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RESEARCH ARTICLE

Translational Physiology

Resistance, but not endurance exercise training, induces changes in cerebrovascular function in healthy young subjects

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Abstract

It is generally considered that regular exercise maintains brain health and reduces the risk of cerebrovascular diseases such as stroke and dementia. Since the benefits of different "types" of exercise are unclear, we sought to compare the impacts of endurance and resistance training on cerebrovascular function. In a randomized and crossover design, 68 young healthy adults were recruited to participate in 3 mo of resistance and endurance training. Cerebral hemodynamics through the internal carotid, vertebral, middle and posterior cerebral arteries were measured using Duplex ultrasound and transcranial Doppler at rest and during acute exercise, dynamic autoregulation, and cerebrovascular reactivity (to hypercapnia). Following resistance, but not endurance training, middle cerebral artery velocity and pulsatility index significantly decreased ($P < 0.01$ and $P = 0.02$, respectively), whereas mean arterial pressure and indices of cerebrovascular resistance in the middle, posterior, and internal carotid arteries all increased ($P < 0.05$). Cerebrovascular resistance indices in response to acute exercise and hypercapnia also significantly increased following resistance ($P = 0.02$), but not endurance training. Our findings, which were consistent across multiple domains of cerebrovascular function, suggest that episodic increases in arterial pressure associated with resistance training may increase cerebrovascular resistance. The implications of long-term resistance training on brain health require future study, especially in populations with pre-existing cerebral hypoperfusion and/or hypotension.

NEW & NOTEWORTHY Three months of endurance exercise did not elicit adaptation in any domain of cerebrovascular function in young healthy inactive volunteers. However, resistance training induced decreased pulsatility in the extracranial arteries and increased indices of cerebrovascular resistance in cerebral arteries. This increase in cerebrovascular resistance, apparent at baseline and in response to both hypercapnia and acute exercise, may reflect a protective response in the face of changes in arterial pressure during resistance exercise.

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cerebral blood flow; cerebrovascular function; endurance training; exercise; resistance training

INTRODUCTION

Regular exercise maintains brain health and reduces the risk of cerebrovascular diseases, such as stroke and dementia (1–7). Despite this, the mechanisms responsible for the benefits of exercise are not well understood. A small number of studies have suggested that habitual training has beneficial effects on cerebrovascular function, such as resting cerebral perfusion (8), and cerebrovascular reactivity (9–12), which may partly explain the protective effect of exercise. However, other studies have reported no impact, or even a detrimental effect, of habitual exercise on some measures of cerebrovascular function (11, 13–18). This disparity may, in part, be attributed to methodological factors such as differences in the type of exercise training performed, particularly where cross-sectional comparisons of different groups (e.g., athletes) have been used as a surrogate for the impacts of training per se. There are known differences in the hemodynamic impacts of resistance (RES) and endurance (END) exercise on vascular structure and function (19). Two studies have compared the effects of habitual RES and END on resting cerebral hemodynamics and cerebrovascular reactivity to hypercapnia

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(20) and dynamic cerebral autoregulation (21), however, no study to our knowledge has examined the impact on cerebrovascular function of supervised and center-based training regimes using these distinct modalities of exercise.

END and RES exercise induce different physiological adaptations (22, 23), including distinct peripheral vascular changes (24–26), possibly due to the different hemodynamic responses associated with each modality (19). For example, END results in sustained elevation in cardiac output and blood pressure, whereas RES induces oscillation in these measures (27). END is associated with improved endothelial function (19, 24) and central arterial stiffness (26, 28, 29), whereas RES training can decrease central arterial compliance (25, 30). Acute bouts of END and RES are also associated with distinct cerebral blood flow (CBF) responses, whereby submaximal END induces an increase in CBF of 15%–25%, whereas CBF during RES exercise reflects changes in blood pressure (27). Given that blood flow and shear stress are fundamental stimuli for vascular adaptation (19, 31), and cerebral vessels are sensitive to these stimuli at rest (32) and during exercise (33), it is possible that different exercise modalities may induce distinct cerebrovascular adaptations.

The aim of this study was to employ a randomized crossover study design to compare the impacts of END- and RES-based exercise programs on cerebrovascular function in healthy subjects. We hypothesized that END training would result in greater benefits in cerebrovascular function than RES training.

METHODS

Full details of the study design and experimental procedures can be found in our protocol paper (34) and in the study registration (ACTRN12616001095459), which was published before recruitment and randomization. Of note, all subjects in this study were pairs of monozygotic and dizygotic twins. However, for the purpose of this report, we present group responses and heritability analyses are not included. Nonetheless, we have adjusted all analyses for twin correlations. These data have not previously been reported.

Participants

Sixty-eight young, healthy adults (25.5 ± 5.4 yr; 62% female; 100% Caucasian) were recruited to participate in the cerebrovascular component of the study. Recruitment was facilitated via newsletters, mail, newspaper advertisements, online and via social media, university email lists, and word-of-mouth referral. Inclusion criteria were healthy, relatively sedentary individuals who did not meet Australian guidelines for physical activity recommendations (<150 min/wk), were nonsmokers, and medication free. This study was approved by the University of Western Australia Human Research Ethics Committee (Reference No. RA/4/7031). Oral and written consent were obtained from all subjects before participation in the study, which conformed to the Declaration of Helsinki. Baseline demographic data are displayed in Table 1.

Study Design

Cerebral and other outcome measures were undertaken by all participants within 14 days of commencing and completing each intervention, as detailed below. Participants were randomized to 3 mo of either RES or END exercise training (Fig. 1), before undergoing a 3-mo washout period, during which they were instructed to return to their usual activities and diet. Participants then crossed over to complete 3 mo of their second, alternate, exercise intervention (RES or END). Fat and lean mass were assessed using dual energy X-ray absorptiometry (22), fitness using a graded exercise $\dot{V}O_{2max}$ test performed on a treadmill and consisting of 3-min stages interspersed with 1-min rest periods. The test commenced at 8 km·h^{-1} and increased by 1 km·h^{-1} per stage until volitional exhaustion and maintained a 1% incline gradient. Peak oxygen consumption was calculated from the four highest consecutive 15-s oxygen uptake values of each stage (34). Strength was assessed using a one-repetition maximum (1RM) test pre and post each exercise intervention (34). Randomization was performed using a website-based randomization tool. To quantify incidental changes in physical activity levels across the study, active energy expenditure (AEE) and total energy expenditure (TEE) was recorded using a physical activity monitor (Actiheart 4, CamNtech Ltd, Cambridge, UK) for a five-day period. This was done in the week before, or immediately following, each exercise intervention (i.e., at *weeks –1* to *0*, *13–14*, *23–24*, and *37–38*) (34). In addition, to assess whether eating habits had remained constant throughout the study, a food diary was given to each participant to complete the week before, or immediately following, each exercise intervention. Participants were instructed to complete the diary on four consecutive days, including one weekend day. Mean total daily energy intake was determined from these records using a commercially available software program (Foodworks 9; Xyris Software, Queensland, Australia) (34).

