42.5 and -167.5 $\mu mol.min^{-1}$ in study 1 and 2 respectively. Plasma $[K^+]_a$ was slightly lower in study 2, despite a higher absolute work rate, which is probably due to the rest periods in between exercise bouts in study 2 (Figure 6.1). The greater $[K^+]_v$ rise above rest in study 2 corresponded to a proportional increase in work rate and blood flow compared to study 1 (Figure 6.1). Also, the undershoot of $[K^+]_v$ below that previously established at rest was consistent between study 1 and 2, and is in keeping with other forms of exercise (McKenna et al 1997a; Nielsen et al 2003; Juel et al 1990 Vøllestad et al 1994) which is likely due to increased NKA activity and also likely to a decreased interstitial [K^+]. Plasma $[K^+]_{a-v}$ decreased (became more negative) during each bout of exercise, with the peak change (most negative $[K^+]_{a-v}$) occurring during the first minute of exercise, which was consistent between studies 1 and 2. During recovery $[K^+]_{a-v}$ was rapidly reversed, due to cessation of K^+ efflux and NKA activity remaining very high. Plasma $[K^+]_{a-v}$ was greatest after the first minute of exercise and gradually diminished as exercise progressed which is consistent with large muscle mass exercise of low and very high intensities (Verberg et al, 1999; Nielsen et al 2003; Vøllestad et al 1994). Depression of maximal in-vitro NKA activity has been frequently observed during a range of exercise modes and intensities during exercise with large muscle mass (McKenna et al, 2006; Petersen et al, 2005; Fraser et al, 2002; Aughey et al 2005, 2006; Leppik et al, 2004; Fowles et al, 2002; Green et al 2007; Sandiford et al, 2005). However this phenomenon is unknown in small intact exercising human muscle. It is possible that NKA activity is not depressed during finger flexion exercise, given that the $[K^+]_{a-v}$ diminishes as exercise progresses in both studies 1 and 2.

The rise in arterial and venous [K^+] from rest to fatigue varied between respective exercise mode and intensity in each study (Figure 6.1). In study 3, lower $[K^+]_v$ and $[K^+]_{a-v}$ were found in comparison to during finger flexion exercise in studies 1 and 2 This was because the forearm muscle during leg cycling exercise was inactive, with subsequent K^+ uptake from the circulation rather than K^+ release, as occurred from the contracting forearm. An interesting observation was that plasma $[K^+]_a$ was lower during leg cycling

exercise at 33% $\dot{V}O_{2peak}$ than in finger flexion exercise despite the 20 and 12- fold difference in absolute power output compared to studies 1 and 2 respectively and that substantially less inactive muscle was available for K^+ clearance. The different [K^+] change is possibly due to muscle fibre recruitment relative to the size of contracting muscle mass, during low intensity cycling exercise.

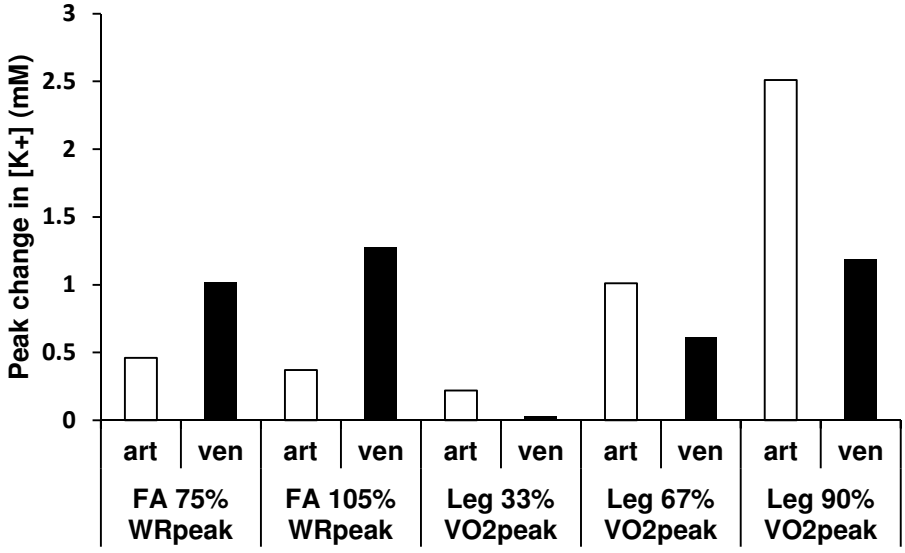

Figure 6.1 Rise in plasma arterial (□) and venous (■) [K^+] from rest to fatigue during submaximal finger flexion exercise (FA 75% WRpeak, ~3W), intermittent supramaximal finger flexion exercise (FA 105% WRpeak, ~5W), submaximal cycling exercise at 33% $\dot{V}O_{2peak,}$ (Leg 33% VO2peak, ~60W), submaximal cycling exercise at 67% $\dot{V}O_{2peak,}$ (Leg 67% VO2peak, ~188W), submaximal cycling exercise at 90% $\dot{V}O_{2peak}$ to fatigue (Leg 90% VO2peak, ~278W).

Blood flow to the inactive forearm was not assessed in study 3, however a 2-3-fold increase in forearm blood flow above resting values during leg exercise would be expected (Ahlborg et al, 1975; Bevegaard and Shepherd, 1966). In study 3, the inactive forearm was carefully secured and oriented to negate even small muscle movements and minimise all contractions, in an attempt to represent true resting muscle. Lindinger et al (1990) carefully secured an upper arm in an attempt to assess the regulatory role of inactive muscle tissue during multiple bouts of leg extension exercise. Plasma [K^+] changes during those experiments were of similar magnitude as described in study 3. Lindinger et al (1990) also extracted muscle samples from the inactive deltoid muscle, and found no change in glycogen or ATP during exercise and recovery; therefore they

could confidently assume that the resting arm muscle was metabolically inactive relative to leg muscle. Subsequently ionic changes reflected net uptake into muscle rather than release. Thus it is highly likely that the positive $[K^+]_{a-v}$ across inactive forearm muscle during cycling exercise in study 1 represented net K^+ uptake into inactive muscle, thus constraining increases in circulating $[K^+]$ due to K^+ loss from exercising muscle. Hence inactive tissue plays a fundamentally crucial role in the regulation of K^+ during exercise.

7.1.3 Changes in Na^+ and Cl^- during small muscle mass exercise with alkalosis

In study 1, with alkalosis, plasma $[Na^+]_a$, $[Cl^-]_v$ and Cl^- fluxes was higher, and $[Na^+]_v$ tended to be higher which collectively may preserve t-tubular $[Na^+]$ and stabilise cell membranes during contractions. Plasma $[Na^+]$ changes during alkalosis are consistent with others for $[Na^+]_v$ (Lindinger et al, 1999; Raymer et al, 2004; Street at al, 2005). Interestingly $[Cl^-]_a$ tended to be higher with digoxin during the first two sub maximal cycling bouts of exercise in study 3, however this did not affect exercise performance outcomes. This Cl^- observation is novel and has not been previously observed with digoxin, for which the mechanism is currently unknown and requires further investigation. However Cl^- changes were less in DIG compared to the clear effects observed in ALK. Therefore the impact of possible elevated Cl^- conductance and consequent cell membrane stabilization effects (Cairns et al, 2004) would be substantially less in DIG compared to ALK.

7.1.4 Reduced glycolysis during small and large muscle mass exercise with digoxin is not caused by any apparent NKA inhibition

In studies 2 and 3, it was hypothesized that digoxin inhibition of NKA activity would reduce NKA glycolytic energy demands and subsequently reduce lactate production in contracting skeletal muscle. This was on the basis that NKA has a preference for ATP via glycolysis (Clausen 2003), and increased NKA activation is associated with increased lactate production (James et al, 1999; Bundgaard et al, 2002), whereas inhibition of NKA by ouabain is associated with reduced lactate production (James et al, 1999).

Plasma $[Lac^-]_v$ and $[Lac^-]_{a-v}$ were in fact lower with digoxin in study 2, and plasma Lac^- was also lower at several sub-maximal time points throughout exercise in study 2, but both of these responses not due to any apparent reduced muscle NKA activity. Whilst lactate production and peak workload are lower in CHF patients taking DIG compared to controls during exercise (Okita et al, 1998; Näveri et al, 1997), there is also numerous additional muscle morphology changes in CHF patients that preclude reliable comparisons with healthy muscle exposed to NKA inhibition.

Therefore these observations are either due to reduced Lac^- production or release from muscle. Interestingly, Lac^- flux into plasma at fatigue was greater with alkalosis in study 1, which reflects enhanced glycolytic ATP production, and is likely to be due in part to increased NKA activity. This glycolysis/NKA rationale in alkalosis is consistent with those previously observations made when lactate production increased with increased NKA activation (James et al, 1999; Bundgaard et al, 2002).

The effects of acutely inhibited NKA activity on glycolysis have not been comprehensively explored in healthy human skeletal muscle during exercise, thus require further investigation

7.2 CONCLUSIONS

The key conclusions for this thesis include;

Study 1, Chapter 3

1. Oral sodium bicarbonate induced alkalosis attenuated muscle fatigue, evidenced by a ~25% improvement in submaximal finger flexion exercise performance by in healthy untrained humans.
2. Finger flexion exercise barely perturbed arterial plasma ions and acid-base status, but induced substantial arterio-venous changes.
3. Plasma $[K^+]_a$ and $[K^+]_v$ were systematically reduced with alkalosis, whereas the $[K^+]_{a-v}$ during exercise tended to be greater. Muscle K^+ efflux at fatigue was ~49% greater in alkalosis, consistent with lower $[K^+]$ and a bigger gradient for K^+ release. However the peak K^+ uptake was elevated during recovery in alkalosis, which suggests increased muscle NKA activity.
4. Forearm blood flow, plasma volume, blood volume, muscle O_2 content did not change with alkalosis**.**
5. Alkalosis elevated arterial and venous $[HCO_3^-]$, CO_2 content and PCO_2, and lowered arterial and venous $[H^+]$ at rest, during exercise and recovery. Lower circulating $[K^+]$ and greater muscle K^+ uptake, Na^+ delivery and Cl^- uptake with alkalosis, are all consistent with preservation of membrane excitability during exercise. This suggests that lesser exercise-induced membrane depolarisation may be an important mechanism underlying enhanced exercise performance with alkalosis.
6. During post-exercise recovery under control conditions, K^+ re-uptake across previously exercising muscle demonstrates the important regulatory role that active tissue plays in recovery from K^+ challenge in restoring K^+ homeostasis.

Study 2, Chapter 4

1. Oral digoxin administration for 14 days in healthy humans achieved a clinically relevant serum digoxin concentration, but did not perturb plasma K^+ homeostasis at rest, during exercise or recovery, nor did it contribute to fatigue during intermittent supramaximal finger flexion exercise.
2. Forearm blood flow increased substantially during exercise, but was not affected by DIG; nor were changes in plasma and blood volume, or forearm muscle O_2 uptake and CO_2 output.
3. The plasma $[K^+]_a$ increased slightly and $[K^+]_v$ increased dramatically with each bout of exercise. The $[K^+]_{a-v}$ decreased (more negative) rapidly from rest during the first exercise bout and together with substantial K^+ efflux from muscle, reflected net K^+ loss from contracting muscle throughout exercise. However, no digoxin treatment effects were found for any K^+ measures. A lack of DIG effect on K^+ homeostasis might reflect inadequate digitalisation or adaptive compensatory NKA upregulation.
4. Arterial $[HCO_3^-]$, PCO_2, C_aCO_2 and the $[Lac^-]_{a-v}$ were lower during exercise and recovery in DIG; and venous $[H^+]$ was lower at fatigue.
5. Acid-base disturbances during exercise were decreased with digoxin, possibly associated with a decrease in glycolysis, although unlikely to be associated with a decrease in NKA activity. These changes had no impact on exercise performance.

Study 3, Chapter 5

1. Oral digoxin administration for 14 days in healthy humans did not perturb plasma K^+ homeostasis or contribute to fatigue during submaximal cycling exercise of increasing intensity.
2. Blood flow was not measured across the inactive forearm, however it appears unlikely to have changed with DIG based on forearm blood flow results from study 2, and that exercise $\dot{V}O_2$ did not change with DIG. Plasma volume shifts from rest and across the inactive forearm were unaffected by DIG.
3. Arterial $[K^+]$, venous $[K^+]$ and the arterio-venous $[K^+]$ difference across the inactive forearm were ~6.5, ~5 and ~1.25 mM at fatigue respectively, however $[K^+]_a$, $[K^+]_v$ and $[K^+]_{a-v}$ were not affected by DIG. The lack of DIG effect on plasma K^+ homeostasis during exercise involving large muscle mass was possibly due to adaptive compensatory NKA upregulation in healthy skeletal muscle tissue.

4. Plasma $[Lac^-]_a$ tended to be lower during DIG at 67% $\dot{V}O_{2peak}$, and plasma $[Lac^-]_v$ was lower during DIG at 33% $\dot{V}O_{2peak.}$ However, DIG effects on glycolysis were small, and not associated with altered NKA. The $[SID]_a$ was lower in DIG at rest and 33% $\dot{V}O_{2peak,}$ but did not affect $[H^+]_a$ or exercise performance.
5. Plasma $[Cl^-]_a$ tended to be greater in DIG at rest to 67% $\dot{V}O_{2peak}$, although the associated mechanism is currently unknown.
6. Inactive muscle also plays a substantial role in the regulation of strong ions during sub maximal cycling exercise at increasing intensities
7. Adaptive compensatory NKA upregulation with DIG in healthy humans also demonstrates remarkable self-preservation in otherwise healthy tissue to maintain K^+ homeostasis and subsequent muscle function.

7.3 FUTURE PERSPECTIVES

Whilst these studies were designed to examine altered NKA and resultant plasma K^+ perturbations in young healthy adults, it would be beneficial to investigate NKA functional changes with age, particularly with regard to studies 2 and 3, given that patients suffering CHF that are medicated with DIG are typically from older age groups. Future research should consider exploring the specific role of K^+ transport pumps and K^+-channels, along with H^+ transporters and H^+ exchangers in muscle to uncover the mechanisms associated with improved K^+ homeostasis with alkalosis. This could be best achieved in small muscle mass by integrating arterio-venous $[K^+]$ and $[H^+]$ differences across active contracting tissue with concurrent muscle tissue extraction for respective muscle counterpart analyses. An alternative research design could also adopt the well established microdialysis technique for interstitial analyses, coupled with corresponding muscle analyses. Whilst extracting muscle tissue samples via the needle biopsy technique poses significant technical and safety challenges, the quadriceps may be a more logical site of interest compared to the forearm.

In studies 2 and 3, chronic DIG for 14 days achieved a therapeutic serum DIG concentration, but did not perturb K^+ homeostasis during exercise in healthy participants; likely due to an adaptive compensatory upregulation of NKA . Therefore future researchers should consider the possibility that 1-2 days acute administration of DIG may impair a small fraction of NKA without inducing compensatory upregulation. This should include serum and muscle digoxin concentration analyses at regular intervals within the 1-2 day time frame, and therefore exclude the side effect of compensatory NKA upregulation that appears to co-exist with chronic digoxin treatment in healthy human muscle tissue.

Skeletal muscle fatigue is associated with a complex and comprehensive series of multifactorial physiological processes. The studies within this thesis have focussed on K^+ disturbances in particular, along with numerous coexisting ionic, acid-base and metabolic disturbances in response to small and large exercising muscle mass exercise, and theoretically attenuated/exacerbated by upregulation and downregulation of NKA. Exercise performance improved when K^+ homeostasis was improved and was unchanged when K^+ homeostasis was unchanged. This is consistent with an important link between NKA function and subsequent K^+ homeostasis and exercise performance. Whilst the body of knowledge containing K^+ regulation and skeletal muscle function and fatigue has increased greatly over the previous 2-3 decades, further research in the field of muscle and extracellular K^+ regulation is required to elaborate on key mechanisms which will substantially improve understanding of skeletal muscle function within healthy and diseased tissue across expansive population demographics.

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APPENDICES

The following appendices are attached;

Appendix 1 The Nernst equation

Appendix 2 The Goldman Constant Field Equation

Appendix 3 Digoxin characteristics

Appendix 4A Study 1 subject informed consent and health/medical screening

Appendix 4B Study 2 & 3 subject informed consent and health/medical screening

Appendix 5 Forearm geometric calculation

Appendix 6 Study 2 & 3 dietary guidelines

Appendix 7 **Digoxin upregulates skeletal muscle Na^+,K^+-ATPase but does not alter muscle function in healthy humans**
Michael J. McKenna, Aaron C. Petersen, Xiaofei Gong, Simon Sostaric, Craig Goodman, Andrew Garnham, Juan Aw, Collene Steward, Kate T. Murphy, Kate Carey, Henry Krum, David Cameron-Smith and Rodney J. Snow

Appendix 8A Raw data – study 1

Appendix 8B Raw data – study 2

Appendix 8C Raw data – study 3

APPENDICES

Appendix 1

The Nernst Equation.

$E_K = RT/FZ_K \; ln \; ([K_o^+]/[K_i^+]) = 61.5 \; log \; ([K_o^+]/[K_i^+])$ at 37°C

where E_K= equilibrium potential for K^+; Z_K= valence of K^+ (+1); $[K_o^+] = [K^+]$ outside the cell; $[K_i^+] = [K^+]$ inside the cell; R= gas constant; T= absolute temperature; F= the faraday (number of coulombs per mole of charge).

Appendix 2

The Goldman Constant Field Equation.

$$V = \frac{RT}{F} \; ln \; \frac{P_{K+}[K_o^+] + P_{Na+}[Na_o^+] + P_{Cl-}[Cl_i^-]}{P_{K+}[K_i^+] + P_{Na+}[Na_i^+] + P_{Cl-}[Cl_o^-]}$$

where; V= membrane potential; R= gas constant; T= absolute temperature; F= faraday; P_{K+}, P_{Na+}, P_{Cl-},= permeability of the membrane to K^+, Na^+, and Cl^-; $_i$ and $_o$ = inside and outside of the cell.

Appendix 3 Digoxin characteristics (MIMS annual, 2005)

3.1 Composition

Lanoxin Tablets contain Digoxin 0.250 mg, Lactose, maize starch, rice starch, magnesium stearate.

3.2 Description

Digoxin has the molecular formula $C_{14}H_{64}O_{14}$ (CAS - 20830 - 75 - 5) with a molecular weight of 781.0. It is practically insoluble in water and in ether and slightly soluble in alcohol. Digoxin is obtained from the leaves of Digitalis lanata and occurs as odourless, colourless or white crystals or a white or almost white powder.

3.3 Distribution

With therapeutic plasma concentrations, about 20 - 30 % of digoxin in blood is bound to plasma proteins. Digoxin protein binding is not appreciably changed in uraemic patients. Patients with severe renal impairment have smaller apparent volumes of distribution of digoxin than do normal subjects.

3.4 Elimination

Digoxin has an elimination half-life of 34 - 44 hours. In patients with renal failure the elimination half-life is increased, or example in anephric patients the half-life is about 4.5 days or longer. Elimination half-life is prolonged in hypothyroid patients and decreased in hyperthyroid patients. In undigitalised patients, institution of a fixed daily dose of digoxin maintenance therapy without an initial loading dose results steady-state plasma concentrations after 4 - 5 elimination half lives (about 7 days in patients with normal renal function). In most patients, only small amounts of digoxin are metabolised, but the extent of metabolism is variable and may be substantial in some patients. Some metabolism presumably occurs in the liver, but digoxin is also apparently metabolised by bacteria within the lumen of the large intestine following oral administration and possibly after biliary elimination following parenteral administration. Digoxin is excreted mainly in the urine, principally as unchanged drug, by glomerular filtration and active tubular secretion; tubular resorption may also occur. In most patients, small amounts of reduced metabolites are also excreted in urine. However, in some patients, about 40% or more of orally administered digoxin excreted in urine will consist of reduced metabolites. In healthy individuals, about 50 - 70% of an IV dose is excreted unchanged in urine. Small amounts of cardioactive metabolites and unchanged digoxin are also excreted in the bile and faeces. See Appendix 4 for DIG indications, contraindications, precautions, interactions, dosage & administration.

3.5 Dosing and toxicology

The use of digoxin in heart failure should be based on principles that optimum doses are not necessarily maximum tolerated doses, and that a small dose improves cardiac

performance (MIMS annual, 2005). After oral administration of 0.75-1.5 mg, the onset of digitisation occurs in 30 - 60 minutes. Determining the serum digoxin concentration using radioimmunoassay can assess the suitability of digoxin regimes. Optimum levels are 0.5 - 2 $ng.ml^{-1}$. Digoxin is excreted exponentially, with an elimination half-life of 36-48 hours in patients with normal renal function, resulting in ~ 30% loss daily, therefore 7 days treatment is effective for steady-state (Hauptman and Kelly, 1999).

Digoxin therapy may induce ECG changes, such as premature ventricular contractions (Hauptman and Kelly, 1999). Hyperkalemia may exacerbate digitalis induced conduction delays, but can be treated rapidly with digoxin specific fab antibody fragments (Clausen, 1998). Other symptoms associated with chronic digoxin therapy may include; anaorexia, nausea, vomiting and abdominal pain. While controversy exists with regard to ideal serum digoxin levels, there was a trend of reduction in hospitalisation and death from heart failure in those CHF patients administered therapeutic digoxin doses in the recent prolific Digitalis Investigation Group Trial (1997). This randomised study comprised 6800 patients investigating digoxin therapy vs digoxin withdrawal in patients exhibiting LVEF < 40% in sinus rhythm.

3.6 Serum Digoxin Assay

The Multigent™ Digoxin System assay, (a homogeneous particle enhanced turbidimetric immunoassay) was used for the quantitative *in vitro* measurement of digoxin in human serum. Analyses were completed in the clinical biochemistry laboratory at the Alfred Hospital, Melbourne. Serum was collected by standard venepuncture, allowed to clot and centrifuged at 8000-10000 RCF x 10min. Samples were analysed fresh where possible, otherwise stored for up to 48hrs at 2-8℃ prior to being tested. The Multigent™ Digoxin System assay was calibrated using a full six-point calibration procedure. For quality control, a minimum of two levels of controls spanning the medical range was run every 24hrs. The Multigent™ Digoxin assay accurately quantitates digoxin concentrations in human serum containing up to 6.4 nM (5.0$ng.ml^{-1}$). Further detailed information can be found via the distributor, Abbott Laboratories, Inc. Abbot Park, IL 60064 USA.

Appendix 4A

Appendix 4A.1 Study 1 - subject informed consent

Victoria University of Technology
Standard Consent Form for Subjects
Involved in Experiments

CERTIFICATION BY SUBJECT

I,
of

certify that I have the legal ability to give valid consent and that I am voluntarily giving my consent to participate in the experiment entitled:
"Effect of bicarbonate ingestion on muscle potassium release and fatigability during exercise in humans."

being conducted at Victoria University of Technology by:
Dr Michael McKenna, Mr Simon Sostaric, Dr Steve Selig, Dr Sandford Skinner and Dr David Crankshaw.

I certify that the objectives of the experiment, together with any risks to me associated with the procedures listed hereunder to be carried out in the experiment, have been fully explained to me by:
Mr Simon Sostaric and Dr Michael McKenna
and that I freely consent to participation involving the use on me of these procedures.

Procedures:
1. Anthropometric measurements (forearm size)
2. Maximal incremental forearm exercise
3. Ingestion of either sodium bicarbonate or calcium carbonate
4. Venous occlusion plethysmography measurements (forearm blood flow)
5. Radial artery and antecubital vein catheterisation and blood sampling

I certify that I have had the opportunity to have any questions answered and that I understand that I can withdraw from this experiment at any time and that this withdrawal will not jeopardise me in any way.

I have been informed that the confidentiality of the information I provide will be safeguarded.

Signed: **.....** **}**

Witness other than the experimenter: **}** **Date: .....**

.....}

Any queries or complaints about your participation in this project may be directed to the experimenter, or to the Secretary, Human Research Ethics Committee, Victoria University of Technology, PO Box 14428 MMC, Melbourne, 3000 (telephone no: 03-9688 4710).

Appendix 4A.2 SUBJECT INFORMATION:

Investigators- Dr Michael McKenna, Mr Simon Sostaric, Dr Steve Selig
Department of Physical Education and Recreation, Victoria
University of Technology
Dr Sandford Skinner
Department of Physiology, The University of Melbourne
Dr David Crankshaw
Department of Surgery (Royal Melbourne Hospital),
The University of Melbourne

Aims of study- Potassium is released from muscles during exercise and may lead to fatigue. The aim of the study is to determine whether sodium-bicarbonate ($NaHCO_3$) ingestion may improve potassium regulation and exercise performance.

Subject participation- You will be required to attend V.U.T on three seperate occassions, approximately one week apart. In the 24 hours prior to each visit, you will be asked to avoid any intense exercise and substances such as caffeine, alcohol, or other drugs and to record all exercise, fluid and food intake 24 hours prior to the first trial. This enables the same pre-trial conditions to be duplicated for subsequent trials. Please fast for at least 2hrs before all three trials. Each trial will require about 2 hours of your time.

Forearm exercise tests- A specially made handgrip dynamometer for finger flexion will be used. Whilst lying on your back with forearm supported, you will flex fingers to lift weights via a pulley system. Since you will be unaccustomed to this type of exercise, you may experience some muscle soreness following the first exercise test. However, this is expected to disappear within a few days.

Forearm blood flow- A technique called venous occlusion plethysmography will be used to measure blood flow during exercise. A low pressure cuff is placed around the upper arm and a high pressure cuff placed around the wrist. These cuffs, when inflated briefly, will restrict blood flow leaving the arm and blood flow into the hand (same feeling as having your blood pressure taken). There is no undue risk associated with this procedure and should you experience anything more than discomfort, the cuffs will be immediately deflated (pressure released).

Exercise testing procedures- The study will be conducted in the Human Performance Laboratory at Victoria University of Technology, Footscray Campus (Rm L305, building L). The initial visit will involve forearm measurements to determine volume of muscle; an incremental forearm exercise test to fatigue, necessary to determine work rate peak; and a familiarisation trial, giving the subject and investigators an idea of what to expect in the experimental trial.
During the second and third visits, you will complete incremental forearm exercise to fatigue on a forearm dynamometer under control and experimental conditions. The final two visits involve blood sampling.

Experimental Trial- You will undergo two trials on two separate days. Three hours before the start of the second and third trial, you will ingest sodium bicarbonate **or** calcium carbonate (a placebo) capsules in five equal dosages with a total of 1 litre of water (0.3g/kg.bw).All trials will follow a double blind procedure (neither you or the investigators will know which capsules you ingest).Thirty minutes prior to the commencement of each trial, teflon catheters will be inserted into a vein of the exercising arm and in an artery of the non exercising arm. The total volume of blood taken in each trial will be 140ml, less than one quarter of that taken in a blood bank donation. Blood samples will be taken at rest, during exercise and recovery. Blood samples will be analysed for blood gases, ions, plasma pH, metabolites, catecholamines,

haemoglobin and haematocrit. Blood flow measurements will be made immediately following blood samples.

Venous catheterisation- Blood samples will be taken during rest, exercise and recovery via a catheter placed in the exercising arm. The catheter consists of a needle and teflon tubing. The tubing is fed over the top of the needle on entering the vein. The needle is then withdrawn, leaving only the teflon tubing in your vein for the remainder of the experiment. A tap (stopcock) is placed into the tubing so the flow of blood along the tubing can be altered at will. This procedure allows the taking of multiple blood samples without the need for multiple venepunctures (puncturing of the vein). Each time a blood sample is taken, a small volume of heparinised saline will be injected to clear the catheter and keep it patent. Catheterisation is slightly uncomfortable, with minimal possibility of bruising and infection. The use of sterile, disposable catheters, syringes, single dose vials and aseptic techniques will markedly reduce the possibility of infection. Only qualified and experienced staff will be used in order to prevent complications. Although the possibility of infection and bruising is quite small, if by chance it does eventuate, inform us immediately and then consult your doctor.

Arterial catheterisation for blood sampling- A similar catheter will be used as above, but will be inserted into the radial artery (wrist) of the non exercising arm. Arterial puncture and catheterisation is more difficult and may involve more discomfort and bruising formation than with venous punctures. Pain is minimised by use of a local anaesthetic in the skin and near the artery, whilst bleeding and bruising are minimised through use of appropriate pressure techniques for an adequate amount of time after arterial puncture or removal of the catheter. Infection is unlikely as only sterile, unused disposable instruments, single dose vials and aseptic techniques will be used. All arterial catheterisations will be performed by an experienced medical practitioner, who will remain throughout the entire testing and recovery procedures.

Although the possibility of infection and significant bruising is quite small, you should inform us immediately and consult your doctor if in the 12hrs following the procedure swelling and/or pain increases at the site.
By signing the informed consent form you are indicating that the tests and procedures have been explained to you and are understood by you. Also, it is accepted by the investigators and by yourself that you are participating voluntarily in the study and that you are free to withdraw from the investigation at any time without ill-repute. Thank you for your cooperation.

Contact Numbers:

Mr Simon Sostaric	**(W) 9248 1133**
Dr Michael McKenna	**(W) 9688 4499**
Dr Sandy Skinner	**(W) 9344 5830**
Dr David Crankshaw	**(W) 9342 7925**

Appendix 4A.3 CARDIOVASCULAR RISK FACTOR QUESTIONNAIRE

In order to be eligible to participate in the experiment investigating:**"Effect of bicarbonate ingestion on muscle potassium release and fatigability during exercise in humans"**
You are required to complete the following questionnaire which is designed to assess the risk of having a cardiovascular event occurring during an exhaustive exercise bout.

Name: _____ Date: _____

Age: _____ years Weight: _____ kg Height: _____ cms

Give a brief description of your average activity pattern in the past 2 months:
_____

_____

_____

Circle the appropriate response to the following questions.

1.	Are you overweight?	Yes	No	Don't know
2.	Do you smoke?	Yes	No	Social
3.	Does your family have a history of premature cardiovascular problems (eg. heart attack, stroke)?	Yes	No	Don't Know
4.	Are you an asthmatic	Yes	No	Don't Know
5.	Are you a diabetic?	Yes	No	Don't Know
6.	Do you have a high blood cholesterol level?	Yes	No	Don't Know
7.	Do you have high blood pressure?	Yes	No	Don't Know
8.	Are you on any medication?	Yes	No	

If so, what is the medication? _____

9. Do you think you have any medical complaint or any other reason which you know of which you think may prevent you from participating in strenuous exercise? No
Yes, please elaborate _____

I, _____, believe that the answers to these questions are true and correct.

Signed: _____ Date: _____

APPENDIX 4A.4

ARTERIAL & VENOUS CANNULATION QUESTIONNAIRE:

NAME: _____

ADDRESS: _____
DATE: _____ **AGE:** _____ **years**

1. Have you or your family suffered from any tendency to bleed excessively? (eg. Haemophilia) or bruise very easily? Yes No Don't Know
   If yes, please elaborate..._____
   _____

2. Are you allergic to local anaesthetic? Yes No Don't Know
   If yes, please elaborate..._____
   _____

3. Do you have any skin allergies? Yes No Don't Know
   If yes, please elaborate..._____
   _____

4. Have you any allergies? Yes No Don't Know
   If yes, please elaborate... _____
   _____

5. Are you currently on any medication? Yes No Don't Know
   If yes, what is the medication? _____
   _____

6. Do you have any other medical problem? Yes No
   If yes, please elaborate... _____
   _____

7. Have you ever fainted when you had an injection or blood sample taken? Yes No Don't know
   If yes, please elaborate_____

8. Have you previously had heparin infused or injected? Yes No Don't know
   If yes, please elaborate_____

9. Do you or other members of your family have Raynauds disease, or suffer from very poor circulation in the fingers, leading to painful fingers that turn white/blue? Yes No Don't know

If yes, please elaborate_____

To the best of my knowledge, the above questionnaire has been completely accurately and truthfully.

Signature: _____ Date: _____

Appendix 4B

Appendix 4B.1 Study 3 & 4 subject informed consent

Victoria University of Technology

Consent Form for Participants Involved in Research

INFORMATION TO PARTICIPANTS:

We would like to invite you to be a part of a study investigating the effects of high intensity exercise on skeletal muscle fatigue

CERTIFICATION BY PARTICIPANT

I,
of

certify that I am at least 18 years old and that I am voluntarily giving my consent to participate in the experiment entitled: **"The effects of a standard clinical dose of digoxin on potassium regulation in muscle and blood, and muscle fatigability during exercise in healthy young volunteers"**
being conducted at Victoria University of Technology by:
Associate Professor Michael McKenna; Associate Professor Henry Krum; Mr Simon Sostaric

I certify have read, or had read to me in my first language, and I understand the Participant Information version 1 dated 13th May 2003.

I certify that the researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

I understand that I will be given a copy of the Participant information and Consent Form to keep.

I certify that the objectives of the experiment, together with any risks to me associated with the procedures listed hereunder to be carried out in the experiment, have been fully explained to me by: **Assoc Prof Michael McKenna, Assoc Prof Henry Krum and Simon Sostaric**
and that I freely consent to participation involving the use on me of these procedures.

Procedures:
1. Preliminary participant screening (blood sample plus ECG Analysis)
2. Forearm anthropometry (length and size measurements)
3. Maximal incremental exercise test of the finger flexor muscles
4. Maximal incremental test and submaximal test on a cycle ergometer
5. Blood flow measurements by method of venous occlusion plethysmography
6. Maximal muscle function test on a Cybex isokinetic dynamometer
7. Digoxin and placebo administration under experimental conditions
8. Arterial catheterisation and blood sampling during rest, exercise and recovery
9. Antecubital venous catheterisation and blood sampling during rest, exercise and recovery
10. Muscle biopsies at rest and during maximal incremental exercise

I certify that I have had the opportunity to have any questions answered and that I understand that I can withdraw from this experiment at any time and that this withdrawal will not jeopardise me in any way.

Victoria University of Technology
PO Box 14428
MELBOURNE CITY MC VIC 8001
Australia

Telephone:
(03) 9688 4432
Facsimile:
(03) 9688 4891

School of Human Movement, Recreation and Performance
Footscray Park Campus
Building L, Ballarat Road, Footscray

I have been informed that the information I provide will be kept confidential.

Participant's name: ……..……..…….

Signed: .....…….....…….... Date: ……..……..

Name of witness other than the experimenter: ……

Signed: .....……..... Date: .....…..…….....

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher's Name (printed) ……

Signature Date

* A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the Consent Form must date their own signature.

Appendix 4B.2 PARTICIPANT INFORMATION

Title:

The effects of a standard clinical dose of digoxin on potassium regulation in muscle and blood, and muscle fatigability during exercise in healthy young volunteers

Investigators.
Associate Professor Michael McKenna, Mr Simon Sostaric,
School of Human Movement, Recreation & Performance, Victoria University
Associate Professor Henry Krum
Department of Epidemiology and Preventive Medicine Monash University, Alfred Hospital

You are invited to take part in this research project, which will study the effects of a standard clinical dose of digoxin on potassium regulation in muscle and blood, and muscle fatigability in healthy young volunteers.

This Participant Information and Consent Form is **10** pages long. Please make sure you have all of them. This Participant Information contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the Participant Information and Consent Form to keep as a record.

Aims of study.

Digoxin is a drug taken by many patients with heart failure, to increase the performance of their heart. We anticipate that it might make limb muscles weaker and more easily fatigued. This project therefore investigates the effects of digoxin on muscle strength, fatigue and the regulation of potassium in muscle and blood during exercise, in healthy individuals. The knowledge gained from this study may have important implications for the clinical use of digoxin.

A total of 16 people will participate in this project. You are invited to participate in this research project as a healthy active young adult

This study is being sponsored by Victoria University of Technology. This trial has been initiated by the investigator, Assoc/Prof Michael McKenna. The results of this research may be used to help researcher Simon Sostaric to obtain a degree.

Participant Involvement and Overview of Testing.

Participants will be requested to attend an initial medical screening session, followed by a further eight exercise testing sessions, all over an 11 week period.

Timeframe Overview

Week 1	Initial screening (visit 1)
Weeks 2 and 3	Familiarisation with equipment and testing procedures (visits 2 and 3)
Weeks 4 and 5	Repeat testing to measure variability (visits 4 and 5)

Week 6	Muscle strength, forearm test and leg cycle test (visits 6 and 7)
Week 11	Muscle strength, forearm test and leg cycle test (visits 8 and 9)

Details of Visits

Visit 1. Participants in the study will be asked to attend the Alfred Medical Centre on one occasion for initial screening purposes to ensure that only healthy individuals can enter the study. This will require 30 minutes.

Visits 2 to 9. Participants will then be requested to attend the Human Performance Laboratory at Victoria University of Technology, Footscray Campus (Room L305, building L) on eight separate occasions for exercise testing trials, over a period of approximately 11 weeks.

Visit 2 will involve measures of forearm size, an incremental forearm exercise test and an incremental cycling test; and measures of leg maximal strength and endurance. Details of all tests are given in the next section.

Visit 3 will involve familiarisation trials for forearm, cycling, strength and fatigue testing procedures used for later visits.

Visits 4 and 5. The above tests will be repeated twice to determine how much your exercise test results vary between test sessions.

Visits 2 to 5 will be over a period of about 3-4 weeks and will require about 2 hours on each occasion. Whilst each exercise test is tiring, you will recover very quickly. Please refrain from eating for 2 hours before all exercise trials.

Visits 6 and 8. Participants will be asked to complete the leg muscle strength and fatigue tests on the Cybex. One visit will be after taking the drug digoxin for 12 days, whilst the other visit will be after taking a sugar placebo for 12 days and will be conducted one month apart to ensure digoxin is completely cleared from your body.

Visits 7 and 9. Participants will be asked to complete the forearm test and leg cycle tests two days after the leg muscle strength and fatigue test. These visits will therefore be after taking the drug digoxin or placebo for 14 days and will also be conducted one month apart.

Visits 6 to 9 will be over a period of about 6 weeks. Visits 6 and 8 will require 45 minutes on each occasion for measurement of your muscle strength and fatigue. Visits 7 and 9 will require approximately 5 hours each and will involve (i) a forearm exercise test with blood sampling, (ii) a 2 hour rest, (iii) followed by a cycling exercise test with blood and muscle sampling. In the 24 hours prior to each of Visits 6 to 9, participants will be asked to avoid any intense exercise and substances such as caffeine, alcohol, or other drugs and to record all exercise, fluid and food intake.

Exercise Testing Procedures:

Safety Procedures.

Each exercise test is completed when you become too tired to continue (wish to stop), or unless we stop the test due to you having an abnormal response to exercise, such as unusual heart rhythm, inappropriate heart rate or sweating responses, chest pain or severe shortness of breath. We will closely monitor you and your heart electrical activity (ECG) during exercise to ensure your safety. The most common event associated with maximal exercise testing is fainting. This will be prevented using our standard laboratory procedures outlined in the document titled "Prevention and Management of Vaso-Vagal Attack" which is displayed at several points throughout our laboratory. In the unlikely event of emergency situations, a medical practitioner will be in attendance, two members of the research team have current CPR (cardio pulmonary resuscitation) qualifications and the Western Hospital is minutes away by ambulance.

Forearm exercise tests.

Participants will be asked to undertake forearm exercise over several laboratory visits. This uses a specially made handgrip device for flexing your fingers against a resistance. On Visit 2 you will be asked to perform an incremental forearm test, in which the workrate is progressively increased until your muscles fatigue. On Visits 3 to 5, 7 and 9 you will be asked to perform a forearm test comprising three one minute bouts of exercise, followed by a fourth bout continued until fatigue. Exercise will be performed at the peak workrate attained during the incremental forearm test. As with all unaccustomed exercise, you may experience some muscle soreness after the first forearm exercise test, but this should disappear within a few days.

Forearm Blood Flow Measures.

During and after the forearm exercise tests, forearm blood flow will be measured. This involves placing a blood pressure cuff at the wrist and above the elbow. The wrist cuff is inflated to a similar pressure as when your blood pressure is measured. This pressure is maintained for one minute. The elbow cuff is repeatedly inflated to ¼ of this pressure, for 2 to 30 seconds. When inflated briefly, these cuffs restrict blood from leaving the forearm and flowing into the hand. There is no undue risk associated with this procedure and should participants experience anything more than discomfort, the pressure in the cuffs will be immediately released.

Cycling Exercise Tests Procedures.

Participants will be asked to undertake cycling exercise tests over several laboratory visits. On Visit 2 you will be asked to perform an incremental cycling test, in which the workrate is progressively increased until your muscles fatigue. This test is used to determine your aerobic fitness, by measurement of the peak oxygen consumption (VO_2 peak). On Visits 3 to 5, 7 and 9 you will be asked to perform a cycling test comprising 10 min exercise at workrates corresponding to 33% and 67% of that attained during the incremental cycling test. This will be followed by cycling to fatigue at 90% of your peak workrate. Visits 7 and 9 will include blood sampling and muscle biopsies. The total volume of blood taken in each of these two visits will be ~130ml, less than one quarter of that taken in a blood bank donation.

Digoxin Treatment.

Screening Phase

Participants will be requested to undergo a complete medical history and physical examination. A blood sample will be taken to check for normal electrolytes and kidney function. Your resting ECG will also be assessed to ensure that you have normal heart rate and rhythm.

Treatment and Evaluation

Participants will be given either a sugar tablet (a placebo), or standard-dose digoxin (0.25 mg per day) for 2 weeks, followed by 4 weeks without drug or placebo, and then by taking the alternate treatment (drug or placebo) for a further 2 weeks. The 4 week period is to allow your body to rid itself of digoxin. You take the drug or placebo in random order and will not be informed of this order until the completion of the study. After 7, 12 and 14 days of taking digoxin (or placebo), a blood sample will be taken and digoxin levels in the blood measured, to minimise the risk of accidental overdose and ensure the correct procedures have been followed.

Side Effects

Short-term treatment with digoxin using the standard dose of 0.25mg per day is usually free of side effects. Short-term side effects of digoxin are principally associated with overdose, and may include nausea, vomiting, diarrhoea, lack of appetite. These should respond simply to stopping the drug. Occasionally, too much digoxin may also lead to irregularities of the heart's rhythm. Again this usually responds to stopping the drug. It is possible, although unlikely, that digoxin treatment may adversely affect your ability to undertake heavy exercise, but is unlikely to impact on any lower level day-to-day activity. Although very unlikely, should you experience any adverse effects you should immediately contact the Principal Investigators to review the reported problem and recommend appropriate action. Participants will not be charged for any hospital visits, or for any laboratory measurements.

Muscle Biopsies and Muscle Fatigue Testing:

On Visits 7 and 9, a muscle biopsy will be taken from the thigh muscle of participants, at rest, and following each of the three workrates of the cycling test. Thus four biopsies will be taken on each visit, two from each leg, giving an overall total of eight biopsies. Muscle biopsies are routinely carried out in our laboratory, with no serious adverse effects.

The muscle biopsy procedure is used to obtain small samples of your muscle tissue for analysis of enzymes and energy sources. An injection of a local anaesthetic is made in the skin overlying the muscle in your thigh, and then a small incision (approx. 0.6 cm long) is made in the skin. The 5 mm thick biopsy needle is then inserted into your muscle and a small piece of tissue removed from the muscle. During this part of the procedure you will feel pressure and this will be quite uncomfortable and may cause some pain, but this will last for only about 1-2 seconds. When the small piece of muscle is removed you may also experience a mild muscle cramp, which might also be painful, but this only persists for a few seconds. The size of muscle

removed by the biopsy needle is similar to a grain of rice. This poses no long-term effects for your muscle and will not be noticeable to others apart from a small scar on the skin for a few months. Following the biopsy the incision will be closed using a steri-strip and covered by a transparent waterproof dressing. Then a pressure bandage will be applied which should be maintained for 24-48 hours. Steri-strip closure should be maintained for a few days. You should not exercise for 24 hours after biopsies and you should avoid heavy knocks. It is common for participants to experience some soreness in the muscle over the next 2-3 days, however this passes and does not restrict movement. The soreness is due to slight bleeding within the muscle and is best treated by "ice, compression and elevation". An ice pack will be applied over the biopsy site after the biopsy procedure to minimise any bleeding and therefore soreness. In some rare cases mild haematomas have been reported, but these symptoms disappear within a week. A medical practitioner will perform the whole procedure under sterile conditions. On very rare occasions, some people have reported altered sensation (numbness or tingling) in the skin near the site of the biopsy. This is due to a very small nerve being cut, but this sensation disappears over a period of a few weeks-to-months. Although the possibility of infection, significant bruising and altered sensation is quite small, if by chance it does eventuate, please inform us immediately and we will immediately consult the doctor who performed the biopsy to review the reported problems and recommend appropriate act.

Venous catheterisation

Blood samples will be taken during rest, exercise and recovery via a catheter placed in the exercising arm. The catheter consists of a needle and teflon tubing. The tubing is fed over the top of the needle on entering the vein. The needle is then withdrawn, leaving only the teflon tubing in your vein for the remainder of the experiment. A tap (stopcock) is placed into the tubing so the flow of blood along the tubing can be altered at will. This procedure allows the taking of multiple blood samples without the need for multiple venepuncture (puncturing of the vein). Each time a blood sample is taken, a small volume of fluid will be injected to keep the catheter from clotting. Catheterisation is slightly uncomfortable, with minimal possibility of bruising and infection. The use of sterile, disposable catheters, syringes, single dose vials and aseptic techniques will markedly reduce the possibility of infection. Only staff qualified and experienced in venepuncture will be used in order to prevent complications. Although the possibility of infection, bleeding, local blood clots, local swelling and redness, and bruising are remote, should any one of these conditions eventuate, please inform us immediately and then consult your doctor.

Arterial catheterisation for blood sampling

A similar catheter will be used as above, but will be inserted into the radial artery (wrist) of the non-exercising arm. Arterial puncture and catheterisation is more difficult and may involve more discomfort and bruising formation than with venous punctures. Pain is minimised by use of a local anaesthetic in the skin and near the artery, whilst bleeding and bruising are minimised through use of appropriate pressure techniques for an adequate amount of time after arterial puncture or removal of the catheter. Infection is unlikely as only sterile, unused disposable instruments; single dose vials and aseptic techniques will be used. An experienced medical practitioner, who will remain throughout the entire testing and recovery procedures, will perform all arterial catheterisations.

Timing of blood sampling

During the forearm exercise tests, blood samples will be taken from an artery and a vein before and at the end of each exercise bout, with recovery samples at 1, 2, 5, 10 and 30 min after exercise. Approximately 3 ml of blood will be withdrawn on each occasion (total ~ 60ml). In the leg cycling test, blood samples will be taken from an artery and a vein before and at the end of each exercise bout, with recovery samples at 1, 2, 5, 10 and 30 min after exercise. Approximately 3 ml of blood will be withdrawn on each occasion (total ~ 72ml).

Possible Benefits

There are no direct benefits to the participants in this study with the exception of you gaining information on your fitness levels.

Possible Risks

Although the possibility of infection, significant bruising, bleeding, local blood clot and local swelling and redness, are quite small, you should inform us immediately and consult your doctor if in the 12hrs following the procedure, swelling, temperature, redness and/or pain increases at the site.

The effects of digoxin on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the study. You must not participate in the study if you are pregnant or trying to become pregnant, or breast-feeding. If you are male, you should not father a child. If you are female and child bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the study. Both male and female participants are strongly advised to use effective contraception during the course of the study and for a period of one month after completion of the study. You should discuss methods of effective contraception with your doctor. If you do become pregnant whilst participating in the study you should advise your treating doctor immediately. He/she will withdraw you from the study and advise on further medical attention should this be necessary. You must not continue in the study if you become pregnant.

There may be additional unforeseen or unknown risks.

Compensation

If medical treatment is required following any adverse effects associated with participating in this study, any costs will be reimbursed. In recognition of the large time commitment in participating for this study, participants will be reimbursed a total of $200 at the completion of the study, at a rate equivalent to $10 per hour, for the estimated commitment of approximately 20 hours.

Other Treatments Whilst on Study

It is important to tell your doctor and the research staff about any treatments or medications you may be taking, including non-prescription medications, vitamins or herbal remedies and any changes to these during your participation in the study.

Privacy, Confidentiality and Disclosure of Information

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law. If you give us your permission by signing the Consent Form, we plan to publish the results of this study in peer review journals and present them at conferences. In any publication, information will be provided in such a way that you cannot be identified, this will be done by only reporting data as group averages.

New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

Results of Project

Participants will initially be given a brief written report with their exercise performance results and interpretation. Those interested will also later receive a lay description of major findings of the study.

Further Information or Any Problems

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact the principal researcher or any of the other researchers listed here. The researchers responsible for this project are

Mr Simon Sostaric, (W) 96884160 (mob) 0414 90 7767,
Assoc Prof Michael McKenna (W) 9688 4499 (H) 5422 6089,
Assoc Prof Henry Krum, (W) 9909 0042 (mob) 0417 325 834.

Other Issues

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact.

Name: Rowan Frew
Position: Ethic Manager, Alfred Research and Ethics Unit
Telephone: 9276 3848

Participation Is Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Victoria University of Technology.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

Ethical Guidelines

This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of this Institution.

By signing the informed consent form you are indicating that the tests and procedures have been explained to you and are understood by you. Also, the investigators and yourself accept it that you are participating voluntarily in the study and that you are free to withdraw from the investigation at any time without ill repute. Thank you for your co-operation.

Contact Numbers:

Mr Simon Sostaric	**(W) 96884160**
Assoc Prof Michael McKenna	**(W) 9688 4499**
Assoc Prof Henry Krum	**(W) 9909 0042**

Any queries about your participation in this project may be directed to the researcher (Name: Assoc. Prof. M.McKenna; ph. 9688-4499). If you have any queries or complaints about the way you have been treated, you may contact the Secretary, University Human Research Ethics Committee, Victoria University of Technology, PO Box 14428 MCMC, Melbourne, 8001 (telephone no: 03-9688 4710).

Appendix 4B.3 Revocation of Consent Form

Full Project Title:

The effects of a standard clinical dose of digoxin on potassium regulation in muscle and blood, and muscle fatigability during exercise in healthy young volunteers

I hereby wish to WITHDRAW my consent to participate in the research proposal named above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with Victoria University of Technology.

Participant's Name: …….

Signature: …… Date: …….

Appendix 4B.4 Subject medical alert

Victoria University of Technology
PO Box 14428 Telephone:
MELBOURNE CITY MC VIC 8001 (03) 9688 4432
Australia Facsimile:
(03) 9688 4891
School of Human Movement, Recreation and Performance
Footscray Park Campus
Building L, Ballarat Road, Footscray

Please retain this form in your wallet or purse for easy access for the duration of the study

Date:_____

To whom it may concern, please be advised that Name:_____
is participating as a volunteer in an experiment conducted at Victoria University of Technology.

The experiment is a placebo-controlled investigation into the effects of 0.25 mg/day oral digoxin on muscle strength, exercise performance and plasma potassium concentration.

S/he will be receiving either 0.25 mg/day digoxin OR placebo orally for a 2 week period, commencing on:

Date:_____ through to Date:_____.
S/he will then be receiving the reverse treatment, i.e. either placebo OR 0.25 mg/day digoxin for a 2 week period, commencing on:

Date:_____ through to Date:_____.

For further information in the event of an adverse reaction, please contact the Principal Investigators:	
Associate Professor Henry Krum (MBBS)	**(W) 9909 0042**
Associate Professor Michael McKenna (PhD)	**(W) 9688 4499**
michael.mckenna@vu.edu.au	
or Mr Simon Sostaric (PhD student)	**(W) 96884160**

tear here - - - - - - - - - - - - -- - - - - - - - - - - - - - -- - - - - - - - - - - - - - - -

Appendix 4B.4

CARDIOVASCULAR AND OTHER RISK FACTORS QUESTIONNAIRE

In order to be eligible to participate in the experiment investigating:
" **The effects of a standard clinical dose of digoxin on potassium regulation in muscle and blood, and muscle fatigability during exercise in healthy young volunteers**" you are required to complete the following questionnaire which is designed to assess the risk of you having a cardiovascular event occurring during an exhaustive exercise bout.

Name: _____ Date: _____

Age: _____ years Weight: _____ kg Height: _____ cms
Gender:__M_____F____

Give a brief description of your average activity pattern in the past 2 months:
_____

_____

Circle the appropriate response to the following questions.

1.	Are you overweight?	Yes	No	Don't know
2.	Do you smoke?	Yes	No	Social
3.	Does your family have a history of premature cardiovascular problems (eg. heart attack, stroke)?	Yes	No	Don't Know
4.	Are you an asthmatic	Yes	No	Don't Know
5.	Are you a diabetic?	Yes	No	Don't Know
6.	Do you have a high blood cholesterol level?	Yes	No	Don't Know
7.	Do you have elevated blood pressure?	Yes	No	Don't Know
8.	Are you being treated with diuretics?	Yes	No	
9.	Are you on any other medications?	Yes	No	

List all medications? _____

10. Do you think you have any medical complaint or any other reason which you know of which you think may prevent you from participating in strenuous exercise? Yes No

Yes, please elaborate _____

11. Are you currently pregnant or expect to become pregnant during the time in which this experiment is conducted? Yes No

I, _____, believe that the answers to these questions are true and correct.
Signed: Date:

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Appendix 4B.5

MUSCLE BIOPSY & ARTERIAL- VENOUS CANNULATION QUESTIONNAIRE:

The effects of a standard clinical dose of digoxin on potassium regulation in muscle and blood, and muscle fatigability during exercise in healthy young volunteers

NAME: _____

ADDRESS: _____
DATE: _____ **AGE:** _____ **years**

1. Have you or your family suffered from any tendency to bleed excessively? (eg. Haemophilia) or bruise very easily? Yes No Don't Know
   If yes, please elaborate..._____
   _____

2. Are you allergic to local anaesthetic? Yes No Don't Know
   If yes, please elaborate..._____
   _____

3. Do you have any skin allergies? Yes No Don't Know
   If yes, please elaborate..._____
   _____

4. Have you any allergies? Yes No Don't Know
   If yes, please elaborate... _____
   _____

5. Are you currently on any medication? Yes No Don't Know
   If yes, what is the medication? _____
   _____

6. Do you have any other medical problem? Yes No
   If yes, please elaborate... _____
   _____

7. Have you ever fainted when you had an injection or blood sample taken? Yes No Don't know
   If yes, please elaborate_____

8. Have you previously had heparin infused or injected? Yes No Don't know
   If yes, please elaborate_____

9. Do you or other members of your family have Raynauds disease, or suffer from very poor circulation in the fingers, leading to painful fingers that turn white/blue? Yes No Don't know

If yes, please elaborate_____

To the best of my knowledge, the above questionnaire has been completely accurately and truthfully.

Signature: _____ Date: _____

Appendix 5 Forearm geometric model

Two segments, truncated cone 1 and truncated cone 2 represent the change of forearm volume from resting conditions to exercise and recovery. The assumption during venous occlusion plethysmography is that the forearm shape remains unchanged, causing an increase in size over the complete dimensions; that all expansion occurs across the diameter and not in height;

Truncated Cone 1

(A) The volume of a truncated cone can be re-written as;

$V= (h/12\prod) * (C_1^2+C_2^2+C_1C_2)$, where C_1 = circumference 1 (widest point of forearm, distal to olecronon process); C_2 = circumference 2 (wrist); h = height.

Expansion at $C_1 = x$, and is detected by electronic strain gauge mounted at that point. Following expansion, $C_1 = C_{1i} + x$, or $C_{1f} = C_{1i} + x$, where $_i$ = initial and $_f$ = final.

(B) Expansion at C_2 is equal to the fraction or percent expansion at C_1, therefore;

$\%\Delta C_1 = 100 ((C_1 + x- C_1)/ C_1)$

$\%\Delta C_{1i} = 100 (x/ C_{1i})$ or fractional $\Delta C_1 = x/ C_{1i}$, therefore $C_{2f} = C_{2i} + C_{2i}x/ C_{1i}$

(C) Change in volume of a truncated cone = $\Delta V = V_f-V_i$, where $_i$ = initial and $_f$ = final

$\Delta V = (h/12\prod) * (C_{1f}^2+C_{2f}^2+C_{1f}C_{2f}-C_{1i}^2+C_{2i}^2+C_{1i}C_{2i})$; substitute C_{1f} where $C_{1f} = C_{1i}+x$

$\Delta V = (h/12\prod) * \{2C_{1i}x+x^2+C_{2f}^2+C_{1i}C_{2f}+xC_{2f}-C_{2i}^2-C_{1i}C_{2i}\}$

(D) Substitute for C_{2f} where $C_{2f} = C_{2i} + C_{2i}x/C_{1i}$

$\Delta V = (h/12\prod) * \{2C_{1i}x+x^2+(C_{2i}+C_{2i}x/C_{1i})^2 + C_{1i}(C_{2i}+C_{2i}x/C_{1i}) + x(C_{2i}+C_{2i}x/C_{1i}) - C_{2i}^2-C_{1i}C_{2i})\}$

Omit $_i$, as now only initial circumferences are expressed, where C_1=initial C_1, C_2 = initial C_2

$\Delta V = (h/12\prod) * \{2C_1x+x^2+(C_2+C_2x/C_1)^2 + C_1(C_2+C_2x/C_1) + x(C_2+C_2x/C_1) - C_2^2-C_1C_2)\}$

$\Delta V = (h/12\prod) * \{2C_1x+x^2+2C_2^2x/C_1+ C_2^2x^2/C_1^2+2C_2x + C_2\, x^2/C_1\}$, then remove C_1^2 from denominator, thus ΔV for a single truncated cone is;

$\Delta V = (hx/C_1^2 12\prod) * \{C_1^2(2C_1+2C_2+x) + C_2^2(2C_1+x) + C_1C_2x\}$

Truncated Cone 2 = Truncated Cone 1, substitute circumference 2 (wrist) with circumference around olecronon process.

The rate of change in the two truncated cone segments are added together and converted into blood flow units of $ml.min^{-1}$.

Appendix 6

24 hour Diet Pre-Trial Days: Set Menu

No exercise, alcohol, tobacco, or caffeine in the 24 hours before the trial!! Please bring this sheet with you on test days.

Breakfast:

Cereal	90g
Low fat Milk	333ml
4 slices of toast	120g
Jam/honey	1 tablespoon
Orange juice (tetra pk)	250ml

Lunch:

2 x bread rolls	180g
Half tomato	50g
Lettuce	30g
Cheese	40g
Ham (lean)	60g
Margarine/butter	15g
1 apple	140g
1 can drink (diet or regular)	375ml

Dinner:

Half a packet of pasta	175g
Half a jar of pasta sauce	200ml
1 can tuna (in spring water)	90g
2 x two fruits snacks (or equivalent)	240g
1 can drink (diet or regular)	375ml

Snacks: ***Please record any snacks eaten (type and amount) so that food intake is the same for both trials. Water may be consumed at any time on the day before the trial – as per necessary.***

Possible snacks include:

Banana	140g
Muesli bar	35g
Sultana's	30g
Bread with jam or honey	30g/1 teaspoon

Morning of trial:
Upon waking consume 5ml of water per kilogram of body weight;
Eg – a 70kg person consumes 350ml water
An 83kg person consumes 415ml of water

Snacks:

Appendix 7

Digoxin upregulates skeletal muscle Na^+,K^+-ATPase but does not alter muscle function in healthy humans

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Running Head: Digoxin and muscle Na^+,K^+-pump adaptability

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ABSTRACT

We investigated digoxin effects on skeletal muscle function and Na^+,K^+-ATPase (NKA) content (^{3}H-ouabain binding), activity (3-O-MFPase) and isoforms (α_1-α_3, β_1-β_3 mRNA, protein). Ten active, healthy volunteers received digoxin (DIG, 0.25 mg.d^{-1}) or placebo (CON) for 14 d, in a double-blind, 4 week cross-over design. A muscle biopsy was taken at rest, after cycling 20 min (33%, then 67% $\dot{V}O_{2peak}$), at fatigue (90% $\dot{V}O_{2peak}$) and 3h post-exercise.

Serum digoxin was 0.8±0.2 nM (mean±SD) in DIG. In resting muscle, NKA content and activity were unchanged with DIG, but bound digoxin removal with Digibind® antibodies revealed increased NKA content (P=0.047), indicating a 7% digoxin occupancy. In DIG, total β mRNA increased (P=0.04), α_2 mRNA (P=0.059) and α_2 protein (P=0.08) tended to increase. Muscle strength, fatiguability and cycle fatigue time were unaltered with DIG. Across all times, DIG did not systematically affect NKA content, activity, α_1-α_3 or β_1-β_3 mRNA or protein. NKA content increased above rest at 67% $\dot{V}O_{2peak}$ (P<0.05), tended to increase at fatigue (P<0.06) and was higher than 3h (P<0.05); findings were inconsistent after Digibind®. Exercise increased α_3 mRNA and β_3 mRNA at 3h (P<0.05) and tended to increase α_2 mRNA above rest (P=0.06). Exercise increased α_3 protein at 3h in CON, but reduced α_3 at 3h in DIG (P<0.05). Both β_1 and β_3 protein tended to increase above rest (P=0.07), with β_2 protein increased at fatigue (P=0.04).

Thus, digoxin at therapeutic levels induced 7% occupancy of muscle NKA, and compensatory upregulation of NKA, with consequent maintenance of NKA and muscle function.

INTRODUCTION

The Na^+,K^+-ATPase (NKA, Na^+,K^+-pump) is ubiquitously expressed, with important cellular functions including Na^+/K^+ transport, volume regulation and solute transport (Blanco & Mercer, 1998). In skeletal muscle, NKA is a vital regulator of Na^+ and K^+ gradients across sarcolemmal and transverse tubular membranes, thereby directly modulating membrane potential and excitability (Clausen, 2003). Thus NKA has a fundamental role in the maintenance of skeletal muscle contractility. This role is clearly demonstrated in isolated rat muscles when force is depressed by incubation in high K^+ concentrations, where NKA inhibition by ouabain increased the rate of force decline by as much as 3-fold (Nielsen & Clausen, 1996; Clausen, 2003). Conversely, in these same conditions, NKA stimulation by catecholamines, insulin, CGRP and numerous other hormones, each reduced the rate of force decline (Clausen, 2003). However, it is difficult to extrapolate from these in vitro NKA experiments in isolated rat muscles to study the in-vivo functional effects of NKA in human skeletal muscle. One approach has been to examine the functional effects of NKA upregulation in skeletal muscle. Exercise training for days-to-months, across a range of exercise modalities and conditions, elevate skeletal muscle NKA content in humans, as quantified by ^{3}H-ouabain binding (Green *et al.*, 1993; McKenna *et al.*, 1993; McKenna, 1998; Clausen, 2003; Green *et al.*, 2004; Green *et al.*, 2008). Important functional advantages of NKA upregulation with training are suggested by coincident reductions in K^+ concentration ($[K^+]$) in plasma and muscle interstitium during exercise, and enhanced muscular performance (Green *et al.*, 1993; McKenna *et al.*, 1993; McKenna *et al.*, 1997; Harmer

et al., 2000; Nielsen *et al.*, 2004; Harmer *et al.*, 2006). Muscle NKA content upregulation with dexamethasone reduced plasma [K^+] and muscular K^+ release, and enhanced performance (Nordsborg *et al.*, 2008). The opposite approach is to examine functional effects of lowering human muscle NKA content.

Digoxin is a specific NKA inhibitor, and has been used extensively to treat patients with severe heart failure (Goldberg *et al.*, 2007). Digitalisation achieving low dose serum digoxin concentrations (SDC) has been shown to reduce hospitalisations and mortality in heart failure patients (Ahmed *et al.*, 2006). Digoxin exerts a positive inotropic effect on the myocardium, in large part via inhibition of NKA activity, resulting in elevated myocardial intracellular Na^+, increased Na^+/Ca^{2+} exchange and cytosolic Ca^{2+} (Fozzard & Sheets, 1985; Levi *et al.*, 1994). However, digoxin will also bind to and thus inhibit NKA in skeletal muscle (Schmidt *et al.*, 1991). By far the largest proportion of digoxin binds to skeletal muscle, estimated at ~50% of total body digoxin (Schmidt *et al.*, 1991). Digoxin occupancy in skeletal muscle has been measured in digitalised patients, at ~9% of total NKA binding sites after 3 d treatment (Schmidt *et al.*, 1995), 13% in muscle obtained post-mortem (Schmidt *et al.*, 1993), and as much as 35% in heart failure patients (Green *et al.*, 2001). Thus digoxin-induced skeletal muscle NKA inhibition would occur, lowering functional NKA and thus would be expected to impair Na^+/K^+ exchange and contractility. Indeed K^+ regulation is impaired with digoxin in cardiac patients, with higher plasma [K^+] during exercise (Norgaard *et al.*, 1991; Schmidt *et al.*, 1995) and exacerbated K^+ loss from exercising muscles (Schmidt *et al.*, 1995). However, interpretation of digoxin effects in these patients is complicated, as numerous medications and myopathies might contribute to impaired ion exchange and muscle function (Mettauer *et al.*, 2006). We therefore investigated the effects of digoxin on muscle function and muscle NKA in healthy young adults, where normal muscle function and the absence of disease allow investigation of digoxin-specific effects.

In healthy humans treated with digoxin, exercise both increased muscle digoxin binding, and reduced SDC (Joreteg & Jogestrand, 1983). Increased digoxin binding to contracting muscles might exacerbate the exercise-induced reduction in maximal NKA activity (Green *et al.*, 2007; Green *et al.*, 2008; McKenna *et al.*, 2008), potentially accelerating the onset of muscular fatigue. Thus we investigated whether digoxin inhibits maximal NKA activity in human skeletal muscle at rest, with acute exercise, and whether this is associated with impaired exercise performance.

Finally, combined digitalisation and exercise is of significance, since exercise is an important modulator of NKA gene expression in skeletal muscle (Tsakiridis *et al.*, 1996; Nordsborg *et al.*, 2003; Murphy *et al.*, 2004; Nordsborg *et al.*, 2005; Petersen *et al.*, 2005; Murphy *et al.*, 2006b; Aughey *et al.*, 2007), whilst NKA inhibition by ouabain modulates NKA gene expression in rat EDL muscle (Murphy *et al.*, 2006a) and cardiomyocytes (Huang *et al.*, 1997). It is unknown whether digoxin modulates NKA gene expression in resting or exercised human skeletal muscle. Thus the NKA mRNA responses to both digoxin and exercise were also investigated here.

This study therefore investigated the effects of digoxin on skeletal muscle NKA morphology and regulation at rest and during exercise, as well as effects on muscle function in healthy humans.

The hypotheses tested were that oral digoxin administration would: (i) reduce quadriceps muscle strength, exacerbate muscle fatigue and impair intense cycling exercise performance; (ii) depress skeletal muscle NKA content ([^{3}H]-ouabain binding) and maximal in-vitro activity (3-O-MFPase), at rest and after exercise; (iii) increase NKA mRNA expression in resting muscle; and (iv) exacerbate the effects of exercise on muscle NKA isoform mRNA expression, (v) without acute changes in NKA isoform protein abundance.

METHODS

Subjects

Ten recreationally active subjects (one female, nine male; age, 26.1 ±5.9 yr; height, 178.4 ±9.1 cm; body mass, 75.7 ±11.3 kg; $\dot{V}O_{2peak}$, 3.67 ±0.42 l.min^{-1}; mean ± SD) gave written informed consent and participated in the study. Young rather than older adults were recruited due to ethical considerations. All subjects underwent an initial medical examination to screen for abnormal plasma electrolyte concentrations, kidney function, rest and exercise electrocardiogram, and history of adverse cardiovascular events. All protocols and procedures were approved by the Victoria University Human Research Ethics Committee and Alfred Hospital Ethics Committee, and conformed to the Declaration of Helsinki.

Study design

Subjects were randomly allocated to either a digoxin (DIG) or placebo (CON) treatment group. Subjects were given either a typical clinical oral digoxin dose of 0.25 mg.d^{-1} (Lanoxin, Glaxo Smith Kline) or a placebo for 14 days. Trials were conducted in a randomised, double-blind, crossover, counterbalanced design. For ethical reasons, the attending medical practitioner was non-blinded. On day 13 of treatment subjects performed muscle isokinetic strength and fatigue index tests, whilst on day 14, the cycling exercise test was performed and muscle biopsies were taken. After a four week washout period, the groups switched to the alternative treatment for a further two weeks and then repeated the exercise test and biopsies. Thus, for those subjects taking DIG first, the effective digoxin clearance time was six weeks, i.e. the standard four week washout plus the two weeks of placebo treatment. Similarly, for the placebo group, the time between biopsies was six weeks. This washout period was more than sufficient, as the digoxin clearance half-time from serum after digoxin injection was 45 h (range 32-131 h) (Kramer *et al.*, 1974) and from skeletal muscle after oral digoxin was ~2.2 d (Jogestrand & Sundqvist, 1981).

NKA investigations comprised digoxin effects on the total content and maximal in-vitro activity, as well as isoform gene expression and protein abundance. Digoxin effects on muscle function were assessed via quadriceps muscle strength and fatiguability, time to fatigue during incremental cycling exercise, as well as respiratory muscle function by standard spirometry. This study was part of a larger project, in which the effects of digoxin on arterial [K^+] during exercise, K^+ release from contracting muscle and K^+ uptake into skeletal muscle were also investigated (Sostaric et al. In Preparation).

Quadriceps Muscle Strength and Endurance Test

Subjects performed tests of quadriceps muscle strength and endurance (dominant leg) on an isokinetic dynamometer (Cybex Norm 770, Henley Healthcare, USA) on day 13 of DIG, and

CON treatments, as previously described (Li *et al*., 2002). Three familiarisation trials were conducted at least 2 weeks prior to commencement of the trial, to minimise any training effect. The dynamometer was calibrated for angle, torque and velocity immediately prior to each test. Maximal peak torque was measured at 0, 60, 120, 180, 240, 300 and 360 °/s. Quadriceps muscle fatigue was determined from the percent decline in peak torque during 50 repeated maximal contractions, conducted at 180°/s and expressed as a fatigue index: Fatigue Index (%) = ((Peak torque - Final torque) / Peak torque) x 100. Peak torque was defined as the average of the 5 highest peak torque values of the first 10 contractions, while final torque was the average of the 5 highest values of the last 10 contractions.

Respiratory Muscle Function

The forced expired volume (FEV), forced expired volume in one s (FEV_1) maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) were measured as indices of respiratory function and respiratory muscle strength. Subjects performed an initial test at the commencement of the study, then two variability trials, followed by the DIG and CON trial measurements. The MIPs and MEPs were determined using a respiratory pressure meter (Micro Medical Ltd, Rochester, England), whilst the FVC and FEV_1 were measured using a spirometer (MedGraphics Cardiopulmonary Diagnostic System, Medical Graphics Corporation, Minnesota, USA) which was calibrated prior to each test.

Peak oxygen uptake ($\dot{V}O_2$ peak) test

Participants performed an initial incremental (4min at each of 60, 90, 120 and 150 W, then 25 W increments per min to fatigue, 70 rpm) cycle ergometer exercise to fatigue, to determine peak oxygen uptake ($\dot{V}O_2$ peak), as a marker of aerobic fitness and for calculation of work rates corresponding to 33, 67 and 90% $\dot{V}O_2$ peak. All equipment, procedures and calibration were as previously described (Fraser *et al*., 2002; Li *et al*., 2002). All cycling tests were performed using an electrically braked cycle ergometer (Lode Excalibur, Groningen, Holland), but with subjects partially-recumbent, using a custom-designed seat. This set-up was used to facilitate tissue and blood sampling with the exercise trial.

Cycle Exercise test and Muscle Biopsy Sampling

For invasive studies, the participants cycled for 10 min at 33% $\dot{V}O_{2peak}$ followed by a two min pause, 10 min at 67% $\dot{V}O_{2peak}$, two min pause, and then continued until fatigue at 90% $\dot{V}O_{2peak}$. This test was conducted on day 14 of both DIG and CON trials. A muscle biopsy was taken at rest, immediately after the cycling exercise periods at 67% $\dot{V}O_{2peak}$ and at fatigue, and in recovery at 3 hours post-exercise, giving a total of 4 biopsies per trial and 8 in total. Due to the invasive and complex nature of the experiment, it was judged ethically appropriate to take only a single delayed recovery biopsy. This was performed at 3 hr post-exercise to maximise the opportunity of detecting increases in NKA gene transcripts (Nordsborg *et al*., 2003; Murphy *et al*., 2004). A local anaesthetic (1% Lignocaine) was injected into the skin and subcutaneous tissue over the vastus lateralis muscle, four small incisions (2 per leg) were made through the

skin and fascia, and a muscle sample of approximately 100-120 mg was then excised using a biopsy needle. Samples were immediately frozen in liquid N_2 until assayed later for NKA isoform mRNA expression and protein abundance, maximal in-vitro activity (3-O-MFPase), and content ([^{3}H]ouabain binding site content).

Real-Time RT-PCR measurement of mRNA

Total RNA was extracted from 5-10 mg muscle and transcribed into cDNA using methods previously employed in our laboratory (Murphy *et al.*, 2001; Murphy *et al.*, 2003). Gene expression of the Na^+,K^+-ATPase α_1, α_2, α_3, β_1, β_2 and β_3 isoforms was quantified using Real-Time RT-PCR, using previously described methods (Murphy *et al.*, 2004; Murphy *et al.*, 2006b). The relative expression of the genes compared with resting samples was normalised for input cDNA using the housekeeping gene cyclophilin and were therefore expressed as $2^{-\Delta\Delta CT}$. Neither exercise (P = 0.82) nor digoxin (P = 0.64) had any significant effect on the mRNA expression of cyclophilin, when expressed in the linear (2^{-CT}) form (CON rest, 7.6 x 10^{-9} ± 2.5 x 10^{-9}; CON 67%, 12.3 x 10^{-9} ± 4.2 x 10^{-9}; CON fatigue, 8.2 x 10^{-9} ± 2.6 x 10^{-9}; CON 3 h recovery, 9.0 x 10^{-9} ± 2.3 x 10^{-9}; DIG rest, 7.3 x 10^{-9} ± 1.4 x 10^{-9}; DIG 67%, 7.7 x10^{-9} ± 2.7 x 10^{-9}; DIG Fatigue, 7.7 x 10^{-9} ± 1.7 x 10^{-9}; DIG 3 h recovery, 9.8 x 10^{-9} ± 6.0 x 10^{-9}, all n = 10). Intra-assay variability of 2^{-CT} values for respective isoforms was CV (%): α_1 13.8; α_2 10.6; α_3 12.5; β_1 8.9; β_2 12.7; β_3 14.0; human CYC 8.6, which are within values previously reported (Murphy *et al.*, 2003). The total α mRNA expression was also calculated in resting muscle to compare DIG versus CON, as the sum of α_1, α_2 and α_3 $2^{-\Delta\Delta CT}$ ($\Sigma\alpha_1+\alpha_2+\alpha_3$ mRNA) and the total β mRNA expression as the sum of β_1, β_2 and β_3 $2^{-\Delta\Delta CT}$ ($\Sigma\beta_1+\beta_2+\beta_3$ mRNA).

Western Blotting

Muscle samples (20–30 mg) underwent standard extraction, separation and western blotting procedures as previously fully described (Murphy *et al.*, 2004; Murphy *et al.*, 2006b). Antibodies were for α_1: monoclonal α6F (developed by D. Fambrough and obtained from the Developmental Studies Hybridoma Bank developed under the auspices of the NICHD and maintained by the University of Iowa, Department of Biological Sciences, Iowa City, IA, USA); α_2: polyclonal anti-HERED (kindly donated by T. Pressley, Texas Tech University); α_3: monoclonal MA3-915 (Affinity Bioreagents, Golden, CO, USA); β_1: monoclonal MA3-930 (Affinity Bioreagents); β_2: monoclonal 610915 (Transduction Laboratories, Lexington, KY, USA); and β_3: monoclonal 610993 (Transduction Laboratories).

Muscle 3-O-MFPase assay

Maximal *in-vitro* NKA activity was measured in muscle homogenates using the K^+-stimulated 3-*O*-methylfluorescein phosphatase (3-*O*-MFPase) assay, which is specific for the Na^+,K^+-pump and adapted for human skeletal muscle, as previously described (Fraser & McKenna, 1998; Fraser *et al.*, 2002). Approximately 20 mg of muscle was analysed. All assays were performed at 37 °C, with continuous stirring, on a fluorometer (Photon Technology International, Birmingham, NJ). NKA maximal in-vitro activity results were expressed relative to wet weight, and also to muscle protein content, to correct for any exercise-induced changes in muscle water

content. Skeletal muscle protein content was determined spectrophotometrically (Lowry et al 1951). The intra-assay coefficient of variation (CV) for the 3-O-MFPase assay was 18%.

[^{3}H]ouabain binding site content

Skeletal muscle total NKA content was determined in quadruplicate by vanadate-facilitated [^{3}H]ouabain binding site content analysis, using standard techniques (Nørgaard *et al.*, 1983; Nørgaard *et al.*, 1984), as previously fully described (Petersen *et al.*, 2005). The [^{3}H]ouabain binding site content was expressed as pmol.(g wet wt)$^{-1}$ and pmol.(g protein)$^{-1}$. The intra- and inter-assay CV for the [^{3}H]ouabain binding site assay were 9% and 14%, respectively.

NKA activity-to-content ratio

To determine the exercise effects on NKA activity per pump, the ratio between 3-O-MFPase activity and [^{3}H]ouabain binding site content without removal of bound digoxin (activity/content ratio) was calculated for combined CON and DIG data.

