CIRCUIT RESISTANCE TRAINING IN CHRONIC HEART FAILURE IMPROVES SKELETAL MUSCLE MITOCHONDRIAL ATP PRODUCTION RATE – A RANDOMISED CONTROLLED TRIAL

Resistance Training in Heart Failure

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ABSTRACT

Background. We aimed to determine the role of skeletal muscle mitochondrial ATP production rate (MAPR) in relation to exercise tolerance following resistance training in CHF.

Methods and Results. Thirteen CHF patients (NYHA functional class 2.3 ± 0.5; LVEF 26 ± 8%; age 70 ± 8 years) underwent testing for $\dot{V}O_{2\ peak}$, and resting vastus lateralis muscle biopsy. Patients were then randomly allocated to 11 weeks of RT, (n = 7) or continuance of usual care (C, n = 6) following which testing was repeated. Muscle samples were analysed for MAPR, metabolic enzyme activity and capillary density.

$\dot{V}O_{2\ peak}$ and MAPR in the presence of the pyruvate and malate (P+M) substrate combination, representing carbohydrate metabolism, increased in RT ($p<0.05$) and decreased in C ($p<0.05$) with a significant difference between groups ($\dot{V}O_{2\ peak}$ $p = 0.005$; MAPR $p = 0.03$). There was a strong correlation between the change in MAPR and the change in $\dot{V}O_{2\ peak}$ over the study ($r = 0.875$; $p < 0.0001$), the change in MAPR accounting for 70% of the change in $\dot{V}O_{2\ peak}$.

Conclusions. These findings suggest that mitochondrial ATP production is a major determinant of aerobic capacity in CHF patients and can be favourably altered by muscle strengthening exercise.

KEY WORDS: exercise, oxidative capacity, skeletal muscle.

INTRODUCTION

Chronic heart failure (CHF) is characterized by a low peak oxygen uptake ($\dot{V}O_{2\ peak}$) that is an independent predictor of morbidity and mortality (1, 2). The low $\dot{V}O_{2\ peak}$ is associated with impaired exercise tolerance and early onset of lactic acidosis during incremental exercise (3). Muscle oxidative function is reduced in CHF and it is widely accepted that this is a major cause of exercise intolerance in this patient group. Additionally, muscle atrophy may also contribute to the reduced exercise capacity in CHF patients (3, 4). These patients also exhibit reduced muscle strength due at least partly to the significant muscle atrophy (4). Both the low exercise capacity and the reduced strength contribute to functional impairment in these patients.

Traditionally, endurance training (ET) has been the recommended modality to increase $\dot{V}O_{2\ peak}$ and muscle oxidative capacity. However, this form of training has little influence on muscle mass (5, 6). Conversely, resistance training (RT) results in increases in muscle strength and skeletal muscle hypertrophy in healthy young volunteers (7, 8), but generally has been thought not to change muscle oxidative capacity (9) or capillary density (7). Morphometric changes that occur in response to RT in young participants include a transition from type IIX to IIA fibres (9). Likewise, studies that investigated the effects of RT in healthy elderly subjects reported gains in muscle strength and muscle mass (10, 11) and fibre type transitions from IIX to IIA fibres (11). However, in healthy elderly volunteers, RT has also been demonstrated to increase endurance exercise capacity ($\dot{V}O_{2\ peak}$) in conjunction with increases in skeletal muscle oxidative capacity (10) and the capillary to fibre perimeter exchange index (12).

Previously we have reported significant improvements in both muscle strength and $\dot{V}O_{2\ peak}$ in CHF patients randomized to 11 weeks of RT compared with a control group which had no increase in muscle strength and a slight decrease in $\dot{V}O_2$ (13). The current study investigated a separately stratified cohort of the CHF patients from our previous work with the aim of investigating the effect of resistance exercise training on skeletal muscle mitochondrial ATP production rate (MAPR) as an integrated measure of muscle oxidative capacity, and secondarily to relate changes in MAPR, metabolic enzyme activity and capillary density to changes in $\dot{V}O_{2\ peak}$.