Table 1. *Baseline characteristics of participants enrolled in the study*

	Baseline
n (%female)	68 (62)
Age, yr	25.5 ± 5.4
Height, cm	173.1 ± 6.9
Weight, kg	71 ± 16.5
BMI, kg·m^{-2}	23.6 ± 4.9
HR, beats·min^{-1}	73 ± 9
MAP, mmHg	88 ± 12
SBP, mmHg	120 ± 13
DBP, mmHg	68 ± 11
$P_{ET_{CO_2}}$, mmHg	39.3 ± 4.1
MCAv, cm·s^{-1}	73 ± 16
PCAv, cm·s^{-1}	50 ± 11
ICA flow, mL·min^{-1}	438 ± 115
ICA diameter, cm	0.474 ± 0.047
VA flow, mL·min^{-1}	149 ± 70
VA diameter, cm	0.345 ± 0.049
Total CBF, mL·min^{-1}	1,179 ± 282
PI_{MCA}	0.79 ± 0.14

Values are means ± SD; *n*, number of participants. BMI, body mass index; CBF, cerebral blood flow; DBP, diastolic blood pressure; HR, heart rate; ICA, internal carotid artery; MAP, mean arterial pressure; MCAv, Middle cerebral artery velocity; PCAv, posterior cerebral artery velocity; $P_{ET_{CO_2}}$, partial pressure of carbon dioxide; PI_{MCA}, middle cerebral artery pulsatility index; SBP, systolic blood pressure; TCBF, total cerebral blood flow; VA, vertebral artery.

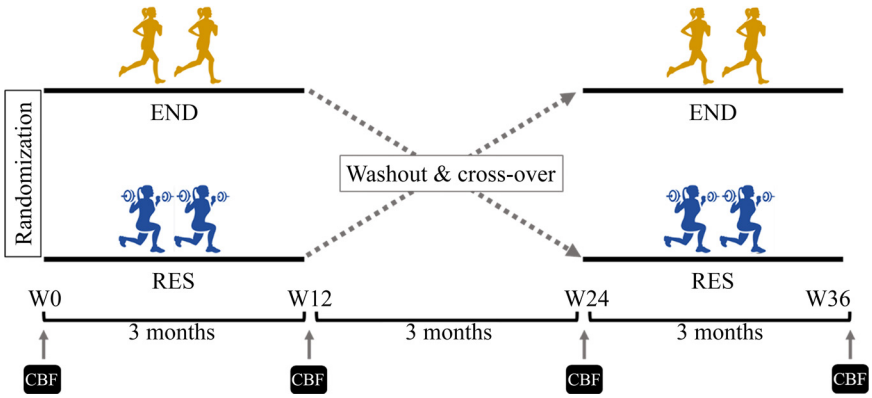


Figure 1. Study design. Participants were randomized to complete 3 mo of each exercise intervention [resistance (RES) or endurance (END) training], 3 mo of a washout period, then crossover to complete 3 mo of the alternate modality. Outcome measures of cerebrovascular function were completed pre and post each exercise intervention (*weeks 0*, *12*, *24*, and *36*). $n = 68$. CBF, cerebral blood flow.

Exercise Interventions

The center-based, supervised exercise interventions consisted of three 1-h sessions per week for 12 wk. The programs were intensity matched between volunteers and progressively overloaded across the 12 wk, consisting of specified training phases.

END used two running and one cycling session per week progressing from 60% to 90% $\dot{V}O_{2max}$, which was monitored via continuous heart rate (HR) using a HR monitor (Polar RS300X HR monitor, Polar Electro Oy, Finland). Target HRs were calculated from HR at a percentage of the initial graded exercise $\dot{V}O_{2max}$ test so that they were individualized, but matched, for intensity between individuals. The 12 wk END program followed a periodized progressive macrocycle plan consisting of three mesocycles of 4 wk each and was interval based (i.e., walking/running/cycling bouts were interspersed with rest periods) in keeping with a recent study which concluded that accumulated change in cerebral blood flow velocity is higher in response to interval rather than continuous exercise (35). The first mesocycle, the "general preparatory" phase (*weeks 1–4*), consisted of low training intensity/volume (lots of walking/jogging at 60% HR, 1–2.5 km running, and/or 15–25 min cycling/running) including a long warm up focusing on running drills, technique, and dynamic stretching. The second mesocycle, the "high intensity" phase (*weeks 5–8*), consisted of higher intensity work with higher HRs (up to 90%), and distance/duration (2.5–5 km running and/or 25–40 min cycling/running). The final mesocycle, the "maintenance and distance" phase (*weeks 9–12*), consisted mostly of maintaining subthreshold HRs (70%–85%) for longer distance/duration (5–7 km running and/or 40 min in *week 9* to 60 min by *week 12* cycling/running). In the mesocycles, a 1:1 structure loading existed with a "hard" loading week followed by an "easier" or "maintenance" week. Within each week there existed a structured load with a "harder" run session, an "easier" run session, and the cycling session was always the longest duration session in each week, adapting many principles from previously published work (36, 37). The exercise modalities were not matched for workload or energy expenditure; we opted to assess the impact of ecologically valid exercise prescriptions used in gymnasia and industry settings.

RES alternated between upper and lower body exercises and sessions progressed from 60% to 90% of 1RM. RES was monitored by recording the number of repetitions, sets and weight completed, as well as a rating of perceived exertion for each set. Individual weights were prescribed from each participant's pretraining 1RM so that they were individualized, but matched, for intensity between individuals and within-twin pairs. The 12-wk RES training program followed a periodized plan consisting of four mesocycles of 3 wk each. The first mesocycle focused on muscular endurance (*weeks 1–3*) where intensity was low (60%–70% 1RM), reps were high (12–15 reps), and rest periods between sets were short (30–60 s). This first mesocycle allowed participants to focus on forming good technique habits, condition muscles, and assist recovery between sessions. The second mesocycle was muscular hypertrophy (*weeks 4–6*) where intensity increased (70%–75%), reps decreased (10–12 reps), while rest periods between sets remained short (30–90 s). *Weeks 7–9* were a progressive step between muscular hypertrophy and strength where intensity increased (75%–80%), reps decreased (8–10 reps), and rest periods between sets increased (60–120 s). The last mesocycle focused on improving muscular strength where intensity increased (80%–90%), reps decreased (5 reps), and rest periods between sets increased (3–5 min). Each session focused on one of the five main exercises (two upper body—bench press and standing military press; three lower body—squats, deadlift, and leg press) that were rotated alternating upper and lower body on separate days. There were secondary exercises performed during each session that used muscle groups that were similar to or would assist in performing, the main exercise of the session (i.e., staggered feet leg press, seated row, lat pulldown). Participants performed a standardized warm up before completing their session and a standardized 5 min core exercises and cool down at the end of the session. To guide participant's progressions, 1RM assessments were repeated halfway through their 12-wk program. A more detailed explanation of the exercise interventions is provided in our protocol paper (34).

