The impact of 6-month land versus water walking on cerebrovascular function in the aging brain

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Abstract

Introduction: To examine the hypothesis that exercise training induces adaptation in cerebrovascular function, we recruited 63 older adults (62±7 yrs, 46 females), to undertake 24 weeks of either land-walking, water-walking, or participate in a non-exercise control group. This is the first multi-interventional study to perform a comprehensive assessment of cerebrovascular function in response to longer term (6-month) training interventions, including water-based exercise, in older healthy individuals. Methods: Intra-cranial blood flow velocities (middle [MCAv] and posterior [PCAv] cerebral arteries) were assessed at rest, and in response to neurovascular coupling, hypercapnic reactivity and cerebral autoregulation. Results: We observed no change in resting MCAv in response to either training intervention (pre v post, mean [95% confidence interval], land-walking: 65 [59-70] to 63 [57-68] cm/s, P=0.33 and water-walking: 63 [58-69] to 61 [55-67] cm/s, P=0.92) compared to controls, and no change in neurovascular coupling (land-walking: P=0.18, water-walking: P=0.17). There was a significant but modest improvement in autoregulatory normalised gain following the intervention in the water-walking compared to the land-walking group (P=0.03). Hypercapnic MCAv reactivity was not different based on exercise group (land: P=0.87, water: P=0.83); however, when data were pooled from the exercise groups, increases in fitness were correlated with decreases in hypercapnic reactivity ($r^2=0.25$, $P=0.003$). Conclusion: While exercise was not associated with systematic changes across multiple domains of cerebrovascular function, our data indicate that exercise may induce modest changes in autoregulation and CO$_2$ reactivity. These findings should encourage further studies of the longer term implications of exercise training on cerebrovascular health.

Keywords (4): exercise training, cerebral blood flow, cerebrovascular function, water immersion.
Introduction

Regular exercise is recommended for the primary and secondary prevention of cerebrovascular disease and for maintaining brain health and cognition (1-3). Exercise improves neural synaptic plasticity (4) and vascular elements of brain health (5); however, the stimuli responsible for these benefits remain unknown. A better understanding of these mechanism/s is key to improving prevention and management strategies for cerebrovascular diseases.

A hallmark of the pathogenesis of cerebrovascular disease is endothelial dysfunction (6). In the peripheral vasculature, it is well established that shear stress is the principal physiological stimulus responsible for direct and beneficial effects of exercise on arterial function and remodelling in humans (7). If this is also true in the cerebral circulation, it would contribute to healthy cerebrovascular and cognitive aging (8). Previous animal studies have confirmed that cerebral vessels are sensitive to changes in blood flow and shear stress both in vitro and in vivo (9, 10), and that exercise training improves endothelium-dependent vasodilation (11). Exercise trained mice exhibit greater blood flow in the ischaemic region following stroke, as well as a more rapid and complete functional recovery compared to untrained animals (12). Exercise trained mice unable to produce endothelium-derived nitric oxide (NO) fail to benefit from the protective effects of exercise on the cerebral vasculature (13). In humans, endothelium-dependent and flow-mediated dilation has been confirmed in the carotid arteries (14), while exercise training has been associated with increased regional brain matter and coupling of angiogenesis and neurogenesis (8, 15). Taken together, this evidence suggests that increases in cerebral blood flow and shear stress may improve endothelial health and play a regulatory role in protecting and/or reversing vascular and cognitive decline.
We recently demonstrated that immersion of the lower body in euthermic water significantly increases (~20%) cerebral blood flow velocity both at rest (16) and during water-based exercise (17). Similar findings have been replicated in other laboratories (18). In addition to minimising the musculoskeletal impact of exercise and the risk of injury, upright exercise performed in the water enhances cerebrovascular haemodynamic stress and may therefore enhance cerebrovascular function and health. To examine this hypothesis, we designed a trial (19) in older adults, to measure the impact of a novel aquatic exercise intervention which aimed to increase the haemodynamic stimulus responsible for improvement in cerebrovascular function. We employed validated techniques to comprehensively assess changes in cerebrovascular function in response to various physiological stimuli (20), before and after a 6 month intervention period during which previously inactive participants were randomised to undertake either land-based walking exercise, intensity-matched water walking exercise, or be part of an inactive control. We hypothesised that water-based walking would improve cerebrovascular function to a greater degree than land-walking.

Methods

The University of Western Australia Human Research Ethics Committee granted approval for all aspects of this study, which was prospectively registered as a clinical trial (ACTRN12614000017628). All participants provided written, informed consent prior to participation. This study conformed to the standards set by the Declaration of Helsinki.