In particular, it was hypothesized that improved skeletal muscle MAPR might explain the improvements in exercise tolerance produced by a program of muscle strengthening exercise in CHF patients.

METHODS

Inclusion criteria were: Patients with left ventricular systolic failure, ejection fraction below 40%, New York Heart Association (NYHA) functional classes II and III, and stable (>2 weeks) pharmacological therapy. All patients were a minimum of six months post any coronary intervention that might lead to improvements in left ventricular function prior to commencement in the study.

Exclusion criteria were: Current angina or occurrence within the previous 6 months of myocardial infarction, cardiac arrest, symptomatic or sustained ventricular tachycardia; musculoskeletal or respiratory problems or other co-morbidity that contraindicate exercise; baseline assessment suggesting unsatisfactory control of heart failure, symptoms preventing the undertaking of exercise, exercise-induced ventricular tachycardia (symptomatic or sustained), or blood pressure drop of ≥ 20 mmHg during baseline exercise testing for $\dot{V}O_{2\,peak}$. Patients were withdrawn if they developed any of the above exclusion criteria during participation in the study.

Patients consenting to skeletal muscle biopsy underwent a separate stratified randomization. Medical management continued throughout the study, and the control group was advised to maintain previous (i.e. pre – study) activity levels which were generally sedentary.

Written informed consent was obtained from all patients prior to their entry into this study that was approved by the Human Research Ethics Committees of Austin Health and Victoria University of Technology and complied with the Declaration of Helsinki.

Resistance training protocol.

Training (three months, 3 sessions per week) was undertaken in the hospital gymnasium using a multi-station hydraulic resistance training system (HydraGym, Belton, USA), arm (Repco, Melbourne, Australia) and leg cycling (Repco, Melbourne, Australia) ergometers, and a set of stairs as previously described (13). Briefly, the graduated resistance training program used the following exercises, alternating between upper and lower body: leg cycling (0.5 - 2 min), elbow extension / flexion (30 s), stair climbing (0.5 - 2 min), arm cycling (0.5 - 2 min), knee extension / flexion (30 s), shoulder press / pull (30 s). Recovery intervals between exercises were determined as the period required to return heart rate to within 10 beats of the pre-exercise (rest) recording. For safety reasons workload intensities were reduced if the heart rate response to a station was within 5 $b.min^{-1}$ of peak heart rate. Exercise progressions were introduced gradually either by increasing intensity (resistance) or the number of sets for a given exercise. Adherence was monitored as attendance. Adverse events were documented. Cardiac rate and rhythm were continuously monitored and recorded during exercise on a four channel (patient) telemetry system (prototype designed by Victoria University bioengineers, Melbourne, Australia).

Exercise Tests and Blood Sampling.

Peak total body oxygen consumption ($\dot{V}O_{2\ peak}$) was determined during a symptom-limited graded exercise test on an electronically braked bicycle ergometer (Ergomed, Siemens, Erlangen, Germany), commencing at 10 W and increasing by 10 $W.min^{-1}$ to volitional fatigue or a level of 17 on the 6-20 point Borg scale of perceived exertion (14). Expired volume and expired oxygen and carbon dioxide concentrations were analysed and used to compute $\dot{V}O_2$, carbon dioxide production (VCO_2), respiratory exchange ratio ($RER = VCO_2/\dot{V}O_2$) and ventilatory equivalents ($V_E/\dot{V}O_2$) as previously described (13). Arterialised blood samples were obtained during the incremental exercise test from a dorsal hand vein via a 20-guage indwelling catheter. Oxygen saturation in the blood samples was consistently in excess of 95%, confirming arterialisation. Details of the exercise testing protocols and measurements have been reported previously (13). Plasma lactate levels were determined and lactate threshold calculated using a log-log transformation plot of plasma lactate concentration versus power output as previously described (3).