Cerebrovascular Outcome Measures

Intracranial blood velocity recordings of the middle (MCAv) and posterior (PCAv) cerebral arteries were measured using noninvasive transcranial Doppler (TCD, Spencer Technologies, Seattle, WA), whereas extracranial measures of CBF were collected using duplex ultrasound (Terason t3300) of the internal carotid (ICA) and vertebral (VA) arteries (diameter and velocity) according to standardized approaches (38). All vessels were measured unilaterally and

simultaneously (ICA and MCAv were measured on the right side and VA and PCAv were measured on the left side). Recordings of MCAv and PCAv were made at a frequency of 100 Hz, at recommended depths, described in TCD guidelines (38) (depth varied between participants). To standardize vessel recording sites within participants, photographs were taken of probe position, TCD settings, and velocity traces, which were used in follow-up testing sessions.

Blood flow was calculated as follows:

$$Q\ (\text{mL}\cdot\text{min}^{-1}) = (\text{peak envelope velocity}/2) \times [\pi(0.5 \times \text{diameter})^2] \times 60$$

while total CBF was calculated as follows:

$$\text{CBF}\ (\text{mL}\cdot\text{min}^{-1}) = 2 \times (Q_{\text{ICA}} + Q_{\text{VA}}).$$

The coefficient of variation for repeated assessment of resting MCAv is 4.5% (8) using TCD and 4.4% for ICA diameter (39) using duplex ultrasound (32). A Finometer (Finometer Pro, Finapres Medical Systems, Amsterdam ZO, The Netherlands) continuously monitored beat-to-beat blood pressure via photoplethysmography from the middle finger of the left hand. A 3-lead ECG was attached to monitor HR (BIO Amp CF, ADInstruments, New South Wales, Australia). Following instrumentation, the participant was seated on a semisupine bench (incline of bench remained consistent to allow optimal reproducibility of blood vessel images) and the procedure was explained to them in detail. Once the participant was in position, a mouthpiece connected to a spirometer (Spirometer, ADInstruments, New South Wales, Australia) was placed in the participant's mouth, with a nose clip, to measure expired gases. Breath-by-breath CO_2 and O_2 were sampled at the mouth and recorded using a calibrated gas analyzer (ML206, ADInstruments, CO). The partial pressures of end-tidal CO_2 and O_2 (i.e., $P_{ET}CO_2$ and $P_{ET}O_2$, respectively) were calculated in LabChart using peak detection analysis with correction for daily barometric pressure. The blood pressure, ECG, and respiratory signals were recorded on LabChart 8 via a 16-channel Powerlab (ADinstruments, Sydney, Australia).

Once instrumented, a 5-min resting baseline of the aforementioned cerebrovascular and cardiorespiratory parameters was recorded and averaged for resting data. Cerebrovascular function was then continuously assessed throughout tests of dynamic cerebral autoregulation, cerebrovascular CO_2 reactivity, and exercise. Tests were performed in the same order to ensure testing conditions were the same across each time point. Exercise tests were performed last as they are the most likely to result in prolonged effects/fatigue of the subjects. All tests were performed by the same sonographer for each participant.

The cerebrovascular resistance index (CVRi) was calculated as mean arterial pressure (MAP) divided by MCA_V or PCAv (in $\text{mmHg}\cdot\text{cm}^{-1}\cdot\text{s}^{-1}$). There is no standardized analytical approach for the calculation of cerebrovascular reactivity (40, 41), therefore, cerebrovascular reactivity was calculated in absolute terms ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$ change in $P_{ET}CO_2$). Middle cerebral artery pulsatility index (PI_{MCA}) was estimated as systolic MCAv minus diastolic MCAv divided by mean MCAv (42).

Dynamic cerebral autoregulation.

Dynamic autoregulation was assessed by measuring MCAv responses to spontaneous blood pressure oscillation. Spontaneous autoregulation was assessed using the 5-min resting baseline data in the very low frequency (0.02–0.07 Hz) and low frequency (0.07–0.20 Hz) range. Where values were identified as wrap-around phase, those data were excluded from analysis (43). These methodological approaches are in accordance with published guidelines on this technique (44).

Cerebrovascular CO_2 reactivity.

Steady-state CO_2 reactivity was assessed by having participants initially breathe room air for a 1-min baseline period, before switching to a Douglas bag containing a mixture of 6% CO_2, 21% O_2, and balanced N_2, for 3 min. The MCAv, ICA, and CVRi responses to elevations in $P_{ET}CO_2$ were analyzed by averaging 30 s of data at baseline and during the last 30 s of the steady-state hypercapnic stimulus. Linear regression analysis was then performed to calculate reactivity slopes ($P_{ET}CO_2$ vs. absolute cerebrovascular measures and CVRi). The use of two points (baseline and peak) in the linear regression analysis was justified based on the understanding that CBF response is highly linear within this physiological range of $P_{ET}CO_2$ [for review, see Hoiland et al. (45)].

Absolute cerebrovascular reactivity (CR) was calculated as:

$$\text{Absolute CR} = (\text{hypercapnic}(6\%CO_2)\text{MCAv} - \text{resting MCAv})/(\text{hypercapnic}(6\%CO_2)P_{ET}CO_2 - \text{resting}\ P_{ET}CO_2).$$

The same calculation was performed to calculate absolute CR for PCAv, ICA flow, MAP, and CVRi for each vessel.

Acute exercise responses.

For this assessment, participants were positioned semisupine on a bench with their feet on a Monark bicycle (Ergomedic 828 E, MONARK, Vansbro, Sweden). Following a 1-min baseline, participants commenced their first 2-min stage at 60 W, followed immediately by 2 min at 90 W and again by 2 min at 120 W. The participants maintained their RPM between 50 and 60 RPM throughout the entire 6-min test. Cerebrovascular measures, MAP and $P_{ET}CO_2$ were continuously measured throughout. The MCAv, ICA, and CVRi responses were analyzed by averaging 30 s of data at baseline and during the last 30 s of each stage. The submaximal exercise test was used to assess whether exercise training impacts CBF responses to common levels of daily exercise, as has been undertaken in previous studies (11).

Statistical Analysis

Cerebrovascular autoregulation and reactivity were analyzed using Ensemble v1.0.0.42 (Elucimed LTD, University of Otago, New Zealand). Statistical analyses were performed with STATA v15 software (StataCorp, College Station, TX). The effects of the exercise interventions (Tables 2 and 3, Figs. 2 and 3, and Supplemental Fig. S1; see https://doi.org/10.6084/m9.figshare.14499018 and Supplemental Fig. S2; see https://doi.org/10.6084/m9.figshare.14499036) were assessed for each outcome measure using a linear mixed model which accounted for the repeated nature of the data, controlling for individual fixed effects which takes into account the twin association, with age and sex as covariates. The fixed effects of the linear mixed model were specified as regression parameters (time, workload, and age) and the random-effects portion of the model were specified by considering the grouping structure of the data (twin pairings).