Study Design

Seventy-two healthy but inactive (<60 mins exercise per week) males and post-menopausal females over 50 years of age with no diagnosed cognitive impairment were recruited from the community.
Health status was thoroughly assessed. When a potential participant expressed interest in participating in the study, a 45 minute telephone screening interview was conducted to assess general health, alcohol use, medications, and medical history, as well as questionnaires related to cognition and mood (TICS-m and GDS – see below and supplementary Table). Exclusion criteria included diagnosed mild cognitive impairment or dementia, smoking (or <12 months cessation), hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg), weekly alcohol intake greater than 280g per week and/or drinking more than 40g ethanol in one session, BMI greater than 40 kg·m$^{-2}$ and total cholesterol greater than 7.0 mmol·L$^{-1}$ (for a full list, see our detailed methodological paper (19)). These data for assessing inclusion were obtained either through the phone interview or from baseline laboratory screening tests. The baseline screening visit included a resting ECG and 12 lead ECG stress test with results assessed by medical practitioners affiliated with the study. Any ECG results of potential concern were communicated to study coordinators and the participant’s GP. To rule out cognitive impairment, a battery of cognitive tests was applied by a qualified neuropsychologist in the screening stages (phone interview and laboratory baseline tests). Participants were excluded if they had a diagnosed cognitive impairment (mild cognitive impairment or dementia) or fell into one of the following categories: Modified Telephone Interview Cognitive Status – TICS-m less than 32, Geriatric Depression Scale - GDS - greater than six, Standardised Mini- Mental State Examination - sMMSE less than 24, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) delayed memory index score more than 1.5 standard deviations below the age-related mean (see supplementary Table).

Following this comprehensive initial screening to confirm eligibility, participants attended the Cardiovascular Research Laboratory at The University of Western Australia for assessment of cerebrovascular function at Week 0 (Baseline) and 24 (immediately post-intervention) (see...
Supplementary Figure). Participants were then randomised into 1 of 3 groups, land-based walking (LW), water-based walking (WW), or a control group (CG). This paper reports the cerebrovascular function responses to the exercise interventions; the cardiopulmonary fitness (21), peripheral vascular (22) and body composition outcomes (23) of this study have previously been reported previously.

Exercise training protocols

All exercise was supervised and centre-based, with intensity monitored using a heart rate watch (Polar RS300X HR monitor, Polar Electro Oy, Finland) and with sessions conducted in small groups in the early morning and evening. A supervised warm-up and cool down interval were included in each session. Land-based walking took place on the university grounds as well as along the adjoining river foreshore and parkland, or on a treadmill if weather indicated. Water-based walking was in a heated (~30 °C) chest deep swimming pool (20 x 30m) located at the University. Duration and intensity of the exercise sessions increased over the course of the study, from an initial 15 mins of exercise, increasing to 50 mins by the end of the 24 weeks. Participants (land and water) were given a personalised target heart rate range, based on heart rate reserve calculated from their initial peak exercise test results. The relationship between heart rate and oxygen consumption during exercise is maintained for water- versus land-based exercise (17). We therefore used heart rate reserve to standardise and match exercise intensity for the land- and water- groups. Each exercise session was guided by an accredited exercise scientist/physiologist (Exercise and Sports Science Australia), and heart rate was monitored and recorded every 5 mins throughout the session.

The second session of each week was an interval training session, with the other two sessions of continuous intensity. The intensity of training started at 40-45% heart rate reserve, building to 55-
65% by week 24. Additional, ‘make-up’ sessions were provided if required, to ensure optimal adherence to the protocol. The two exercise groups (land- and water-based walking) completed three exercise sessions per week for 24 weeks, building to a one-hour duration over the course of the study (see below).

The control group was asked to maintain their usual levels of activity (all participants were sedentary at recruitment), and attended the university every six weeks to participate in an educational seminar of approximately one hour, on a topic which was expected to be of interest but was unrelated to physical activity, lifestyle and health – for example, first aid skills, computer workstation optimal ergonomic set-up, etc.

**Cerebrovascular assessments**

Tests were conducted on non-exercise days, at the same time of day, and the participants were required to have abstained from moderate/vigorous physical activity, caffeine and food, for at least 6 hours prior to the test. Middle (MCAv) and posterior (PCAv) cerebral artery velocities were measured using a 2-MHz, S3 transcranial Doppler ultrasound system (Spencer Technologies, Seattle, WA). Previously published guidelines were closely followed (20) so the procedures will be described briefly here. Throughout all assessments, MCAv, PCAv and end-tidal CO₂ (P\text{ET}CO₂) were continuously recorded along with beat to beat blood pressure via photoplethysmography (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). After instrumentation and a minimum of 20 min supine rest, a 5 min baseline recording of all variables was performed.
Neurovascular coupling

A 4 min baseline was collected (2 mins eyes open, 2 mins eyes closed), followed by 5 cycles of 30 secs eyes open, 30 secs eyes closed. During the eyes open cycles, a tablet was positioned in front of the participant’s eyes and they were instructed to watch a 0.5Hz chequerboard visual stimulus. The neurovascular coupling response was calculated as the average peak %PCA\text{v} change across the 5 trials. The last 10 secs of eyes closed was averaged and used as the baseline for the subsequent peak PCA\text{v} during eyes open.