Unilateral (right leg) skeletal muscle strength for knee extension/flexion were assessed using an isokinetic dynamometer (MERAC, Universal, Cedar Rapids, Iowa), with microprocessor, as described previously (3, 13, 15, 16)

Muscle Biopsy.

Approximately 4 days after both the baseline and final incremental exercise tests for measuring $\dot{V}O_{2\ peak}$, resting muscle biopsies were obtained from the vastus lateralis. These were separated and stored as described previously (3). Fresh muscle (35-40mg) was placed on ice and immediately taken to the laboratory for the determination of MAPR. A second piece of muscle (15-20mg) was immediately frozen in liquid nitrogen for later analyses of enzyme activities. A third piece (15-20mg) was embedded in Tissue Tek mounting medium and immediately immersed in isopentane that had been cooled in liquid nitrogen, and then stored in liquid nitrogen for later histochemical analysis.

Analytical Measurements.

Muscle samples were used to determine MAPR. Fresh muscle was placed on a plate over ice, dissected free of visible connective tissue, minced finely with a scalpel blade, and then transferred to a ground glass tissue homogenizing tube (Kontes, New Jersey) for weighing and homogenization as described previously (3). The homogenizing solutions and the procedures for the preparation of the mitochondrial suspension have previously been described by Wibom and Hultman (17).

In brief, MAPR was determined at 25^{o}C by a chemiluminescence method using a combination of pyruvate and malate (P+M) representing pathways of carbohydrate metabolism as the principal substrate. Four other substrate combinations representing fat (palmitoyl carnitine and malate; PC+M), protein (alphaketoglutarate; α-kg), complex II of the electron transport chain (succinate and rotenone; S+R) and a mixture of carbohydrate, protein and fat metabolism (pyruvate, palmitoyl carnitine, malate and alphaketoglutarate; PPKM) were secondarily tested. All measurements of MAPR were

made in duplicate, completed within 4 h of biopsy and are expressed as $mmol.min^{-1}.kg^{-1}$ wet weight of muscle. ATP production by the adenylate kinase reaction and other non-specific reactions was determined from a blank containing ADP and mitochondrial suspension alone. Methods for determining the activity of oxidative enzymes citrate synthase (CS) and β-hydroxyacyl coenzyme A dehydrogenase (HAD), and glycolytic enzymes phosphofructokinase (PFK) and lactate dehydrogenase (LDH), and the method for quantitating capillary density, have been previously described (3).

Capillary Density

Cross-sections (16mm) of the muscle were stained for capillary density using the periodic acid Schiff-amylase method (18). The capillary to fibre ratio was determined by dividing the number of capillaries in a section by the number of muscle fibres and were determined from sections containing 197 ± 13 (mean ± SEM) fibres.

Statistical Analysis.

Data was analysed using two-way repeated measures analysis of variance (ANOVA) with group and time factors (SPSS v 11.0; Chicago, Illinois). Where significant main effects (group or time) were identified by ANOVA, t-tests were used to locate the specific effects. Multiple regression analyses of muscle variables and exercise tolerance were also conducted. Data are expressed as means ± SEM. A p value of less than 0.05 was designated to indicate statistical significance.

RESULTS

Patient Characteristics.

Of 39 CHF patients who were randomized into resistance training or control groups, 13 (12 male/1 female; 70 ± 8 years, 84 ± 18 kg, body mass index 29 ± 6 kg/m^2; mean ± SD) agreed to skeletal muscle biopsy and underwent a separate stratified randomization according to a generated random number method (19). The patients were in NYHA functional class II (n = 9) & III (n = 4) and had left ventricular ejection (LVEF) of 26 ± 8% by radionuclide gated blood pool scanning. The average time since diagnosis of CHF in the patients was 36 ± 40 months (mean ± SD). These two groups (RT: n = 7; C: n = 6) were well-matched at baseline (Table 1), and to the full patient cohort. Exercise data for the complete cohort are presented in table 2 and have been included due to their relevance to the overall findings. Paired biopsies from all 13 patients were available for MAPR, CS and capillary density but in a single case insufficient muscle sample was available for the other analytical procedures.