Table 2. *Variables at rest in response to resistance and endurance training*

	Pre-RES	Post-RES	Pre-END	Post-END	ΔRES vs. ΔEND (*P* Value)
HR, beats·min^{-1}	73 ± 9	72 ± 9*	72 ± 9	68 ± 9*	0.01
MAP, mmHg	88 ± 12	91 ± 11*	87 ± 11	89 ± 12	0.21
SBP, mmHg	119 ± 13	122 ± 13*	119 ± 13	120 ± 14	0.29
DBP, mmHg	67 ± 11	71 ± 10*	67 ± 10	68 ± 11	0.24
$P_{ET_{CO_2}}$, mmHg	39.2 ± 3.9	39.6 ± 2.7	39.4 ± 3.7	39.8 ± 3.2	0.97
MCAv, cm·s^{-1}	74 ± 15	71 ± 14*	72 ± 15	71 ± 14	0.10
MCAv CVRi, mmHg·cm^{-1}·s^{-1}	1.25 ± 0.30	1.34 ± 0.32*	1.28 ± 0.35	1.31 ± 0.34	0.03
PCAv, cm·s^{-1}	51 ± 11	52 ± 9	50 ± 11	51 ± 10	0.99
PCAv CVRi, mmHg·cm^{-1}·s^{-1}	1.80 ± 0.43	1.82 ± 0.39	1.83 ± 0.43	1.83 ± 0.46	0.43
ICA flow, mL·min^{-1}	429 ± 100	432 ± 114	428 ± 117	424 ± 112	0.94
ICA flow CVRi, mmHg·mL^{-1}·min^{-1}	0.21 ± 0.06	0.23 ± 0.07	0.22 ± 0.08	0.22 ± 0.07	0.16
ICA diameter, cm	0.472 ± 1.143	0.469 ± 1.117	0.469 ± 1.107	0.474 ± 1.049	0.01
VA flow, mL·min^{-1}	142 ± 69	144 ± 67	142 ± 66	135 ± 63	0.46
VA flow CVRi, mmHg·mL^{-1}·min^{-1}	0.87 ± 0.71	0.82 ± 0.62	0.83 ± 0.63	0.86 ± 0.54	0.18
VA diameter, cm	0.347 ± 0.050	0.343 ± 0.051*	0.340 ± 0.050	0.339 ± 0.047*	0.85
Total CBF, mL·min^{-1}	1,143 ± 264	1,148 ± 302	1,145 ± 279	1,119 ± 289	0.67
PI_{MCA}	0.77 ± 0.14	0.74 ± 0.09*	0.79 ± 0.11	0.78 ± 0.10	0.32

Values are means ± SD from raw data. *P* values are from linear mixed models (intention to treat; n = 6) analysis, which accounted for the repeated nature of the data and pairing within the twins, with age and sex as covariates. CBF, cerebral blood flow; CVRi, cerebrovascular resistance; DBP, diastolic blood pressure; END, endurance training; HR, heart rate; ICA, internal carotid artery; MAP, mean arterial pressure; MCAv, Middle cerebral artery velocity; PCAv, posterior cerebral artery velocity; $P_{ET_{CO_2}}$, partial pressure of carbon dioxide; PI_{MCA}, middle cerebral artery pulsatility index; RES, resistance training; SBP, systolic blood pressure; VA, vertebral artery. *$P < 0.05$, significantly different change from preexercise to postexercise.

There have been few longitudinal training studies of cerebrovascular outcomes on which to base a power test. However, based on the effect size and standard deviations reported by Murrell et al. (11), which reported a significant effect of 12 wk of aerobic training on cerebrovascular reactivity in 10 subjects, our sample size of 68 subjects possessed >80% power, assuming ∝ 0.05 and two-tailed tests. Based on the effect size and standard deviations reported by Ivey et al. (12), which reported a significant change in cerebral vasomotor reactivity after aerobic exercise in 19 stroke survivors (and 19 in control group), our study of 68 subjects possessed 99% power. G*Power was used to perform these power calculations.

RESULTS

Participant Characteristics

Baseline characteristics for the 68 participants included in this study are provided in Table 1.

Exercise Training Efficacy

Attendance at training sessions was 94% for RES and 95% for END. As previously published (23), cardiorespiratory fitness ($\dot{V}O_{2max}$) significantly increased by 3.61 ± 3.77 mL·kg^{-1}·min^{-1} in response to END ($P < 0.005$) (0.25 ± 0.26 L·min^{-1}, $P < 0.005$), but not in response to RES (0.03 ± 3.57 mL·kg^{-1}·min^{-1}) (0.04 ± 0.25 L·min^{-1}). In contrast, 1RM significantly increased in response to RES (leg press: +47.0 ± 29.4 kg, $P < 0.01$, bench press: +5.1 ± 5.0 kg, $P < 0.01$) but not in response to END (leg press: +3.0 ± 26.4 kg, bench press: −0.4 ± 3.4 kg). Both RES and END significantly increased total lean mass (1,156 ± 1,132 g, $P < 0.001$ and 430 ± 1,111 g, $P = 0.002$, respectively) and decreased total fat mass (−495 ± 1,464 g, $P = 0.006$ and −351 ± 1,403 g, $P < 0.05$, respectively) (22). Lastly, there were no significant changes following RES or END training in daily caloric intake, AEE or TEE (22), indicating a stable diet and levels of incidental activity (outside of the training interventions) throughout the study; there was no evidence of any

Table 3. *Spontaneous and dynamic cerebral autoregulation changes in response to resistance and endurance training*

	Pre-RES	Post-RES	Pre-END	Post-END	ΔRES vs. ΔEND (*P* Value)
LF					
Coherence	0.767 ± 0.135	0.763 ± 0.118	0.796 ± 0.123	0.758 ± 0.133*	0.212
Phase, radians	0.479 ± 0.233	0.458 ± 0.196	0.473 ± 0.221	0.447 ± 0.203	0.575
Gain, cm·s^{-1}·mmHg^{-1}	0.942 ± 0.257	0.898 ± 0.260	0.965 ± 0.274	0.916 ± 0.275	0.857
*n*Gain, %·mmHg^{-1}	1.297 ± 0.331	1.258 ± 0.291	1.361 ± 0.340	1.294 ± 0.299	0.663
VLF					
Coherence	0.481 ± 0.144	0.451 ± 0.140	0.464 ± 0.132	0.473 ± 0.135	0.233
Phase, radians	0.790 ± 0.448	0.831 ± 0.437	0.800 ± 0.444	0.747 ± 0.371	0.163
Gain, cm·s^{-1}·mmHg^{-1}	0.730 ± 0.264	0.719 ± 0.295	0.715 ± 0.220	0.704 ± 0.228	0.960
*n*Gain, %·mmHg^{-1}	0.998 ± 0.330	1.022 ± 0.415	1.014 ± 0.326	0.986 ± 0.268	0.362

Values are means ± SD from linear mixed models (intention to treat; n = 68) analysis incorporating pre- and postdata. END, endurance training; LF, low frequency; nGain, normalized gain; RES, resistance training; VLF, very low frequency. *$P < 0.05$, significantly different change from preexercise to postexercise.