Digoxin Binding and Occupancy

As digoxin and ouabain bind competitively to the digitalis receptors on the NKA, the [^{3}H]ouabain binding assay will not detect any NKA that are occupied by digoxin. Thus, the [^{3}H]ouabain binding assay was performed with and without prior incubation in digoxin antibody fragments (F_{ab}, Digibind®, GlaxoSmithKline, Melbourne, Australia), using previously described procedures (Schmidt & Kjeldsen, 1991; Schmidt *et al.*, 1993). This method has been shown to remove ~97% of bound digoxin from skeletal muscle (Schmidt & Kjeldsen, 1991). Briefly, muscle samples were incubated for 16 h at 30ºC in tris-vanadate-sucrose (TVS) buffer containing 0.5 µM F_{ab}, after which the standard [^{3}H]ouabain binding site content assay was performed. The skeletal muscle digoxin occupancy was calculated as the difference in [^{3}H]ouabain binding with F_{ab} incubation minus the standard [^{3}H]ouabain binding (ie without F_{ab}), expressed as a proportion of total [^{3}H]ouabain binding sites: [(Ouabain binding+Fab) – (ouabain binding)] x 100 / (Ouabain binding+Fab) (Schmidt *et al.*, 1993).

F_{ab} Control Experiments

Two control experiments were conducted to test the efficacy of the digoxin F_{ab} method in detecting bound NKA in our laboratory. These were to verify that use of F_{ab} would enable recovery of bound NKA and that the 16 h incubation would not affect [^{3}H]ouabain binding site content in healthy human skeletal muscle.

Recovery. Muscle samples from three healthy subjects were each divided into three portions, for incubation in digoxin, digoxin+F_{ab}, and control (n = 3 per group). The digoxin and digoxin+F_{ab} samples were incubated in 10 nM digoxin for 60 min at 37ºC. The digoxin+F_{ab} samples were subsequently incubated overnight in 0.5 µM digoxin F_{ab}, whilst the control samples did not undergo any incubation. The digoxin, digoxin+F_{ab}, and control samples were then analysed for [^{3}H]ouabain binding site content, as described above. The clearance of bound digoxin was calculated from the [^{3}H]ouabain binding results of the digoxin, digoxin+F_{ab}, and control samples, using the formula: [(digoxin+F_{ab} – digoxin) / (control – digoxin)] × 100 (Schmidt & Kjeldsen, 1991). Incubation in 10 nM digoxin reduced [^{3}H]ouabain binding sites by 32% compared to control (P < 0.05), whereas following incubation in F_{ab}, the [^{3}H]ouabain binding site content was

not different to control (P = 0.92). Thus the F_{ab} removed 96% of bound digoxin (i.e. 96% of the difference between control and digoxin) and enabled almost complete NKA quantification, similar to previous reports (Schmidt & Kjeldsen, 1991).

Incubation effects. To ensure that the additional 16 h overnight incubation with F_{ab} did not effect [^{3}H]ouabain binding site content, an additional three human skeletal muscle samples, from different subjects, were tested. To compare the effect of incubation in F_{ab} versus incubation in standard TVS buffer, samples were incubated for 16 h at 30ºC in standard TVS buffer or buffer containing 0.5 µM F_{ab} (n = 3 per group). To determine if the 16 h incubation in F_{ab} or TVS buffer affected subsequent [^{3}H]ouabain binding, an additional 3 samples did not undergo any incubation (control). The TVS buffer, F_{ab}, and control samples were then analysed for [^{3}H]ouabain binding site content. Overnight incubation in standard TVS buffer or in buffer containing F_{ab} had no effect on [^{3}H]ouabain binding site content, indicating that the overnight incubation did not result in any loss of NKA (P = 0.93), similar to previous reports (Schmidt & Kjeldsen, 1991).

Statistical Analyses

All data are presented as mean±SD. Muscle data were analysed using a repeated-measures two-way ANOVA (digoxin treatment – digoxin vs. placebo; exercise time – rest, 67%, fatigue, 3h recovery). For the digoxin F_{ab} verification experiments a one-way ANOVA was used, and for comparison of [^{3}H]ouabain binding site content performed with and without digoxin F_{ab}, a paired t-test was used. Treatment-by-exercise interaction effects were not significant unless indicated. Post hoc analyses were determined using the least significant difference test. The resting muscle total α or β subunit mRNA expression, digoxin occupancy were compared between digoxin and placebo using a paired-samples student t-test. Correlations were determined by least squares linear regression. Variability of test measures was determined for the two variability trials using the coefficient of variation (CV). Statistical significance was accepted at $P < 0.05$. Statistics were performed using SPSS version 15. The effect size for paired comparisons close to significance was calculated using Cohen's d [d = ($mean_1$ – $mean_2$)/SD], where the SD was pooled when the SD's were unequal (Cohen, 1988). The effect size was also calculated for selected exercise and DIG effects and interactions using partial Eta squared (η_p^2) value given in SPSS. Cohen's conventions for effect size were adopted for interpretations, where values for η2p of 0, 0.2, 0.5 and 0.8 are considered as trivial, small, moderate and large, respectively (Cohen, 1988). Trivial effect sizes were generally not reported. A moderate to large effect size represents a functional effect of an intervention.

RESULTS

Serum digoxin concentration

Serum digoxin concentration (SDC) at rest on days 7, 13 and 14 in DIG was 0.7±0.2, 0.7±0.2 and 0.8±0.2 nM, respectively. In CON, SDC was below the detection limit (<0.4 nM) in six subjects, and below a lower SDC detection limit of <0.2nM for the final three subjects. SDC in one subject was at the detection limit of 0.4 nM in CON, whilst his corresponding SDC in DIG was 0.9-1.0 nM.

Digoxin effects on muscle strength, fatiguability and incremental exercise performance

Quadriceps Muscle Strength

The peak torque at each velocity during isokinetic contractions was highly reproducible during variability trials (CV 4.3%–7.9%). Peak torque declined with increased velocity (P=0.001), but no significant differences were found between DIG and CON (Figure 1A). Whilst a significant treatment-by-velocity interaction was found (P=0.008), no differences could be detected between DIG and CON trials at any velocity.

Quadriceps Muscle Fatiguae

Peak quadriceps muscle torque declined during 50 repeated contractions (P<0.05, Figure 1B) and the calculated fatigue index was highly reproducible during variability trials (CV=4.7%). There were no differences in fatigue index between DIG and CON (53.6±9.0 vs 57.4±10.0 %, respectively, P=0.14).

Respiratory Muscle Function.

The respiratory muscle strength and respiratory function measures had excellent reproducibility during variability trials (CV, MIP 4.4%, MEP 4.0%, FVC 2.3%, FEV1 2.2%). There were no differences between DIG and CON, respectively, for MIP (153.0±19.2 vs 152.7±23.3 cmH_2O), MEP (182.1±34.5 vs 180.6±35.1 cmH_2O), FVC (5.33±0.74 vs 5.31±0.73 l), or FEV_1 (4.22±0.68 vs 4.28±0.56 l).

Incremental Exercise Performance and $\dot{V}O_2$

The initial incremental cycling exercise $\dot{V}O_{2peak}$ was 3.67±0.42 $L.min^{-1}$. The time to fatigue cycling at 90% $\dot{V}O_{2peak}$ was reproducible (CV=5.9%) and did not differ between DIG and CON (262±156 and 254±125 s, respectively). There were also no differences between DIG and CON for $\dot{V}O_2$ during exercise at 33% (1.21±0.20 vs 1.19±0.21, CV=2.2%); 67% $\dot{V}O_{2peak}$ (2.63±0.51 vs 2.68±0.54, CV=1.9%); or 90% $\dot{V}O_{2peak}$ (3.61±0.28 vs 3.55±0.67, CV=4.4%), respectively.

Digoxin effects on NKA in muscle obtained at Rest

NKA content ([^{3}H]ouabain binding sites) in rest muscle

Ouabain binding without F_{ab}

Despite SDC being elevated to therapeutic levels, the muscle [^{3}H]ouabain binding site content did not differ in resting muscle between DIG and CON (352±54 vs 353±42 pmol.g wet $weight^{-1}$, respectively). There was no effect of digoxin on skeletal muscle total protein content, thus [^{3}H]ouabain binding site content expressed relative to muscle total protein was also unaltered in resting muscle (DIG, 1789±367, vs CON, 1831±378 pmol.g $protein^{-1}$).

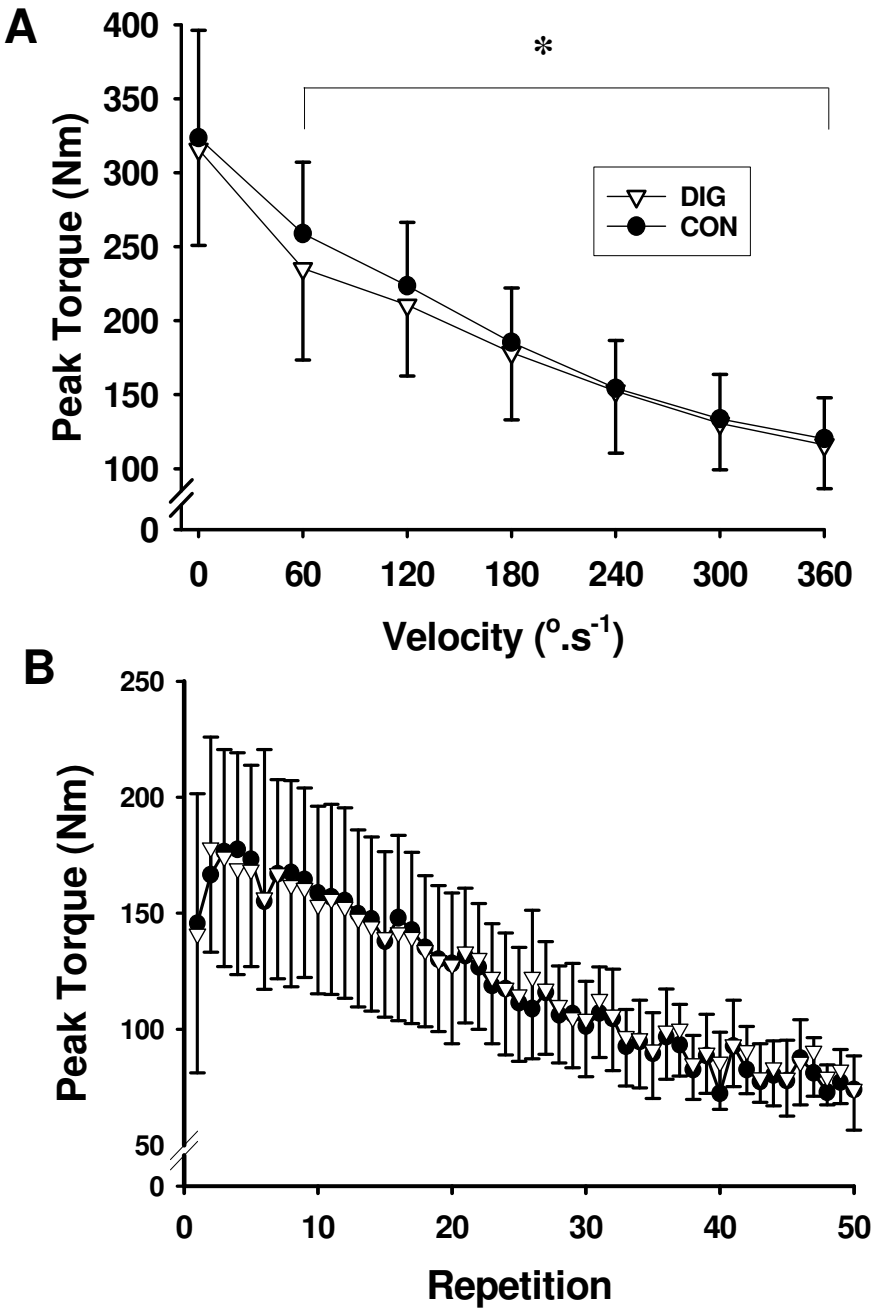

Figure 1. Quadriceps muscle torque-velocity relationship (A) and peak torque during repeated (B) during isokinetic contractions. **Digoxin (DIG; ∇) and control (CON; •).** Values are mean±SD, n=10. Torque-velocity relationship: * All values less than 0 $^{o}.s^{-1}$, *P*<0.001, main effect. Effect sizes: treatment 0.22, time 0.95 and treatment x time 0.27.

Ouabain binding after incubation in F_{ab} (Digibind)

When measured in a separate muscle piece following clearance of bound digoxin by 16 h incubation in F_{ab}, the muscle [^{3}H]ouabain binding site content again did not differ between DIG and CON, expressed either relative to muscle wet weight (381±53 vs 369±41 pmol.g wet weight^{-1}), or protein (1941±403 vs 1913±362 pmol.g protein^{-1}, respectively).

Comparisons of ouabain binding with versus without incubation in F_{ab} (± F_{ab})

In the DIG trial, the muscle [^{3}H]ouabain binding site content was 8.2% higher when measured with F_{ab} (Digibind) compared to without F_{ab} (381±53 vs 352±54 pmol.g wet weight^{-1}, respectively, P=0.047, moderate effect size, d=0.54), indicating a digoxin occupancy for the DIG trial of 7.0%. In the CON trial, no difference was seen in [^{3}H]ouabain binding site content when measured comparing ±F_{ab} (P=0.20) and the calculated "apparent digoxin occupancy" for the CON trial was 3.3%.

NKA maximal activity (3-O-MFPase activity) in rest muscle

The maximal in-vitro 3-O-MFPase activity in resting muscle was not different between DIG and CON when expressed relative to muscle wet weight (300±53 vs. 297±79 nmol.min^{-1}.g wet weight^{-1}, respectively), or protein content (1533±372 vs. 1514±369 pmol.min^{-1}.g protein^{-1}, respectively).

NKA α mRNA and β mRNA expression in rest muscle

α isoforms. Related to CON rest muscle (1.00 a.u.), there was no significant change with DIG in individual isoform mRNA, but each with a moderate effect size, for α_1 (1.70±1.72, P=0.23, d=0.58) or α_3 (1.85±2.25, P=0.52, d=0.53), but α_2 mRNA tended to increase with DIG (2.27±2.27, P=0.08, d=0.79). The total α mRNA expression ($\Sigma\alpha_1+\alpha_2+\alpha_3$) strongly tended to increase in DIG compared to CON (2.01±1.85, P=0.059) with a moderate effect size (d=0.77).

β isoforms. Related to CON rest, there were no significant changes with DIG in individual isoforms for β_1 (2.04±2.03, P=0.14, d=0.72), β_2 (1.19±0.75, P=0.44, d=0.36) or β_3 (1.57±1.22, P=0.17, d=0.66) mRNA. However, DIG increased the total β mRNA expression ($\Sigma\beta_1+\beta_2+\beta_3$) compared to CON (1.64±0.87, P=0.04).

Crude homogenate NKA α and β subunit protein abundance in rest muscle.

α isoforms. Related to CON rest, there was no significant change in α_1 (1.14±0.61, P=0.50, d=0.13), or α_3 (1.12±0.58, P=0.52, d=0.30) protein abundance with DIG. The α_2 protein tended to increase with DIG in rest muscle (1.44±0.74, P=0.08) with a large effect size (d=0.83).

β isoforms. Related to CON rest, there was no significant change in β_1 (1.19±0.58, P=0.32, d=0.47), β_2 (1.86±1.81, P=0.17, d=0.67) or β_3 (0.85±0.52, P=0.39, d=0.40) protein abundance with DIG in resting muscle.

DIGOXIN PLUS EXERCISE EFFECTS ON MUSCLE NKA CONTENT

MUSCLE TOTAL PROTEIN CONTENT

Total protein content was assessed to enable expression of pump content and activity relative to muscle protein; this was unchanged by DIG. Protein content was slightly reduced (P<0.01, g

protein.g muscle wet weight^{-1}) after exercise at 67% $\dot{V}O_{2peak}$ (0.183±0.009) and fatigue (0.182±0.007), compared to rest (0.197±0.008) and +3 h (0.204±0.007).

Muscle [^{3}H]ouabain binding site content with no F_{ab}

When compared across all four biopsy time points, the [^{3}H]ouabain binding site content measured using the standard binding assay (-F_{ab}) was not different between CON and DIG, regardless of whether expressed relative to muscle wet weight, or per g protein, indicating no systematic effects of DIG on measured NKA content (Figure 2). Effect sizes for ANOVAs are reported in the figure legends.

The [^{3}H]ouabain binding site content (-F_{ab}) expressed relative to muscle wet weight, tended to be higher at 67% $\dot{V}O_{2peak}$ than at rest (10%, *P*=0.051) and was higher than at 3h post-exercise (12%, *P* =0.005); at fatigue also tended to be higher than at 3h (5%, *P*=0.092, Figure 2).

Relative to muscle protein content, [^{3}H]ouabain binding site content (-F_{ab}) showed a similar pattern (Figure 2). Compared to rest, [^{3}H]ouabain binding (-F_{ab}) was increased by 21% at 67% $\dot{V}O_{2peak}$ (*P*=0.006) and tended to be higher at fatigue (16%, *P*=0.059); and was also higher at fatigue and 67% $\dot{V}O_{2peak}$ than 3h recovery by 20% and 25%, respectively (*P*=0.005).

Muscle [^{3}H]ouabain binding site content measured after clearance of bound digoxin by F_{ab}

When compared across all trial points, the [^{3}H]ouabain binding site content measured after clearance of bound digoxin by F_{ab}, did not differ between DIG and CON trials, whether expressed relative to muscle wet weight, or protein content (Figure 3). These results were thus consistent with the lack of systematic effect of DIG on the standard [^{3}H]ouabain binding measures (without F_{ab}).

However, no exercise effect could be detected when [^{3}H]ouabain binding site content was measured after clearance of bound digoxin by F_{ab} and when expressed relative to muscle wet weight. Thus, [^{3}H]ouabain binding site content with F_{ab} did not differ across all times (Figure 3). When expressed per g protein, some exercise effects were still

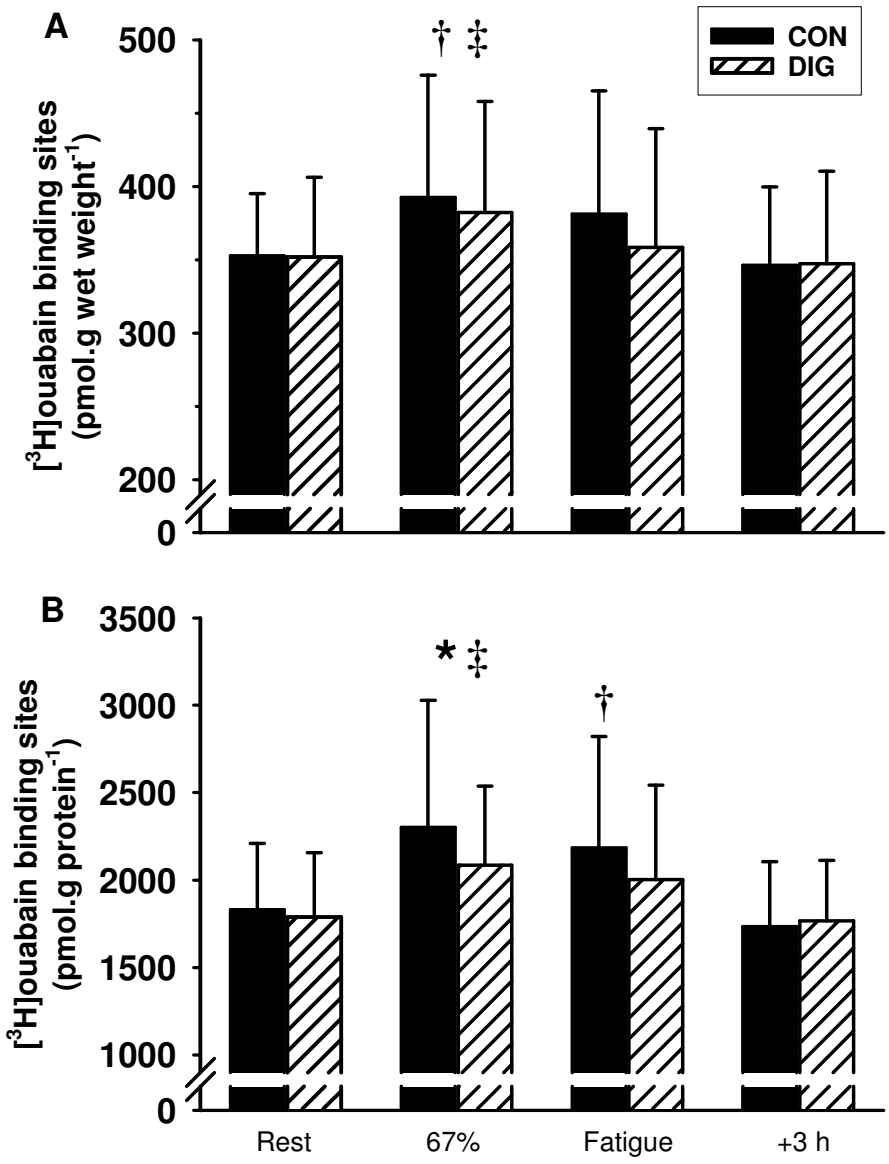

Figure 2. Effects of digoxin treatment and acute exercise on NKA content in human skeletal muscle (*without* F_{ab}). NKA content was measured by [^{3}H]ouabain binding sites without F_{ab} incubation, after 14 d digoxin (DIG) or placebo (CON) and expressed relative to (A) muscle wet weight and (B) muscle protein content. Biopsies samples were taken at rest, after cycling at 67% $\dot{V}O_{2peak}$, immediately following cycling at 90% $\dot{V}O_{2peak}$ to fatigue, and at 3 h post-fatigue. Data are mean ±SD, n = 10.

‡ greater than +3 h (P < 0.05), * > rest (P < 0.01), **†** tended to be > rest (P < 0.06), § tended to be > +3h (P < 0.10).

Effect sizes: per wet weight, treatment 0.05, time 0.30, treatment x time 0.08; per protein, treatment 0.19, time 0.46, treatment x time 0.17.

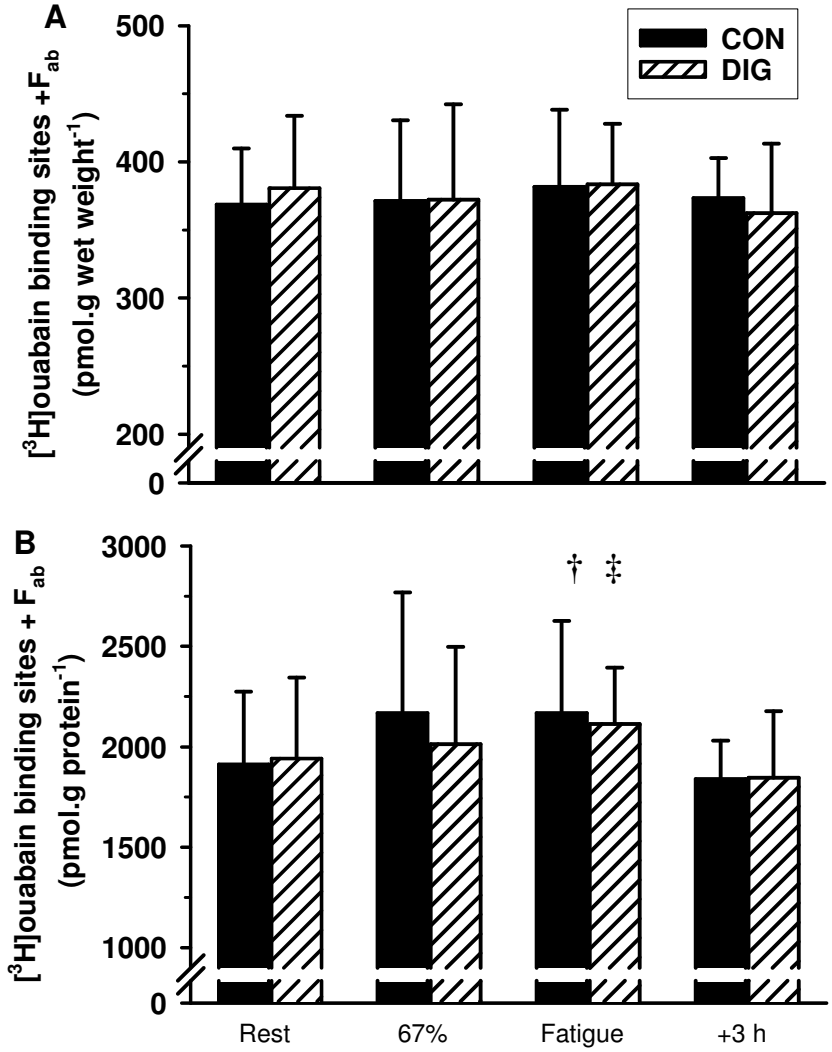

Figure 3. Effects of digoxin treatment and acute exercise on NKA content in human skeletal muscle, measured after clearance of bound digoxin by F_{ab} (ouabain binding + F_{ab}).

NKA content was measured by [^{3}H]ouabain binding sites after prior incubation in F_{ab}, after 14 d digoxin (DIG) or placebo (CON) and expressed relative to (A) muscle wet weight and (B) muscle protein content. Biopsies samples were taken at rest, after cycling at 67% $\dot{V}O_{2peak}$, immediately following cycling at 90% $\dot{V}O_{2peak}$ to fatigue, and at 3 h post-fatigue. Data are mean ±SD, n = 10. ‡ > +3h (P < 0.05), † tended to be > rest (P < 0.06). Effect sizes: per wet weight, treatment 0.01, time 0.05, treatment x time 0.04; per protein, treatment 0.031, time 0.27, treatment x time 0.09

apparent; [^{3}H]ouabain binding plus F_{ab} tended to be higher at fatigue than at rest (11%, *P* =0.058) and was higher than at 3 h post-exercise (17%, *P*=0.013, Figure 3).

Comparison of [^{3}H]ouabain binding site content with versus without F_{ab}

Pooling of [^{3}H]ouabain binding site measures across trial time points (i.e. rest, exercise and recovery) performed without prior incubation in digoxin F_{ab} (364 ± 68 pmol.(g wet weight)$^{-1}$), did not differ from pooled [^{3}H]ouabain binding site measured after incubation in F_{ab} (374 ± 50 pmol.(g wet weight)$^{-1}$, *n* = 80, *P*=0.60). Similarly, when expressed relative to muscle protein content, pooled [^{3}H]ouabain binding did not differ without prior incubation in F_{ab} (1962 ±513 pmol.g protein^{-1}) compared to with F_{ab} (2000 ± 409 pmol.g protein^{-1}, *n* = 80, *P*=0.36).

Calculations of digoxin occupancy across all trial time points indicated no systematic effects of either treatment (P=0.49) or exercise (P=0.22), or digoxin x exercise interactions (P=0.37).

DIGOXIN PLUS EXERCISE EFFECTS ON MUSCLE MAXIMAL IN-VITRO NKA ACTIVITY

All 3-O-MFPase activity assays were performed without F_{ab}. When compared across all trial points, maximal 3-O-MFPase activity was not different between CON and DIG when expressed relative to wet weight, or protein (Figure 4). Maximal 3-O-MFPase activity (per g wet weight) was depressed at fatigue by 15% from rest (*P* < 0.05) and had recovered at +3h (*P* < 0.01, Figure 4). When expressed relative to muscle protein content however, maximal in 3-O-MFPase activity did not change significantly as a result of exercise (-6% lower at fatigue, Figure 4).

Muscle NKA activity-to-content ratio

The activity-to-content ratio (per g wet weight) was unaffected by digoxin, but was reduced from rest by ~18% at 67%VO_{2peak} (P=0.022) and at fatigue (*P* =0.049), and had fully recovered (*P*<0.05) by 3 h (86.6 ±21.9, 71.0 ±15.0, 71.4 ±19.1, 88.1 ±26.1 a.u., respectively). The activity-to-content ratio (per g protein) was similarly reduced at 67%VO_{2peak} (P=0.01) and at fatigue (*P* =0.049) and had fully recovered (*P*<0.05) by 3 h (data not shown).

DIGOXIN PLUS EXERCISE EFFECTS ON MUSCLE NKA ISOFORM MRNA EXPRESSION

NKA α mRNA expression.

α_1. There was no significant effect of DIG on α_1 mRNA expression (Figure 5). The α_1 mRNA was increased above rest at 3 h post-exercise (P=0.035) and tended to be greater at fatigue (P=0.071). The treatment x time interaction tended to significance (P=0.09), but no differences were detected, although within CON α_1 mRNA at 3h tended to be greater than at rest (P=0.08, Figure 5).

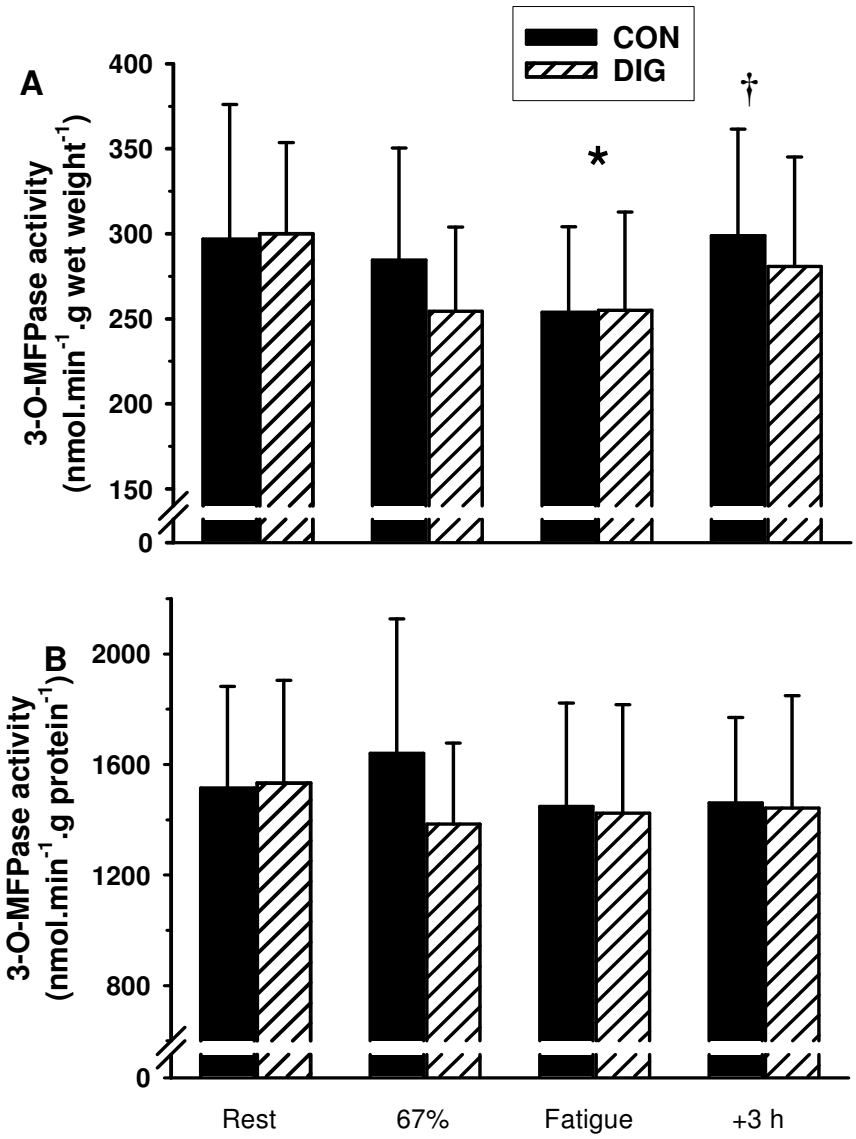

Figure 4. Effects of digoxin treatment and acute exercise on maximal in-vitro NKA activity.

NKA activity was measured by maximal in-vitro 3-O-MFPase activity, after 14 d digoxin (DIG) or placebo (CON) and expressed relative to (A) muscle wet weight and (B) muscle protein content. Biopsies samples were taken at rest, after cycling at 67% $\dot{V}O_{2peak}$, immediately following cycling at 90% $\dot{V}O_{2peak}$ to fatigue, and at 3 h post-fatigue. Data are mean ±SD, n = 10.

* less than rest (P < 0.05), † greater than fatigue (P < 0.01). Effect sizes: per wet weight, treatment 0.15, time 0.25, treatment x time 0.08; per protein, treatment 0.18, time 0.06, treatment x time 0.13.

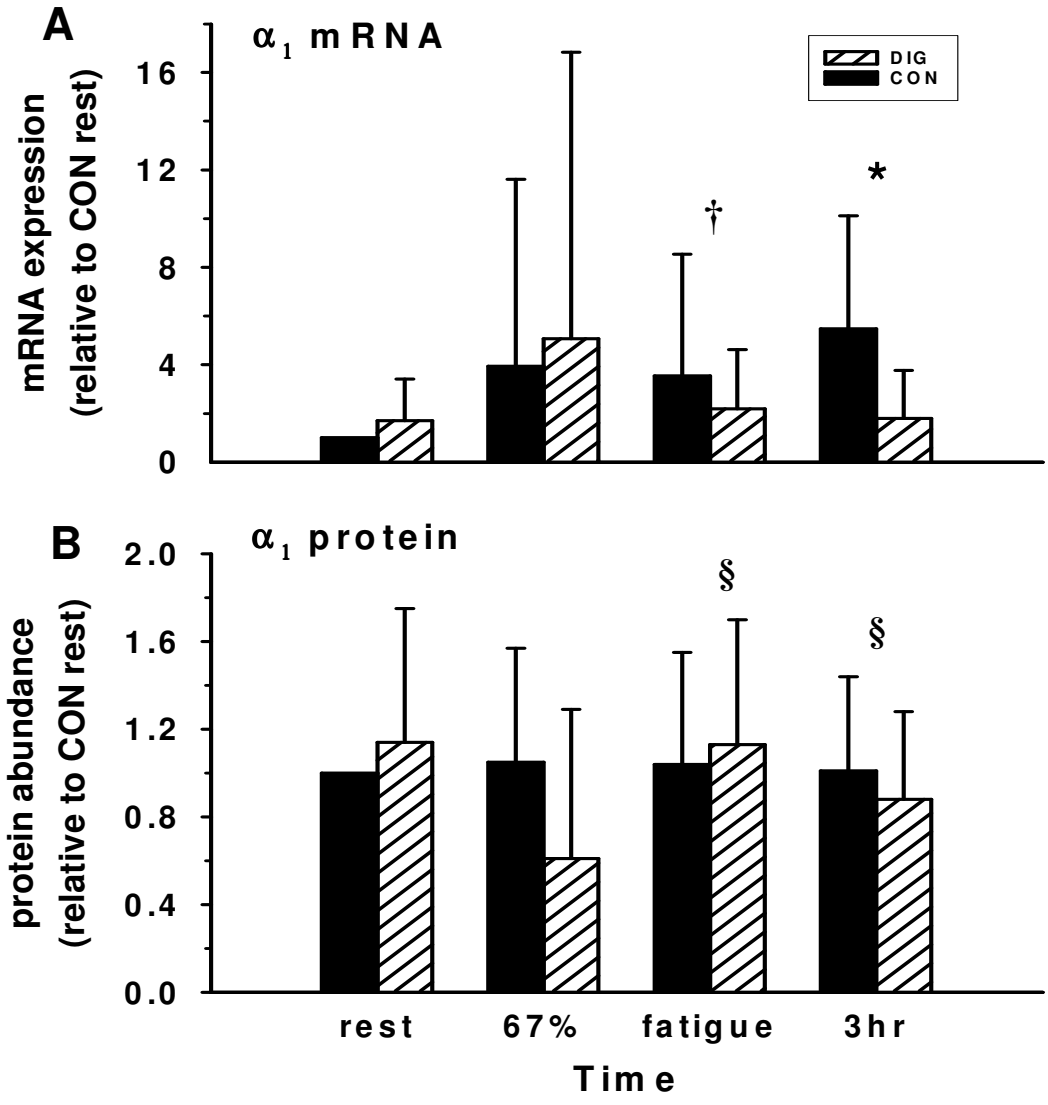

Figure 5. Muscle Na^+,K^+-ATPase α_1 mRNA expression and protein abundance before and after cycling exercise.

Biopsies samples were taken at rest, after cycling at 67% $\dot{V}O_{2peak}$, immediately following cycling at 90% $\dot{V}O_{2peak}$ to fatigue, and at 3 h post-fatigue. All results were normalised against resting CON values. Data are mean±SD, n=10.

* greater than rest ($P < 0.05$), **†** tended to greater than rest ($P < 0.08$), **§** tended to differ from rest ($P < 0.10$).

Effect sizes: α_1 mRNA: treatment 0.22, time 0.09, time x treatment 0. 21; α_1 protein: treatment 0.12, time 0.11, time x treatment 0.12.

α_2. There were no significant main effects of DIG or exercise on α_2 mRNA expression (Figure 6). Tendencies toward a significant digoxin-by-time interaction effect was detected for α_2 mRNA

(P=0.058), such that α_2 mRNA tended to be greater than CON rest, at each of CON Fatigue (P=0.06), CON 3 hr recovery (P=0.09) and DIG rest (P=0.08, Figure 6).

α_3. There was no significant effect of DIG on α_3 mRNA expression (Figure 7). An exercise main effect for α_3 mRNA expression was observed (P=0.007); α_3 mRNA was higher at 3 h post-exercise than after exercise at 67% $\dot{V}O_{2peak}$ and fatigue (78% and 43%, *P*=0.02 and P=0.005, respectively, Figure 7) and at fatigue tended to be less than at rest (36%, P=0.09). The CON +3h α_3 mRNA was also higher than at all other times (P<0.05) except DIG rest.

NKA β mRNA expression.

β_1. When compared across all trial points, there was no significant effect of DIG on β_1 isoform mRNA expression (Figure 8). There was no effect of exercise or recovery on β_1 mRNA expression. A tendency towards toward significant digoxin-by-time interaction effects were detected for β_1 mRNA (P=0.089).

β_2. There was no significant effect of DIG or exercise on β_2 isoform mRNA expression (Figure 9).

β_3. There was no significant effect of DIG on β_3 isoform mRNA expression (Figure 10). Exercise increased β_3 mRNA expression (P=0.004), being greater at 3 h post-exercise, compared to rest (78%), 67% $\dot{V}O_{2peak}$ exercise (43%) and fatigue (65%) (*P*<0.05, Figure 12). At 67% $\dot{V}O_{2peak}$ β_3 mRNA tended to be greater than at rest (25%, *P*=0.097). Within CON, fatigue and 3 h recovery β_3 mRNA were greater than at rest (156% and 171%, respectively, P<0.05).

DIGOXIN PLUS EXERCISE EFFECTS ON MUSCLE NKA ISOFORM PROTEIN EXPRESSION

NKA α subunit protein abundance

α_1. When compared across all trial points, there were no significant effects of DIG or exercise on crude muscle homogenate α_1 protein abundance, although tendencies of increase at fatigue (9%) and decline at 3 h post-exercise (12%) were found (P<0.10) (Figure 5).

α_2. A digoxin-by-time interaction effect was observed for α_2 protein abundance (*P*=0.031, Figure 6). In DIG there was a tendency towards increased α_2 at rest when compared to CON (44%, *P*=0.08, *d*=0.78). In CON α_2 protein was increased at 3 h post-exercise (60%, *P*=0.017). In contrast, in the DIG trial, α_2 at 3 h was reduced compared to rest (37%, *P*=0.034) and was less than in CON (43%, *P*=0.006).

α_3. There were no significant effects of DIG or exercise on α_3 protein abundance (Figure 7).

NKA β subunit protein abundance

β_1. When compared across all trial points, β_1 protein abundance was unchanged by DIG (Figure 8). The β_1 protein abundance at 3 h post-exercise was greater than 67% $\dot{V}O_{2peak}$ (42%, *P*=0.003) and fatigue (51%, *P*=0.006) and also tended to be greater than rest (44%, *P*=0.070, Figure 8).

β_2. The β_2 protein abundance was not altered by DIG (Figure 9), but was increased at fatigue compared to both rest (88%, *P*=0.02) and 67% $\dot{V}O_{2peak}$ (77%, *P*=0.043, Figure 9).

β_3. There were no significant main effects of digoxin on β_3 protein abundance. The β_3 protein abundance was increased above rest at 67% $\dot{V}O_{2peak}$ (46%, *P*=0.049) and 3 h post-exercise (57%, *P*=0.021, Figure 10) and tended to be higher at fatigue (58%, *P*=0.076). The β_3 protein abundance was greater at 3 h post-exercise in DIG than in CON (77%, *P*=0.034).

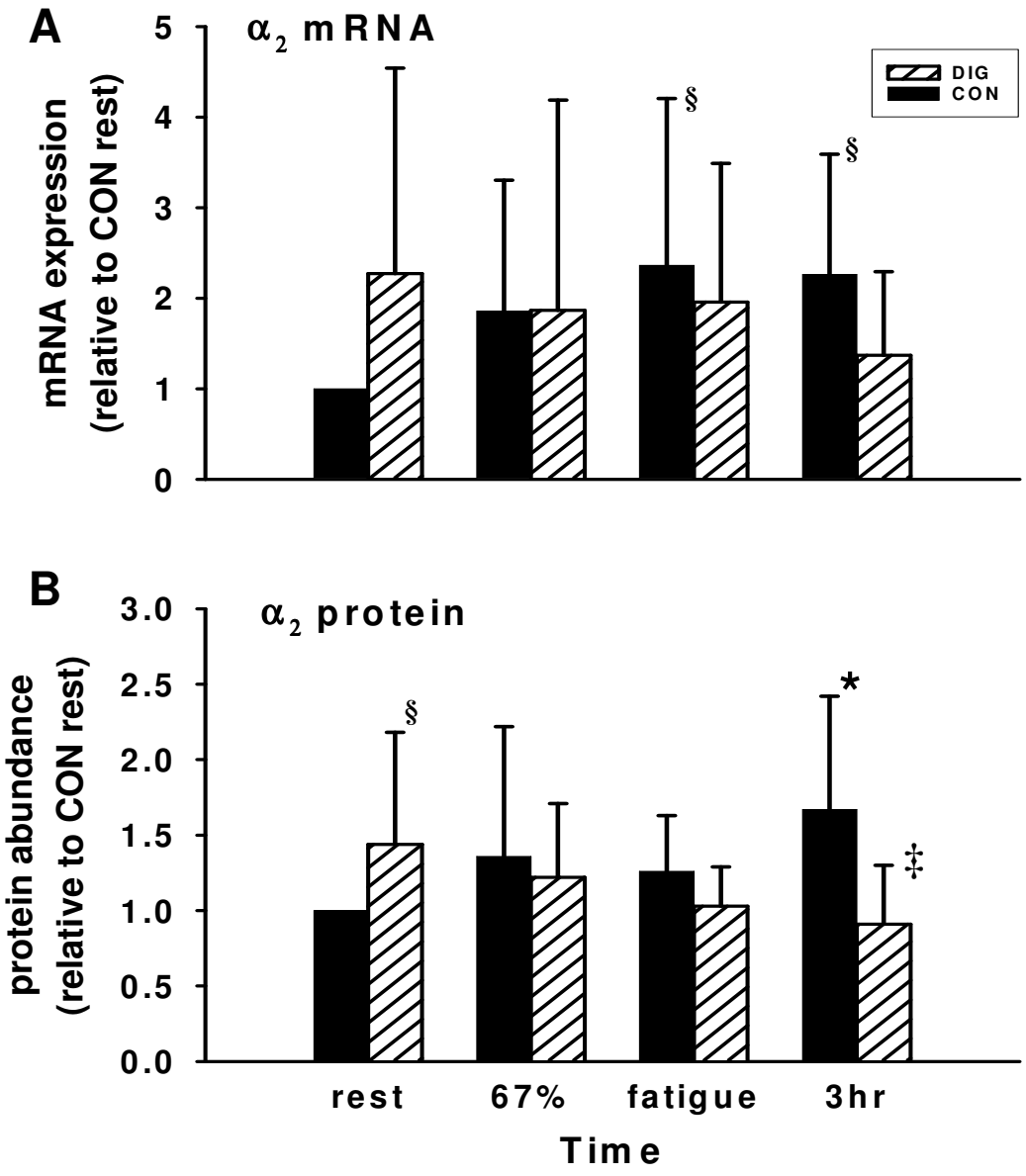

Figure 6. Muscle Na^+,K^+-ATPase α_2 mRNA expression and protein abundance before and after cycling exercise.

Biopsies samples were taken at rest, after cycling at 67% $\dot{V}O_{2peak}$, immediately following cycling at 90% $\dot{V}O_{2peak}$ to fatigue, and at 3 h post-fatigue. All results were normalised against resting CON values. Data are mean±SD, n=10. A tendency for a treatment-by-time interaction was observed for α_2 mRNA expression (*P*= 0.058) and α_2 protein abundance (*P*= 0.074). **§** tended to greater than Rest (*P* <0.10); * greater than CON Rest; ‡ less than DIG Rest and less than CON Rest P<0.05. Effect sizes: α_2 mRNA: treatment 0.00, time 0.06, time x treatment 0.238 (P=0.058); α_2 protein: treatment 0.24, time 0.03, time x treatment 0.28 (P=0.031).

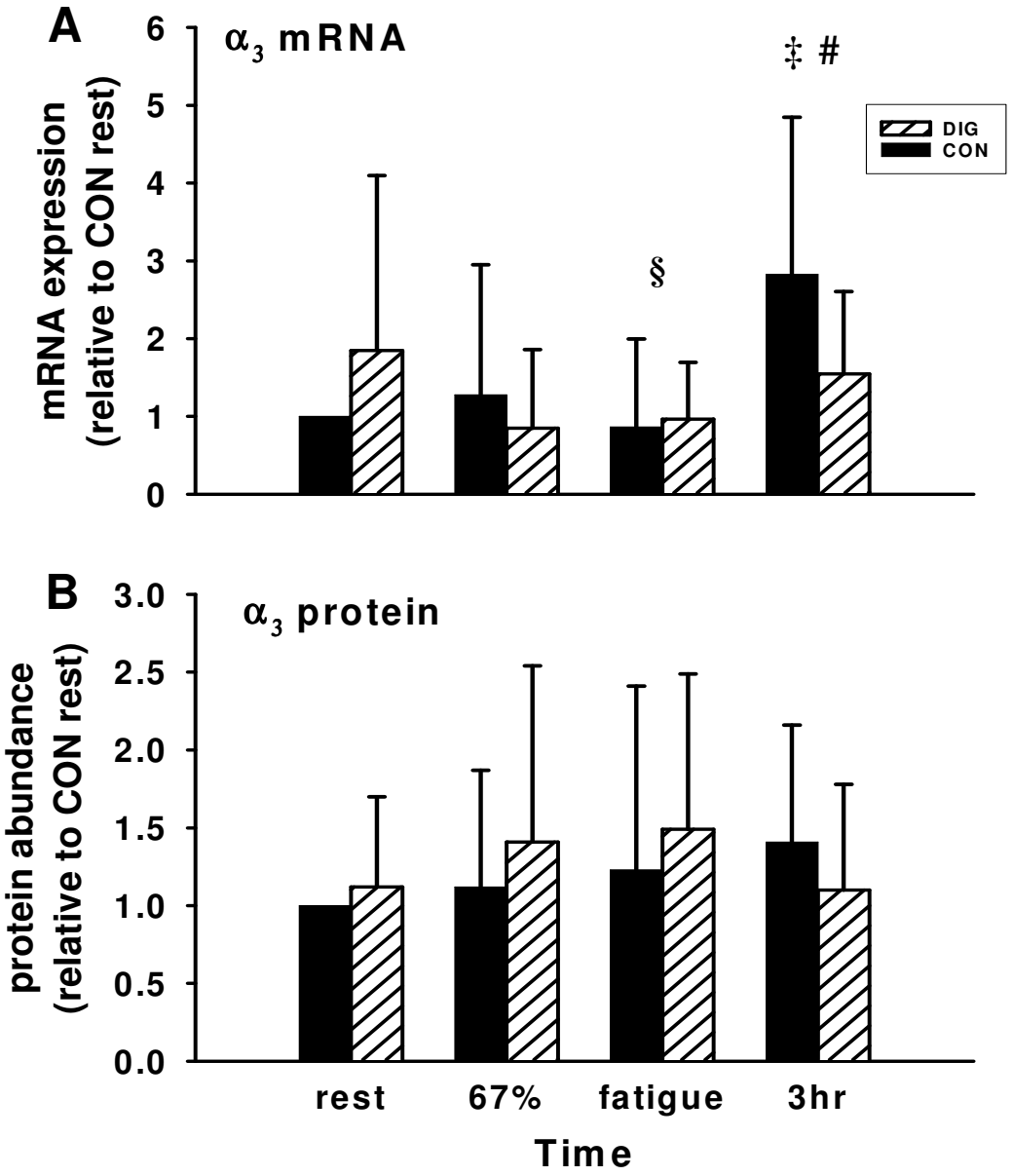

Figure 7. Muscle Na^+,K^+-ATPase α_3 mRNA expression and protein abundance before and after cycling exercise.

Biopsies samples were taken at rest, after cycling at 67% $\dot{V}O_{2peak}$, immediately following cycling at 90% $\dot{V}O_{2peak}$ to fatigue, and at 3 h post-fatigue. All results were normalised against resting values. Data are mean±SD, n=10.

‡ $P<0.05$ greater than $\dot{V}O_{2peak}$ 67%, # $P<0.01$ greater than fatigue, **§** tended to less than Rest ($P<0.10$).

Effect sizes: α_3 mRNA: treatment 0.07, time 0.36, time x treatment 0.23 (P=0.069); α_3 protein: treatment 0.05, time 0.08, time x treatment 0.13.

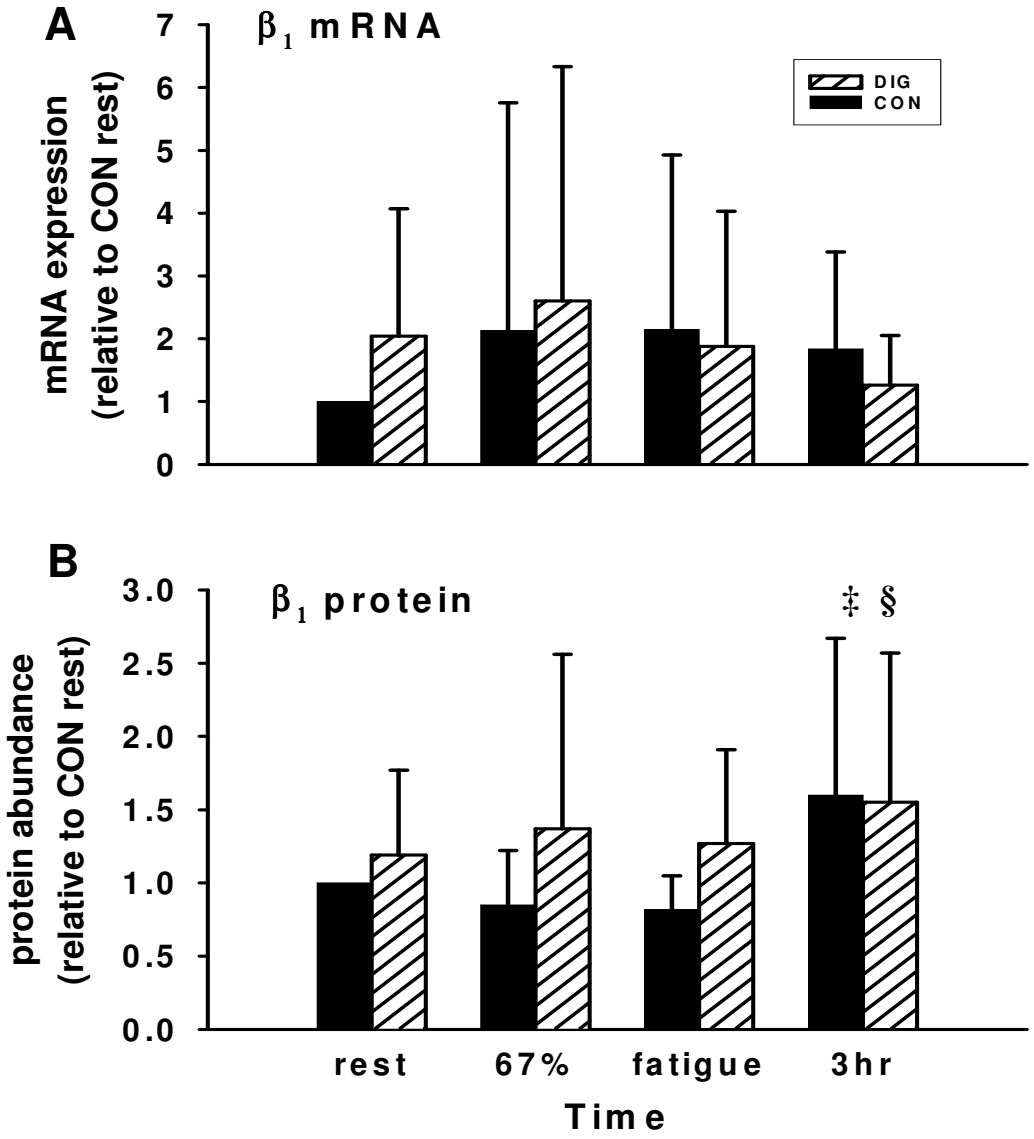

Figure 8. Muscle Na^+,K^+-ATPase β_1 mRNA and protein expression before and after cycling exercise.

Biopsies samples were taken at rest, after cycling at 67% $\dot{V}O_{2peak}$, immediately following cycling at 90% $\dot{V}O_{2peak}$ to fatigue, and at 3 h post-fatigue. All results were normalised against resting CON values. Data are mean±SD, n=10.

‡ *P*< 0.005 greater than 67% $\dot{V}O_{2peak}$ and than fatigue, **§** tended greater than Rest P<0.08.
Effect sizes: β_1 mRNA: treatment 0.06, time 0.07, time x treatment 0. 21 (P=0.089); β_1 mRNA: treatment 0.20, time 0.33, time x treatment 0.06.

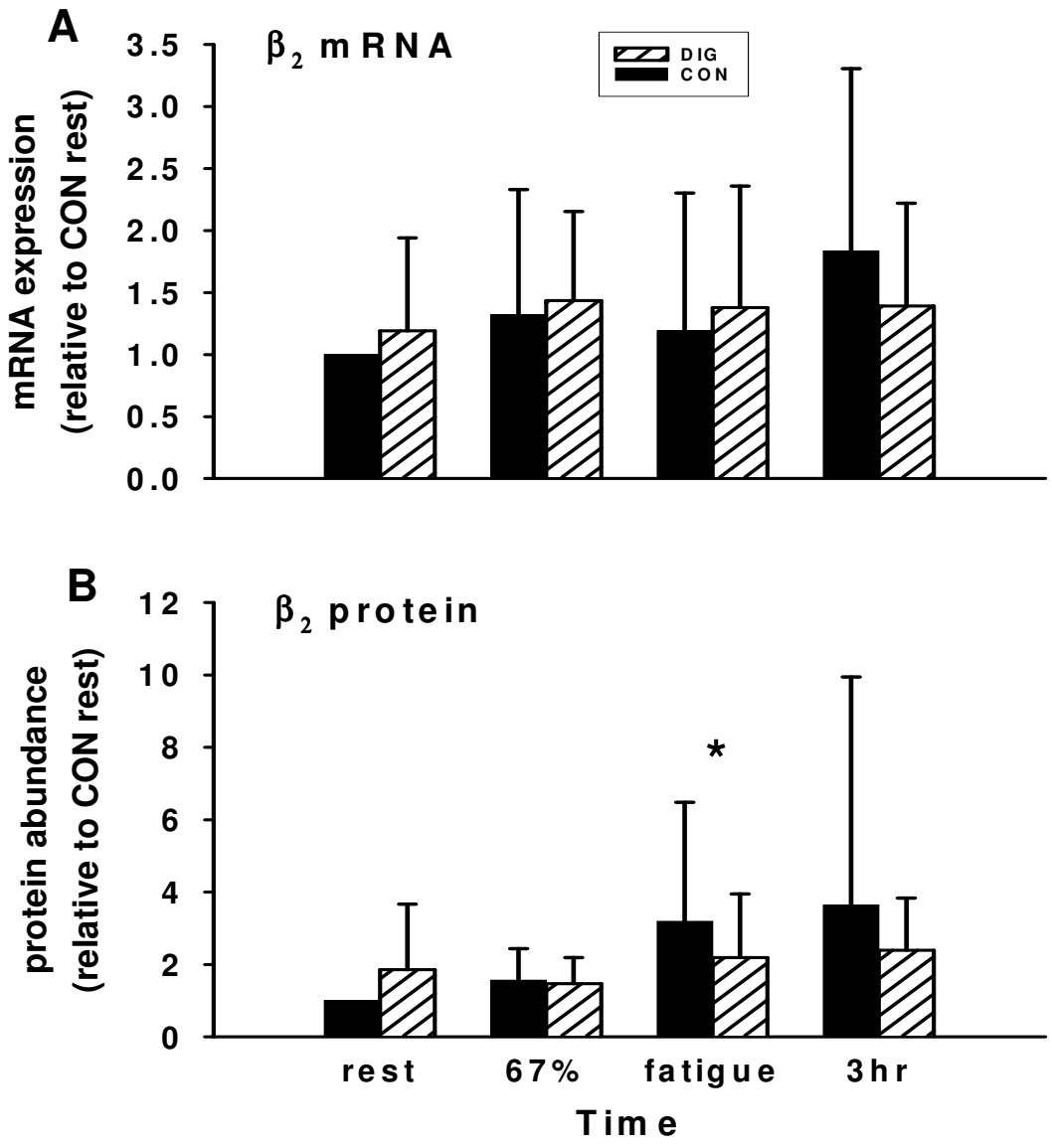

Figure 9. Muscle Na^+,K^+-ATPase β_2 mRNA expression and protein abundance before and after cycling exercise.

Biopsies samples were taken at rest, after cycling at 67% $\dot{V}O_{2peak}$, immediately following cycling at 90% $\dot{V}O_{2peak}$ to fatigue, and at 3 h post-fatigue. All results were normalised against resting CON values. Data are mean±SD, n=10.

* $P < 0.05$ greater than Rest and 67% $\dot{V}O_{2peak}$. Effect sizes: β_2 mRNA: treatment 0.00, time 0.13, time x treatment 0.08; β_2 protein: treatment 0.06, time 0.21 (P=0.096), time x treatment 0.68.

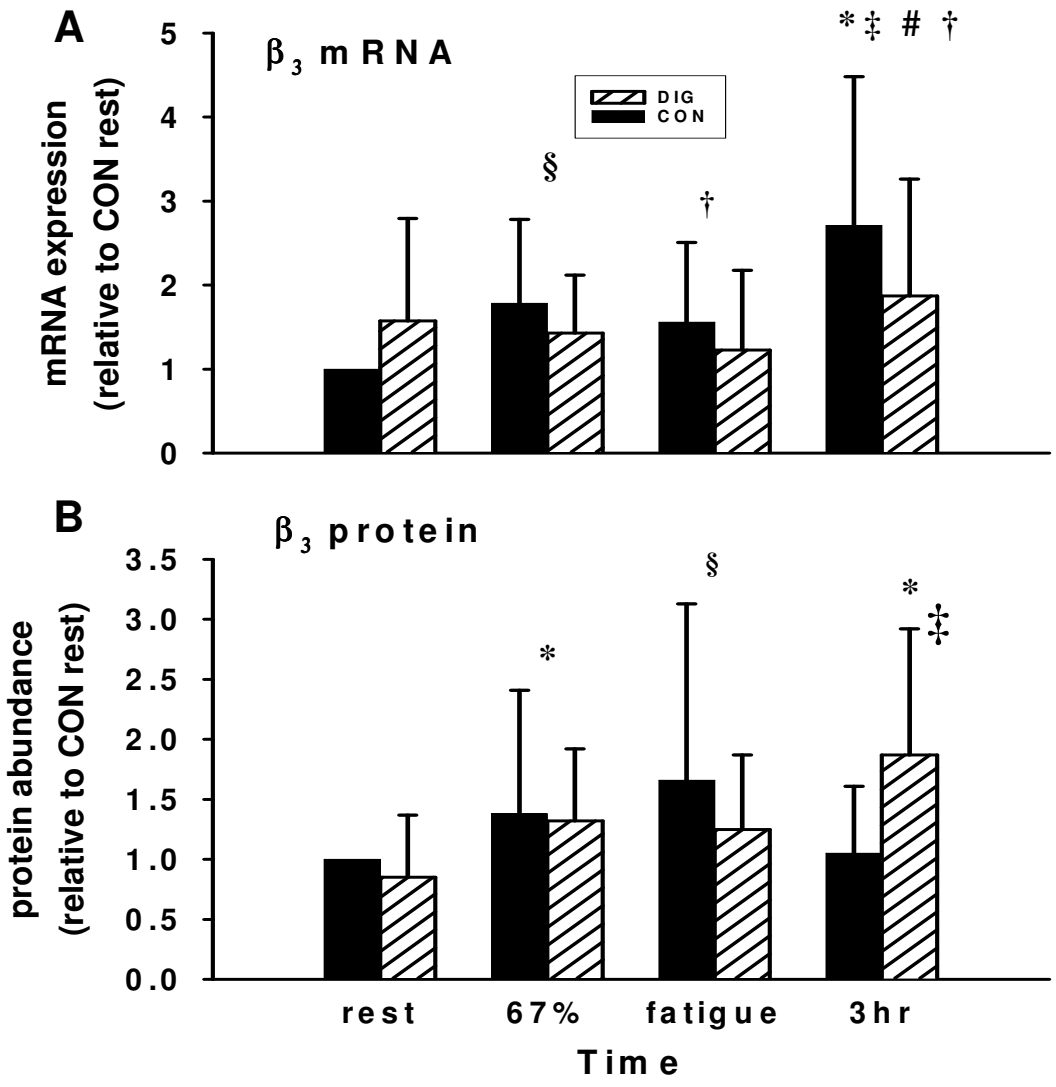

Figure 10. Muscle Na^+,K^+-ATPase β_3 mRNA and protein expression before and after cycling exercise.

Biopsies samples were taken at rest, after cycling at 67% $\dot{V}O_{2peak}$, immediately following cycling at 90% $\dot{V}O_{2peak}$ to fatigue, and at 3 h post-fatigue. All results were normalised against resting CON values. Data are mean±SD, n=10.

* *P*<0.05 greater than rest, ‡ *P*<0.05 greater than 67% $\dot{V}O_{2peak}$, # *P*<0.05 greater than fatigue, **§** tend greater than Rest *P*<0.10, **†** *P*<0.05CON greater than CON Rest. ‡ *P*<0.05DIG 3 h greater than CON 3 h.

Effect sizes: β_3 mRNA: treatment 0.18, time 0.38, time x treatment 0.60; β_3 protein: treatment 0.02, time 0.27 (P=0.016), time x treatment 0.23 (P=0.063).

DISCUSSION

Digoxin is a specific Na^+,K^+-ATPase (NKA) inhibitor that has been used to treat heart failure for more than two centuries. There is renewed clinical interest in digoxin, since low serum digoxin concentration (SDC) is associated with reduced hospitalisation and all-cause mortalities in patients with heart failure (Ahmed *et al.*, 2006). This is the first study to investigate the effects of digoxin on skeletal muscle NKA content, digoxin occupancy and NKA activity in healthy humans. We administered digoxin for 14 d, aiming to produce similarly low SDC, in healthy humans, thereby avoiding any complicating disease, inactivity or medication effects. Our skeletal muscle NKA analyses were comprehensive, including NKA content, maximal in-vitro activity, isoform mRNA expression and isoform protein abundance, all measured at rest, with exercise and recovery. Since NKA is integral to muscle contractile performance, we also investigated the effects of digoxin on human skeletal muscle strength, fatiguability and endurance. We show several novel and surprising findings.

Clinically relevant digoxin levels induces NKA upregulation in resting muscle, thus maintaining NKA morphology and function

The SDC attained in these healthy young adults with digoxin (0.8 $nmol.l^{-1}$, ~0.62 $ng.ml^{-1}$) was similar to SDC (0.9 $nmol.l^{-1}$) reported in healthy males after an identical dosage (Schenck-Gustafsson *et al.*, 1987), and within the optimal therapeutic range (0.5-0.9 $ng.ml^{-1}$, ~0.65–1.15 nM) (Ahmed *et al.*, 2006). Hence, with therapeutic levels of digoxin achieved, interpretation of any muscle NKA and functional changes with digoxin is clinically relevant. We hypothesised that muscle NKA content and thus also maximal in-vitro activity would be reduced with digoxin, given digoxin binding to skeletal muscle (Jogestrand & Sundqvist, 1981), plus the reported lack of compensatory NKA upregulation in skeletal muscle with digitalisation (Schmidt *et al.*, 1993; Green *et al.*, 2001). However, digoxin did not reduce NKA content or maximal in-vitro activity in rest muscle. Rather, we found a 7% digoxin occupancy of NKA, with an upregulation in NKA content evident after removal of digoxin from muscle. Furthermore, there was a corresponding tendency towards increased α_2 isoform protein abundance in rest muscle with DIG (P=0.08).

In contrast to our hypothesis, muscle NKA content measured by the standard [^{3}H]ouabain binding site method was not depressed, but was unchanged by digoxin. As [^{3}H]ouabain binds to all functional $\alpha\beta$ complexes in human muscle, this method would normally enable complete quantification of NKA content (Nørgaard *et al.*, 1983). In muscle exposed to digoxin, however, some NKA will already be bound by digoxin and thus unavailable for [^{3}H]ouabain binding, thereby underestimating true NKA content (Schmidt & Kjeldsen, 1991). We therefore used digoxin antibody fragments (F_{ab}) to first clear any digoxin bound in muscle, followed by [^{3}H]ouabain binding, to determine the digoxin-NKA occupancy and detect any NKA upregulation with digitalisation (Schmidt & Kjeldsen, 1991). We first confirmed that the F_{ab} wash methodology enabled almost complete NKA recovery (96%) in healthy human muscle biopsy samples incubated in digoxin, consistent with 97% recovery in skeletal muscle obtained post-mortem (Schmidt & Kjeldsen, 1991). Any compensatory NKA upregulation with DIG should be revealed via an increased [^{3}H]ouabain binding site content when measured after clearance of bound

digoxin by F_{ab} incubation. In rest muscle samples, a significantly higher [^{3}H]ouabain binding was detected in the DIG trial after F_{ab} incubation, compared to with no F_{ab} wash, indicating both a digoxin occupancy rate of 7 % in DIG, and that NKA upregulation had in fact occurred during the 14 d DIG trial. Our findings of 7% digoxin occupancy in the DIG trial are quite consistent with the NKA occupancy by digoxin of 9% in skeletal muscle obtained from living heart failure patients digitalised for 3 days, and 13% in muscle obtained post-mortem from previously digitalised patients, after similar digoxin dosages (Schmidt *et al.*, 1993; Schmidt *et al.*, 1995). Extremely high digoxin occupancy of 35% has been reported in heart failure patients taking digoxin (Green *et al.*, 2001), but the reason for such a large discrepancy is not evident. As previous studies in healthy individuals have demonstrated digoxin uptake in quadriceps muscle with digitalisation (Joreteg & Jogestrand, 1983), occurring in both slow and fast twitch fibers (Joreteg, 1986), digoxin binding to muscle was certainly expected here. The slightly higher occupancy (9-13%) in previous studies could have ensued from the higher SDC (1.2–2.3 nM) and because they were conducted with heart failure patients (Schmidt *et al.*, 1993; Schmidt *et al.*, 1995), who already had depressed NKA content (Norgaard *et al.*, 1990) and probably reduced muscle mass due to cachexia, with digoxin distributed over a smaller tissue volume than in the young, active subjects tested here.

Interestingly, no increase was detected in [^{3}H]ouabain binding site content between CON and DIG trials, when compared across all time points, with similar [^{3}H]ouabain binding between treatments in muscle measured either with, or without F_{ab} incubation. This is not surprising and most likely reflects: (i) the small magnitude of upregulation with DIG after F_{ab} incubation; (ii) a slightly higher [^{3}H]ouabain binding after F_{ab} incubation in CON of 3.3%; and (iii) variability of the [^{3}H]ouabain binding assay. Others have also reported a tendency to higher [^{3}H]ouabain binding after F_{ab} incubation in muscle not previously exposed to digoxin, compared to no F_{ab} incubation, with an “apparent digoxin occupancy rate” of 5.2% (Schmidt & Kjeldsen, 1991), 6.2% (Schmidt *et al.*, 1993), and 5.1% (Green *et al.*, 2001), similar to ours of 3.3%. This does not appear to be an artefact of the long (16h) incubation period used with F_{ab} as this did not affect [^{3}H]ouabain binding, consistent with other findings (Schmidt & Kjeldsen, 1991; Green *et al.*, 2001). It is unlikely that the 7% digoxin occupancy in the DIG trial simply reflects a similar increment as in control muscle after F_{ab} incubation (Schmidt & Kjeldsen, 1991; Schmidt *et al.*, 1993; Green *et al.*, 2001). First, none of these three studies, or the present one, reported significantly greater [^{3}H]ouabain binding in control muscle after F_{ab} incubation. In our study, the significant elevation in [^{3}H]ouabain binding after F_{ab} was found only after digoxin, as would be expected. Second, the non-significant difference of 3% in CON should be contrasted against the two-fold higher 7% digoxin occupancy in the DIG trial. The observed difference in [^{3}H]ouabain binding between with and without F_{ab} conditions, representing digoxin binding, was 29 pmol.g^{-1} wet weight, slightly greater than muscle digoxin content of ~32 -39 nmol.kg^{-1} dry weight (~8-10 pmol.g^{-1} wet weight) previously measured by radioimmunoassay, in digitalised healthy males with a similar SDC (Ericsson *et al.*, 1981; Jogestrand & Sundqvist, 1981; Schenck-Gustafsson *et al.*, 1987).

One reason that previous studies failed to find skeletal muscle NKA upregulation with digitalisation might be because these studies were conducted in heart failure patients (Schmidt *et al.*, 1993; Schmidt *et al.*, 1995; Green *et al.*, 2001). However, pre- and post-digitalisation biopsies were not obtained in any of these studies, as in the present study, in which the effects were demonstrated. Our findings of compensatory upregulation of NKA content in skeletal muscle are consistent with upregulation in erythrocytes following digitalisation in humans (Ford *et al.*, 1979). The NKA maximal activity was unchanged, not depressed with digoxin, as would be anticipated. Thus the lack of change in NKA activity is consistent with the small compensatory NKA upregulation with digoxin detected by [^{3}H]ouabain binding±F_{ab}. Importantly, our finding of unchanged NKA activity in human muscle clearly contrasts with the 30% elevation in NKA activity reported with digitoxin in guinea pig myocardium after only 10-15 days (Bonn & Greeff, 1978).

That neither muscle NKA content nor maximal activity were reduced after clinically relevant digitalisation in healthy humans points to resilience of skeletal muscle NKA in healthy adults undergoing a digoxin challenge. This is not apparent in heart failure patients, where substantially lower *functional* NKA content is evident in muscle – i.e. [^{3}H]ouabain binding in muscle not subjected to F_{ab} incubation was significantly reduced (Schmidt & Kjeldsen, 1991; Schmidt *et al.*, 1993; Green *et al.*, 2001). The maintenance of muscle NKA content and activity with digoxin in these healthy individuals presents an intriguing scenario of NKA regulation. The constant NKA content despite 7% digoxin-NKA occupancy, indicates increased NKA synthesis and/or reduced NKA degradation, that was sufficient to reverse depressed functional NKA to pre-digoxin levels, but not beyond this. The mechanism for this effect is unclear, but would allow for muscle NKA stability to compensate for any functional NKA reductions due to e.g. binding by digoxin, with the consequence of unchanged muscle NKA content or activity. This possibility is strongly suggested by adaptive responses to DIG evident at the NKA isoform gene and protein expression levels.

We hypothesised that digoxin, by inhibiting a fraction of NKA, would increase NKA isoform mRNA expression in human skeletal muscle. An important and novel finding was that in muscle biopsies taken at rest digoxin increased NKA total β mRNA expression ($\Sigma\beta_1+\beta_2+\beta_3$) by 0.6-fold. This is consistent with increased NKA β gene transcription with digoxin, although might also reflect reduced degradation or translation. The total NKA α mRNA expression ($\Sigma\alpha_1+\alpha_2+\alpha_3$) also tended to be 1.0-fold higher with DIG, with a moderate effect size (0.74) suggesting an effect of DIG also on NKA α isoform gene expression. Since there were no significant changes in mRNA expression detected for individual α or β isoforms, underlying changes cannot be confirmed. Nonetheless, the increased total β mRNA clearly indicate, and the tendency to increased total α mRNA strongly suggest, activation of NKA isoform gene expression in healthy skeletal muscle with digoxin. Furthermore, there was a tendency for digoxin to increase α_2 protein abundance in rest muscle (44%, P=0.08), consistent with increased NKA content detected after F_{ab} incubation. Since α_2 is the dominant α-subunit, representing ~75-85% NKA in skeletal muscle (Hansen, 2001), the magnitude of increase in α_2 protein exceeds that of [^{3}H]ouabain binding, a

discrepancy which we cannot explain. Nonetheless, NKA adaptation to DIG is clearly evident in healthy muscle. These findings may give some insight into muscle adaptation in heart failure patients. We speculate that an enhanced NKA turnover effect evident in control muscle might be absent or diminished in advanced heart failure, eventually contributing to their loss of muscle NKA content (Norgaard *et al.*, 1990), and consistent with their lack of NKA adaptation in response to digoxin and physical training (Green *et al.*, 2001).

There is evidence for cardiac glycosides differentially affecting NKA isoform mRNA, and transcription rates, although these are difficult to apply to the current study, being studied in other species, tissues and cell preparations, and with different glycoside concentrations. Chronic digoxin injections in rats stimulated increased myocardial α_3 isoform mRNA, without significant change in α_1 or α_2 mRNA (Wang *et al.*, 2000). Conversely, in neonatal rat cardiomyocytes, non-toxic ouabain concentrations (5-100 μM) decreased α_3 mRNA expression, in a dose- and time-dependent manner (Huang *et al.*, 1997; Kometiani *et al.*, 2000), depressed α_3 transcription rates and α_3 protein levels (Huang *et al.*, 1997), but also increased β_1 mRNA expression (Kometiani *et al.*, 2000). Exposure of rat cardiomyocytes to a high ouabain concentration (1 mM) induced a rapid two - to four-fold increase in α_1, α_2, α_3 and β_1 mRNA expression, with an increased $\alpha_1$protein abundance (Yamamoto et al., 1993). In contrast, incubation of isolated rat EDL muscle in high ouabain (1 mM) depressed β_2 and β_3 mRNA and tended to lower α_2 and α_3 mRNA (Murphy *et al.*, 2006a). Despite obvious difficulties in extrapolating these findings to digitalisation effects in skeletal muscle in healthy humans, these studies do provide an evidential basis consistent with digoxin-induced regulation of NKA α and β subunit isoform expression.

EXERCISE AND DIGOXIN EFFECTS ON NA^+,K^+-ATPASE IN HUMAN SKELETAL MUSCLE

The combined effects of digoxin plus exercise and recovery were studied on NKA content, activity, gene expression and protein abundance, as each has been shown to exert effects on these variables.

Digoxin did not exacerbate increased NKA isoform mRNA expression with exercise

Exercise. The NKA isoform responses to exercise (10 min submaximal bouts at each of 33% and 67% $\dot{V}O_{2peak}$ then a third bout continued until fatigue at 90% $\dot{V}O_{2peak}$) differed to what we and others have previously found. Only the α_1, α_3 and β_3 mRNA transcripts were increased with exercise, and only at 3 h post-exercise, although strong tendencies towards increased α_2 mRNA (P=0.06) and increased α_1 mRNA at fatigue (P=0.06) were observed. These findings clearly contrast earlier studies, where each of the α_1-α_3, and β_1-β_3 isoform mRNA expression were increased after brief, intense exercise (Murphy *et al.*, 2004; Petersen *et al.*, 2005), and where intense, and intermittent exercise protocols elevated the α_1, α_2 and α_3 isoform mRNA after exercise (Murphy *et al.*, 2004; Nordsborg *et al.*, 2005; Petersen *et al.*, 2005; Murphy *et al.*, 2006b; Aughey *et al.*, 2007). One reason for the fewer significant exercise effects observed here might relate to the lower, submaximal exercise intensities employed. The findings that gene

activation was not induced for all six NKA isoforms, and with increases observed in α_1 and α_3 mRNA, are consistent with our previous prolonged submaximal (75% $\dot{V}O_{2peak}$) exercise study (Murphy *et al.*, 2006b). However, findings differ for exercise effects on β isoforms. Here we found increased β_3 mRNA, whereas previously with submaximal exercise we reported only β_2 mRNA was elevated (Murphy *et al.*, 2006b). Others have also reported an increased β_3 mRNA after prolonged exercise at intensities similar to used here, but unfortunately did not probe other isoforms (Mahoney *et al.*, 2005). In rats, 1 h of treadmill running exercise increased the α_1 mRNA in red-type I muscle and the β_2 mRNA in white-type IIb muscles, but the α_2 and β_1 mRNA levels were unaffected by exercise; neither α_3 nor β_3 mRNA expression were detected (Tsakiridis *et al.*, 1996). It seems unlikely that these differences might simply be because we missed the time course of NKA gene activation, as most studies that have examined NKA gene expression with exercise report mRNA changes within the first 0-3 h post-exercise (Nordsborg *et al.*, 2003; Murphy *et al.*, 2004; Nordsborg *et al.*, 2005; Murphy *et al.*, 2006b). Finally, we cannot exclude the possibility that variability in the Real-Time RT-PCR method prevented detection of some changes, as might be suggested from tendencies to higher mean data at fatigue for α_1 mRNA. Only trivial effect sizes (0-0.2) were observed for exercise main effects for non-significant mRNA responses (α_2, β_1 and β_3). However, there was a tendency toward higher mRNA observed at rest in DIG for α_2 and β_1 isoforms, which may have obscured a possible rise in the CON trial suggested with exercise. Further, whilst digoxin-by-exercise interaction effects for NKA α_2, β_1 and β_3 isoform mRNA expression were non significant, strong tendencies were found for both α_2 (P=0.058) and β_1 (P=0.089) mRNA expression. In addition, a small effect size (0.2-0.5) for interactions for α_2 and β_1, also point to possible undetected changes. We therefore cannot exclude the possibilities of Type II errors in failing to detect exercise and DIG effects on NKA gene activation, at least for α_2 and β_1.