Training Compliance and Medication Status.

All of the participants in the RT group were compliant and completed a minimum of 33 training sessions. Participants randomized to control complied with the request to maintain previous activity levels. Minimal changes in medications occurred among patients in either group during or in the month prior to commencement of the study (Table 1).

Exercise Tests.

There were no baseline differences in either $\dot{V}O_{2\ peak}$, or lactate threshold between groups. There was an increase in $\dot{V}O_{2\ peak}$ in the RT group and a decrease in the C participants (Table 2; $p<0.01$) after the intervention, concordant with the full cohort. Lactate threshold (W) increased significantly in the RT group (28 ± 4 vs 45 ± 4 W; $p<0.01$) but remained unaltered in C (25 ± 2 vs 28 ± 4 W) following the intervention (Table 2) and again this also occurred in the full cohort. No changes were observed in either group for peak RER or peak (V_E/VO_2) following the intervention (Table 2).

There were no significant differences in either quadriceps ($p = 0.42$) or hamstrings ($p = 0.47$) muscle strength between patients randomised to RT or C at baseline prior to the intervention. There were trends towards increases in both quadriceps and hamstrings strength in the group of patients randomised to the training group (Table 2).

Muscle Oxidative Capacity.

Using the substrate combination pyruvate and malate (P+M), MAPR increased in the training group ($p<0.05$) and decreased in the control group ($p<0.05$) (Table 3) during the 11 week intervention, with a significant difference between groups ($p = 0.03$). No significant difference was found in the response to any of the other MAPR substrates between the groups or within the groups (Table 3). CS activity increased ($p<0.01$) in the training group and there was a trend towards an increase in HAD ($p<0.05$) (Table 3). The activities of CS and HAD were unchanged in the control group following the intervention period, with trained patients having significantly greater increase in CS activity than

controls (p = 0.02). There were no changes in the activities of either of the glycolytic enzymes PFK or LDH following the intervention period in either group. Changes in $\dot{V}O_{2\ peak}$ as a result of the intervention were significantly correlated with changes to both MAPR (P+M: Figure 1; $p < 0.0001$) and the oxidative enzyme HAD ($p < 0.05$). Multivariate analysis of metabolic variables revealed that the change in MAPR, using the P+M substrate combination accounted for 75% of the change in $\dot{V}O_{2\ peak}$.**Capillary Density.**

Capillary to fibre ratio increased significantly more (p = 0.039) in the training group (1.01 ± 0.05 to 1.17 ± 0.03) than in the control group (1.15 ± 0.03 and 1.14 ± 0.03) over 11 weeks (Table 4).

DISCUSSION

The main finding of the current study was that RT was associated with increases in several indices of muscle oxidative capacity, including CS activity and, in particular, intact mitochondrial maximally-activated ATP production rate (MAPR). Significantly, the observed changes in muscle oxidative capacity using MAPR were strongly related to changes in $\dot{V}O_{2\ peak}$ (Figure 1), a finding not previously reported, and explaining most of the improvement in $\dot{V}O_{2\ peak}$ produced by this exercise program. This suggests that improvements in mitochondrial ATP production rate may be a major determinant of exercise-induced increases in aerobic capacity in heart failure patients. Whilst aerobic training has previously been shown to increase volume density of mitochondria (20) and RT has been shown to increase the activity of CS in female CHF patients (21) and male heart transplant recipients (22), this is the first study to examine the effects of RT on

MAPR, an integrated measure of ATP production rate in intact mitochondria and considered a more robust indicator of muscle oxidative capacity than activities of oxidative enzymes (3). In addition to the improvement in MAPR, the circuit resistance exercise training program, when compared with controls, resulted in marked improvement in both lactate threshold ($p = 0.012$) and $\dot{V}O_{2\ peak}$ ($p = 0.005$).