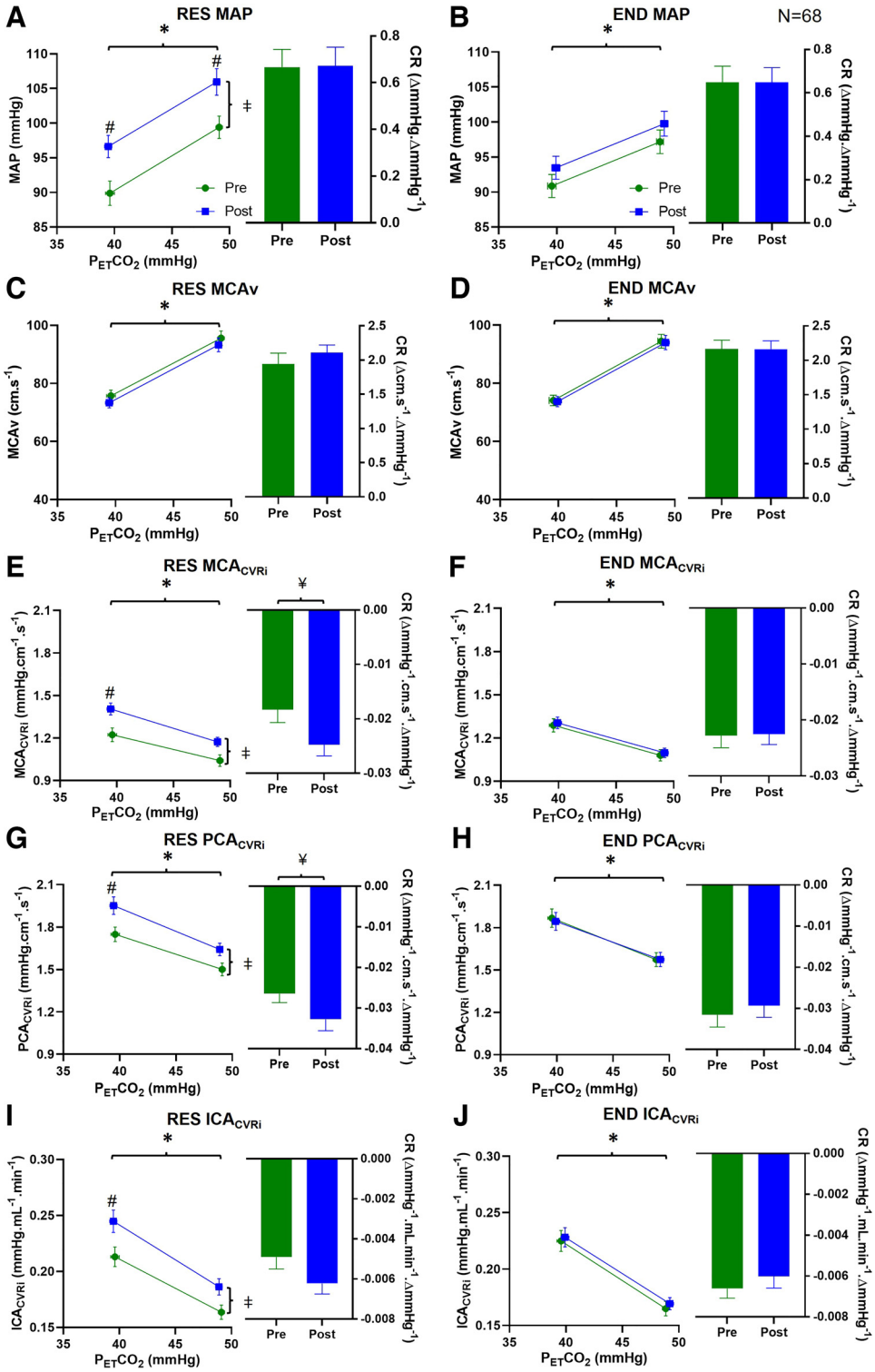


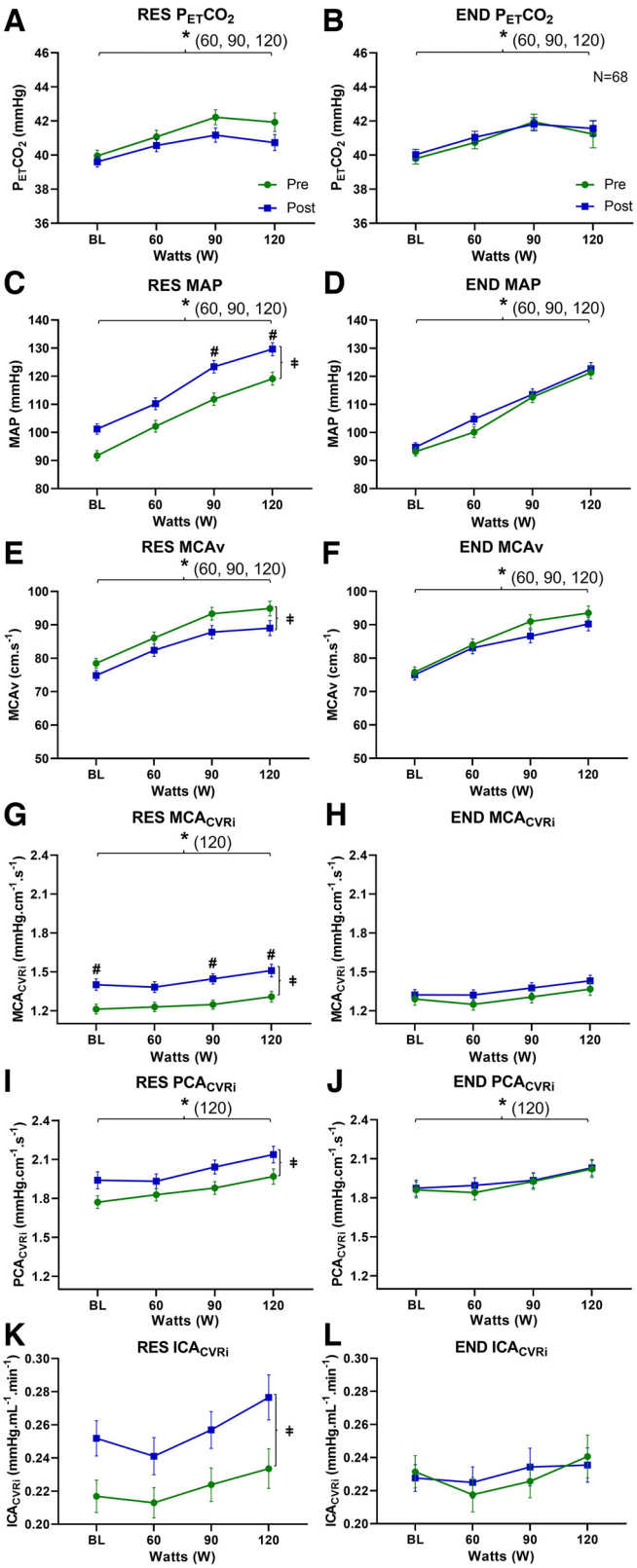
Figure 2. Cerebrovascular reactivity (CR) to 6% CO_2; resistance (RES; *left*) and endurance (END; *right*) training responses for MAP (*A* and *B*), MCAv (*C* and *D*), MCA_{CVRi} (*E* and *F*), PCA_{CVRi} (*G* and *H*), and ICA_{CVRi} (*I* and *J*), respectively. *Significant main effect for hypercapnic stimulus. ǂSignificant main effect of training. #Significant effect of training at an individual workload. ¥Significant difference in mean absolute reactivity with training. Data are means ± SE from linear mixed models (intention to treat) analysis incorporating pre- and postdata and accounted for the repeated nature of the data and pairing within the twins, with age as a covariate. n = 68. CVRi, cerebrovascular resistance; ICA, internal carotid artery; MAP, mean arterial pressure; MCA, middle cerebral artery; MCAv, middle cerebral artery velocity; PCA, posterior cerebral artery.