Digoxin. No significant main effects were detected for any NKA isoform mRNA with DIG, indicating no widespread up/down-regulation of any NKA gene with DIG and exercise, which contrasts the large α_3 downregulation with DIG in cardiomyocytes (Huang *et al.*, 1997). Our analyses are complicated by the possible interactions of both digoxin and of exercise on mRNA response to exercise. Thus the tendency toward higher mRNA at rest in DIG for the dominant α_2 and β_1 isoforms may have prevented a possible rise with exercise, as suggested in the CON trial. This suggests that DIG might desensitise NKA transcription in skeletal muscle to activating stimuli invoked by exercise. This may be important in explaining why heart failure patients did not upregulate NKA content with DIG or exercise training (Green *et al.*, 2001), a well established training adaptation (McKenna, 1998).

Exercise increased NKA content and isoform protein abundance

The [^{3}H]ouabain binding content fully quantifies NKA in non-digitalised human skeletal muscle biopsy pieces (Nørgaard *et al.*, 1984) and we have previously found this to be unchanged with acute exercise in humans (for review see (McKenna *et al.*, 2008)), and also in rat muscles after electrical stimulation (McKenna *et al.*, 2003). Thus the observed transient increase in

[^{3}H]ouabain binding of 5-10% per muscle wet weight (16-21% per muscle protein) after only 20-30 minutes of exercise was surprising, suggesting an increased number of NKA in muscle with exercise. Whilst consistent with a 13% increase in muscle [^{3}H]ouabain binding after ~10 hours running, attributed to synthesis of new Na^+,K^+-pumps (Overgaard *et al.*, 2002), synthesis of~35-70 pmol NKA per gram muscle seems too rapid and thus unlikely after only 20-30 min of exercise. This increase is unlikely to reflect an increased rate of ouabain binding due to increased NKA activity with exercise, since the assay conditions ensure saturation of [^{3}H]-ouabain binding (Nørgaard *et al.*, 1984). An alternative explanation for an increase in [^{3}H]ouabain binding site with exercise could be increased recruitment of NKA subunits to the sarcolemma and t-tubules (Benziane & Chibalin, 2008), from undefined intracellular stores, as reported in membrane fractions following exercise (Tsakiridis *et al.*, 1996; Juel *et al.*, 2000; Juel *et al.*, 2001), or possibly from caveolae (Kristensen *et al.*, 2008). However, this conflicts with a previous study, where we were unable to detect increases in [^{3}H]ouabain binding sites in stimulated rat muscle, which would be expected if an increased availability of NKA occurred (McKenna *et al.*, 2003). Importantly, when measured after removal of bound digoxin by F_{ab} and expressed per g wet weight, we did not detect any increase in [^{3}H]ouabain binding with exercise. However, a tendency to elevation was still present at fatigue after measures with F_{ab}, when expressed per g protein. The similar results when expressed per gram protein with and without the F_{ab} suggest that the result cannot be excluded as an artefact, perhaps caused by variability of the assay. Finally, we anticipated that digoxin binding to muscle would be increased with exercise in the DIG trial, and to a greater extent with increased exercise intensity, of up to 20% (Joreteg & Jogestrand, 1983). This effect would lower [^{3}H]ouabain binding, the opposite of the increase we observed; the reason for the lack of this effect is not clear. Thus our [^{3}H]ouabain binding results are not consistent and whilst they cannot be interpreted to conclusively support increased NKA recruitment with exercise; nonetheless they are intriguing and consistent with this possibility.

If there is an increased NKA availability in these cut muscle pieces, due to synthesis, or recruitment from secluded cellular locations, then increased α and β subunit protein abundance should also be apparent with exercise in crude muscle homogenates. None of α_1, α_2 or α_3 isoform protein abundance were significantly increased at 67% VO_{2peak} or at fatigue, when NKA content was increased. However, α_1 protein tended to increase at fatigue (9%) and decline at 3 h post-exercise. Clear and surprising findings were the increases detected in each of β_1, β_2 and β_3 isoform protein abundance with exercise, suggesting an increased overall availability of β subunits with exercise. Thus these results are consistent with unchanged NKA α_{1-3} protein, but contrast the unchanged β_{1-3} isoform protein abundance 0-3 h after brief, exhaustive exercise (Murphy *et al.*, 2004), or prolonged submaximal exhaustive exercise (Murphy *et al.*, 2006b).

Reduced NKA maximal in-vitro activity to content ratio with exercise

The maximal NKA activity, as measured by the in-vitro 3-O-MFPase activity assay, was reversibly depressed with exhaustive exercise, similar to previous findings (for review see (McKenna *et al.*, 2008)). Surprisingly, this effect was absent when activity was expressed per

gram protein. The reason for this discrepancy is unclear, as numerous studies have reported reduced maximal in-vitro 3-O-MFPase activity following fatiguing exercise when expressed relative to muscle protein content (Fowles *et al.*, 2002; Fraser *et al.*, 2002; Leppik *et al.*, 2004; Sandiford *et al.*, 2004; Aughey *et al.*, 2005; Aughey *et al.*, 2006; Murphy *et al.*, 2006b; Green *et al.*, 2007; Green *et al.*, 2008). Nonetheless, a clear finding was that the NKA activity/content ratio in muscle was reversibly depressed with exercise, confirming an NKA inactivation effect. The underlying mechanism likely involves free radicals modulating maximal NKA activity (McKenna *et al.*, 2006), but potentially also other factors such as increased intracellular [Ca^{2+}] or α subunit phosphorylation.

Therapeutic digoxin levels do not impair skeletal muscle function in healthy young adults

Unchanged muscle strength.

We comprehensively evaluated whether digoxin inducing typical therapeutic SDC would impair skeletal muscle strength, fatigability, cycling exercise performance and effort-dependent parameters of respiratory muscle function, in healthy adult volunteers. This was investigated since impaired limb or respiratory muscle function with digoxin could counter cardiac benefits during physical activity in heart failure patients, and previous studies had design limitations. Important research design features included careful control of test procedures, familiarisation and determination of within-subject variability for each test. This was essential since previous reports suggested tendencies to deterioration in muscle strength, although results were not significantly different after digoxin (Bruce *et al.*, 1968; Sundqvist *et al.*, 1983). Muscle strength during isokinetic contractions at very slow - slow limb velocities was unchanged by digoxin (Sundqvist *et al.*, 1983), although mean values were 5-6% less, no familiarisation was indicated, nor was the typical test variability reported. In addition, the well-trained subjects utilised (Sundqvist *et al.*, 1983) may have had elevated muscle NKA content (McKenna, 1998; Murphy *et al.*, 2007), and with digoxin hence likely to have had lesser effects. An older study also found no significant change with digoxin on peak muscle handgrip strength, but tested only four subjects (Bruce *et al.*, 1968). Finally, others have reported that intra-arterial injection of high-dose ouabain enhanced electrically evoked muscle strength, whereas low-dose did not (Smulyan & Eich, 1976). Our strength test results are convincing and clearly indicate that in healthy young adults, peak voluntary muscle strength across a range of limb velocities, including isometric, was unchanged after digoxin at low therapeutic SDC. Further, DIG did not affect respiratory muscle strength - dependent measures, maximal inspiratory and expiratory pressure development, suggesting no adverse effect of DIG on the respiratory muscles.

Unchanged muscle fatigue and endurance.

We report for the first time the effects of DIG on fatiguability during dynamic exercise restricted to a major muscle group. The rationale was that any reduction in muscle strength with DIG would be exacerbated during exercise due to the increased muscle binding of digoxin during exercise (Joreteg & Jogestrand, 1983), leading to increased fatigability, as occurs in isolated muscle preparations with ouabain inhibition (Clausen, 2003). Importantly, digoxin had no effect on the fatiguability of the knee extensors during repeated maximal contractions, with no change

in the fatigue index. This finding is consistent with the lack of effect of digoxin on isometric endurance during sustained handgrip contractions at 30% MVC (Bruce *et al*., 1968).

We also investigated digoxin effects on large muscle mass exercise, finding unchanged performance time and $\dot{V}O_{2peak}$ during cycling to exhaustion at 90% $\dot{V}O_{2peak}$. This contrasts worsened incremental treadmill running time with digoxin in four healthy adults (Bruce *et al*., 1968), but is consistent with unchanged $\dot{V}O_{2max}$ with digoxin (SDC ~1.0 nM) in well-trained (Sundqvist *et al*., 1983) and untrained men (Russell & Reeves, 1963). Two studies were performed after short-term, higher dose digitalisation (Russell & Reeves, 1963; Bruce *et al*., 1968), suggesting extent of digitalisation cannot explain the different findings.

The strength, fatiguability and cycling performance tests were all reproducible, no trends were apparent and performance measures were internally consistent. Thus we reject the overall hypothesis that performance measures dependent on muscle strength and endurance would be worsened with oral digoxin administration in healthy individuals. An important question is why wasn't muscle function in healthy humans impaired with elevated SDC, since digoxin binds to and inhibits NKA in skeletal muscle. NKA inhibition with DIG would be anticipated to impair muscle contractile performance in humans, as muscle maximal in-vitro NKA activity is related to $\dot{V}O_{2peak}$ (Fraser *et al*., 2002) and time to fatigue during submaximal cycling (Leppik *et al*., 2004), and is depressed with exercise (McKenna *et al*., 2008). The lack of effect of digoxin on muscle function is consistent with unchanged *functional* muscle NKA, measured by unchanged content (measured without F_{ab}) and maximal in-vitro activity. Although digoxin increased plasma [K^+] during exercise in cardiac patients (Norgaard *et al*., 1991; Schmidt *et al*., 1995), upregulation of NKA with DIG in healthy individuals would protect against any K^+ disturbances that could impact adversely on fatigue (Sejersted & Sjogaard, 2000; Clausen, 2003; McKenna *et al*., 2008). However, since NKA content was upregulated with DIG, we cannot evaluate from this study whether a functional reduction in NKA acutely impairs muscle strength or fatiguability.

PERSPECTIVES AND CONCLUSIONS

Despite achieving therapeutic SDC, functional measurements were each unchanged by digoxin, comprising quadriceps muscle strength and fatiguability, maximal inspiratory and expiratory pressures, cycling time to fatigue and peak oxygen uptake. Importantly, NKA content and maximal in-vitro activity were not depressed but were in fact unchanged with digoxin. Use of digoxin-specific antibody fragments revealed a skeletal muscle digoxin occupancy of NKA of 7%, and although protein abundance of NKA isoforms was not significantly increased, there was a tendency towards increased α_2 protein with digoxin. Further, the total mRNA expression for β subunits (and tendency for α subunits) was increased with digoxin. Collectively these indicate a compensatory Na^+,K^+-ATPase upregulation with digoxin in resting skeletal muscle in healthy individuals. These adaptive changes likely compensated for the expected initial functional depression in NKA with digoxin, with the consequent increase in total overall NKA in resting muscle maintaining ouabain binding content and maximal NKA activity, thus preserving functional NKA. The unchanged functional NKA in muscle with digoxin was then consistent with

the observed maintenance of muscle function. These findings point to resilience of skeletal muscle NKA function, and indeed of muscle function in healthy adults when undergoing a digoxin challenge. Interestingly, this does not appear to occur in heart failure patients (Green *et al.*, 2001). Unravelling the underlying mechanisms may be important in determining why muscle NKA appears unresponsive to either digoxin or training in these patients (Green *et al.*, 2001), as this may be important in contributing to their poor exercise tolerance. Since patients with severe chronic heart failure are typically in older age groups, it is important to determine whether these differences might also relate to ageing.

A surprising finding was that exercise caused a transient increase in NKA content, but this was not entirely consistent across ouabain binding measures with and without digoxin-specific antibody fragments, and in results expressed per gram wet weight or per gram protein. Exercise depressed the NKA activity-to-content ratio, which recovered after 3 h. Exercise increased the mRNA expression of the α_1, α_3 and β_3 isoforms, and also elevated the protein abundance of β_1 and β_3 isoforms. Finally, although muscle contractions typically increase muscle in vivo NKA activity, digoxin binding, NKA gene expression, but reduce in-vitro maximal NKA activity, we could not detect additional effects of digoxin on these NKA functional characteristics in muscle with exercise.

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Appendix 8A Raw data Chapter 3 (Study 1)

Table 8A.1 Participant information and initial finger flexion performance variability trials; units are watts (w), newton (N); coefficient of variation (CV, %).

	Age	**Mass**	**Height**	**Power Output (W)**			**Force (N)**			**Time to fatigue (min)**		
Subject	yrs	kg	cm	Test 1	Test 2	CV%	Test 1	Test 2	CV%	Test 1	Test 2	CV%
1	21	70.4	175	2.3	2.6	7.5	14.9	15.3	1.9	14.2	14.0	0.8
2	31	60.2	159	3.0	2.9	2.2	14.1	15.4	6.5	7.6	7.4	2.0
3	21	66.1	176	3.1	3.2	2.7	17.0	16.4	2.5	11.6	11.8	1.1
4	25	72.5	153	2.5	2.4	2.6	12.9	13.6	3.7	9.9	10.0	0.7
5	17	74.4	181	3.3	3.4	2.8	20.6	21.9	4.5	10.2	10.2	0.2
6	19	69.4	171	2.3	2.4	2.1	16.8	17.0	0.9	9.5	9.4	0.7
7	22	78.1	180	3.7	3.5	3.5	17.4	16.2	5.1	10.9	11.0	0.2
8	22	62.5	174	3.1	3.0	1.4	20.1	19.4	2.4	11.9	12.1	1.4
9	26	81.6	186	2.6	2.7	3.3	16.1	16.5	1.9	5.6	5.8	2.7
n	9	9	9	9	9	9	9	9	9	9	9	9
Mean	22.7	70.6	172.8	2.9	2.9	3.1	16.6	16.9	3.3	10.1	10.2	1.1
stdev	4.2	7.0	10.6	0.5	0.4	1.8	2.6	2.5	1.8	2.5	2.5	0.8
SEM	1.4	2.3	3.5	0.2	0.1	0.6	0.9	0.8	0.6	0.8	0.8	0.3

Table 8A.2 Control (CON) and Alkalosis (ALK) finger flexion exercise performance.

	Power Output			**Force**			**Time to fatigue**	
	CON	**ALK**		**CON**	**ALK**		**CON**	**ALK**
Subject	(W)	(W)	CV%	N	N	CV%	min	min
1	2.7	2.9	4.5	13.3	12.9	2.0	14.1	17.3
2	2.8	3.1	7.3	14.6	14.8	0.8	7.3	11.3
3	3.1	3.1	0.7	17.1	15.7	5.9	12.6	18.9
4	2.4	2.3	2.1	12.8	14.9	10.6	10.3	9.4
5	3.3	2.9	7.8	20.6	20.4	0.6	10.4	14.2
6	2.8	2.3	12.2	18.2	16.9	5.2	9.4	9.7
7	3.7	3.8	3.0	16.6	18.7	8.6	11.3	12.0
8	3.0	3.5	9.2	19.1	19.5	1.5	10.2	11.6
9	2.8	2.9	1.2	16.5	17.2	2.8	6.3	9.7
n	9	9	9	9	9	9	9	9
Mean	2.9	3.0	5.3	16.5	16.8	4.2	10.2	12.7
stdev	0.4	0.5	4.0	2.6	2.4	3.6	2.4	3.4
SEM	0.1	0.2	1.3	0.9	0.8	1.2	0.8	1.1

Table 8A.3 Control & Alkalosis forearm blood flow (ml.min^{-1}), at rest, fatigue and recovery (+1 to +10min).

CON			**Recovery**				**ALK**		**Recovery**			
Subject	Rest	Fatigue	+1	+2	+5	+10	Rest	Fatigue	+1	+2	+5	+10
1	4.4	75.8	83.1	75.9	50.0	32.8	8.4	96.7	26.9	51.7	25.0	26.0
4	7.8	214.0	75.5	38.2	27.4	23.5	7.5	210.2	112.4	27.1	26.4	42.4
5	9.4	283.1	90.8	49.2	23.6	17.0	8.6	283.0	95.0	55.8	28.4	19.9
6	5.0	104.6	72.6	69.4	36.5	28.4	5.2	61.3	53.4	52.4	24.3	8.2
7	8.0	155.3	75.4	22.0	20.8	17.7	9.0	156.1	85.9	59.1	45.0	38.7
8	10.8	141.5	105.2	80.5	47.2	34.8	12.2	166.0	120.8	122.8	76.2	47.8
n	6	6	6	6	6	6	6	6	6	6	6	6
av	7.6	162.4	83.8	55.9	34.3	25.7	8.5	162.2	82.4	61.5	37.5	30.5
stdev	2.5	75.6	12.4	23.2	12.3	7.5	2.3	79.3	36.0	32.1	20.4	15.1
sem	1.0	30.8	5.1	9.5	5.0	3.1	0.9	32.4	14.7	13.1	8.3	6.2

Fluid Shifts (Control). Arterial (art) and venous (ven) Haemoglobin ([Hb]), hematocrit (Hct); changes from resting levels in arterial (art) and venous (ven) plasma volume (ΔPV) and blood volume (ΔBV); and changes in venous compared to arterial plasma (ΔPV_{a-v}) and blood volume (ΔBV_{a-v}) across the forearm calculated at rest, during submaximal finger flexion exercise (e1-e6) to fatigue (F), and recovery (+1 to +10min). Units are g dl^{-1} haemoglobin and % for Hct; percent change for ΔPV_a, ΔBV_a, ΔPV_{a-v}, ΔBV_{a-v}.

Table 8A.4

Hb art				Exercise					Recovery			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	12.6	12.7	12.6	12.3	12.8	12.9	13.0	13.0	12.8	12.8	12.6	12.4
2	12.1	12.6	12.7	12.7	12.8	12.6	12.7	12.8	12.7	12.6	12.5	12.7
3	12.9	13.2	13.2	13.2	13.3	13.1	13.3	13.3	13.4	13.3	13.2	13.1
4	13.2	13.3	13.3	13.4	13.3	13.3	13.5	13.5	13.4	13.8	13.9	13.5
5	14.1	14.1	14.3	14.2	14.3	14.4	14.4	14.5	14.6	14.5	14.2	14.1
6	14.0	14.0	14.2	14.1	14.1	14.0	14.0	14.4	14.2	14.2	14.2	14.2
7	14.1	14.2	14.2	14.1	14.2	14.3	14.1	14.1	14.1	14.0	14.1	14.0
8	15.6	16.1	16.0	16.0	16.1	16.1	16.1	16.3	16.3	16.1	15.8	16.0
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	13.6	13.8	13.8	13.8	13.9	13.8	13.9	14.0	13.9	13.9	13.8	13.8
stdev	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.2	1.1	1.1	1.1
SEM	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4

Table 8A.4

Hb ven				Exercise					Recovery			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	12.7	13.0	13.1	13.0	13.3	13.7	13.7	12.8	13.2	13.1	12.6	12.4
2	12.2	12.9	12.9	13.2	12.9	13.0	12.8	12.9	12.5	12.6	12.6	12.6
3	13.0	13.2	13.2	13.4	13.3	13.4	13.4	13.5	13.1	13.1	13.0	12.7
4	13.1	13.5	13.6	13.5	13.5	13.4	13.3	13.5	13.3	13.1	13.1	13.1
5	13.9	14.4	14.3	14.7	14.5	14.5	14.4	14.4	14.5	14.3	14.1	14.0
6	13.7	13.8	13.9	14.2	14.3	14.0	14.5	15.2	14.8	14.6	14.1	13.8
7	14.0	14.3	14.3	14.3	14.1	14.1	13.9	14.0	14.0	13.7	13.6	13.6
8	15.8	15.7	15.8	15.8	16.0	16.2	16.0	16.3	16.1	16.1	15.8	15.4
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	13.6	13.9	13.9	14.0	14.0	14.0	14.0	14.1	13.9	13.8	13.6	13.5
stdev	1.1	0.9	0.9	0.9	1.0	1.0	1.0	1.2	1.2	1.1	1.1	1.0
SEM	0.4	0.3	0.3	0.3	0.3	0.4	0.3	0.4	0.4	0.4	0.4	0.3

Table 8A.5

Hct art				Exercise					Recovery			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	35.5	36.0	35.9	35.3	36.4	36.6	36.9	36.9	36.6	36.5	36.2	35.4
2	35.0	34.8	35.5	35.5	36.0	36.2	35.7	35.8	35.9	35.5	35.1	35.3
3	35.8	36.8	36.4	36.4	37.3	36.4	36.8	36.5	37.3	38.0	37.3	36.9
4	34.2	35.8	36.5	36.7	36.4	36.4	36.9	36.9	35.8	37.3	37.5	36.1
5	38.8	39.2	39.6	39.7	39.4	38.8	40.0	40.6	40.9	40.0	40.3	39.7
6	41.1	40.7	41.9	41.1	40.6	40.8	39.9	41.0	41.1	41.0	41.3	40.5
7	40.8	41.1	40.4	40.7	41.2	41.5	40.2	40.9	40.8	40.1	40.2	40.4
8	46.9	47.5	47.5	47.3	48.3	48.3	48.3	49.0	47.6	48.2	47.6	47.5
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	38.5	39.0	39.2	39.1	39.5	39.4	39.3	39.7	39.5	39.6	39.4	39.0
stdev	4.3	4.2	4.1	4.0	4.1	4.2	4.0	4.3	4.0	4.0	3.9	4.1
SEM	1.5	1.5	1.4	1.4	1.5	1.5	1.4	1.5	1.4	1.4	1.4	1.4

Table 8A.6

Hct ven				Exercise					Recovery			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	36.3	36.6	37.6	38.0	37.2	38.8	40.3	36.7	37.9	36.2	35.8	35.6
2	34.2	36.0	36.6	36.7	36.3	37.0	37.3	37.0	36.0	35.9	35.7	35.4
3	36.3	37.0	37.2	37.5	37.0	36.9	37.9	38.2	36.8	36.4	35.9	35.6
4	36.0	36.7	37.4	36.8	36.7	36.6	36.4	37.3	36.1	36.0	35.2	36.3
5	38.4	40.5	40.0	40.8	40.9	40.9	40.6	40.8	40.8	40.1	39.5	38.5
6	39.8	40.0	40.3	40.8	41.1	40.3	40.5	41.8	40.4	39.6	40.7	40.2
7	40.7	41.0	41.5	41.1	41.1	41.3	40.7	41.3	40.8	40.0	39.4	39.6
8	46.2	46.9	47.0	47.0	48.0	48.4	48.8	47.6	47.7	47.6	46.3	45.1
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	38.5	39.3	39.7	39.8	39.8	40.0	40.3	40.1	39.6	39.0	38.6	38.3

stdev	3.8	3.6	3.4	3.4	3.9	3.9	3.8	3.7	3.9	4.0	3.8	3.4
SEM	1.3	1.3	1.2	1.2	1.4	1.4	1.4	1.3	1.4	1.4	1.3	1.2

Table 8A.7

PV art					**Exercise**					**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0	-1.6	-0.6	2.8	-2.9	-4.0	-5.2	-5.2	-3.2	-3.1	-1.1	1.8
2	0	-3.6	-5.5	-5.5	-6.9	-5.7	-5.8	-6.6	-6.0	-4.7	-3.3	-5.2
3	0	-3.8	-3.2	-3.2	-5.3	-2.4	-4.5	-4.1	-6.0	-6.3	-4.6	-3.2
4	0	-3.2	-4.2	-5.2	-4.1	-4.1	-6.2	-6.2	-3.9	-8.9	-9.8	-5.0
5	0	-0.7	-2.7	-2.2	-2.4	-2.1	-4.0	-5.6	-6.7	-4.7	-3.1	-1.5
6	0	0.7	-2.7	-0.7	0.1	0.5	2.0	-2.6	-1.4	-1.2	-1.7	-0.4
7	0	-1.2	0.0	0.2	-1.4	-2.6	1.0	-0.2	0.0	1.9	1.0	1.4
8	0	-4.2	-3.6	-3.2	-5.7	-5.7	-5.7	-8.1	-5.6	-5.5	-2.6	-3.6
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	-2.2	-2.8	-2.1	-3.6	-3.3	-3.5	-4.8	-4.1	-4.1	-3.2	-2.0
stdev	0.0	1.8	1.8	2.8	2.4	2.1	3.2	2.5	2.4	3.3	3.2	2.7
SEM	0.0	0.6	0.6	1.0	0.8	0.7	1.1	0.9	0.9	1.2	1.1	1.0

Table 8A.8

PV ven					**Exercise**					**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0	-2.8	-5.0	-4.9	-5.9	-10.9	-13.1	-1.4	-6.2	-2.9	1.6	3.5
2	0	-8.0	-8.9	-11.1	-8.4	-10.1	-9.2	-9.5	-5.1	-5.7	-5.4	-4.9
3	0	-2.6	-2.9	-4.8	-3.3	-3.9	-5.4	-6.6	-1.5	-0.9	0.6	3.5
4	0	-4.0	-5.8	-4.2	-4.0	-3.2	-2.1	-4.9	-1.7	0.0	1.3	-0.5
5	0	-6.8	-5.3	-9.1	-8.0	-8.0	-6.9	-7.2	-7.9	-5.5	-3.2	-0.9
6	0	-1.1	-2.3	-5.1	-6.3	-3.3	-6.6	-12.9	-8.4	-5.9	-4.3	-1.4
7	0	-2.6	-3.4	-2.8	-1.4	-1.7	0.7	-1.0	-0.2	3.4	5.2	4.9
8	0	-0.7	-1.5	-1.5	-4.6	-6.5	-6.0	-5.6	-4.6	-4.4	-0.2	4.7
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	-3.6	-4.4	-5.4	-5.2	-5.9	-6.1	-6.1	-4.4	-2.7	-0.5	1.1
stdev	0.0	2.6	2.4	3.2	2.4	3.5	4.2	3.9	3.0	3.3	3.5	3.5
SEM	0.0	0.9	0.8	1.1	0.8	1.2	1.5	1.4	1.1	1.2	1.2	1.3

Table 8A.9

BV art					**Exercise**					**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0	-0.8	0.0	2.4	-1.6	-2.3	-3.1	-3.1	-1.6	-1.6	0.0	1.6
2	0	-4.0	-4.7	-4.7	-5.5	-4.0	-4.7	-5.5	-4.7	-4.0	-3.2	-4.7
3	0	-2.3	-2.3	-2.3	-3.0	-1.5	-3.0	-3.0	-3.7	-3.0	-2.3	-1.5
4	0	-0.8	-0.8	-1.5	-0.8	-0.8	-2.2	-2.2	-1.5	-4.3	-5.0	-2.2
5	0	0.0	-1.4	-0.7	-1.4	-2.1	-2.1	-2.8	-3.4	-2.8	-0.7	0.0
6	0	0.0	-1.4	-0.7	-0.7	0.0	0.0	-2.8	-1.4	-1.4	-1.4	-1.4
7	0	-0.7	-0.7	0.0	-0.7	-1.4	0.0	0.0	0.0	0.7	0.0	0.7
8	0	-3.1	-2.5	-2.5	-3.1	-3.1	-3.1	-4.3	-4.3	-3.1	-1.3	-2.5
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	-1.4	-1.7	-1.2	-2.1	-1.9	-2.3	-3.0	-2.6	-2.4	-1.7	-1.3
stdev	0.0	1.5	1.5	2.1	1.7	1.3	1.6	1.6	1.7	1.6	1.7	2.0
SEM	0.0	0.5	0.5	0.7	0.6	0.4	0.6	0.6	0.6	0.6	0.6	0.7

Table 8A.10

BV ven					**Exercise**					**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0	-2.3	-3.1	-2.3	-4.5	-7.3	-7.3	-0.8	-3.8	-3.1	0.8	2.4
2	0	-5.4	-5.4	-7.6	-5.4	-6.2	-4.7	-5.4	-2.4	-3.2	-3.2	-3.2
3	0	-1.5	-1.5	-3.0	-2.3	-3.0	-3.0	-3.7	-0.8	-0.8	0.0	2.4
4	0	-3.0	-3.7	-3.0	-3.0	-2.2	-1.5	-3.0	-1.5	0.0	0.0	0.0
5	0	-3.5	-2.8	-5.4	-4.1	-4.1	-3.5	-3.5	-4.1	-2.8	-1.4	-0.7
6	0	-0.7	-1.4	-3.5	-4.2	-2.4	-5.5	-9.9	-7.4	-6.2	-2.8	-0.7
7	0	-2.1	-2.1	-2.1	-0.7	-0.7	0.7	0.0	0.0	2.2	2.9	2.9
8	0	0.6	0.0	0.0	-1.3	-2.5	-1.3	-3.1	-1.9	-1.9	0.0	2.6
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	-2.2	-2.5	-3.4	-3.2	-3.6	-3.2	-3.7	-2.7	-2.0	-0.5	0.7
stdev	0.0	1.8	1.6	2.3	1.7	2.2	2.6	3.0	2.4	2.5	2.0	2.2
SEM	0.0	0.6	0.6	0.8	0.6	0.8	0.9	1.1	0.8	0.9	0.7	0.8

Table 8A.11

PV a-v					**Exercise**					**Recovery**		

Subject	rest	e1	e2	e3	e4	e5	e6	F	+1	+2	+5	+10
1	-2.02	-3.2	-6.4	-9.3	-5.0	-9.1	-10.2	1.9	-5.0	-1.8	0.6	-0.3
2	0.40	-4.2	-3.2	-5.6	-1.2	-4.3	-3.3	-2.6	1.4	-0.6	-1.7	0.6
3	-1.54	-0.3	-1.3	-3.2	0.5	-3.0	-2.5	-4.1	3.1	4.1	3.8	5.3
4	-1.99	-2.9	-3.6	-0.9	-1.9	-1.1	2.3	-0.6	0.3	7.5	10.0	2.7
5	2.10	-4.2	-0.7	-5.2	-3.8	-4.1	-1.0	0.4	0.9	1.2	2.1	2.7
6	4.45	2.6	5.0	-0.2	-2.2	0.5	-4.4	-6.5	-2.9	-0.4	1.7	3.4
7	0.88	-0.5	-2.5	-2.1	0.9	1.8	0.6	0.0	0.7	2.4	5.1	4.3
8	0.04	3.7	2.2	1.8	1.2	-0.8	-0.3	2.7	1.0	1.2	2.5	8.6
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.289	-1.1	-1.3	-3.1	-1.5	-2.5	-2.4	-1.1	-0.1	1.7	3.0	3.4
stdev	2.232	3.0	3.6	3.5	2.2	3.4	3.8	3.1	2.6	3.0	3.5	2.8
SEM	0.789	1.1	1.3	1.3	0.8	1.2	1.4	1.1	0.9	1.1	1.2	1.0

Table 8A.12

BV a-v					Exercise						Recovery	
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	-0.8	-2.3	-3.8	-5.4	-3.8	-5.8	-5.1	1.6	-3.0	-2.3	0.0	0.0
2	-0.8	-2.3	-1.6	-3.8	-0.8	-3.1	-0.8	-0.8	1.6	0.0	-0.8	0.8
3	-0.8	0.0	0.0	-1.5	0.0	-2.2	-0.7	-1.5	2.3	1.5	1.5	3.1
4	0.8	-1.5	-2.2	-0.7	-1.5	-0.7	1.5	0.0	0.8	5.3	6.1	3.1
5	1.4	-2.1	0.0	-3.4	-1.4	-0.7	0.0	0.7	0.7	1.4	0.7	0.7
6	2.2	1.4	2.2	-0.7	-1.4	-0.3	-3.4	-5.3	-4.1	-2.7	0.7	2.9
7	0.7	-0.7	-0.7	-1.4	0.7	1.4	1.4	0.7	0.7	2.2	3.7	2.9
8	-1.3	2.5	1.3	1.3	0.6	-0.6	0.6	0.0	1.2	0.0	0.0	3.9
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.2	-0.6	-0.6	-2.0	-0.9	-1.5	-0.8	-0.6	0.0	0.7	1.5	2.2
stdev	1.3	1.8	1.9	2.1	1.5	2.2	2.3	2.1	2.3	2.6	2.3	1.4
SEM	0.4	0.6	0.7	0.7	0.5	0.8	0.8	0.7	0.8	0.9	0.8	0.5

Fluid Shifts (Alkalosis). Arterial (art) and venous (ven) Haemoglobin ([Hb]), hematocrit (Hct); changes from resting levels in arterial (art) and venous (ven) plasma volume (ΔPV) and blood volume (ΔBV); and changes in venous compared to arterial plasma (ΔPV_{a-v}) and blood volume (ΔBV_{a-v}) across the forearm calculated at rest, during submaximal finger flexion exercise (e1-e6) to fatigue (F), and recovery (+1 to +10min). Units are g dl^{-1} haemoglobin and % for Hct; percent change for ΔPV_a, ΔBV_a, ΔPV_{a-v}, ΔBV_{a-v}.

Table 8A.13

Hb art					Exercise						Recovery	
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	13.5	13.7	13.8	13.8	14.1	13.5	13.8	14.4	14.2	13.3	13.5	13.5
2	12.1	12.6	12.7	12.6	12.8	12.7	12.8	13.1	13.2	12.9	12.2	12.6
3	12.4	12.5	13.3	12.6	12.5	12.6	12.7	13.2	12.6	13.1	12.9	12.4
4	13.4	13.7	13.7	13.7	13.8	13.8	13.7	13.7	13.5	13.4	13.4	13.5
5	13.8	13.9	13.9	13.9	14.0	14.0	14.0	14.2	14.4	14.0	13.9	13.8
6	13.0	13.4	13.3	13.5	13.4	13.5	13.6	13.7	13.5	13.7	13.4	13.3
7	13.7	13.8	13.8	13.7	13.5	13.8	13.9	14.1	14.1	14.1	14.0	14.0
8	15.5	15.7	15.7	15.8	15.8	15.9	15.7	15.9	15.9	15.8	15.6	16.0
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	13.4	13.7	13.8	13.7	13.7	13.7	13.8	14.0	13.9	13.8	13.6	13.6
stdev	1.0	1.0	0.9	1.0	1.0	1.0	0.9	0.9	1.0	0.9	1.0	1.1
SEM	0.4	0.3	0.3	0.4	0.4	0.4	0.3	0.3	0.4	0.3	0.3	0.4

Table 8A.14

Hb ven					Exercise						Recovery	
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	13.2	13.9	14.0	14.0	14.1	13.6	14.0	14.3	14.2	13.3	13.4	13.1
2	12.3	12.8	12.9	13.2	12.9	13.0	13.2	12.9	12.1	12.9	13.0	12.0
3	12.5	12.7	12.8	12.9	12.9	13.3	13.4	12.4	13.7	14.1	14.0	12.7
4	13.6	13.9	13.9	13.7	13.7	14.1	13.8	13.8	13.4	13.3	13.1	13.3
5	13.7	13.9	14.0	14.2	14.2	14.1	14.1	14.2	13.9	13.9	13.8	13.8
6	12.9	13.5	13.6	13.6	13.6	13.4	13.6	13.6	13.4	13.4	13.2	13.1
7	13.5	13.9	14.1	13.9	13.9	14.2	14.0	14.1	13.9	14.1	13.8	13.7
8	15.4	15.6	15.9	15.9	16.0	16.0	15.9	15.7	15.5	15.5	15.4	15.2
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	13.4	13.8	13.9	13.9	13.9	14.0	14.0	13.9	13.8	13.8	13.7	13.4
stdev	1.0	0.9	1.0	0.9	1.0	0.9	0.8	1.0	0.9	0.8	0.8	0.9
SEM	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3	0.3	0.3	0.3

Table 8A.15

Hct art				Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	37.8	38.0	37.8	38.6	38.7	37.3	39.3	38.9	37.7	37.9	39.1	39.0
2	35.9	37.8	38.3	38.4	37.7	35.8	38.6	39.0	44.3	44.1	42.6	40.3
3	34.5	34.0	35.7	34.8	34.2	39.0	34.3	35.6	34.6	40.9	35.4	34.8
4	36.2	36.4	36.8	36.9	36.8	37.4	37.0	36.5	36.7	37.0	36.1	35.6
5	37.4	38.2	38.2	38.3	38.5	38.5	38.6	38.5	39.0	39.0	38.0	38.5
6	35.8	37.1	37.4	37.5	37.2	37.1	37.0	37.8	37.2	37.3	36.9	36.7
7	39.2	39.2	39.9	38.6	38.5	39.7	39.5	40.0	40.2	40.3	39.3	39.8
8	43.0	43.4	43.9	44.2	44.7	44.3	43.7	44.8	44.9	44.2	44.1	43.8
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	37.5	38.0	38.5	38.4	38.3	38.6	38.5	38.9	39.3	40.1	38.9	38.6
stdev	2.7	2.7	2.5	2.7	3.0	2.6	2.7	2.8	3.6	2.9	3.1	2.9
SEM	0.9	0.9	0.9	0.9	1.1	0.9	1.0	1.0	1.3	1.0	1.1	1.0

Table 8A.16

Hct ven				Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	37.6	39.3	40.0	39.1	40.5	38.1	39.1	39.6	40.5	38.0	37.1	36.9
2	37.4	38.2	39.4	41.8	39.3	39.1	39.5	39.2	39.1	38.5	38.5	36.5
3	34.9	35.0	35.2	35.4	35.6	35.9	36.5	33.0	36.3	38.5	37.3	35.3
4	36.9	37.8	37.5	37.2	37.1	37.8	37.6	37.7	35.8	35.9	35.2	36.4
5	37.8	38.7	39.0	39.1	39.1	40.0	39.4	39.4	37.4	37.5	37.6	37.8
6	35.5	37.1	37.5	37.7	37.4	36.8	37.4	37.7	36.7	36.7	36.1	36.3
7	38.2	40.0	39.6	39.9	40.0	41.0	40.1	40.7	39.7	40.4	39.1	39.0
8	42.8	43.9	44.3	44.2	44.6	44.8	45.1	44.5	44.1	43.0	42.8	42.9
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	37.6	38.7	39.1	39.3	39.2	39.2	39.3	39.0	38.7	38.6	38.0	37.6
stdev	2.4	2.6	2.6	2.7	2.7	2.8	2.6	3.2	2.8	2.2	2.3	2.4
SEM	0.8	0.9	0.9	1.0	1.0	1.0	0.9	1.1	1.0	0.8	0.8	0.8

Table 8A.17

PV art				Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0	-1.8	-2.2	-3.4	-5.6	0.8	-4.5	-7.9	-4.8	1.3	-2.1	-1.9
2	0	-6.8	-8.4	-7.8	-8.2	-4.7	-9.5	-12.2	-20.4	-18.3	-11.3	-10.7
3	0	0.0	-8.5	-2.0	-0.3	-8.3	-2.1	-7.6	-1.7	-14.6	-5.2	-0.5
4	0	-2.5	-3.1	-3.3	-3.8	-4.7	-3.4	-2.6	-1.5	-1.3	0.2	0.2
5	0	-2.0	-2.0	-2.1	-3.2	-3.2	-3.3	-4.5	-6.6	-3.9	-1.7	-1.8
6	0	-4.9	-4.7	-6.3	-5.1	-5.7	-6.2	-8.1	-5.8	-7.3	-4.6	-3.6
7	0	-0.7	-1.9	1.0	2.6	-1.5	-1.9	-4.1	-4.4	-4.6	-2.3	-3.1
8	0	-2.0	-2.8	-4.0	-4.8	-4.7	-2.5	-5.6	-5.8	-4.0	-2.6	-4.5
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	-2.6	-4.2	-3.5	-3.5	-4.0	-4.2	-6.6	-6.4	-6.6	-3.7	-3.2
stdev	0.0	2.2	2.8	2.7	3.4	2.8	2.6	3.0	6.0	6.7	3.5	3.4
SEM	0.0	0.8	1.0	0.9	1.2	1.0	0.9	1.1	2.1	2.4	1.2	1.2

Table 8A.18

PV ven				Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0	-7.6	-9.3	-8.0	-10.7	-3.7	-8.0	-10.7	-11.4	-1.4	-0.7	1.9
2	0	-5.1	-7.6	-13.4	-7.5	-8.0	-9.9	-7.4	-1.1	-6.3	-7.0	4.0
3	0	-1.7	-2.8	-3.8	-4.1	-7.5	-9.0	3.7	-10.7	-16.2	-14.0	-2.2
4	0	-3.6	-3.1	-1.2	-1.0	-4.9	-2.5	-2.7	3.3	3.9	6.6	3.1
5	0	-2.9	-4.0	-5.5	-5.5	-6.3	-5.3	-6.0	-0.8	-1.0	-0.4	-0.7
6	0	-6.8	-8.1	-8.4	-7.9	-5.7	-7.9	-8.4	-5.5	-5.5	-3.2	-2.7
7	0	-5.7	-6.4	-5.5	-5.7	-9.2	-6.5	-8.1	-5.2	-7.7	-3.6	-2.7
8	0	-3.2	-5.7	-5.5	-6.8	-7.1	-7.0	-4.8	-2.9	-1.0	0.0	1.1
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	-4.6	-5.9	-6.4	-6.2	-6.5	-7.0	-5.5	-4.3	-4.4	-2.8	0.2
stdev	0.0	2.1	2.4	3.6	2.9	1.8	2.3	4.5	5.0	6.1	6.0	2.7
SEM	0.0	0.7	0.9	1.3	1.0	0.6	0.8	1.6	1.8	2.1	2.1	0.9

Table				Exercise						Recovery		

8A.19
BV art

Subject	rest	e1	e2	e3	e4	e5	e6	F	+1	+2	+5	+10
1	0	-1.5	-2.2	-2.2	-4.3	0.0	-2.2	-6.3	-4.9	1.5	0.0	0.0
2	0	-4.0	-4.7	-4.0	-5.5	-4.7	-5.5	-7.6	-8.3	-6.2	-0.8	-4.0
3	0	-0.8	-6.8	-1.6	-0.8	-1.6	-2.4	-6.1	-1.6	-5.3	-3.9	0.0
4	0	-2.2	-2.2	-2.2	-2.9	-2.9	-2.2	-2.2	-0.7	0.0	0.0	-0.7
5	0	-0.7	-0.7	-0.7	-1.4	-1.4	-1.4	-2.8	-4.2	-1.4	-0.7	0.0
6	0	-3.0	-2.3	-3.7	-3.0	-3.7	-4.4	-5.1	-3.7	-5.1	-3.0	-2.3
7	0	-0.7	-0.7	0.0	1.5	-0.7	-1.4	-2.8	-2.8	-2.8	-2.1	-2.1
8	0	-1.3	-1.3	-1.9	-1.9	-2.5	-1.3	-2.5	-2.5	-1.9	-0.6	-3.1
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	-1.8	-2.6	-2.0	-2.3	-2.2	-2.6	-4.4	-3.6	-2.7	-1.4	-1.5
stdev	0.0	1.2	2.1	1.3	2.1	1.6	1.5	2.1	2.3	2.7	1.4	1.6
SEM	0.0	0.4	0.7	0.5	0.8	0.6	0.5	0.7	0.8	1.0	0.5	0.6

Table 8A.20
BV ven — **Exercise** — **Recovery**

Subject	rest	e1	e2	e3	e4	e5	e6	F	+1	+2	+5	+10
1	0	-5.0	-5.7	-5.7	-6.4	-2.9	-5.7	-7.7	-7.0	-0.8	-1.5	0.8
2	0	-3.9	-4.7	-6.8	-4.7	-5.4	-6.8	-4.7	1.7	-4.7	-5.4	2.5
3	0	-1.6	-2.3	-3.1	-3.1	-6.0	-6.7	0.8	-8.8	-11.3	-10.7	-1.6
4	0	-2.2	-2.2	-0.7	-0.7	-3.5	-1.4	-1.4	1.5	2.3	3.8	2.3
5	0	-1.4	-2.1	-3.5	-3.5	-2.8	-2.8	-3.5	-1.4	-1.4	-0.7	-0.7
6	0	-4.4	-5.1	-5.1	-5.1	-3.7	-5.1	-5.1	-3.7	-3.7	-2.3	-1.5
7	0	-2.9	-4.3	-2.9	-2.9	-4.9	-3.6	-4.3	-2.9	-4.3	-2.2	-1.5
8	0	-1.3	-3.1	-3.1	-3.8	-3.8	-3.1	-1.9	-0.6	-0.6	0.0	1.3
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	-2.8	-3.7	-3.9	-3.8	-4.1	-4.4	-3.5	-2.7	-3.1	-2.4	0.2
stdev	0.0	1.5	1.4	1.9	1.7	1.2	2.0	2.6	3.8	4.1	4.2	1.7
SEM	0.0	0.5	0.5	0.7	0.6	0.4	0.7	0.9	1.3	1.4	1.5	0.6

Table 8A.21
PV a-v — **Exercise** — **Recovery**

Subject	rest	e1	e2	e3	e4	e5	e6	F	+1	+2	+5	+10
1	2.6	-3.5	-4.9	-2.2	-2.9	-2.0	-1.1	-0.5	-4.5	-0.2	4.1	6.6
2	-4.0	-2.2	-3.2	-9.8	-3.4	-7.3	-4.5	1.2	19.3	10.0	0.5	11.7
3	-1.4	-3.1	4.7	-3.2	-5.2	-0.4	-8.4	10.7	-10.4	-3.3	-10.6	-3.1
4	-2.6	-3.6	-2.5	-0.5	0.3	-2.8	-1.7	-2.6	2.2	2.5	3.7	0.2
5	0.1	-0.8	-2.0	-3.4	-2.4	-3.1	-2.0	-1.5	6.3	3.2	1.4	1.1
6	1.2	-0.7	-2.4	-1.1	-1.8	1.2	-0.6	0.9	1.5	3.2	2.8	2.2
7	3.2	-2.0	-1.6	-3.5	-5.2	-4.9	-1.7	-1.2	2.3	-0.2	1.8	3.5
8	1.0	-0.2	-2.0	-0.6	-1.1	-1.5	-3.7	1.8	4.1	4.1	3.7	6.9
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	-2.0	-1.7	-3.0	-2.7	-2.6	-3.0	1.1	2.6	2.4	0.9	3.7
stdev	2.5	1.3	2.8	3.0	1.9	2.6	2.6	4.2	8.6	3.9	4.8	4.6
SEM	0.9	0.5	1.0	1.1	0.7	0.9	0.9	1.5	3.0	1.4	1.7	1.6

Table 8A.22
BV a-v — **Rest** — **Exercise** — **Recovery**

Subject	rest	e1	e2	e3	e4	e5	e6	F	+1	+2	+5	+10
1	2.3	-1.4	-1.4	-1.4	0.0	-0.7	-1.4	0.7	0.0	0.0	0.7	3.1
2	-1.6	-1.6	-1.6	-4.5	-0.8	-2.3	-3.0	1.6	9.1	0.0	-6.2	5.0
3	-0.8	-1.6	3.9	-2.3	-3.1	-5.3	-5.2	6.5	-8.0	-7.1	-7.9	-2.4
4	-1.5	-1.4	-1.4	0.0	0.7	-2.1	-0.7	-0.7	0.7	0.8	2.3	1.5
5	0.7	0.0	-0.7	-2.1	-1.4	-0.7	-0.7	0.0	3.6	0.7	0.7	0.0
6	0.8	-0.7	-2.2	-0.7	-1.5	0.7	0.0	0.7	0.7	2.2	1.5	1.5
7	1.5	-0.7	-2.1	-1.4	-2.9	-2.8	-0.7	0.0	1.4	0.0	1.4	2.2
8	0.6	0.6	-1.3	-0.6	-1.3	-0.6	-1.3	1.3	2.6	1.9	1.3	5.3
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.3	-0.9	-0.9	-1.7	-1.3	-1.7	-1.6	1.2	1.3	-0.2	-0.7	2.0
stdev	1.4	0.8	2.0	1.4	1.3	1.8	1.7	2.2	4.7	2.9	3.9	2.5
SEM	0.5	0.3	0.7	0.5	0.5	0.6	0.6	0.8	1.7	1.0	1.4	0.9

Electrolytes (Control). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [K^+], [Na^+], [Cl^-], [Lac^-] and [SID] at rest (R), during submaximal finger flexion exercise (e1 to e6) to fatigue (F), and recovery (1 to 10min). Units are mM; a-v has been corrected for the arterio-venous ΔPV.

Table 8A.23

K+ art				Exercise					Recovery			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	3.89	4.03	4.33	4.28	4.26	4.3	4.35	4.4	4.21	4.26	4.09	4.07
2	3.46	3.47	3.65	3.73	3.82	3.85	3.89	3.85	3.91	3.88	3.81	3.72
3	3.63	3.61	3.68	3.73	3.87	4.07	3.94	4.33	4.57	4.07	3.98	3.87
4	3.54	3.58	3.74	3.79	3.75	3.81	3.9	4.06	3.97	3.91	3.91	3.86
5	3.79	3.94	3.91	4.03	4.19	4.24	4.14	4.44	4.24	4.11	3.91	3.97
6	3.62	3.96	3.98	3.93	3.97	4.06	4.06	3.99	3.98	3.93	3.82	3.67
7	3.73	3.89	3.89	3.99	4.02	4.12	4.13	4.16	4.17	4.15	4.11	4.07
8	3.92	3.93	4.01	3.99	4.02	4.03	4.07	4.02	3.98	3.95	3.83	3.76
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	3.70	3.80	3.90	3.93	3.99	4.06	4.06	4.16	4.13	4.03	3.93	3.87
stdev	0.16	0.21	0.22	0.18	0.18	0.17	0.15	0.21	0.22	0.14	0.12	0.15
SEM	0.06	0.08	0.08	0.07	0.06	0.06	0.05	0.08	0.08	0.05	0.04	0.05

Table 8A.24

K+ ven				Exercise					Recovery			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	3.78	5.25	4.91	5.17	5.33	5.24	5.07	4.81	3.73	3.75	3.69	3.74
2	3.46	4.58	4.78	4.72	4.45	4.77	4.54	4.45	3.45	3.56	3.39	3.61
3	3.71	4.21	4.11	4.34	4.41	4.43	4.54	4.86	3.71	3.69	3.47	3.52
4	3.36	4.77	4.58	4.29	4.34	4.27	4.27	4.31	3.61	3.4	3.24	3.32
5	3.88	4.65	4.88	4.69	4.76	4.74	4.76	4.73	4.09	3.77	3.53	3.59
6	3.62	4.64	4.78	4.70	5.0	4.74	4.68	4.8	3.56	3.54	3.6	3.49
7	3.74	4.6	4.73	4.74	4.79	4.52	4.52	4.43	3.55	3.49	3.39	3.51
8	3.85	5.15	5	4.93	4.98	5.2	5.08	5.19	3.12	2.62	2.51	2.37
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	3.68	4.73	4.72	4.70	4.76	4.74	4.68	4.70	3.60	3.48	3.35	3.39
stdev	0.18	0.33	0.28	0.29	0.34	0.34	0.28	0.29	0.27	0.37	0.37	0.43
SEM	0.07	0.12	0.10	0.10	0.12	0.12	0.10	0.10	0.10	0.13	0.13	0.15

Table 8A.25

K+a-v				Exercise					Recovery			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.19	-1.09	-0.29	-0.45	-0.85	-0.51	-0.22	-0.49	0.70	0.59	0.37	0.34
2	-0.01	-0.96	-1.01	-0.77	-0.58	-0.75	-0.43	-0.48	0.40	0.34	0.49	0.09
3	-0.02	-0.59	-0.38	-0.49	-0.56	-0.23	-0.50	-0.34	0.72	0.22	0.36	0.16
4	0.25	-1.08	-0.70	-0.47	-0.52	-0.42	-0.46	-0.22	0.35	0.24	0.31	0.44
5	-0.17	-0.54	-0.94	-0.44	-0.40	-0.32	-0.58	-0.31	0.11	0.29	0.30	0.27
6	-0.15	-0.78	-0.99	-0.76	-0.94	-0.56	-0.52	-0.53	0.54	0.41	0.15	0.06
7	-0.04	-0.69	-0.74	-0.67	-0.81	-0.47	-0.41	-0.27	0.59	0.56	0.52	0.39
8	0.07	-1.36	-1.08	-1.01	-1.01	-1.14	-1.00	-1.28	0.82	1.28	1.23	1.09
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.01	-0.89	-0.77	-0.63	-0.71	-0.55	-0.52	-0.49	0.53	0.49	0.47	0.35
stdev	0.15	0.29	0.30	0.21	0.22	0.28	0.22	0.34	0.23	0.35	0.33	0.33
SEM	0.05	0.10	0.11	0.07	0.08	0.10	0.08	0.12	0.08	0.12	0.12	0.12

Table 8A.26

Na+ art				Exercise					Recovery			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	136.4	134.9	134.5	137.9	136.7	136.6	137	136	135.5	136.3	135.9	136.5
2	134.7	133.7	135.9	136.4	136.8	135.7	135.8	135.1	137.6	134.1	135.9	135.6
3	134.6	134.2	134.5	135.1	135.4	135	135.7	135.6	135.5	134.3	134.2	134.2

4	131.6	127.9	131.2	133.5	133	133.3	133.2	132.9	132.1	132.1	131.9	132
5	129.5	133.1	131.2	132.4	131.4	132	133.3	132.4	133.2	133.9	134	133.5
6	131	132.5	132.8	132	132.5	134.4	135.0	131.9	133.7	132.8	133.1	133.1
7	132.3	133.8	133.1	133.3	132.7	135.3	135.3	134.3	121.2	134.5	135.3	135.6
8	132.9	133	133.1	132.9	133.3	132.7	134.6	133.5	134.2	133.7	132.1	132.6
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	132.9	132.9	133.3	134.2	134.0	134.4	135.0	134.0	132.9	134.0	134.1	134.1
stdev	2.3	2.1	1.6	2.1	2.0	1.6	1.3	1.5	5.0	1.2	1.6	1.6
SEM	0.8	0.8	0.6	0.7	0.7	0.6	0.5	0.5	1.8	0.4	0.6	0.6

Table 8A.27

Na+ ven				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	135.1	138.2	139.2	141.6	140.9	141	139.9	137.6	134.6	134.5	135.4	136.3
2	135.8	141.3	141.1	141.2	140.1	138.7	139.4	137.9	135.9	134.3	134.2	128.3
3	135.9	137.5	137.7	138.5	138.5	138	138	138.3	133	132.3	132.7	132.5
4	133.1	135.7	137.7	137.1	136.7	136.3	135.6	133.7	132.8	130.2	130.8	132
5	130.6	135.4	135.7	135.6	135.7	135.4	135.7	136	134.2	132	132	132.3
6	132.2	135.3	138.1	138.5	137.6	137.7	137.4	135.1	131.6	127.9	132.6	133
7	134.6	138.6	139.4	138.8	135.9	137.2	137.1	136.8	134.8	134.4	135.3	135.8
8	133.9	135.1	135.6	136.4	135.6	137.4	136	142.7	135.7	133.9	132.5	133.7
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	133.9	137.1	138.1	138.5	137.6	137.7	137.4	137.3	134.1	132.4	133.2	133.0
stdev	1.9	2.2	1.9	2.1	2.0	1.7	1.6	2.7	1.5	2.4	1.6	2.5
SEM	0.7	0.8	0.7	0.8	0.7	0.6	0.6	0.9	0.5	0.8	0.6	0.9

Table 8A.28

Na+a-v				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	4.1	1.2	4.4	10.5	2.9	9.3	12.7	-4.1	8.1	4.3	-0.3	0.6
2	-1.6	-1.7	-0.7	3.3	-1.6	3.1	4.2	1.4	-0.3	0.6	4.1	6.4
3	0.8	-2.9	-1.5	1.1	-3.7	1.2	1.1	3.1	-1.6	-3.3	-3.4	-5.0
4	1.2	-4.0	-1.6	-2.4	-1.1	-1.6	-5.4	0.0	-1.1	-7.3	-10.9	-3.5
5	-3.8	3.5	-3.6	4.0	0.9	2.2	-1.1	-4.1	-2.1	0.3	-0.7	-2.3
6	-6.8	-6.2	-11.5	-6.2	-2.1	0.7	0.9	6.0	6.1	5.5	-1.8	-4.3
7	-3.5	-4.1	-2.8	-2.7	-4.4	-4.2	-2.6	-2.5	-14.5	-3.0	-6.5	-5.8
8	-1.0	-6.9	-5.4	-5.9	-3.9	-3.6	-0.9	-12.8	-2.9	-1.7	-3.6	-11.7
n	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
mean	-1.3	-2.6	-2.8	0.2	-1.6	0.9	1.1	-1.6	-1.0	-0.6	-2.9	-3.2
stdev	3.4	3.5	4.5	5.7	2.5	4.3	5.5	5.7	6.8	4.2	4.5	5.2
SEM	1.2	1.3	1.6	2.0	0.9	1.5	1.9	2.0	2.4	1.5	1.6	1.8

Table 8A.29

Cl- art				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	100	100	98	95	99	98	96	102	102	100	100	95
2	101	99	100	100	97	101	98	99	101	103	99	99
3	108	111	110	109	109	107	108	108	108	108	108	111
4	104	101	99	100	100	98	97	105	104	103	103	103
5	104	104	103	100	99	97	96	104	105	105	106	103
6	109	108	108	109	108	101	100	107	107	106	105	105
7	110	108	117	116	104	101	99	102	105	101	99	98
8	107	108	107	108	107	107	108	106	106	107	107	107
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	105.4	104.9	105.3	104.6	102.9	101.3	100.3	104.1	104.8	104.1	103.4	102.6
stdev	3.7	4.5	6.5	6.9	4.7	3.9	5.0	3.0	2.4	2.9	3.7	5.2
SEM	1.3	1.6	2.3	2.4	1.7	1.4	1.8	1.1	0.8	1.0	1.3	1.8

Table				**Exercise**						**Recovery**		

8A.30
Cl- ven

Subject	rest	e1	e2	e3	e4	e5	e6	F	+1	+2	+5	+10
1	101	99	96	96	95	93	93	99	101	101	101	100
2	101	98	97	95	99	98	95	95	101	99	101	103
3	106	108	108	107	107	105	105	106	104	104	105	109
4	102	97	98	96	96	94	94	103	100	101	104	100
5	102	101	97	95	94	93	92	100	101	101	103	103
6	105	106	102	99	100	98	97	104	107	101	103	104
7	109	106	109	100	100	98	98	100	100	100	101	100
8	108	105	107	105	106	105	105	95	101	104	104	105
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	104.3	102.5	101.7	99.1	99.6	98.0	97.4	100.3	101.9	101.4	102.8	103.0
stdev	3.2	4.2	5.5	4.6	4.8	4.8	5.1	4.0	2.4	1.8	1.6	3.1
SEM	1.1	1.5	1.9	1.6	1.7	1.7	1.8	1.4	0.9	0.6	0.6	1.1

Table 8A.31
Cl-a-v

				Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	1.1	4.3	8.7	8.8	9.2	14.8	13.9	1.1	6.4	0.9	-1.6	-4.7
2	-0.4	5.3	6.3	10.9	-0.8	7.5	8.6	7.1	-1.4	4.6	-0.3	-4.6
3	3.7	3.4	3.4	5.6	1.5	5.3	5.7	6.6	0.7	-0.3	-1.0	-3.6
4	4.1	7.0	4.7	4.9	6.0	5.0	0.8	2.7	3.7	-5.2	-10.4	0.3
5	-0.1	7.5	6.7	10.4	8.9	8.1	5.0	3.6	3.1	2.7	0.9	-2.7
6	-0.6	-0.8	1.2	10.1	10.9	6.4	5.3	10.5	3.2	5.5	0.2	-2.5
7	0.0	2.6	11.0	18.4	3.1	1.2	0.4	2.0	4.3	-1.3	-6.8	-6.1
8	-1.0	-0.9	-2.3	1.0	-0.3	2.9	3.4	8.2	3.9	1.8	0.4	-6.5
n	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
mean	0.8	3.6	5.0	8.8	4.8	6.4	5.4	5.2	3.0	1.1	-2.3	-3.8
stdev	2.0	3.2	4.2	5.2	4.6	4.1	4.4	3.3	2.4	3.4	4.1	2.2
SEM	0.7	1.1	1.5	1.8	1.6	1.4	1.5	1.2	0.8	1.2	1.4	0.8

Table 8A.32
Lac- art

				Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.5	1.3	0.7	0.8	0.8	0.8	0.8	0.8	1.2	0.9	1.2	0.8
2	0.6	2.0	1.1	0.9	1.1	1.2	1.1	1.0	1.3	1.3	1.5	1.2
3	1.1	0.6	1.0	2.2	0.7	0.9	1.1	1.0	1.9	1.3	0.6	1.0
4	0.7	0.7	0.7	0.7	0.8	0.9	0.8	0.9	1.0	0.9	0.8	0.7
5	0.6	0.7	0.7	0.8	0.8	0.9	1.0	1.4	1.1	1.2	1.3	0.9
6	0.7	0.8	0.7	0.8	0.9	1.2	0.9	1.1	1.1	1.2	1.3	1.1
7	0.7	0.7	0.7	0.6	0.7	0.7	0.8	0.8	0.8	0.9	0.8	0.8
8	0.9	1.1	0.8	1.0	1.0	1.2	1.0	1.5	1.4	1.6	1.3	1.7
n	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
mean	0.7	1.0	0.8	1.0	0.9	1.0	0.9	1.1	1.2	1.2	1.1	1.0
stdev	0.2	0.5	0.2	0.5	0.1	0.2	0.1	0.3	0.3	0.3	0.3	0.3
SEM	0.1	0.2	0.1	0.2	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.1

Table 8A.33
Lac- ven

				Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.4	3.6	4.0	4.6	5.2	4.2	5.0	3.7	3.0	3.4	2.7	1.7
2	0.6	3.5	4.7	4.5	5.1	5.5	5.9	4.0	5.0	5.4	4.4	2.3
3	1.3	2.7	2.8	3.0	3.3	3.5	4.7	5.0	4.9	4.9	3.7	2.9
4	0.5	2.8	2.8	3.0	2.6	2.3	2.2	2.1	2.6	1.4	1.4	0.9
5	0.8	1.7	2.5	2.1	1.7	1.8	2.2	2.0	4.4	4.6	3.1	1.6
6	0.6	0.7	1.0	2.4	1.7	3.4	3.8	1.8	1.9	2.6	3.2	1.7
7	0.8	2.3	2.6	3.2	3.2	2.8	2.7	2.5	2.2	2.3	1.6	1.1

8	1.2	2.5	2.9	3.3	3.9	3.7	4.1	5.8	5.5	5.5	4.7	2.8
n	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
mean	0.8	2.5	2.9	3.3	3.3	3.4	3.8	3.4	3.7	3.8	3.1	1.9
stdev	0.3	0.9	1.1	0.9	1.3	1.1	1.3	1.5	1.4	1.5	1.2	0.7
SEM	0.1	0.3	0.4	0.3	0.5	0.4	0.5	0.5	0.5	0.5	0.4	0.3

Table 8A.34

Lac-a-v				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.1	-2.2	-3.3	-3.7	-4.4	-3.3	-4.1	-2.9	-1.8	-2.5	-1.5	-0.9
2	0.0	-1.4	-3.6	-3.5	-3.9	-4.2	-4.7	-2.9	-3.7	-4.1	-2.9	-1.2
3	-0.2	-2.1	-1.9	-0.7	-2.6	-2.6	-3.6	-4.0	-3.0	-3.6	-3.1	-2.0
4	0.2	-2.0	-2.0	-2.2	-1.7	-1.4	-1.4	-1.2	-1.6	-0.6	-0.8	-0.2
5	-0.1	-1.0	-1.7	-1.3	-0.9	-0.9	-1.2	-0.5	-3.3	-3.4	-1.8	-0.7
6	0.0	0.0	-0.3	-1.6	-0.8	-2.2	-2.9	-0.6	-0.7	-1.3	-1.9	-0.6
7	-0.1	-1.7	-1.9	-2.5	-2.5	-2.2	-2.0	-1.6	-1.4	-1.5	-0.9	-0.3
8	-0.4	-1.5	-2.1	-2.3	-2.8	-2.5	-3.1	-4.3	-4.1	-3.9	-3.4	-1.2
n	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
mean	0.0	-1.5	-2.1	-2.2	-2.4	-2.4	-2.9	-2.3	-2.5	-2.6	-2.0	-0.9
stdev	0.2	0.7	1.0	1.0	1.3	1.0	1.3	1.5	1.2	1.3	1.0	0.6
SEM	0.1	0.3	0.4	0.4	0.5	0.4	0.4	0.5	0.4	0.5	0.4	0.2

Table 8A.35

SID art				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	39.8	37.6	40.2	46.3	41.2	42.1	44.6	37.6	36.5	39.7	38.8	44.8
2	36.5	36.1	38.4	39.2	42.5	37.3	40.6	39.0	39.2	33.7	39.2	39.1
3	29.2	26.2	27.2	27.6	29.5	31.2	30.5	30.9	30.1	29.0	29.6	26.1
4	30.4	29.7	35.2	36.5	35.9	38.2	39.3	31.0	31.1	32.1	32.0	32.1
5	28.7	32.3	31.4	35.7	35.8	38.3	40.4	31.4	31.3	31.8	30.6	33.6
6	25.0	27.7	28.0	26.2	27.6	35.9	37.8	27.7	29.6	29.5	30.6	30.7
7	25.3	29.0	19.3	20.7	32.0	37.7	39.7	35.6	19.6	36.8	39.6	40.9
8	29.0	27.8	29.3	27.9	29.3	28.5	29.7	30.0	30.8	29.1	27.6	27.6
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	30.5	30.8	31.1	32.5	34.2	36.2	37.8	32.9	31.0	32.7	33.5	34.4
stdev	5.2	4.2	6.8	8.4	5.6	4.3	5.1	4.0	5.8	3.9	4.9	6.6
SEM	1.8	1.5	2.4	3.0	2.0	1.5	1.8	1.4	2.0	1.4	1.7	2.3

Table 8A.36

SID ven				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	37.5	40.9	44.1	46.2	46.0	49.1	47.0	39.8	34.3	33.8	35.4	38.4
2	37.7	44.3	44.1	46.4	40.5	40.0	43.1	43.4	33.4	33.5	32.2	26.6
3	32.3	31.0	31.0	32.8	32.6	33.9	32.9	32.2	27.8	27.1	27.4	24.1
4	33.9	40.7	41.5	42.4	42.5	44.2	43.6	32.9	33.8	31.2	28.6	34.5
5	31.7	37.3	41.1	43.2	44.8	45.3	46.2	38.8	32.9	30.2	29.5	31.3
6	30.2	33.2	40.1	41.6	41.4	41.0	40.8	34.1	26.3	27.9	30.0	30.8
7	28.5	34.9	32.5	40.4	37.5	40.9	40.9	38.7	36.2	35.6	36.1	38.2
8	28.5	32.7	30.7	33.1	30.7	33.9	32.0	47.1	32.3	27.1	26.3	28.3
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	32.6	36.9	38.1	40.8	39.5	41.0	40.8	38.4	32.1	30.8	30.7	31.5
stdev	3.6	4.7	5.8	5.3	5.5	5.3	5.6	5.2	3.4	3.3	3.6	5.2
SEM	1.3	1.7	2.0	1.9	2.0	1.9	2.0	1.8	1.2	1.2	1.3	1.8

Table 8A.37

SID a-v				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	2.3	-3.3	-4.0	0.2	-4.9	-7.0	-2.5	-2.1	2.3	5.8	3.4	6.4
2	-1.1	-8.2	-5.7	-7.2	2.0	-2.7	-2.5	-4.4	5.8	0.2	7.1	12.6

3	-3.2	-4.8	-3.8	-5.2	-3.0	-2.7	-2.3	-1.2	2.4	2.0	2.1	2.0
4	-3.5	-10.9	-6.3	-5.9	-6.6	-6.1	-4.4	-1.8	-2.7	1.0	3.5	-2.3
5	-3.1	-5.0	-9.7	-7.5	-9.0	-7.0	-5.8	-7.4	-1.5	1.6	1.1	2.3
6	-5.3	-5.5	-12.1	-15.5	-13.8	-5.1	-3.0	-6.3	3.3	1.6	0.6	-0.1
7	-3.2	-5.8	-13.2	-19.7	-5.5	-3.1	-1.2	-3.1	-16.6	1.2	3.6	2.6
8	0.4	-4.9	-1.4	-5.2	-1.4	-5.3	-2.3	-17.1	-1.6	2.0	1.3	-0.6
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-2.1	-6.1	-7.0	-8.2	-5.3	-4.9	-3.0	-5.4	-1.1	1.9	2.8	2.8
stdev	2.4	2.4	4.2	6.3	4.8	1.8	1.4	5.2	6.9	1.7	2.1	4.7
SEM	0.9	0.9	1.5	2.2	1.7	0.6	0.5	1.8	2.4	0.6	0.7	1.7

ELECTROLYTES (Alkalosis). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [K^+], [Na^+], [Cl^-], [Lac^-] and [SID] at rest (R), during submaximal finger flexion exercise (e1 to e6) to fatigue (F), and recovery (1 to 10min). Units are mM; a-v has been corrected for the arterio-venous ΔPV.