In the current study, $\dot{V}O_{2\ peak}$ increased significantly in the RT group and decreased in the control patients. Improved sub-maximal exercise tolerance and muscle efficiency following RT protocols of 10 and 11 weeks have been reported, suggesting improvement in the functional capacity of the patients (15, 21). While the increase in $\dot{V}O_{2\ peak}$ in the RT group was significant in terms of improving functional capacity in CHF, the decrease in $\dot{V}O_{2\ peak}$ in those randomized to the control group has negative implications for CHF patients not involved in exercise training. Many prospective randomized studies of aerobic and/or resistance training have reported no deterioration in $\dot{V}O_{2\ peak}$ in the non-exercise control groups (20, 21, 23). However several studies have reported decreases in $\dot{V}O_{2\ peak}$ in non exercising controls.(24, 25) Kiilavuori and colleagues (26) indicated that there were falls in $\dot{V}O_{2\ peak}$ for their control group in an endurance training study, but did not present this data . Possible explanations for the decrease in $\dot{V}O_{2\ peak}$ in our inactive volunteers include clinical deterioration, onset of cardiac cachexia, decreased aerobic power due to continued deconditioning of these generally otherwise sedentary patients, decreased effort on the part of the patients at endpoint, or technical problems with the accuracy or reliability of the cardiorespiratory

data measurements. We have previously discounted the latter two explanations. (16) There was little evidence of changed clinical condition: most of the patients studied over the three-month period maintained stable medication regimes and all patients in the control group returned for endpoint testing. Mean weight of the control group increased by 1 kg, arguing against a cachexia mechanism. Therefore, the fall in VO_{2peak} in the control patients was probably due to deterioration of aerobic power due to prolongation of inactivity or progression of the disease. The patients were instructed to maintain their pre-study activity habits, and this was monitored. The implication of this finding is that exercise training in CHF patients not only improves exercise tolerance, but prevents a decline that underlines its value for CHF patients.

MAPR in the presence of the substrate combination P+M increased significantly in the training group and decreased in the control group over the intervention period. While this was the only substrate combination (of the five trialled) to increase in response to the training stimulus, it is the substrate that we postulated to be the most responsive in the context of this study. This is because the P+M substrate combination simulates the effect of carbohydrate metabolism. During training, patients exercised at heart rates approaching the peak heart rates they obtained during incremental exercise testing (>85% of peak) indicating that the exercise was of relatively high intensity. The majority of the increased demand for ATP resynthesis via oxidative mechanisms would be met by carbohydrate metabolism, as lipid metabolism has been demonstrated to be negligible at high exercise intensities (27). The changes in MAPR (P+M) were significantly related to changes in $\dot{V}O_{2\,peak}$. In addition, the results indicate that skeletal muscle oxidative

capacity is increased following circuit resistance training in CHF patients and that training also offsets the decline in oxidative capacity that was observed in patients randomized to the control group. We have previously suggested that muscle oxidative capacity in untrained CHF patients, at a single point in time, might not be dissimilar to that of sedentary controls (3). However, the rapid decrease of oxidative capacity and $\dot{V}O_{2\ peak}$ in the current control group of CHF patients suggests that these patients deteriorate over time and that this deterioration can be reversed by circuit resistance training.

Previously, we have speculated that the lower $\dot{V}O_{2\ peak}$ in CHF patients may be due at least in part to lower rates of oxidative phosphorylation during incremental exercise (3). This may be due to a number of factors including reduced muscle blood flow during exercise or muscle fibre transformations resulting in early onset of lactic acidosis. Training resulted in a significant increase in the lactate threshold, with no change in the control group following the intervention period. Jubrias et al (28) have demonstrated that intracellular acidosis inhibits ATP supply from oxidative phosphorylation in contracting skeletal muscle, thus limiting sustained oxidative flux to rates below true mitochondrial capacity. Consequently the later onset of lactic acidosis after training indicates that flux through oxidative phosphorylation is likely to be maintained for longer during incremental exercise.