carryover effects of initial exercise interventions into the washout phase.

Resting Cerebrovascular, Respiratory, and Hemodynamic Variables

All resting data are presented in Table 2. Following RES training there was an increase in MAP (P = 0.01), whereas there was no change following END training (P = 0.52). Resting HR decreased with RES and END training (P = 0.04 and $P < 0.001$, respectively), with a greater reduction observed following END compared with RES training (P = 0.01). RES training was associated with a significant reduction in resting MCAv (P = 0.024) and PI_{MCA} ($P < 0.01$), whereas END training had no impact on these measures (P =

0.76, and P = 0.17, respectively). These changes in resting MCAv and MAP following RES training resulted in a significant increase in MCA cerebrovascular resistance (CVRi) ($P <$ 0.001), which was not apparent following END (P = 0.47).



There were no significant impacts of either RES or END training on resting PCAv, total CBF, ICA or VA flows, or CVRi data for these vessels (Table 2). However, there was a significant magnitude of change between RES and END interventions (P = 0.01) for ICA diameter, reflecting a trend for a decrease in ICA diameter following RES training (P = 0.088) and a trend for an increase following END training (P = 0.089). There was no change in resting $P_{ET}CO_2$ following either intervention (RES: P = 0.185 and END: P = 0.268).

There were no carryover effects present when the two baseline periods were compared (*week 0* vs. *24*) for any variable (all $P > 0.05$).

Dynamic Cerebral Autoregulation

No differences were observed in phase, gain, or normalized gain within the low-frequency (LF) and very low-frequency (VLF) domains in response to spontaneous blood pressure oscillations following either RES or END training (Table 3). There was a significant reduction in coherence in the LF range following END training (P = 0.02), whereas there were no significant differences in coherence in the VLF range following END or the LF and VLF range following RES training.

Cerebrovascular CO_2 Reactivity

As illustrated in Fig. 2 and Supplemental Fig. S1; see https://doi.org/10.6084/m9.figshare.14499018, Supplemental Fig. S3; see https://doi.org/10.6084/m9.figshare.16416825, and Supplemental Fig. S4; see https://doi.org/10.6084/m9.figshare.16416831, the impact of RES on resting MAP and CVRi was also apparent in response to the 6% hypercapnic stimulus. END did not impact on these variables at rest or in response to hypercapnia. In terms of the reactivity of response to changes in $P_{ET}CO_2$, Fig. 2 and Supplemental Fig. S1 (*right axis*) indicates that no changes were apparent in MCAv, PCAv, or ICA CO_2 reactivity following RES or END training. However, both MCA_{CVRi} and PCA_{CVRi} reactivity significantly increased following RES training (Fig. 2, *E* and *G*, P = 0.02 and P = 0.02), whereas no change was evident following END training (Fig. 2, *F* and *H*). The ICA_{CVRi} reactivity showed a similar tendency for change with RES (P = 0.06) but not END training (P = 0.62) (Fig. 2, *I* and *J*).

Acute Exercise Responses

Figure 3 and Supplemental Figs. S2; see https://doi.org/10.6084/m9.figshare.14499036, Supplemental Fig. S5; see https://doi.org/10.6084/m9.figshare.16416834, and Supplemental Fig. S6; see https://doi.org/10.6084/m9.figshare.16416837 illustrate responses to acute exercise bouts

Figure 3. Cerebrovascular responses to acute exercise; resistance (RES; *left*) and endurance (END; *right*) training responses for partial pressure of carbon dioxide ($P_{ET}CO_2$; *A* and *B*), MAP (*C* and *D*), MCAv (*E* and *F*), MCA_{CVRi} (*G* and *H*), PCA_{CVRi} (*I* and *J*), and ICA_{CVRi} (*K* and *L*), respectively. *Significant main effect for acute exercise stimulus. ‡Significant main effect of training. #Significant effect of training at an individual workload. Data are means ± SE from linear mixed models (intention to treat) analysis incorporating pre- and postdata and accounted for the repeated nature of the data and pairing within the twins, with age as a covariate. n = 68. CVRi, cerebrovascular resistance; ICA, internal carotid artery; MAP, mean arterial pressure; MCA, middle cerebral artery; MCAv, middle cerebral artery velocity; PCA, posterior cerebral artery.

performed before and after RES and END training. Following RES training there was no difference in the ICA or PCAv response to acute exercise; however, the MCAv response was significantly lower (P = 0.046) post-RES training, suggesting a regional adaptation in response to exercise. Consistent with the resting and CO_2 response data presented earlier, RES training increased MAP during incremental exercise (main effect of training P = 0.001). Consequently, CVRi for MCA, PCA, and ICA were all significantly increased following RES training (Fig. 3, *G*, *I*, and *K*, $P < 0.001$, P = 0.012 and P = 0.001, respectively). There was no difference in $P_{ET}CO_2$ during exercise as a result of RES (Fig. 3*A*). No changes were apparent in any of these variables following END (Fig. 3 and Supplemental Fig. S1, *right column*).

DISCUSSION

Several lines of evidence suggest that exercise is beneficial for brain health, with impacts on the risk of stroke and dementia (1–7). Despite this evidence, surprisingly little is known regarding the impacts of different forms of exercise training on cerebrovascular physiology. This study investigated the hypothesis that exercise training may enhance cerebrovascular function. To this end, we compared three months of center-based and closely supervised END and RES training, separated by a three-month washout. This crossover design enabled within-subjects comparison of training modalities that have distinct hemodynamic effects on the cardiovascular system. Cerebrovascular function was assessed across a number of regulatory domains, including resting function, dynamic autoregulation, reactivity to hypercapnia, and acute exercise. Our principal findings are that, at rest, RES induced changes in intracranial PI, MAP, and CVRi, with the latter variables similarly modified across multiple cerebrovascular domains. In contrast, END did not modify cerebrovascular parameters in response to any stimuli. These findings suggest that RES training, associated with oscillatory increases in blood pressure (27), induces an adaptive response that decreases intracranial PI and increases CVRi, while global perfusion is maintained.