Table 8A.38

K+ art	**Rest**			**Exercise**					**Recovery**			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	2.83	3.11	3.18	3.19	3.26	3.33	3.43	3.43	3.32	3.29	3.92	3.3
2	3.1	3.07	3.16	3.19	3.22	3.28	3.19	3.5	3.41	3.4	3.3	3.12
3	3.31	3.2	3.39	3.44	3.52	3.54	3.56	3.74	3.81	3.77	3.49	3.36
4	3.42	3.37	3.35	3.43	3.54	3.56	3.55	4.05	4.13	4.55	3.97	4.02
5	3.39	3.48	3.54	3.53	3.62	3.69	3.68	3.89	3.88	3.51	3.64	3.68
6	2.78	2.96	2.9	2.95	3.02	3.09	3.13	3.16	3.1	3.06	2.98	2.87
7	3.4	3.39	3.53	3.58	3.56	3.58	3.64	4.01	3.81	3.82	3.74	3.71
8	3.43	3.48	3.49	3.52	3.59	3.61	3.56	3.58	3.48	3.9	3.34	3.31
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	3.21	3.26	3.32	3.35	3.42	3.46	3.47	3.67	3.62	3.66	3.55	3.42
stdev	0.27	0.20	0.22	0.22	0.22	0.20	0.20	0.31	0.34	0.46	0.34	0.37
SEM	0.10	0.07	0.08	0.08	0.08	0.07	0.07	0.11	0.12	0.16	0.12	0.13

Table 8A.39

K+ ven	**Rest**			**Exercise**					**Recovery**			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	2.92	4.65	4.62	4.39	4.31	4.26	4.11	3.95	2.94	2.9	2.88	2.82
2	3.17	3.93	4.07	4.04	4.12	4.1	4.16	4.17	3.17	3.12	2.89	2.74
3	3.29	4.1	3.92	4.2	4.05	4.07	4.06	4.33	3.3	3.21	3.17	3.13
4	3.28	4.23	3.92	4.25	4.19	4.2	4.05	4.81	3.71	3.74	3.58	3.6
5	3.41	4.06	4.19	4.37	4.38	4.13	4.17	4.3	3.34	3.32	3.16	3.26
6	3.02	4.44	4.86	4.76	4.83	4.54	4.38	4.31	2.63	2.48	2.28	2.18
7	3.27	4.47	4.28	4.42	4.15	4.44	4.48	4.5	3.39	3.3	3.24	3.29
8	3.77	5.07	4.87	4.99	4.72	4.95	4.44	4.8	2.56	2.65	2.54	2.6
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	3.27	4.37	4.34	4.43	4.34	4.34	4.23	4.40	3.13	3.09	2.97	2.95
stdev	0.26	0.37	0.39	0.31	0.29	0.30	0.17	0.30	0.39	0.40	0.41	0.45
SEM	0.09	0.13	0.14	0.11	0.10	0.11	0.06	0.10	0.14	0.14	0.15	0.16

Table 8A.40

K+a-v	**Rest**			**Exercise**					**Recovery**			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	-0.16	-1.43	-1.28	-1.13	-0.95	-0.86	-0.64	-0.50	0.54	0.40	0.89	0.28
2	0.06	-0.79	-0.80	-0.50	-0.79	-0.56	-0.82	-0.71	-0.31	-0.03	0.39	0.05
3	0.07	-0.80	-0.68	-0.65	-0.34	-0.51	-0.17	-0.95	0.95	0.69	0.73	0.34
4	0.23	-0.73	-0.48	-0.80	-0.66	-0.54	-0.44	-0.65	0.33	0.70	0.25	0.41
5	-0.02	-0.55	-0.58	-0.72	-0.67	-0.32	-0.41	-0.35	0.46	0.08	0.43	0.38
6	-0.27	-1.46	-1.89	-1.78	-1.76	-1.49	-1.23	-1.18	0.42	0.48	0.62	0.63

7	0.03	-1.01	-0.69	-0.71	-0.39	-0.68	-0.78	-0.44	0.33	0.53	0.43	0.29
8	-0.37	-1.58	-1.31	-1.45	-1.09	-1.28	-0.74	-1.28	0.78	1.10	0.68	0.49
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-0.06	-1.04	-0.96	-0.97	-0.83	-0.78	-0.65	-0.76	0.44	0.49	0.55	0.36
stdev	0.20	0.39	0.48	0.45	0.45	0.41	0.32	0.34	0.37	0.36	0.21	0.17
SEM	0.07	0.14	0.17	0.16	0.16	0.14	0.11	0.12	0.13	0.13	0.07	0.06

Table 8A.41

Na+ art	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	138.1	134	139.1	138.1	138.1	137.7	137.3	135.6	136.5	134.8	136.7	138
2	129.8	137.7	135.6	134.8	135.1	134.8	134.8	135.8	135.2	135.4	136.3	135.9
3	134.7	135	134.5	134	135.8	135.7	136.4	137	136.3	136.6	138.3	140.4
4	135.5	133.3	134.9	135.1	136.4	137.4	136.5	134.7	134	133.8	133.6	134.6
5	132.4	133.3	135.8	131.7	133.9	135.1	134.6	134.4	135.5	135.6	134.6	134.8
6	130.4	133.2	131.3	132.4	133.6	132.2	134.7	134.9	132.8	133.8	133.8	134.6
7	135.4	134.8	135.1	135.4	136.9	136.2	137.2	136.9	136.6	136.8	136.4	136
8	132.9	133	133.2	134.8	134.2	134.1	133.1	133.8	133.3	139.6	133.3	135.9
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	133.7	134.3	134.9	134.5	135.5	135.4	135.6	135.4	135.0	135.8	135.4	136.3
stdev	2.8	1.6	2.2	2.0	1.6	1.8	1.5	1.2	1.5	1.9	1.8	2.0
SEM	1.0	0.6	0.8	0.7	0.6	0.6	0.5	0.4	0.5	0.7	0.6	0.7

Table 8A.42

Na+ ven	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	138.3	144.2	144.8	143.9	142.5	141.2	141.1	138.8	134.6	134.8	136.8	137.8
2	134.7	137.5	139.3	138.5	139.1	137.7	139	138.8	135.1	134.5	134.2	135.5
3	136.7	138.5	137.1	138.9	138.9	138.8	139.6	139.6	133.1	133.8	136	136.7
4	135.6	138.8	138.8	140.4	139.9	139.3	139	135.9	131.4	132.5	134.6	133.3
5	134.9	138.7	139.9	139.1	140.6	138	139.8	137	134.2	133.8	133.6	133.9
6	134.6	138.3	139.1	137.9	139.4	137.9	136.2	135.8	133.3	132.4	134.3	135.2
7	136.9	137.7	137.7	139.8	139.4	139.3	138.9	137.3	135.6	135.4	136.2	136.8
8	137.6	137.2	137.4	136.4	137.7	138.7	130.2	137.6	131.5	132.2	133.4	134.4
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	136.2	138.9	139.3	139.4	139.7	138.9	138.0	137.6	133.6	133.7	134.9	135.5
stdev	1.4	2.2	2.4	2.2	1.4	1.1	3.4	1.4	1.6	1.2	1.3	1.6
SEM	0.5	0.8	0.9	0.8	0.5	0.4	1.2	0.5	0.6	0.4	0.5	0.6

Table 8A.43

Na+a-v	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	-3.70	-5.33	1.49	-2.65	-0.22	-0.69	-2.27	-2.58	8.32	0.22	-5.43	-8.35
2	0.51	3.29	0.82	10.97	0.69	7.76	2.15	-4.63	-21.75	-11.43	1.36	-13.88
3	-0.08	0.77	-8.66	-0.44	4.29	-2.49	9.30	-15.90	19.05	7.49	18.64	8.21
4	3.45	-0.51	-0.40	-4.65	-3.84	1.99	-0.18	2.40	-0.26	-1.98	-5.81	0.97
5	-2.61	-4.31	-1.33	-2.79	-3.45	1.47	-2.45	-0.60	-1.36	-2.40	-0.82	-0.62
6	-5.80	-4.11	-4.62	-4.09	-3.37	-7.30	-0.64	-2.10	-2.52	-2.77	-4.15	-3.46
7	-5.64	-0.11	-0.35	0.55	5.08	3.94	0.67	1.22	-2.05	1.63	-2.19	-5.46
8	-6.02	-3.87	-1.53	-0.75	-2.05	-2.53	8.03	-6.20	-3.41	1.87	-4.80	-7.33
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-2.49	-1.77	-1.82	-0.48	-0.36	0.27	1.83	-3.55	-0.50	-0.92	-0.40	-3.74
stdev	3.48	3.06	3.32	4.97	3.50	4.59	4.49	5.74	11.51	5.39	8.08	6.70
SEM	1.23	1.08	1.17	1.76	1.24	1.62	1.59	2.03	4.07	1.91	2.86	2.37

Table 8A.44

Cl- art	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**

1	109	108	106	107	107	106	105	106	106	107	106	106
2	110	112	113	110	110	111	112	109	110	109	109	111
3	110	112	111	111	110	110	110	109	109	108	109	109
4	106	106	106	106	105	104	105	105	108	107	107	104
5	108	105	102	104	107	104	104	103	110	113	111	109
6	107	105	107	112	105	106	105	104	104	105	105	105
7	100	97	95	94	107	106	104	103	105	105	108	107
8	108	104	105	99	107	106	104	104	105	118	106	108
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	107.3	106.1	105.6	105.4	107.3	106.6	106.1	105.4	107.1	109.0	107.6	107.4
stdev	3.2	4.8	5.5	6.2	1.9	2.6	3.1	2.4	2.4	4.4	2.0	2.3
SEM	1.1	1.7	1.9	2.2	0.7	0.9	1.1	0.9	0.9	1.6	0.7	0.8

Table 8A.45

Cl- ven	**Rest**			**Exercise**					**Recovery**			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	106	108	107	106	106	105	104	104	102	102	102	104
2	109	110	110	110	110	109	109	106	106	105	106	108
3	110	111	111	109	110	109	107	107	106	107	106	106
4	105	106	106	103	103	103	104	110	106	104	103	104
5	106	102	99	98	100	103	100	107	109	109	110	112
6	103	111	104	103	103	103	101	100	98	99	100	102
7	100	95	93	103	105	100	101	98	104	104	108	108
8	108	106	106	103	96	103	97	97	100	101	105	106
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	105.9	106.1	104.5	104.4	104.1	104.4	102.9	103.6	103.9	103.9	105.0	106.3
stdev	3.27	5.44	5.93	3.85	4.76	3.16	3.91	4.75	3.64	3.23	3.25	3.11
SEM	1.16	1.92	2.10	1.36	1.68	1.12	1.38	1.68	1.29	1.14	1.15	1.10

Table 8A.46

Cl-a-v	**Rest**			**Exercise**					**Recovery**			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.24	3.92	4.48	3.44	4.24	3.17	2.17	2.48	8.99	5.17	-0.13	-4.56
2	5.59	4.51	6.77	11.97	3.82	10.78	8.28	1.69	-13.78	-5.93	2.40	-8.66
3	1.57	4.54	-5.00	5.70	5.99	1.50	13.08	-8.58	15.68	4.71	15.88	6.50
4	3.78	3.97	2.75	3.51	1.74	3.94	2.78	-2.20	-0.30	0.38	0.15	-0.25
5	1.91	3.86	5.08	9.64	9.60	4.36	6.13	-2.47	-1.16	0.50	-0.50	-4.23
6	2.68	-5.22	5.59	10.19	3.91	1.72	4.67	3.08	4.41	2.73	2.14	0.77
7	-3.05	4.01	3.58	-5.56	7.92	11.48	4.80	6.22	-1.35	1.18	-1.89	-4.67
8	-1.07	-1.74	1.10	-3.37	12.16	4.63	11.01	5.14	0.89	12.32	-2.74	-5.02
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	1.45	2.23	3.04	4.44	6.17	5.20	6.61	0.67	1.67	2.63	1.91	-2.51
stdev	2.74	3.65	3.69	6.34	3.48	3.84	3.89	4.85	8.60	5.20	5.91	4.68
SEM	0.97	1.29	1.30	2.24	1.23	1.36	1.37	1.71	3.04	1.84	2.09	1.65

Table 8A.47

Lac- art	**Rest**			**Exercise**					**Recovery**			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.60	0.71	0.70	0.65	0.76	0.79	0.92	0.78	0.90	0.57	3.52	3.19
2	0.59	0.87	0.73	0.79	0.90	1.11	0.73	1.3	1.3	1.1	3.8	3.6
3	1.00	1.00	1.08	0.90	1.06	1.18	1.20	1.15	1.15	0.87	3.70	3.42
4	1.56	1.49	1.40	1.28	1.54	1.49	1.57	1.41	1.37	1.33	3.50	3.46
5	0.29	0.35	0.29	0.30	0.32	0.42	0.35	1.06	0.79	0.63	3.35	3.20
6	1.26	1.33	1.45	1.56	1.62	2.04	1.68	1.70	1.82	1.66	3.81	3.65
7	0.58	0.58	0.32	0.70	0.74	0.70	0.79	0.64	0.74	0.64	3.03	2.93
8	1.39	1.45	1.49	1.76	1.50	1.54	1.65	2.08	2.24	1.94	4.45	4.16
n	8	8	8	8	8	8	8	8	8	8	8	8

mean	0.91	0.97	0.93	0.99	1.06	1.16	1.11	1.26	1.29	1.09	3.64	3.44
stdev	0.46	0.42	0.49	0.50	0.46	0.52	0.49	0.47	0.52	0.51	0.41	0.37
SEM	0.16	0.15	0.17	0.18	0.16	0.18	0.17	0.17	0.18	0.18	0.15	0.13

Table 8A.48

Lac- ven	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.34	5.58	4.79	4.08	3.56	4.24	3.27	4.02	3.27	1.53	5.88	4.15
2	0.76	2.48	2.98	3.59	3.74	4.51	4.38	3.95	3.48	1.75	5.77	4.04
3	1.05	1.68	1.60	2.03	2.18	2.23	2.46	3.96	1.63	2.11	4.10	4.58
4	1.68	4.14	4.09	4.05	2.31	4.06	4.08	2.97	2.10	2.06	4.05	4.01
5	0.69	3.01	3.44	2.68	2.63	2.92	3.93	4.09	3.44	1.81	5.59	3.96
6	0.81	3.18	4.81	5.22	5.45	5.36	4.81	5.05	3.48	2.10	5.46	4.09
7	0.77	2.05	2.70	2.90	2.94	3.35	3.49	3.80	2.41	1.32	4.70	3.61
8	1.47	3.05	4.22	5.34	5.11	6.09	6.10	6.22	3.73	2.71	6.19	5.17
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.95	3.14	3.58	3.74	3.49	4.10	4.06	4.26	2.94	1.93	5.22	4.20
stdev	0.44	1.24	1.12	1.18	1.24	1.26	1.09	0.97	0.78	0.42	0.83	0.47
SEM	0.16	0.44	0.39	0.42	0.44	0.45	0.39	0.34	0.28	0.15	0.29	0.17

Table 8A.49

Lac-a-v	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.25	-4.84	-4.06	-3.42	-2.78	-3.43	-2.34	-3.24	-2.32	-0.96	-2.50	-1.16
2	-0.14	-1.59	-2.23	-2.71	-2.82	-3.31	-3.61	-2.67	-2.40	-0.79	-2.01	-0.86
3	-0.04	-0.65	-0.57	-1.10	-1.06	-1.05	-1.15	-2.93	-0.35	-1.21	0.03	-1.05
4	-0.09	-2.59	-2.66	-2.77	-0.77	-2.53	-2.48	-1.53	-0.76	-0.76	-0.68	-0.56
5	-0.40	-2.66	-3.15	-2.36	-2.31	-2.48	-3.58	-3.01	-2.67	-1.20	-2.29	-0.80
6	0.44	-1.84	-3.33	-3.65	-3.80	-3.35	-3.12	-3.36	-1.68	-0.49	-1.76	-0.52
7	-0.21	-1.45	-2.37	-2.18	-2.16	-2.62	-2.70	-3.15	-1.68	-0.68	-1.72	-0.78
8	-0.09	-1.60	-2.71	-3.56	-3.60	-4.52	-4.39	-4.17	-1.58	-0.84	-1.89	-1.28
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-0.03	-2.15	-2.63	-2.72	-2.41	-2.91	-2.92	-3.01	-1.68	-0.87	-1.60	-0.88
stdev	0.26	1.26	1.02	0.85	1.08	1.01	0.99	0.74	0.80	0.25	0.85	0.27
SEM	0.09	0.45	0.36	0.30	0.38	0.36	0.35	0.26	0.28	0.09	0.30	0.10

Table 8A.50

SID art				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	31.3	28.4	35.6	33.6	33.6	34.2	34.8	32.3	32.9	30.5	31.1	32.1
2	22.3	27.9	25.0	27.2	27.4	26.0	25.3	29.0	27.3	28.7	26.8	24.5
3	27.0	25.2	25.8	25.5	28.3	28.1	28.8	30.6	30.0	31.5	29.1	31.3
4	31.4	29.2	30.9	31.3	33.4	35.5	33.5	32.3	28.8	30.0	27.1	31.2
5	27.5	31.4	37.1	30.9	30.2	34.4	33.9	34.2	28.6	25.5	23.9	26.3
6	24.9	29.8	25.8	21.8	30.0	27.3	31.2	32.4	30.1	30.2	28.0	28.8
7	38.2	40.6	43.3	44.3	32.7	33.1	36.1	37.3	34.7	35.0	29.1	29.8
8	26.9	31.0	30.2	37.6	29.3	30.2	31.0	31.3	29.5	23.6	26.2	27.0
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	28.7	30.4	31.7	31.5	30.6	31.1	31.8	32.4	30.2	29.4	27.7	28.9
stdev	4.9	4.5	6.5	7.1	2.4	3.7	3.5	2.5	2.4	3.5	2.2	2.7
SEM	1.7	1.6	2.3	2.5	0.8	1.3	1.3	0.9	0.9	1.3	0.8	1.0

Table 8A.51

SID ven				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	34.9	35.3	37.6	38.2	37.2	36.2	37.9	34.7	32.3	34.2	31.8	32.5
2	28.1	29.0	30.4	29.0	29.5	28.3	29.8	33.0	28.8	30.9	25.3	26.2
3	28.9	29.9	28.4	32.1	30.8	31.6	34.2	33.0	28.8	27.9	29.1	29.3
4	32.2	32.9	32.6	37.6	38.8	36.4	35.0	27.7	27.0	30.2	31.1	28.9
5	31.6	37.8	41.6	42.8	42.3	36.2	40.0	30.2	25.1	26.3	21.2	21.2
6	33.8	28.6	35.1	34.4	35.8	34.1	34.8	35.1	34.5	33.8	31.1	31.3

7	39.4	45.1	46.3	38.3	35.6	40.4	38.9	40.0	32.6	33.4	26.7	28.5
8	31.9	33.2	32.0	33.0	41.3	34.6	31.5	39.2	30.3	31.1	24.8	25.8
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	32.6	34.0	35.5	35.7	36.4	34.7	35.3	34.1	29.9	31.0	27.6	28.0
stdev	3.5	5.5	6.0	4.4	4.6	3.6	3.6	4.1	3.1	2.8	3.8	3.5
SEM	1.3	2.0	2.1	1.5	1.6	1.3	1.3	1.5	1.1	1.0	1.3	1.3

Table 8A.52

SID a-v				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	-3.6	-6.9	-2.0	-4.6	-3.6	-2.0	-3.1	-2.5	0.6	-3.6	-0.7	-0.4
2	-5.8	-1.1	-5.4	-1.8	-2.1	-2.3	-4.5	-4.0	-1.5	-2.1	1.5	-1.7
3	-1.9	-4.7	-2.6	-6.5	-2.5	-3.6	-5.4	-2.4	1.2	3.6	0.0	2.1
4	-0.8	-3.7	-1.8	-6.3	-5.4	-1.0	-1.5	4.6	1.7	-0.2	-4.1	2.3
5	-4.1	-6.3	-4.6	-11.9	-12.1	-1.8	-6.1	4.0	3.5	-0.8	2.7	5.1
6	-8.9	1.3	-9.4	-12.6	-5.8	-6.8	-3.6	-2.7	-4.4	-3.6	-3.1	-2.5
7	-1.2	-4.5	-3.0	6.0	-2.9	-7.3	-2.8	-2.7	2.1	1.6	2.4	1.3
8	-5.0	-2.2	-1.8	4.5	-12.0	-4.4	-0.5	-7.9	-0.8	-7.6	1.4	1.2
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-3.9	-3.5	-3.8	-4.2	-5.8	-3.7	-3.5	-1.7	0.3	-1.6	0.0	0.9
stdev	2.7	2.7	2.6	6.8	4.1	2.4	1.9	4.1	2.5	3.5	2.5	2.4
SEM	1.0	1.0	0.9	2.4	1.4	0.8	0.7	1.5	0.9	1.2	0.9	0.9

Acid-base (Control). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for $[H^+]$, $[HCO_3^-]$; arterial and venous PCO_2, PO_2 at rest (R), during submaximal finger flexion exercise (e1 to e6) to fatigue (F), and recovery (1 to 10min). Units are mM for $[H^+]$, $[HCO_3^-]$ and mmHg for PCO_2, PO_2.

Table 8A.53

H+ art				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	37.0	36.8	36.6	37.8	36.9	37.1	34.8	35.1	34.5	34.3	37.2	38.3
2	35.4	33.9	35.2	35.1	35.9	34.5	36.1	34.8	35.4	33.8	35.5	34.1
3	33.1	33.9	34.8	35.0	35.1	36.1	36.6	33.7	31.3	31.7	32.6	31.5
4	36.6	35.2	35.6	36.4	36.2	36.3	36.6	36.1	37.0	35.5	35.9	35.0
5	37.3	38.0	37.1	36.3	36.2	33.7	38.1	35.8	35.6	39.4	37.1	38.5
6	35.2	36.7	35.5	35.5	35.8	34.7	36.5	35.5	34.9	35.0	35.9	36.1
7	34.8	36.7	37.2	36.0	35.4	36.7	37.1	37.2	35.6	36.1	37.4	39.8
8	36.3	34.9	35.3	35.4	35.2	35.9	36.1	36.1	34.7	34.9	35.7	35.5
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	35.7	35.8	35.9	35.9	35.8	35.6	36.5	35.6	34.9	35.1	35.9	36.1
stdev	1.4	1.5	0.9	0.9	0.6	1.2	1.0	1.1	1.7	2.2	1.5	2.7
SEM	0.5	0.5	0.3	0.3	0.2	0.4	0.3	0.4	0.6	0.8	0.5	1.0

Table 8A.54

H+ ven				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	41.2	49.8	53.6	53.6	52.0	53.3	52.7	49.2	47.1	42.9	41.0	40.3
2	38.5	47.1	49.1	51.6	51.2	49.3	49.5	48.0	48.0	44.2	40.5	39.4
3	40.2	43.7	47.5	48.5	50.7	51.3	50.7	50.1	45.8	41.0	40.0	38.2
4	41.7	46.6	51.6	53.3	51.3	50.7	49.0	48.5	46.9	44.2	42.1	39.6
5	43.0	44.6	48.4	47.0	48.4	45.4	46.6	46.0	51.5	47.1	45.3	42.9
6	39.3	39.6	46.8	49.0	50.2	51.3	50.1	52.5	49.0	45.7	42.7	40.4
7	40.0	40.0	44.7	48.6	48.5	48.3	48.9	47.3	49.5	46.9	44.2	42.4
8	38.4	41.5	47.3	48.5	49.4	51.2	53.3	55.0	48.1	44.3	40.7	39.8
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	40.3	44.1	48.6	50.0	50.2	50.1	50.1	49.6	48.2	44.5	42.0	40.4
stdev	1.6	3.6	2.8	2.5	1.3	2.4	2.2	2.9	1.8	2.0	1.9	1.5
SEM	0.6	1.3	1.0	0.9	0.5	0.9	0.8	1.0	0.6	0.7	0.7	0.5

Table 8A.55

H+ a-v				**Exercise**						**Recovery**		

Subject	rest	e1	e2	e3	e4	e5	e6	F	+1	+2	+5	+10
1	-4.2	-13.0	-16.9	-15.8	-15.1	-16.3	-18.0	-14.1	-12.6	-8.6	-3.8	-2.0
2	-3.1	-13.2	-13.9	-16.6	-15.3	-14.8	-13.5	-13.1	-12.6	-10.4	-5.0	-5.2
3	-7.1	-9.8	-12.8	-13.5	-15.6	-15.1	-14.1	-16.5	-14.6	-9.3	-7.4	-6.7
4	-5.1	-11.3	-16.0	-16.9	-15.1	-14.4	-12.4	-12.4	-9.9	-8.7	-6.2	-4.6
5	-5.6	-6.5	-11.3	-10.7	-12.2	-11.7	-8.5	-10.2	-15.9	-7.7	-8.2	-4.3
6	-4.0	-2.9	-11.3	-13.5	-14.4	-16.6	-13.6	-16.9	-14.1	-10.7	-6.8	-4.3
7	-5.2	-3.3	-7.5	-12.7	-13.1	-11.6	-11.8	-10.1	-13.9	-10.7	-6.7	-2.6
8	-2.1	-6.6	-12.0	-13.1	-14.2	-15.3	-17.3	-18.8	-13.4	-9.4	-5.1	-4.3
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-4.5	-8.3	-12.7	-14.1	-14.4	-14.5	-13.6	-14.0	-13.4	-9.4	-6.1	-4.3
stdev	1.6	4.1	3.0	2.2	1.2	1.9	3.0	3.2	1.8	1.1	1.5	1.5
SEM	0.6	1.4	1.0	0.8	0.4	0.7	1.1	1.1	0.6	0.4	0.5	0.5

Table 8A.56
HCO3 art

				Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	27.6	27.3	27.7	28.3	27.6	28.9	27.8	27.3	28.0	26.7	28.1	28.2
2	27.4	28.2	28.0	28.0	28.3	27.9	28.8	28.8	26.5	26.5	27.4	27.4
3	26.0	25.2	25.3	24.2	24.9	23.5	25.0	24.8	24.4	24.0	24.4	24.5
4	25.8	28.4	28.7	28.0	27.6	28.2	28.2	27.7	28.0	27.8	27.7	27.8
5	27.6	25.0	26.9	26.5	26.9	26.3	26.8	25.3	26.1	26.5	25.9	26.0
6	29.2	27.4	27.4	27.2	27.3	26.9	27.2	27.3	27.4	26.8	27.8	28.0
7	27.4	28.5	29.5	29.7	29.7	30.1	30.0	29.6	27.9	29.2	29.5	29.6
8	28.0	28.0	28.5	27.7	28.3	28.0	27.5	27.7	27.1	27.0	27.2	27.2
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	27.4	27.3	27.8	27.5	27.6	27.5	27.7	27.3	26.9	26.8	27.2	27.3
stdev	1.1	1.4	1.3	1.6	1.4	2.0	1.5	1.6	1.2	1.5	1.5	1.5
SEM	0.4	0.5	0.5	0.6	0.5	0.7	0.5	0.6	0.4	0.5	0.5	0.5

Table 8A.57
HCO3 ven

	Rest			Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	30.5	33.3	32.3	33.5	34.1	32.5	32.9	31.1	28.8	27.1	27.8	28.3
2	28.8	29.8	33.5	31.7	29.8	30.2	30.5	30.9	26.7	26.9	28.0	27.3
3	29.0	29.0	29.6	29.6	29.5	28.8	29.2	28.7	24.5	25.0	24.2	26.6
4	29.6	32.0	31.8	32.0	32.6	31.7	31.7	31.0	29.0	28.0	28.5	28.9
5	30.3	29.9	32.2	32.3	32.0	31.4	32.2	31.5	30.2	28.0	27.8	28.7
6	27.5	31.3	31.5	31.8	32.0	31.5	32.1	32.3	29.7	28.2	27.9	28.2
7	31.8	32.2	33.6	32.4	33.4	33.1	33.2	33.3	32.1	31.6	30.4	31.5
8	27.8	32.9	31.9	31.2	32.1	30.5	33.4	33.5	28.5	27.9	27.8	29.0
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	29.4	31.3	32.1	31.8	31.9	31.2	31.9	31.5	28.7	27.8	27.8	28.6
stdev	1.4	1.6	1.3	1.1	1.6	1.4	1.4	1.5	2.3	1.8	1.7	1.4
SEM	0.5	0.6	0.4	0.4	0.6	0.5	0.5	0.5	0.8	0.7	0.6	0.5

Table 8A.58
HCO3 a-v

	Rest			Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	-2.9	-6	-4.6	-5.2	-6.5	-3.6	-5.1	-3.8	-0.8	-0.4	0.3	-0.1
2	-1.4	-1.6	-5.5	-3.7	-1.5	-2.3	-1.7	-2.1	-0.2	-0.4	-0.6	0.1
3	-3	-3.8	-4.3	-5.4	-4.6	-5.3	-4.2	-3.9	-0.1	-1	0.2	-2.1
4	-3.8	-3.6	-3.1	-4	-5	-3.5	-3.5	-3.3	-1	-0.2	-0.8	-1.1
5	-2.7	-4.9	-5.3	-5.8	-5.1	-5.1	-5.4	-6.2	-4.1	-1.5	-1.9	-2.7
6	1.7	-3.9	-4.1	-4.6	-4.7	-4.6	-4.9	-5.0	-2.3	-1.4	-0.1	-0.2
7	-4.4	-3.7	-4.1	-2.7	-3.7	-3.0	-3.2	-3.7	-4.2	-2.4	-0.9	-1.9
8	0.2	-4.9	-3.4	-3.5	-3.8	-2.5	-5.9	-5.8	-1.4	-0.9	-0.6	-1.8

n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-2.0	-4.1	-4.3	-4.4	-4.4	-3.7	-4.2	-4.2	-1.8	-1.0	-0.6	-1.2
stdev	2.1	1.3	0.8	1.1	1.4	1.2	1.4	1.4	1.6	0.7	0.7	1.1
SEM	0.7	0.5	0.3	0.4	0.5	0.4	0.5	0.5	0.6	0.3	0.3	0.4

Table 8A.59

pO2 art				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	96.6	122.4	119.8	118.6	120.8	125.6	139.5	119.8	100.6	118.6	79.5	78.5
2	76.1	84.3	86.1	97.3	101.7	102.9	85.5	84.0	86.5	107.0	84.8	115.2
3	111.0	109.3	104.8	110.6	120.9	104.5	102.8	105.2	104.0	118.6	131.0	96.5
4	104.2	104.8	109.7	105.9	107.7	113.0	107.4	117.0	115.0	115.1	113.4	110.4
5	101.2	107.2	114.2	120.3	116.9	133.3	100.1	116.1	125.3	97.0	95.6	109.6
6	91.3	86.5	105.6	108.6	111.2	110.8	105.4	100.6	101.9	109.7	85.8	90.3
7	88.5	88.8	95.0	99.3	97.8	91.0	95.1	98.3	99.8	102.1	89.3	81.4
8	99.6	109.2	109.8	108.3	112.5	105.3	107.7	100.6	82.2	109.7	85.8	90.3
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	96.1	101.6	105.6	108.6	111.2	110.8	105.4	105.2	101.9	109.7	95.6	96.5
stdev	10.7	13.5	10.7	8.1	8.5	13.4	15.6	12.0	13.9	7.7	17.6	13.9
SEM	3.8	4.8	3.8	2.9	3.0	4.7	5.5	4.3	4.9	2.7	6.2	4.9

Table 8A.60

pO2 ven				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	26.1	23.3	28	29.3	28.4	27.8	29.5	27.7	43.2	49.5	41.2	41.6
2	31.2	26.9	31.8	33.8	33.1	33.2	33.2	32.3	45.4	52.6	46.6	53.1
3	24.9	20.9	23.1	22.8	23.5	23.9	23.2	29.5	46.3	46.2	38.4	41
4	25.1	20	22.4	23.9	23.2	24.8	24.4	24.5	42.5	44.6	40.7	38.8
5	22.6	18.7	20.8	19.1	19.2	19.9	18.8	21.8	41.2	44.1	44.5	41.8
6	37.4	30.4	25.8	24.8	24.2	22.8	23.0	25.4	40.5	44.6	41.4	41.5
7	24.2	21	20.1	20.8	22.1	21.5	22	21.3	32	29.5	31.3	29.1
8	33.6	24	20.4	19.5	19.9	19.4	19	27.00	43.00	43.90	40.10	40.60
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	28.1	23.2	24.1	24.3	24.2	24.2	24.1	26.2	41.8	44.4	40.5	40.9
stdev	5.3	3.9	4.2	5.1	4.6	4.6	5.0	3.7	4.4	6.7	4.5	6.5
SEM	1.9	1.4	1.5	1.8	1.6	1.6	1.8	1.3	1.6	2.4	1.6	2.3

Table 8A.61

pCO2 art				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	42.4	41.7	42.1	44.3	42.2	44.5	39.6	39.7	40.9	38	43.4	44.8
2	39.8	39.6	41	40.7	42.1	40	42.7	41.6	38.9	37.1	40.3	38.8
3	36.2	36.1	36.8	34.9	36.4	33.3	38.3	34.8	31.8	31.6	33.1	28.8
4	39.2	41.5	42.5	42.2	41.4	42.5	42.7	41.5	43	40.9	41.2	40.3
5	42.7	39.5	41.3	39.3	40.4	37.1	42.4	37.6	38.6	43.2	39.9	41.5
6	42.7	41.8	41.5	41.0	41.1	40.5	42.0	41.8	41.0	40.2	41.0	41.8
7	39.6	43.4	45.4	44.3	43.6	45.9	46.2	45.8	41.2	43.8	45.8	48.9
8	42.1	40.6	41.7	40.7	41.4	41.7	41.1	39.00	37.50	38.10	40.20	39.00
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	40.6	40.5	41.5	40.9	41.1	40.7	41.9	40.2	39.1	39.1	40.6	40.5
stdev	2.3	2.2	2.4	3.0	2.1	4.0	2.4	3.3	3.4	3.9	3.6	5.8
SEM	0.8	0.8	0.8	1.1	0.7	1.4	0.8	1.2	1.2	1.4	1.3	2.0

Table 8A.62

pCO2 ven				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	51.9	68.7	71.7	74.4	73.6	72	71.9	63.5	56.2	48.2	47.3	47.2
2	45.8	58.2	68.3	67.9	63.2	61.8	62.6	61.4	53.1	49.2	47	44.6
3	48.5	52.6	57.4	59.4	61.6	60.5	61.3	59.8	45.6	42.5	40.2	42.2
4	51.1	63.3	68.1	70.9	69.3	66.6	64.4	62.4	58.1	51.2	49.8	47.5
5	53.9	55.2	64.9	63	64.2	59.1	62.1	60.2	64.6	54.7	52.3	51
6	44.8	51.7	64.0	65.9	66.4	65.0	65.8	63.1	58.8	53.0	49.4	48.2
7	52.7	59.7	68.9	66	66.9	66.6	66.6	65.5	66	61.4	55.7	55.4
8	44.2	56.7	62.7	62.5	65.9	64.7	74	60.70	56.20	49.60	47.80	47.90

n	8	8	8	8	8	8	8	8	8	8	8	8
mean	49.1	58.3	65.8	66.3	66.4	64.5	66.1	62.1	57.3	51.2	48.7	48.0
stdev	3.8	5.6	4.5	4.8	3.8	4.1	4.6	1.9	6.4	5.5	4.5	4.0
SEM	1.3	2.0	1.6	1.7	1.3	1.5	1.6	0.7	2.3	1.9	1.6	1.4

Acid-base (Alkalosis). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for $[H^+]$, $[HCO_3^-]$; arterial and venous PCO_2, PO_2 at rest (R), during submaximal finger flexion exercise (e1 to e6) to fatigue (F), and recovery (1 to 10min). Units are mM for $[H^+]$, $[HCO_3^-]$ and mmHg for PCO_2, PO_2.

Table 8A.63

H+ art				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	32.2	31.3	31.0	31.3	31.8	31.1	30.8	29.7	29.2	26.8	30.8	31.8
2	33.3	32.7	32.8	33.1	33.6	30.6	32.8	31.5	29.0	30.5	34.0	33.2
3	31.9	33.1	33.8	33.8	34.7	34.8	34.9	31.5	29.6	27.9	33.7	35.0
4	32.6	32.3	32.4	33.0	32.4	33.0	32.7	33.3	32.7	31.8	33.1	33.6
5	33.8	34.2	35.7	33.7	33.6	34.8	34.8	33.1	34.4	34.8	36.0	36.5
6	32.4	33.4	33.0	33.0	33.1	33.6	33.5	33.6	33.8	31.0	33.3	33.3
7	33.6	34.0	34.0	34.4	34.7	34.1	34.8	34.4	35.3	34.8	35.1	34.4
8	32.4	34.6	35.6	36.0	34.1	35.0	34.8	36.4	36.1	35.6	35.8	35.2
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	32.8	33.2	33.5	33.5	33.5	33.4	33.6	32.9	32.5	31.7	34.0	34.1
stdev	0.7	1.1	1.6	1.4	1.0	1.7	1.5	2.0	2.9	3.3	1.7	1.5
SEM	0.2	0.4	0.6	0.5	0.4	0.6	0.5	0.7	1.0	1.2	0.6	0.5

Table 8A.64

H+ ven				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	36.5	45.8	51.9	49.7	46.3	46.2	45.9	43.0	40.5	36.5	35.5	33.5
2	35.0	41.8	46.6	46.5	47.9	48.4	49.8	49.1	40.2	39.5	37.2	36.0
3	36.7	39.6	42.3	44.2	45.0	45.0	45.9	45.5	40.7	36.3	38.7	38.3
4	37.5	46.1	49.1	49.3	48.9	48.6	49.3	46.0	43.0	40.0	37.9	36.5
5	37.9	43.3	47.5	49.2	48.9	47.3	50.2	44.2	48.5	44.7	41.1	37.4
6	37.6	43.0	49.0	52.6	54.6	53.5	51.1	49.0	53.2	43.1	39.9	37.2
7	37.1	39.8	42.8	48.2	49.3	47.9	48.9	48.8	49.7	45.4	41.6	38.0
8	35.8	42.3	45.2	47.5	48.4	53.7	51.8	59.2	59.2	47.3	39.4	37.2
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	36.8	42.7	46.8	48.4	48.7	48.8	49.1	48.1	46.9	41.6	38.9	36.8
stdev	1.0	2.4	3.3	2.5	2.8	3.2	2.2	5.0	7.0	4.1	2.0	1.5
SEM	0.3	0.9	1.2	0.9	1.0	1.1	0.8	1.8	2.5	1.5	0.7	0.5

Table 8A.65

H+ a-v				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	-4.3	-14.6	-20.9	-18.4	-14.6	-15.1	-15.2	-13.2	-11.2	-9.7	-4.6	-1.7
2	-1.7	-9.0	-13.7	-13.3	-14.3	-17.8	-17.0	-17.6	-11.2	-9.0	-3.1	-2.8
3	-4.8	-6.5	-8.5	-10.4	-10.3	-10.2	-11.0	-14.0	-11.1	-8.4	-5.1	-3.3
4	-4.9	-13.8	-16.7	-16.3	-16.5	-15.6	-16.7	-12.8	-10.3	-8.2	-4.8	-2.9
5	-4.1	-9.1	-11.8	-15.5	-15.3	-12.6	-15.5	-11.0	-14.1	-9.9	-5.1	-0.9
6	-5.2	-9.5	-16.0	-19.6	-21.5	-19.9	-17.6	-15.4	-19.4	-12.0	-6.6	-4.0
7	-3.5	-5.8	-8.8	-13.8	-14.6	-13.7	-14.0	-14.3	-14.3	-10.6	-6.5	-3.6
8	-3.4	-7.7	-9.5	-11.6	-14.3	-18.7	-16.9	-22.8	-23.0	-11.8	-3.6	-2.0
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-4.0	-9.5	-13.3	-14.9	-15.2	-15.5	-15.5	-15.1	-14.3	-9.9	-4.9	-2.6
stdev	1.1	3.2	4.4	3.2	3.1	3.3	2.1	3.6	4.6	1.4	1.2	1.0
SEM	0.4	1.1	1.6	1.1	1.1	1.2	0.8	1.3	1.6	0.5	0.4	0.4

Table 8A.66

HCO3 art	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	27.9	32.3	32	31.9	31.6	30.4	30.9	31.2	30.5	29.2	30.7	30.4
2	31.1	27.4	28.8	28.5	28.6	27.9	28.9	28.8	27.3	27.4	29	28.5
3	29.8	28.4	30.4	30.3	30.1	30.3	28.7	30	29.1	24.9	27.3	27.6
4	29.2	32.7	32.3	31.4	32.2	32.3	32.2	33.4	30.9	32.6	31.3	32.1

5	31.6	31	31.4	31.3	30.2	31.1	31.8	30.1	30.2	28.5	29.6	30.7
6	34.7	33.5	33.6	34.2	34.2	30.9	32.2	32.6	31.8	30.6	31.2	30.7
7	32.7	33.1	33.1	33.6	31.9	31.9	32.2	32.7	30.3	31.3	30.8	31.8
8	31.3	29.8	31	30.8	31.6	30.7	32.1	30.7	30.6	31	31.3	28.7
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	31.0	31.0	31.6	31.5	31.3	30.7	31.1	31.2	30.1	29.4	30.2	30.1
stdev	2.1	2.3	1.5	1.8	1.7	1.3	1.5	1.6	1.4	2.5	1.4	1.6
SEM	0.7	0.8	0.5	0.6	0.6	0.5	0.5	0.6	0.5	0.9	0.5	0.6

Table 8A.67

HCO3 ven	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	32.4	35.1	36.3	36.5	36.7	35.7	35.9	34.5	32.2	30.8	27.4	31.4
2	32.4	29	31.6	32.3	32.2	31.3	31.9	31.5	28.2	27.5	27.7	29
3	31.3	32.8	33.7	33.6	33.2	33.6	33.2	28.9	29	26.7	26.5	29.2
4	34.9	35.8	35.5	35.3	36.4	36	35.3	35.8	33.8	32.7	32.6	33.4
5	33.3	33.3	34.1	36.4	35.1	35.1	35.2	35.2	32.5	31.4	30.7	30.5
6	36.2	36.1	37.8	37.4	37.4	34.2	34.5	34.3	31.6	29.5	29.3	31.1
7	34.5	36.6	35.5	35.1	34.4	36.1	36.5	36.5	33	32.1	31.8	32.1
8	32	29.9	32.5	36	36.1	35.2	35.3	36.3	32.2	31.7	30.1	28.5
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	33.4	33.6	34.6	35.3	35.2	34.7	34.7	34.1	31.6	30.3	29.5	30.7
stdev	1.7	2.9	2.0	1.7	1.8	1.6	1.5	2.6	2.0	2.2	2.2	1.7
SEM	0.6	1.0	0.7	0.6	0.6	0.6	0.5	0.9	0.7	0.8	0.8	0.6

Table 8A.68

HCO3 a-v	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	-4.5	-2.8	-4.3	-4.6	-5.1	-5.3	-5	-3.3	-1.7	-1.6	3.3	-1
2	-1.3	-1.6	-2.8	-3.8	-3.6	-3.4	-3	-2.7	-0.9	-0.1	1.3	-0.5
3	-1.5	-4.4	-3.3	-3.3	-3.1	-3.3	-4.5	1.1	0.1	-1.8	0.8	-1.6
4	-5.7	-3.1	-3.2	-3.9	-4.2	-3.7	-3.1	-2.4	-2.9	-0.1	-1.3	-1.3
5	-1.7	-2.3	-2.7	-5.1	-4.9	-4	-3.4	-5.1	-2.3	-2.9	-1.1	0.2
6	-1.5	-2.6	-4.2	-3.2	-3.2	-3.3	-2.3	-1.7	0.2	1.1	1.9	-0.4
7	-1.8	-3.5	-2.4	-1.5	-2.5	-4.2	-4.3	-3.8	-2.7	-0.8	-1	-0.3
8	-0.7	-0.1	-1.5	-5.2	-4.5	-4.5	-3.2	-5.6	-1.6	-0.7	1.2	0.2
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-2.3	-2.6	-3.1	-3.8	-3.9	-4.0	-3.6	-2.9	-1.5	-0.9	0.6	-0.6
stdev	1.8	1.3	0.9	1.2	0.9	0.7	0.9	2.1	1.2	1.2	1.6	0.7
SEM	0.6	0.5	0.3	0.4	0.3	0.2	0.3	0.7	0.4	0.4	0.6	0.2

Table 8A.69

pO2 art	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	93.6	102.9	102	101	97	98.5	112.2	105.2	109	105	93.1	86
2	98.9	103.1	102.8	103	104.5	103	105.2	109.4	111.1	108.5	102.5	98.00
3	101.0	103.9	103.2	102.4	103.9	104.5	105.1	112	112.8	107.1	101	96.90
4	105.9	104	106.4	106.9	107.8	104.5	104.8	111.4	119.8	117	111.4	112.3
5	105	105.6	98.6	105.2	108.7	109	100.8	118.3	110	96.4	98.7	95
6	102.5	104.9	99.6	103.2	103.8	106.1	106.6	112.2	116.5	101.2	99.5	97.77
7	99.6	102.3	103.5	106.5	107.7	104	106.1	108.9	111.2	107.1	101.8	95.50
8	105.0	107.1	102.1	107	103	102.9	106.9	114.4	112.8	105.9	100.9	99.10
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	101.4	104.2	102.3	104.4	104.6	104.1	106.0	111.5	112.9	106.0	101.1	97.6
stdev	4.1	1.6	2.4	2.3	3.7	3.0	3.2	3.9	3.6	5.9	5.1	7.2
SEM	1.5	0.6	0.8	0.8	1.3	1.1	1.1	1.4	1.3	2.1	1.8	2.6

Table 8A.70

pO2 ven	**Rest**			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	27.7	16.1	21	21	21.8	23.6	24.2	23.6	46.7	51.2	43.5	44.8
2	34.7	28	29.6	28.9	29.4	29.4	29.4	27.9	50.2	53.3	44.9	41.9
3	30.6	18.2	21.9	22.2	18.8	20.4	20.7	20.7	40.2	44.5	34.1	32.2
4	28.2	22.9	24.1	22.7	23.8	24.6	24	22.6	45.3	46.3	43.2	42.6

5	34.2	24.8	22.6	23.3	23.3	23.4	24.7	21.3	35.4	40.8	43.7	40.6
6	23.2	22.4	24.9	23	24.8	22.7	23.2	23.1	49.7	54.3	40.3	36.4
7	27.2	24.3	26	22.7	21.9	21.3	23.6	20	36.8	42.4	45.2	41.8
8	39.1	23.1	22.3	21.3	20.6	20.8	19.9	21.6	45.2	46.2	46.6	44.7
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	30.6	22.5	24.1	23.1	23.1	23.3	23.7	22.6	43.7	47.4	42.7	40.6
stdev	5.1	3.8	2.8	2.5	3.2	2.9	2.9	2.5	5.6	5.0	3.9	4.3
SEM	1.8	1.3	1.0	0.9	1.1	1.0	1.0	0.9	2.0	1.8	1.4	1.5

Table 8A.71 pCO2 art

	Rest			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	37.3	41.9	41.1	41.4	41.6	39.2	39.4	39.2	37.8	33.9	37.4	40.5
2	42.9	37.2	39.2	39.1	39.8	35.5	39.3	37.6	32.8	34.7	41	39.2
3	39.6	39	42.6	42.5	43.3	43.7	41.6	36.7	35.8	28.8	38.1	40.1
4	39.5	43.8	43.3	43	43.2	44.2	43.6	46.4	41.8	43.1	43	44.7
5	44.3	44	46.5	43.8	42.1	44.8	45.9	41.4	43.1	41.1	44.2	46.5
6	46.6	46.5	46.1	46.9	47	43.1	44.7	45.4	44.6	39.4	43	42.4
7	45.5	46.7	46.6	48	45.9	45.2	46.5	46.7	44.4	45.3	44.8	45.4
8	42.4	42.7	45.8	46	44.7	44.5	46.4	46.3	45.9	45.7	46.5	41.8
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	42.3	42.7	43.9	43.8	43.5	42.5	43.4	42.5	40.8	39.0	42.3	42.6
stdev	3.2	3.3	2.8	3.0	2.4	3.4	3.0	4.2	4.7	6.0	3.2	2.7
SEM	1.1	1.2	1.0	1.1	0.8	1.2	1.1	1.5	1.7	2.1	1.1	0.9

Table 8A.72 pCO2 ven

	Rest			**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	49	66.8	78.1	75.1	70.5	68.4	68.3	61.4	54.1	46.6	40.3	43.6
2	47.1	50.3	61.1	62.2	64	62.9	65.8	64.2	47	45.1	42.7	43.3
3	48	53.9	59	61.6	61.9	62.7	63.2	63.9	49	40.2	42.6	46.3
4	54.3	68.6	72.3	72.3	73.7	72.7	72.3	68.8	60.2	54.2	51.5	50.5
5	52.4	59.7	67.3	74.2	71.1	68.9	73.4	59.6	63.2	56.9	52.1	46.6
6	56.5	64.3	76.8	81.5	84.6	75.8	73	69.7	69.8	52.7	48.5	48.1
7	53	60.4	62.9	70.1	70.3	71.7	74	73.9	67.9	60.5	54.9	50.7
8	47.6	52.4	60.9	70.9	72.5	78.4	75.9	89.2	79.1	62.2	49.2	44
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	51.0	59.6	67.3	71.0	71.1	70.2	70.7	68.8	61.3	52.3	47.7	46.6
stdev	3.5	6.8	7.6	6.6	6.8	5.6	4.5	9.5	11.0	7.8	5.3	3.0
SEM	1.2	2.4	2.7	2.3	2.4	2.0	1.6	3.3	3.9	2.7	1.9	1.0

Ion fluxes (Control). Net ion fluxes into or out of forearm musculature for [K^+], [Na^+], [Cl^-], [Lac^-], [$Blac^-$], [H^+] and [HCO_3^-] at rest (R), fatigue (F), and recovery (1 to 10min). Units are $\mu M.min^{-1}$ except for for [H^+] which is $pM.min^{-1}$.

Table 8A.73
K+ flux

Subject	R	F	+1	+2	+5	+10
1	0.5	-23.5	37.0	28.4	12.0	7.3
4	1.3	-30.3	16.9	5.7	5.4	6.6
5	-1.0	-51.4	6.1	8.6	4.2	2.8
6	-0.5	-32.7	23.1	16.7	3.3	1.0
7	-0.2	-24.9	57.4	7.4	6.5	4.1
8	0.4	-92.2	45.1	53.6	30.3	19.9
n	6	6	6	6	6	6
mean	0.1	-42.5	30.9	20.1	10.3	7.0
stdev	0.8	26.3	19.0	18.5	10.3	6.8
SEM	0.3	10.7	7.8	7.5	4.2	2.8

Table 8A.74
Na+ flux

Subject	R	F	+1	+2	+5	+10
1	11.6	-196.9	424.5	209.1	-11.1	13.2
4	6.1	6.5	-51.9	-176.0	-186.7	-52.7
5	-21.6	-684.2	-114.6	8.1	-9.9	-23.9
6	-19.9	373.0	261.5	224.2	-38.1	-72.5
7	-16.5	-233.4	-645.3	-39.5	-81.2	-61.5
8	-6.0	-921.5	-159.5	-72.2	-89.0	-212.8
n	6	6	6	6	6	6
mean	-7.7	-276.1	-47.5	25.6	-69.3	-68.4
stdev	14.0	467.4	372.2	159.9	66.6	77.2
SEM	5.7	190.8	152.0	65.3	27.2	31.5

Table 8A.75
Cl- flux

Subject	R	F	+1	+2	+5	+10
1	3.0	53.3	336.6	41.6	-51.8	-99.8
4	21.2	360.6	179.7	-124.8	-177.6	3.9
5	-0.8	610.6	166.6	80.4	12.1	-27.9
6	-1.9	648.0	137.4	223.5	4.4	-41.7
7	0.2	180.5	189.9	-17.5	-84.3	-64.1
8	-5.9	589.6	215.0	74.0	10.1	-119.0
n	6	6	6	6	6	6
mean	2.6	407.1	204.2	46.2	-47.8	-58.1
stdev	9.6	249.6	69.7	115.5	74.7	45.8
SEM	3.9	101.9	28.5	47.2	30.5	18.7

Table 8A.76
Lac- flux

Subject	R	F	+1	+2	+5	+10
1	0.4	-138.0	-95.2	-120.6	-48.7	-18.2
4	1.3	-161.3	-78.2	-15.1	-13.0	-2.4
5	-0.8	-91.6	-178.1	-99.0	-25.2	-7.5
6	0.1	-38.3	-32.0	-53.8	-40.4	-10.4
7	-0.6	-150.5	-61.0	-19.4	-11.0	-3.0
8	-2.1	-313.3	-224.7	-163.4	-85.3	-22.4
n	6	6	6	6	6	6
mean	-0.3	-148.8	-111.5	-78.6	-37.3	-10.6
stdev	1.1	92.5	74.2	59.2	27.8	8.1
SEM	0.5	37.8	30.3	24.2	11.4	3.3

Table 8A.77
H+ flux

Subject	R	F	+1	+2	+5	+10
1	-9.8	-707.1	-566.7	-382.6	-128.1	-39.7
4	-22.6	-1641.9	-484.8	-267.3	-161.8	-83.6
5	-36.7	-1739.1	-868.3	-242.5	-126.4	-54.6
6	-16.2	-892.1	-559.2	-430.3	-158.0	-93.1
7	-26.0	-925.7	-532.1	-187.6	-140.4	-63.4
8	-11.9	-1492.1	-757.1	-410.4	-146.9	-130.3
n	6	6	6	6	6	6
mean	-20.5	-1233.0	-628.0	-320.1	-143.6	-77.4
stdev	10.0	442.2	150.1	100.6	14.8	32.3
SEM	4.1	180.5	61.3	41.1	6.0	13.2

Table 8A.78
HCO3- flux

Subject	R	F	+1	+2	+5	+10
1	-6.6	-206.0	69.1	4.7	4.0	-0.3
4	-16.9	-421.8	-95.9	-51.4	-56.9	-27.6
5	-18.7	-1057.6	-231.9	-53.7	-34.1	-34.7
6	1.3	-189.6	-63.2	-53.2	-12.3	-19.0
7	-22.1	-349.6	-196.3	-40.5	-28.9	-33.1
8	1.1	-508.2	-92.7	-50.4	-31.5	-72.4
n	6	6	6	6	6	6
mean	-10.3	-455.5	-101.8	-40.8	-26.6	-31.2
stdev	10.3	319.5	106.5	22.8	20.7	23.8
SEM	4.2	130.5	43.5	9.3	8.4	9.7

Table 8A.79
Blood Lac- flux

Subject	R	F	+1	+2	+5	+10
1	0.1	-161.5	-110.6	-119.2	-72.0	-22.6
4	0.1	-166.9	-99.9	-59.7	-24.2	-9.0
5	0.4	-112.7	-175.0	-71.0	-27.6	-11.0
6	-2.4	-42.7	-46.4	-60.3	-40.5	-13.8
7	1.6	-199.4	-78.0	-22.7	-12.3	-6.2
8	-1.1	-410.4	-294.0	-194.9	-104.3	-47.3
n	6	6	6	6	6	6
mean	-0.2	-182.3	-134.0	-88.0	-46.8	-18.3
stdev	1.4	124.4	89.2	60.8	34.8	15.3
SEM	0.6	50.8	36.4	24.8	14.2	6.2

Ion fluxes (Alkalosis). Net ion fluxes into or out of forearm musculature for [K^+], [Na^+], [Cl^-], [Lac^-], [$Blac^-$], [H^+] and [HCO_3^-] at rest (R), fatigue (F), and recovery (1 to 10min). Units are $\mu M.min^{-1}$ except for for [H^+] which is $pM.min^{-1}$.

Table 8A.80
K+ flux

Subject	R	F	+1	+2	+5	+10
1	-0.8	-29.8	9.0	12.7	13.5	4.4
4	1.1	-87.0	23.6	11.9	4.2	11.2
5	-0.1	-61.3	17.9	2.8	7.6	4.6
6	-0.9	-44.9	14.2	15.9	9.5	3.3
7	0.1	-41.5	17.2	18.6	11.9	6.8
8	-2.6	-117.7	52.2	75.1	29.0	13.3
n	6	6	6	6	6	6
mean	-0.5	-63.7	22.4	22.8	12.6	7.3
stdev	1.2	33.1	15.4	26.1	8.7	4.1
SEM	0.5	13.5	6.3	10.7	3.5	1.7

Table 8A.81
Na+ flux

Subject	R	F	+1	+2	+5	+10
1	-19.3	-152.4	139.3	7.0	-82.7	-132.6
4	16.5	319.9	-18.3	-33.7	-97.8	26.6
5	-14.1	-105.1	-391.2	-81.7	-14.5	-7.5
6	-19.4	-80.0	-84.7	-91.0	-63.5	-17.9
7	-30.8	113.9	-105.5	57.5	-59.9	-127.4
8	-41.7	-567.9	-227.2	127.9	-204.3	-196.9
n	6	6	6	6	6	6
mean	-18.1	-78.6	-114.6	-2.3	-87.1	-75.9
stdev	19.7	297.2	181.0	84.6	63.9	88.4
SEM	8.0	121.3	73.9	34.5	26.1	36.1

Table 8A.82
Cl- flux

Subject	R	F	+1	+2	+5	+10
1	1.2	146.7	150.4	165.9	-2.0	-72.5
4	18.0	1059.6	-21.5	6.5	2.6	-6.9
5	10.3	972.8	-320.8	17.0	-8.9	-51.7
6	9.0	117.2	148.1	89.6	32.7	4.0
7	-16.7	582.1	-69.2	41.5	-51.7	-108.8
8	-7.4	470.8	59.5	844.3	-116.5	-134.7
n	6	6	6	6	6	6
mean	2.4	558.2	-8.9	194.1	-24.0	-61.8
stdev	12.7	398.8	176.5	323.8	52.9	54.9
SEM	5.2	162.8	72.1	132.2	21.6	22.4

Table 8A.83
Lac- flux

Subject	R	F	+1	+2	+5	+10
1	1.3	-210.6	-44.2	-103.9	-36.6	-15.8
4	-0.4	-299.5	-133.1	-27.2	-13.1	-20.0
5	-2.2	-426.0	-217.9	-104.2	-46.9	-14.5
6	1.4	-98.2	-112.0	-111.8	-26.2	-2.5
7	-1.1	-225.8	-165.3	-111.5	-46.0	-16.4
8	-0.6	-512.8	-367.6	-289.3	-66.8	-24.1
n	6	6	6	6	6	6
mean	-0.3	-295.5	-173.4	-124.7	-39.3	-15.5
stdev	1.4	151.9	111.2	86.9	18.6	7.3
SEM	0.6	62.0	45.4	35.5	7.6	3.0

Table 8A.84
H+ flux

Subject	R	F	+1	+2	+5	+10
1	-19.5	-840.9	-164.7	-301.3	-77.2	-27.4
4	-20.9	-1664.5	-749.2	-176.2	-129.1	-102.9
5	-25.4	-1876.4	-808.1	-346.0	-99.6	-22.8
6	-20.2	-471.8	-578.8	-367.1	-102.6	-24.6
7	-20.2	-1321.8	-742.2	-402.3	-221.0	-115.7
8	-21.9	-2009.9	-1480.9	-773.4	-179.7	-120.3
n	6	6	6	6	6	6
mean	-21.3	-1364.2	-754.0	-394.4	-134.9	-69.0
stdev	2.1	606.9	426.5	201.5	54.9	48.6
SEM	0.9	247.8	174.1	82.3	22.4	19.8

Table 8A.85
HCO3- flux

Subject	R	F	+1	+2	+5	+10
1	-21.2	-236.5	-1.5	-34.6	49.6	-32.5
4	-25.2	-290.1	-215.4	-40.4	-68.4	-58.4
5	-12.4	-875.3	-143.6	-108.7	-28.8	-7.3
6	-9.1	-459.4	36.3	38.1	19.5	-6.9
7	-11.1	-351.5	-148.3	-53.9	-66.9	-37.4
8	-4.6	-543.6	-121.4	-67.1	17.7	-52.3
n	6	6	6.00	6.00	6.00	6.00
mean	-13.9	-459.4	-99.0	-44.4	-12.9	-32.5
stdev	7.7	232.4	96.2	48.3	49.3	21.8
SEM	3.2	94.9	39.3	19.7	20.1	8.9

Table 8A.86
Blood Lac- flux

Subject	R	F	+1	+2	+5	+10
1	-0.5	-174.4	-65.8	-92.0	-40.4	-16.9
4	-0.8	-263.0	-104.5	-35.6	-24.4	-16.8
5	-6.8	-458.5	-205.2	-128.1	-44.0	-17.3
6	3.5	-90.9	-65.3	-99.5	-23.4	-1.0
7	-1.2	-290.3	-153.1	-113.5	-53.6	-15.3
8	0.0	-844.9	-360.2	-400.4	-159.8	-81.5
n	6	6	6	6	6	6
mean	-1.0	-353.7	-159.0	-144.9	-57.6	-24.8
stdev	3.3	270.5	112.3	129.1	51.4	28.5

SEM	1.4	110.4	45.9	52.7	21.0	11.6

Metabolism (Control). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [$Blac^-$], blood CO_2 content (CCO_2), blood O_2 content (CO_2); forearm muscle VCO_2 ($mVCO_2$) and VO_2 (mVO_2) at rest (R), during submaximal finger flexion exercise (e1 to e6) to fatigue (F), and recovery (1 to 10min). Units are mM for [$Blac^-$]; $ml.min^{-1}$ for CCO_2, CO_2, $mVCO_2$ and mVO_2. $[Blac^-]_{a-v}$ was corrected for arterio-venous ΔBV.

Table 8A.87

BLac-art				**Exercise**					**Recovery**			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.51	0.65	0.69	0.69	0.65	0.54	0.51	0.65	0.91	0.85	0.77	0.69
2	0.82	1.07	0.97	1.01	0.94	0.94	0.98	1.01	1.09	1.30	1.14	1.00
3	1.17	1.09	0.70	0.67	0.89	0.90	0.79	0.84	1.08	0.97	0.75	0.72
4	0.73	0.72	0.98	0.72	0.71	0.73	0.72	0.68	0.49	0.46	0.40	0.40
5	0.86	0.92	0.96	0.91	0.91	0.86	0.79	1.16	1.09	1.02	1.05	0.91
6	0.59	0.85	0.84	0.83	0.85	1.00	0.77	0.93	0.96	1.10	1.04	0.93
7	0.65	0.64	0.67	0.63	0.56	0.63	0.65	0.57	0.60	0.65	0.60	0.63
8	0.93	0.97	0.98	0.01	1.04	1.02	0.97	1.33	1.10	1.23	1.05	1.06
n	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
mean	0.78	0.86	0.85	0.68	0.82	0.83	0.77	0.90	0.91	0.95	0.85	0.79
stdev	0.21	0.18	0.14	0.30	0.16	0.18	0.16	0.26	0.24	0.29	0.26	0.22
SEM	0.07	0.06	0.05	0.11	0.06	0.06	0.06	0.09	0.08	0.10	0.09	0.08

Table 8A.88

BLac ven				**Exercise**					**Recovery**			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.49	2.53	2.72	3.69	2.81	2.52	2.75	2.77	2.27	2.44	2.21	1.38
2	0.42	2.65	3.20	3.38	3.66	3.61	3.60	3.49	3.53	3.53	3.34	2.10
3	1.29	2.35	1.74	2.19	2.57	1.60	1.84	3.43	3.64	3.07	3.36	1.76
4	0.71	2.23	2.19	2.33	2.13	1.98	1.96	1.46	1.81	2.00	1.26	0.77
5	0.80	1.30	1.54	1.42	1.39	1.35	1.43	1.55	3.01	2.45	2.21	1.55
6	1.06	0.83	0.58	1.29	1.37	2.28	2.40	1.39	1.64	2.00	2.14	1.39
7	0.45	1.55	2.00	2.28	2.13	1.96	2.14	1.85	1.63	1.67	1.17	0.96
8	1.04	1.88	2.21	2.20	2.92	2.94	3.10	4.23	3.88	3.65	3.26	2.38
n	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
mean	0.78	1.91	2.02	2.35	2.37	2.28	2.40	2.52	2.68	2.60	2.37	1.54
stdev	0.33	0.64	0.79	0.84	0.78	0.74	0.71	1.10	0.95	0.74	0.89	0.54
SEM	0.12	0.23	0.28	0.30	0.28	0.26	0.25	0.39	0.34	0.26	0.31	0.19

Table 8A.89

BLac a-v				**Exercise**					**Recovery**			
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.02	-1.87	-2.00	-2.96	-2.14	-1.95	-2.22	-2.13	-1.33	-1.57	-1.43	-0.69
2	0.41	-1.55	-2.22	-2.32	-2.71	-2.64	-2.57	-2.46	-2.46	-2.23	-2.19	-1.11
3	-0.11	-1.25	-1.04	-1.51	-1.68	-0.68	-1.04	-2.58	-2.59	-2.12	-2.63	-1.07
4	0.02	-1.50	-1.19	-1.60	-1.41	-1.24	-1.25	-0.78	-1.33	-1.56	-0.89	-0.39
5	0.05	-0.36	-0.57	-0.48	-0.47	-0.48	-0.64	-0.40	-1.93	-1.44	-1.17	-0.65
6	-0.49	0.01	0.25	-0.45	-0.50	-1.27	-1.62	-0.41	-0.64	-0.86	-1.11	-0.49
7	0.20	-0.90	-1.33	-1.64	-1.57	-1.34	-1.50	-1.28	-1.03	-1.03	-0.59	-0.35
8	-0.10	-0.93	-1.24	-2.19	-1.89	-1.91	-2.13	-2.90	-2.79	-2.42	-2.21	-1.35
n	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
mean	0.00	-1.04	-1.17	-1.65	-1.55	-1.44	-1.62	-1.62	-1.76	-1.65	-1.53	-0.76
stdev	0.26	0.63	0.77	0.87	0.77	0.71	0.65	1.02	0.79	0.56	0.73	0.37
SEM	0.09	0.22	0.27	0.31	0.27	0.25	0.23	0.36	0.28	0.20	0.26	0.13

Table 8A.90

CCO2 art	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	675.1	666.9	676.4	690.5	673.5	706.9	671.3	666.8	698.1	653.1	686.2	688.8
2	661.9	688.7	685.4	683.5	690.9	682.7	697.5	703.7	647.3	646.5	668.9	670.0
3	644.4	628.0	624.1	587.7	611.6	542.8	615.8	609.7	600.4	588.2	599.1	539.8
4	631.7	694.1	702.6	683.3	673.4	689.7	688.3	676.7	685.0	679.7	676.8	678.9

5	674.5	612.5	657.0	647.3	657.7	643.7	656.1	619.4	638.9	647.3	634.7	634.7
6	714.9	671.2	690.6	681.5	675.7	689.0	679.4	693.8	693.8	676.6	673.4	683.2
7	670.7	696.9	720.5	726.2	726.5	737.1	734.9	725.1	681.6	714.6	721.8	724.1
8	684.8	687.3	697.7	679.4	694.4	686.5	673.5	637.7	638.3	645.8	666.0	649.2
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	669.7	668.2	681.8	672.4	675.5	672.3	677.1	666.6	660.4	656.5	665.9	658.6
stdev	25.25	31.6	29.9	40.4	33.0	58.4	34.1	41.3	34.5	36.4	36.2	54.9
SEM	8.93	11.2	10.6	14.3	11.7	20.6	12.0	14.6	12.2	12.9	12.8	19.4

Table 8A.91 CCO2

ven	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	752.2	834.7	806.1	833.4	853.9	814.5	820.4	773.1	705.7	663.4	680.3	691.1
2	706.6	740.2	831.1	784.1	735.6	746.8	753.1	761.8	653.7	657.1	685.6	668.0
3	721.2	728.9	726.7	738.3	732.6	710.5	730.4	712.9	587.8	611.6	594.4	654.0
4	733.3	831.7	799.8	802.6	816.9	790.9	791.0	772.9	732.9	685.0	699.7	708.7
5	754.0	756.0	812.4	818.6	809.6	791.4	815.9	800.7	744.8	688.1	683.5	704.9
6	676.8	476.6	826.9	813.1	799.3	765.5	796.1	726.7	712.4	687.0	686.1	706.0
7	790.2	908.1	939.2	825.7	836.8	839.1	827.7	842.3	793.3	781.0	750.2	779.1
8	685.2	830.5	810.2	792.9	821.2	782.7	866.1	669.6	693.5	663.6	695.6	713.4
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	727.4	763.3	819.0	801.1	800.7	780.2	800.1	757.5	703.0	679.6	684.4	703.1
stdev	38.0	130.5	58.4	30.3	44.4	39.8	43.0	53.8	61.8	47.9	42.8	37.2
SEM	13.4	46.1	20.6	10.7	15.7	14.1	15.2	19.0	21.8	16.9	15.1	13.2

Table 8A.92 CCO2 a-

v	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	-77.1	-167.7	-129.7	-143.0	-180.5	-107.5	-149.0	-106.2	-7.6	-10.3	5.9	-2.3
2	-44.6	-51.5	-145.6	-100.6	-44.7	-64.1	-55.6	-58.2	-6.4	-10.5	-16.6	2.0
3	-76.8	-100.8	-102.6	-150.5	-121.0	-167.8	-114.6	-103.2	12.5	-23.4	4.7	-114.2
4	-101.6	-137.6	-97.2	-119.3	-143.5	-101.2	-102.7	-96.2	-47.9	-5.4	-22.9	-29.8
5	-79.6	-143.5	-155.4	-171.3	-151.9	-147.7	-159.8	-181.3	-105.9	-40.8	-48.8	-70.2
6	38.1	194.6	-136.3	-131.6	-123.6	-76.6	-116.7	-32.9	-18.6	-10.4	-12.6	-22.8
7	-119.6	-211.2	-218.7	-99.5	-110.3	-102.0	-92.9	-117.2	-111.7	-66.4	-28.4	-55.0
8	-0.5	-143.2	-112.5	-113.6	-126.8	-96.1	-192.6	-31.8	-55.2	-17.7	-29.6	-64.2
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-57.7	-95.1	-137.2	-128.7	-125.3	-107.9	-123.0	-90.9	-42.6	-23.1	-18.5	-44.6
stdev	52.9	126.0	38.8	25.3	39.3	34.4	42.9	49.6	46.5	20.7	18.2	39.0
SEM	18.7	44.5	13.7	8.9	13.9	12.2	15.2	17.5	16.4	7.3	6.4	13.8

Table 8A.93

				Exercise						**Recovery**		
CO2 art	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	165.6	169.2	167.7	163.5	170.1	171.8	173.5	173.5	170.8	170.7	165.6	162.8
2	157.0	164.8	166.6	167.1	168.9	166.8	166.1	167.7	167.5	167.3	164.0	168.1
3	171.5	175.6	174.2	175.3	177.0	174.0	176.6	177.5	178.7	177.3	176.2	174.0
4	174.6	176.8	176.6	177.6	176.3	176.4	178.7	179.3	177.9	182.7	184.2	178.4
5	186.5	186.9	189.7	188.8	190.3	191.8	190.6	192.6	194.5	190.6	187.6	186.1
6	182.2	182.0	188.4	187.2	186.7	185.6	185.0	191.2	188.9	188.8	188.4	187.4
7	186.1	186.9	188.2	186.1	187.6	188.2	186.3	187.1	187.6	185.2	185.7	182.3
8	206.5	212.9	212.0	212.3	213.2	212.5	213.6	216.0	216.7	213.2	208.8	210.5
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	178.7	181.9	182.9	182.2	183.8	183.4	183.8	185.6	185.3	184.5	182.6	181.2
stdev	15.2	14.8	15.0	15.3	14.3	14.6	14.3	15.0	15.6	14.2	14.3	14.6
SEM	5.4	5.2	5.3	5.4	5.1	5.2	5.1	5.3	5.5	5.0	5.1	5.2

Table 8A.94 CO2

				Exercise						**Recovery**		
ven	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	81.0	59.2	66.4	72.5	65.2	69.0	74.3	73.8	134.6	153.4	139.8	141.7
2	98.7	74.8	82.1	92.2	93.3	91.1	90.4	93.7	134.5	146.0	138.4	150.8
3	84.1	61.6	68.5	66.4	66.1	68.8	64.1	61.0	143.6	146.4	130.1	119.5
4	81.3	51.6	60.3	66.0	63.7	69.5	70.0	73.4	136.7	138.9	134.3	133.9
5	79.2	60.4	63.0	61.7	59.8	65.5	57.7	57.1	132.7	140.8	143.8	136.2
6	123.7	104.5	68.0	70.4	70.9	69.8	69.8	79.4	140.4	145.8	136.4	137.8

7	86.5	65.2	62.1	61.9	63.3	60.3	61.1	60.0	107.5	97.3	106.2	99.9
8	144.2	77.4	68.4	61.2	62.0	59.0	52.1	84.7	162.0	170.4	165.4	156.4
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	97.3	69.3	67.3	69.0	68.0	69.1	67.4	72.9	136.5	142.4	136.8	134.5
stdev	24.0	16.5	6.7	10.2	10.7	9.8	11.8	12.9	15.0	20.7	16.3	17.9
SEM	8.5	5.8	2.4	3.6	3.8	3.5	4.2	4.6	5.3	7.3	5.8	6.3

Table 8A.95

				Exercise						Recovery		
CO2a-v	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	84.6	109.9	101.3	91.0	104.9	102.8	99.2	99.7	36.2	17.2	25.8	21.1
2	58.2	89.9	84.5	75.0	75.6	75.7	75.7	74.1	33.0	21.3	25.5	17.4
3	87.3	114.1	105.8	108.9	110.9	105.2	112.5	116.5	35.1	30.9	46.0	54.5
4	93.3	125.2	116.3	111.6	112.6	106.9	108.7	105.8	41.2	43.8	49.9	44.4
5	107.3	126.5	126.7	127.1	130.4	126.3	132.9	135.4	61.8	49.8	43.8	49.9
6	58.4	77.5	120.4	116.8	115.8	115.8	115.2	111.8	48.5	43.0	52.0	49.7
7	99.6	121.7	126.1	124.2	124.3	127.9	125.2	127.0	80.1	87.9	79.5	82.5
8	62.4	135.5	143.7	151.1	151.2	153.5	161.5	131.3	54.7	42.7	43.4	54.1
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	81.4	112.5	115.6	113.2	115.7	114.3	116.4	112.7	48.8	42.1	45.8	46.7
stdev	19.3	19.7	18.2	23.1	21.7	22.8	25.1	20.0	16.2	21.8	16.9	20.5
SEM	6.8	7.0	6.4	8.2	7.7	8.0	8.9	7.1	5.7	7.7	6.0	7.2

Table 8A.96 mVCO2

Subject	R	F	+1	+2	+5	+10
1	0.34	8.06	0.63	0.78	0.29	0.07
4	0.80	20.59	3.61	0.21	0.63	0.70
5	0.74	51.32	9.62	2.01	1.15	1.19
6	0.19	3.44	1.35	0.72	0.46	0.65
7	0.96	18.19	8.42	1.46	0.59	0.98
8	0.01	4.51	5.81	1.43	1.40	2.23
n	6	6	6	6	6	6
mean	0.51	17.69	4.91	1.10	0.75	0.97
stdev	0.38	17.94	3.69	0.65	0.43	0.72
sem	0.15	7.32	1.51	0.26	0.17	0.30

Table 8A.97 mVO2

R	F	+1	+2	+5	+10
0.37	7.56	3.01	1.31	1.29	0.69
0.73	22.65	3.11	1.68	1.37	1.05
1.00	38.34	5.61	2.45	1.03	0.85
0.29	22.23	4.49	1.84	1.35	1.07
0.80	19.72	6.04	1.93	1.66	1.46
0.67	22.85	4.49	1.84	1.35	1.07
6	6	6	6	6	6
0.64	22.23	4.46	1.84	1.34	1.03
0.27	9.81	1.24	0.37	0.20	0.26
0.11	4.01	0.51	0.15	0.08	0.11

Metabolism (Alkalosis). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [Blac$^-$], blood CO_2 content (CCO_2), blood O_2 content (CO_2); forearm muscle VCO_2 ($mVCO_2$) and VO_2 (mVO_2) at rest (R), during submaximal finger flexion exercise (e1 to e6) to fatigue (F), and recovery (1 to 10min). Units are mM for [Blac$^-$]; ml.min^{-1} for CCO_2, CO_2, $mVCO_2$ and mVO_2. $[Blac^-]_{a-v}$ was corrected for arterio-venous ΔBV.

Table 8A.98

BLac-art				Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.54	0.43	0.64	0.53	0.65	0.62	0.62	0.87	0.73	0.68	3.34	3.30
2	0.56	0.65	0.64	0.67	0.64	0.46	0.74	0.91	0.80	0.61	3.29	3.10
3	0.95	1.03	1.01	0.98	1.06	1.11	1.10	0.98	0.80	0.77	3.35	3.32
4	1.33	1.26	1.14	1.34	0.99	1.26	1.14	0.83	1.08	1.08	3.21	3.21
5	0.27	0.29	0.36	0.32	0.45	0.62	0.56	0.91	0.76	0.67	3.32	3.23
6	1.33	1.41	1.41	1.74	1.54	1.78	1.66	1.80	1.64	1.62	3.62	3.61
7	0.52	0.52	0.81	0.64	0.55	0.51	0.51	0.73	0.63	0.70	2.92	2.99
8	1.32	1.42	1.40	1.49	1.53	1.45	1.42	1.64	1.39	1.71	3.61	3.93
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.85	0.88	0.93	0.96	0.93	0.98	0.97	1.08	0.98	0.98	3.33	3.33
stdev	0.43	0.46	0.38	0.51	0.43	0.49	0.43	0.40	0.36	0.45	0.22	0.30
SEM	0.15	0.16	0.13	0.18	0.15	0.17	0.15	0.14	0.13	0.16	0.08	0.11

Table 8A.99

BLac-ven				Exercise						Recovery		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	0.59	4.05	2.37	2.93	2.21	2.76	2.46	2.65	2.34	1.31	4.95	3.93
2	0.72	1.86	2.50	2.58	2.92	3.28	3.30	3.21	2.14	1.42	4.43	3.70

3	0.93	1.13	1.46	1.33	1.86	1.97	1.82	3.72	2.38	0.13	4.85	2.60
4	1.46	2.82	2.50	2.97	2.41	2.90	3.16	2.14	1.98	1.46	3.94	3.41
5	1.06	2.47	2.62	2.32	2.23	2.45	2.43	3.20	2.30	1.54	4.45	3.69
6	0.65	2.08	3.38	3.64	3.70	3.58	3.66	3.66	2.58	1.72	4.57	3.70
7	0.65	1.55	2.03	2.22	2.47	2.39	2.10	2.65	1.81	1.08	4.10	3.36
8	1.31	2.49	3.62	3.80	3.86	4.05	4.68	4.87	3.47	3.33	5.93	5.79
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.92	2.31	2.56	2.72	2.71	2.92	2.95	3.26	2.38	1.50	4.65	3.77
stdev	0.33	0.89	0.69	0.80	0.73	0.69	0.94	0.84	0.50	0.89	0.62	0.91
SEM	0.12	0.32	0.24	0.28	0.26	0.24	0.33	0.30	0.18	0.31	0.22	0.32

Table 8A.100

BLac-a-v				**Exercise**						**Recovery**		
Subject	**rest**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	-0.06	-3.61	-1.72	-2.40	-1.56	-2.14	-1.83	-1.79	-1.61	-0.63	-1.63	-0.73
2	-0.15	-1.19	-1.86	-1.88	-2.28	-2.82	-2.53	-2.31	-1.41	-0.82	-0.92	-0.75
3	0.03	-0.08	-0.49	-0.32	-0.76	-0.79	-0.66	-2.80	-1.52	0.69	-1.22	0.80
4	-0.11	-1.54	-1.34	-1.63	-1.43	-1.61	-2.01	-1.30	-0.91	-0.39	-0.80	-0.25
5	-0.79	-2.19	-2.25	-1.99	-1.77	-1.82	-1.87	-2.29	-1.57	-0.88	-1.16	-0.46
6	0.67	-0.66	-1.94	-1.88	-2.14	-1.81	-2.00	-1.88	-0.96	-0.13	-1.00	-0.15
7	-0.14	-1.02	-1.20	-1.57	-1.90	-1.87	-1.59	-1.93	-1.20	-0.38	-1.23	-0.44
8	0.00	-1.08	-2.19	-2.30	-2.31	-2.60	-3.24	-3.26	-2.12	-1.66	-2.37	-2.06
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-0.07	-1.42	-1.62	-1.75	-1.77	-1.93	-1.97	-2.19	-1.41	-0.52	-1.29	-0.51
stdev	0.40	1.08	0.59	0.64	0.52	0.62	0.74	0.61	0.39	0.67	0.50	0.80
SEM	0.14	0.38	0.21	0.23	0.18	0.22	0.26	0.22	0.14	0.24	0.18	0.28

Table 8A.101

				Exercise							**Recovery**	
CCO2 art	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	683.3	791.4	783.7	782.0	773.3	743.7	756.5	780.1	764.5	748.9	716.3	752.4
2	759.7	669.8	704.3	695.9	698.7	684.0	706.1	704.8	668.8	670.3	709.6	696.0
3	731.4	694.1	745.9	740.8	735.6	740.8	702.0	688.0	712.7	609.7	667.5	675.0
4	715.1	800.6	789.6	767.9	787.9	789.4	787.7	822.8	755.0	798.7	765.8	785.2
5	773.0	758.9	767.4	766.1	739.9	760.3	779.0	738.0	738.9	697.6	724.4	751.5
6	849.3	820.7	825.0	839.5	837.2	757.2	787.2	797.7	778.1	749.4	762.4	751.7
7	799.5	811.3	809.5	822.2	780.5	781.5	787.3	800.1	741.6	767.2	753.4	777.8
8	773.0	730.1	759.8	755.9	775.0	752.0	787.5	751.9	750.5	759.4	767.2	703.2
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	760.5	759.6	773.1	771.3	766.0	751.1	761.7	760.4	738.8	725.1	733.3	736.6
stdev	51.5	56.5	38.0	45.1	41.5	32.0	37.1	48.1	34.2	61.6	35.3	40.2
SEM	18.2	20.0	13.4	15.9	14.7	11.3	13.1	17.0	12.1	21.8	12.5	14.2

Table 8A.102

				Exercise							**Recovery**	
CCO2 ven	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	800.7	929.3	924.0	926.5	926.8	894.5	898.4	863.5	791.0	754.6	671.1	769.2
2	796.9	717.1	782.5	800.2	798.5	775.9	790.3	782.9	689.5	672.7	678.7	710.6
3	775.4	831.8	842.7	842.2	839.9	848.1	836.6	851.8	711.5	654.3	652.3	716.8
4	863.8	899.9	888.9	888.4	911.3	900.2	884.9	906.1	828.1	800.4	802.1	818.6
5	819.9	829.5	857.1	913.5	881.9	880.1	882.1	818.0	773.6	754.0	749.0	736.3
6	907.3	909.6	947.0	942.6	940.8	860.6	865.8	859.5	776.2	722.0	718.4	764.4
7	854.9	915.1	883.7	876.0	859.6	903.0	909.2	918.4	813.2	790.0	780.2	788.6
8	788.1	748.4	818.1	909.7	918.0	898.1	905.6	948.1	796.2	777.9	737.4	700.7
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	825.9	847.6	868.0	887.4	884.6	870.1	871.6	868.5	772.4	740.7	723.7	750.7
stdev	45.3	80.4	54.3	47.1	49.0	43.0	40.4	54.1	48.2	53.7	53.6	41.5
SEM	16.0	28.4	19.2	16.7	17.3	15.2	14.3	19.1	17.1	19.0	18.9	14.7

Table 8A.103

				Exercise							**Recovery**	
CCO2 a-v	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	-117.3	-137.9	-140.4	-144.5	-153.5	-150.8	-142.0	-83.4	-26.5	-5.7	45.2	-16.7
2	-37.2	-47.3	-78.2	-104.2	-99.8	-91.9	-84.1	-78.1	-20.6	-2.4	30.9	-14.5
3	-44.0	-137.6	-96.8	-101.4	-104.2	-107.3	-134.7	-163.9	1.2	-44.6	15.2	-41.8
4	-148.7	-99.3	-99.3	-120.5	-123.4	-110.8	-97.2	-83.2	-73.1	-1.7	-36.3	-33.4

5	-47.0	-70.5	-89.7	-147.4	-142.0	-119.8	-103.0	-80.1	-34.6	-56.5	-24.6	15.2
6	-58.0	-88.9	-122.0	-103.2	-103.6	-103.4	-78.6	-61.8	1.9	27.4	44.0	-12.7
7	-55.4	-103.9	-74.2	-53.8	-79.0	-121.6	-121.8	-118.3	-71.7	-22.8	-26.8	-10.9
8	-15.2	-18.3	-58.3	-153.8	-143.0	-146.0	-118.1	-196.1	-45.6	-18.5	29.8	2.5
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	-65.4	-88.0	-94.9	-116.1	-118.6	-118.9	-109.9	-108.1	-33.6	-15.6	9.7	-14.1
stdev	44.6	41.7	26.5	33.0	26.0	20.5	23.0	47.8	28.9	26.4	33.7	18.1
SEM	15.8	14.7	9.4	11.7	9.2	7.2	8.1	16.9	10.2	9.3	11.9	6.4

Table 8A.104

		Exercise							Recovery			
CO2 art	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	178.4	181.6	182.5	182.5	186.1	178.5	183.6	191.2	189.1	177.0	176.7	178.2
2	157.8	166.6	167.5	165.8	168.8	169.2	169.3	173.3	176.2	171.3	156.8	166.6
3	160.2	163.3	174.1	164.8	163.1	164.1	166.1	174.6	166.8	174.0	167.3	160.5
4	177.4	181.9	182.1	181.9	183.3	183.3	182.3	181.9	179.8	178.1	178.1	178.9
5	183.3	184.4	184.0	184.2	185.5	185.5	185.2	188.8	185.8	185.2	183.8	182.1
6	169.7	174.7	174.5	176.9	176.1	177.6	179.3	180.8	177.3	181.6	175.6	174.7
7	177.9	180.3	180.7	178.8	177.1	181.8	183.3	186.1	185.2	185.9	184.4	184.8
8	195.0	195.4	195.7	199.2	199.4	200.9	200.1	203.9	205.8	204.9	201.7	202.8
n	8	8	8	8	8	8	8	8	8	8	8	8
mean	174.9	178.5	180.1	179.3	179.9	180.1	181.1	185.1	183.3	182.2	178.1	178.6
stdev	12.2	10.2	8.4	10.9	11.3	11.1	10.4	9.9	11.5	10.5	13.1	12.7
SEM	4.3	3.6	3.0	3.9	4.0	3.9	3.7	3.5	4.1	3.7	4.6	4.5

Table 8A.105

		Exercise							Recovery			
CO2 ven	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	97.8	35.4	51.4	53.1	59.5	64.7	69.8	73.4	150.9	149.9	151.2	149.6
2	115.5	90.0	87.1	84.2	82.6	83.6	83.7	76.4	139.4	152.1	143.9	128.0
3	105.4	48.7	61.2	61.4	49.8	55.4	56.7	51.7	141.2	163.4	131.5	112.1
4	99.0	66.1	69.8	62.2	66.3	75.4	68.8	63.8	143.5	145.8	141.7	141.2
5	121.7	79.0	66.2	66.8	66.0	69.5	71.2	67.2	118.5	139.1	148.5	160.0
6	65.0	58.8	66.2	56.7	59.6	58.0	62.5	66.0	146.2	160.9	137.4	129.2
7	91.0	73.8	82.2	73.6	71.3	74.8	81.2	65.8	112.3	133.2	149.4	145.2
8	163.6	87.6	79.5	72.0	66.7	62.6	58.8	46.5	147.3	177.2	182.4	174.8
n	8	8	8	8	8	8	8	8	8	8	8	8
average	107.4	67.4	70.5	66.2	65.2	68.0	69.1	63.8	137.4	152.7	148.3	142.5
stdev	28.5	19.1	11.8	10.1	9.6	9.6	9.8	10.1	14.1	14.1	15.3	19.7
SEM	10.1	6.7	4.2	3.6	3.4	3.4	3.5	3.6	5.0	5.0	5.4	7.0

Table 8A.106

		Exercise							Recovery			
CO2a-v	**R**	**e1**	**e2**	**e3**	**e4**	**e5**	**e6**	**F**	**+1**	**+2**	**+5**	**+10**
1	80.6	146.2	131.1	129.4	126.6	113.9	113.8	117.8	38.2	27.1	25.5	28.6
2	42.2	76.6	80.3	81.6	86.1	85.5	85.6	96.9	36.7	19.2	12.9	38.6
3	54.8	114.6	112.8	103.4	113.4	108.7	109.4	122.9	25.6	10.5	35.8	48.4
4	78.4	115.8	112.3	119.7	117.0	107.9	113.5	118.1	36.3	32.3	36.5	37.8
5	61.5	105.4	117.8	117.4	119.5	116.0	113.9	121.6	67.4	46.0	35.3	22.2
6	104.7	115.9	108.3	120.2	116.6	119.6	116.8	114.9	31.1	20.7	38.2	45.5
7	86.9	106.5	98.5	105.2	105.8	107.0	102.0	120.4	72.8	52.7	35.0	39.6
8	31.4	107.9	116.2	127.2	132.8	138.3	141.3	157.4	58.6	27.8	19.3	28.1
n	8	8	8	8	8	8	8	8	8	8	8	8
average	67.6	111.1	109.7	113.0	114.7	112.1	112.0	121.2	45.9	29.5	29.8	36.1
stdev	24.5	19.1	15.0	15.7	14.1	14.8	15.5	16.8	17.8	14.0	9.4	9.0
SEM	8.6	6.7	5.3	5.6	5.0	5.2	5.5	5.9	6.3	5.0	3.3	3.2

Table 8A.107 mVCO2

Subject	R	F	+1	+2	+5	+10
1	1.0	8.1	2.2	4.3	2.1	2.2
4	1.1	23.3	12.5	3.0	2.9	4.7
5	0.4	22.7	7.6	4.5	2.3	1.6
6	0.3	3.8	3.3	3.2	1.5	0.5
7	5.0	18.5	10.2	7.0	5.3	4.9
8	2.0	32.6	23.7	24.1	14.9	9.4
n	6	6	6	6	6	6

Table 8A.108 mVO2

Rest	F	+1	+2	+5	+10
0.7	11.4	1.0	1.4	0.6	0.7
0.6	24.8	4.1	0.9	1.0	1.6
0.5	34.4	6.4	2.6	1.0	0.4
0.5	7.0	1.7	1.1	0.9	0.4
0.8	18.8	6.3	3.1	1.6	1.5
0.4	26.1	7.1	3.4	1.5	1.3
6	6	6	6	6	6

mean	1.6	18.1	9.9	7.7	4.8	3.9	0.6	20.4	4.4	2.1	1.1	1.0
stdev	1.7	10.6	7.8	8.2	5.1	3.2	0.1	10.1	2.6	1.1	0.4	0.6
sem	0.7	4.3	3.2	3.3	2.1	1.3	0.1	4.1	1.1	0.4	0.1	0.2

Appendix 8B Raw data Chapter 4 (Study 2)

Table 8B.1 Participant and exercise variability (Var) performance data. V

					Finger flexion variability tests								
					Var 1	Var 2		Var 1	Var 2		Var 1	Var 2	
	Age	Height	mass	VO_{2peak}	PO	PO	PO	Force	Force	Force	Fatigue	Fatigue	Fatigue
Subject	yrs	cm	kg	L.min	W	W	CV%	N	N	CV%	sec	sec	CV%
1	28	175	68.7	3.43	3.82	3.81	0.09	26.9	27.2	0.8	444	407	6.1
2	21	180.5	73.0	3.64	5.60	5.44	1.95	31.1	33.3	4.7	204	230	8.5
3	21	173.5	64.8	3.11	4.30	4.11	3.15	28.6	28.3	0.9	500	575	9.9
4	40	189.25	104.0	3.78	6.13	6.05	0.84	50.2	55.0	6.1	65	61	4.5
5	20	179	76.5	3.42	5.25	5.29	0.47	29.1	29.5	1.0	286	224	17.2
6	24	188	82.7	4.32	4.59	4.60	0.23	31.1	33.1	4.2	300	306	1.4
7	30	179.5	81.2	4.24	6.11	6.19	0.92	35.5	36.0	1.0	456	310	27.0
8	23	173	67.5	3.93	5.78	5.84	0.76	37.5	35.3	4.3	183	300	34.3
9	28	188	68.8	3.74	7.32	7.30	0.19	59.0	54.4	6.0	66	73	7.1
10	26	158.5	74.7	3.11	4.41	4.31	1.58	30.8	28.3	6.1	403	455	8.6
n	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	26.1	178.4	76.2	3.67	5.33	5.3	1.0	36.0	36.0	3.5	290.7	294.1	12.4
stdev	6.0	9.2	11.4	0.42	1.06	1.1	1.0	10.5	10.3	2.3	159.1	159.9	10.5
SEM	1.9	2.9	3.6	0.13	0.34	0.3	0.3	3.3	3.3	0.7	50.3	50.6	3.3

Table 8B.2 Exercise performance data during Control (CON) and Digoxin (DIG) trials.