It is possible that the change in lactate threshold may be the result of alterations in muscle blood flow during exercise. We have previously demonstrated that resistance

training results in increased forearm blood flow at rest and in response to submaximal exercise and limb ischemia in CHF patients (13). In the current study the capillary to fibre ratio was increased in the training group following the intervention period, which would explain the previously demonstrated increase in skeletal muscle blood flow (13).

Skeletal Muscle Strength. Previously we have reported significant improvements in the strength of chronic heart failure patients following a resistance training intervention (13). These changes are consistent with those reported in previous studies (15, 21). The current study utilised a prospectively stratified sub group of patients, part of the previously reported cohort (13), who were willing to undergo muscle biopsies prior to and following the intervention. While the increases in strength following training in this sub-group did not reach statistical significance, the changes in strength were similar to those previously reported in the full cohort (13) and it is therefore our contention that strength increased with resistance training in the current study.

Study Limitations

The training component of the current study included stationary cycling on a bicycle ergometer in which patients were instructed to exercise at a high intensity for periods not exceeding two minutes. The short duration at high intensity was designed to maximize muscle strengthening and to minimize aerobic training. Nevertheless, it is possible, though considered unlikely, that the increases observed in $\dot{V}O_{2\ peak}$ and muscle oxidative capacity that were observed in the current study could be the result of an aerobic training stimulus from the cycle exercise.

Conclusions

Circuit RT in CHF patients resulted in improvements in $\dot{V}O_{2\ peak}$ and that this alteration was likely due to an increase in MAPR and alterations in capillary density. The increases in $\dot{V}O_{2\ peak}$ were strongly related to increased skeletal muscle oxidative capacity and lactate threshold. The former mechanism has not been previously described, and may be an important mechanism explaining the exercise training adaptations in these patients.

The increased skeletal muscle blood flow from resistance exercise training was associated with increased muscle capillarisation that is probably associated with increased muscle fibre size. It would also seem that mitochondrial ATP production is a strong predictor of aerobic capacity in heart failure patients and is favorably altered by a program of predominantly muscle strengthening exercise.

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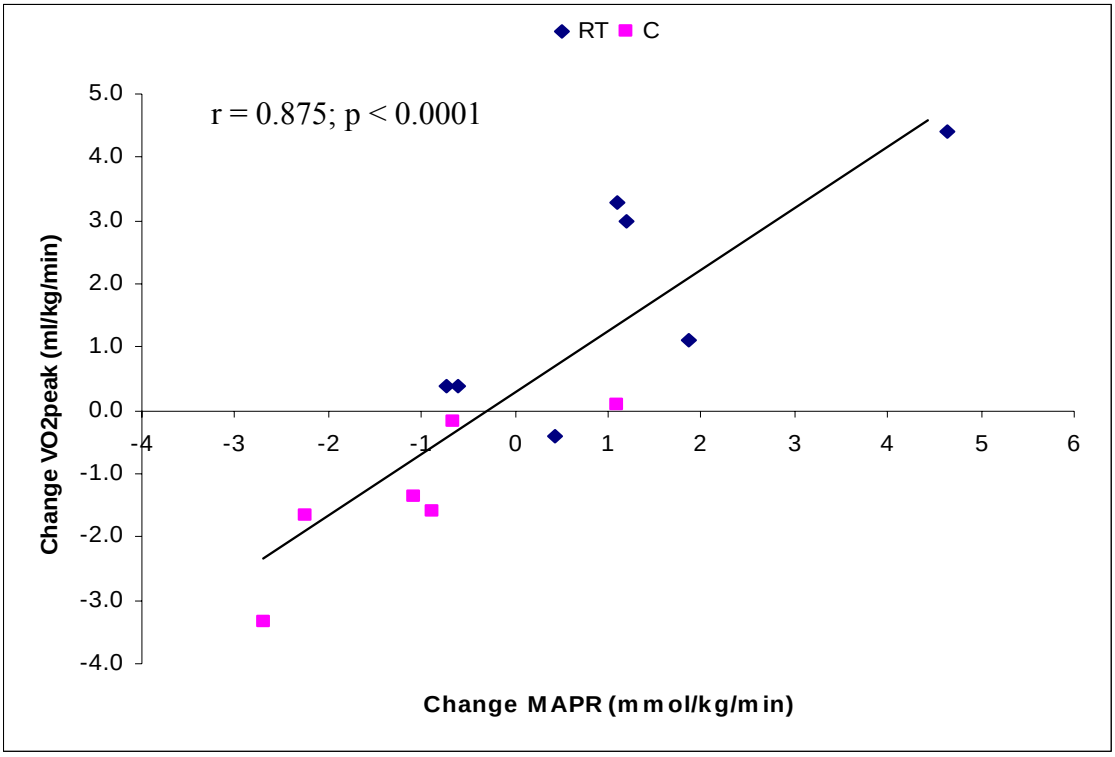