Cerebral perfusion is regulated by multiple mechanisms. For example, intrinsic and neural autoregulatory features of cerebral blood vessels allow for the relative maintenance of cerebral perfusion in the face of changes in blood pressure. Rickards et al. (46) have pointed out that there is a high linearity between arterial pressure and cerebral blood flow variations, and cerebral perfusion becomes increasingly passive to higher frequency changes in pressure. Typically, the spontaneous pressure-to-perfusion relationship is assessed in humans by measuring the relationship between MAP and CBF during a resting period. This autoregulation index (assessed via commonly used transfer function analysis) and resting $P_{ET}CO_2$ were unaltered by END or RES in the current study. Nonetheless, we observed evidence of an underlying change in the regulation of cerebral perfusion at baseline and in response to CO_2 and exercise following RES (Figs. 2 and 3). RES is known to increase arterial pressure (47) and in the current study MAP was modestly but significantly higher following RES at rest, and also in response to hypercapnia and during submaximal exercise. Despite this increase in pressure, cerebral perfusion was maintained at pretraining levels, and vascular resistance was consequently increased. In addition, there was a decrease in both MCAv and PI_{MCA} at rest following RES training, and a significant difference between the magnitude of change in ICA diameter when RES and END were compared. One interpretation of this data is that the cerebral circulation may exhibit vasoconstriction of the vasculature and a decrease in the amplitude of the pulsatile waveform to protect downstream microvessels. Although speculative, we propose that the brain may be responsive to the potential detrimental impacts of episodic increases in MAP associated with RES training. Previous studies indicate that peripheral arterial compliance is negatively impacted by RES training (19) and it is also possible that sympathetic neural regulation of conduit artery tone may be involved in RES-based adaptation (48). It is also possible that the impact of increases in blood pressure during the RES training outweigh any impacts on arterial shear stress (19). Although there is some literature on the competing impacts of changes in transmural wall pressure gradient, versus shear stress, in humans (49), this is derived from peripheral arteries and the relative impacts of pressure and shear-driven adaptation in cerebral vessels in vivo requires further investigation.

Cerebrovascular reactivity is abnormal in clinical populations such as patients with Alzheimer's disease (50) and, in some studies it has been predictive of stroke risk and cardiovascular-related mortality (51, 52). It is unclear, based on extant literature, what effect exercise training has on cerebrovascular reactivity to CO_2 in humans. Previous studies that investigated the impact of lifelong activity and exercise training on CO_2 reactivity are equivocal, with increases (11, 12), decreases (15), and no change (16) reported. The discrepancy may be due to different imaging (MR vs. TCD) or methodological approaches (breath holding vs. steady state vs. rebreathing, etc.) and/or the type of exercise performed. In a previous 6-mo aerobic training study (53), there was a small but significant reduction in CVRi during hypercapnia that was also apparent during submaximal exercise. In contrast, we observed a significant increase in MCA_{CVRi} and PCA_{CVRi} reactivity to hypercapnia (Fig. 2) and significantly decreased MCAv and increased MCA_{CVRi}, PCA_{CVRi}, and ICA_{CVRi} during acute exercise following RES but not END training (Fig. 3). Notably, MAP was higher at rest and in response to hypercapnia (Fig. 2), despite a similar CR response pre- and post-training, indicating that a change occurred in the underlaying relationship between MAP and CO_2 as a result of RES, rather than in the functional response to CO_2 exposure. As indicated earlier, this increase in CVRi in response to hypercapnia could potentially be a protective mechanism to protect the cerebral vasculature. A previous study that reported lower cerebrovascular reactivity in masters athletes (who participated in aerobic exercise), compared with matched controls, was undertaken using 3 T MRI (54). That study concluded that blood vessels in the athletes were less responsive to hypercapnic-induced vasodilation and that this effect was spatially nonspecific and present throughout the brain. The authors speculated that elevated CO_2 exposure as a result of repeated exercise may downregulate CO_2 sensitivity as a protective mechanism to prevent blood vessels in the brain from over-dilating during exercise, when most cardiac

output should be redistributed to the limbs (15). This finding is generally consistent with our observations related to the impact of RES in the current study.

The current study reported no change in cerebral reactivity in response to END exercise, however, we employed a 12-wk intervention in young healthy individuals, whereas Thomas et al. used master athletes who had been training for "life." The benefits of END training in peripheral arteries are known to be extensive (19) and include improvement in the nitric oxide-mediated dilator function, arterial remodeling, reduced arterial stiffness, and higher stroke volume (19, 55). While it may appear surprising that we did not observe any adaptations in the cerebrovasculature following END training, it is worth pointing out that many exercise training studies performed in healthy asymptomatic subjects have also failed to register adaptations in peripheral artery structure and function (56), possibly due to the difficulty in inducing physiological adaptation in vessels that are functioning optimally a priori. We think it unlikely that our END training was performed at insufficient intensity, given that Smith and Ainslie (27) concluded that increases in velocity and peak flow are observed at an intensity of ~70% maximum workload, whereas higher intensities cause a modest "peaking over" in CBF. Our training intervention was informed by this observation regarding the optimal intensity zone, and used intensities of between 60% and 90% maximum workload. We conclude that in young inactive adults, END training of 3 mo duration does not directly influence CO_2 reactivity, whereas RES training of 3 mo duration may stimulate some protective adaptations.

Previous research pertaining to RES training effects on cerebrovascular function is limited. A recent cross-sectional (i.e., nontraining) study by Corkery et al. (20) evaluated cerebrovascular hemodynamics and function at rest and in response to hypercapnia in RES trained (n = 13), END trained (n = 13), and untrained adults (n = 13). They found that, at rest, there was no difference in MCAv between groups; however, RES trained adults had greater cerebrovascular MCA conductance compared with END trained adults. However, there were no differences in MCAv or MCA conductance in response to hypercapnia between the groups. As indicated earlier, we also observed a similar difference in resting cerebrovascular function in the current study, however observed an increase in MCA_{CVRi} and PCA_{CVRi} in response to hypercapnia following RES training. Importantly, we employed a training intervention, which allowed us to accurately monitor and measure the RES training stimulus. Cross-sectional studies are unable to accurately characterize the training stimulus or whether training per se, versus myriad other factors that vary between individuals, are causal. It is possible that the RES training intervention undertaken by participants in the current study was of different intensity and frequency than that experienced by subjects in the study of Corkery et al. (20). In addition, different durations of training are associated with distinct changes in arterial function and structure (19, 31), with arterial remodeling superseding initial functional adaptation. It is also worth noting that the effects of RES training on CVRi may be exaggerated in older individuals or those with hypo- or hypertension, compared with the normotensive healthy young subjects we examined. Future studies should investigate the impact of RES on cerebrovascular adaptation and regulation in such populations. A second cross-sectional study by Perry et al. (21) evaluated resting cerebral hemodynamics and dynamic cerebral autoregulation in RES trained (n = 12), END trained (n = 12), and sedentary healthy young adults (n = 12). They reported no significant effects of either exercise modality on autoregulation, using forced blood pressure oscillations. These results are consistent with the results of the current study. Both of these studies used young healthy individuals; future research should investigate the effects of exercise training in different populations groups.