Finger flexion exercise performance								
	CON	DIG		CON	DIG		CON	DIG
	PO	PO		Force	Force		Time to fatigue	
Subject	(W)	(W)	CV%	N	N	CV%	sec	sec
1	4.06	3.64	7.8	28.89	26.07	7.3		
2	6.02	6.55	6.0	34.73	37.75	5.9	108	128
3	3.49	3.75	5.2	28.54	29.88	3.3	74	100
4	7.11	7.95	7.9	52.62	56.98	5.6	82	80
5	6.51	5.31	14.3	36.58	31.01	11.7	367	329
6	4.06	4.59	8.6	29.32	31.84	5.8	173	94
7	5.59	6.05	5.6	33.07	40.54	14.4	655	140
8	6.41	6.35	0.7	38.81	35.18	6.9	180	86
9	7.18	6.56	6.4	57.61	55.80	2.3	70	65
10	3.23	3.63	8.2	22.20	28.68	18.0	416	391
n	10	10	10	10	10	10	9	9
mean	5.36	5.44	7.1	36.23	37.37	8.1	236.1	157.0
stdev	1.52	1.49	3.4	11.07	10.90	5.0	201.9	118.4
sem	0.5	0.5	1.1	3.5	3.4	1.6	67.3	39.5

Table 8B.3 Serum digoxin concentration. Units are nM.

	DIG			CON		
Subject	day 7	day 13	day 14	day 7	day 13	day 14
1	0.8	0.7	0.7	<0.4	<0.4	<0.4
2	0.7	0.8			<0.4	<0.4
3	<0.4	0.5	0.5	<0.4	<0.4	<0.4
4	0.9	0.9	1.1	<0.4	<0.4	
5	0.7	0.7	0.8	<0.4	<0.4	<0.4
6	0.8	0.6	0.8	<0.4	<0.4	<0.4
7	0.4	0.4	0.6	<0.02	<0.02	<0.02
8	1	1	0.9	<0.4	<0.4	<0.4
9	0.7	0.8	0.8	<0.02		<0.02
10	0.5	0.5	0.7	<0.02	<0.02	<0.02
n	9	10	9	9	9	9
mean	0.7	0.7	0.8			
stdev	0.2	0.2	0.2			
sem	0.1	0.1	0.1			

*lower detection limits were revised from <0.4 to <0.2 by Alfred Hospital pathology

Forearm blood flow for Control (CON) and Digoxin (DIG) at rest (R), during exercise (e1-pe4) to fatigue (F) and in recovery (1 to 30min). Units are ml.min^{-1}.

Table 8B.4

CON				Exercise (bouts)					Recovery (min)				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1	14.2	78.0	63.7	77.9	70.7	85.0	84.8	184.9	81.6	74.4	31.9	14.2	14.2
2	10.6	116.9	56.6	170.0	94.5	170.2	68.1	98.5	41.6	34.1	26.5	15.1	11.3
3	41.3	331.2	248.3	529.0	487.0	674.5	591.0	679.9	414.8	347.3	243.3	119.1	72.4
4	16.1	140.9	32.2	116.8	60.3	153.0	68.6	206.4	101.1	48.5	48.5	32.3	20.2
5	38.3	167.7	71.9	167.7	81.6	278.1	86.3	443.8	86.4	62.4	67.2	38.3	23.9
6	26.1	196.0	73.9	230.7	82.6	234.9	108.7	275.1	113.3	78.7	52.3	39.2	21.8
7	16.1	141.2	96.8	173.6	129.1	230.7	153.7	263.6	154.3	60.8	40.5	32.4	24.3
8	33.5	201.1	87.9	243.2	117.4	226.8	63.0	311.3	130.6	75.8	46.3	16.8	21.0
9	16.3	114.3	40.8	102.0	53.0	118.5	61.4	155.0	85.9	61.3	49.0	12.3	20.4
10	15.3	107.1	26.8	126.3	15.3	130.1	30.6	172.3	45.9	15.3	15.3	19.1	11.5
n	10	10	10	10	10	10	10	10	10	10	10	10	10
mean	22.8	159.4	79.9	193.7	119.1	230.2	131.6	279.1	125.6	85.9	62.1	33.9	24.1
stdev	11.2	71.9	63.5	129.2	133.2	167.6	164.7	170.8	107.3	94.0	65.3	31.7	17.6
sem	3.5	22.7	20.1	40.8	42.1	53.0	52.1	54.0	33.9	29.7	20.7	10.0	5.6

Table 8B.5

DIG				Exercise (bouts)					Recovery (min)				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1	11.3	88.4	53.0	67.3	70.7	113.3	91.9	191.5	42.5	14.2	17.7	35.4	14.1
2	11.3	120.9	67.9	155.1	79.3	192.8	79.3	87.0	56.7	45.4	18.9	11.3	11.3
3	31.0	326.6	217.5	347.5	321.4	425.7	415.0	415.0	196.9	155.3	181.1	103.4	62.0
4	12.1	128.8	68.4	153.0	64.4	201.5	84.6	222.3	125.3	60.6	48.5	20.2	12.1
5	28.7	153.3	81.5	162.9	124.8	268.6	43.2	432.3	76.6	76.8	19.2	38.4	19.1
6	30.5	183.0	47.8	252.5	108.7	261.0	91.3	283.9	78.4	78.7	43.6	30.5	26.1
7	20.1	92.6	60.4	165.4	112.9	274.2	120.9	234.3	170.0	89.0	44.5	20.2	16.1
8	31.4	236.1	134.8	257.9	143.6	237.1	93.0	385.7	114.1	63.3	54.8	21.1	16.8
9	17.1	97.6	20.3	130.0	61.1	142.4	32.6	162.8	24.4	12.2	12.2	16.2	20.3
10	15.3	95.7	49.7	111.0	30.6	99.5	23.0	149.4	38.3	23.0	15.3	11.5	15.3
n	10	10	10	10	10	10	10	10	10	10	10	10	10
mean	20.9	152.3	80.1	180.3	111.8	221.6	107.5	256.4	92.3	61.8	45.6	30.8	21.3
stdev	8.6	77.3	56.6	82.5	81.2	95.8	112.4	119.4	58.0	42.8	50.2	27.2	14.9
sem	2.7	24.4	17.9	26.1	25.7	30.3	35.5	37.8	18.3	13.5	15.9	8.6	4.7

Fluid Shifts (Control). Arterial (art) and venous (ven) Haemoglobin ([Hb]), hematocrit (Hct); changes from resting levels in arterial (art) and venous (ven) plasma volume (ΔPV) and blood volume (ΔBV); and changes in venous compared to arterial plasma (ΔPV_{a-v}) and blood volume (ΔBV_{a-v}) across the forearm calculated at rest (R), during supramaximal finger flexion exercise (e1-e4+1) to fatigue (F), and recovery (1 to 30min). Units are g dl^{-1} haemoglobin and % for Hct; percent change for ΔPV_a, ΔBV_a, ΔPV_{a-v}, ΔBV_{a-v}.

Table 8B.6 Hb art

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	14.7	14.8	14.9	14.9	15.0	15.0	14.9	15.1	15.1	15.1	15.1	14.9	14.8	14.8
3	12.8	12.9	13.1	13.1	13.1	13.1	13.3	13.2	13.2	13.2	13.2	13.0	13.0	12.9
4	14.4	14.4	14.5	14.5	14.6	14.6	14.7	14.7	14.9	15.0	14.9	14.7	14.5	14.6
5	15.2	15.0	15.1	15.1	15.1	15.1	15.1	15.2	15.3	15.3	15.3	15.3	15.1	15.1
6	15.2	14.9	15.1	15.1	15.0	15.1	15.1	14.8	15.0	15.1	14.7	15.1	15.0	14.6
7	14.5	14.7	14.6	14.8	14.8	14.8	14.9	14.4	14.9	15.0	15.0	14.8	14.7	14.4
8	14.4	15.0	14.8	14.5	14.7	14.9	14.9	15.2	15.2	14.9	14.8	14.8	14.6	14.4
9	13.6	13.6	13.7	13.7	13.8	13.8	13.9	13.9	13.9	14.0	13.9	13.8	13.5	13.5
10	12.9	12.9	12.9	13.1	12.9	12.7	12.8	12.9	13.0	13.1	13.1	12.9	12.8	12.9
n	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	14.2	14.2	14.3	14.3	14.3	14.3	14.4	14.4	14.5	14.5	14.4	14.3	14.2	14.1
stdev	0.9	0.9	0.8	0.8	0.8	0.9	0.8	0.9	0.9	0.9	0.8	0.9	0.9	0.8
SEM	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Table 8B.7 Hb ven

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	13.6	14.1	13.8	14.0	13.7	14.1	13.8	14.1	14.7	13.7	13.6	13.6	13.1	13.2
2														
3	12.8	13.3	13.1	13.4	13.1	13.3	13.1	13.5	13.5	13.1	13.1	13.0	12.9	12.9
4														
5	15.2	15.2	14.9	15.3	15.0	15.1	15.0	15.2	15.5	15.3	15.3	15.0	14.9	14.8
6	15.0	15.3	15.4	15.3	15.1	15.2	15.1	15.3	15.5	15.1	15.1	15.2	15.1	15.0
7	14.5	15.2	15.2	14.8	14.8	15.1	15.0	14.4	15.3	15.0	14.9	14.7	14.5	14.4
8	14.0	14.9	14.5	15.1	14.9	15.1	14.9	15.6	15.6	15.0	14.9	14.6	14.4	14.1
9														
10	12.7	13.1	12.9	13.0	12.9	12.9	12.8	13.0	13.1	12.9	12.8	12.9	12.8	12.7
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	14.0	14.4	14.2	14.4	14.2	14.4	14.2	14.4	14.7	14.3	14.2	14.1	13.9	13.9
stdev	1.0	0.9	1.0	0.9	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.9
SEM	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4

Table 8B.8 Hct art

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	40.6	41.9	41.5	41.6	41.9	42.5	41.7	42.3	42.3	42.9	42.5	42.0	41.7	41.3
3	36.8	37.2	38.1	37.4	37.2	38.1	37.7	38.1	38.1	38.5	38.4	37.4	37.4	37.0
4	41.5	41.8	41.9	41.8	42.0	41.9	42.2	42.0	43.1	42.9	42.6	42.5	41.6	41.6
5	41.8	41.6	41.9	41.6	42.1	41.3	41.9	42.0	42.4	42.3	42.7	42.2	41.8	42.0
6	40.9	40.6	40.7	40.9	40.4	40.5	40.2	39.2	40.1	40.6	39.7	40.2	40.3	39.3
7	40.7	40.7	40.8	41.3	41.7	40.8	41.4	40.5	41.7	41.4	41.9	41.5	40.9	40.1
8	40.1	42.3	41.2	40.9	41.9	41.8	42.6	43.0	43.0	42.5	42.3	41.5	41.1	40.9
9	38.1	38.0	38.5	38.6	38.9	39.0	39.5	39.6	39.6	39.5	39.6	39.1	38.6	38.2
10	37.4	37.7	37.8	36.9	37.1	37.4	37.6	37.6	37.8	38.1	38.2	38.1	37.4	37.8
n	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	39.7	40.2	40.2	40.1	40.3	40.3	40.5	40.5	40.9	40.9	40.9	40.5	40.1	39.8
stdev	1.9	2.0	1.7	1.9	2.1	1.8	1.9	2.0	2.0	1.9	1.9	1.9	1.8	1.8
SEM	0.6	0.7	0.6	0.6	0.7	0.6	0.6	0.7	0.7	0.6	0.6	0.6	0.6	0.6

Table 8B.9 Hct ven

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	39.5	41.0	39.7	40.6	40.0	41.1	40.5	41.6	41.7	40.6	40.4	39.7	36.4	37.4

2														
3	36.5	38.2	37.5	38.5	38.0	38.7	38.4	39.2	39.2	38.1	37.8	37.8	37.5	37.6
4														
5	42.1	41.8	42.1	42.6	41.8	41.9	41.6	42.7	42.6	42.3	42.5	41.5	41.9	41.1
6	40.5	41.6	41.4	41.4	41.0	41.4	41.0	41.4	42.1	40.5	41.2	41.2	40.6	40.6
7	41.2	43.6	42.0	41.9	41.3	43.1	42.0	41.2	43.1	42.0	41.8	41.3	41.2	40.7
8	39.6	41.7	41.1	42.5	41.9	43.1	42.5	44.4	44.4	43.1	42.5	41.6	40.7	40.2
9														
10	37.1	38.6	38.3	38.1	37.5	37.8	37.1	38.0	38.6	37.9	37.5	37.7	37.2	36.8
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	39.5	40.9	40.3	40.8	40.2	41.0	40.4	41.2	41.7	40.6	40.5	40.1	39.3	39.2
stdev	2.1	1.9	1.8	1.8	1.8	2.0	2.0	2.1	2.1	2.0	2.1	1.7	2.2	1.8
SEM	0.8	0.7	0.7	0.7	0.7	0.8	0.8	0.8	0.8	0.8	0.8	0.7	0.8	0.7

Table 8B.10 PV art

				Exercise							**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	0	-2.9	-2.8	-2.7	-4.2	-4.8	-2.8	-5.1	-5.2	-6.5	-5.8	-3.7	0.7	1.4
3	0	-1.4	-4.3	-3.3	-3.0	-4.4	-5.2	-5.1	-5.1	-5.3	-5.5	-2.5	-1.1	3.3
4	0	-0.9	-1.7	-1.5	-2.1	-2.0	-3.1	-2.9	-6.2	-6.2	-5.2	-4.0	-0.3	0.2
5	0	1.3	0.6	0.8	-0.2	1.5	0.2	-0.7	-1.7	-1.4	-2.5	-1.3	-0.6	-0.3
6	0	2.4	1.2	0.7	2.5	-3.8	-4.4	5.9	2.7	1.4	5.8	2.2	0.0	5.7
7	0	-1.4	-1.2	-3.4	-4.1	-2.3	-3.9	-3.2	-4.7	-4.6	-5.6	-3.4	-0.6	2.2
8	0	-7.8	-4.5	-1.9	-4.9	-6.3	-7.7	-10.2	-10.2	-7.5	-6.2	-5.0	4.9	3.0
9	0	-0.2	-1.7	-1.9	-3.0	-3.2	-4.7	-4.9	-4.9	-5.4	-4.5	-3.0	-0.2	2.0
10	0	-0.8	-0.9	-0.6	0.2	1.1	0.3	-0.5	-1.7	-2.6	-2.7	-1.4	1.7	0.4
n	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	0.0	-1.3	-1.7	-1.6	-2.1	-2.7	-3.5	-3.0	-4.1	-4.2	-3.6	-2.5	0.5	2.0
stdev	0.0	2.9	2.0	1.5	2.5	2.6	2.5	4.4	3.6	2.8	3.8	2.1	1.8	1.9
SEM	0.0	1.0	0.7	0.5	0.8	0.9	0.8	1.5	1.2	0.9	1.3	0.7	0.6	0.6

Table 8B.11 PV ven

				Exercise							**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	-5.7	-1.5	-4.4	-1.3	-5.8	-2.8	-6.6	-8.4	-2.6	-1.6	-0.4	15.6	8.2
2														
3	0	-6.7	-4.2	-7.9	-5.0	-7.2	-5.7	-9.2	-9.2	-5.1	-4.7	-3.6	4.2	1.4
4														
5	0	0.5	2.1	-1.2	1.9	1.0	2.2	-0.9	-2.8	-1.0	-1.0	2.5	1.9	2.4
6	0	-3.8	-3.7	-3.2	-1.4	-6.3	-6.4	-6.4	-6.4	-0.7	-1.4	-2.5	3.5	3.6
7	0	-7.9	-5.5	-3.0	-1.8	-6.8	-4.5	-7.3	-7.8	-4.4	-3.6	-1.4	8.6	8.2
8	0	-9.0	-5.5	-11.4	-9.3	-12.7	-10.6	-17.1	-17.1	-12.1	-10.2	-7.3	5.2	4.0
9														
10	0	-5.0	-2.7	-3.6	-1.5	-2.4	0.0	-3.4	-4.7	-2.5	-0.7	-2.2	5.0	3.6
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean		-5.4	-3.0	-5.0	-2.6	-5.7	-4.0	-7.3	-8.0	-4.1	-3.3	-2.1	6.3	4.5
stdev		3.1	2.7	3.5	3.5	4.3	4.2	5.1	4.6	3.9	3.4	3.0	4.6	2.7
SEM		1.2	1.0	1.3	1.3	1.6	1.6	1.9	1.7	1.5	1.3	1.1	1.7	1.0

Table 8B.12 BV art

				Exercise							**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	0	-0.7	-1.3	-1.0	-2.0	-1.7	-1.0	-2.3	-2.3	-2.6	-2.6	-1.3	0.3	1.0
3	0	-0.8	-2.3	-2.3	-2.3	-2.3	-3.8	-3.0	-3.0	-2.7	-3.0	-1.5	-0.8	1.6
4	0	-0.3	-1.0	-1.0	-1.4	-1.4	-2.0	-2.0	-3.7	-4.0	-3.4	-2.4	-0.7	-0.3
5	0	1.0	0.7	0.3	0.3	0.7	0.3	-0.3	-0.7	-0.7	-1.0	-0.7	-0.3	0.0
6	0	1.8	0.9	0.7	1.6	-2.2	-2.6	3.0	1.3	0.9	3.7	1.0	-0.5	3.2
7	0	-1.4	-1.0	-2.4	-2.4	-2.1	-2.8	-1.6	-3.0	-3.3	-3.7	-2.1	-0.3	1.2
8	0	-4.3	-2.7	-0.7	-2.0	-3.7	-3.7	-5.6	-5.6	-3.7	-2.7	-2.7	2.7	2.4
9	0	-0.4	-1.1	-1.1	-1.8	-1.8	-2.5	-2.5	-2.5	-3.2	-2.2	-1.5	0.7	1.5
10	0	-0.2	-0.2	-1.4	-0.2	1.1	0.5	-0.2	-1.0	-1.5	-1.4	-0.2	1.2	0.4

n	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	0.00	-0.6	-0.9	-1.0	-1.1	-1.5	-1.9	-1.6	-2.3	-2.3	-1.8	-1.3	0.3	1.2
stdev	0.00	1.7	1.2	1.0	1.4	1.5	1.6	2.3	2.0	1.6	2.2	1.2	1.1	1.1
SEM	0.00	0.6	0.4	0.3	0.5	0.5	0.5	0.8	0.7	0.5	0.7	0.4	0.4	0.4

Table 8B.13 BV ven — **Exercise** — **Recovery (min)**

Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	-3.2	-1.1	-2.5	-0.4	-3.2	-1.1	-3.2	-4.8	-0.7	0.0	0.0	7.3	4.2
2														
3	0	-4.1	-2.7	-4.9	-2.7	-3.8	-2.7	-5.2	-5.2	-2.7	-2.7	-1.5	3.1	1.6
4														
5	0	0.0	2.0	-0.3	1.3	0.7	1.3	0.0	-1.9	-0.7	-0.3	1.3	2.0	0.7
6	0	-2.0	-2.3	-1.7	-0.7	-3.7	-3.3	-2.0	-3.2	-0.7	-0.3	-1.3	1.7	2.3
7	0	-4.1	-4.2	-1.8	-1.6	-3.8	-3.1	-3.9	-4.7	-3.1	-2.7	-1.2	4.3	5.6
8	0	-5.7	-3.1	-7.0	-5.7	-7.3	-6.0	-10.0	-10.0	-6.7	-5.7	-4.1	3.5	2.5
9														
10	0	-2.8	-0.9	-2.1	-0.9	-1.3	-0.2	-2.1	-2.5	-1.3	-0.2	-1.3	2.7	1.2
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	0.00	-3.1	-1.7	-2.9	-1.5	-3.2	-2.2	-3.8	-4.6	-2.3	-1.7	-1.2	3.5	2.6
stdev	0.00	1.8	2.0	2.3	2.2	2.5	2.4	3.2	2.7	2.2	2.1	1.7	1.9	1.8
SEM	0.00	0.7	0.8	0.9	0.8	0.9	0.9	1.2	1.0	0.8	0.8	0.6	0.7	0.7

Table 8B.14 PVa-v — **Exercise** — **Recovery (min)**

Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	0.9	-4.6	1.0	-4.0	-1.2	-2.1	0.4	-3.5	-3.5	1.0	1.7	-0.3	0.5	-0.9
4														
5	-0.8	-1.7	0.7	-2.8	1.2	-1.3	1.2	-1.1	-2.0	-0.4	0.7	2.9	0.8	3.4
6	2.0	-4.1	-2.9	-1.9	-1.9	-2.2	-1.3	-6.9	-6.5	0.0	-4.9	-2.6	-0.7	-4.8
7	-1.5	-7.9	-5.8	-1.0	0.9	-6.0	-2.0	-1.8	-4.7	-1.3	0.6	0.6	0.6	-0.3
8	3.4	2.1	2.3	-6.6	-1.3	-3.6	0.2	-4.6	-4.6	-1.8	-1.0	0.9	2.3	3.3
9														
10	1.5	-2.9	-0.3	-1.5	-0.3	-2.0	1.2	-3.4	-3.7	-0.8	-0.4	0.6	0.3	0.1
n	6	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	0.9	-3.2	-0.8	-3.0	-0.4	-2.9	-0.1	-3.6	-4.2	-0.5	-0.6	0.4	0.6	0.1
stdev	1.8	3.3	3.0	2.1	1.3	1.7	1.3	2.1	1.5	1.0	2.3	1.8	1.0	3.0
SEM	0.7	1.4	1.2	0.8	0.5	0.7	0.5	0.8	0.6	0.4	1.0	0.7	0.4	1.2

Table 8B.15 BVa-v — **Exercise** — **Recovery (min)**

Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	-0.9	-1.4	-1.0	-1.3	-1.0	-1.2	-0.8	-1.3	-1.3	-0.9	-0.9	-0.9	-0.9	-1.0
4														
5	-1.1	-1.2	-0.9	-1.2	-0.9	-1.1	-0.9	-1.0	-1.3	-1.1	-0.9	-0.8	-0.8	-0.8
6	-0.8	-1.4	-1.3	-1.2	-1.1	-1.1	-1.0	-1.5	-1.5	-1.0	-1.4	-1.2	-1.1	-1.4
7	-1.1	-1.5	-1.6	-1.0	-1.0	-1.3	-1.1	-1.1	-1.4	-1.1	-0.9	-0.9	-0.8	-0.9
8	-0.7	-0.9	-0.7	-1.6	-1.2	-1.2	-1.0	-1.4	-1.4	-1.1	-1.1	-0.9	-0.8	-0.7
9														
10	-0.9	-1.5	-0.9	-0.9	-0.9	-1.2	-0.9	-1.1	-1.1	-0.9	-1.0	-0.9	-0.9	-1.0
n	6	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	-0.9	-1.3	-1.1	-1.2	-1.0	-1.2	-1.0	-1.2	-1.3	-1.0	-1.0	-0.9	-0.9	-1.0
stdev	0.2	0.2	0.3	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.2	0.1	0.1	0.2
SEM	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.1	0.0	0.1	0.1	0.0	0.1

Fluid Shifts (Digoxin). Arterial (art) and venous (ven) Haemoglobin ([Hb]), hematocrit (Hct); changes from resting levels in arterial (art) and venous (ven) plasma volume (ΔPV) and blood volume (ΔBV); and changes in venous compared to arterial plasma (ΔPV_{a-v}) and blood volume (ΔBV_{a-v}) across the forearm

calculated at rest (R), during supramaximal finger flexion exercise (e1-e4+1) to fatigue (F), and recovery (1 to 30min). Units are g dl^{-1} haemoglobin and % for Hct; percent change for ΔPV_a, ΔBV_a, $\Delta PV_{a\text{-}v}$, $\Delta BV_{a\text{-}v}$.

Table 8B.16 Hb art

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	14.7	15.3	14.9	15.4	15.2	15.2	15.3	14.5	15.4	15.2	15.0	15.3	15.2	14.8
3	12.7	12.8	12.9	13.0	13.1	13.1	13.1	13.2	13.2	13.2	13.2	13.1	12.9	13.1
4	14.5	14.7	14.6	14.6	14.2	14.6	14.4	14.5	14.8	14.8	14.8	14.7	14.6	14.7
5	14.6	14.4	14.6	14.9	14.7	14.9	14.8	15.0	15.0	14.7	15.0	14.8	14.4	14.8
6	15.4	15.4	15.4	15.6	15.6	15.6	15.7	15.7	15.8	15.7	15.7	15.6	15.6	15.6
7	14.8	15.0	15.1	15.2	15.3	15.2	15.4	15.2	15.3	15.4	15.5	15.3	15.1	14.9
8	13.2	13.3	13.2	13.2	13.2	13.3	13.4	13.3	13.3	13.5	13.4	13.3	13.1	12.9
9	14.4	14.7	14.7	14.7	14.8	15.0	14.9	14.9	15.5	15.4	15.4	15.2	14.8	14.9
10	12.6		12.4	12.6	12.6	12.5	12.6							
n	9	8	9	9	9	9	9	8	8	8	8	8	8	8
mean	14.1	14.4	14.2	14.3	14.3	14.4	14.4	14.5	14.8	14.7	14.7	14.6	14.4	14.4
stdev	1.0	0.9	1.1	1.1	1.1	1.1	1.1	0.9	1.0	0.9	0.9	1.0	1.0	1.0
SEM	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Table 8B.17 Hb ven

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	14.4	13.9	13.7	13.7	12.8	14.3	13.5	14.4	14.4	14.5	14.4	14.2	14.1	14.1
2														
3	12.8	13.1	13.0	13.2	13.2	13.3	13.1	13.3	13.3	13.2	12.9	12.9	12.9	12.9
4														
5	14.6	14.8	14.5	15.0	14.7	15.1	14.8	15.0	15.0	14.9	14.9	15.0	14.0	15.0
6	15.3	16.0	15.7	15.9	15.5	15.5	15.5	15.4	15.8	15.5	15.3	14.9	15.1	15.4
7	14.8	15.4	15.2	15.5	15.2	15.4	15.1	15.4	15.6	15.3	15.3	15.1	15.0	14.7
8	13.0	13.6	13.3	13.6	13.3	13.6	13.4	13.6	13.6	13.2	13.1	12.9	12.9	12.8
9														
10	12.5	13.0	12.5	12.7	12.6	12.9	12.6	12.8	12.7	12.5	12.5	12.6	12.3	12.4
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	13.9	14.3	14.0	14.2	13.9	14.3	14.0	14.3	14.3	14.2	14.0	13.9	13.7	13.9
stdev	1.1	1.1	1.2	1.2	1.2	1.1	1.1	1.1	1.2	1.2	1.2	1.1	1.1	1.2
SEM	0.4	0.4	0.4	0.5	0.4	0.4	0.4	0.4	0.5	0.4	0.5	0.4	0.4	0.5

Table 8B.18 Hct art

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	40.1	41.9	40.7	41.5	41.4	41.5	41.2	41.0	42.0	41.1	40.5	41.6	40.4	39.1
3	36.5	37.5	38.0	38.2	38.2	38.4	38.7	38.7	38.7	38.5	38.9	38.4	38.9	38.6
4	40.2	40.0	40.9	40.6	40.9	41.5	40.4	40.8	41.7	41.9	41.9	41.3	41.3	40.7
5	41.0	40.4	40.5	40.9	40.0	41.5	41.2	41.9	41.9	41.4	42.0	42.0	40.3	41.5
6	40.9	41.6	41.8	42.3	42.1	42.1	41.9	42.1	42.5	42.4	42.3	42.1	41.8	41.9
7	41.5	42.6	42.6	43.1	42.6	43.3	43.4	43.2	43.0	43.8	43.8	43.4	43.2	41.8
8	37.4	38.2	37.5	37.5	37.1	37.6	38.6	38.3	38.3	39.1	39.1	38.3	37.6	37.1
9	40.0	41.0	41.1	41.2	41.7	41.7	41.7	42.0	42.9	42.5	43.3	42.5	41.6	41.6
10	36.2		36.2	36.3	36.0	36.2	36.0							
n	9	8	9	9	9	9	9	8	8	8	8	8	8	8
mean	39.3	40.4	39.9	40.1	40.0	40.4	40.3	41.0	41.4	41.3	41.4	41.2	40.6	40.3
stdev	2.0	1.8	2.2	2.3	2.3	2.4	2.2	1.7	1.8	1.8	1.8	1.8	1.8	1.8
SEM	0.7	0.6	0.7	0.8	0.8	0.8	0.7	0.6	0.7	0.6	0.6	0.7	0.6	0.6

Table 8B.19 Hct ven

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	40.2	39.4	38.5	38.7	40.2	40.1	38.4	40.9	41.1	40.8	41.0	39.6	40.2	39.6
2														
3	37.9	39.0	38.3	38.8	38.9	39.5	39.0	39.8	39.8	39.1	38.6	38.4	38.5	38.4
4														

5	40.8	41.8	40.4	42.3	40.7	41.8	41.1	42.2	42.2	42.1	42.0	41.9	39.5	42.4
6	41.1	43.5	41.9	42.4	42.3	41.9	40.9	41.5	42.7	41.8	41.4	40.4	40.6	41.6
7	41.2	43.7	43.2	44.1	43.3	43.8	42.7	43.5	44.4	43.4	43.2	42.4	42.4	41.9
8	37.7	39.5	38.7	39.2	38.5	39.4	38.8	39.2	39.2	38.7	38.4	37.5	37.1	37.0
9														
10	35.9	37.3	36.0	36.7	36.1	36.9	36.0	36.6	36.6	36.3	35.9	36.1	35.6	35.7
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	39.3	40.6	39.6	40.3	40.0	40.5	39.5	40.5	40.8	40.3	40.1	39.5	39.1	39.5
stdev	2.1	2.4	2.4	2.6	2.4	2.2	2.2	2.3	2.6	2.4	2.6	2.3	2.3	2.6
SEM	0.8	0.9	0.9	1.0	0.9	0.8	0.8	0.9	1.0	0.9	1.0	0.9	0.9	1.0

Table 8B.20 PV art

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	0	-6.7	-2.2	-6.3	-5.3	-5.4	-5.2	-3.9	-7.1	-4.4	-2.5	-6.2	3.6	3.4
3	0	-2.7	-4.3	-5.2	-6.0	-6.3	-6.8	-7.5	-3.4	-7.2	-7.7	-6.0	-3.1	-2.0
4	0	-1.1	-2.3	-1.7	0.5	-3.2	-3.5	-1.3	-4.8	-4.9	-5.2	-3.5	-1.7	-0.3
5	0	2.8	1.1	-1.3	1.4	-2.2	-1.4	-3.6	-3.6	-1.2	-3.7	-2.7	0.4	-3.0
6	0	-1.5	-1.8	-3.9	-3.2	-3.8	-4.4	-3.9	-5.2	-4.8	-4.5	-3.5	-1.3	-1.1
7	0	-3.4	-3.8	-5.2	-5.0	-5.6	-7.3	-5.8	-5.8	-7.9	-8.2	-6.3	-1.8	2.3
8	0	-2.0	-0.2	-0.2	0.5	-1.0	-3.4	-2.1	-2.1	-4.9	-4.2	-2.2	3.0	3.4
9	0	-3.6	-3.9	-4.0	-5.5	-6.8	-5.8	-3.2	-11.4	-10.4	-11.3	-8.9	-1.9	-1.8
10	0		1.5	0.1	0.2	0.7	0.6							
n	9	8	9	9	9	9	9	8	8	8	8	8	8	8
mean	0.0	-2.3	-1.8	-3.1	-2.5	-3.7	-4.1	-3.9	-5.4	-5.7	-5.9	-4.9	-0.3	0.1
stdev	0.0	2.7	2.1	2.4	3.1	2.6	2.6	2.0	2.9	2.8	2.9	2.3	2.5	2.6
SEM	0.0	0.9	0.7	0.8	1.0	0.9	0.9	0.7	1.0	1.0	1.0	0.8	0.9	0.9

Table 8B.21 PV ven

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	5.1	8.1	7.7	12.6	1.3	9.9	-6.0	-5.9	-1.6	-1.3	2.5	-2.8	-4.7
2														
3	0	-3.9	-1.8	-4.1	-4.2	-5.8	-3.6	-2.8	-4.9	-4.9	-1.8	-1.6	2.8	0.6
4														
5	0	-3.5	1.4	-5.4	-0.5	-4.9	-1.9	-6.4	-5.1	-4.7	-4.0	-4.5	10.1	-6.6
6	0	-7.9	-4.0	-5.9	-3.2	-6.3	-6.4	-6.4	-6.4	-2.4	-0.5	3.7	11.0	2.7
7	0	-8.0	-5.7	-9.0	-5.8	-7.9	-4.3	0.6	-10.3	-6.9	-6.3	-3.7	5.0	5.5
8	0	-7.1	-3.7	-6.3	-3.6	-6.7	-4.3	0.8	-6.4	-3.1	-1.5	1.6	9.9	6.7
9														
10	0	-6.6	-0.6	-3.2	-1.5	-5.0	-1.3	-3.3	-3.0	-0.9	0.1	-1.7	8.8	1.4
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	0.0	-4.6	-0.9	-3.7	-0.9	-5.0	-1.7	-3.4	-6.0	-3.5	-2.2	-0.5	6.4	0.8
stdev	0.0	4.6	4.6	5.4	6.2	3.0	5.4	3.1	2.2	2.1	2.2	3.2	5.0	4.9
SEM	0.0	1.7	1.7	2.0	2.3	1.1	2.0	1.2	0.8	0.8	0.8	1.2	1.9	1.9

Table 8B.22 BV art

				Exercise							Recovery (min)			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	0	-3.7	-1.1	-4.0	-3.1	-3.1	-3.4	5.3	-4.0	-2.8	-1.8	-3.7	1.0	0.7
3	0	-1.2	-1.9	-2.7	-3.4	-3.4	-3.4	-4.2	-2.3	-4.2	-4.2	-3.1	-0.8	-1.1
4	0	-1.4	-1.0	-1.0	1.8	-1.0	0.4	-0.3	-2.4	-2.0	-2.4	-1.7	0.3	-0.7
5	0	1.8	0.2	-1.5	-0.3	-1.5	-1.1	-2.1	-2.1	-0.5	-2.1	-1.1	0.1	-1.4
6	0	-0.3	-0.3	-1.6	-1.3	-2.2	-2.6	-1.9	-2.5	-2.4	-2.2	-1.6	-1.0	-1.0
7	0	-1.7	-2.0	-2.6	-3.3	-2.6	-4.2	-3.0	-3.3	-4.2	-4.5	-3.3	-0.7	1.0
8	0	-0.8	0.0	0.0	0.0	-0.8	-1.5	-0.8	-0.8	-2.2	-1.5	-0.8	1.9	2.7
9	0	-1.8	-2.0	-2.0	-2.7	-4.0	-3.0	-1.5	-6.8	-6.5	-6.2	-5.0	-0.9	-1.0
10	0		1.6	0.3	0.0	0.8	0.4							
n	9	8	9	9	9	9	9	8	8	8	8	8	8	8
mean	0.0	-1.1	-0.7	-1.7	-1.4	-2.0	-2.1	-1.1	-3.0	-3.1	-3.1	-2.5	0.0	-0.1
stdev	0.0	1.6	1.2	1.4	1.9	1.5	1.7	2.8	1.8	1.8	1.7	1.5	1.0	1.4

SEM	0.0	0.6	0.4	0.5	0.6	0.5	0.6	1.0	0.6	0.6	0.6	0.5	0.4	0.5

Table 8B.23

BV ven				**Exercise**							**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	3.6	5.1	5.1	12.5	1.1	6.7	-3.5	-3.1	-0.7	0.0	1.4	-1.4	-3.0
2														
3	0	-2.3	-1.2	-2.7	-2.7	-3.4	-1.9	-1.5	-3.8	-3.0	-0.8	-0.8	1.9	0.8
4														
5	0	-1.9	0.7	-3.0	-0.7	-3.3	-1.4	-2.8	-2.8	-2.5	-2.0	-2.7	5.9	-3.3
6	0	-4.1	-2.7	-3.8	-1.3	-3.7	-3.3	-0.8	-3.3	-1.3	0.0	2.5	5.6	2.1
7	0	-3.9	-2.3	-4.2	-2.3	-3.6	-1.7	0.3	-5.1	-3.3	-3.0	-1.7	2.7	3.1
8	0	-4.4	-2.3	-4.1	-2.3	-4.1	-2.6	0.4	-4.1	-1.5	-0.4	1.2	5.8	3.9
9														
10	0	-4.5	-0.4	-2.0	-1.2	-3.5	-1.2	-2.4	-2.0	-0.4	0.0	-1.4	5.9	0.8
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	0.0	-2.5	-0.4	-2.1	0.3	-2.9	-0.8	-1.5	-3.5	-1.8	-0.9	-0.2	3.8	0.6
stdev	0.0	2.9	2.7	3.3	5.4	1.8	3.4	1.5	1.0	1.1	1.2	1.9	2.8	2.8
SEM	0.0	1.1	1.0	1.2	2.1	0.7	1.3	0.6	0.4	0.4	0.4	0.7	1.1	1.1

Table 8B.24

PVa-v				**Exercise**							**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	-3.4	-4.6	-0.9	-2.2	-1.4	-2.8	0.0	-2.5	-2.5	-1.0	2.8	1.2	1.1	1.8
4														
5	0.9	-5.3	1.2	-3.3	-1.0	-1.8	0.5	-0.7	-0.7	-2.7	0.6	-0.9	3.8	-2.5
6	-0.1	-6.5	-2.3	-2.2	0.0	0.4	2.9	2.5	-0.9	2.5	4.1	7.5	2.3	1.5
7	0.3	-4.5	-1.8	-3.7	-0.6	-2.2	3.6	-1.5	-4.6	1.4	2.3	3.0	2.1	1.3
8	1.1	-4.2	-2.6	-5.2	-3.0	-4.8	0.1	-3.4	-3.4	2.9	3.9	4.9	2.3	0.6
9														
10	1.6		-0.5	-1.7	-0.2	-4.2	-0.3							
n	6	5	6	6	6	6	6	5	5	5	5	5	5	5
mean	0.1	-5.0	-1.1	-3.0	-1.0	-2.6	1.1	-1.1	-2.4	0.6	2.7	3.1	2.3	0.5
stdev	1.8	0.9	1.4	1.3	1.1	1.8	1.7	2.3	1.7	2.4	1.4	3.3	0.9	1.8
SEM	0.7	0.4	0.6	0.5	0.4	0.8	0.7	1.0	0.7	1.1	0.6	1.5	0.4	0.8

Table 8B.25

BVa-v				**Exercise**							**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	-1.2	-1.3	-1.1	-1.2	-1.1	-1.2	-1.0	-1.1	-1.1	-1.0	-0.7	-0.9	-0.9	-0.8
4														
5	-0.9	-1.5	-0.9	-1.2	-1.0	-1.2	-0.9	-1.0	-1.0	-1.2	-0.9	-1.2	-0.8	-1.2
6	-1.0	-1.6	-1.3	-1.3	-0.9	-1.0	-0.8	-0.8	-1.1	-0.8	-0.6	-0.3	-0.5	-0.9
7	-1.1	-1.4	-1.1	-1.3	-0.9	-1.2	-0.7	-1.2	-1.4	-0.9	-0.8	-0.8	-0.9	-0.8
8	-0.8	-1.3	-1.1	-1.4	-1.1	-1.3	-0.9	-1.3	-1.3	-0.7	-0.7	-0.5	-0.8	-1.0
9														
10	-0.9		-1.1	-1.1	-1.0	-1.4	-1.1							
n	6	5	6	6	6	6	6	5	5	5	5	5	5	5
mean	-1.0	-1.4	-1.1	-1.2	-1.0	-1.2	-0.9	-1.1	-1.2	-0.9	-0.7	-0.7	-0.8	-0.9
stdev	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.2	0.1	0.2	0.1	0.3	0.2	0.1
SEM	0.1	0.0	0.1	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Electrolytes (Control). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [K^+], [Na^+], [Cl^-], [Lac^-] and [SID] at rest (R), during supramaximal finger flexion exercise (e1 to e4+1) to fatigue (F), and recovery (1 to 30min). Units are mM; a-v has been corrected for the arterio-venous ΔPV.

Table 8B.26

K+ art			**Exercise**								**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	4.2	4.0	4.2	4.2	4.2	4.2	4.1	4.2	4.4	4.5	4.3	4.3	4.2	3.8

2	4.2	3.9	4.2	4.0	4.3	4.1	4.1	4.2	4.3	4.0	4.4	4.2	4.0	3.8
3	3.8	3.9	4.2	4.1	4.3	4.2	4.3	4.2	4.2	4.2	4.3	4.0	3.9	3.9
4	4.1	3.9	4.0	4.0	4.1	4.1	4.0	4.1	4.5	4.3	4.2	4.1	3.9	3.8
5	4.0	3.9	3.9	3.9	4.0	4.0	4.0	4.1	4.3	4.2	4.1	4.0	3.9	3.9
6	3.6	3.7	3.8	3.7	3.7	3.8	3.9	3.9	3.9	3.8	3.9	3.8	3.8	3.6
7	3.7	4.0	4.0	3.9	4.1	4.1	4.2	4.2	4.2	4.1	4.1	3.9	4.0	4.0
8	3.7	3.8	3.9	3.9	4.0	4.1	4.1	4.6	4.6	4.0	3.9	3.7	3.8	3.8
9	3.6	3.6	3.6	3.7	3.9	3.8	4.0	3.9	3.9	4.1	3.9	3.7	3.7	3.7
10	3.9	4.1	4.1	4.2	4.3	4.3	4.3	4.3	4.4	4.4	4.3	4.4	4.4	4.3
n	10	10	10	10	10	10	10	10	10	10	10	10	10	10
mean	3.9	3.9	4.0	4.0	4.1	4.1	4.1	4.2	4.3	4.2	4.1	4.0	4.0	3.8
stdev	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2
SEM	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Table 8B.27

K+ ven			**Exercise**									**Recovery (min)**		
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	4.3	5.3	4.3	4.8	4.1	4.8	4.0	5.0	4.6	3.9	3.6	3.5	3.6	3.6
2														
3	4.0	5.3	4.3	5.3	4.4	5.2	4.2	5.2	5.2	4.0	4.0	4.2	4.1	4.2
4														
5	3.8	4.9	4.1	4.5	4.0	4.5	3.9	4.7	4.8	3.9	4.0	3.9	4.0	4.0
6	3.8	4.8	3.8	4.9	3.7	4.7	3.8	4.5	3.9	3.2	3.3	3.3	3.3	3.6
7	3.9	5.9	4.1	5.7	4.0	5.8	4.1	5.4	5.5	3.9	3.8	3.7	3.8	4.0
8	3.7	5.6	3.7	5.7	3.8	5.6	3.7	6.5	6.5	3.6	3.5	3.4	3.4	3.5
9	3.7	5.5	3.7	5.6	3.8	5.8	3.7	5.8	5.8	3.8	3.5	3.4	3.4	3.5
10	4.1	5.2	4.1	5.2	4.0	4.9	4.0	4.9	5.2	4.0	3.8	4.1	4.1	4.2
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8
mean	3.9	5.3	4.0	5.2	4.0	5.2	3.9	5.3	5.2	3.8	3.7	3.7	3.7	3.8
stdev	0.2	0.4	0.2	0.5	0.2	0.5	0.2	0.6	0.8	0.3	0.2	0.3	0.3	0.3
SEM	0.1	0.1	0.1	0.2	0.1	0.2	0.1	0.2	0.3	0.1	0.1	0.1	0.1	0.1

Table 8B.28

K+ a-v			**Exercise**								**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	-0.2	-1.3	-0.1	-1.1	0.0	-0.9	0.1	-0.9	-0.9	0.1	0.2	-0.2	-0.2	-0.2
4														
5	0.2	-1.0	-0.2	-0.5	0.0	-0.5	0.1	-0.5	-0.5	0.3	0.1	0.0	-0.1	-0.2
6	-0.3	-1.0	0.0	-1.1	0.1	-0.8	0.1	-0.4	0.2	0.6	0.8	0.7	0.5	0.2
7	-0.1	-1.6	0.2	-1.8	0.1	-1.5	0.2	-1.1	-1.1	0.3	0.3	0.2	0.2	-0.1
8	-0.2	-1.9	0.0	-1.5	0.2	-1.3	0.3	-1.7	-1.7	0.5	0.5	0.3	0.2	0.1
9														
10	-0.2	-1.0	0.1	-1.0	0.3	-0.5	0.2	-0.5	-0.7	0.3	0.4	0.3	0.3	0.0
n	6	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	-0.1	-1.3	0.0	-1.2	0.1	-0.9	0.2	-0.9	-0.8	0.4	0.4	0.2	0.2	0.0
stdev	0.2	0.4	0.2	0.4	0.1	0.4	0.1	0.5	0.6	0.2	0.2	0.3	0.3	0.2
SEM	0.1	0.2	0.1	0.2	0.1	0.2	0.0	0.2	0.3	0.1	0.1	0.1	0.1	0.1

Table 8B.29

Na+ art				**Exercise**										
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	139.7	140.6	140.9	140.9	140.8	139.5	140.1	139.8	139.1	139.6	139.3	138.3	136.9	138.3
2	137.7	138.6	137.6	137.7	137.7	138.1	138.2	137.5	138.2	137.4	138.1	137.5	137.9	137.5
3	142.2	142	140.9	141.8	141.4	141.9	143.9	141.3	141.3	142	142.5	140.8	141.6	141.3
4	136.8	136.5	137.9	134.8	137.2	136.5	137.3	137.2	136.6	131.9	136.2	137.7	138.4	137
5	139	138.5	138.9	139	139.4	139.4	139	139.8	139.6	139.2	139.9	138.8	139.5	138.9
6	139.2	140.2	140	139.6	140.1	140.2	139.4	140.2	141.8	138.9	140.9	140.4	139.6	140.4
7	140.7	140.4	137.5	140.5	141.5	141	140.4	139.4	140.2	141.1	140.7	140.8	140.5	139.7
8	138.5	139.5	140.8	137.6	140.3	138.7	139.8	138.4	138.4	139.7	140.1	139.5	139.4	138.4
9	145.5	143.9	144.6	144.7	145.7	144.5	146.2	144	144	141.9	143	145	141.2	141.4
10	136.9	137	137.6	137	138.1	136.9	136.9	136.5	137.6	134.8	136.6	136.8	138.5	137.1
n	10	10	10	10	10	10	10	10	10	10	10	10	10	10

mean	139.6	139.7	139.7	139.4	140.2	139.7	140.1	139.4	139.7	138.7	139.7	139.6	139.4	139.0
stdev	2.7	2.2	2.3	2.8	2.5	2.4	2.9	2.2	2.2	3.2	2.3	2.4	1.5	1.6
SEM	0.8	0.7	0.7	0.9	0.8	0.8	0.9	0.7	0.7	1.0	0.7	0.8	0.5	0.5

Table 8B.30

Na+ ven			**Exercise**								**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	140.6	149.6	142.1	142.6	141.1	141.6	142	143.4	143.8	138.7	134.2	133.9	139.1	139.6
2														
3	142.2	142	144.5	146.1	145.8	145.8	145.8	144.9	144.9	146.4	143	141.2	141.3	140.9
4	138.1	142.5	138.3	141.1	143.3	141.2	141	141.4	140	144.9	139.6	138.3	135.7	135.6
5	140.8	140.9	141.1	141.1	141.3	140	141.4	141.7	143	141.3	141.6	138.8	139.5	139
6	140.1	143.8	143.4	142.1	141.6	142.1	141.6	142	140.9	137.4	136.7	139.3	139.5	140.5
7	138.6	149.5	144.5	147.7	142.9	144.6	143.5	143.4	145.4	139.9	139.2	138.2	138.9	139.9
8	139.4	146.1	141.8	145.4	143.1	145.3	142	147	147	142.6	138.6	137.2	137.9	138.5
9	146.6	152.4	152.6	150.9	150.4	151.1	149.6	147.2	147.2	143.8	141	140.9	141.3	139.9
10	137.4	140.9	141.6	141.2	140.4	140.3	138.1	139.7	141.7	138.3	135.9	135.4	134.3	137.8
n	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	140.4	145.3	143.3	144.2	143.3	143.6	142.8	143.4	143.8	141.5	138.9	138.1	138.6	139.1
stdev	2.7	4.3	4.0	3.5	3.1	3.6	3.3	2.6	2.6	3.2	2.9	2.4	2.3	1.6
SEM	0.9	1.4	1.3	1.2	1.0	1.2	1.1	0.9	0.9	1.1	1.0	0.8	0.8	0.5

Table 8B.31

Na+ av			**Exercise**								**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	-1.2	6.8	-5.0	1.5	-2.7	-0.9	-2.5	1.6	1.6	-5.9	-2.9	0.0	-0.5	1.6
4														
5	-0.6	-0.1	-3.1	1.8	-3.5	1.3	-4.0	-0.3	-0.6	-1.5	-2.6	-3.9	-1.2	-4.6
6	-3.7	2.4	0.8	0.2	1.2	1.3	-0.4	8.7	10.7	1.6	11.5	4.9	1.2	7.0
7	4.2	3.0	1.4	-5.7	-2.7	5.4	-0.2	-0.1	1.7	3.0	0.6	1.7	0.8	0.2
8	-5.5	-9.4	-4.2	1.9	-0.9	-1.4	-2.4	-2.0	-2.0	-0.4	2.9	1.0	-1.7	-4.6
9														
10	-2.5	0.1	-3.5	-2.1	-1.9	-0.6	-2.8	-1.1	-1.9	-5.6	-3.9	0.5	3.8	-4.4
n	6	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	-1.6	0.5	-2.3	-0.4	-1.7	0.9	-2.1	1.1	1.6	-1.5	0.9	0.7	0.4	-0.8
stdev	3.3	5.4	2.7	3.0	1.7	2.5	1.5	3.9	4.7	3.7	5.8	2.9	2.0	4.7
SEM	1.4	2.2	1.1	1.2	0.7	1.0	0.6	1.6	1.9	1.5	2.4	1.2	0.8	1.9

Table 8B.32

Cl- art					**Exercise**					**Recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	105	106	106	106	105	106	106	106	105	104	105	105	106	106
2	106	109	106	108	106	108	109	108	107	109	106	108	109	109
3	110	109	107	108	106	111	109	110	110	110	108	110	110	109
4	104	105	104	104	104	104	104	104	104	104	105	104	104	104
5	106	107	108	106	107	106	107	106	104	105	104	104	104	106
6	108	108	108	108	109	108	108	108	110	109	108	108	108	109
7	109	109	112	112	111	112	108	106	108	108	108	110	109	109
8	103	105	106	105	106	106	105	105	105	104	104	103	105	105
9	106	108	108	109	108	107	108	107	107	107	107	104	107	108
10	105	104	104	105	104	104	104	104	103	106	104	104	103	104
n	10	10	10	10	10	10	10	10	10	10	10	10	10	10
mean	106.2	107.0	106.9	107.1	106.6	107.2	106.8	106.4	106.3	106.6	105.9	106.0	106.5	106.9
stdev	2.2	1.9	2.3	2.4	2.2	2.7	1.9	1.9	2.5	2.3	1.7	2.7	2.5	2.1
SEM	0.7	0.6	0.7	0.8	0.7	0.8	0.6	0.6	0.8	0.7	0.5	0.9	0.8	0.7

Table 8B.33

Cl- ven					**Exercise**					**Recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	105	102	104	105	107	106	104	105	105	102	99	99	104	105
2														
3	107	109	106	107	108	109	107	108	108	106	105	106	107	108
4	103	101	109	106	105	104	100	102	104	100	100	99	101	103
5	106	107	106	107	105	106	104	104	105	103	103	103	104	105
6	106	108	105	107	105	106	105	107	105	104	103	106	106	108

7	111	109	109	109	108	111	104	105	106	103	103	103	105	107
8	102	105	103	105	104	104	102	103	103	99	98	99	100	104
9	105	109	105	107	105	106	104	105	105	104	102	101	104	107
10	103	105	105	103	103	105	102	104	102	101	101	103	106	105
n	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	105.3	106.1	105.8	106.2	105.6	106.3	103.6	104.7	104.8	102.4	101.6	102.1	104.1	105.8
stdev	2.7	3.1	2.0	1.7	1.7	2.3	2.0	1.9	1.7	2.2	2.2	2.8	2.3	1.8
SEM	0.9	1.0	0.7	0.6	0.6	0.8	0.7	0.6	0.6	0.7	0.7	0.9	0.8	0.6

Table 8B.34

Cl- a-v								**Exercise**					
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	2.1	5.2	0.0	5.4	-0.7	4.4	1.6	6.0	6.0	2.9	1.1	4.3	2.4	2.0
4														
5	0.9	1.8	1.3	2.0	0.7	1.5	1.7	3.2	1.1	2.4	0.3	-1.9	-0.9	-2.4
6	-0.1	4.6	6.2	3.1	6.1	4.5	4.4	9.1	12.6	5.1	10.6	4.9	2.8	6.5
7	-0.4	9.4	9.9	4.2	2.0	8.2	6.2	4.7	7.4	6.4	4.3	6.3	3.4	2.3
8	-2.4	-2.1	0.6	7.4	3.4	6.0	2.8	7.0	7.0	6.9	7.1	3.0	2.6	-2.4
9														
10	0.5	2.1	-0.6	3.6	1.3	1.2	0.8	1.6	2.7	3.3	-0.5	0.3	-3.3	-3.8
n	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
mean	0.1	3.5	2.9	4.3	2.2	4.3	2.9	5.3	6.1	4.5	3.8	2.8	1.2	0.4
stdev	1.5	3.9	4.2	1.9	2.4	2.7	2.0	2.7	4.0	1.9	4.4	3.1	2.7	3.9
SEM	0.6	1.6	1.7	0.8	1.0	1.1	0.8	1.1	1.7	0.8	1.8	1.3	1.1	1.6

Table 8B.35

Lac- art					**exercise**					**recovery (min)**
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1	2.1	2.3	2.2	2.4	2.2	2.9	2.8	2.6	2.3	2.2
2	0.6	0.3	0.5	0.4	0.4	0.5	0.6	0.6	0.9	0.6
3	0.5	0.6	0.3	0.9	1.2	2.6	1.2	1.5	0.9	0.9
4	1.0	1.2	1.3	1.1	1.3	2.1	2.4	1.5	1.7	1.7
5	1.8	2.0	1.9	1.9	1.2	1.9	1.9	2.1	2.5	2.3
6										
7	0.9	0.9	1.4	1.5	2.0	2.7	1.7	1.7	1.9	1.4
8	0.8	1.4	1.8	2.3	2.5	2.5	2.7	2.4	1.9	1.3
9	1.1	1.6	2.1	3.5	5.3	6.3	5.1	5.9	6.8	4.3
10	1.4	1.9	2.3	4.8	3.0	2.4	2.4	2.4	2.3	3.3
n	9	9	9	9	9	9	9	9	9	9
mean	1.1	1.4	1.5	2.1	2.1	2.7	2.3	2.3	2.3	2.0
stdev	0.5	0.7	0.7	1.4	1.4	1.5	1.3	1.5	1.8	1.2
SEM	0.2	0.2	0.2	0.5	0.5	0.5	0.4	0.5	0.6	0.4

Table 8B.36

Lac-ven			**exercise**				**recovery (min)**			
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.8	3.7	3.1	2.8	3.3	5.2	4.8	4.7	5.4	2.7
2										
3	0.8	4.0	5.4	3.8	3.8	6.2	7.0	3.9	3.8	3.5
4	1.2	3.3	4.5	4.7	5.0	6.9	6.6	5.5	5.6	3.5
5	2.1	3.0	2.9	2.6	3.1	4.9	4.6	5.1	4.2	5.3
6										
7	1.1	6.5	7.7	8.1	5.0	6.2	6.1	6.4	7.4	7.0
8	1.0	6.0	6.5	7.7	6.5	6.8	8.2	6.1	4.1	1.6
9	1.3	5.7	7.4	8.1	8.8	11.5	13.1	12.5	10.7	7.2
10	0.9	4.4	5.1	4.6	3.4	5.8	5.2	5.5	4.4	2.8
n	8	8	8	8	8	8	8	8	8	8
mean	1.3	4.6	5.3	5.3	4.9	6.7	6.9	6.2	5.7	4.2
stdev	0.5	1.3	1.8	2.3	2.0	2.1	2.8	2.6	2.3	2.1
SEM	0.2	0.5	0.6	0.8	0.7	0.7	1.0	0.9	0.8	0.7

Table 8B.37

Lac-av			**exercise**				**recovery (min)**			

Subject	R	eb1	eb2	eb3	F	1	2	5	10	30
1										
2										
3	-0.3	-3.4	-5.1	-2.9	-2.6	-3.6	-5.8	-2.5	-2.9	-2.5
4										
5	-0.4	-1.0	-0.9	-0.6	-1.9	-3.0	-2.7	-3.1	-1.7	-3.1
6										
7	-0.1	-5.5	-6.2	-6.5	-2.9	-3.5	-4.4	-4.7	-5.5	-5.6
8	-0.3	-4.6	-4.5	-5.4	-3.9	-4.2	-5.5	-3.8	-2.2	-0.3
9										
10	0.5	-2.4	-2.7	0.3	-0.4	-3.4	-2.9	-3.2	-2.1	0.4
n	5	5	5	5	5	5	5	5	5	5
mean	-0.1	-3.4	-3.9	-3.0	-2.3	-3.5	-4.3	-3.4	-2.9	-2.2
stdev	0.4	1.8	2.1	2.9	1.3	0.5	1.4	0.8	1.6	2.4
SEM	0.2	0.8	0.9	1.3	0.6	0.2	0.6	0.4	0.7	1.1

Table 8B.38 SID art — exercise — recovery (min)

Subject	R	eb1	eb2	eb3	F	1	2	5	10	30
1	38.6	38.2	38.9	37.4	37.6	38.5	37.0	36.9	34.5	34.7
2	34.8	32.7	32.4	32.9	33.5	28.9	35.2	32.0	31.4	31.2
3	34.8	35.5	36.8	33.9	36.7	34.6	37.6	33.3	33.4	35.4
4	35.9	34.3	34.0	35.6	36.6	30.6	34.1	36.3	36.6	35.3
5	35.2	32.6	34.1	34.2	36.4	36.2	36.7	35.5	36.2	34.1
6										
7	34.4	34.5	31.4	31.7	34.9	35.8	35.1	33.6	34.2	33.5
8	38.8	38.2	35.8	35.4	37.0	35.4	33.4	37.6	36.3	37.1
9	40.3	36.5	35.9	38.3	39.9	35.2	36.2	39.5	34.2	34.2
10	35.1	35.8	35.5	36.6	36.3	29.7	34.4	36.6	36.9	35.9
n	9	9	9	9	9	9	9	9	9	9
mean	36.4	35.4	35.0	35.1	36.5	33.9	35.5	35.7	34.9	34.6
stdev	2.2	2.1	2.3	2.1	1.8	3.3	1.4	2.4	1.8	1.7
SEM	0.7	0.7	0.8	0.7	0.6	1.1	0.5	0.8	0.6	0.6

Table 8B.39 SID ven — exercise — recovery (min)

Subject	R	eb1	eb2	eb3	F	1	2	5	10	30
1	38.1	49.2	39.3	37.6	38.5	35.4	34.1	33.7	33.3	35.7
2										
3	38.4	34.3	39.1	38.2	39.2	37.5	35.1	35.4	34.6	34.6
4										
5	36.5	35.8	35.8	35.9	38.1	37.3	38.0	34.6	35.4	32.6
6										
7	30.4	39.9	36.8	31.3	38.1	34.0	33.9	32.5	30.3	30.0
8	40.1	40.7	39.6	39.1	39.1	40.5	35.9	35.4	37.3	36.4
9	44.0	43.2	42.1	42.7	41.6	32.1	29.4	30.8	30.0	29.2
10	37.6	36.7	38.4	35.6	37.8	35.6	33.5	30.9	28.0	34.2
n	7	7	7	7	7	7	7	7	7	7
mean	37.8	40.0	38.7	37.2	38.9	36.0	34.3	33.3	32.7	33.2
stdev	4.1	5.1	2.0	3.5	1.3	2.7	2.6	2.0	3.3	2.8
SEM	1.5	1.9	0.8	1.3	0.5	1.0	1.0	0.7	1.3	1.0

Table 8B.40 SIDa-v — exercise — recovery (min)

Subject	R	eb1	eb2	eb3	F	1	2	5	10	30
1										
2										
3	-3.9	2.9	-0.9	-3.6	-1.1	-3.3	1.8	-2.0	-1.4	1.1
4										
5	-1.0	-2.6	-0.7	-1.2	-0.9	-0.9	-1.5	-0.1	0.6	0.4
6										

7	4.6	-2.5	-5.0	2.4	-1.5	2.3	1.0	0.9	3.7	3.6
8	-2.6	-3.3	-1.3	-2.4	-0.2	-4.4	-2.2	1.8	-1.8	-0.5
9										
10	-3.0	0.1	-2.3	1.7	-1.0	-6.3	-0.3	5.4	8.7	0.8
n	5	5	5	5	5	5	5	5	5	5
mean	-1.2	-1.1	-2.0	-0.6	-0.9	-2.5	-0.2	1.2	2.0	1.1
stdev	3.4	2.6	1.8	2.6	0.5	3.3	1.7	2.8	4.4	1.5
SEM	1.5	1.2	0.8	1.2	0.2	1.5	0.7	1.2	2.0	0.7

Electrolytes (Digoxin). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [K^+], [Na^+], [Cl^-], [Lac^-] and [SID] at rest (R), during supramaximal finger flexion exercise (e1 to e4+1) to fatigue (F), and recovery (1 to 30min). Units are mM; a-v has been corrected for the arterio-venous ΔPV.