Figure 1. The relationship between changes in $\dot{V}O_{2\ peak}$ and skeletal muscle oxidative capacity over the 3 month exercise training intervention (RT = Resistance Training; C = Control; MAPR = Mitochondrial ATP Production Rate using substrates indicative of carbohydrate metabolism).

Table 1: Descriptive characteristics of CHF patients (mean ± SD)

Characteristic	RT group (n = 7)	Control group (n = 6)	P value
Age, yr	67 ± 9 (64 ± 10)	74 ± 4 (66 ± 9)	0.09
Weight (kg)	88 ± 19 (80 ± 15)	80 ± 18 (80 ± 14)	0.44
Body Mass Index (kg/m^2)	30 ± 6 (30 ± 5)	27 ± 5 (28 ± 5)	0.32
LVEF %	26 ± 8 (28 ± 7)	27 ± 9 (27 ± 7)	0.82
NYHA functional class	2.4 ± 0.5 (2.3 ± 0.5)	2.2 ± 0.4 (2.3 ± 0.5)	0.34
Etiology			
Ischaemic heart disease	4 (57%) 11 (61%)	4 (67%) 14 (67%)	
Dilated cardiomyopathy	3 (43%) 7 (39%)	1 (17%) 6 (28%)	
Valvular	0	1 (17%) 1 (17%)	
Medications (Pre/Post)			
Angiotensin converting enzyme inhibitor	6/5 (14/13)	4/4 (16/16)	
Angiotensin receptor blocker	1/2 (3/4)	2/2 (2/3)	
Diuretic	6/6 (15/15)	6/6 (17/17)	
Beta-blocker	5/5 (7/7)	2/3 (9/10)	
Digoxin	4/4 (7/7)	3/3 (9/9)	
Aspirin	4/4 (11/11)	5/4 (12/10)	
Warfarin	3/2 (7/6)	2/3 (10/11)	
Amiodarone	0/2 (1/4)	2/2 (5/4)	
Nitrates	2/2 (4/3)	2/3 (6/7)	
Calcium channel antagonist	1/1 (1/1)	0/0 (2/2)	

Numbers in parentheses are data from the full cohort of patients

Table 2. Cardiovascular, metabolic and strength changes following 11 week intervention (mean ± SEM).