There is disparity in the literature regarding the effects of END training on cerebrovascular function. Studies have reported positive impacts on cerebrovascular function (9, 11, 12, 57), no impact (16, 18, 57), or attenuated responses (15). This inconsistency is likely due to differences in methodology used to stimulate responses, equipment used to measure vessel responses, and/or the quality and regulation of training stimulus (many studies used cross-sectional comparisons). The current study is one of few that has employed an END training intervention to accurately measure adaptations in dynamic volumetric cerebrovascular function. In contrast to the current study, both Ivey et al. (12) and Murrell et al. (11) reported small improvements in cerebrovascular reactivity following END interventions and Anazodo et al. (57) reported improvements in resting CBF in some regions of the brain associated with cognition following an END training cardiac rehabilitation program. However, Ivey et al. studied hemiparetic stroke survivors and Anazodo et al. studied patients with coronary artery disease who may have had impaired CBF before participating in the END intervention, in addition to employing a 6-mo training intervention. Murrell et al. studied both young and older individuals and employed a 3-mo intervention, however, their intervention was not center-based and involved a mixture of circuit modalities with consequently inconsistent hemodynamic stimuli. In addition, Murrell et al. (11) studied a smaller sample of subjects (n = 10) than the current study (n = 68), which may have also influenced the results. The current study suggests that END training does not impact cerebrovascular function in young healthy adults, but it is possible that more intensive or prolonged exercise programs may induce adaptation in this population. Nonetheless, our END intervention was sufficiently demanding to stimulate adaptation in $\dot{V}O_{2max}$, resting HR, total fat mass, and total lean mass (22, 23). Another relevant point is that different forms of exercise are associated with distinct changes in artery shear stress (58) (and transmural wall pressure) (49), and the interval type END we used may present a different stimulus for adaptation compared with studies which adopted continuous modes of END training. Future studies will be needed to address the possible beneficial impacts of distinct forms of END and also changes that may occur in individuals with a priori compromised cerebrovascular function.

This study possessed several limitations. The use of transcranial Doppler to assess CBF in the MCA and PCA relies on the assumption that the diameter of these vessels does not change during cerebrovascular assessments (CO_2 reactivity, autoregulation, and acute exercise), or in response to the training interventions. Although structural remodeling of the cerebrovasculature has not been confirmed, there is

convincing evidence suggesting that exercise remodels peripheral blood vessels in humans (19, 31, 59–62). In an attempt to overcome the limitation of transcranial Doppler in measuring vessel diameter, we added the use of simultaneously collected duplex ultrasound of the ICA and VA to measure both velocity and diameter. A second limitation is that some authors argue that maneuvers that induce large changes in blood pressure, such as a sit-to-stand protocol, are more representative of fluctuations experienced in day-to-day life and may also be less affected by noise. It is therefore a limitation that we only report spontaneous pressure-flow relationships to index autoregulation. However, it should be noted there is no gold-standard approach to assess autoregulation in humans and few metrics of autoregulation can be used interchangeably (63). Some authors argue that spontaneous measures of dynamic autoregulation are sufficient to accurately quantify autoregulatory capacity (64, 65), since consistent patient breathing is maintained and the risk of changes occurring as a result of alterations in the partial pressure of carbon dioxide ($P_{ET_{CO_2}}$) is minimized (64). Other researchers contend that more robust measures can be obtained using maneuvers that induce larger changes in blood pressure (66, 67) and that these measures are more representative of daily life and are less affected by "noise" in the signal recordings (64). Ideally, future research should report both spontaneous and forced blood pressure perturbations when investigating dynamic cerebral autoregulation. A further limitation of this study is that we used hypercapnia alone to test cerebral reactivity; future research should consider using both hypercapnia and hypocapnia. In addition, while the use of an acute aerobic exercise bout in the testing sessions enabled investigations into the effects of exercise interventions on responses to END exercise, the addition of an acute bout of RES exercise would have also been of interest and should be incorporated in future research to examine the influence of exercise interventions on the increases in pressure seen with RES exercise. The acute exercise bout assessed during the cerebrovascular testing sessions involved three stages at set Watt levels at each of the four testing time points. In future, the use of relative intensity stages should be considered to eliminate the possibility of a lower relative intensity postintervention influencing the cerebrovascular responses. Finally, although research surrounding young healthy populations is critical in determining mechanisms surrounding cerebrovascular adaptation to exercise training, we cannot extrapolate our findings to older populations or patients with impaired cerebrovascular function, such as reduced cognitive function, stroke, or dementia.

This study is the first to assess a comprehensive array of cerebrovascular measures using a randomized crossover design involving two distinct exercise modalities. These modalities, and the programs we designed, are ecologically valid in that they emulate guideline-based (68, 69) programs similar to those typically and widely adopted in the community to enhance fitness or muscular strength and hypertrophy. Our study was designed as a superiority trial: it did not include a group that had no exercise as a comparator. Our findings suggest that the different hemodynamic stimuli experienced in response to RES versus END may induce distinct cerebrovascular adaptation, particularly in response to the impacts of, and regulatory responses to, blood pressure. Future research should investigate the impact of longer duration exercise interventions to determine whether END training can positively impact cerebrovascular adaptation. In addition, the effect of RES training interventions in older populations and in patients who suffer from hypertension or cognitive decline, stroke, and dementia should be investigated.

SUPPLEMENTAL DATA

Supplemental Fig. S1: https://doi.org/10.6084/m9.figshare.14499018.
Supplemental Fig. S2: https://doi.org/10.6084/m9.figshare.14499036.
Supplemental Fig. S3: https://doi.org/10.6084/m9.figshare.16416825.
Supplemental Fig. S4: https://doi.org/10.6084/m9.figshare.16416831.
Supplemental Fig. S5: https://doi.org/10.6084/m9.figshare.16416834.
Supplemental Fig. S6: https://doi.org/10.6084/m9.figshare.16416837.

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DISCLAIMERS

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

L.H.N., K.J.S., and D.J.G. conceived and designed research; H.J.T., C.E.M., and K.J.S. performed experiments; H.J.T. analyzed data; H.J.T., P.N.A., K.J.S., H.H.C., and D.J.G. interpreted results of experiments; H.J.T. prepared figures; H.J.T. drafted manuscript; H.J.T., C.E.M., L.H.N., P.N.A., K.J.S., H.H.C., and D.J.G. edited and revised manuscript; H.J.T., C.E.M., L.H.N., P.N.A., K.J.S., H.H.C., and D.J.G. approved final version of manuscript.

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