Table 8B.41

K+ art			**Exercise**							**Recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	4.1	4.0	4.1	4.1	4.1	4.1	4.2	4.2	3.9	3.9	3.8	3.8	3.6	3.8
2	4.2	4.2	4.2	4.3	4.4	4.4	4.3	4.2	4.4	4.4	4.4	4.3	4.4	4.1
3	4.0	3.8	4.0	4.1	4.2	4.2	4.3	4.2	4.2	4.2	4.3	3.8	3.7	3.9
4	3.9	3.8	4.1	4.2	4.2	4.2	4.2	4.2	4.4	4.4	4.3	4.0	4.0	4.0
5	3.8	3.6	4.5	4.3	4.4	4.4	4.4	4.4	4.4	4.2	4.4	4.2	4.2	4.2
6	3.6	3.4	3.5	3.4	3.5	3.5	3.5	3.4	3.5	3.6	3.5	3.5	3.4	3.5
7	4.1	3.9	4.1	4.2	4.2	4.2	4.3	4.2	4.4	4.4	4.3	4.2	4.0	3.8
8	3.8	4.1	4.1	4.1	4.0	4.1	4.2	4.2	4.2	4.0	3.8	3.8	3.8	3.9
9	3.6	3.6	3.7	3.7	3.2	3.7	3.9	3.9	4.6	4.1	3.8	3.8	3.9	3.9
10	3.6	3.7	2.8	3.4	3.4	3.4	3.6							
n	10	10	10	10	10	10	10	9	9	9	9	9	9	9
mean	3.87	3.81	3.91	3.97	3.94	4.01	4.09	4.11	4.23	4.15	4.07	3.93	3.88	3.90
stdev	0.19	0.27	0.28	0.28	0.30	0.28	0.27	0.30	0.33	0.29	0.33	0.27	0.32	0.20
SEM	0.06	0.09	0.09	0.09	0.09	0.09	0.09	0.10	0.11	0.10	0.11	0.09	0.11	0.07

Table 8B.42

K+ ven			**Exercise**							**Recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	4.6	5.0	4.2	5.0	4.0	4.8	3.9	4.9	4.3	3.3	3.2	3.1	3.1	3.7
2														
3	4.0	5.4	4.2	5.4	4.0	5.1	4.2	5.2	5.2	4.0	3.9	3.9	3.9	3.9
4														
5	3.9	4.5	4.3	4.8	4.3	4.9	4.2	5.2	5.2	4.2	4.3	4.4	4.0	3.9
6	3.8	5.4	3.7	5.0	3.4	4.7	3.4	4.6	4.1	3.3	3.1	3.4	3.4	3.4
7	3.9	5.8	4.1	5.7	4.0	5.5	3.9	5.3	5.5	3.9	3.8	3.7	3.8	3.9
8	3.8	5.9	4.1	5.7	3.8	5.6	4.0	5.3	5.3	3.5	3.4	3.3	3.5	3.7
9	3.7	5.5	3.7	5.4	3.7	5.8	3.8	5.9	6.3	3.9	3.5	3.6	3.7	3.9
10	4.1	4.7	3.6	4.4	3.6	4.4	3.6	4.5	4.9	3.5	3.5	3.6	3.6	3.5
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8
mean	3.97	5.28	3.98	5.16	3.84	5.08	3.86	5.09	5.09	3.69	3.60	3.62	3.62	3.73
stdev	0.27	0.49	0.26	0.47	0.29	0.48	0.27	0.44	0.68	0.34	0.39	0.40	0.29	0.21
SEM	0.09	0.17	0.09	0.17	0.10	0.17	0.10	0.16	0.24	0.12	0.14	0.14	0.10	0.07

Table 8B.43

K+ a-v			**Exercise**							**Recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	0.2	-1.3	-0.1	-1.2	0.3	-0.8	0.1	-0.8	-0.8	0.3	0.3	-0.1	-0.3	-0.1
4														
5	-0.2	-0.7	0.2	-0.3	0.2	-0.4	0.2	-0.8	-0.8	0.1	0.0	-0.1	0.1	0.4
6	-0.2	-1.8	-0.2	-1.5	0.1	-1.2	0.0	-1.3	-0.5	0.2	0.3	-0.1	-0.2	0.1
7	0.1	-1.8	0.1	-1.4	0.3	-1.1	0.2	-1.0	-0.9	0.4	0.4	0.3	0.1	-0.1
8	0.0	-1.6	0.1	-1.4	0.2	-1.3	0.3	-0.9	-0.9	0.4	0.3	0.3	0.2	0.2
9														

10	-0.5	-1.0	-0.7	-0.9	-0.2	-0.9	0.0							
n	6	6	6	6	6	6	6	5	5	5	5	5	5	5
mean	-0.1	-1.4	-0.1	-1.1	0.1	-1.0	0.1	-1.0	-0.8	0.3	0.3	0.1	0.0	0.1
stdev	0.3	0.4	0.3	0.5	0.2	0.3	0.1	0.2	0.2	0.1	0.1	0.2	0.2	0.2
SEM	0.1	0.2	0.1	0.2	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Table 8B.44

Na+ art			**Exercise**								**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	138.4	138.4	140.5	140.1	136.5	139.5	142.8	139.0	138.1	139.8	138.3	143	137.6	139.0
2	137.8	137.8	137.6	138.6	137.5	138.5	138.6	140.0	138.5	138.2	137.4	138.2	138.1	137.1
3	143.6	143.8	142.5	144	143.7	143.2	144.3	143.8	143.8	144.4	143.1	143.7	143.3	143.2
4	136.7	136.5	136	136.4	135.8	136	135.4	135.9	137.9	136.8	136.9	137.6	137.5	136.8
5	139.8	141.1	139.4	137.5	140.3	138.4	140	138.9	138.9	140.3	140.4	139.8	140.2	138.8
6	138.9	138.3	136.9	138.7	138.8	138.9	138.1	139.1	138.3	138.8	137.9	138.2	139.2	138.6
7	142.5	141.9	141.7	142.3	142.8	142.2	142.7	142.9	143.2	142.4	140.1	139.6	140.6	139.9
8	138.4	138.9	139.2	139.1	139.8	139.7	140.1	139.6	139.2	138.7	139.6	137.8	138.6	139.0
9	139.4	138.2	138.7	137.6	138.4	133.1	139	137.6	138.9	139.6	140.4	139.5	138.6	138.8
10	136.3	139.4	138	138.2	135.1	136.4	134.3							
n	10	10	10	10	10	10	10	9	9	9	9	9	9	9
mean	139.2	139.4	139.1	139.3	138.9	138.6	139.5	139.6	139.6	139.9	139.3	139.7	139.3	139.0
stdev	2.4	2.4	2.3	2.5	2.8	2.3	2.9	2.5	2.4	2.4	2.0	2.4	1.9	2.0
SEM	0.8	0.8	0.7	0.8	0.9	0.7	0.9	0.8	0.8	0.8	0.7	0.8	0.6	0.7

Table 8B.45

Na+ ven			**Exercise**								**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	140.2	141.6	143.1	145.8	139.1	141.7	140.1	142.1	142.7	138	137.7	138	137.6	138.4
2														
3	144	149.5	148.7	149.8	148.3	148.4	146.9	149.1	149.1	145.8	143.4	142.9	142.8	143.6
4	138.2	137.3	139	137.2	139.2	138.7	138.8	137.8	139.9	140.1	138.6	138.1	136.9	136.8
5	140.4	141.1	141.8	141.3	141.1	141.5	142.2	142.9	142.9	141.1	140.8	141.4	139.6	136.2
6	139.6	143	142.8	141.7	140	140.4	140.2	140.3	141.4	138.8	136.7	137.4	138.3	139
7	144.6	150	149.9	150	148	148.1	144.8	147.7	148.4	142	140	139.3	139.1	140.8
8	139.9	146.3	148.2	147.2	144.8	144.5	142.4	143.2	137.9	137.3	137.9	137.5	138.8	138.4
9	140.6	143	141.9	142.3	142.1	143.7	144.4	142.5	144.2	146.3	138.2	137.9	137.9	138.7
10	137.7	141.5	135.7	136.4	137.9	139.3	135.4	137.2	136.4	133.7	133.6	133.7	134.7	134.2
n	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	140.6	143.7	143.5	143.5	142.3	142.9	141.7	142.5	142.5	140.3	138.5	138.5	138.4	138.5
stdev	2.3	4.2	4.7	5.0	3.9	3.5	3.5	4.0	4.3	4.0	2.7	2.6	2.2	2.7
SEM	0.8	1.4	1.6	1.7	1.3	1.2	1.2	1.3	1.4	1.3	0.9	0.9	0.7	0.9

Table 8B.46

Na+ av			**Exercise**								**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	4.6	1.3	-5.0	-2.6	-2.5	-1.0	-2.6	-1.7	-1.7	0.0	-4.2	-0.9	-1.1	-2.9
4														
5	-1.8	7.9	-4.1	0.8	0.7	-0.5	-2.8	-3.0	-3.0	3.0	-1.2	-0.3	-4.5	6.2
6	-0.6	4.9	-2.7	0.1	-1.2	-2.0	-6.0	-4.6	-1.9	-3.4	-4.3	-8.8	-5.9	-2.5
7	-2.5	-1.4	-5.6	-2.2	-4.4	-2.7	-7.0	-2.6	1.6	-1.5	-3.1	-3.8	-1.4	-2.7
8	-2.9	-1.3	-5.3	-0.5	-0.7	2.2	-2.5	1.2	6.1	-2.6	-3.5	-6.2	-3.3	-0.2
9														
10	-3.5	2.8	3.0	4.2	-2.5	3.1	-0.7							
n	6	6	6	6	6	6	6	5	5	5	5	5	5	5
mean	-1.1	2.4	-3.3	0.0	-1.8	-0.2	-3.6	-2.1	0.2	-0.9	-3.3	-4.0	-3.2	-0.4
stdev	3.0	3.7	3.2	2.5	1.8	2.3	2.4	2.2	3.7	2.5	1.2	3.6	2.1	3.9
SEM	1.2	1.5	1.3	1.0	0.7	1.0	1.0	1.0	1.7	1.1	0.6	1.6	0.9	1.7

Table 8B.47

Cl- art			**Exercise**								**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	105	106	104	105	108	105	104	105	106	105	105	103	105	104

2	107	107	108	105	101	100	100	105	98	98	98	98	98	98
3	107	109	107	108	108	108	108	108	108	107	107	109	111	108
4	105	106	104	103	103	105	104	103	103	103	102	104	104	104
5	108	110	105	107	105	106	105	106	106	106	105	106	106	106
6	104	107	106	106	106	105	106	107	107	106	106	106	108	105
7	105	106	104	104	104	104	104	105	105	104	105	104	106	106
8	105	105	104	105	107	106	105	105	106	105	106	104	105	105
9	104	105	104	105	104	108	104	104	105	103	102	102	103	103
10	105		113	108	109	108	106							
n	10	9	10	10	10	10	10	9	9	9	9	9	9	9
mean	105.5	106.8	105.9	105.6	105.5	105.5	104.6	105.4	104.9	104.1	104.0	104.0	105.1	104.4
stdev	1.39	1.69	1.58	1.60	2.49	2.30	2.26	1.48	3.14	2.82	2.92	3.15	3.70	2.92
SEM	0.44	0.56	0.50	0.51	0.79	0.73	0.71	0.49	1.05	0.94	0.97	1.05	1.23	0.97

Table 8B.48

Cl- ven			**Exercise**								**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	102	104	102	102	105	104	103	104	102	103	102	105	105	104
2	109	108	105	102	100	106	101	104	99	98	98	102	99	98
3	107	109	107	108	107	107	105	106	106	105	105	106	106	107
4	107	109	111	106	105	106	106	106	103	104	104	103	102	104
5	107	106	108	105	104	104	107	104	104	103	103	104	106	105
6	103	106	102	103	101	103	101	103	104	100	100	102	103	104
7	104	106	103	105	102	102	101	104	102	103	102	101	104	105
8	103	106	105	104	103	104	103	101	103	99	100	101	101	104
9	103	104	106	103	101	102	100	102	101	99	97	97	99	102
10	106	101	106	103	103	104	101	105	103	100	101	102	103	104
n	10	10	10	10	10	10	10	10	10	10	10	10	10	10
mean	105.1	105.9	105.5	104.1	103.1	104.2	102.8	103.9	102.7	101.4	101.2	102.3	102.8	103.7
stdev	2.4	2.5	2.8	1.9	2.2	1.7	2.4	1.6	1.9	2.5	2.5	2.5	2.6	2.4
SEM	0.8	0.8	0.9	0.6	0.7	0.5	0.8	0.5	0.6	0.8	0.8	0.8	0.8	0.7

Table 8B.49

Cl- a-v			**Exercise**								**Recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	3.7	5.3	0.9	2.4	2.6	4.1	3.0	4.7	4.7	3.1	-0.9	1.7	3.8	-0.9
4														
5	0.0	10.2	-4.3	5.6	2.1	4.0	-2.5	2.7	2.7	5.9	1.4	3.0	-3.8	3.7
6	1.1	8.4	6.5	5.4	5.0	1.6	2.0	1.4	3.9	3.4	1.8	-3.4	-0.3	-0.6
7	0.7	5.0	2.9	3.1	2.6	4.3	-0.6	2.6	8.0	-0.4	0.6	-0.1	-0.2	-0.3
8	0.9	3.6	1.8	6.7	7.3	7.3	1.6	7.6	6.7	3.0	2.1	-1.9	1.7	0.4
9														
10	-2.7		7.6	6.9	6.2	8.7	5.3							
n	6.0	5.0	6.0	6.0	6.0	6.0	6.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
mean	0.6	6.5	2.6	5.0	4.3	5.0	1.5	3.8	5.2	3.0	1.0	-0.1	0.2	0.5
stdev	2.0	2.7	4.2	1.9	2.2	2.6	2.7	2.5	2.1	2.2	1.2	2.6	2.8	1.9
SEM	0.8	1.2	1.7	0.8	0.9	1.1	1.1	1.1	1.0	1.0	0.5	1.2	1.3	0.8

Table 8B.50

Lac- art			**exercise**				**recovery (min)**			
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1	0.3	0.4	0.1	0.4	1.8	1.6	1.5	0.7	0.6	1.5
2	1.1	0.9	1.3	1.3	2.2	3.0	1.3	1.7	1.5	1.0
3	1.2	1.3	1.1	1.2	1.3	1.6	1.2	1.5	2.2	0.8
4	1.0	1.1	0.8	1.0	1.1	1.6	1.3	1.5	1.7	1.5
5	1.8	2.7	2.8	3.1	2.8	2.1	3.3	3.4	3.2	2.7
6										
7	1.0	0.9	1.0	1.4	1.7	1.4	1.7	1.1	1.3	1.2
8	0.4	0.2	0.7	1.5	2.3	2.3	6.7	2.6	4.9	0.1
9	2.8	3.0	3.4	3.0	3.3	3.8	3.6	5.2	3.7	2.9
10	0.7		0.7	0.6				0.6		
n	9	8	9	9	8	8	8	9	8	8

mean	1.1	1.3	1.3	1.5	2.1	2.2	2.6	2.0	2.4	1.5
stdev	0.5	0.8	0.8	0.8	0.6	0.6	2.0	0.9	1.4	0.8
SEM	0.2	0.3	0.3	0.3	0.2	0.2	0.7	0.3	0.5	0.3

Table 8B.51

Lac-ven			**exercise**				**recovery (min)**			
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.3	2.8	2.1	3.0	3.2	3.1	2.3	1.3	1.4	1.9
2	1.8	2.3	3.4	4.9	1.6	4.8	2.8	2.2	2.5	2.0
3	1.3	4.0	4.9	5.8	5.0	4.0	4.6	3.7	2.9	0.8
4	1.3					2.6			3.3	2.4
5	3.3	4.3	3.7	2.7	3.6	5.5	1.9	3.5	3.7	3.0
6										
7	0.6	11.3	7.4	5.8	5.9	5.4	6.6	5.2	5.5	3.5
8	0.2	2.1	4.1	6.0	8.4	8.9	7.4	6.8	4.1	0.2
9	1.8	6.8	7.3	10.0	6.9	8.4	11.4	9.5	6.0	2.5
10	0.8	2.6	2.1	2.0	1.9	2.6	2.9	3.0	2.3	1.5
n	9	8	8	8	8	9	8	8	9	9
mean	1.4	4.5	4.4	5.0	4.6	5.0	5.0	4.4	3.5	2.0
stdev	0.9	3.1	2.1	2.5	2.4	2.3	3.3	2.7	1.5	1.0
SEM	0.3	1.1	0.7	0.9	0.8	0.8	1.2	0.9	0.5	0.3

Table 8B.52

Lac-a-v			**exercise**				**recovery (min)**			
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1										
2										
3	0.0	-2.6	-3.7	-4.6	-3.6	-2.3	-3.4	-2.3	-0.7	0.0
4										
5	-1.5	-1.4	-0.8	0.5	-0.8	-3.3	1.3	-0.1	-0.6	-0.2
6										
7	0.4	-10.3	-6.4	-4.3	-4.2	-4.0	-4.9	-4.2	-4.2	-2.4
8	0.2	-1.9	-3.4	-4.5	-5.9	-6.6	-1.0	-4.3	0.7	-0.1
9										
10	-0.1		-1.4	-1.4				-2.4		
n	5	4	5	5	4	4	4	5	4	4
mean	-0.2	-4.1	-3.1	-2.9	-3.6	-4.0	-2.0	-2.6	-1.2	-0.7
stdev	0.8	4.2	2.2	2.3	2.1	1.8	2.8	1.7	2.1	1.1
SEM	0.3	2.1	1.0	1.0	1.1	0.9	1.4	0.8	1.1	0.6

Table 8B.53

SID art			**exercise**				**recovery (min)**			
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1	36.2	35.1	38.0	37.4	41.1	37.3	35.2	42.2	34.8	37.1
2	34.1	34.2	36.8	41.6	41.5	42.9	42.6	43.4	43.2	42.3
3	39.6	37.9	39.0	38.3	39.2	40.1	39.2	37.3	34.5	38.2
4	34.4	33.3	36.7	33.7	35.2	37.2	37.7	36.6	36.6	36.1
5	32.8	31.8	32.1	33.8	36.4	35.5	36.9	35.3	35.9	34.2
6										
7	41.4	38.2	42.0	41.5	42.1	42.5	38.7	38.7	37.5	37.3
8	36.8	36.9	37.4	36.3	38.2	35.5	34.6	34.8	34.7	36.1
9	37.3	33.1	32.8	25.3	36.9	37.2	37.5	38.6	36.8	36.6
10	34.2		32.3	31.1						
n	9	8	9	9	8	8	8	8	8	8
mean	36.3	35.1	36.4	35.4	38.8	38.5	37.8	38.3	36.8	37.2
stdev	2.8	2.4	3.4	5.2	2.6	2.9	2.5	3.1	2.8	2.3
SEM	0.9	0.8	1.1	1.7	0.9	1.0	0.9	1.1	1.0	0.8

Table 8B.54

SID ven			**exercise**				**recovery (min)**			
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1	41.4	39.8	46.7	39.4	38.2	35.2	36.6	34.8	34.3	36.5
2										
3	39.7	41.8	42.3	40.7	42.1	40.8	37.6	37.1	37.8	39.7

4										
5	34.0	35.3	37.3	39.6	36.8	36.8	40.2	38.3	33.9	32.1
6										
7	43.9	38.6	43.3	45.8	43.4	37.6	35.2	36.8	33.4	36.2
8	40.5	44.0	44.8	40.0	36.5	32.9	33.9	33.0	37.2	38.0
9	39.5	37.7	37.4	37.5	43.8	42.8	33.3	35.0	36.6	38.1
10	35.0	42.6	35.7	37.7	37.3	34.6	33.2	32.3	33.0	32.2
n	7	7	7	7	7	7	7	7	7	7
mean	39.15	39.99	41.08	40.11	39.73	37.25	35.72	35.33	35.17	36.11
stdev	3.50	3.05	4.24	2.77	3.23	3.50	2.60	2.21	1.99	2.94
SEM	1.32	1.15	1.60	1.05	1.22	1.32	0.98	0.84	0.75	1.11

Table 8B.55

SIDa-v			**exercise**				**recovery (min)**			
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1										
2										
3	1.3	-2.1	-2.4	-1.2	-1.9	-0.3	0.5	-0.2	-3.7	-2.2
4										
5	-1.5	-1.7	-4.2	-5.2	-0.2	-0.3	-3.6	-2.7	0.7	3.0
6										
7	-2.6	1.4	0.3	-3.4	0.7	4.3	2.7	0.7	3.4	0.7
8	-4.0	-5.6	-5.4	-2.0	3.0	1.6	-0.6	0.2	-3.3	-2.0
9										
10	-1.3		-2.9	-5.3						
n	5	4	5	5	4	4	4	4	4	4
mean	-1.63	-1.99	-2.90	-3.41	0.41	1.31	-0.26	-0.51	-0.75	-0.13
stdev	1.95	2.85	2.13	1.83	2.03	2.21	2.60	1.52	3.40	2.48
SEM	0.87	1.43	0.95	0.82	1.01	1.10	1.30	0.76	1.70	1.24

Acid-base (Control). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for $[H^+]$, $[HCO_3^-]$; arterial and venous PCO_2, PO_2 at rest (R), during supramaximal finger flexion exercise (e1 to e4+1) to fatigue (F), and recovery (1 to 30min). Units are mM for $[H^+]$, $[HCO_3^-]$ and mmHg for PCO_2, PO_2.

Table 8B.56

H+ art				**exercise**						**recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	39.2	38.7	38.0	39.6	37.9	38.6	39.4	39.4	39.3	39.3	39.7	38.4	39.5	39.5
2	39.5	39.4	37.8	38.7	39.3	39.0	37.2	38.6	37.8	39.3	39.6	38.7	39.2	36.5
3	37.8	37.9	37.7	37.0	37.6	37.9	35.6	36.7	36.7	39.5	40.6	38.3	38.6	36.1
4	38.3	35.8	38.3	38.6	38.5	37.1	38.6	37.0	31.5	31.8	33.1	38.3	39.4	37.7
5	40.3	39.9	40.6	40.6	40.6	40.8	41.4	41.5	39.4	40.9	41.8	42.8	40.7	41.6
6	37.5	37.9	36.7	38.4	38.1	38.6	37.8	38.6	35.3	39.2	37.8	35.1	36.1	38.8
7	39.0	37.6	38.4	38.1	38.5	38.5	38.2	38.6	35.3	38.2	36.4	38.3	39.0	38.5
8	36.6	37.8	37.7	36.9	38.2	31.3	38.9	29.3	29.3	38.5	37.5	39.5	38.3	37.2
9	42.8	37.2	39.5	32.5	42.8	34.3	40.9	30.8	30.8	40.6	40.8	42.1	43.6	40.8
10	38.2	37.7	37.4	39.7	37.8	37.8	37.9	36.5	37.4	37.9	37.9	38.4	38.3	37.6
N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
mean	38.9	38.0	38.2	38.0	38.9	37.4	38.6	36.7	35.3	38.5	38.5	39.0	39.3	38.4
SD	1.7	1.1	1.1	2.3	1.6	2.7	1.7	3.8	3.6	2.5	2.6	2.2	1.9	1.8
SEM	0.5	0.4	0.3	0.7	0.5	0.9	0.5	1.2	1.1	0.8	0.8	0.7	0.6	0.6

Table 8B.57

H+ ven				**exercise**						**recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	44.9	48.2	49.8	47.2	50.7	47.9	53.6	49.1	52.2	51.6	50.6	43.4	42.0	42.4
2														
3	43.0	45.8	56.4	47.9	59.0	51.2	56.8	51.8	51.8	53.3	51.2	44.6	42.1	42.0
4	43.0	46.2	62.7	48.2	60.5	49.1	63.5	53.2	56.5	58.1	47.4	48.8	44.7	39.2
5	44.3	46.5	50.5	47.4	53.5	49.3	53.1	50.4	52.8	54.8	54.5	49.1	44.4	43.6
6	42.6	48.1	60.1	49.7	56.8	48.9	56.0	49.9	51.3	47.6	43.2	40.9	40.6	38.5
7	41.9	52.2	61.2	56.2	57.1	54.1	58.5	51.1	59.2	50.6	45.9	47.2	43.4	41.0
8	42.8	46.3	52.7	48.1	60.4	50.6	60.1	56.4	56.4	59.8	54.2	49.4	44.1	40.9

9	47.9	58.7	73.1	57.5	67.6	56.8	65.8	54.1	54.1	63.7	59.7	54.8	49.1	45.8
10	42.2	48.3	56.0	48.4	58.3	47.6	56.4	47.9	55.3	61.1	53.3	42.3	41.3	41.0
N	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	43.6	48.9	58.0	50.1	58.2	50.6	58.2	51.5	54.4	55.6	51.1	46.7	43.5	41.6
SD	1.9	4.2	7.3	3.9	4.8	3.0	4.3	2.7	2.6	5.4	5.0	4.4	2.5	2.2
SEM	0.6	1.4	2.4	1.3	1.6	1.0	1.4	0.9	0.9	1.8	1.7	1.5	0.8	0.7

Table 8B.58

H+ a-v				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-5.7	-9.5	-11.8	-7.6	-12.8	-9.2	-14.1	-9.7	-13.0	-12.4	-10.9	-5.0	-2.4	-2.8
2														
3	-5.2	-7.9	-18.7	-10.9	-21.4	-13.2	-21.1	-15.0	-15.0	-13.8	-10.5	-6.3	-3.4	-5.8
4	-4.7	-10.4	-24.4	-9.6	-22.1	-12.0	-24.9	-16.2	-25.0	-26.2	-14.3	-10.5	-5.2	-1.5
5	-4.0	-6.5	-9.9	-6.9	-12.9	-8.5	-11.7	-8.9	-13.5	-13.9	-12.7	-6.3	-3.6	-2.0
6	-5.1	-10.2	-23.4	-11.3	-18.6	-10.2	-18.2	-11.3	-16.0	-8.5	-5.3	-5.9	-4.6	0.3
7	-2.9	-14.7	-22.9	-18.1	-18.7	-15.6	-20.3	-12.5	-23.8	-12.4	-9.5	-8.9	-4.4	-2.5
8	-6.2	-8.6	-15.1	-11.2	-22.2	-19.3	-21.2	-27.1	-27.1	-21.3	-16.7	-9.9	-5.8	-3.7
9	-5.1	-21.6	-33.6	-25.0	-24.9	-22.5	-24.8	-23.3	-23.3	-23.1	-18.9	-12.8	-5.5	-5.0
10	-4.0	-10.6	-18.6	-8.7	-20.6	-9.8	-18.4	-11.4	-17.9	-23.2	-15.4	-3.9	-3.0	-3.4
N	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	-4.8	-11.1	-19.8	-12.1	-19.4	-13.4	-19.4	-15.0	-19.4	-17.2	-12.7	-7.7	-4.2	-2.9
SD	1.0	4.5	7.3	5.8	4.1	4.9	4.4	6.3	5.4	6.3	4.1	2.9	1.2	1.8
SEM	0.3	1.5	2.4	1.9	1.4	1.6	1.5	2.1	1.8	2.1	1.4	1.0	0.4	0.6

Table 8B.59

HCO3- art				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	27.3	24.9	27	25.6	26.6	25.7	26.5	26	26.4	25.4	26.8	25.5	25.2	24.5
3	28.9	28.3	30.3	29.3	29.9	26.8	26.8	27.8	26.3	27.4	28	26.2	27.1	26.4
4														
5	26.6	27.1	27.1	27.3	27	26.9	26.7	25.8	25	26.5	26	26	25.4	25.3
6	25.6	27.8	26.3	27.9	26.4	28.1	27.9	28	27.2	27.8	28.4	27.2	27.5	28.4
7	28.4	28.5	28.2	27.2	28	27	26.8	27.2	26	27.4	26.8	26.1	27.8	28.1
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	27.4	27.3	27.8	27.5	27.6	26.9	26.9	27.0	26.2	26.9	27.2	26.2	26.6	26.5
stdev	1.3	1.5	1.6	1.3	1.4	0.9	0.6	1.0	0.8	1.0	1.0	0.6	1.2	1.7
SEM	0.6	0.7	0.7	0.6	0.6	0.4	0.2	0.5	0.4	0.4	0.4	0.3	0.5	0.8

Table 8B.60

HCO3- ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	32.4	33.9	35.6	34.7	31.7	31.6	31.8	32.0	32	30	29.3	28.9	28.8	30.3
4														
5	29.8	30.6	31.5	30.6	31	30.8	28.7	30.2	30.4	29.1	28.6	27.2	27.8	27.1
6	29.1	31.5	32.4	31.6	32.6	31.2	32.4	31.3	31.9	29.5	29.3	29.2	30	30.7
7	32.3	33.9	34.8	32.1	32.5	32.5	33.3	32.8	34.9	29.3	26.5	27.1	28.5	29.8
8														
9														
10														
n	4	4	4	4	4	4	4	4	4	4	4	4	4	4
mean	30.9	32.5	33.6	32.3	32.0	31.5	31.6	31.6	32.3	29.5	28.4	28.1	28.8	29.5
stdev	1.7	1.7	1.9	1.7	0.8	0.7	2.0	1.1	1.9	0.4	1.3	1.1	0.9	1.6

SEM	0.8	0.8	1.0	0.9	0.4	0.4	1.0	0.5	0.9	0.2	0.7	0.6	0.5	0.8

Table 8B.61

HCO3- a-v				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	-3.5	-5.6	-5.3	-5.4	-1.8	-4.8	-5	-4.1	-5.7	-2.6	-1.3	-2.7	-1.7	-3.9
4														
5	-3.2	-3.5	-4.4	-3.3	-4	-3.9	-2	-4.4	-5.4	-2.6	-2.6	-1.2	-2.4	-1.8
6	-3.5	-3.7	-6.1	-3.7	-6.2	-3.1	-4.5	-3.3	-4.7	-1.7	-0.9	-2	-2.5	-2.3
7	-3.9	-5.4	-6.6	-4.9	-4.5	-5.5	-6.5	-5.6	-8.9	-1.9	0.3	-1	-0.7	-1.7
8														
9														
10														
n	4	4	4	4	4	4	4	4	4	4	4	4	4	4
mean	-3.5	-4.6	-5.6	-4.3	-4.1	-4.3	-4.5	-4.4	-6.2	-2.2	-1.1	-1.7	-1.8	-2.4
stdev	0.3	1.1	1.0	1.0	1.8	1.0	1.9	0.9	1.9	0.5	1.2	0.8	0.8	1.0
SEM	0.1	0.6	0.5	0.5	0.9	0.5	0.9	0.5	0.9	0.2	0.6	0.4	0.4	0.5

Table 8B.62

PCO2 art				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	43.4	41	40.5	42.9	39	40.9	43.3	42.4	42.5	41.6	42.7	40.7	41.9	41
2	44.8	40.6	42.4	41.2	43.3	41.5	40.9	41.6	41.5	41.3	44	40.9	41	37
3	45.2	44.6	47.3	44.9	46.6	42.1	39.7	40.1	40.1	44.9	47.2	41.6	43.5	39.6
4	29.7	41.6	48.1	49.9	53.2	50.8	54.7	52.6	39.8	38	40.5	54	57.7	52.9
5	44.4	44.8	45.6	45.9	45.4	45.6	45.9	44.4	40.8	45	45.1	46.2	43	43.7
6	39.8	43.7	40	44.4	41.7	45	43.7	44.8	39.9	45.1	44.6	39.6	41.1	45.7
7	45.9	44.4	44.9	43	44.6	43	42.5	41.2	38.1	43.4	40.4	41.5	44.9	44.9
8	42.9	46.6	45	41.9	44.3	33.8	46.1	29.8	29.8	40.9	40.1	45.4	45.3	46.6
9	45.8	37.2	40	31	48	32.2	42.9	28.1	28.1	41.7	41.9	44	44.1	42.9
10														
N	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	42.5	42.7	43.8	42.8	45.1	41.7	44.4	40.6	37.8	42.4	42.9	43.8	44.7	43.8
SD	5.1	2.9	3.1	5.1	4.0	5.7	4.4	7.5	5.2	2.4	2.5	4.4	5.1	4.6
SEM	1.7	1.0	1.0	1.7	1.3	1.9	1.5	2.5	1.7	0.8	0.8	1.5	1.7	1.5

Table 8B.63

PCO2 ven				**exercise**						**recovery (min)**				
Subjec t	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	56.2	60.9	62.2	58.4	59.8	58.9	65.5	58.7	65.0	60.8	58.6	46.1	46.5	48.1
2														
3	57.8	64.5	83.3	68.9	77.7	67.1	74.9	68.8	68.8	66.4	62.2	53.4	50.3	52.8
4	38.6	63.6	98.7	66.7	93.9	77.0	108.4	79.9	91.9	91.1	65.2	65.5	60.6	55.4
5	54.7	58.9	65.9	60.1	68.7	63.1	63.2	63.0	66.7	66.1	64.5	55.4	51.2	48.9
6	51.3	62.9	80.9	65.0	76.8	63.2	75.3	64.8	67.8	58.3	52.5	49.5	50.5	49.1
7	56.0	73.4	88.4	74.8	77.1	72.8	80.8	67.8	85.6	61.4	50.5	53.0	51.3	50.7
8	58.0	68.2	74.2	68.1	84.1	69.0	79.1	72.8	72.8	68.7	60.1	56.3	53.8	55.5
9	59.9	79.2	103.4	74.7	91.4	71.7	85.7	66.8	66.8	78.2	66.0	57.1	53.3	53.5
10														
N	8	8	8	8	8	8	8	8	8	8	8	8	8	8
mean	54.1	66.5	82.1	67.1	78.7	67.9	79.1	67.8	73.2	68.9	60.0	54.5	52.2	51.8
SD	6.7	6.8	14.6	6.0	11.2	6.0	14.0	6.4	10.0	10.9	5.8	5.7	4.1	3.0
SEM	2.4	2.4	5.2	2.1	4.0	2.1	5.0	2.3	3.5	3.8	2.1	2.0	1.4	1.0

Table 8B.64

PO2 art				**exercise**							**recovery**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	109.6	118	118.9	106	122.9	115.7	114.7	110.2	91.3	97.8	107	109.2	113.8	112.6
2	101.4	111.7	114.2	109.8	111.2	109.3	120.9	112.5	123.5	110.7	105.6	117.3	109.1	104.3
3	91.5	93.4	97.1	96.7	105.3	91.3	110.2	104.5	104.5	79.2	101	84.5	89.3	106.2
4	107.7	123.2	99.1	121	106.3	121.5	108.2	119.6	141.3	153.8	145.2	94.6	84.1	102
5	116.8	104.5	99.3	104.2	105.4	108.9	104.9	104.3	123.3	101.2	107.9	104.8	107.7	106.7
6	109	114.8	116.6	103	113	100.8	111.2	102.2	123.7	96.6	104.8	114.9	104.7	105.5

7	118.4	119.4	110	118.8	112.5	111.9	113.7	112.0	127.9	112.8	119.1	101.9	103.9	96.4
8	114.4	109.9	111	122.1	126.4	133.3	98.6	135.4	135.4	108.3	110.9	98.4	100.2	96.5
9	107.3	130.3	118.8	142.1	98	138.9	103.5	141.7	141.7	84.3	87.3	107.3	112.9	125.9
10	81.7	82.7	88.8	85.6	81.7	81.3	91.1	87.2	97.1	83.6	87.9	84.5	87.8	75.8
N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
mean	105.8	110.8	107.4	110.9	108.3	111.3	107.7	113.0	121.0	102.8	107.7	101.7	101.4	103.2
SD	11.5	14.2	10.5	15.8	12.6	17.6	8.6	16.0	17.8	21.4	16.4	11.4	10.7	12.8
SEM	3.6	4.5	3.3	5.0	4.0	5.6	2.7	5.1	5.6	6.8	5.2	3.6	3.4	4.0

Table 8B.65

PO2 ven			**exercise**							**recovery**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	35.1	25	31.8	25	32.2	24.6	37	25.1	23	39.4	45.9	47	46.9	40.2
2														
3	33.9	23.9	30.6	23.6	29.7	23.4	34.4	25.6	25.6	39.6	43.1	38.8	41.3	36.4
4	32.4	19.9	37.5	24.5	36.9	39	21.4	44.2	23.8	25.9	50.7	60.7	59.2	60
5	35.2	23.9	26.2	24.5	28.7	25.8	29	25.2	26.8	36.7	33.9	43.2	44	44.1
6	40.5	24.3	38.1	22	39.6	21.8	38.3	23.2	29.2	46.3	49.1	48.8	43.3	48.2
7	32.6	25.7	40.4	24.7	45.9	24.5	41.3	27.7	30.7	49.8	54.6	47	44.1	37.5
8	27.3	22.4	34.7	23.3	42.1	25.4	41.1	24.8	24.8	55	57.5	46.6	39.8	32.2
9	33.2	22.9	40.8	22.3	41.4	20.6	40.7	22	22	40.4	57.6	54.4	43	42.6
10	39.4	24.1	32.1	22.3	36.9	22.8	40.3	26.3	24.7	43.6	51.4	54.8	41.9	39.9
N	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	34.4	23.6	34.7	23.6	37.0	25.3	35.9	27.1	25.6	41.9	49.3	49.0	44.8	42.3
SD	3.9	1.7	4.9	1.2	5.9	5.4	6.8	6.6	2.8	8.3	7.6	6.6	5.7	8.1
SEM	1.3	0.6	1.6	0.4	2.0	1.8	2.3	2.2	0.9	2.8	2.5	2.2	1.9	2.7

Acid-base (Digoxin). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for $[H^+]$, $[HCO_3^-]$; arterial and venous PCO_2, PO_2 at rest (R), during supramaximal finger flexion exercise (e1 to e4+1) to fatigue (F), and recovery (1 to 30min). Units are mM for $[H^+]$, $[HCO_3^-]$ and mmHg for PCO_2, PO_2.

Table 8B.66

H+ art				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	37.3	36.1	37.2	34.9	36.4	33.4	33.3	36.7	24.1	26.7	28.2	31.5	32.5	39.8
2	40.0	38.9	38.5	39.7	38.7	39.5	38.7	36.4	39.1	38.8	41.5	39.1	40.1	40.6
3	38.6	38.0	38.3	38.3	40.4	39.1	37.4	35.6	35.6	39.3	38.7	39.6	37.9	38.2
4	38.0	38.1	37.8	38.4	37.8	39.6	37.6	39.3	38.5	35.5	37.1	40.3	39.8	39.2
5	40.5	37.8	40.2	39.1	39.6	39.9	38.4	39.6	39.6	40.5	40.2	40.6	40.1	38.5
6	36.2	35.9	35.5	36.7	36.9	37.1	36.5	36.5	37.6	34.8	35.6	35.1	37.6	35.5
7	40.6	39.9	39.7	39.3	39.2	39.2	37.2	36.2	32.5	33.7	33.3	36.3	39.2	40.8
8	40.3	34.7	39.4	34.8	37.1	34.1	37.2	37.8	34.1	40.5	39.0	39.5	39.4	40.2
9	42.1	32.4	37.8	31.2	35.6	27.0	34.8	28.3	29.0	38.2	40.8	41.4	42.3	40.8
10	38.0		37.1	37.2	37.6	37.5	38.1							
N	10	9	10	10	10	10	10	9	9	9	9	9	9	9
mean	39.2	36.9	38.1	37.0	37.9	36.6	36.9	36.3	34.5	36.4	37.2	38.2	38.8	39.3
SD	1.8	2.3	1.4	2.7	1.5	4.1	1.7	3.3	5.2	4.4	4.2	3.2	2.7	1.7
SEM	0.6	0.8	0.4	0.8	0.5	1.3	0.5	1.1	1.7	1.5	1.4	1.1	0.9	0.6

Table 8B.67

H+ ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	42.0	44.4	47.8	45.4	52.1	45.1	49.4	51.9	33.5	34.4	33.3	32.8	33.8	42.7
2														
3	43.7	50.4	59.6	53.5	60.5	51.6	57.1	51.5	51.5	54.7	48.4	45.7	43.6	42.1
4	44.3	44.3	47.4	45.5	44.2	46.5	45.1	45.6	46.2	45.7	43.6	45.0	42.4	42.2
5	45.0	45.9	46.2	48.6	50.6	48.6	48.1	48.6	48.6	53.2	49.1	44.0	43.3	43.0
6	40.1	47.8	59.0	49.7	60.1	46.8	56.1	48.6	51.4	55.3	48.4	42.3	40.8	39.6
7	46.0	58.9	75.3	59.2	71.4	55.0	59.8	53.2	56.5	48.8	45.8	43.6	44.3	41.4
8	44.1	55.8	70.0	56.6	62.4	51.9	55.0	63.2	51.5	58.7	57.3	49.9	45.2	43.8
9	45.5	51.2	61.7	54.3	64.4	53.8	57.5	54.1	55.8	70.5	62.1	56.8	48.4	42.7
10	42.1	47.2	51.6	44.4	54.3	43.6	61.7	47.9	51.3	56.9	50.1	43.8	42.2	41.1
N	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	43.6	49.5	57.6	50.8	57.8	49.2	54.4	51.6	49.6	53.1	48.7	44.9	42.6	42.0

SD	1.9	5.1	10.3	5.3	8.3	4.0	5.6	5.1	6.8	9.9	8.1	6.4	4.0	1.2
SEM	0.6	1.7	3.4	1.8	2.8	1.3	1.9	1.7	2.3	3.3	2.7	2.1	1.3	0.4

Table 8B.68

H+ a-v				**exercise**							**recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-4.7	-8.2	-10.6	-10.5	-15.7	-11.7	-16.2	-15.2	-9.4	-7.6	-5.1	-1.3	-1.3	-2.8
2														
3	-5.0	-12.3	-21.3	-15.2	-20.2	-12.6	-19.7	-15.9	-15.9	-15.4	-9.7	-6.1	-5.6	-3.9
4	-6.2	-6.2	-9.6	-7.1	-6.4	-6.8	-7.5	-6.3	-7.7	-10.2	-6.5	-4.7	-2.6	-3.0
5	-4.5	-8.2	-6.1	-9.6	-11.0	-8.7	-9.7	-9.0	-9.0	-12.8	-8.9	-3.3	-3.2	-4.5
6	-3.9	-11.9	-23.5	-12.9	-23.2	-9.7	-19.6	-12.2	-13.8	-20.6	-12.8	-7.2	-3.2	-4.1
7	-5.4	-19.0	-35.6	-19.9	-32.3	-15.8	-22.6	-17.0	-24.0	-15.1	-12.5	-7.2	-5.1	-0.6
8	-3.8	-21.2	-30.5	-21.8	-25.3	-17.8	-17.8	-25.4	-17.4	-18.3	-18.3	-10.4	-5.8	-3.6
9	-3.4	-18.8	-23.8	-23.1	-28.9	-26.8	-22.7	-25.8	-26.9	-32.3	-21.3	-15.4	-6.2	-1.8
10	-4.1		-14.6	-7.2	-16.7	-6.1	-23.6							
N	9	8	9	9	9	9	9	8	8	8	8	8	8	8
mean	-4.5	-13.2	-19.5	-14.1	-20.0	-12.9	-17.7	-15.8	-15.5	-16.5	-11.9	-6.9	-4.1	-3.0
SD	0.9	5.7	10.0	6.2	8.4	6.5	5.7	7.0	7.1	7.6	5.6	4.4	1.8	1.3
SEM	0.3	2.0	3.3	2.1	2.8	2.2	1.9	2.5	2.5	2.7	2.0	1.5	0.6	0.5

Table 8B.69

HCO3- art				**exercise**							**recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	25.8	24.8	24.9	23.7	25.4	24.4	24.2	25.5	24.8	24.7	25	24.8	25.5	24.4
3	26.9	26.2	26.6	26.9	25.9	25.4	26.2	26	26.1	27.2	26	25.5	24.4	26.3
4														
5	24.9	25	27.3	26.6	27.1	26.6	26.8	25.1	25.2	26.9	27.4	26.5	26.9	26.8
6	27.7	26	26.6	26.7	27.4	27	26.2	25.8	25.9	26.7	26.5	25.8	26.9	26.9
7	27.6	26.5	27.1	27.5	27.7	26.8	26.3	26.7	24.6	24.7	25.7	26.7	26.6	27.2
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	26.6	25.7	26.5	26.3	26.7	26.0	25.9	25.8	25.3	26.0	26.1	25.9	26.1	26.3
stdev	1.2	0.8	0.9	1.5	1.0	1.1	1.0	0.6	0.7	1.2	0.9	0.8	1.1	1.1
SEM	0.5	0.3	0.4	0.7	0.4	0.5	0.4	0.3	0.3	0.6	0.4	0.3	0.5	0.5

Table 8B.70

HCO3- ven				**exercise**							**recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	28.9	31.6	32.5	31.4	31.7	30.1	31.3	31.2	30.5	29.7	27.2	27	27	28.9
4														
5	29.2	29.1	29.4	29.4	30.6	30.4	28.4	31.5	31.8	31	29.9	30.5	26.4	26.9
6	31.2	32.4	34.1	32.4	32	31.2	32.7	31.5	32	31.3	28.2	30	29.9	30.4
7	31.1	33.7	34.2	32.5	33	30.7	30	30.6	31.5	27.5	25.4	26.2	27.5	29.4
8														
9														
10														
n	4	4	4	4	4	4	4	4	4	4	4	4	4	4
mean	30.1	31.7	32.6	31.4	31.8	30.6	30.6	31.2	31.5	29.9	27.7	28.4	27.7	28.9
stdev	1.2	1.9	2.2	1.4	1.0	0.5	1.8	0.4	0.7	1.7	1.9	2.1	1.5	1.5
SEM	0.6	1.0	1.1	0.7	0.5	0.2	0.9	0.2	0.3	0.9	0.9	1.1	0.8	0.7

Table 8B.71

HCO3- a-v				**exercise**							**recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2														
3	-2	-5.4	-5.9	-4.5	-5.8	-4.7	-5.1	-5.2	-4.4	-2.5	-1.2	-1.5	-2.6	-2.6
4														
5	-4.3	-4.1	-2.1	-2.8	-3.5	-3.8	-1.6	-6.4	-6.6	-4.1	-2.5	-4	0.5	-0.1
6	-3.5	-6.4	-7.5	-5.7	-4.6	-4.2	-6.5	-5.7	-6.1	-4.6	-1.7	-4.2	-3	-3.5
7	-3.5	-7.2	-7.1	-5	-5.3	-3.9	-3.7	-3.9	-6.9	-2.8	0.3	0.5	-0.9	-2.2

8														
9														
10														
n	4	4	4	4	4	4	4	4	4	4	4	4	4	4
mean	-3.3	-5.8	-5.7	-4.5	-4.8	-4.2	-4.2	-5.3	-6.0	-3.5	-1.3	-2.3	-1.5	-2.1
stdev	1.0	1.3	2.5	1.2	1.0	0.4	2.1	1.1	1.1	1.0	1.2	2.2	1.6	1.4
SEM	0.5	0.7	1.2	0.6	0.5	0.2	1.0	0.5	0.6	0.5	0.6	1.1	0.8	0.7

Table 8B.72

PCO2 art				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	45	44	46.2	41.8	42.5	38.8	38.8	38.9	24.1	28.3	31.2	34	36.3	43.6
2	42.7	40.1	39.8	39.1	40.8	40	38.5	39.5	40.2	39.7	43	40.2	42.4	41
3	42.57	41.3	42.2	42.7	43.3	41.1	40.6	38.6	38.6	44.3	41.7	42	38.4	41.7
4	42	41.5	43.8	43.6	43.1	47	42.7	45.1	41.9	37.9	40.4	44.1	43.2	43
5	41.75	39.2	45.8	43.2	44.6	44.1	42.6	41.5	41.5	45.1	45.7	44.6	44.8	42.8
6	41.55	39.4	39.2	40.7	42	41.5	39.6	39	40.4	38.5	39.2	37.5	41.9	39.6
7	46.5	43.8	44.7	44.8	45	43.6	40.7	43.3	33.2	34.5	35.4	40.2	43.3	46.1
8	48.4	37.2	45.2	37.2	39.5	35.2	39.6	40.3	33.5	44.6	42.5	44	42.3	45.4
9	44.2	31.7	39.7	29.5	36.5	25	36.5	25.5	26.4	39.1	43.1	41.6	44.7	45.8
10														
N	9	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	43.9	39.8	43.0	40.3	41.9	39.6	40.0	39.1	35.5	39.1	40.2	40.9	41.9	43.2
SD	2.4	3.7	2.8	4.7	2.7	6.4	2.0	5.5	6.7	5.4	4.5	3.5	2.8	2.2
SEM	0.8	1.2	0.9	1.6	0.9	2.1	0.7	1.8	2.2	1.8	1.5	1.2	0.9	0.7

Table 8B.73

PCO2 ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	56.1	61.7	65.1	63.2	69.1	62.0	65.0	64.8	41.0	39.7	38.3	39.8	41.7	50.2
2	48.9	53.7	63.0	56.4	57.9	46.5	51.7	63.5	54.5	53.5	53.1	51.0	46.2	45.2
3	52.7	65.9	80.2	69.7	79.7	64.5	74.2	65.1	65.1	67.3	54.6	51.1	48.7	50.5
4	52.0	49.5	49.7	53.0	53.9	56.0	54.3	53.2	55.0	54.8	50.8	51.5	49.5	49.1
5	54.6	55.4	56.3	61.6	64.3	61.4	56.7	64.2	64.2	68.4	60.9	55.6	47.4	47.9
6	52.0	64.1	83.4	66.8	79.8	60.6	76.1	63.6	68.3	71.9	56.7	52.6	50.6	50.0
7	59.4	82.2	106.9	79.8	97.8	70.0	74.5	67.5	73.9	55.7	48.2	47.3	50.4	50.5
8	56.4	76.3	102.3	73.9	84.0	67.1	66.1	81.4	64.6	69.7	65.9	55.7	54.1	53.8
9	53.4	64.4	81.1	66.5	83.7	64.4	72.1	64.8	69.8	87.9	63.4	57.1	52.2	51.2
10	51.6	62.7	63.8	57.1	67.9	56.4	67.9	56.4	61.8	66.0	54.6	46.0	46.5	47.3
N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
mean	53.7	63.6	75.2	64.8	73.8	60.9	65.9	64.5	61.8	63.5	54.7	50.8	48.7	49.6
SD	3.0	9.9	19.0	8.3	13.5	6.7	8.9	7.4	9.5	13.1	8.0	5.2	3.5	2.4
SEM	1.0	3.1	6.0	2.6	4.3	2.1	2.8	2.3	3.0	4.2	2.5	1.7	1.1	0.7

Table 8B.74

PO2 art				**exercise**							**recovery**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1														
2	114.4	115.0	111.1	112.5	111.2	117.5	118.7	117.0	115.6	103.3	102.2	104.8	107.0	100.3
3	94.6	102.5	101.9	100.9	104.1	108.3	101.7	110.4	110.4	89.1	102.3	93.7	100.5	100.9
4	131.7	117.5	112.4	112.8	123.7	107.5	136.4	114.9	119.9	139.8	133.2	99.4	110.7	104.4
5	100.9	107.5	100.1	107.3	107.2	104.8	109.3	115.2	115.2	102.7	101.6	103.8	109.2	110.2
6	91.7	92.5	111.2	95.7	107.1	89.4	106.8	102.1	108.1	107.7	118.3	127.2	99.6	104.7
7	110.6	113.8	120.2	118.2	115.8	119.7	127.2	117.7	142.4	131.0	144.2	111.7	104.2	103.4
8	95.3	120.9	97.4	123.3	116.4	125.5	109.4	113.8	124.9	86.9	87.8	108.6	119.8	115.7
9	104.3	139.2	111.8	134.5	124.8	146.4	117.9	142.6	149.8	87.5	83.0	97.3	106.1	106.2
10	80.4		103.7	88.8	85.3	105.6	79.5							
N	9	8	9	9	9	9	9	8	8	8	8	8	8	8
mean	102.7	113.6	107.8	110.4	110.6	113.9	111.9	116.7	123.3	106.0	109.1	105.8	107.1	105.7
SD	14.9	13.8	7.4	14.1	11.9	16.1	16.2	11.6	15.1	19.9	21.3	10.5	6.4	5.1
SEM	5.0	4.9	2.5	4.7	4.0	5.4	5.4	4.1	5.4	7.0	7.5	3.7	2.3	1.8

Table 8B.75

PO2 ven				**exercise**							**recovery**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	41.9	23	30	22.1	35.4	22.1	34.8	27.90	19.5	33.5	33.8	33	40.5	38.2
2	38													

3	35.6	22	32.5	24.8	37	24.5	36.6	25.2	25.2	39	40.8	41.9	39.6	29.5
4	36.1	35.7	36.5	38.6	38.3	38.1	41.3	39.3	41.2	42.1	46.7	51.3	50.2	46.6
5	35.6	25	26.7	27	32.5	26.7	27.7	25.9	25.9	33	30.6	40	48.4	47.6
6	28.8	19.2	30.8	20.9	42	20.1	39.9	21.2	26.7	42.6	38.6	41.3	34.2	30.3
7	35.1	26.5	40.6	26	46.7	24.7	43.3	25.8	27	45.5	51.8	51.6	40.8	33.6
8	28.2	23.6	36.8	24.7	35.3	25.3	36.66	44.3	24.8	44	48	39.8	35.8	39.2
9	33.2	25.3	31.1	23.4	39.2	23	35.2	21.8	23	40.6	52.3	57.6	52	38.5
10	30.2	22.5	44.5	22.5	33.7	21.5	36.1	22	21.2	41.2	47.1	46.9	34.8	26.9
N	10	9	9	9	9	9	9	9	9	9	9	9	9	9
mean	34.3	24.8	34.4	25.6	37.8	25.1	36.8	28.2	26.1	40.2	43.3	44.8	41.8	36.7
SD	4.3	4.6	5.7	5.3	4.4	5.3	4.5	8.1	6.2	4.3	7.8	7.6	6.8	7.3
SEM	1.4	1.5	1.9	1.8	1.5	1.8	1.5	2.7	2.1	1.4	2.6	2.5	2.3	2.4

Ion fluxes (Control). Net ion fluxes into or out of forearm musculature for [K^+], [Na^+], [Cl^-], [Lac^-], [$Blac^-$], [H^+] and [HCO_3^-] at rest (R), during exercise (e1 to pe4), fatigue (F), and recovery (1 to 30min). Units are $\mu M.min^{-1}$ except for for [H^+] which is $pM.min^{-1}$.

Table 8B.76

K+ flux				**exercise**					**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1													
2													
3	-5.8	-272.0	-12.4	-368.6	6.8	-380.2	30.7	-369.4	37.7	48.5	-30.5	-13.5	-11.2
4													
5	5.0	-95.5	-10.3	-49.9	-2.2	-79.3	2.7	-118.9	15.3	4.7	1.8	-2.3	-2.2
6	-5.3	-112.2	1.4	-144.3	4.0	-110.8	8.4	30.6	40.5	36.1	20.5	12.4	3.1
7	-0.6	-132.6	11.9	-179.3	7.8	-199.3	15.8	-168.3	22.9	9.4	4.2	3.8	-1.0
8	-3.1	-218.0	1.1	-220.7	16.7	-172.6	11.7	-307.1	36.4	23.2	8.0	2.4	1.7
9													
10	-1.6	-64.0	1.6	-77.7	2.6	-44.2	4.8	-71.7	9.7	3.6	2.6	3.5	0.0
n	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	-1.9	-149.0	-1.1	-173.4	5.9	-164.4	12.3	-167.5	27.1	20.9	1.1	1.1	-1.6
stdev	3.9	79.5	8.9	114.6	6.3	120.3	10.2	149.0	12.9	18.4	16.9	8.6	5.1
SEM	1.6	32.5	3.6	46.8	2.6	49.1	4.2	60.8	5.3	7.5	6.9	3.5	2.1

Table 8B.77

Cl- flux				**exercise**					**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1													
2													
3	53.7	1081.8	-4.1	1804.6	-219.8	1824.6	582.1	2532.6	223.2	452.8	499.4	254.8	180.9
4													
5	20.1	176.2	54.0	197.2	35.1	236.8	87.5	274.3	-28.4	46.2	-74.9	3.1	-46.9
6	-2.1	541.6	273.5	419.3	301.3	626.4	284.4	2075.5	339.7	505.5	248.2	65.9	98.7
7	-3.6	788.0	565.7	423.6	150.7	1118.9	560.7	1130.9	306.4	153.1	102.4	121.7	63.2
8	-48.7	-246.1	30.0	1064.7	235.3	789.0	101.9	1246.4	294.1	265.7	136.3	16.2	19.9
9													
10	4.4	138.4	-10.8	288.9	12.6	93.9	14.7	284.9	-17.6	13.3	22.1	8.0	-41.5
n	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	4.0	413.3	151.4	699.7	85.9	781.6	271.9	1257.4	186.2	239.4	155.6	78.3	45.7
stdev	33.5	483.8	228.6	621.3	186.7	631.7	248.5	919.1	166.5	206.4	200.5	97.6	87.5
SEM	13.7	197.5	93.3	253.6	76.2	257.9	101.5	375.2	68.0	84.2	81.8	39.8	35.7

Table 8B.78

Na+ flux				**exercise**					**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1													
2													
3	-32.0	1409.3	-761.5	510.5	-823.0	-363.4	-903.3	1412.3	-861.0	-1463.4	-20.7	-85.6	70.5
4													
5	-13.8	-7.0	-129.9	181.2	-167.1	213.5	-201.9	94.8	-91.0	-108.5	-219.1	-25.6	-62.9
6	-56.4	283.5	35.2	24.9	60.3	184.1	-27.9	1223.3	-143.6	413.1	251.1	50.6	94.7
7	40.2	253.0	81.8	-585.9	-201.2	744.5	-19.2	593.6	-117.2	11.5	14.6	34.0	29.7
8	-110.5	-	-217.9	273.1	-60.4	-185.4	-88.3	796.5	26.0	-64.1	5.3	-8.9	-37.2

		1093.4											
9													
10	-24.0	9.9	-58.8	-165.7	-18.2	-46.3	-53.8	107.6	-95.3	-76.3	-1.7	11.5	3.0
n	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	-32.8	142.6	-175.2	39.7	-201.6	91.2	-215.8	704.7	-213.7	-214.6	4.9	-4.0	16.3
stdev	49.7	800.5	307.1	382.1	319.2	388.0	343.3	551.2	322.4	641.5	149.4	48.6	61.0
SEM	20.3	326.8	125.4	156.0	130.3	158.4	140.1	225.0	131.6	261.9	61.0	19.8	24.9

Table 8B.79

Lac- flux			**exercise**				**recovery (min)**			
Subject	**R**	**e1**	**e2**	**e3**	**F**	**1**	**2**	**5**	**10**	**30**
1										
2										
3	-7.39	-700.20	-1652.79	-1190.61	-1086.09	-1071.87	-1233.78	-375.79	-219.05	-528.73
4										
5	-8.14	-95.65	-89.80	-105.07	-474.23	-147.80	-95.16	-119.98	-36.86	-43.72
6										
7	-1.30	-459.66	-635.44	-886.23	-404.00	-374.13	-155.93	-111.63	-106.11	-81.34
8	-5.98	-538.36	-654.43	-714.93	-687.44	-317.33	-239.37	-102.29	-22.05	-3.92
9										
10	4.88	-157.01	-217.09	25.16	-43.07	-95.50	-27.51	-30.25	-25.23	2.85
n	5	5	5	5	5	5	5	5	5	5
mean	-3.6	-390.2	-649.9	-574.3	-539.0	-401.3	-350.4	-148.0	-81.9	-131.0
stdev	5.4	256.9	613.8	518.8	384.0	392.2	500.0	132.2	84.0	224.9
SEM	2.4	114.9	274.5	232.0	171.7	175.4	223.6	59.1	37.6	100.6

Table 8B.80

Blac- flux			**exercise**				**recovery (min)**			
Subject	**R**	**e1**	**e2**	**e3**	**F**	**1**	**2**	**5**	**10**	**30**
1										
2										
3	0.25	-590.45	-920.62	-1470.73	-2869.59	-1459.28	-543.15	-335.83	-109.46	-8.62
4										
5	10.68	-65.16	-113.92	-333.40	-481.92	-152.09	-116.68	-125.19	-27.24	-21.23
6										
7	-5.70	-454.76	-642.83	-851.55	-618.76	-542.68	-172.13	-83.23	-0.64	-69.39
8	-6.66	-566.85	-355.85	-716.02	-796.98	-547.43	-207.71	-138.20	-3.08	-3.11
9										
10	-10.53	-417.01	-222.28	-14.26	-246.00	-177.40	-23.30	-24.60	-38.40	-7.37
n	5	5	5	5	5	5	5	5	5	5
mean	-2.4	-418.8	-451.1	-677.2	-1002.6	-575.8	-212.6	-141.4	-35.8	-21.9
stdev	8.3	210.8	328.8	552.1	1062.9	529.3	197.5	117.4	44.2	27.4
SEM	3.7	94.3	147.0	246.9	475.3	236.7	88.3	52.5	19.8	12.2

Table 8B.81

H+ flux				**exercise**					**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1													
2													
3	-144.4	-1264.4	-2930.6	-3098.5	-6417.1	-5188.6	-7822.7	-5762.4	-3933.5	-3099.5	-1588.4	-483.8	-141.1
4													
5	-81.2	-575.5	-425.4	-560.9	-632.1	-1294.1	-610.1	-3247.6	-665.0	-506.6	-537.8	-149.3	-68.7
6	-89.6	-992.8	-976.4	-1438.5	-881.8	-1306.8	-1153.8	-2229.9	-1072.7	-305.3	-133.9	-130.8	-36.6
7	-22.0	-955.5	-1176.5	-1807.2	-1433.1	-1796.8	-1757.6	-3396.7	-2114.6	-446.3	-231.2	-175.2	-61.5
8	-148.7	-1085.7	-822.7	-1235.3	-1480.0	-2398.3	-769.5	-4552.3	-1994.0	-915.0	-461.9	-106.9	-86.9
9													
10	-43.4	-635.5	-307.0	-644.1	-197.1	-735.0	-360.7	-1856.3	-526.4	-231.2	-148.1	-48.1	-29.0
n	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	-88.2	-918.3	-1106.4	-1464.1	-1840.2	-2119.9	-2079.1	-3507.5	-1717.7	-917.3	-516.9	-182.4	-70.6
stdev	51.5	265.4	952.1	930.6	2294.4	1603.8	2855.7	1457.0	1271.8	1095.2	550.6	153.9	40.5
SEM	21.0	108.4	388.7	379.9	936.7	654.7	1165.8	594.8	519.2	447.1	224.8	62.8	16.5

Table 8B.82

HCO3- flux				**exercise**					**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1													
2													

3	-98.0	-884.8	-859.84	-1388.5	-439.9	-1765.2	-1878.9	-1994.8	-735.3	-381.2	-401.4	-137.5	-167.2
4													
5	-66.3	-298.1	-191.27	-247.5	-203.9	-576.6	-115.9	-1252.9	-124.2	-99.2	-75.1	-58.3	-36.4
6	-61.9	-291.7	-232.65	-431.3	-280.0	-343.4	-269.6	-465.2	-113.5	27.2	-39.5	-53.7	-11.4
7	-33.2	-246.1	-279.43	-470.7	-357.7	-514.8	-536.2	-1170.5	-139.9	4.7	-27.6	-16.5	-23.4
8													
9													
10													
n	4	4	4	4	4	4	4	4	4	4	4	4	4
mean	-64.9	-430.2	-390.8	-634.5	-320.4	-800.0	-700.2	-1220.8	-278.3	-112.1	-135.9	-66.5	-59.6
stdev	26.5	304.0	314.8	512.0	101.5	651.0	804.8	625.4	304.9	187.6	178.1	50.9	72.5
SEM	13.3	152.0	157.4	256.0	50.7	325.5	402.4	312.7	152.5	93.8	89.1	25.5	36.2

Ion fluxes (Digoxin). Net ion fluxes into or out of forearm musculature for [K^+], [Na^+], [Cl^-], [Lac^-], [$Blac^-$], [H^+] and [HCO_3^-] at rest (R), during exercise (e1 to pe4), fatigue (F), and recovery (1 to 30min). Units are $\mu M.min^{-1}$ except for for [H^+] which is $pM.min^{-1}$.

Table 8B.83

K+ flux				**exercise**					**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1													
2													
3	3.1	-272.4	-18.2	-248.8	49.8	-198.9	13.0	-214.6	38.9	25.9	-8.3	-17.1	-2.3
4													
5	-3.1	-65.4	8.1	-26.4	13.2	-67.4	5.8	-198.5	5.6	2.0	-1.6	2.0	4.2
6	-4.5	-189.9	-5.0	-214.8	5.7	-183.6	-0.4	-86.5	9.2	11.4	-3.6	-3.0	1.6
7	1.8	-96.3	3.3	-128.8	17.8	-178.2	15.9	-121.4	40.2	19.7	8.5	1.4	-1.4
8	0.4	-235.3	10.8	-228.9	22.0	-192.1	15.1	-220.3	28.1	11.5	10.8	2.3	1.8
9													
10	-5.0		-23.4	-65.8	-4.0	-57.9	0.6						
n	6	5	6	6	6	6	6	5	5	5	5	5	5
mean	-1.2	-171.9	-4.1	-152.3	17.4	-146.3	8.3	-168.3	24.4	14.1	1.2	-2.9	0.8
stdev	3.4	88.8	14.1	92.7	18.3	65.3	7.3	60.5	16.3	9.1	8.2	8.2	2.6
SEM	1.4	39.7	5.8	37.9	7.5	26.6	3.0	27.1	7.3	4.1	3.6	3.7	1.2

Table 8B.84

Cl- flux				**exercise**					**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1													
2													
3	73.0	1081.9	126.3	517.2	509.5	1083.2	770.4	1453.8	492.1	-89.5	85.9	112.7	115.6
4													
5	0.8	931.0	-206.2	539.8	156.9	626.1	-63.0	-321.2	39.4	106.1	33.1	-42.4	30.8
6	19.2	902.6	179.7	783.9	316.4	241.2	108.5	964.8	109.7	81.8	-34.4	-21.3	50.9
7	8.6	265.6	100.3	287.5	168.1	670.0	-41.4	1063.9	152.5	-67.1	-2.2	10.1	6.3
8	17.8	523.1	147.6	1081.2	661.7	1079.5	93.8	1287.9	-84.3	80.8	34.6	8.9	36.2
9													
10	-25.9		239.7	487.3	121.9	555.1	78.4						
n	6	5	6	6	6	6	6	5	5	5	5	5	5
mean	15.6	740.9	97.9	616.1	322.4	709.2	157.8	889.8	141.9	22.4	23.4	13.6	48.0
stdev	32.6	336.1	156.6	277.3	219.8	325.0	308.7	703.4	215.3	92.8	45.1	59.6	41.1
SEM	13.3	150.3	63.9	113.2	89.7	132.7	126.0	314.6	96.3	41.5	20.2	26.7	18.4

Table 8B.85

Na+ flux				**exercise**					**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1													
2													
3	90.1	262.8	-667.7	-557.0	-500.2	-275.0	-651.8	261.3	-142.7	-509.9	-217.0	-50.8	-77.8
4													
5	-31.1	725.6	-197.0	80.4	49.6	-80.8	-72.2	-311.0	73.4	-72.1	10.0	-153.0	47.4
6	-11.0	526.3	-75.9	15.9	-73.5	-308.1	-315.9	-149.2	-246.4	-249.8	-211.7	-106.1	-18.6
7	-29.1	-75.5	-195.3	-203.1	-284.5	-426.1	-482.3	629.8	-385.1	-140.4	-101.2	-29.3	-2.5
8	-57.8	-194.8	-447.8	-87.0	-59.3	321.5	-141.7	610.6	-438.3	-144.9	-164.2	-36.6	-10.1

9													
10	-34.7		94.5	298.5	-49.5	196.4	-9.8						
n	6	5	6	6	6	6	6	5	5	5	5	5	5
mean	-12.2	248.9	-248.2	-75.4	-152.9	-95.3	-279.0	208.3	-227.8	-223.4	-136.8	-75.2	-12.3
stdev	52.3	389.4	271.4	290.1	202.4	298.7	251.3	430.0	204.6	172.3	94.4	52.9	44.7
SEM	21.4	174.1	110.8	118.4	82.6	121.9	102.6	192.3	91.5	77.1	42.2	23.7	20.0

Table 8B.86

Lac- flux			**exercise**				**recovery (min)**			
Subject	**R**	**e1**	**e2**	**e3**	**F**	**1**	**2**	**5**	**10**	**30**
1										
2										
3	0.16	-541.09	-804.59	-1200.42	-923.02	-283.72	-326.80	-252.53	-46.97	-0.55
4										
5	-25.62	-131.00	-75.94	73.36	-200.50	-146.95	59.75	-0.80	-13.57	-2.26
6										
7	4.68	-546.89	-598.44	-669.77	-554.19	-378.52	-246.70	-104.60	-48.51	-22.13
8	3.17	-283.07	-541.86	-668.68	-1411.30	216.04	-36.93	-146.95	8.93	-1.05
9										
10	-0.70		-96.68	-87.81						
n	5	4	5	5	4	4	4	4	4	4
mean	-3.7	-375.5	-423.5	-510.7	-772.3	-148.3	-137.7	-126.2	-25.0	-6.5
stdev	12.5	204.2	323.1	511.4	518.2	260.8	179.6	104.2	27.8	10.4
SEM	5.6	102.1	144.5	228.7	259.1	130.4	89.8	52.1	13.9	5.2

Table 8B.87

Blac- flux			**exercise**				**recovery (min)**			
Subject	**R**	**e1**	**e2**	**e3**	**F**	**1**	**2**	**5**	**10**	**30**
1										
2										
3	0.36	-726.31	-754.15	-1073.80	-797.26	-441.05	-326.75	-304.26	-114.94	6.99
4										
5	-9.71	-61.13	-177.60	-191.37	-265.79	-140.44	-83.31	-14.40	-20.53	-13.06
6										
7	0.44	-203.61	-773.18	-1140.01	-587.24	-811.98	-353.64	-150.33	-116.19	-91.83
8	6.31	-272.52	-423.16	-630.60	-2104.62	-374.76	-165.94	-164.08	29.99	79.00
9										
10	3.00		-23.44	-80.62						
n	5	4	5	5	4	4	4	4	4	4
mean	0.1	-315.9	-430.3	-623.3	-938.7	-442.1	-232.4	-158.3	-55.4	-4.7
stdev	6.0	287.4	336.1	487.6	807.4	278.3	129.4	118.5	72.5	70.2
SEM	2.7	143.7	150.3	218.1	403.7	139.1	64.7	59.2	36.2	35.1

Table 8B.88

H+ flux				**exercise**					**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1													
2													
3	-72.4	-2142.0	-2824.6	-3078.0	-3890.5	-2995.6	-5018.6	-3811.4	-1879.9	-1568.2	-1130.8	-412.2	-239.9
4													
5	-82.6	-551.4	-317.0	-793.1	-789.6	-1256.9	-251.5	-2197.2	-355.8	-578.8	-95.1	-109.7	-23.8
6	-69.2	-1000.4	-632.3	-1765.4	-1461.5	-1489.8	-1096.1	-2203.4	-665.7	-997.5	-385.3	-158.2	-58.0
7	-64.7	-910.3	-1211.0	-1729.9	-2078.7	-2317.7	-1635.3	-2995.4	-2335.2	-793.7	-340.7	-91.6	-52.4
8	-82.6	-2868.8	-2484.2	-3207.5	-2182.1	-2378.0	-945.0	-3862.9	-1277.2	-763.1	-680.2	-147.8	-63.9
9													
10	-45.4	-517.8	-456.7	-463.4	-326.4	-279.6	-344.3	-1446.4	-382.8	-284.6	-128.7	-46.0	-35.6
n	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	-69.5	-1331.8	-1321.0	-1839.5	-1788.1	-1786.3	-1548.5	-2752.8	-1149.4	-831.0	-460.1	-160.9	-78.9
stdev	13.8	956.9	1082.2	1132.4	1257.0	972.9	1774.9	972.5	825.5	433.4	390.2	129.6	80.2
SEM	5.6	390.6	441.8	462.3	513.2	397.2	724.6	397.0	337.0	176.9	159.3	52.9	32.8

Table 8B.89

HCO3- flux				**exercise**					**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**F**	**1**	**2**	**5**	**10**	**30**
1													
2													
3	-21.0	-843.2	-764.1	-838.4	-1077.6	-1039.3	-1295.7	-952.5	-270.2	-181.8	-200.0	-181.5	-116.9

4													
5	-76.6	-245.9	-117.6	-183.2	-241.0	-519.4	-43.8	-1615.6	-150.9	-118.5	-41.8	-10.9	6.7
6	-62.7	-490.5	-191.6	-743.8	-289.2	-651.1	-383.9	-959.4	-237.1	-124.9	-151.4	-76.7	-59.4
7	-42.1	-316.8	-229.3	-370.1	-333.5	-513.7	-315.6	-764.5	-299.6	-13.9	-7.2	-16.6	-23.9
8													
9													
10													
n	4	4	4	4	4	4	4	4	4	4	4	4	4
mean	-50.6	-474.1	-325.7	-533.9	-485.3	-680.9	-509.8	-1073.0	-239.5	-109.8	-100.1	-71.4	-48.4
stdev	24.3	266.7	296.0	309.1	396.7	247.2	544.2	372.8	64.3	70.0	90.6	79.2	53.1
SEM	12.1	133.3	148.0	154.5	198.3	123.6	272.1	186.4	32.2	35.0	45.3	39.6	26.5

Metabolism (Control). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [$Blac^-$], blood CO_2 content (CCO_2), blood O_2 content (CO_2); forearm muscle VCO_2 ($mVCO_2$) and VO_2 (mVO_2) at rest (R), during submaximal finger flexion exercise (e1 to e4+1) to fatigue (F), and recovery (1 to 30min). Units are mM for [$Blac^-$]; $ml.min^{-1}$ for CCO_2, CO_2, $mVCO_2$ and mVO_2. $[Blac^-]_{a-v}$ was corrected for arterio-venous ΔBV.

Table 8B.90

CCO2 art				**exercise**						**recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	653.0	623.9	627.7	637.9	606.6	624.2	647.6	635.2	639.1	625.3	634.8	626.5	625.2	612.2
2	669.1	608.5	661.1	627.6	650.7	627.9	648.1	635.4	647.2	620.7	655.2	623.2	617.4	598.6
3	705.0	692.4	739.6	715.2	730.4	653.7	656.4	643.2	643.2	669.0	683.9	640.0	663.1	645.4
4	666.5	685.3	741.0	761.6	815.8	808.4	835.0	839.0	747.3	705.3	722.3	832.1	862.8	828.3
5	651.5	662.3	663.4	667.8	660.5	658.8	654.1	653.8	611.7	648.8	636.9	637.6	622.7	619.8
6	626.4	679.7	642.8	682.8	645.7	687.2	683.0	683.9	667.0	679.2	695.1	666.6	672.8	694.3
7	694.1	696.8	690.2	665.7	684.1	659.5	656.4	651.5	636.8	670.4	655.2	639.5	679.2	686.9
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	666.5	664.2	680.8	679.8	684.8	674.3	682.9	677.4	656.0	659.8	669.1	666.5	677.6	669.4
stdev	26.7	34.8	45.0	46.1	69.1	62.8	68.1	73.1	43.4	30.2	32.5	74.4	85.6	79.1
SEM	10.1	13.2	17.0	17.4	26.1	23.7	25.7	27.6	16.4	11.4	12.3	28.1	32.3	29.9

Table 8B.91

CCO2 ven				**exercise**						**recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	742.2	757.5	743.7	742.4	702.0	740.5	726.4	718.2	753.5	698.1	685.3	628.3	653.8	671.1
2														
3	797.4	834.9	888.5	860.0	794.4	783.0	795.7	791.1	799.0	738.1	719.3	708.7	706.3	744.1
4														
5	733.6	752.0	783.3	759.4	771.4	764.2	713.4	747.3	758.4	723.0	704.7	671.4	683.1	664.1
6	713.7	791.2	802.7	794.2	805.4	786.4	800.6	786.0	791.0	724.3	719.3	715.1	735.1	753.1
7	794.6	835.9	871.3	791.7	815.7	799.0	837.0	787.9	868.0	718.6	649.8	664.1	699.9	732.0
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	756.3	794.3	817.9	789.5	777.8	774.6	774.6	766.1	794.0	720.4	695.7	677.5	695.6	712.9
stdev	37.7	40.4	60.8	45.1	45.4	22.8	52.7	32.2	45.9	14.5	29.2	35.4	30.0	42.1
SEM	16.9	18.1	27.2	20.2	20.3	10.2	23.5	14.4	20.5	6.5	13.1	15.8	13.4	18.8

Table 8B.92

CCO2 a-v				**exercise**						**recovery (min)**			
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-89.2	-133.6	-116.0	-104.5	-95.4	-116.4	-78.8	-83.0	-114.4	-72.8	-50.5	-1.8	-28.6	-59.0
2														
3	-92.5	-142.5	-148.9	-144.8	-64.0	-129.3	-139.4	-147.9	-155.8	-69.2	-35.3	-68.7	-43.2	-98.7
4														
5	-82.1	-89.6	-119.9	-91.6	-110.8	-105.4	-59.3	-93.5	-146.6	-74.2	-67.8	-33.8	-60.4	-44.3
6	-87.3	-111.5	-159.9	-111.4	-159.8	-99.2	-117.6	-102.1	-124.0	-45.1	-24.1	-48.5	-62.3	-58.8
7	-100.5	-139.0	-181.2	-126.0	-131.6	-139.5	-180.6	-136.3	-231.3	-48.3	5.4	-24.7	-20.7	-45.1
8														
9														

10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	-90.3	-123.2	-145.2	-115.7	-112.3	-117.9	-115.1	-112.6	-154.4	-61.9	-34.5	-35.5	-43.0	-61.2
stdev	6.8	22.3	27.5	20.5	36.2	16.6	48.3	28.1	46.1	14.1	27.7	25.1	18.6	22.2
SEM	3.0	10.0	12.3	9.2	16.2	7.4	21.6	12.6	20.6	6.3	12.4	11.2	8.3	9.9

Table 8B.93

CO2 art				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	184.8	181.4	179.3	181.4	197.5	189.7	197.3	188.6	205.1	200.1	211.0	212.7	197.5	206.1
2	192.8	194.6	195.9	195.4	195.8	195.5	195.2	195.6	195.6	197.9	198.1	194.7	192.7	192.7
3	167.7	169.7	172.2	172.2	172.2	173.3	175.0	174.9	174.8	171.1	174.0	170.5	170.5	170.4
4	189.2	190.5	190.6	191.8	191.5	192.6	193.0	194.3	198.9	199.5	198.2	192.4	187.9	191.5
5	201.0	198.2	198.2	198.9	198.9	198.4	198.7	200.4	201.9	200.9	201.7	201.1	198.6	198.6
6	201.2	197.9	198.6	199.7	197.1	199.7	198.4	195.8	197.6	198.8	194.1	198.6	198.2	194.1
7	190.9	193.8	192.7	195.5	195.3	195.0	196.7	190.6	197.5	198.1	198.0	194.6	193.2	190.1
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	189.7	189.4	189.6	190.7	192.6	192.0	193.5	191.5	195.9	195.2	196.4	195.0	191.2	191.9
stdev	11.4	10.4	10.1	10.2	9.3	8.9	8.4	8.2	9.8	10.7	11.2	12.7	9.9	10.9
SEM	4.3	3.9	3.8	3.9	3.5	3.4	3.2	3.1	3.7	4.0	4.2	4.8	3.7	4.1

Table 8B.94

CO2 ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	128.3	87.7	111.3	84.3	110.2	78.5	124.1	82.8	71.5	136.3	153.6	153.1	157.3	143.3
2														
3	124.6	129.3	79.5	95.9	72.6	98.1	73.2	115.6	83.0	140.1	152.7	142.5	150.6	138.6
4	133.2	65.6	119.2	78.9	113.4	59.3	135.1	70.7	76.0	159.5	181.1	177.9	178.1	169.8
5	141.3	151.3	96.5	100.6	94.7	111.0	99.2	113.4	96.6	99.8	136.7	129.3	161.7	165.2
6	153.0	78.4	132.2	71.2	134.1	69.6	134.7	73.7	108.1	164.6	172.3	171.0	161.0	167.1
7	121.0	131.1	81.5	133.3	76.4	153.8	74.5	145.9	105.2	167.4	177.9	162.2	156.5	141.5
8														
9														
10														
n	6	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	133.6	107.2	103.4	94.0	100.2	95.1	106.8	100.3	90.1	144.6	162.4	156.0	160.9	154.3
stdev	11.9	34.5	21.2	22.1	23.6	34.4	28.6	29.6	15.4	25.5	17.4	18.1	9.3	14.5
SEM	4.8	14.1	8.6	9.0	9.6	14.0	11.7	12.1	6.3	10.4	7.1	7.4	3.8	5.9

Table 8B.95

CO2 a-v				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	56.5	93.7	68.0	97.1	87.3	111.1	73.3	105.8	133.6	63.8	57.4	59.6	40.1	62.8
2														
3	43.2	40.4	92.7	76.3	99.6	75.2	101.8	59.3	91.8	31.0	21.3	28.0	20.0	31.8
4														
5	59.7	46.9	101.8	98.3	104.2	87.4	99.5	87.0	105.3	101.1	65.0	71.7	36.9	33.4
6	48.2	119.5	66.3	128.5	63.0	130.1	63.7	122.1	89.5	34.2	21.8	27.7	37.2	27.0
7	69.9	62.6	111.2	62.2	118.9	41.2	122.3	44.7	92.2	30.7	20.1	32.4	36.7	48.6
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	55.5	72.6	88.0	92.5	94.6	89.0	92.1	83.8	102.5	52.2	37.1	43.9	34.2	40.7
stdev	10.4	33.3	20.1	25.2	21.0	34.1	23.6	32.0	18.5	30.7	22.1	20.4	8.1	14.8
SEM	4.6	14.9	9.0	11.2	9.4	15.3	10.5	14.3	8.3	13.7	9.9	9.1	3.6	6.6

Table 8B.96

VmO2				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0.8	7.3	4.3	7.6	6.2	9.5	6.2	19.6	24.7	5.2	4.3	1.9	0.6	0.9
2														
3	1.8	13.4	23.0	40.4	48.5	50.7	60.2	40.3	62.4	12.9	7.4	6.8	2.4	2.3

4														
5	2.3	7.9	7.3	16.5	8.5	24.3	8.6	38.6	46.7	8.7	4.1	4.8	1.4	0.8
6	1.3	23.4	4.9	29.6	5.2	30.6	6.9	33.6	24.6	3.9	1.7	1.4	1.5	0.6
7	1.1	8.8	10.8	10.8	15.4	9.5	18.8	11.8	24.3	4.7	1.2	1.3	1.2	1.2
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	1.5	12.2	10.1	21.0	16.8	24.9	20.1	28.8	36.6	7.1	3.7	3.3	1.4	1.2
stdev	0.6	6.7	7.7	13.7	18.2	17.1	22.9	12.5	17.4	3.7	2.5	2.5	0.7	0.7
SEM	0.3	3.0	3.4	6.1	8.1	7.7	10.3	5.6	7.8	1.7	1.1	1.1	0.3	0.3

Table 8B.97

VmCO2				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.3	10.4	7.4	8.1	6.7	9.9	6.7	15.4	21.2	5.9	3.8	0.1	0.4	0.8
2														
3	3.8	47.2	37.0	76.6	31.2	87.2	82.4	100.5	105.9	28.7	12.3	16.7	5.1	7.1
4														
5	3.1	15.0	8.6	15.4	9.0	29.3	5.1	41.5	65.1	6.4	4.2	2.3	2.3	1.1
6	2.3	21.9	11.8	25.7	13.2	23.3	12.8	28.1	34.1	5.1	1.9	2.5	2.4	1.3
7	1.6	19.6	17.5	21.9	17.0	32.2	27.8	35.9	61.0	7.4	0.3	1.0	0.7	1.1
8														
9														
10														
n	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
mean	2.4	22.8	16.5	29.5	15.4	36.4	26.9	44.3	57.4	10.7	4.5	4.5	2.2	2.3
stdev	1.1	14.3	12.1	27.1	9.6	29.7	32.2	32.9	32.7	10.1	4.6	6.9	1.9	2.7
SEM	0.5	6.4	5.4	12.1	4.3	13.3	14.4	14.7	14.6	4.5	2.1	3.1	0.8	1.2

Table 8B.98

bLac-art			**exercise**				**recovery (min)**			
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.6	1.4	1.5	0.9	1.7	2.1	1.9	1.9	1.7	1.4
2	0.5	0.1	0.3	0.2	0.5	0.3	0.7	0.2	0.4	0.4
3	0.6	0.5	0.7	0.9	0.6	1.3	1.1	0.9	0.7	0.5
4	0.8	0.8	0.9	1.0	1.2	1.6	1.8	1.7	1.4	1.1
5	1.8	1.8	1.8	2.0	1.9	1.9	2.0	2.1	2.3	1.8
6										
7	0.6	0.6	0.7	1.4	1.2	1.7	0.9	1.5	1.2	1.3
8	0.9	1.6	1.9	1.6	2.5	1.8	2.2	2.2	2.9	1.3
9	1.4	0.1	1.0	1.4	1.0	2.2	1.3	0.6	3.0	1.0
10	1.4	1.4	2.1	2.6	1.6	2.0	2.4	3.1	2.2	2.0
n	9	9	9	9	9	9	9	9	9	9
mean	1.1	0.9	1.2	1.3	1.4	1.6	1.6	1.6	1.7	1.2
stdev	0.5	0.6	0.6	0.7	0.6	0.6	0.6	0.9	0.9	0.5
SEM	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.2

Table 8B.99

bLac- ven			**exercise**				**recovery (min)**			
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.9	2.9	2.5	2.5	3.0	4.4	2.7	4.0	3.0	2.2
2										
3	0.6	2.3	2.5	3.1	4.8	5.2	2.7	2.3	1.7	0.6
4										
5	1.5	2.2	2.5	3.2	3.0	3.6	3.9	4.0	3.0	2.7
6										
7	0.9	3.8	4.4	5.1	3.5	4.9	3.8	3.6	1.3	4.2
8	1.1	4.5	3.4	4.8	5.1	6.0	5.0	5.2	3.1	1.4
9	1.2	7.4	5.6	4.0	4.3	7.1	6.3	6.2	7.5	3.3
10	2.1	5.3	3.8	2.7	2.8	5.9	4.0	4.8	4.3	2.7
n	7	7	7	7	7	7	7	7	7	7
mean	1.3	4.1	3.5	3.6	3.8	5.3	4.0	4.3	3.4	2.4
stdev	0.5	1.9	1.2	1.0	0.9	1.1	1.3	1.3	2.1	1.2
SEM	0.2	0.7	0.4	0.4	0.4	0.4	0.5	0.5	0.8	0.4

Table 8B.100 bLac-a-v

		exercise				recovery (min)				
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1										
2										
3	0.0	-1.8	-1.7	-2.2	-4.2	-3.9	-1.6	-1.4	-0.9	-0.1
4										
5	0.3	-0.4	-0.7	-1.2	-1.1	-1.8	-1.9	-1.9	-0.7	-0.9
6										
7	-0.4	-3.2	-3.7	-3.7	-2.3	-3.2	-2.8	-2.1	0.0	-2.9
8	-0.2	-2.8	-1.5	-3.2	-2.6	-4.2	-2.7	-3.0	-0.2	-0.1
9										
10	-0.7	-3.9	-1.8	-0.1	-1.2	-3.9	-1.5	-1.6	-2.0	-0.6
n	5	5	5	5	5	5	5	5	5	5
mean	-0.2	-2.4	-1.9	-2.1	-2.3	-3.4	-2.1	-2.0	-0.8	-0.9
stdev	0.4	1.4	1.1	1.5	1.3	1.0	0.6	0.6	0.8	1.1
SEM	0.2	0.6	0.5	0.6	0.6	0.4	0.3	0.3	0.4	0.5

Metabolism (Digoxin). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [$Blac^-$], blood CO_2 content (CCO_2), blood O_2 content (CO_2); forearm muscle VCO_2 ($mVCO_2$) and VO_2 (mVO_2) at rest (R), during submaximal finger flexion exercise (e1 to e4+1) to fatigue (F), and recovery (1 to 30min). Units are mM for [$Blac^-$]; $ml.min^{-1}$ for CCO_2, CO_2, $mVCO_2$ and mVO_2. $[Blac^-]_{a-v}$ was corrected for arterio-venous ΔBV.