	Training Group		Control Group		P Value	
	Baseline	**Endpoint**	**Baseline**	**Endpoint**	**Time**	**Group X Time**
$\dot{V}O_{2peak}$ (ml.kg^{-1}.min^{-1})	13.8 ± 1.1	15.5 ± 0.6*	14.8 ± 1.4	13.5 ± 1.3*	0.646	0.005
Peak RER	1.13 ± 0.07	1.15 ± 0.05	1.15 ± 0.05	1.22 ± 0.07	0.096	0.298
Peak (V_E/VO_2)	44.2 ± 4.0	45.0 ± 4.5	44.7 ± 3.2	47.5 ± 3.4	0.241	0.511
Peak Workrate (W)	61 ± 9	76 ± 10	60 ± 10	58 ± 11	0.057	0.021
Lactate threshold (W)♣	28 ± 4	45 ± 4†	25 ± 2	28 ± 4	0.003	0.012
Peak Lactates (mmol.L^{-1}) ♣	5.9 ± 0.8	6.8 ± 0.9$^{\#}$	4.7 ± 0.6	4.0 ± 0.6*	0.615	0.012
Peak Heart Rate (beats/min)	111 ± 5	114 ± 4	134 ± 8	122 ± 7	0.176	0.029
Quadriceps Strength (Nm)	92 ± 16	101 ± 17	110 ± 14	111 ± 11	0.069	0.201
Hamstrings Strength (Nm)	41 ± 6	51 ± 8	49 ± 9	52 ± 11	0.057	0.323

♣NB. Training group n=6,control group n=5. *Denotes $p < 0.05$ vs. baseline; †Denotes $p < 0.01$ vs. baseline; #Denotes a trend from baseline $p = 0.09$

Table 3. Indices of muscle metabolism. Substrate combinations: pyruvate + malate (P+M, carbohydrate), palmitoyl-L-carnitine + malate (PC+M, fat), α-ketoglutarate (α-KG, protein), succinate + rotenone (S+R) and pyruvate + palmitoyl-L-carnitine + α-ketoglutarate + malate (PPKM, carbohydrate, fat and protein).

	Training Group		Control Group		P Value	
	Baseline	**Endpoint**	**Baseline**	**Endpoint**	**Time**	**Group X Time**
MAPR (mmol ATP.min^{-1}.kg^{-1} WW)						
P+M	3.78 ± 0.76	4.91 ± 0.95*	4.79 ± 0.88	3.71 ± 0.63*	0.954	0.032
PC+M	1.83 ± 0.46	1.90 ± 0.28	2.28 ± 0.52	1.57 ± 0.37	0.304	0.215
α-KG	3.22 ± 0.92	3.79 ± 0.61	3.49 ± 0.64	2.85 ± 0.70	0.949	0.251
S+R	3.21 ± 0.94	4.00 ± 0.60	2.08 ± 0.59	2.75 ± 0.69	0.218	0.920
PPKM	5.02 ± 0.99	4.89 ± 0.73	4.26 ± 0.67	4.21 ± 0.82	0.855	0.933
Metabolic Enzymes (mmol.min^{-1}.kg^{-1} WW)						
CS	13.06 ± 1.03	18.24±1.63†	14.16 ± 0.75	15.25 ± 0.97	0.002	0.021
HAD	12.10 ± 1.00	17.16 ± 2.61	12.95 ± 1.75	12.55 ± 1.57	0.097	0.058
PFK	29.37 ± 1.45	29.19 ± 1.41	25.67 ± 2.24	28.80 ± 0.86	0.292	0.242
LDH	67.1 ± 16.7	65.0 ± 14.0	50.5 ± 6.7	36.1 ± 9.2	0.124	0.241

*Denotes $p < 0.05$ from baseline. †Denotes $p < 0.01$ from baseline. Note for HAD, PFK and LDH in the training group (n = 6)

Table 4. Capillarity changes following 11-week intervention.

	Training Group (n = 7)		Control Group (n = 6)		P Value	
	Baseline	**Endpoint**	**Baseline**	**Endpoint**	**Time**	**Group X Time**
Capillary to fibre ratio	1.01 ± 0.05	1.17 ± 0.03*	1.15 ± 0.03	1.14 ± 0.03	0.063	0.039

†Denotes $p < 0.01$ from baseline.