Table 8B.101

CCO2 art				exercise						recovery (min)				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	711.3	718.2	733.5	706.7	689.1	685.6	688.8	632.6	594.6	627.7	653.9	638.3	659.4	650.1
2	629.7	608.3	610.5	580.9	621.7	596.9	591.3	632.7	607.0	603.6	611.3	607.0	624.1	596.4
3	648.6	639.6	649.1	656.9	631.7	619.3	639.2	638.1	638.1	664.5	634.2	624.2	596.1	643.0
4	651.5	642.4	682.7	670.2	673.0	699.4	670.0	677.3	641.2	630.4	643.0	645.9	639.9	647.4
5	608.6	612.3	672.2	652.0	663.8	651.9	654.9	617.8	617.8	657.4	671.0	647.2	658.9	656.5
6	677.3	648.2	652.5	654.4	672.2	661.0	641.2	631.5	634.8	654.6	649.6	631.6	658.2	659.2
7	674.8	647.6	663.9	673.2	677.9	656.7	645.1	653.7	603.6	605.8	628.9	653.6	652.2	666.0
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	657.4	645.2	666.4	656.3	661.3	653.0	647.2	640.5	619.6	634.9	641.7	635.4	641.3	645.5
stdev	33.8	36.1	37.5	38.1	25.0	35.5	30.4	19.4	18.6	24.7	19.2	16.0	23.7	23.0
SEM	12.8	13.7	14.2	14.4	9.4	13.4	11.5	7.3	7.0	9.4	7.3	6.0	9.0	8.7

Table 8B.102

CCO2 ven				exercise						recovery (min)				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	790.9	822.5	805.3	836.7	789.0	833.6	780.9	760.1	729.7	701.7	697.9	720.3	731.6	698.6
2														
3	714.7	791.3	803.6	784.6	784.2	751.0	772.2	750.5	758.1	730.1	666.9	660.5	660.9	713.0
4														
5	720.0	715.6	728.8	757.2	760.2	751.4	705.3	788.4	788.4	770.5	738.5	753.6	648.2	659.1
6	773.7	801.8	870.7	807.3	813.1	769.6	831.3	777.1	811.9	782.5	695.1	738.6	734.2	749.9
7	766.6	843.5	852.5	816.2	819.0	768.4	740.8	764.8	788.5	676.7	622.0	641.9	674.4	724.6
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	753.2	794.9	812.2	800.4	793.1	774.8	766.1	768.2	775.3	732.3	684.1	703.0	689.8	709.0
stdev	33.9	48.6	55.1	30.6	23.7	34.0	47.0	14.8	31.9	44.8	43.1	49.2	40.4	33.7
SEM	15.2	21.8	24.6	13.7	10.6	15.2	21.0	6.6	14.3	20.0	19.3	22.0	18.1	15.1

Table 8B.103

CCO2 a-v				exercise						recovery (min)				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-79.6	-104.2	-71.8	-130.0	-100.0	-147.9	-92.1	-127.5	-135.0	-74.0	-44.0	-82.0	-72.2	-48.5

2														
3	-66.1	-151.6	-154.5	-127.7	-152.5	-131.7	-132.9	-112.4	-120.1	-65.5	-32.7	-36.4	-64.7	-70.0
4														
5	-111.5	-103.4	-56.6	-105.1	-96.4	-99.5	-50.3	-170.6	-170.6	-113.1	-67.5	-106.4	10.7	-2.6
6	-96.4	-153.5	-218.1	-152.9	-140.9	-108.5	-190.1	-145.7	-177.2	-127.9	-45.5	-107.0	-75.9	-90.8
7	-91.9	-195.9	-188.6	-143.0	-141.2	-111.7	-95.6	-111.1	-184.9	-70.9	6.8	11.8	-22.3	-58.6
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	-89.1	-141.7	-137.9	-131.7	-126.2	-119.9	-112.2	-133.4	-157.6	-90.3	-36.6	-64.0	-44.9	-54.1
stdev	17.2	38.9	71.2	18.0	26.0	19.6	52.4	25.0	28.4	28.2	27.3	51.2	37.8	32.8
SEM	7.7	17.4	31.8	8.1	11.6	8.8	23.5	11.2	12.7	12.6	12.2	22.9	16.9	14.7

Table 8B.104

CO2 art				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	199.9	186.6	185.7	189.2	188.2	191.1	189.8	194.1	198.5	195.7	191.7	193.7	187.5	192.9
2	194.8	202.4	197.1	203.2	200.4	201.2	201.3	191.8	201.8	200.2	197.4	201.3	199.6	195.1
3	166.6	168.8	170.1	171.4	173.1	173.4	173.4	174.8	175.1	173.7	174.2	171.7	170.3	172.1
4	191.5	193.2	192.3	192.5	188.6	192.9	190.5	191.2	195.5	195.5	195.9	193.0	192.5	193.4
5	192.5	189.1	193.1	195.6	193.8	195.8	194.9	197.1	197.5	193.4	196.7	194.8	189.2	195.3
6	201.0	203.1	202.0	205.5	203.4	205.2	205.9	206.4	207.9	208.0	208.1	205.1	204.6	206.1
7	194.5	198.0	198.8	200.2	201.5	200.8	204.5	201.0	202.5	204.3	205.6	201.7	199.5	196.3
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	191.5	191.6	191.3	194.0	192.7	194.4	194.3	193.8	197.0	195.8	195.7	194.5	191.9	193.0
stdev	11.5	11.8	10.7	11.5	10.6	10.5	11.2	10.0	10.5	11.1	11.0	11.0	11.4	10.2
SEM	4.4	4.5	4.1	4.3	4.0	4.0	4.2	3.8	4.0	4.2	4.2	4.2	4.3	3.9

Table 8B.105

CO2 ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	157.0	160.9	177.2	84.7	111.2	77.8	127.5	70.4	126.5	78.1	153.6	145.7	142.6	162.5
2														
3	131.1	66.7	103.0	75.4	116.7	78.1	119.3	121.0	83.2	132.9	145.5	151.9	146.6	114.8
4	132.2	132.7	129.0	142.7	138.6	138.3	147.2	143.0	150.2	150.8	165.4	171.3	160.3	165.9
5	143.5	152.2	102.9	111.4	106.3	129.0	105.3	111.4	103.1	127.3	121.4	157.0	175.8	177.7
6	113.0	117.4	57.2	100.8	62.3	143.2	60.9	139.7	67.5	90.2	146.7	140.4	155.2	134.1
7	115.7	74.2	113.3	71.7	127.4	75.5	130.2	76.3	78.6	142.6	153.0	151.4	133.6	113.9
8														
9														
10														
n	6	6	6	6	6	6	6	6	6	6	6	6	6	6
mean	132.1	117.4	113.8	97.8	110.4	107.0	115.1	110.3	101.5	120.3	147.6	153.0	152.4	144.8
stdev	16.6	39.4	39.2	26.7	26.3	33.0	29.9	31.0	31.7	29.4	14.7	10.6	14.8	27.6
SEM	6.8	16.1	16.0	10.9	10.7	13.5	12.2	12.6	12.9	12.0	6.0	4.3	6.1	11.3

Table 8B.106

CO2 a-v				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	43.0	25.7	8.5	104.6	77.0	113.3	62.4	123.7	71.9	117.6	38.1	48.0	44.9	30.4
2														
3	35.5	102.1	67.1	96.1	56.4	95.4	54.2	53.8	91.9	40.8	28.7	19.8	23.6	57.2
4														
5	49.0	36.9	90.2	84.2	87.5	66.8	89.6	85.7	94.4	66.1	75.4	37.7	13.4	17.7
6	87.9	85.6	144.8	104.7	141.0	62.1	145.0	66.7	140.4	117.8	61.3	64.7	49.4	71.9
7	78.8	123.8	85.5	128.4	74.1	125.2	74.3	124.8	123.9	61.7	52.6	50.3	65.9	82.4
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5

mean	58.8	74.8	79.2	103.6	87.2	92.6	85.1	90.9	104.5	80.8	51.2	44.1	39.4	51.9
stdev	23.1	42.1	49.0	16.2	32.1	27.8	36.1	32.5	27.3	35.0	18.5	16.7	21.0	27.3
SEM	10.3	18.8	21.9	7.3	14.4	12.5	16.1	14.5	12.2	15.7	8.3	7.5	9.4	12.2

Table 8B.107

VmO2				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0.5	2.3	0.5	7.0	5.4	12.8	5.7	23.7	13.8	5.0	0.5	0.8	1.6	0.4
2														
3	1.1	33.3	14.6	33.4	18.1	40.6	22.5	22.3	38.1	8.0	4.5	3.6	2.4	3.6
4														
5	1.4	5.7	7.4	13.7	10.9	17.9	3.9	37.0	40.8	5.1	5.8	0.7	0.5	0.3
6	2.7	15.7	6.9	26.4	15.3	16.2	13.2	18.9	39.8	9.2	4.8	2.8	1.5	1.9
7	1.6	11.5	5.2	21.2	8.4	34.3	9.0	29.2	29.0	10.5	4.7	2.2	1.3	1.3
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	1.5	13.7	6.9	20.4	11.6	24.4	10.9	26.2	32.3	7.6	4.1	2.0	1.5	1.5
stdev	0.8	12.1	5.1	10.4	5.1	12.3	7.4	7.1	11.4	2.5	2.0	1.2	0.7	1.3
SEM	0.4	5.4	2.3	4.6	2.3	5.5	3.3	3.2	5.1	1.1	0.9	0.6	0.3	0.6

Table 8B.108

VmCO2				**exercise**						**recovery (min)**				
Subject	**R**	**e1**	**pe2**	**e2**	**pe3**	**e3**	**pe4**	**e4+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.0	11.8	6.1	7.0	6.7	13.2	7.2	15.9	21.9	3.1	0.7	0.0	1.0	0.8
2														
3	2.9	46.6	32.4	50.3	20.6	55.0	57.8	61.4	64.7	13.6	5.5	12.4	4.5	6.1
4														
5	2.4	13.7	9.8	14.9	13.8	28.3	2.6	40.4	63.4	5.7	5.2	0.6	2.3	0.8
6	2.7	20.4	7.6	28.1	17.4	25.9	10.7	29.0	35.2	3.5	1.9	2.1	1.9	1.5
7	2.0	12.9	10.9	20.8	14.9	38.2	21.8	31.9	54.2	8.2	0.5	1.1	0.4	0.7
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	2.18	21.08	13.38	24.25	14.67	32.13	20.04	35.72	47.87	6.83	2.76	3.27	2.02	2.01
stdev	0.73	14.63	10.78	16.50	5.14	15.61	22.29	16.82	18.69	4.30	2.42	5.18	1.55	2.32
SEM	0.33	6.54	4.82	7.38	2.30	6.98	9.97	7.52	8.36	1.92	1.08	2.32	0.70	1.04

Table 8B.109

bLac- art			**exercise**					**recovery (min)**		
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1	0.3	0.3	0.2	0.2	0.6	0.4	0.9	0.6	0.4	1.8
2	0.9	0.9	1.1	1.3	1.5	1.8	1.2	1.1	1.2	0.9
3	1.0	0.7	1.1	1.1	1.3	1.6	1.2	1.3	1.5	1.0
4	1.2	1.1	0.8	1.1	0.6	1.0	1.5	1.0	0.9	0.7
5	2.8	2.9	2.7	2.9	3.0	3.0	2.9	2.7	2.5	2.7
6										
7	0.2	1.6	0.5	1.0	1.0	0.3	0.7	1.1	1.1	0.4
8	0.4	0.1	0.8	1.6	1.2	2.2	2.8	1.6	4.7	4.8
9	1.7	3.7	3.4	3.5	2.8	3.6	4.7	2.7	2.7	3.1
10	0.7	0.6		0.7				0.6		
n	9	9	8	9	8	8	8	9	8	8
mean	1.0	1.3	1.3	1.5	1.5	1.7	2.0	1.4	1.9	1.9
stdev	0.9	1.0	0.8	0.8	0.8	1.0	0.9	0.7	1.5	1.6
SEM	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.5	0.6

Table 8B.110

bLac- ven			**exercise**			**recovery (min)**				
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.0	1.4	1.5	1.4	1.7	1.7	0.9	0.8	0.9	2.3
2										
3	1.0	2.8	3.3	3.6	3.3	3.8	3.3	3.0	2.6	0.9
4										
5	3.2	3.4	3.8	3.7	3.7	4.9	4.0	3.5	3.1	3.4
6										

7	0.1	3.8	5.1	5.1	3.5	5.1	4.7	4.5	6.8	6.1
8	0.2	1.2	2.4	4.2	7.0	5.5	5.5	4.6	3.3	0.2
9	2.9	6.7	7.6	8.5	6.0	6.6	6.6	6.7	4.7	1.9
10	0.5	1.7	1.6	1.5	1.8	2.1	2.3	2.1	2.3	2.2
n	7	7	7	7	7	7	7	7	7	7
mean	1.3	3.0	3.6	4.0	3.8	4.2	3.9	3.6	3.4	2.4
stdev	1.3	1.9	2.2	2.4	2.0	1.8	1.9	1.9	1.9	1.9
SEM	0.5	0.7	0.8	0.9	0.8	0.7	0.7	0.7	0.7	0.7

Table 8B.111

bLac-a-v			**exercise**			**recovery (min)**				
Subject	**R**	**eb1**	**eb2**	**eb3**	**F**	**1**	**2**	**5**	**10**	**30**
1										
2										
3	0.0	-2.1	-2.2	-2.5	-1.9	-2.2	-2.1	-1.7	-1.1	0.1
4										
5	-0.3	-0.4	-1.1	-0.7	-0.6	-1.8	-1.1	-0.8	-0.5	-0.7
6										
7	0.0	-2.2	-4.7	-4.2	-2.5	-4.8	-4.0	-3.4	-5.8	-5.7
8	0.2	-1.2	-1.6	-2.6	-5.8	-3.3	-2.6	-3.0	1.4	4.7
9										
10	0.2	-1.1		-0.8				-1.5		
n	5	5	4	5	4	4	4	5	4	4
mean	0.0	-1.4	-2.4	-2.2	-2.7	-3.0	-2.4	-2.1	-1.5	-0.4
stdev	0.2	0.7	1.6	1.4	2.2	1.3	1.2	1.1	3.0	4.3
SEM	0.1	0.3	0.8	0.6	1.1	0.7	0.6	0.5	1.5	2.1

Appendix 8C Raw data Chapter 5 (Study 3)

Table 8C.1 Exercise and VO_2 variability trials

	33% VO2peak				67% VO2peak				90% VO2peak				fatigue time		
		Var 1	Var 2			Var 1	Var 2			Var 1	Var 2		Var 1	Var 2	
	PO	VO2	VO2		PO	VO2	VO2		PO	VO2	VO2				
Subject	(W)	(L.min)	(L.min)	CV%	(W)	(L.min)	(L.min)	CV%	(W)	(L.min)	(L.min)	CV%	sec	sec	CV%
1	42	0.95	0.94	0.7	145	2.13	2.06	2.4	214	3.41	3.37	0.8	573	530	5.5
2	50	1.23	1.12	6.6	185	2.73	2.66	1.8	276	3.56	3.75	3.7	356	285	15.7
3	48	0.99	1.01	1.4	159	2.14	2.21	2.3	234	2.91	3.32	9.3	307	300	1.6
4	61	1.24	1.19	2.9	205	2.82	2.77	1.3	303	3.97	3.87	1.8	315	289	6.1
5	49	1.03	1.03	0.0	170	2.42	2.46	1.2	252	3.37	3.78	8.1	308	307	0.2
6	81	1.50	1.58	3.7	212	3.16	3.21	1.1	300	4.50	4.68	2.8	375	381	1.1
7	76	1.58	1.58	0.0	251	3.65	3.83	3.4	369	4.14	4.64	8.1	148	145	1.4
8	79	1.38	1.71	15.1	213	2.97	3.18	4.8	303	3.73	3.94	3.9	225	282	15.9
9	67	1.09	1.07	1.3	181	2.37	2.25	3.7	257	3.57	3.31	5.3	579	610	3.7
10	48	0.97	1.06	6.3	159	1.59	1.64	2.2	234	2.16	2.17	0.3	230	257	7.8
n	10	10	10	10.0	10	10	10	10.0	10	10	10	10.0	10	10	10
mean	58.1	1.2	1.2	2.2	189.6	2.7	2.7	1.9	278.3	3.5	3.7	4.4	5.7	5.6	5.9
stdev	15.1	0.2	0.3	2.4	36.1	0.6	0.6	0.8	51.8	0.7	0.7	3.2	2.3	2.3	5.7
SEM	4.8	0.1	0.1	0.8	11.4	0.2	0.2	0.3	16.4	0.2	0.2	1.0	0.74	0.72	1.82

Table 8C.2 Digoxin and Control exercise trials: VO_2 and time to fatigue

	DIGOXIN				CONTROL			
	EB1 33% VO2peak	EB2 67% VO2peak	EB3	Fatigue time	EB1 33% VO2peak	EB2 67% VO2peak	EB3	Fatigue time
	VO2(l.min)	VO2(l.min)	90% VO2peak VO2(l.min)	sec	VO2(l.min)	VO2(l.min)	90% VO2peak VO2(l.min)	sec
Subject								
1	1.00	2.12	3.52	609	1.00	2.26	3.58	438
2	1.13	2.67	3.41	182	1.22	2.71	3.83	262
3	1.04	2.38	3.22	223	0.98	2.33	3.01	210
4	1.26	2.82	3.91	246	1.34	2.87	4.11	272
5	1.11	2.54	3.64	290	1.11	2.68	3.47	179
6	1.53	3.01	3.64	193.8	1.50	3.06	4.22	343
7	1.30	3.50	3.95	121	1.47	3.64	3.99	112
8	1.54	3.10		108	1.27	3.06		78
9	1.04	2.35	3.19	451	1.14	2.49	3.65	445
10	1.14	1.77		197	0.87	1.67	2.05	199
n	10	10	8	10	10	10	9	10
mean	1.21	2.63	3.61	266.40	1.19	2.68	3.55	253.80
SD	0.20	0.51	0.26	160.09	0.21	0.54	0.42	107.77
Sem	0.06	0.16	0.09	50.62	0.07	0.17	0.14	34.08

Fluid shifts (Control). Arterial (art) and venous (ven) Haemoglobin ([Hb]), hematocrit (Hct); changes from resting levels in arterial (art) and venous (ven) plasma volume (ΔPV) and blood volume (ΔBV); and changes in venous compared to arterial plasma (ΔPV_{a-v}) and blood volume (ΔBV_{a-v}) across the forearm calculated at rest (R), during submaximal cycling exercise (e1 to e3+1) to fatigue (F), and recovery (1 to 30min). Units are g dl^{-1} haemoglobin and % for Hct; percent change for ΔPV_a, ΔBV_a, ΔPV_{a-v}, ΔBV_{a-v}.

Table 8C.3

Hb art				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	14.1	14.6	14.4	14.3	14.5	15.2	14.6	14.8	15.8	15.6	15.5	15.3	15.2	14.0
2	15.3	15.4	15.4	15.2	15.7	16.5	16.2	16.5	17.3	16.9	16.8	16.5	16.2	15.2
3	13.5	13.7	13.7	13.7	13.9	14.2	14.1	14.1	14.9	14.6	14.3	13.7	13.8	13.0
4	14.6	14.9	14.9	14.8	15.0	16.0	15.7	16.1	16.6	16.2	16.2	16.0	15.6	14.7
5	15.5	15.5	15.5	15.5	15.6	16.5	16.3	16.7	17.6	17.1	17.0	16.6	16.3	15.5
6	15.4	15.9	15.7	15.6	16.1	16.9	16.9	17.4	17.5	17.2	17.4	16.0	15.3	14.7
7	16.1	15.9	15.6	15.9	17.1	17.4	16.6	17.1	17.5	17.5	17.5	16.7	16.5	15.5
8	15.0	15.3	15.0	15.0	15.3	15.7	15.5	15.8	16.3	16.2	16.1	15.9	15.6	14.7
9	14.1	14.5	14.6	14.5	14.8	15.5	15.2	15.6	15.8	15.3	15.2	15.2	14.9	14.1
10	13.2	13.4	13.2	13.0	13.3	13.7	13.5	13.8	14.0		13.5	13.3	13.2	12.7
n	10	10	10	10	10	10	10	10	10	9	10	10	10	10
mean	14.7	14.9	14.8	14.7	15.1	15.7	15.5	15.8	16.3	16.3	15.9	15.5	15.2	14.4
stdev	0.9	0.9	0.8	0.9	1.1	1.2	1.1	1.2	1.2	1.0	1.3	1.2	1.1	1.0
SEM	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.3	0.4	0.4	0.3	0.3

Table 8C.4

Hb ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	13.6	14.1	14.0	15.3	13.7	14.5	14.3	14.5	15.3	15.4	15.4	14.8	14.7	14.0
2														
3	13.5	13.6	13.4	13.7	13.5	14.0	14.4	14.5	14.3	14.8	12.8	14.3	14.1	12.9
4														
5	15.3	15.3	15.3	15.4	15.3	16.7	16.6	16.7	16.3	17.4	17.7	16.0	16.3	15.4
6	15.7	15.2	15.6	15.5	16.0	16.9	17.4	17.2	17.2	17.3	17.2	17.1	17.1	15.3
7	15.6	15.3	16.5	18.0	17.8	16.8	17.3	17.2	18.4	17.2	16.5	16.6	16.8	16.5
8	14.8	14.7	14.8	14.9	14.8	15.8	15.8	15.7	16.4	16.3	16.1	15.9	15.6	14.7
9	14.0	13.9	14.3	14.3	14.7	14.9	15.6	15.5	15.6	15.0	14.9	15.0	14.9	13.8
10	12.7	12.8	13.1	12.9	12.9	13.5	13.4	13.5	13.7	13.5	13.6	13.4	13.2	12.6
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8
mean	14.4	14.4	14.6	15.0	14.8	15.4	15.6	15.6	15.9	15.8	15.5	15.4	15.3	14.4
stdev	1.1	0.9	1.1	1.5	1.6	1.3	1.5	1.4	1.5	1.4	1.7	1.2	1.4	1.3
SEM	0.4	0.3	0.4	0.5	0.6	0.5	0.5	0.5	0.5	0.5	0.6	0.4	0.5	0.5

Table 8C.5

Hct art				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	40.8	41.9	42.0	40.9	42.2	43.9	42.5	42.8	46.4	45.9	45.8	45.6	44.7	40.8
2	42.0	42.8	43.5	42.2	44.3	46.4	45.3	46.6	49.2	48.7	48.0	47.5	46.7	42.9
3	39.6	39.5	39.3	38.6	40.3	41.4	40.5	40.4	42.5	42.0	41.4	38.8	40.0	37.4
4	41.3	42.0	42.3	41.9	43.0	46.0	44.9	46.1	47.7	46.8	47.0	46.7	45.2	42.3
5	43.1	43.0	42.8	43.2	43.4	45.8	45.8	47.1	49.8	48.4	48.4	47.6	45.9	43.3
6	40.9	42.5	41.7	41.9	42.7	45.6	46.5	47.0	47.5	46.8	46.9	44.8	44.0	40.5
7	42.0	41.6	42.2	41.2	42.2	43.9	41.5	45.0	48.3	49.0	48.7	46.8	47.0	42.6
8	42.4	43.2	43.1	42.9	44.1	45.0	45.0	45.5	47.4	47.3	46.8	46.7	45.1	41.2
9	39.6	40.7	41.0	40.8	41.8	44.5	43.2	43.4	44.8	44.5	43.7	44.3	42.6	33.9
10	38.3	39.0	38.3	38.3	37.9	39.3	39.6	40.6	41.2		40.0	39.7	38.2	36.5
n	10	10	10	10	10	10	10	10	10	9	10	10	10	10
mean	41.0	41.6	41.6	41.2	42.2	44.2	43.5	44.4	46.5	46.6	45.7	44.8	43.9	40.1
stdev	1.5	1.5	1.7	1.6	1.9	2.2	2.4	2.5	2.8	2.2	3.0	3.1	2.9	3.2
SEM	0.5	0.5	0.5	0.5	0.6	0.7	0.8	0.8	0.9	0.7	0.9	1.0	0.9	1.0

Table 8C.6

Hct ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	39.0	40.3	40.7	44.2	39.7	42.1	42.0	42.4	45.1	45.4	45.1	43.9	43.1	41.4
2														
3	39.2	39.1	38.4	39.3	38.8	40.4	40.8	41.2	41.3	42.2	36.1	41.6	41.3	36.5
4														
5	42.0	42.2	42.1	42.2	42.7	45.8	46.4	47.0	47.0	49.0	49.6	46.6	46.6	43.3
6	42.3	41.4	42.3	42.1	43.6	46.0	47.6	47.0	47.6	47.4	47.3	46.6	46.7	41.5
7	39.4	40.6	43.3	48.5	49.5	46.3	47.0	48.0	48.0	48.1	46.2	46.9	47.4	44.3
8	41.5	41.9	41.8	42.6	42.1	44.7	45.2	44.6	47.3	47.4	46.4	45.1	45.4	41.9
9	39.2	39.2	40.6	40.0	44.5	44.0	42.1	44.6	45.0	42.9	43.1	42.7	42.5	39.4
10	37.1	37.7	38.4	37.8	38.2	39.8	39.6	39.7	40.3	40.3	40.2	39.2	38.9	37.0
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8
mean	39.9	40.3	41.0	42.1	42.4	43.6	43.8	44.3	45.2	45.3	44.2	44.1	44.0	40.6
stdev	1.8	1.6	1.8	3.3	3.7	2.6	3.1	3.0	2.9	3.2	4.3	2.8	3.0	2.8
SEM	0.6	0.5	0.6	1.2	1.3	0.9	1.1	1.1	1.0	1.1	1.5	1.0	1.1	1.0

Table				**exercise**						**recovery (min)**				

8C.7

PV art													
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	-4.8	-3.8	-0.9	-4.5	-11.5	-5.8	-7.6	-19.0	-17.0	-16.4	-15.1	-13.1	1.3
2	0	-2.1	-3.2	0.1	-6.8	-14.3	-11.2	-14.7	-22.6	-19.9	-18.7	-16.4	-13.6	-1.2
3	0	-1.3	-0.6	0.1	-4.1	-8.0	-5.3	-5.6	-13.5	-11.0	-8.1	-0.5	-2.9	7.3
4	0	-3.3	-3.8	-2.4	-5.6	-16.1	-13.0	-16.8	-21.7	-18.3	-19.0	-17.2	-12.7	-3.0
5	0	0.2	0.9	0.1	-1.2	-10.5	-9.5	-13.8	-22.1	-17.8	-17.6	-13.8	-9.4	-0.1
6	0	-5.3	-3.4	-2.9	-7.1	-16.2	-17.4	-20.2	-21.6	-19.5	-20.1	-10.0	-4.5	5.6
7	0	1.6	2.9	2.4	-6.4	-10.4	-2.4	-10.9	-18.0	-19.1	-18.6	-11.8	-11.1	2.5
8	0	-3.1	-1.3	-0.6	-4.9	-8.9	-7.6	-10.3	-16.0	-15.1	-14.0	-12.8	-8.1	4.1
9	0	-4.1	-5.5	-4.2	-7.8	-16.4	-12.7	-15.3	-18.4	-15.3	-13.5	-14.4	-10.0	9.5
10	0	-2.2	0.5	1.6	-0.1	-4.9	-4.3	-7.8	-10.1		-4.9	-3.0	0.6	7.0
n	10	10	10	10	10	10	10	10	10	9	10	10	10	10
mean	0.0	-2.4	-1.7	-0.7	-4.9	-11.7	-8.9	-12.3	-18.3	-17.0	-15.1	-11.5	-8.5	3.3
stdev	0.0	2.2	2.6	2.0	2.5	3.9	4.7	4.6	4.1	2.8	5.1	5.6	4.8	4.1
SEM	0.0	0.7	0.8	0.6	0.8	1.2	1.5	1.5	1.3	0.9	1.6	1.8	1.5	1.3

Table 8C.8

PV ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	-5.4	-5.6	-18.9	-2.1	-10.6	-9.5	-11.5	-20.2	-20.9	-20.2	-15.2	-13.8	-6.7
2														
3	0	-0.9	1.6	-1.7	0.7	-5.8	-8.7	-10.0	-8.8	-13.5	11.0	-9.6	-7.6	9.3
4														
5	0	-0.3	-0.3	-0.8	-1.3	-14.2	-14.8	-16.4	-14.0	-22.7	-24.9	-12.1	-13.6	-3.0
6	0	4.3	0.1	1.3	-4.2	-13.0	-18.1	-16.2	-17.4	-17.3	-16.7	-15.3	-15.5	3.8
7	0	-0.5	-11.5	-26.4	-27.2	-17.9	-21.3	-22.3	-27.5	-22.3	-16.2	-17.6	-19.4	-13.3
8	0	-0.3	-0.9	-3.0	-1.4	-11.5	-12.6	-10.8	-18.8	-18.6	-16.1	-13.0	-11.5	-0.6
9	0	0.3	-4.7	-3.5	-13.4	-13.8	-14.9	-18.1	-19.2	-12.4	-12.4	-12.4	-11.5	0.8
10	0	-1.7	-5.1	-2.7	-3.3	-10.0	-8.6	-9.5	-11.8	-10.5	-11.0	-8.2	-6.6	1.4
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	-0.6	-3.3	-7.0	-6.5	-12.1	-13.6	-14.3	-17.2	-17.3	-13.3	-12.9	-12.4	-1.0
stdev	0.0	2.7	4.3	10.0	9.4	3.6	4.6	4.6	5.8	4.7	10.7	3.1	4.1	6.8
SEM	0.0	0.9	1.5	3.5	3.3	1.3	1.6	1.6	2.0	1.7	3.8	1.1	1.5	2.4

Table 8C.9

BV art				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	-3.0	-1.9	-0.8	-2.2	-6.7	-3.0	-4.3	-10.6	-9.2	-8.7	-7.6	-7.0	1.3
2	0	-0.7	-0.7	0.5	-2.9	-7.3	-5.9	-7.3	-11.6	-9.5	-9.2	-7.6	-5.9	0.3
3	0	-1.5	-1.1	-1.5	-2.9	-5.1	-3.9	-4.3	-9.1	-7.2	-5.3	-1.7	-2.2	3.6
4	0	-2.0	-2.0	-1.4	-2.7	-8.8	-7.3	-9.3	-12.1	-9.9	-10.2	-8.8	-6.4	-1.2
5	0	0.0	0.3	0.3	-0.6	-6.1	-4.9	-7.2	-11.7	-9.4	-9.0	-6.3	-4.6	0.3
6	0	-2.7	-1.9	-1.1	-4.2	-8.9	-8.7	-11.1	-11.6	-10.4	-11.1	-3.6	0.8	5.0
7	0	0.9	3.1	0.9	-6.1	-7.5	-3.3	-6.1	-8.0	-8.0	-8.0	-3.9	-2.7	3.5
8	0	-1.6	0.0	0.3	-2.0	-4.5	-3.2	-5.1	-8.0	-7.1	-6.8	-5.7	-3.5	2.0
9	0	-2.4	-3.4	-2.4	-4.4	-9.0	-7.2	-9.6	-10.8	-7.8	-7.2	-7.2	-5.4	0.0
10	0	-1.1	0.4	1.5	-0.8	-3.3	-2.2	-4.3	-5.7		-2.2	-0.8	0.4	3.9
n	10	10	10	10	10	10	10	10	10	9	10	10	10	10
mean	0.0	-1.4	-0.7	-0.4	-2.9	-6.7	-5.0	-6.9	-9.9	-8.7	-7.8	-5.3	-3.7	1.9
stdev	0.0	1.2	1.8	1.3	1.7	2.0	2.2	2.5	2.1	1.2	2.6	2.7	2.7	2.1
SEM	0.0	0.4	0.6	0.4	0.5	0.6	0.7	0.8	0.7	0.4	0.8	0.9	0.9	0.6

Table 8C.10

BV ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	-3.3	-2.9	-11.3	-0.9	-5.9	-4.9	-6.2	-11.3	-11.7	-11.4	-7.8	-7.5	-2.9
2														
3	0	-1.1	0.4	-1.5	0.0	-3.9	-6.3	-6.9	-5.6	-9.1	5.5	-5.9	-4.3	4.6
4														
5	0	0.0	0.0	-0.3	0.0	-8.1	-7.8	-8.4	-6.1	-12.1	-13.6	-4.4	-6.1	-0.6
6	0	2.8	0.1	1.0	-1.9	-7.1	-9.9	-8.7	-9.0	-9.3	-8.7	-8.5	-8.5	2.3
7	0	1.5	-5.4	-13.6	-12.7	-7.4	-10.1	-9.5	-15.6	-9.3	-5.7	-6.0	-7.2	-5.7
8	0	0.3	-0.3	-1.0	-0.3	-6.3	-6.6	-5.8	-9.8	-9.5	-8.4	-7.2	-5.1	0.1
9	0	0.4	-2.4	-2.1	-5.1	-6.4	-10.6	-10.0	-10.6	-6.7	-6.4	-7.0	-6.4	1.1
10	0	-0.8	-3.1	-1.6	-1.6	-5.9	-4.9	-5.6	-7.0	-5.6	-6.3	-5.0	-3.8	1.2
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8
mean	0.0	0.0	-1.7	-3.8	-2.8	-6.4	-7.6	-7.6	-9.4	-9.1	-6.9	-6.5	-6.1	0.0
stdev	0.0	1.8	2.1	5.4	4.3	1.3	2.3	1.7	3.3	2.2	5.7	1.4	1.6	3.2
SEM	0.0	0.6	0.7	1.9	1.5	0.4	0.8	0.6	1.2	0.8	2.0	0.5	0.6	1.1

Table 8C.11

PV a-v				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	7.1	6.5	5.1	-12.4	9.8	8.2	2.8	2.6	5.5	2.1	2.2	6.9	6.2	-1.4
2														
3	1.0	1.3	3.2	-0.9	5.9	3.3	-2.6	-3.7	6.4	-1.9	21.9	-8.3	-3.9	2.8

4														
5	3.3	2.7	2.1	2.3	3.1	-1.0	-2.8	0.2	13.6	-2.9	-5.9	5.4	-1.5	0.3
6	-3.8	6.0	-0.4	0.4	-0.8	-0.2	-4.6	1.1	1.4	-1.2	0.4	-9.5	-14.8	-5.5
7	7.7	5.5	-7.3	-3.0	-3.1	-1.3	-13.1	-6.1	-4.8	3.5	10.9	0.7	-2.4	-8.8
8	3.3	6.2	3.7	0.9	7.0	0.2	-2.3	2.6	-0.2	-1.0	0.8	3.0	-0.5	-1.4
9	1.9	6.5	2.8	2.7	-4.2	5.0	-0.7	-1.5	0.9	5.4	3.2	4.2	0.2	-6.3
10	6.0	6.5	0.1	1.5	2.6	0.4	1.2	4.2	4.0		-0.7	0.4	-1.6	0.5
n	8	8	8	8	8	8	8	8	8	7	8	8	8	8
mean	3.3	5.2	1.2	-1.1	2.5	1.8	-2.8	-0.1	3.4	0.6	4.1	0.4	-2.3	-2.5
stdev	3.8	2.0	3.9	4.9	5.0	3.4	4.8	3.5	5.5	3.1	8.6	6.1	5.9	4.0
SEM	1.3	0.7	1.4	1.7	1.8	1.2	1.7	1.2	1.9	1.2	3.0	2.2	2.1	1.4

Table 8C.12

BV a-v				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-0.5	-0.5	-0.6	-2.1	-0.3	-0.3	-0.7	-0.7	-0.5	-0.8	-0.9	-0.4	-0.5	-1.1
2														
3	-0.9	-0.9	-0.8	-1.0	-0.5	-0.8	-1.3	-1.4	-0.4	-1.3	0.5	-1.6	-1.3	-0.8
4														
5	-0.8	-0.8	-0.9	-0.9	-0.7	-1.2	-1.3	-1.0	0.3	-1.3	-1.7	-0.4	-1.1	-1.0
6	-1.2	-0.4	-0.9	-0.9	-0.9	-0.9	-1.5	-0.8	-0.7	-1.0	-0.8	-2.1	-2.8	-1.6
7	-0.5	-0.4	-1.9	-3.1	-1.7	-0.4	-1.7	-1.1	-2.0	-0.7	-0.1	-0.9	-1.3	-2.0
8	-0.8	-0.4	-0.8	-1.0	-0.5	-1.1	-1.3	-0.9	-1.1	-1.2	-1.0	-1.0	-1.0	-1.0
9	-0.9	-0.5	-0.7	-0.8	-0.9	-0.4	-1.4	-0.9	-0.8	-0.6	-0.7	-0.8	-1.0	-0.7
10	-0.5	-0.5	-0.9	-0.9	-0.6	-0.9	-0.9	-0.6	-0.7		-1.1	-1.1	-1.1	-0.9
n	8	8	8	8	8	8	8	8	8	7	8	8	8	8
mean	-0.8	-0.5	-0.9	-1.3	-0.8	-0.7	-1.3	-0.9	-0.7	-1.0	-0.7	-1.0	-1.2	-1.1
stdev	0.3	0.2	0.4	0.8	0.4	0.3	0.3	0.2	0.6	0.3	0.7	0.6	0.7	0.4
SEM	0.1	0.1	0.1	0.3	0.2	0.1	0.1	0.1	0.2	0.1	0.2	0.2	0.2	0.2

Fluid Shifts (Digoxin). Arterial (art) and venous (ven) Haemoglobin ([Hb]), hematocrit (Hct); changes from resting levels in arterial (art) and venous (ven) plasma volume (ΔPV) and blood volume (ΔBV); and changes in venous compared to arterial plasma (ΔPV_{a-v}) and blood volume (ΔBV_{a-v}) across the forearm calculated at rest (R), during submaximal cycling exercise (e1 to e3+1) to fatigue (F), and recovery (1 to 30min). Units are g dl^{-1} haemoglobin and % for Hct; percent change for ΔPV_a, ΔBV_a, ΔPV_{a-v}, ΔBV_{a-v}.

Table 8C.13

Hb art				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	14.6	14.7	14.6	14.4	14.7	14.9	14.6	15.7	15.6	15.5	15.4	15.3	14.8	14.6
2	15.6	16.8	17.1	17.0	17.1	17.1	17.9	18.4	17.9	17.1	16.5	16.0	15.7	14.7
3	13.5	13.6	13.6	13.5	13.7	14.1	14.1	14.4	14.9	15.0	14.7	14.3	14.0	13.0
4	15.1	15.7	15.3	15.1	15.4	16.2	15.8	16.2	16.9	16.6	16.7	16.2	15.7	15.1
5	15.2	15.3	15.3	15.3	15.4	16.7	16.5	16.7	17.4	17.0	17.0	16.8	16.3	15.4
6	15.9	16.3	16.4	16.3	16.6	17.6	17.6	17.8	18.1	17.9	18.0	17.8	17.3	15.9
7	15.5	15.8	15.6	15.5	15.9	16.8	16.7	16.7	17.2	17.1	17.2	16.9	16.5	15.4
8	13.5	13.8	13.6	13.7	13.8	14.4	14.3	14.5	15.0	14.8	14.6	14.5	14.2	13.3
9	14.8	15.3	15.3	15.3	15.6	16.4	15.7	16.2	16.5	15.9	15.7	15.5	15.2	14.6
10	12.4	11.8	12.7	12.7	12.4	13.0	12.1					12.9		
n	10	10	10	10	10	10	10	9	9	9	9	10	9	9
mean	14.6	14.9	14.9	14.9	15.0	15.7	15.5	16.3	16.6	16.3	16.2	15.6	15.5	14.6
stdev	1.1	1.5	1.3	1.3	1.4	1.5	1.8	1.3	1.2	1.1	1.1	1.4	1.1	0.9
SEM	0.4	0.5	0.4	0.4	0.4	0.5	0.6	0.4	0.4	0.4	0.4	0.5	0.4	0.3

Table 8C.14

Hb ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	14.4	14.4	15.4	15.2	14.8	15.1	15.2	16.1	16.0	16.8	16.5	15.7	15.7	14.9
2														
3	13.2	13.4	13.5	13.6	13.6	14.4	14.3	13.9	14.7	14.9	14.6	14.4	14.4	13.2
4														
5	15.1				15.2	16.6	16.7					17.0		15.9
6	15.8	15.8	15.6	15.9	15.9	17.4	17.3	17.6	17.7	18.1	17.3	17.3	17.2	15.8
7	15.0	15.4	15.4	15.4	15.3	16.8	16.5	16.8	17.0	16.8	16.7	16.7	16.4	15.3
8	13.5	13.4	13.5	13.4	13.5	14.3	14.1	14.1	14.9	14.8	14.7	14.4	14.0	13.3
9	14.5	14.7	14.9	15.0	14.3	16.1	16.1	15.3	16.1	16.1	15.9	15.3	15.1	14.7
10	12.2	12.3	12.7	12.5	12.5	12.9	12.8	13.0	12.8	12.9	12.9	12.6		
n	8	7	7	7	8	8	8	7	7	7	7	8	6	7
mean	14.2	14.2	14.4	14.4	14.3	15.4	15.4	15.2	15.6	15.8	15.5	15.4	15.4	14.7
stdev	1.2	1.2	1.2	1.3	1.1	1.5	1.5	1.7	1.6	1.7	1.5	1.6	1.2	1.1
SEM	0.4	0.5	0.4	0.5	0.4	0.5	0.5	0.6	0.6	0.6	0.6	0.6	0.5	0.4

Table 8C.15

Hct art				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	41.4	41.8	41.5	41.2	42.7	42.8	42.0	45.5	45.0	45.2	44.4	44.1	41.3	41.2
2	41.9	45.5	47.1	45.9	46.8	47.2	49.3	50.7	49.9	46.4	46.6	45.0	44.2	42.5

3	39.3	40.0	39.8	39.7	40.7	41.0	41.8	42.3	44.1	46.4	43.4	42.5	41.0	38.3
4	51.5	43.3	42.6	42.1	42.8	45.5	44.2	46.2	48.4	47.4	47.0	46.5	44.9	42.7
5	42.3	43.1	42.7	42.6	43.3	47.2	46.6	47.1	50.1	48.7	48.2	48.2	47.0	42.8
6	42.5	43.3	43.7	43.6	44.5	47.7	47.7	48.0	48.3	48.7	48.6	47.9	46.7	42.3
7	44.3	44.4	43.6	43.5	44.7	47.7	46.5	47.7	49.0	49.1	48.8	48.3	46.9	43.3
8	38.5	38.9	39.4	39.3	39.2	42.1	40.9	41.8	43.9	43.3	42.8	42.9	41.0	38.5
9	41.4	42.7	42.2	42.8	43.6	45.9	44.7	45.9	46.7	45.7	45.1	43.9	43.4	41.1
10	35.0	33.9	36.2	36.2	35.7	37.8	35.1					37.8		
n	10	10	10	10	10	10	10	9	9	9	9	10	9	9
mean	41.8	41.7	41.9	41.7	42.4	44.5	43.9	46.1	47.3	46.7	46.1	44.7	44.0	41.4
stdev	4.3	3.4	2.9	2.7	3.1	3.4	4.1	2.8	2.4	1.9	2.3	3.2	2.5	1.8
SEM	1.4	1.1	0.9	0.9	1.0	1.1	1.3	0.9	0.8	0.6	0.8	1.0	0.8	0.6

Table 8C.16

Hct ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	41.4	41.3	42.7	42.5	42.1	42.2	43.0	45.4	45.2	47.7	45.6	44.1	43.6	41.6
2														
3	39.7	40.1	40.2	40.6	40.1	42.3	42.3	41.3	43.7	43.7	42.6	42.4	42.4	38.8
4														
5	42.4				42.3	47.1	47.6					48.3		44.3
6	42.1	42.2	42.2	43.1	42.8	46.9	46.3	47.2	47.7	49.1	47.1	46.6	46.6	42.3
7	42.3	44.4	43.4	43.4	43.8	47.7	46.7	47.3	48.6	47.8	47.7	47.9	47.1	43.6
8	37.7	38.6	38.1	38.2	38.4	40.9	40.5	40.0	42.9	42.6	42.5	42.0	40.9	38.5
9	40.5	40.9	41.5	41.7	40.3	45.5	45.1	44.4	45.4	45.0	44.8	43.7	43.7	41.6
10	35.2	35.3	36.2	35.6	36.3	37.6	36.6		38.2	37.3	37.6	37.0	36.4	
n	8	7	7	7	8	8	8	6	7	7	7	8	7	7
mean	40.1	40.4	40.6	40.7	40.7	43.7	43.5	44.3	44.5	44.7	44.0	44.0	42.9	41.5
stdev	2.6	2.9	2.6	2.9	2.5	3.6	3.7	3.0	3.4	4.0	3.5	3.7	3.6	2.2
SEM	0.9	1.1	1.0	1.1	0.9	1.3	1.3	1.2	1.3	1.5	1.3	1.3	1.4	0.8

Table 8C.17

PV art				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	-1.4	-0.1	1.7	-2.9	-3.9	-0.7	-13.2	-11.9	-11.9	-10.0	-8.7	-0.8	1.4
2	0	-12.6	-16.9	-14.7	-16.3	-17.0	-23.7	-28.0	-24.6	-15.5	-13.1	-7.7	-4.6	5.0
3	0	-1.9	-1.6	-0.3	-3.7	-6.5	-8.1	-10.6	-16.3	-20.5	-14.4	-10.8	-6.3	5.6
4	0	12.5	16.8	19.4	15.7	4.8	9.8	3.2	-5.4	-1.6	-1.0	2.7	9.1	18.4
5	0	-2.1	-1.4	-0.9	-3.1	-16.5	-14.6	-16.6	-24.4	-20.5	-19.6	-18.6	-14.3	-2.2
6	0	-3.4	-5.1	-3.9	-7.2	-17.8	-17.6	-19.2	-20.8	-20.5	-20.8	-19.0	-14.8	0.7
7	0	-2.2	0.3	1.1	-3.2	-13.6	-11.0	-13.2	-17.7	-17.4	-17.3	-15.0	-10.5	2.4
8	0	-2.4	-2.2	-2.7	-3.3	-11.7	-9.3	-11.8	-17.9	-15.9	-14.0	-13.6	-8.5	1.5
9	0	-5.1	-4.5	-5.2	-8.5	-16.6	-11.2	-15.6	-18.0	-13.7	-11.6	-8.5	-5.8	2.4
10	0	6.4	-4.6	-4.5	-1.6	-9.2	1.9					-8.1		
n	10	10	10	10	10	10	10	9	9	9	9	10	9	9
mean	0.0	-1.2	-1.9	-1.0	-3.4	-10.8	-8.4	-13.9	-17.5	-15.3	-13.5	-10.7	-6.3	3.9
stdev	0.0	6.7	8.2	8.6	8.0	7.3	9.8	8.3	6.0	6.0	5.9	6.3	7.3	5.9
SEM	0.0	2.1	2.6	2.7	2.5	2.3	3.1	2.8	2.0	2.0	2.0	2.0	2.4	2.0

Table 8C.18

PV ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	-0.1	-8.5	-7.1	-3.8	-6.3	-8.1	-16.7	-16.1	-23.7	-19.2	-12.7	-11.7	-3.9
2														
3	0	-1.9	-3.0	-4.5	-3.3	-12.3	-11.4	-7.4	-16.2	-17.3	-14.0	-12.1	-12.1	1.4
4														
5	0				-0.5	-16.7	-18.0					-20.6		-8.2
6	0	0.0	1.0	-2.4	-1.8	-16.6	-15.1	-18.0	-19.2	-23.1	-16.6	-15.7	-15.1	-0.1
7	0	-6.5	-4.9	-4.9	-4.5	-19.4	-16.1	-18.6	-21.7	-19.5	-18.7	-19.2	-16.2	-4.3
8	0	-0.7	-0.6	-0.1	-1.0	-10.5	-8.9	-8.1	-17.0	-16.0	-15.2	-12.7	-8.8	0.2
9	0	-2.4	-4.5	-5.7	1.4	-17.7	-17.3	-9.6	-17.7	-17.0	-15.7	-10.3	-9.6	-3.4
10	0	-1.0	-5.4	-3.0	-4.1	-9.3	-7.1		-9.5	-8.9	-9.5	-5.9		
n	8	7	7	7	8	8	8	6	7	7	7	8	6	7
mean	0.0	-1.8	-3.7	-3.9	-2.2	-13.6	-12.8	-13.1	-16.8	-17.9	-15.6	-13.7	-12.3	-2.6
stdev	0.0	2.2	3.2	2.3	2.1	4.7	4.4	5.2	3.7	5.0	3.2	4.8	2.9	3.3
SEM	0.0	0.8	1.2	0.9	0.7	1.7	1.6	2.1	1.4	1.9	1.2	1.7	1.2	1.3

Table 8C.19

BV art				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	-0.7	0.0	1.4	-0.7	-1.7	0.3	-6.7	-6.1	-5.8	-5.2	-4.3	-1.0	0.4
2	0	-6.9	-8.8	-8.4	-8.7	-8.8	-12.7	-15.2	-12.6	-8.5	-5.5	-2.5	-0.6	6.1
3	0	-0.7	-0.7	0.4	-1.5	-3.9	-4.3	-5.9	-9.1	-9.3	-8.2	-5.8	-3.6	3.8
4	0	-3.8	-1.3	0.1	-2.0	-6.7	-4.7	-7.0	-11.0	-9.3	-9.5	-7.0	-4.1	0.1
5	0	-0.7	-0.7	-0.3	-1.3	-8.7	-7.6	-9.0	-12.6	-10.6	-10.3	-9.3	-6.6	-1.3
6	0	-2.2	-3.0	-2.2	-3.9	-9.7	-9.4	-10.7	-11.9	-10.9	-11.4	-10.7	-8.1	0.3
7	0	-1.9	-1.0	-0.3	-2.5	-8.0	-7.2	-7.5	-10.2	-9.6	-9.9	-8.3	-6.1	0.7
8	0	-1.8	-0.7	-1.5	-2.2	-6.3	-5.6	-6.9	-10.0	-8.8	-7.5	-6.9	-4.6	1.5
9	0	-3.0	-3.3	-3.0	-4.9	-9.8	-5.9	-5.9	-10.0	-6.9	-5.7	-4.5	-2.6	1.7

10	0	4.7	-2.8	-2.8	-0.4	-5.0	2.1					-3.9		
n	10	10	10	10	10	10	10	9	9	9	9	10	9	9
mean	0.0	-1.7	-2.2	-1.7	-2.8	-6.9	-5.5	-8.3	-10.4	-8.9	-8.1	-6.3	-4.1	1.5
stdev	0.0	2.9	2.6	2.8	2.5	2.7	4.3	3.0	2.0	1.6	2.3	2.6	2.5	2.2
SEM	0.0	0.9	0.8	0.9	0.8	0.8	1.4	1.0	0.7	0.5	0.8	0.8	0.8	0.7

Table 8C.20

BV ven				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0	-0.3	-6.5	-5.3	-2.7	-5.0	-5.6	-10.6	-10.3	-14.6	-13.0	-8.3	-8.3	-3.4
2														
3	0	-1.1	-2.2	-2.9	-2.6	-8.3	-7.4	-4.8	-10.2	-11.4	-9.6	-8.0	-8.0	0.0
4														
5	0				-0.7	-9.3	-9.9					-11.5		-5.0
6	0	0.1	1.1	-0.8	-0.6	-9.1	-8.6	-10.1	-10.7	-12.6	-8.8	-8.6	-8.0	0.1
7	0	-2.9	-2.9	-2.9	-2.0	-11.0	-9.1	-10.7	-12.1	-11.0	-10.2	-10.5	-8.6	-2.0
8	0	0.7	0.0	0.7	0.0	-5.6	-4.6	-4.6	-9.4	-8.8	-8.2	-6.3	-3.9	1.5
9	0	-1.7	-2.8	-3.7	1.0	-10.2	-10.4	-3.9	-7.6	-10.2	-9.1	-5.2	-4.5	-1.7
10	0	-0.8	-4.0	-2.4	-2.4	-5.8	-5.1	-6.2	-5.1	-5.8	-6.0	-3.2		
n	8	7	7	7	8	8	8	7	7	7	7	8	6	7
mean	0.0	-0.9	-2.5	-2.5	-1.2	-8.1	-7.6	-7.3	-9.3	-10.6	-9.3	-7.7	-6.9	-1.5
stdev	0.0	1.2	2.5	2.0	1.4	2.3	2.3	3.1	2.3	2.8	2.1	2.7	2.1	2.2
SEM	0.0	0.5	0.9	0.7	0.5	0.8	0.8	1.2	0.9	1.1	0.8	1.0	0.9	0.8

Table 8C.21

PV a-v				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.7	3.0	-6.8	-7.1	0.8	-0.7	-5.8	-2.4	-3.1	-11.9	-8.6	-2.8	-9.5	-2.4
2														
3	1.7	1.7	0.2	-2.6	2.0	-4.6	-2.0	5.3	1.8	5.8	2.1	0.1	-4.7	-2.3
4														
5	0.8				3.5	0.5	-3.2					-1.7		-5.3
6	1.5	5.2	8.0	3.1	7.4	3.1	4.6	3.1	3.6	-1.9	6.9	5.7	1.2	0.7
7	7.1	2.4	1.6	0.7	5.6	-0.1	0.8	0.5	2.0	4.4	5.2	1.7	0.2	0.1
8	1.7	3.4	3.3	4.4	4.0	3.1	2.1	5.9	2.8	1.6	0.3	2.6	1.3	0.4
9	4.0	7.0	4.0	3.6	15.3	2.6	-3.1	8.8	4.5	0.0	-0.7	2.0	-0.2	-1.9
10	1.3	-5.6	0.5	3.0	-1.3	1.2	-7.7					3.8		
n	8	7	7	7	8	8	8	6	6	6	6	8	6	7
mean	2.5	2.4	1.5	0.7	4.7	0.6	-1.8	3.5	1.9	-0.3	0.9	1.4	-1.9	-1.5
stdev	2.1	4.0	4.5	4.2	5.1	2.6	4.1	4.0	2.7	6.3	5.5	2.8	4.3	2.1
SEM	0.7	1.5	1.7	1.6	1.8	0.9	1.4	1.6	1.1	2.6	2.2	1.0	1.8	0.8

Table 8C.22

BV a-v				**exercise**						**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-0.8	-0.7	-1.8	-1.8	-1.1	-1.3	-1.7	-1.4	-1.5	-2.3	-2.1	-1.4	-1.9	-1.3
2														
3	-0.7	-0.8	-0.9	-1.2	-0.9	-1.4	-1.2	-0.5	-0.9	-0.9	-0.9	-1.0	-1.4	-1.2
4														
5	-0.9				-0.8	-1.0	-1.3					-1.3		-1.5
6	-0.9	-0.5	-0.2	-0.7	-0.3	-0.8	-0.7	-0.8	-0.6	-1.2	-0.4	-0.4	-0.8	-0.9
7	-0.5	-0.7	-0.8	-0.9	-0.4	-1.0	-0.8	-1.1	-0.8	-0.7	-0.5	-0.8	-0.9	-0.9
8	-0.9	-0.6	-0.9	-0.7	-0.6	-0.9	-0.8	-0.6	-0.9	-0.9	-1.1	-0.9	-0.9	-0.9
9	-0.6	-0.4	-0.6	-0.8	0.3	-0.7	-1.4	-0.1	-0.7	-1.2	-1.2	-0.8	-0.9	-1.2
10	-0.8	-1.5	-1.0	-0.8	-1.1	-0.9	-1.7					-0.7		
n	8	7	7	7	8	8	8	6	6	6	6	8	6	7
mean	-0.8	-0.7	-0.9	-0.9	-0.6	-1.0	-1.2	-0.7	-0.9	-1.2	-1.0	-0.9	-1.1	-1.1
stdev	0.1	0.3	0.5	0.4	0.4	0.2	0.4	0.4	0.3	0.6	0.6	0.3	0.4	0.2
SEM	0.1	0.1	0.2	0.1	0.2	0.1	0.1	0.2	0.1	0.2	0.3	0.1	0.2	0.1

Electrolytes (Control). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [K^+], [Na^+], [Cl^-], [Lac^-] and [SID] at rest (R), during submaximal cycling exercise (e1 to e3+1) to fatigue (F), and recovery (1 to 30min). Units are mM; a-v has been corrected for the arterio-venous ΔPV.

Table 8C.23

K+ art			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	4.16	4.26	4.25	4.2	4.47	4.89	4.19	4.75	7.29	5.19	4.4	4.1	4.04	4.02
2	4	4.1	4.15	4.26	4.63	5.24	3.74	4.57	6.93	4.88	3.79	3.5	3.5	3.83
3	4.06	4.03	4.23	4.08	4.31	4.9	4.27	4.3	6.13	4.93	4.2	3.78	3.76	3.52
4	3.77	3.81	4.02	3.87	4.23	5.15	3.92	5.31	7.41	4.82	4.22	3.65	3.78	3.85
5	3.93	4.24	4.22	4.15	4.52	5.01	4.21	4.93	6.51	4.71	3.92	3.79	4.15	4.21
6	3.75	4.20	3.96	3.81	4.45	5.19	3.9	4.56	6.5	5.1	4.02	3.43	3.61	3.6
7	3.97	4.24	4.28	4.21	4.39	5.01	4.06	4.5	7.26	5.14	3.89	3.7	3.85	4.09
8	3.8	4	3.99	3.81	4.37	4.65	3.77	4.4	6.13	4.85	3.82	3.37	3.47	3.65
9	4.08	4.57	4.48	4.1	4.84	4.90	3.88	6.03	5.22	4.55	3.67	3.49	3.59	3.46
10	3.94	4.06	4.08	3.94	4.11	4.52	3.99	4.33	5.18	4.90	4.08	3.82	4.08	3.89
n	10	10	10	10	10	10	10	10	10	10	10	10	10	10
mean	3.95	4.15	4.17	4.04	4.43	4.95	3.99	4.77	6.46	4.91	4.00	3.66	3.78	3.81
stdev	0.14	0.20	0.16	0.17	0.21	0.23	0.18	0.54	0.81	0.20	0.23	0.22	0.24	0.25
SEM	0.04	0.06	0.05	0.05	0.06	0.07	0.06	0.17	0.25	0.06	0.07	0.07	0.08	0.08

Table 8C.24

K+ ven			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	3.85	3.81	3.81	3.95	3.82	4.11	4.11	4.25	5.64	6.87	4.68	4.05	5.37	4.33
2														
3	4.02	4.05	3.75	4.13	3.64	4.25	4.17	4.17	4.09	4.20	4.48	3.91	3.92	3.80
4														
5	3.91	3.99	4.14	4.77	4.05	5.84	5.59	5.64	5.10	4.66	5.50		4.22	4.68
6	3.85	3.51	3.71	3.71	4.19	4.27	4.02	3.98	5.12	4.39	3.96	3.84	3.64	3.78
7	3.94	3.79	4.00	3.87	3.87	4.31	4.15	4.08	5.78	7.21	5.91	4.12	4.08	4.11
8	3.52	3.47	3.64	3.62	3.75	4.20	3.81	3.97	5.01	4.66	4.60	3.57	3.40	3.70
9	3.84	3.51	3.92	3.78	3.14	4.50	4.36	2.95	5.00	2.89	3.97	3.60	3.65	3.79
10	3.74	3.69	3.96	4.01	3.82	4.15	4.05	4.16	4.49	4.32	4.18	4.04	4.08	3.97
n	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	7.00	8.00	8.00
mean	3.83	3.73	3.87	3.98	3.79	4.45	4.28	4.15	5.03	4.90	4.66	3.88	4.05	4.02
stdev	0.15	0.22	0.17	0.36	0.31	0.57	0.55	0.73	0.55	1.44	0.71	0.22	0.60	0.34
SEM	0.05	0.08	0.06	0.13	0.11	0.20	0.19	0.26	0.19	0.51	0.25	0.08	0.21	0.12

Table 8C.25

K+a-v			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	0.03	0.19	0.23	0.84	0.25	0.41	-0.03	0.38	1.27	-1.79	-0.37	-0.21	-1.57	-0.25
2														
3	0.00	-0.07	0.35	-0.01	0.43	0.49	0.21	0.30	1.67	0.83	-1.03	0.21	-0.01	-0.38
4														
5	-0.10	0.14	-0.01	-0.71	0.33	-0.78	-1.26	-0.72	0.63	0.19	-1.34	3.60	-0.01	-0.48
6	0.05	0.45	0.27	0.09	0.29	0.93	0.07	0.53	1.29	0.77	0.04	-0.05	0.60	0.03
7	-0.25	0.23	0.62	1.57	1.37	0.77	0.52	0.71	1.84	-2.25	-2.40	-0.45	-0.14	0.38
8	0.16	0.30	0.21	0.16	0.33	0.44	0.05	0.32	1.13	0.24	-0.81	-0.30	0.09	0.00
9	0.16	0.78	0.44	0.21	1.91	0.17	-0.45	3.17	0.17	1.43	-0.41	-0.25	-0.07	-0.10
10	-0.02	0.12	0.11	-0.13	0.19	0.35	-0.11	0.00	0.49		-0.07	-0.23	0.07	-0.10
n	8	8	8	8	8	8	8	8	8	7	8	8	8	8
mean	0.00	0.27	0.28	0.25	0.64	0.35	-0.12	0.59	1.06	-0.08	-0.80	0.29	-0.13	-0.11
stdev	0.14	0.26	0.19	0.68	0.64	0.51	0.54	1.13	0.58	1.39	0.80	1.35	0.62	0.27
SEM	0.05	0.09	0.07	0.24	0.23	0.18	0.19	0.40	0.21	0.53	0.28	0.48	0.22	0.09

Table 8C.26

Na+ art			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	137.6	139.6	139.1	138.6	139.4	141.2	136	139.3	149.1	144.2	143.2	141.3	138.5	138.1
2	139.9	140.3	139.9	138.9	141.8	144.9	139.6	141.6	151.6	148.9	146.8	144.5	141.7	139.1
3	140.7	141.5	142.5	141.8	143.3	143.3	141.1	141.7	149.2	145.2	144.1	142.8	141.5	141.6
4	136.5	138	137.1	136.1	138.8	142.9	137.9	144.6	152	144.8	142.9	139.8	138.7	136.2
5	139	139.9	138.7	138	138.1	141.5	139	142.2	148.3	144.1	142.8	141.2	138.9	138.8
6	139.1	140.1	140.3	139.5	141.9	142.6	141.4	144.1	148.9	146	144	142.1	140.3	139
7	139.8	139.7	140.9	140.5	139.7	143.9	140.4	141.6	149.4	147.7	144.4	142.6	140.2	138
8	140.2	140.2	139.3	139.3	141.2	141.1	138.9	141.6	146.9	142.7	140.5	136.8	135.1	134
9	143.7	144.4	144	143.4	146	143.0	144.1	151.8	149.3	147.7	146.5	146.1	142.3	141.2
10	136.9	137	137.5	135.7	136.7	139.5	137.2	137.8	141.7		137.7	136.3	137.1	136.6
n	10	10	10	10	10	10	10	10	10	9	10	10	10	10
mean	139.3	140.1	139.9	139.2	140.7	142.4	139.6	142.6	148.6	145.7	143.3	141.4	139.4	138.3
stdev	2.1	2.0	2.1	2.4	2.7	1.6	2.3	3.8	2.8	2.0	2.7	3.1	2.2	2.3
SEM	0.7	0.6	0.7	0.7	0.9	0.5	0.7	1.2	0.9	0.7	0.8	1.0	0.7	0.7

Table 8C.27

Na+ ven			exercise							recovery (min)				

Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	139.2	140.4	139.2	139.6	139.2	141.9	139.2	140.6	144.8	133.4	142.6	141.6	140.3	135.1
2														
3	141.6	143.1	141.6	141.5	142.4	143.5	140.6	144.2	144.3	145.9	145.8	143.9	143.3	142
4														
5	139.5	139.1	138.3	138.1	139.3	141.5	139.4	141.8	143.0	146	145.9	142.0	140.8	140.6
6	139.7	140.8	140.2	139.8	141.3	143.1	143.1	143.8	145.5	145.3	143.7	142.6	141.6	140.9
7	141.4	140.4	141.1	141.5	140.6	142.2	141.4	141.9	146.3	142.1	141.2	143.7	140.6	141.7
8	141.1	140.3	140.1	139.9	140.6	141.3	140.5	141.2	143.9	143.9	142.9	137	134.9	133.6
9	145.5	144	145.3	146.5	141.9	141.1	146.5	148.6	144.5	142.5	145.7	145.7	143.6	141.9
10	138.2	139	137.3	137.8	137.2	139.1	137.8	139.7	140.2	140.2	137.3	139	137.6	137.5
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8
mean	140.8	140.9	140.4	140.6	140.3	141.7	141.1	142.7	144.1	142.4	143.1	141.9	140.3	139.2
stdev	2.2	1.8	2.4	2.7	1.7	1.4	2.7	2.8	1.8	4.2	2.9	2.8	2.9	3.3
SEM	0.8	0.6	0.9	1.0	0.6	0.5	1.0	1.0	0.7	1.5	1.0	1.0	1.0	1.2

Table 8C.28

Na+ a-v			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-10.7	-9.3	-6.8	18.5	-12.2	-11.4	-6.9	-4.8	-3.5	7.9	-2.5	-9.4	-9.9	4.9
2														
3	-2.2	-3.4	-3.6	1.5	-7.1	-4.8	4.2	3.0	-4.1	2.2	-27.6	11.7	4.0	-4.3
4														
5	-4.9	-2.9	-2.5	-3.2	-5.4	1.4	3.6	0.1	-12.5	2.4	5.8	-8.0	0.2	-2.2
6	4.9	-8.7	0.7	-0.8	1.7	-0.3	5.1	-1.2	1.4	2.5	-0.3	14.4	23.1	6.1
7	-11.6	-8.0	10.9	3.3	26.1	3.6	20.2	8.9	10.6	0.5	-11.0	-2.1	3.0	9.7
8	-5.4	-8.3	-5.7	-1.8	-8.6	-0.5	1.7	-3.2	3.3	0.3	-3.4	-4.2	0.8	2.3
9	-4.5	-8.4	-5.2	-6.9	10.5	-4.8	-1.4	5.5	3.4	-2.3	-3.7	-5.5	-1.5	8.7
10	-9.1	-10.4	0.0	-4.1	-4.0	-0.1	-2.2	-7.4	-4.0		1.4	-3.2	1.7	-1.5
n	8	8	8	8	8	8	8	8	8	7	8	8	8	8
mean	-5.4	-7.4	-1.5	0.8	0.1	-2.1	3.0	0.1	-0.7	1.9	-5.2	-0.8	2.7	3.0
stdev	5.3	2.7	5.7	7.8	12.6	4.7	8.0	5.4	6.9	3.1	10.2	8.9	9.3	5.3
SEM	1.9	1.0	2.0	2.8	4.5	1.7	2.8	1.9	2.4	1.2	3.6	3.1	3.3	1.9

Table 8C.29

Cl- art			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	98	98	97	97	98	97	102	103	105	101	99	98	99	104
2	106	108	108	105	107	107	104	105	109	107	104	101	101	102
3	109	109	110	108	111	108	107	107	110	106	105	104	107	110
4	103	104	103	103	103	104	101	103	108	103	101	100	98	99
5	104	104	105	105	106	106	102	105	108	104	102	102	101	104
6	106	105.0	107	107	106	106	100	103	107	104	102	101	100	105
7	105	105	105	105	106	105	100	102	107	102	100	102	102	104
8	103	104	104	104	106	104	102	105	104	101	100	100	100	102
9	106	107	106	107	108	106.0	102	111	107	104	103	102	102	105
10	103	105	105	105	104	105	104	106	107		102	102	103	104
n	10	10	10	10	10	10	10	10	10	9	10	10	10	10
mean	104.3	104.9	105.0	104.6	105.5	104.8	102.4	105.0	107.2	103.6	101.8	101.2	101.3	103.9
stdev	2.9	3.0	3.5	3.1	3.4	3.0	2.1	2.6	1.8	2.1	1.9	1.6	2.5	2.8
SEM	0.9	0.9	1.1	1.0	1.1	1.0	0.7	0.8	0.6	0.7	0.6	0.5	0.8	0.9

Table 8C.30

Cl- ven			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	98	98	98	97	98	98	105	104	104	97	102	104	102	103
2														
3	106	107	108	107	111	106	106	107	107	107	104	106	105	107
4														
5	104	103	104	108	106	108	104	105	105.0	120	106	104.0	101	104
6	106	104	105	105	104	104	101	103	105	103	102	102	103	103
7	103	104	103	102	103	102	102	101	103	101	103	103	103	104
8	102	103	103	103	103	103	102	102	102	102	103.0	102	102	102
9	104	107	106	107	108	104.0	104	117	105.0	110	104	104	103	104
10	104	105	105	104	105	106	105	107	106	105	105	104	104	103
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8
mean	103.4	103.9	104.0	104.1	104.8	103.9	103.6	105.8	104.6	105.6	103.6	103.6	102.9	103.8
stdev	2.6	2.9	2.9	3.6	3.8	3.0	1.8	5.0	1.6	7.0	1.4	1.3	1.2	1.5
SEM	0.9	1.0	1.0	1.3	1.4	1.1	0.6	1.8	0.6	2.5	0.5	0.5	0.4	0.5

Table 8C.31

Cl-a-v			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-6.5	-5.9	-5.7	13.7	-8.7	-8.4	-5.8	-3.6	-4.5	1.9	-5.1	-12.3	-8.8	2.4
2														
3	2.0	0.6	-1.5	1.9	-6.2	-1.5	3.8	4.1	-3.6	1.1	-17.8	7.4	6.4	0.0
4														
5	-3.3	-1.8	-1.2	-5.4	-3.2	-0.9	0.9	-0.2	-10.0	-12.9	2.4	-7.2	1.5	-0.3
6	4.2	-4.9	2.4	1.6	2.8	2.2	3.8	-1.1	0.5	2.2	-0.4	9.6	14.4	8.1
7	-5.5	-4.5	10.2	6.2	23.5	4.4	13.1	7.6	9.4	-2.5	-12.8	-1.7	1.5	10.1

8	-2.3	-5.1	-2.7	0.1	-3.9	0.8	2.4	0.3	2.2	0.0	-3.7	-4.9	-1.5	1.4
9	0.0	-6.5	-2.9	-2.8	4.8	-3.0	-1.3	-4.3	1.0	-11.3	-4.2	-6.2	-1.2	8.0
10	-6.9	-6.4	-0.1	-0.6	-3.6	-1.4	-2.2	-5.2	-3.2		-2.3	-2.4	0.7	0.5
n	8	8	8	8	8	8	8	8	8	7	8	8	8	8
mean	-2.28	-4.32	-0.17	1.85	0.66	-0.98	1.85	-0.29	-1.01	-3.06	-5.50	-2.21	1.61	3.77
stdev	4.07	2.49	4.81	5.88	10.22	3.79	5.62	4.39	5.71	6.40	6.65	7.37	6.70	4.23
SEM	1.44	0.88	1.70	2.08	3.61	1.34	1.99	1.55	2.02	2.42	2.35	2.61	2.37	1.50

Table 8C.32

Lac- art		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.3	1.7	10.0	9.8	17.7	17.0	17.8	18.2	13.7	9.6
2	1.0	1.7	12.5	12.7	12.5	17.7	22.7	22.3	20.2	10.9
3										
4	1.5	1.7	13.2	14.1	20.9	22.1	21.9	21.5	20.9	11.4
5	1.3	0.8	10.9	9.4	20.0	20.2	20.1	20.5	17.8	5.3
6	0.8	1.7	17.8	15.3	19.3	21.5	20.0	19.1	10.9	5.1
7										
8	1.9	1.7	9.1	8.4	12.7	13.7	19.9	22.5	19.0	7.9
9	1.8	2.3	20.3	17.4	22.5	21.1	17.5	16.6	7.5	7.9
10	1.5	2.9	13.2	9.0	9.5	14.6	18.1	12.4	11.4	8.8
n	8	8	8	8	8	8	8	8	8	8
mean	1.4	1.8	13.4	12.0	16.9	18.5	19.7	19.1	15.2	8.4
stdev	0.4	0.6	3.9	3.4	4.7	3.2	1.9	3.4	5.0	2.3
SEM	0.1	0.2	1.4	1.2	1.7	1.1	0.7	1.2	1.8	0.8

Table 8C.33

Lac- ven		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	2.0	1.7	6.0	7.0	15.4	12.2	17.5	14.6	13.1	7.2
2										
3										
4										
5	1.2	2.0	10.1	9.3	10.1	19.1	14.2	13.8	17.5	6.6
6	0.8	0.8	6.5	11.1	10.7	9.0	9.9	13.2	10.8	4.6
7										
8	2.4	6.3	5.3	5.3	5.2	9.9	13.3	13.8	11.7	6.7
9	2.5	2.6	6.7	10.8	10.1	10.1	18.3	14.0	7.3	5.5
10	2.8	3.0	6.4	6.4	8.1	7.2	9.1	7.8	6.4	3.5
n	6	6	6	6	6	6	6	6	6	6
mean	1.9	2.7	6.8	8.3	9.9	11.2	13.7	12.9	11.1	5.7
stdev	0.8	1.9	1.7	2.4	3.4	4.2	3.8	2.5	4.1	1.4
SEM	0.3	0.8	0.7	1.0	1.4	1.7	1.5	1.0	1.7	0.6

Table 8C.34

Lac-a-v		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-0.83	-0.08	3.51	2.07	1.85	3.89	-0.06	3.21	-0.27	1.76
2										
3										
4										
5	0.03	-1.28	0.57	0.25	9.88	-1.33	6.42	7.97	-0.67	-1.28
6	0.07	0.84	11.33	4.28	8.43	12.14	10.37	5.80	1.21	1.47
7										
8	-0.54	-4.65	3.55	3.06	7.24	3.83	6.74	8.56	6.77	1.21
9	-0.66	-0.41	13.13	5.86	12.75	10.89	-1.63	2.08	-0.06	2.39
10	-1.34	-0.17	6.75	2.59	1.08	6.81	9.02	4.71	4.96	5.44
n	6	6	6	6	6	6	6	6	6	6
mean	-0.5	-1.0	6.5	3.0	6.9	6.0	5.1	5.4	2.0	1.8
stdev	0.5	1.9	4.9	1.9	4.6	5.0	4.9	2.6	3.1	2.2
SEM	0.2	0.8	2.0	0.8	1.9	2.0	2.0	1.1	1.3	0.9

Table 8C.35

SID art		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	42.5	44.7	39.1	31.3	33.7	31.4	30.8	29.2	29.9	28.6
2	36.9	34.4	30.6	28.5	37.0	29.1	23.9	24.7	24.0	30.0
3										
4	35.8	36.5	30.9	32.8	30.5	24.5	24.2	21.9	23.6	29.7
5	37.7	37.2	29.7	32.7	26.8	24.6	24.7	22.5	24.3	33.7
6	36.0	35.6	24.0	30.4	29.1	25.6	26.0	25.4	33.1	32.5
7										
8	39.1	37.6	32.6	32.6	36.3	32.9	24.5	17.6	19.6	27.7
9	39.9	40.2	21.6	29.4	25.0	27.1	29.6	31.0	36.4	31.8
10	36.3	33.7	25.8	27.2	30.4		21.7	25.7	26.8	27.7
n	8	8	8	8	8	7	8	8	8	8
mean	38.0	37.5	29.3	30.6	31.1	27.9	25.7	24.8	27.2	30.2
stdev	2.3	3.5	5.5	2.1	4.3	3.3	3.1	4.2	5.5	2.2
SEM	0.8	1.3	1.9	0.8	1.5	1.3	1.1	1.5	2.0	0.8

Table 8C.36 **exercise** **recovery (min)**

SID ven										
Subject	R	e1	e2	e3+1	F	1	2	5	10	30
1	43.0	43.4	42.0	33.9	31.1	31.0	27.8	27.1	30.6	29.2
2										
3										
4										
5	38.2	36.4	29.3	33.2	33.0	11.6	31.2	24.2	26.5	34.6
6	36.8	38.1	36.8	33.7	34.9	37.7	35.8	31.2	31.5	37.1
7										
8	40.2	34.5	37.2	37.9	41.7	36.7	31.2	24.8	24.6	28.6
9	42.9	40.6	34.9	23.8	34.4	25.3	27.4	31.3	37.0	36.2
10	35.2	33.2	30.8	30.5	30.6	32.4	27.4	31.3	31.3	35.0
n	6	6	6	6	6	6	6	6	6	6
mean	39.4	37.7	35.2	32.2	34.3	29.1	30.1	28.3	30.2	33.4
stdev	3.2	3.8	4.6	4.7	4.0	9.7	3.3	3.4	4.3	3.7
SEM	1.3	1.6	1.9	1.9	1.6	3.9	1.4	1.4	1.8	1.5

Table 8C.37

SIDa-v		exercise				recovery (min)				
Subject	R	e1	e2	e3+1	F	1	2	5	10	30
1	-3.4	-0.8	-5.9	-3.4	0.9	-0.3	2.4	0.3	-2.5	-0.2
2										
3										
4										
5	-1.7	0.0	0.7	-0.5	-9.4	13.8	-5.0	-2.8	-1.8	-1.0
6	0.7	-2.3	-12.8	-3.7	-6.2	-11.7	-9.9	-3.1	7.4	-2.8
7										
8	-2.4	1.8	-4.7	-6.1	-5.4	-3.5	-6.9	-7.6	-5.0	-0.4
9	-3.7	-1.5	-14.4	6.0	-9.6	0.4	1.3	-1.6	-0.7	-2.3
10	-0.9	0.4	-5.1	-4.4	-1.5		-5.6	-5.6	-4.1	-7.4
n	6	6	6	6	6	5	6	6	6	6
mean	-1.9	-0.4	-7.0	-2.0	-5.2	-0.3	-3.9	-3.4	-1.1	-2.4
stdev	1.6	1.5	5.6	4.3	4.2	9.2	4.8	2.8	4.4	2.7
SEM	0.7	0.6	2.3	1.8	1.7	4.1	2.0	1.2	1.8	1.1

Electrolytes (Digoxin). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [K^+], [Na^+], [Cl^-], [Lac^-] and [SID] at rest (R), during submaximal cycling exercise (e1 to e3+1) to fatigue (F), and recovery (1 to 30min). Units are mM; a-v has been corrected for the arterio-venous ΔPV.

Table 8C.38

K+ art			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	3.94	3.97	4.01	4.04	4.25	4.64	4.79	6.34	6.69	5.46	4.78	4.36	4.41	4.32
2	4.04	4.3	4.33	4.16	4.47	5.06	3.97	4.56	6.9	4.92	4.01	3.5	3.66	4.07
3	3.9	4.17	4.19	4.13	4.17	5.05	4.25	4.9	6.6	3.83	4.51	3.65	3.42	3.90
4	3.95	4	4.12	4.09	4.52	4.77	3.96	4.72	7.09	5.72	4.35	3.68	3.45	3.92
5	4.29	4.25	4.19	3.95	4.5	5.3	3.97	4.49	6.86	4.6	3.79	3.74	4.09	4.14
6	3.48	3.49	3.72	3.56	3.88	5.23	3.76	4.17	6.36	5.24	4.03	3.33	3.5	3.56
7	4.05	4.25	4.36	4.03	4.59	5.09	3.9	4.68	6.75	5.16	4.08	3.56	3.76	4
8	3.94	4.04	4.19	3.91	4.36	4.64	3.98	4.6	6.63	4.8	3.86	3.48	3.54	3.54
9	3.88	4.19	4.17	4.08	4.99	5.16	3.82	4.93	4.93	3.83	3.73	3.57	3.76	3.53
10	3.71	3.78	3.53	3.86	4.41	4.4	4.04					3.93		
n	10	10	10	10	10	10	10	9	9	9	9	10	9	9
mean	3.92	4.04	4.08	3.98	4.41	4.93	4.04	4.82	6.53	4.84	4.13	3.68	3.73	3.89
stdev	0.23	0.26	0.20	0.19	0.23	0.26	0.32	0.65	0.22	0.58	0.34	0.31	0.35	0.27
SEM	0.07	0.08	0.06	0.06	0.07	0.08	0.10	0.22	0.07	0.19	0.11	0.10	0.12	0.09

Table 8C.39

K+ ven			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	3.8	3.84	3.85	3.9	3.95	4.21	4.68	5.62	5.96	5.28	5.09	4.58	4.55	4.98
2														
3	3.9	3.82	4	4.09	4.16	4.30	4.29	4.42	4.59	4.5	4.4	4.17	3.78	3.79
4														
5	2.84				4.33	4.55	4.33			5.42		4.1	4.16	
6	3.28	3.31	3.32	3.13	3.23	4.15	3.6	3.77	4.96	4.15	3.64	3.41	3.39	3.69
7	3.76	3.81	4.14	3.95	3.91	4.8	4.15	4.23	5.54	5.01	4.16	3.86	3.81	4.03
8	3.69	3.58	3.77	3.71	3.8	4.15	3.99	3.91	4.25	4.14	3.83	3.65	3.6	3.75
9	3.74	3.88	3.86	3.92	3.99	3.98	3.85	4.14	4.14	3.79	3.78	3.69	3.72	3.68
10	3.73	3.56	4.03	3.87	3.79	4.2	3.9	4.31	3.92	3.91	3.7	3.89	3.82	3.05
n	8	7	7	7	8	8	8	7	7	8	7	8	8	7
mean	3.59	3.69	3.85	3.80	3.90	4.29	4.10	4.34	4.77	4.53	4.09	3.92	3.85	3.85
stdev	0.35	0.21	0.27	0.31	0.32	0.26	0.34	0.61	0.76	0.63	0.52	0.36	0.36	0.58
SEM	0.13	0.08	0.10	0.12	0.11	0.09	0.12	0.23	0.29	0.22	0.20	0.13	0.13	0.22

Table 8C.40

Na+ art			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30

1	139.9	140	138.5	139.4	140.3	141.9	138	143.9	145.9	142.8	142.1	140.3	139.6	139.5
2	137.1	139	138.5	137.6	138	142.1	137.6	139.3	147.3	142.6	143.2	139.3	137.9	138.7
3	142.2	143.1	143.6	143.3	142.8	144.9	142.6	144.8	150.2	142.4	144.4	141.9	142	140.0
4	136.9	136.9	137.8	137.3	136.6	140.5	137.5	141.2	149.3	147.9	144.5	141.6	140.7	137.4
5	139.4	136.1	138.7	137.5	140.3	145.7	141	142.6	149.8	145.9	145.3	144.7	140.8	139.6
6	139.4	140	140.2	138.9	139.8	145.3	141.7	142	148.4	147	144.3	142.6	139.7	140.8
7	140.9	142	141.7	140.4	141.3	146.1	142.1	143.7	151	146.9	145.7	143.1	141.7	140.6
8	139.4	139.7	140.4	139.2	141.7	144	140.2	143.5	146.6	145.7	144.1	141.5	141.8	140.1
9	139.2	140	139.7	138.8	141.3	142.5	139	141.9	141.9	139.5	139.8	138	138	138.4
10	133.5	134.5	136.5	134.1	142.8	137.6	139.2					134.2		
n	10	10	10	10	10	10	10	9	9	9	9	10	9	9
mean	138.8	139.1	139.6	138.7	140.5	143.1	139.9	142.5	147.8	144.5	143.7	140.7	140.2	139.5
stdev	1.8	2.3	2.0	2.0	2.0	2.1	2.1	1.8	1.8	2.2	1.1	1.7	1.4	1.1
SEM	0.6	0.7	0.6	0.6	0.6	0.7	0.7	0.6	0.6	0.7	0.4	0.5	0.5	0.4

Table 8C.41

Na+ ven			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	139.3	139.6	139.8	140.5	140.5	141.5	140.4	144.9	143.5	144.0	143.2	141.9	140.9	140.4
2														
3	143.8	143.1	144.0	143.1	143.6	143.0	144.7	144.5	147.2	147.2	146.1	146.1	141.1	140.7
4														
5	140.5				139.5	144.9	142.4			143.6		144.8	141.0	
6	139.1	140.3	141.4	141.9	141.8	144.4	143.2	143.7	146.6	144.8	143.2	143.9	142.7	140.3
7	143.3	140.9	142.3	141.0	142.6	145.3	144.9	145.1	147.5	145.2	144.8	144.9	144.1	143.3
8	140.6	141.6	140.7	140.8	140.7	143.8	143.0	142.2	144.9	144.5	143.4	143.3	142.6	142.4
9	140.3	141.0	140.7	141.6	142.1	142.1	140.3	141.5	141.5	141.0	142.2	140.4	138.8	140.0
10	134.6	135.0	137.9	135.6	136.1	136.9	136.3		139.1	137.1	138.1	136.7	135.9	135.0
n	8.0	7.0	7.0	7.0	8.0	8.0	8.0	6.0	7.0	8.0	7.0	8.0	8.0	7.0
mean	140.2	140.2	141.0	140.6	140.9	142.7	141.9	143.7	144.3	143.4	143.0	142.8	140.9	140.3
stdev	2.8	2.5	1.9	2.4	2.3	2.7	2.8	1.5	3.2	3.1	2.5	3.0	2.6	2.6
SEM	1.0	1.0	0.7	0.9	0.8	1.0	1.0	0.6	1.2	1.1	0.9	1.1	0.9	1.0

Table 8C.42

Na+ a-v			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-1.8	-3.7	8.9	9.5	-1.3	1.4	6.2	2.5	7.0	18.0	12.3	2.4	13.4	2.5
2														
3	-4.0	-2.4	-0.6	4.1	-3.7	8.9	0.8	-7.0	0.3	-12.6	-4.7	-4.4	7.9	2.6
4														
5	-2.2				-4.0	0.1	3.3					2.3	-0.2	
6	-1.8	-7.2	-11.6	-7.2	-11.7	-3.5	-7.7	-5.9	-3.3	5.0	-8.2	-8.9	-4.6	-0.5
7	-11.7	-2.2	-2.8	-1.6	-8.8	0.9	-4.0	-2.1	0.6	-4.5	-6.3	-4.2	-2.7	-2.9
8	-3.5	-6.5	-4.8	-7.5	-4.5	-4.2	-5.7	-6.7	-2.3	-1.1	0.3	-5.4	-2.7	-2.8
9	-6.5	-10.2	-6.4	-7.6	-19.5	-3.2	3.2	-11.1	-5.7	-1.5	-1.4	-5.1	-0.6	1.0
10	-2.9	7.5	-2.0	-5.4	8.5	-0.9	14.4					-7.4		
n	8	7	7	7	8	8	8	6	6	6	6	8	7	6
mean	-4.3	-3.5	-2.8	-2.2	-5.6	-0.1	1.3	-5.0	-0.6	0.6	-1.3	-3.8	1.5	0.0
stdev	3.4	5.7	6.3	6.7	8.2	4.2	7.2	4.7	4.4	10.3	7.4	4.2	6.6	2.5
SEM	1.2	2.1	2.4	2.5	2.9	1.5	2.5	1.9	1.8	4.2	3.0	1.5	2.5	1.0

Table 8C.43

Cl- art			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	105	105	105	104	105	104	101	104	104	101	99	99	99	101
2	106	107	106	106	109	109	106	107	114	108	107	106	106	112
3	108	109	110	109	108	110	107	110	111	105	105	107	111	105
4	104	106	106	105	107	106	103	106	109	106	104	102	104	100
5	106	105	105	104	105	105	102	104	108	104	101	101	99	103
6	104	107	106	107	107	104	102	104	108	105	103	102	101	104
7	107	107	107	107	108	107	103	105	109	105	103	103	103	104
8	105	106	105	105	106	106	101	104	106	101	101	100	101	105
9	103	104	104	104	105	104	99	98	98	99	98	98	98	101
10	106	106	110	108	109	106	106					104	102.4	103.8
n	10	10	10	10	10	10	10	9	9	9	9	10	10	10
mean	105.4	106.2	106.4	105.9	106.9	106.1	103.0	104.7	107.4	103.8	102.3	102.2	102.4	103.9
stdev	1.4	1.3	1.7	1.7	1.5	2.2	2.2	2.1	3.0	2.4	2.5	2.8	4.0	3.6
SEM	0.4	0.4	0.5	0.5	0.5	0.7	0.7	0.7	1.0	0.8	0.8	0.9	1.3	1.1

Table 8C.44

Cl- ven			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	104	104	104	104	104	103	102	102	102	102	101	101	101	102
2														
3	107	107	108	109	108	105.0	108	106	108	107	108	107	102.0	110
4														
5	113				104	108	103			108		102	102	
6	102	104	104	106	106	104	104	103	106	102	102	102	103	102
7	105	105	105	105	106	105	103	104	106	103	103	103	103	105
8	103	105	103	103	104	103	102	104	107	102	104	101	101	102
9	103	102	103	102	102	102	100	98	98	100	99	100	98	99
10	104	106	104	104	105	106	106		105	104	106	104	104	115
n	8	7	7	7	8	8	8	6	7	8	7	8	8	7

mean	105.1	104.7	104.4	104.7	104.9	104.5	103.5	102.8	104.6	103.5	103.3	102.5	101.8	105.0
stdev	3.5	1.6	1.7	2.3	1.8	1.9	2.5	2.7	3.5	2.7	3.0	2.2	1.8	5.6
SEM	1.2	0.6	0.6	0.9	0.6	0.7	0.9	1.1	1.3	1.0	1.1	0.8	0.6	2.1

Table 8C.45

Cl-a-v			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-0.8	-2.1	8.7	7.9	0.2	1.7	5.3	4.6	5.3	12.6	7.3	0.9	8.4	1.5
2														
3	-0.8	0.2	1.8	2.9	-2.2	10.3	1.2	-1.5	1.0	-7.8	-5.2	-0.1	14.4	-2.5
4														
5	-7.9				-2.6	-3.5	2.4			-4.0		0.7	-3.0	
6	0.4	-2.3	-5.8	-2.2	-6.4	-3.1	-6.4	-2.1	-1.7	5.0	-5.6	-5.5	-3.2	1.3
7	-5.0	-0.5	0.3	1.2	-3.8	2.1	-0.9	0.5	0.9	-2.4	-5.1	-1.7	-0.2	-1.1
8	0.3	-2.5	-1.3	-2.4	-2.1	-0.2	-3.1	-5.8	-3.9	-2.6	-3.3	-3.6	-1.3	2.6
9	-4.0	-4.8	-3.0	-1.6	-10.9	-0.7	2.2	-7.9	-4.2	-1.0	-0.3	-3.9	0.2	3.9
10	0.6	6.3	5.5	0.9	5.4	-1.2	8.8					-3.8	-1.6	-11.3
n	8	7	7	7	8	8	8	6	6	7	6	8	8	7
mean	-2.15	-0.81	0.88	0.96	-2.79	0.67	1.18	-2.06	-0.44	-0.02	-2.03	-2.12	1.72	-0.81
stdev	3.12	3.53	4.98	3.65	4.72	4.37	4.75	4.46	3.60	6.75	4.98	2.40	6.31	5.09
SEM	1.10	1.33	1.88	1.38	1.67	1.54	1.68	1.82	1.47	2.55	2.03	0.85	2.23	1.92

Table 8C.46

Lac-art		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0.6	0.8	8.5	12.5	15.8	13.0	13.6	12.6	6.6	9.1
2	0.6	1.2	2.2	9.0	9.4	13.8	16.0	18.5	17.7	14.6
3										
4	0.8	1.3	6.2	9.8	14.3	16.6	15.1	14.7	12.4	14.6
5	1.4	3.4	14.2	14.5	22.5	20.4	21.3	22.0	19.4	7.3
6	2.5	1.8	17.0	15.1	23.5	22.6	21.0	18.3	8.2	4.1
7										
8	0.5	0.8	8.4	7.6	13.0	12.2	11.1	10.8	8.8	6.9
9	2.5	1.8	18.0	18.1	15.2	22.9	23.2	21.1	19.6	7.7
10	1.7	1.7	5.2					7.2		
n	8	8	8	7	7	7	7	8	7	7
mean	1.3	1.6	10.0	12.3	16.2	17.3	17.3	15.7	13.3	9.2
stdev	0.8	1.0	5.4	3.1	5.5	4.2	4.1	4.2	5.3	4.3
SEM	0.3	0.4	1.9	1.2	2.1	1.6	1.5	1.5	2.0	1.6

Table 8C.47

Lac- ven		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0.6	0.6	3.9	11.9	13.2	11.6	13.7	13.0	13.6	6.9
2										
3										
4										
5	1.5		11.1					17.7		9.3
6	1.6	1.6	8.7	11.3	14.5	9.3	9.5	8.4	9.1	4.1
7										
8	0.7	0.7	5.7	5.4	16.5	13.5	12.5	13.6	13.4	5.3
9	1.5	2.5	6.1	8.4	11.9	7.5	9.9	14.2	12.2	8.8
10	1.5	1.6	4.2		4.2	4.8	5.2	5.8	4.5	6.5
n	6	5	6	4	5	5	5	6	5	6
mean	1.2	1.4	6.6	9.2	12.1	9.3	10.2	12.1	10.6	6.8
stdev	0.5	0.8	2.8	3.0	4.7	3.4	3.3	4.3	3.9	2.0
SEM	0.2	0.3	1.1	1.5	2.1	1.5	1.5	1.8	1.7	0.8

Table 8C.48

Lac-a-v		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-0.01	0.20	4.63	0.92	3.12	3.06	1.09	0.04	-6.25	2.40
2										
3										
4										
5	-0.07		3.06					4.67		-1.60
6	0.89	0.05	7.71	3.30	8.16	13.74	10.17	8.91	-1.06	0.01
7										
8	-0.27	0.09	2.48	1.77	-3.85	-1.48	-1.42	-3.02	-4.74	1.52
9	0.90	-0.81	11.43	8.19	2.60	15.37	13.42	6.46	7.48	-0.91
10	0.17	0.05	0.90					1.18		
n	6	5	6	4	4	4	4	6	4	5
mean	0.3	-0.1	5.0	3.5	2.5	7.7	5.8	3.0	-1.1	0.3
stdev	0.5	0.4	3.9	3.2	4.9	8.2	7.1	4.4	6.1	1.7
SEM	0.2	0.2	1.6	1.6	2.5	4.1	3.6	1.8	3.1	0.7

Table 8C.49

SID art		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**

1	38.3	36.7	34.0	33.8	32.8	34.3	34.3	33.0	38.4	33.7
2	34.6	35.6	36.0	27.9	30.8	25.7	24.3	18.3	17.8	16.2
3										
4	36.1	34.7	33.1	30.1	33.1	31.0	29.8	28.6	27.7	26.8
5	36.3	34.5	31.8	28.6	26.1	26.2	26.8	25.5	26.5	33.5
6	36.3	36.1	29.6	27.1	23.3	24.7	24.3	25.6	34.0	36.2
7										
8	37.9	38.8	34.2	36.5	34.2	37.3	35.8	34.2	35.5	31.8
9	37.6	38.1	25.7	30.8	33.7	21.4	22.4	22.5	24.1	33.2
10	29.5	28.3	30.9					26.9		
n	8	8	8	7	7	7	7	8	7	7
mean	35.8	35.3	31.9	30.7	30.6	28.7	28.2	26.8	29.2	30.2
stdev	2.8	3.2	3.2	3.4	4.2	5.7	5.2	5.2	7.2	6.8
SEM	1.0	1.1	1.1	1.3	1.6	2.2	2.0	1.8	2.7	2.6

Table 8C.50 SID ven

		exercise				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	38.5	39.0	38.8	36.6	34.3	35.7	33.6	32.5	30.9	36.5
2										
3										
4										
5	28.8		30.4					29.2		
6	38.8	39.1	35.8	33.2	31.1	37.7	35.3	36.9	33.9	37.9
7										
8	40.6	40.7	39.2	36.7	25.6	33.2	30.7	32.4	31.8	38.8
9	39.6	39.1	38.0	39.2	35.7	36.2	37.1	29.9	32.3	35.9
10	32.8	36.3	30.9		33.8	32.2	30.6	30.8	31.3	16.6
n	6	5	6	4	5	5	5	6	5	5
mean	36.52	38.84	35.51	36.44	32.11	34.98	33.45	31.96	32.04	33.13
stdev	4.63	1.60	3.96	2.49	3.99	2.25	2.84	2.76	1.20	9.34
SEM	1.89	0.72	1.62	1.25	1.78	1.01	1.27	1.13	0.54	4.18

Table 8C.51 SIDa-v

		exercise				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-0.9	0.4	-4.5	-2.1	-0.4	3.3	4.0	1.5	11.5	-1.9
2										
3										
4										
5	7.1		1.3					-3.3		
6	-3.0	-5.7	-7.1	-6.9	-8.6	-12.5	-12.6	-12.6	-0.3	-1.9
7										
8	-3.3	-3.2	-6.1	-2.2	7.6	3.6	5.0	0.9	3.3	-7.2
9	-3.4	-2.4	-13.0	-11.0	-3.5	-14.8	-14.5	-7.8	-8.2	-2.1
10	-3.7	-8.1	-0.4					-4.9		
n	6	5	6	4	4	4	4	6	4	4
mean	-1.20	-3.80	-4.97	-5.53	-1.22	-5.12	-4.53	-4.39	1.59	-3.27
stdev	4.19	3.23	5.09	4.24	6.79	9.90	10.48	5.35	8.19	2.61
SEM	1.71	1.45	2.08	2.12	3.39	4.95	5.24	2.19	4.09	1.30

Acid-base (Control). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for $[H^+]$, $[HCO_3^-]$; arterial and venous PCO_2, PO_2 at rest (R), during submaximal cycling exercise (e1 to e3+1) to fatigue (F), and recovery (1 to 30min). Units are mM for $[H^+]$, $[HCO_3^-]$ and mmHg for PCO_2, PO_2.

Table 8C.52

H+ art			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	37.2	37.6	37.3	39.3	37.5	42.8	45.2	43.5	59.0	66.2	72.1	71.1	69.3	45.5
2	39.8	39.4	39.2	39.0	40.6	45.2	48.9	47.1	53.5	60.0	60.0	67.1	70.6	48.5
3	38.9	38.9	38.5	38.7	37.2	40.9	38.6	39.6	45.1	49.0	50.2	53.7	49.9	39.4
4	38.5	38.4	39.6	35.6	39.4	44.8	48.8	46.0	49.5	55.2	57.7	63.4	63.4	45.8
5	41.2	42.1	42.3	41.3	40.6	47.3	48.8	48.0	64.4	63.1	65.5	69.0	64.3	43.1
6	37.8	39.0	39.5	37.6	39.7	49.5	56.0	50.4	55.8	62.5	64.4	68.2	62.4	42.6
7	40.3	40.6	39.4	38.2	40.2	45.6	45.3	43.7	59.3	60.3	67.3	73.1	72.1	47.9
8	38.3	37.2	37.2	37.9	38.9	40.1	38.9	40.2	58.7	60.5	60.8	62.7	58.3	41.3
9	40.7	40.4	38.8	37.4	39.6	43.8	60.7	61.5	53.8	69.7	74.8	78.5	71.3	48.6
10	39.1	37.8	37.2	37.2	37.6	39.7	40.8	38.8	43.3		46.8	48.1	43.2	38.8
n	10	10	10	10	10	10	10	10	10	9	10	10	10	10
mean	37.0	39.1	38.9	38.2	39.1	44.0	47.2	45.9	54.2	60.7	62.0	65.5	62.5	44.1
stdev	17.0	1.5	1.5	1.5	1.3	3.2	7.1	6.7	6.7	6.0	8.9	9.0	9.6	3.7
SEM	5.4	0.5	0.5	0.5	0.4	1.0	2.3	2.1	2.1	2.0	2.8	2.9	3.0	1.2

Table 8C.53

H+ven			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	41.5	40.8	42.2	42.1	42.1	46.5	48.5	47.8	55.7	59.7	61.7	63.7	65.2	45.3
2														
3	44.2	43.5	44.5	45.8	42.7	45.4	46.1	45.6	47.5	51.9	53.0	52.0	52.2	41.1
4														
5	43.7	43.8	44.6	44.9	45.5	48.5	49.9	49.1	54.0	57.1	64.9	61.0	66.1	46.9
6	41.0	44.8	44.9	45.2	44.7	51.9	52.5	52.5	57.1	63.5	61.1	62.1	62.4	45.4
7	49.1	48.2	46.7	49.3	48.0	51.4	52.2	52.0	57.1	57.9	61.2	70.0	54.8	67.3
8	39.9	40.1	40.6	39.9	40.7	43.3	42.7	42.9	56.6	55.8	59.9	56.6	56.5	43.1
9	48.5	47.6	47.5	46.3	48.4	47.4	60.8	58.6	52.9	62.5	71.8	73.6	69.8	53.5
10	43.2	43.0	40.9	43.6	42.1	42.8	42.8	40.1	44.4	45.0	47.3	47.4	45.9	41.5
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8
mean	43.9	44.0	44.0	44.6	44.3	47.1	49.4	48.6	53.2	56.7	60.1	60.8	59.1	48.0
stdev	20.6	2.9	2.6	2.8	2.9	3.4	6.0	5.9	4.8	6.0	7.4	8.7	8.1	8.7
SEM	7.3	1.0	0.9	1.0	1.0	1.2	2.1	2.1	1.7	2.1	2.6	3.1	2.9	3.1

Table 8C.54

H+a-v			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	-4.3	-3.2	-4.8	-2.8	-4.6	-3.7	-3.3	-4.3	3.3	6.5	10.5	7.4	4.2	0.2
2														
3	-5.3	-4.5	-6.0	-7.1	-5.4	-4.5	-7.5	-6.0	-2.5	-2.9	-2.7	1.7	-2.4	-1.8
4														
5	-2.4	-1.7	-2.3	-3.6	-4.9	-1.2	-1.1	-1.1	10.4	5.9	0.6	8.0	-1.8	-3.8
6	-3.3	-5.8	-5.3	-7.6	-4.9	-2.3	3.5	-2.1	-1.3	-1.0	3.3	6.1	0.0	-2.8
7	-8.8	-7.6	-7.3	-11.1	-7.8	-5.8	-6.9	-8.3	2.1	2.3	6.1	3.1	17.3	-19.4
8	-1.6	-2.9	-3.4	-2.0	-1.8	-3.2	-3.8	-2.7	2.1	4.7	0.9	6.0	1.9	-1.7
9	-7.8	-7.3	-8.7	-8.9	-8.8	-3.6	-0.1	2.9	0.9	7.1	3.0	4.9	1.5	-4.8
10	-4.1	-5.1	-3.7	-6.3	-4.5	-3.0	-1.9	-1.3	-1.1		-0.5	0.7	-2.8	-2.7
n	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	7.0	8.0	8.0	8.0	8.0
mean	-4.7	-4.8	-5.2	-6.2	-5.3	-3.4	-2.7	-2.9	1.8	3.2	2.6	4.8	2.2	-4.6
stdev	2.5	2.1	2.1	3.2	2.1	1.4	3.6	3.4	4.0	3.9	4.1	2.7	6.5	6.2
SEM	0.9	0.7	0.8	1.1	0.8	0.5	1.3	1.2	1.4	1.5	1.5	0.9	2.3	2.2

Table 8C.55

HCO3- art			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	27.1	26.1	26.7	26.5	25.7	19.5	17.4	19.9	10.7	9.3	8.9	8	6.6	15.1
2	24.6	23.6	23.2	24.2	23.8	15	13.6	14.8	9.7	7	7.2	8	8.3	16.9
3	26	26	27.1	26.1	27.3	17.4	18.5	20.3	14.4	13.3	14	10.3	12.7	24.9
4	27.1	26.8	26.5	25.2	27.4	16.6	16.2	16.8	12.8	10.1	10	9	10.1	18.8
5	25	25.3	24.6	23.8	23.4	17.7	17.1	19	12.1	9.9	10.4	11.5	12.5	23.2
6	25.8	26.2	26	24.5	14.2	14.6	13.6	12.4	9.8	10.1	10.4	12.4	23.3	18.6
7	25.5	26.3	27	26.4	26.9	18.2	17.2	18.2	15.3	11.4	9.6	10.1	10.2	11.7
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	25.9	25.8	25.9	25.2	24.1	17.0	16.2	17.3	12.1	10.2	10.1	9.9	12.0	18.5
stdev	1.0	1.1	1.5	1.1	4.7	1.7	1.9	2.9	2.2	1.9	2.1	1.7	5.4	4.5
SEM	0.4	0.4	0.5	0.4	1.8	0.7	0.7	1.1	0.8	0.7	0.8	0.6	2.1	1.7

Table 8C.56

HCO3- ven			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30

1	28.0	28.2	28.5	29.3	27.2	24.1	22.8	23.4	18.8	20.3	19.0	16.6	12.1	18.9
2														
3	31.3	32.3	30.4	30.1	21.6	23.8	24.0	25.7	26.7	24.4	16.7	17.5	23.5	28.6
4														
5	26.9	26.9	28.1	24.7	26.5	17.8	18.6	19.5	21.0	13.0	15.6	18.9	14.3	26.4
6	27.8	30.5	30.0	29.7	29.9	23.0	24.9	22.0	20.1	22.3	22.4	19.4	19.3	26.8
7	31.4	31.6	32.6	32.0	32.3	27.5	28.9	28.0	20.0	26.5	26.0	22.4	24.4	21.0
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	29.1	29.9	29.9	29.2	27.5	23.2	23.8	23.7	21.3	21.3	19.9	19.0	18.7	24.3
stdev	2.1	2.3	1.8	2.7	4.0	3.5	3.7	3.3	3.1	5.2	4.3	2.2	5.4	4.2
SEM	0.9	1.0	0.8	1.2	1.8	1.6	1.7	1.5	1.4	2.3	1.9	1.0	2.4	1.9

Table 8C.57

HCO3-av			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-0.9	-2.1	-1.8	-2.8	-1.5	-4.6	-5.4	-3.5	-8.1	-11.0	-10.1	-8.6	-5.5	-3.8
2														
3	-5.3	-6.3	-3.3	-4.0	5.7	-6.4	-5.5	-5.4	-12.3	-11.1	-2.7	-7.2	-10.8	-3.7
4														
5	-1.9	-1.6	-3.5	-0.9	-3.1	-0.1	-1.5	-0.5	-8.9	-3.1	-5.2	-7.4	-1.8	-3.2
6	-2.0	-4.3	-4.0	-5.2	-15.7	-8.4	-11.3	-9.6	-10.3	-12.2	-12.0	-7.0	4.0	-8.2
7	-5.9	-5.3	-5.6	-5.6	-5.4	-9.3	-11.7	-9.8	-4.7	-15.1	-16.4	-12.3	-14.2	-9.3
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	-3.2	-3.9	-3.6	-3.7	-4.0	-5.8	-7.1	-5.8	-8.9	-10.5	-9.3	-8.5	-5.7	-5.6
stdev	2.2	2.0	1.4	1.9	7.7	3.7	4.3	4.0	2.8	4.5	5.4	2.2	7.2	2.9
SEM	1.0	0.9	0.6	0.9	3.5	1.6	1.9	1.8	1.3	2.0	2.4	1.0	3.2	1.3

Table 8C.58

PCO2art			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	41.2	40.7	41.3	43.2	40.0	34.5	32.7	35.9	26.3	25.5	26.6	23.5	19.1	28.5
2	40.4	38.5	37.7	39.1	40.1	28.1	27.5	29.0	21.5	17.4	17.8	22.2	24.4	34.0
3	41.3	42.0	43.2	41.9	42.2	29.6	29.6	33.3	27.0	27.1	29.1	22.9	26.3	40.7
4	43.1	42.6	43.6	37.2	44.8	30.8	32.8	32.1	26.4	23.1	24.0	23.6	26.6	35.8
5	42.1	44.2	43.2	40.8	39.5	34.8	34.6	37.8	32.4	25.8	28.3	32.9	33.4	41.5
6	39.8	42.2	43.0	40.6	40.4	29.1	33.9	28.5	28.7	25.3	27.1	29.5	32.2	41.1
7	42.6	44.2	44.0	41.8	44.9	34.5	32.3	33.0	28.0	24.0	28.3	30.8	34.9	39.8
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	41.5	42.1	42.3	40.7	41.7	31.6	31.9	32.8	27.2	24.0	25.9	26.5	28.1	37.3
stdev	1.2	2.0	2.2	2.0	2.3	2.9	2.5	3.4	3.3	3.2	3.9	4.4	5.6	4.8
SEM	0.4	0.8	0.8	0.8	0.9	1.1	0.9	1.3	1.2	1.2	1.5	1.7	2.1	1.8

Table 8C.59

PCO2ven			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	48.2	47.7	49.9	51.1	47.5	46.4	45.8	46.3	43.4	50.3	48.5	43.9	31.4	35.6
2														
3	57	58.2	56	57.2	38.2	44.8	45.9	48.7	52.7	52.5	36.8	37.8	50.9	48.8
4														
5	48.2	48.9	51.9	46	50	35.8	38.5	39.8	47.9	30.9	41.9	49.1	39.1	51.4
6	56.6	56.6	55.9	55.6	55.4	49.4	54.1	47.8	47.6	58.8	56.8	50	49.9	50.5
7	64	63.2	63.2	65.4	64.3	61.2	62.6	60.5	47.4	63.8	66	65	55.5	58.5
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	54.8	54.9	55.4	55.1	51.1	47.5	49.4	48.6	47.8	51.3	50.0	49.2	45.4	49.0
stdev	6.7	6.5	5.1	7.2	9.7	9.2	9.2	7.5	3.3	12.6	11.7	10.1	9.9	8.3
SEM	3.0	2.9	2.3	3.2	4.3	4.1	4.1	3.4	1.5	5.6	5.2	4.5	4.4	3.7

Table 8C.60

PO2art			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	110.1	107.6	119.3	105.7	113.7	113.3	124.7	96.8	115.0	126.0	123.0	123.7	118.3	82.9
2	95.8	99.1	100.4	99.0	86.2	96.8	110.9	88.1	94.3	118.9	114.3	116.9	117.6	94.5
3	101.9	84.5	90.0	94.4	83.1	83.4	115.3	88.5	91.8	116.7	114.9	124.3	100.5	70.0
4	100.5	97.7	101.8	119.3	93.4	107.4	117.5	97.2	112.4	118.3	120.2	122.0	127.3	85.2
5	107.1	89.9	97.2	116.9	101.4	107.2	125.0	84.7	90.8	110.5	111.2	103.0	106.4	90.1
6	119.0	93.0	99.1	112.3	101.7	102.9	110.2	106.7	105.5	121.3	117.2	119.9	117.1	84.7
7	111.8	102.0	105.2	119.2	103.7	110.0	126.7	105.1	119.5	133.6	127.3	129.0	118.4	106.7
8	92.2	94.2	97.5	98.4	91.0	111.1	125.0	95.4	99.4	120.9	119.0	123.3	115.0	86.9
9	109.3	91.4	101.0	118.6	89.7	103.1	123.8	90.3	96.2	123.1	125.7	116.1	122.9	88.8
10	77.0	69.4	86.1	95.3	81.3	93.9	98.8	84.9	92.8		97.1	101.7	90.0	82.2
n	10	10	10	10	10	10	10	10	10	9	10	10	10	10

mean	102.4	92.9	99.8	107.9	94.5	102.9	117.8	93.8	101.8	121.0	117.0	118.0	113.4	87.2
stdev	12.0	10.5	8.9	10.5	10.3	9.2	9.1	7.8	10.6	6.4	8.7	9.0	11.2	9.4
SEM	3.8	3.3	2.8	3.3	3.3	2.9	2.9	2.5	3.3	2.1	2.7	2.9	3.5	3.0

Table 8C.61

PO2ven			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	32.9	31.5	27.9	26.9	34.7	33.8	33.4	38.6	32.5	27.4	32.8	31.5	30.3	31.4
2														
3	23.7	22.9	26.4	36.6	33.0	29.2	35.7	35.0	19.5	28.4	39.2	36.7	30.2	28.8
4														
5	41.0	39.9	40.6	46.1	37.6					43.4	54.3		76.7	27.4
6	26.4	25.7	24.7	31.1	29.1	28.7	18.1	31.1	35.5	22.9	22.5	31.5	29.5	25.9
7	20.1	22.0	21.5	21.8	22.7	26.8	20.1	24.8	46.4	18.1	23.4	30.0	34.2	36.3
8	30.5	32.0	29.7	31.5	35.2	40.0	37.4	41.1	39.9	32.6	35.1	33.5	39.5	30.7
9	20.8	28.0	39.4	41.2	32.4	32.0	39.4	53.4	35.0	28.1	38.8	32.7	39.1	25.3
10	27.0	33.2	34.9	30.0	30.2	34.8	39.4	64.9	32.8	26.7	32.5	37.3	34.5	29.1
n	8	8	8	8	8	7	7	7	7	8	8	7	8	8
mean	27.79	29.40	30.64	33.15	31.86	32.19	31.93	41.27	34.51	28.45	34.83	33.31	39.25	29.36
stdev	6.93	5.96	6.96	7.83	4.60	4.48	9.03	13.70	8.20	7.40	10.04	2.75	15.62	3.52
SEM	2.45	2.11	2.46	2.77	1.63	1.69	3.41	5.18	3.10	2.61	3.55	1.04	5.52	1.24

Acid-base (Digoxin). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for $[H^+]$, $[HCO_3^-]$; arterial and venous PCO_2, PO_2 at rest (R), during submaximal cycling exercise (e1 to e3+1) to fatigue (F), and recovery (1 to 30min). Units are mM for $[H^+]$, $[HCO_3^-]$ and mmHg for PCO_2, PO_2.

Table 8C.62

H+art			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	36.1	35.9	36.7	36.3	37.0	41.3	40.1	51.6	57.1	64.6	68.5	70.1	62.7	42.6
2	37.8	39.9	39.2	38.8	41.0	48.2	48.8	48.3	55.7	59.6	64.1	68.4	66.8	43.9
3	37.9	38.8	37.0	37.1	39.0	40.8	40.5	37.1	43.3	48.0	48.6	47.4	38.8	43.6
4	39.4	38.8	39.5	36.8	41.0	45.4	49.8	44.0	57.7	62.1	66.4	71.0	71.3	48.8
5	40.6	42.4	40.5	42.2	40.8	51.3	52.0	49.3	60.1	62.7	60.5	69.5	64.4	42.9
6	36.6	38.9	36.9	36.7	35.8	45.7	49.7	45.3	51.1	56.8	57.7	59.8	57.8	41.9
7	39.2	39.6	39.9	39.7	40.6	46.2	48.5	46.0	50.6	53.8	57.4	62.1	57.8	43.2
8	39.3	38.9	38.4	36.6	39.5	43.4	43.3	41.7	60.7	62.4	63.5	67.6	59.6	40.3
9	40.3	40.7	39.6	37.8	39.9	45.1	60.0	54.6	54.6	72.9	70.8	65.5	57.3	45.7
10	37.8	36.2	37.5	35.8	37.4	40.5	39.7					43.6		
n	10	10	10	10	10	10	10	9	9	9	9	10	9	9
mean	38.5	39.0	38.5	37.8	39.2	44.8	47.2	46.4	54.5	60.3	62.0	62.5	59.6	43.6
stdev	1.5	1.9	1.4	1.9	1.9	3.4	6.4	5.3	5.5	7.1	6.8	9.7	9.1	2.4
SEM	0.5	0.6	0.4	0.6	0.6	1.1	2.0	1.8	1.8	2.4	2.3	3.1	3.0	0.8

Table 8C.63

H+ven			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	40.8	39.9	41.1	41.4	42.2	43.9	46.9	51.5	56.5	57.8	62.7	64.9	61.1	45.5
2														
3	44.7	44.1	42.2	42.8	42.2	48.1	45.4	46.1	48.2	50.4	54.6	53.0	54.9	43.2
4														
5	44.0				45.0	50.6	50.5			64.1		66.4	46.1	
6	44.3	43.3	43.6	43.0	43.6	48.3	50.4	49.4	50.1	54.8	59.8	56.8	55.7	42.1
7	46.2	45.6	47.4	47.1	47.8	50.7	54.5	52.1	56.8	61.5	62.7	62.2	60.0	48.8
8	43.2	43.9	43.9	44.9	44.8	46.6	47.2	46.6	55.6	56.0	58.5	60.8	59.6	44.4
9	47.6	46.7	48.8	47.4	47.9	55.6	55.8	63.1	63.1	65.9	65.9	65.6	61.0	52.4
10	41.2	41.9	41.3	41.4	42.3	42.7	42.7		44.3	56.9	45.1	46.3	43.8	40.2
n	8	7	7	7	8	8	8	6	7	8	7	8	8	7
mean	44.0	43.6	44.0	44.0	44.4	48.3	49.2	51.5	53.5	58.4	58.5	59.5	55.3	45.2
stdev	2.3	2.3	3.0	2.5	2.4	4.1	4.5	6.2	6.3	5.1	6.9	7.0	6.8	4.2
SEM	0.8	0.9	1.1	1.0	0.8	1.5	1.6	2.5	2.4	1.8	2.6	2.5	2.4	1.6

Table 8C.64

H+a-v			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-4.8	-4.0	-4.4	-5.1	-5.2	-2.5	-6.8	0.1	0.7	6.8	5.9	5.3	1.6	-2.9
2														
3	-6.7	-5.2	-5.2	-5.7	-3.2	-7.3	-4.9	-9.1	-4.9	-2.4	-5.9	-5.5	-16.0	0.5
4														
5	-3.3				-4.1	0.7	1.5			-1.5		3.1		
6	-7.6	-4.4	-6.7	-6.2	-7.7	-2.6	-0.7	-4.1	0.9	1.9	-2.2	3.1	2.1	-0.2
7	-7.1	-6.0	-7.5	-7.4	-7.2	-4.5	-5.9	-6.1	-6.2	-7.7	-5.2	-0.1	-2.2	-5.6
8	-3.9	-4.9	-5.5	-8.2	-5.2	-3.2	-4.0	-4.9	5.1	6.4	5.1	6.8	0.0	-4.1
9	-7.4	-5.9	-9.1	-9.6	-8.0	-10.5	4.1	-8.5	-8.5	7.0	4.9	-0.2	-3.7	-6.7
10	-3.5	-5.7	-3.8	-5.6	-4.9	-2.2	-2.9					-2.8		
n	8.0	7.0	7.0	7.0	8.0	8.0	8.0	6.0	6.0	7.0	6.0	8.0	6.0	6.0
mean	-5.5	-5.2	-6.0	-6.8	-5.7	-4.0	-2.4	-5.4	-2.2	1.5	0.4	1.2	-3.0	-3.2
stdev	1.9	0.8	1.9	1.6	1.8	3.5	3.8	3.3	5.2	5.6	5.5	4.1	6.7	2.9
SEM	0.7	0.3	0.7	0.6	0.6	1.2	1.3	1.4	2.1	2.1	2.2	1.5	2.8	1.2

Table 8C.65

HCO3- art			exercise						recovery (min)					
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	27.6	27.3	27.6	27.4	28.1	22.1	20.1	13.8	11.7	11.1	10.6	10.2	11.3	22.3
2	27.2	27.3	26.6	25.8	27	16.6	16.4	17.7	7.4	6.9	7.9	8.2	7.9	14.1
3	26.7	26.7	26.8	26.7	26.5	22.3	21.7	22.9	16.1	13.3	14.5	16.5	23.2	19.60
4	30.4	30	30.1	29.7	30	22.1	21.3	22.8	12.5	9.8	10.5	10	10.7	16.5
5	26.2	17.7	18.2	19.3	20.8	13.3	13.1	14.7	11.1	8.9	8.6	9.8	10.7	21.3
6	24.3	24.3	24.8	25.3	25.2	15.7	15.6	15.8	13.1	10.4	10.9	10.6	13.3	23.4
7	25.2	25.1	25.7	25.2	25.6	17.7	16.7	17.3	13.6	12.4	12	11.4	13	20.9
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	26.8	25.5	25.7	25.6	26.2	18.5	17.8	17.9	12.2	10.4	10.7	11.0	12.9	19.7
stdev	2.0	3.9	3.7	3.2	2.9	3.6	3.2	3.7	2.7	2.2	2.2	2.6	4.9	3.3
SEM	0.7	1.5	1.4	1.2	1.1	1.4	1.2	1.4	1.0	0.8	0.8	1.0	1.8	1.3

Table 8C.66

HCO3- ven			exercise						recovery (min)					
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	31.5	31.5	31.3	31	31.4	29.1	26.6	21	19.8	21.1	19	17.8	18.9	25.2
2														
3	29.9	29.9	29.3	30.2	28.8	24.0	26.7	27.7	26.3	25.6	22.7	21.7	20.5	15.9
4														
5	23.8				24.9	16.8	20.1			14.4		13.3	20.6	
6	29.3	29.1	29.6	29.9	29.6	24	25.4	22.4	18.7	25	24.3	24.1	22.6	25.3
7	30	29.9	30.4	30.2	30.1	26.1	25.7	24.2	23.1	25	23.2	21.9	21.3	23.1
8														
9														
10														
n	5	4	4	4	5	5	5	4	4	5	4	5	5	4
mean	28.9	30.1	30.2	30.3	29.0	24.0	24.9	23.8	22.0	22.2	22.3	19.8	20.8	22.4
stdev	3.0	1.0	0.9	0.5	2.5	4.5	2.7	2.9	3.4	4.7	2.3	4.3	1.3	4.4
SEM	1.3	0.5	0.4	0.2	1.1	2.0	1.2	1.4	1.7	2.1	1.1	1.9	0.6	2.2

Table 8C.67

HCO3-av			exercise						recovery (min)					
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	-3.9	-4.2	-3.7	-3.6	-3.3	-7.0	-6.5	-7.2	-8.1	-10.0	-8.4	-7.6	-7.6	-2.9
2														
3	-3.2	-3.2	-2.5	-3.5	-2.3	-1.7	-5.0	-4.8	-10.2	-12.3	-8.2	-5.2	2.7	3.7
4														
5	2.4				-4.1	-3.5	-7.0			-5.5		-3.5	-9.9	
6	-5.0	-4.8	-4.8	-4.6	-4.4	-8.3	-9.8	-6.6	-5.6	-14.6	-13.4	-13.5	-9.3	-1.9
7	-4.8	-4.8	-4.7	-5.0	-4.5	-8.4	-9.0	-6.9	-9.5	-12.6	-11.2	-10.5	-8.3	-2.2
8														
9														
10														
n	5	4	4	4	5	5	5	4	4	5	4	5	5	4
mean	-2.9	-4.3	-3.9	-4.2	-3.7	-5.8	-7.5	-6.4	-8.4	-11.0	-10.3	-8.1	-6.5	-0.8
stdev	3.0	0.8	1.1	0.7	0.9	3.0	1.9	1.1	2.0	3.5	2.5	4.0	5.2	3.0
SEM	1.4	0.4	0.5	0.4	0.4	1.4	0.9	0.5	1.0	1.6	1.2	1.8	2.3	1.5

Table 8C.68

PCO2art			exercise						recovery (min)					
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	41.3	40.7	42	41.1	43.1	37.9	33.4	29.6	27.8	29.6	30.1	29.7	29.3	39.4
2	42.4	45.2	43.2	41.5	46	33.2	33.2	35.4	17.2	17.1	20.9	23.3	22	25.7
3	42.2	41.7	43	41.1	41.1	42.9	37.7	36.4	35.2	28.9	26.5	29.2	32.5	37.4
4	49.7	48.3	49.4	45.3	51	41.6	43.9	41.6	30	25.3	28.8	29.5	31.6	33.3
5	44.1	31.1	30.6	33.7	35.2	28.2	28.2	30.1	27.7	23.2	21.6	28.2	28.6	37.8
6	36.9	36.8	38	38.5	37.5	29.8	32.2	29.6	27.7	24.4	26.1	26.2	32	40.7
7	40.7	41.3	42.5	41.5	43.1	33.9	33.6	33	28.5	27.7	28.5	29.3	31.1	37.4
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	42.5	40.7	41.2	40.4	42.4	35.4	34.6	33.7	27.7	25.2	26.1	27.9	29.6	36.0
stdev	3.9	5.6	5.8	3.6	5.3	5.6	5.0	4.5	5.4	4.3	3.6	2.4	3.6	5.1
SEM	1.5	2.1	2.2	1.3	2.0	2.1	1.9	1.7	2.0	1.6	1.3	0.9	1.4	1.9

Table 8C.69

PCO2ven			exercise						recovery (min)					
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	53.4	52.1	53.3	53.3	55.0	52.9	51.8	44.9	46.3	50.5	49.3	47.9	48.0	47.6
2														
3	55.5	55.3	54.7	51.2	53.6	50.3	48.7	50.3	53.1	52.6	53.5	51.5	47.7	43.9
4														
5	43.5	43.1				46.5	35.2	42.0			38.3		36.6	39.4

6	53.4	52.2	53.4	53.3	53.4	48.1	53.0	45.9	38.8	56.8	60.2	56.7	52.2	44.1
7	57.6	56.5	59.8	59.0	59.6	54.8	58.1	52.4	54.3	63.7	60.3	56.5	52.9	46.7
8														
9														
10														
n	5	5	4	4	4	5	5	5	4	4	5	4	5	5
mean	52.7	51.8	55.3	54.2	55.4	50.5	49.4	47.1	48.1	55.9	52.3	53.2	47.5	44.3
stdev	5.4	5.3	3.1	3.3	2.9	3.4	8.6	4.2	7.1	5.8	9.1	4.2	6.5	3.2
SEM	2.4	2.3	1.5	1.7	1.4	1.5	3.9	1.9	3.6	2.9	4.1	2.1	2.9	1.4

Table 8C.70

PO2art			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	72.1	68.2	78.0	96.9	77.6	96.9	105.6	115.0	107.4	112.8	112.4	111.7	111.2	83.5
2	131.8	89.0	97.9	103.2	84.2	96.7	111.0	82.9	95.7	112.2	112.6	114.6	130.8	158.1
3	99.9	86.8	102.2	110.2	89.8	83.5	110.1	104.8	104.7	133.1	157.9	98.0	81.3	98.0
4	91.8	90.5	91.6	103.9	84.7	90.4	102.3	86.4	96.9	104.8	105.6	107.2	103.5	90.4
5	98.4	97.2	109.0	109.8	84.3	101.2	115.3	92.3	103.5	117.2	120.7	109.6	109.9	81.9
6	108.1	105.4	108.3	114.6	123.7	101.6	118.1	104.0	106.9	123.1	141.9	121.7	124.0	79.1
7	108.8	102.5	105.5	110.4	102.7	110.7	125.5	105.1	119.5	129.3	126.8	137.1	124.6	98.4
8	104.1	97.7	100.4	118.4	101.2	107.1	126.3	102.4	144.5	121.3	119.2	132.7	113.8	106.3
9	107.0	102.7	101.2	117.3	94.9	102.5	115.7	100.3	100.3	105.4	114.2	119.3	106.1	84.6
10	48.8	54.6	49.0	77.3	73.2	73.0	54.5					80.5		
n	10	10	10	10	10	10	10	9	9	9	9	10	9	9
mean	97.1	89.5	94.3	106.2	91.6	96.4	108.4	99.2	108.8	117.7	123.5	113.2	111.7	97.8
stdev	22.6	16.3	18.3	12.1	14.7	11.3	20.5	10.2	15.1	9.9	16.6	16.4	14.6	24.4
SEM	7.2	5.2	5.8	3.8	4.7	3.6	6.5	3.4	5.0	3.3	5.5	5.2	4.9	8.1

Table 8C.71

PO2ven			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	27.8	28.2	22.5	26.4	29.9	33.7	30.7	40.4	37.3	31.9	39.2	36.3	33.5	29.6
2														
3	28.4	28.8	34.6	33.1	35.7	34.00	37.3	37.7	27.6	27.6	35.6	34.7	35.20	33.2
4														
5	28				35.3	55.9	35.6			64.2		70	45.7	
6	21.8	24.5	21.3	21.5	25.7	29.6	23.6	34.9	50	20.9	19.4	18.7	23.2	34.2
7	23.1	24.8	24.7	24.5	25.5	27.1	28.1	31.5	28.4	22.7	20.7	25.8	33.4	25.9
8	26.2	25.5	25.9	30.3	28.3	28.8	29	35.1	28.9	19.7	32	33.9	29.2	23.7
9	22.9	27.9	23.4	26.4	28.8	25.4	17	41.6	41.6	22.1	29.1	42.6	53.1	29.1
10	22.4	25.3	25.5	29.9	32.2	36.7	27.3		17.1	23.7	24.4	28.6	30.1	32.6
n	8	7	7	7	8	8	8	6	7	8	7	8	8	7
mean	25.08	26.43	25.41	27.44	30.18	33.90	28.58	36.87	32.99	29.10	28.63	36.33	35.43	29.76
stdev	2.80	1.80	4.37	3.92	3.93	9.67	6.44	3.78	10.81	14.72	7.50	15.41	9.58	3.91
SEM	0.99	0.68	1.65	1.48	1.39	3.42	2.28	1.54	4.09	5.20	2.84	5.45	3.39	1.48

Metabolism (Control). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [$Blac^-$], blood CO_2 content (CCO_2), blood O_2 content (CO_2); at rest (R), during submaximal cycling exercise (e1 to e3+1) to fatigue (F), and recovery (1 to 30min). Units are mM for [$Blac^-$]; $ml.min^{-1}$ for CCO_2, CO_2. $[Blac^-]_{a-v}$ was corrected for arterio-venous ΔBV.

Table 8C.72

CCO2 art		exercise							recovery (min)					
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	653.8	638.7	652.6	648.6	629.1	476.1	426.8	487.4	264.1	228.9	219.9	196.8	163.9	369.3
2	598.9	577.4	568.0	591.7	582.5	367.4	332.6	363.9	238.2	172.1	176.1	196.7	205.9	413.7
3	625.4	636.2	662.0	637.6	668.2	426.4	451.6	495.4	353.4	326.5	341.9	251.8	311.0	609.2
4	661.0	655.0	649.0	615.9	670.0	406.2	397.4	411.9	315.0	247.7	246.5	221.0	249.1	461.1
5	602.9	620.1	603.2	582.9	573.6	434.6	419.4	465.8	299.2	242.9	257.1	283.9	308.7	568.9
6	622.2	637.2	642.1	637.8	600.7	347.3	358.8	335.0	304.6	240.4	250.2	257.3	306.2	569.6
7	624.6	643.6	659.9	646.3	660.5	447.3	421.4	446.8	280.2	236.4	250.4	251.5	288.7	491.0
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	627.0	629.7	633.8	623.0	626.4	415.1	401.1	429.5	293.5	242.1	248.9	237.0	261.9	497.6
stdev	23.4	25.3	35.1	26.7	41.2	45.1	41.7	61.7	37.2	45.2	49.8	33.0	58.0	89.1
SEM	8.8	9.6	13.3	10.1	15.6	17.0	15.8	23.3	14.1	17.1	18.8	12.5	21.9	33.7

Table 8C.73

CCO2 ven		exercise							recovery (min)					
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	688.7	693.6	705.6	726.3	669.2	593.1	560.7	574.9	464.9	507.7	471.4	413.9	289.5	467.5
2														
3	772.8	805.7	751.8	740.0	531.0	588.2	590.2	633.6	674.5	605.9	413.8	432.4	580.7	705.1
4														
5	653.6	661.9	696.3	606.4	650.6	436.1	456.4	479.6	542.0	321.8	384.8	489.1	352.0	653.3
6	814.4	758.3	745.5	733.6	739.3	568.2	615.3	545.5	497.9	567.7	570.7	484.4	482.5	667.4
7	798.5	796.6	824.8	811.6	816.9	717.5	741.7	704.7	494.2	695.8	659.3	562.2	604.7	522.2
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	745.6	743.2	744.8	723.6	681.4	580.6	592.9	587.7	534.7	539.8	500.0	476.4	461.9	603.1
stdev	70.7	63.4	50.9	73.9	106.6	100.0	102.8	85.7	82.8	139.7	113.9	58.0	138.5	102.5
SEM	31.6	28.3	22.7	33.1	47.7	44.7	46.0	38.3	37.1	62.5	50.9	25.9	61.9	45.8

Table 8C.74

CCO2 a-v		exercise							recovery (min)					
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	-34.9	-54.8	-53.0	-77.6	-40.1	-117.0	-133.9	-87.6	-200.9	-278.8	-251.5	-217.0	-125.6	-98.2
2														
3	-147.3	-169.4	-89.8	-102.3	137.1	-161.8	-138.7	-138.2	-321.1	-279.4	-72.0	-180.6	-269.7	-95.9
4														
5	-50.7	-41.8	-93.1	-23.5	-77.0	-1.5	-37.0	-13.8	-242.8	-78.9	-127.8	-205.2	-43.3	-84.5
6	-192.2	-121.1	-103.5	-95.8	-138.6	-220.9	-256.5	-210.6	-193.3	-327.3	-320.5	-227.1	-176.3	-97.8
7	-173.9	-153.0	-164.9	-165.4	-156.4	-270.2	-320.3	-257.9	-213.9	-459.3	-408.9	-310.8	-316.0	-31.1
8														
9														
10														
n	5	5	5	5	5	5	5	5	5	5	5	5	5	5
mean	-119.8	-108.0	-100.9	-92.9	-55.0	-154.3	-177.3	-141.6	-234.4	-284.8	-236.1	-228.1	-186.2	-81.5
stdev	72.3	57.4	40.6	51.0	117.1	103.3	111.6	96.9	52.0	136.7	137.7	49.3	109.6	28.7
SEM	32.3	25.7	18.1	22.8	52.4	46.2	49.9	43.3	23.3	61.1	61.6	22.1	49.0	12.8

Table 8C.75

CO2 art		exercise							recovery (min)					
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	186.9	192.3	190.5	188.3	190.9	200.0	192.9	193.8	207.7	204.9	202.9	200.7	198.6	180.9
2	200.1	201.8	201.8	199.6	204.9	215.1	213.0	213.8	224.2	220.8	220.4	215.6	211.7	198.6
3	178.2	179.0	178.5	179.9	181.0	185.9	185.8	184.2	194.6	192.2	188.1	180.3	181.2	167.3
4	191.3	194.8	195.2	195.1	196.5	209.9	207.2	210.6	218.0	212.7	213.4	209.9	204.4	190.1
5	204.6	203.1	203.1	204.3	205.9	217.3	215.1	218.2	227.8	224.6	224.8	216.4	213.4	203.5
6	203.9	208.3	207.6	205.9	211.5	223.7	222.8	226.9	229.3	225.8	227.1	209.0	200.7	191.7
7	211.6	209.2	205.6	210.3	225.5	228.8	219.8	225.2	228.9	229.9	228.7	219.3	215.6	204.0
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	196.6	198.4	197.5	197.6	202.3	211.5	208.1	210.4	218.6	215.8	215.1	207.3	203.7	190.9
stdev	11.7	10.6	10.3	10.7	14.5	14.6	13.9	16.0	13.1	13.4	14.9	13.4	11.8	13.2
SEM	4.4	4.0	3.9	4.0	5.5	5.5	5.2	6.0	5.0	5.1	5.6	5.1	4.5	5.0

Table 8C.76

CO2 ven		exercise							recovery (min)					
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	122.5	123.5	102.2	109.9	126.6	128.6	123.4	139.3	122.0	91.2	111.9	99.6	98.7	112.2
2														

3	82.5	74.0	90.1	126.5	118.8	103.2	132.5	132.8	62.1	98.4	92.0	120.1	106.7	101.3
4														
5	166.3	162.4	108.7	173.8	165.9	217.5	215.1	210.8	126.1	180.7	209.9	120.1	208.2	124.2
6	206.6	97.6	109.6	123.2	131.1	142.2	149.7	128.5	145.2	76.0	73.8	119.8	110.2	97.8
7	64.2	72.5	78.7	84.2	89.4	102.4	66.1	94.7	191.9	51.5	73.4	101.2	138.1	127.1
8														
9														
10														
n	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
mean	128.4	106.0	97.9	123.5	126.3	138.8	137.4	141.2	129.5	99.6	112.2	112.2	132.4	112.5
stdev	58.7	37.8	13.2	32.7	27.4	47.2	53.6	42.5	46.8	48.8	56.9	10.8	44.9	13.2
SEM	26.3	16.9	5.9	14.6	12.3	21.1	24.0	19.0	20.9	21.8	25.4	4.8	20.1	5.9

Table 8C.77

CO2 a-v			**exercise**							**recovery (min)**				
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	64.4	68.8	88.2	78.4	64.3	71.4	69.5	54.4	85.7	113.7	91.0	101.1	99.9	68.8
2														
3	95.6	105.0	88.4	53.4	62.3	82.7	53.3	51.4	132.6	93.9	96.1	60.2	74.5	65.9
4														
5	38.3	40.8	94.4	30.5	40.0	-0.2	0.0	7.4	101.6	43.9	14.9	96.3	5.2	79.3
6	-2.7	110.7	98.0	82.7	80.3	81.5	73.1	98.4	84.1	149.8	153.4	89.2	90.5	93.9
7	147.4	136.7	126.9	126.1	136.1	126.3	153.7	130.5	37.0	178.4	155.3	118.1	77.5	76.8
8														
9														
10														
n	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
mean	68.6	92.4	99.2	74.2	76.6	72.4	69.9	68.4	88.2	115.9	102.1	93.0	69.5	76.9
stdev	56.9	37.7	16.0	35.8	36.2	45.7	55.2	47.4	34.6	51.8	57.5	21.2	37.4	11.0
SEM	25.5	16.9	7.2	16.0	16.2	20.5	24.7	21.2	15.5	23.2	25.7	9.5	16.7	4.9

Table 8C.78

Blac- art		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.6	1.1	2.1	7.2	11.7	15.9	18.3	20.6	16.1	7.1
2	0.7	1.2	9.2	9.2	17.0	15.8	16.8	15.3	15.0	8.3
3										
4	1.0	1.2	11.0	10.9	15.8	16.0	16.4	17.9	14.6	7.0
5	1.1	1.4	7.2	6.9	14.5	14.4	12.6	12.3	13.0	6.5
6	0.7	1.0	10.8	7.3	14.3	19.8	10.6	13.9	8.9	4.3
7										
8	1.9	1.9	7.0	6.6	17.9	15.9	15.2	14.7	12.8	6.6
9	1.9	1.5	12.4	15.1	16.4	12.2	13.8	11.8	13.1	6.3
10	1.5	4.7	9.0	6.4	12.7	15.4	10.5	15.4	9.0	3.8
n	8	8	8	8	8	8	8	8	8	8
mean	1.3	1.7	8.6	8.7	15.0	15.7	14.3	15.2	12.8	6.2
stdev	0.5	1.2	3.2	3.0	2.1	2.1	2.9	2.9	2.6	1.5
SEM	0.2	0.4	1.1	1.1	0.8	0.7	1.0	1.0	0.9	0.5

Table 8C.79

Blac- ven		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	1.2	2.9	4.5	4.8	11.1	10.2	12.2	12.2	11.3	6.8
2										
3										
4										
5	1.1	1.5	6.5	7.3	10.3	11.7	9.0	9.1	11.5	4.9
6	0.6	0.8	7.2	8.5	8.9	7.5	8.6	10.1	8.9	3.2
7										
8	2.6	2.0	6.0	4.5	9.0	9.9	11.6	9.0	13.6	8.3
9	1.8	7.4	12.8	16.7	15.3	15.2	19.3	17.4	13.0	5.3
10	1.8	1.7	7.1	7.8	6.2	6.5	7.2	5.9	5.6	2.4
n	6	6	6	6	6	6	6	6	6	6
mean	1.5	2.7	7.4	8.2	10.1	10.2	11.3	10.6	10.6	5.1
stdev	0.7	2.4	2.8	4.4	3.0	3.1	4.4	3.9	3.0	2.2
SEM	0.3	1.0	1.2	1.8	1.2	1.3	1.8	1.6	1.2	0.9

Table 8C.80

Blac-a-v		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0.4	-1.8	-2.4	2.4	0.7	5.8	6.3	8.6	4.9	0.3
2										
3										
4										
5	0.0	-0.1	0.8	-0.2	4.4	2.6	3.7	3.4	1.5	1.7
6	0.1	0.2	3.7	-1.1	5.5	12.5	2.1	3.9	0.2	1.2
7										
8	-0.7	-0.1	1.0	2.2	9.1	6.2	3.7	5.9	-0.7	-1.7
9	0.1	-5.9	-0.4	-1.5	1.2	-3.0	-5.4	-5.4	0.2	1.1
10	-0.3	3.0	2.0	-1.3	6.5	9.0	3.4	9.7	3.5	1.5
n	6	6	6	6	6	6	6	6	6	6
mean	-0.1	-0.8	0.8	0.1	4.6	5.5	2.3	4.3	1.6	0.7
stdev	0.4	3.0	2.1	1.8	3.2	5.3	4.0	5.4	2.2	1.3

SEM	0.2	1.2	0.9	0.7	1.3	2.2	1.6	2.2	0.9	0.5

Metabolism (Digoxin). Arterial (art), venous (ven) and changes in venous compared to arterial plasma (a-v) across the forearm for [$Blac^-$], blood CO_2 content (CCO_2), blood O_2 content (CO_2); at rest (R), during submaximal cycling exercise (e1 to e3+1) to fatigue (F), and recovery (1 to 30min). Units are mM for [$Blac^-$]; $ml.min^{-1}$ for CCO_2, CO_2. $[Blac^-]_{a-v}$ was corrected for arterio-venous ΔBV.

Table 8C.81

CCO2 art			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	675.7	669.1	674.5	667.6	687.5	541.1	491.2	338.8	288.0	272.3	261.3	252.1	277.3	546.0
2	661.4	669.3	652.0	632.1	662.8	407.4	403.0	433.8	183.0	170.4	193.7	202.8	195.7	345.7
3	655.5	633.1	685.2	653.3	621.1	619.4	549.3	579.1	480.1	355.6	321.5	363.2	493.6	505.6
4	743.4	734.6	737.3	726.2	733.8	541.3	521.1	559.1	308.3	241.9	258.1	247.8	264.2	403.3
5	640.2	433.2	446.3	471.5	508.8	325.3	320.8	360.9	273.5	219.9	211.8	241.7	263.8	520.6
6	594.8	594.8	608.6	619.4	619.1	385.6	383.7	386.6	321.3	255.0	268.5	259.9	328.2	573.8
7	613.2	615.3	628.7	616.7	627.5	433.3	409.3	423.7	333.4	304.7	294.3	280.2	318.8	511.5
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	654.9	621.3	633.2	626.7	637.2	464.8	439.8	440.3	312.5	260.0	258.4	264.0	306.0	486.6
stdev	48.1	94.6	92.3	78.0	70.3	104.6	82.5	94.2	89.0	59.5	44.2	49.6	93.4	81.7
SEM	18.2	35.8	34.9	29.5	26.6	39.5	31.2	35.6	33.6	22.5	16.7	18.8	35.3	30.9

Table 8C.82

CCO2 ven			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	779.3	777.8	780.8	768.6	776.3	716.5	659.7	518.2	489.1	524.7	473.1	442.0	470.4	625.4
2														
3	739.5	747.2	768.6	710.3	752.9	620.5	636.3	646.1	658.9	625.8	583.6	578.5	518.6	601.8
4														
5	589.7					544.4	415.0						462.2	
6	730.0	726.9	745.4	755.4	737.6	597.4	639.4	554.1	459.4	642.6	631.2	628.2	572.2	623.6
7	751.6	745.6	759.2	755.3	750.4	650.2	641.6	601.3	576.0	631.9	595.6	551.8	528.8	571.0
8														
9														
10														
n	5	4	4	4	4	5	5	4	4	4	4	4	5	4
mean	718.0	749.4	763.5	747.4	754.3	625.8	598.4	579.9	545.9	606.3	570.9	550.1	510.4	605.4
stdev	74.1	21.1	15.0	25.6	16.1	63.8	102.9	55.7	90.2	54.8	68.3	78.7	45.2	25.3
SEM	33.1	10.5	7.5	12.8	8.1	28.5	46.0	27.9	45.1	27.4	34.1	39.4	20.2	12.7

Table 8C.83

CCO2 a-v			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	-103.6	-108.7	-106.3	-101.0	-88.9	-175.4	-168.4	-179.4	-201.1	-252.4	-211.8	-189.9	-193.0	-79.4
2														
3	-84.0	-114.1	-83.4	-56.9	-131.7	-1.1	-87.1	-67.0	-178.9	-270.2	-262.1	-215.2	-24.9	-96.2
4														
5	50.5					-219.1	-94.3						-198.4	
6	-135.2	-132.0	-136.7	-136.0	-118.5	-211.8	-255.7	-167.5	-138.1	-387.6	-362.8	-368.3	-243.9	-49.8
7	-138.3	-130.3	-130.5	-138.7	-122.9	-216.9	-232.3	-177.6	-242.7	-327.2	-301.4	-271.6	-210.0	-59.5
8														
9														
10														
n	5.0	4.0	4.0	4.0	4.0	5.0	5.0	4.0	4.0	4.0	4.0	4.0	5.0	4.0
mean	-82.1	-121.3	-114.2	-108.2	-115.5	-164.9	-167.6	-147.9	-190.2	-309.4	-284.5	-261.3	-174.1	-71.2
stdev	77.5	11.7	24.4	38.2	18.6	93.3	77.2	54.2	43.6	61.1	63.8	79.1	85.7	20.7
SEM	34.7	5.8	12.2	19.1	9.3	41.7	34.5	27.1	21.8	30.6	31.9	39.5	38.3	10.4

Table 8C.84

CO2 art			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30
1	194.9	195.0	195.1	192.6	196.0	198.4	194.4	207.4	202.7	202.5	201.0	199.0	192.1	189.3
2	206.9	222.2	223.6	223.4	225.0	222.0	234.5	241.4	230.3	221.4	215.4	208.6	206.0	193.2
3	178.0	178.0	179.5	177.5	179.5	182.8	185.9	189.2	195.4	198.2	194.8	187.2	182.0	170.2
4	197.6	206.1	201.0	199.2	200.7	211.9	208.1	211.0	221.6	218.0	217.1	211.9	203.9	195.4
5	199.8	200.9	201.5	201.1	200.8	218.2	217.6	217.5	226.9	222.8	222.6	218.6	212.3	200.2
6	210.3	213.6	216.2	214.5	219.1	230.4	230.7	233.3	236.1	233.9	236.0	233.3	227.0	208.1
7	203.5	207.7	205.5	204.6	209.2	221.5	220.0	219.8	226.3	225.5	225.9	222.0	216.5	201.6
8														
9														
10														
n	7	7	7	7	7	7	7	7	7	7	7	7	7	7
mean	198.7	203.4	203.2	201.8	204.3	212.2	213.0	217.1	219.9	217.5	216.1	211.5	205.7	194.0
stdev	10.6	14.2	14.3	14.8	15.2	16.4	18.0	17.2	15.0	12.7	14.2	15.2	15.1	12.2
SEM	4.0	5.4	5.4	5.6	5.7	6.2	6.8	6.5	5.7	4.8	5.4	5.8	5.7	4.6

Table 8C.85

CO2 ven			exercise							recovery (min)				
Subject	R	e1+1	e1	pe2	e2+1	e2	pe3	e3+1	F	1	2	5	10	30

1	110.2	113.3	90.5	113.7	120.6	136.8	112.8	151.4	134.9	116.6	135.8	120.3	109.3	103.8
2														
3	97.5	99.3	124.6	120.3	128.0	127.3	136.0	131.6	100.1	97.6	123.6	121.1	110.2	122.8
4														
5	119.2				143.9	199.8	156.6					208.0		125.9
6	84.1	93.7	75.3	76.1	97.8	123.0	89.5	151.2	197.2	68.9	55.9	54.6	79.7	139.5
7	80.7	90.8	89.4	86.3	91.1	107.6	106.2	129.1	109.8	79.2	61.8	85.9	120.5	121.2
8														
9														
10														
n	5	4	4	4	5	5	5	4	4	4	4	5	4	5
mean	98.3	99.3	94.9	99.1	116.3	138.9	120.2	140.8	135.5	90.6	94.3	118.0	104.9	122.6
stdev	16.5	10.0	21.0	21.3	21.8	35.6	26.3	12.2	43.7	21.0	41.3	57.4	17.5	12.8
SEM	7.4	5.0	10.5	10.6	9.7	15.9	11.8	6.1	21.9	10.5	20.6	25.7	8.8	5.7

Table 8C.86

CO2 a-v			**exercise**								**recovery (min)**			
Subject	**R**	**e1+1**	**e1**	**pe2**	**e2+1**	**e2**	**pe3**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	84.7	81.7	104.5	78.9	75.4	61.6	81.5	56.0	67.9	85.9	65.2	78.6	82.9	85.5
2														
3	80.5	78.8	54.9	57.2	51.5	55.5	50.0	57.6	95.3	100.6	71.2	66.1	71.8	47.4
4														
5	80.6				56.9	18.5	60.9					10.6		74.2
6	126.2	119.9	141.0	138.4	121.3	107.4	141.2	82.1	38.8	165.0	180.1	178.7	147.2	68.6
7	122.8	116.9	116.1	118.3	118.1	113.9	113.7	90.7	116.5	146.2	164.1	136.0	96.0	80.4
8														
9														
10														
n	5	4	4	4	5	5	5	4	4	4	4	5	4	5
mean	99.0	99.3	104.1	98.2	84.6	71.4	89.5	71.6	79.6	124.4	120.2	94.0	99.5	71.2
stdev	23.4	22.1	36.2	36.8	33.2	39.6	37.8	17.4	33.7	37.3	60.4	65.0	33.3	14.7
SEM	10.5	11.0	18.1	18.4	14.9	17.7	16.9	8.7	16.9	18.7	30.2	29.1	16.7	6.6

Table 8C.87

Blac-art		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0.2	0.4	6.2	13.8	15.5	16.2	17.0	6.9	8.9	5.1
2	0.4	0.9	0.8	7.8	6.0	12.1	14.3	13.6	13.5	13.8
3										
4	0.5	2.2	3.1	7.4	18.6	16.6	18.4	17.6	15.5	10.1
5	1.5	3.0	11.5	11.5	17.0	18.2	17.0	19.2	16.1	7.7
6	1.7	0.9	10.9	9.5	5.7	16.4	14.2	13.0	12.6	4.6
7										
8	0.8	1.3	6.5	6.0	19.6	19.3	16.2	17.1	13.6	9.9
9	1.3	1.5	14.7	15.8	17.6	15.6	19.8	16.7	16.2	8.2
10	1.1	1.5	5.3					6.2		
n	8	8	8	7	7	7	7	8	7	7
mean	0.9	1.4	7.4	10.3	14.3	16.4	16.7	13.8	13.8	8.5
stdev	0.6	1.0	4.2	2.9	6.3	2.5	1.7	4.4	2.5	3.5
SEM	0.2	0.3	1.5	1.1	2.4	0.9	0.6	1.6	1.0	1.3

Table 8C.88

Blac- ven		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	0.4	0.5	10.9	10.0	8.9	11.2	10.5	10.8	11.5	5.1
2										
3										
4										
5	2.4		10.2					16.1		9.2
6	2.0	1.6	7.4	8.9	10.4	6.8	8.9	8.1	6.9	3.6
7										
8	0.7	0.8	3.4	6.1	14.5	15.8	11.2	6.7	10.4	6.4
9	2.4	2.1	7.7	8.4	10.4	9.2	10.9	9.8	9.2	8.1
10	0.9	1.1	3.8		3.6	3.8	4.3	4.3	4.2	6.4
n	6	5	6	4	5	5	5	6	5	6
mean	1.5	1.2	7.2	8.3	9.6	9.4	9.2	9.3	8.4	6.5
stdev	0.9	0.6	3.1	1.6	3.9	4.5	2.9	4.1	2.9	2.0
SEM	0.4	0.3	1.3	0.8	1.8	2.0	1.3	1.7	1.3	0.8

Table 8C.89

Blac-a-v		**exercise**				**recovery (min)**				
Subject	**R**	**e1**	**e2**	**e3+1**	**F**	**1**	**2**	**5**	**10**	**30**
1	-0.2	-0.1	-4.6	4.0	6.8	5.5	6.8	-3.8	-2.4	0.0
2										
3										
4										
5	-0.9		1.4					3.3		-1.4
6	-0.4	-0.7	3.6	0.7	-4.7	9.8	5.4	5.0	5.8	1.0
7										
8	0.2	0.5	3.2	-0.1	5.3	3.7	5.2	10.6	3.3	3.5
9	-1.1	-0.5	7.1	7.4	7.3	6.6	9.2	7.0	7.2	0.2
10	0.3	0.4	1.6					2.0		
n	6	5	6	4	4	4	4	6	4	5

mean	-0.4	-0.1	2.0	3.0	3.7	6.4	6.6	4.0	3.5	0.7
stdev	0.6	0.5	3.9	3.4	5.7	2.6	1.8	4.9	4.2	1.8
SEM	0.2	0.2	1.6	1.7	2.8	1.3	0.9	2.0	2.1	0.8