Cerebrovascular CO\textsubscript{2} reactivity

Following a 5 min rest period breathing room air via a 2-way mouthpiece, participants inhaled 3% CO\textsubscript{2} for 4 mins and then 6% CO\textsubscript{2} for 4 mins (both 21% O\textsubscript{2}, balanced N\textsubscript{2}) via a Douglas bag. The MCA\textsubscript{v} and cerebrovascular conductance (CVC; calculated as MCA\textsubscript{v}/MAP) response to elevations in P\textsubscript{ET}CO\textsubscript{2} was analysed by averaging 30 seconds of data at baseline and during the last 30 seconds of each hypercapnic stimulus. Linear regression analysis was then performed to calculate reactivity slopes (P\textsubscript{ET}CO\textsubscript{2} vs MCA\textsubscript{v} and CVC).

Dynamic cerebral autoregulation

Precisely controlled blood pressure oscillations were induced by a lower body negative pressure chamber (to -70 mmHg) (Vacustyler – Weyergans, Dueren, Germany) across a 4 min period of 10 secs-on:10 secs-off (0.05 Hz). Transfer function analysis was performed using the commercially available software Ensemble-R (Elucimed Ltd, Wellington, New Zealand) that incorporates internationally recommended guidelines for autoregulation analysis (24).
Statistical analysis

Analyses were conducted using SPSS Version 23.0 (IBM Corporation, Armonk, NY, USA) and STATA Version 15.0 (STATA Corporation LP, College Station, TX, USA). Unadjusted means, standard deviations and confidence intervals were calculated for the cerebrovascular and respiratory outcome variables at Weeks 0 and 24. Due to the repeated measure nature of the data, separate linear mixed models were used to investigate the relationship between the cerebrovascular function variables, group (CG, LW and WW) and time (Week 0 and 24), using two-tailed tests. These analyses accounted for time invariant covariates, including age and sex, and an interaction between group and time. A random intercept was included in each model to account for the repeated nature of the data. Statistical significance was set at P <0.05.

Results

Subject characteristics

Seventy-two participants were recruited and randomised into the study, as detailed in our comprehensive methodology manuscript (19). Of these, cerebral data was not collected in eight participants due to poor transcranial Doppler velocity signals, while a further participant withdrew from the study (see Supplementary CONSORT figure). Baseline characteristics for the 63 participants included in this study are provided in Table 1.

Exercise training - efficacy

Average attendance rate for the LW group was 83.2% ± 4.7%, and 79.2% ± 4.8% for the WW group. As previously published (21), cardiorespiratory fitness was improved in both exercise groups, with increases in $\dot{V}O_2$max of 0.57±0.62 ml/kg/min (LW) and 0.93±0.75 ml/kg/min (WW) compared to the
CG (−1.75 ± 0.78 ml/kg/min; group*time, P < 0.05). LW showed improved peripheral (brachial artery) endothelial function compared to the CG, with an increase in flow-mediated dilation (FMD) from 5.39 ± 0.71% to 7.77 ± 0.78%, P = 0.009 vs CG: 5.87 ± 0.73% to 5.78 ± 0.78% over the 24 weeks (22).

Improvements in body composition were also evident, with a reduction in central adiposity in both exercise groups, and an increased lower limb lean mass in the WW group (23).

Resting intra-cranial velocities
All resting cerebrovascular and respiratory data are presented in Table 2. Compared to the control group, there was no change in resting MCAv or PCAv in the land-based (group*time interaction, P = 0.33 and P = 0.92, respectively) or water-based group following the 6-month intervention (P = 0.25 and P = 0.86). No difference was evident in MCAv or PCAv between the water and land-based exercise groups (P = 0.85 and P = 0.78, respectively). Importantly, resting $P_{\text{ETCO}_2}$ (LW: P = 0.42 and WW: P = 0.52) and MAP (P = 0.24 and P = 0.58) were also unchanged across both the land and water group interventions compared to controls. The change in $P_{\text{ETCO}_2}$ and MAP was also not different between the two exercise groups (P = 0.15 and P = 0.09, respectively). Both MCA and PCA conductance were also unchanged from Week 0 to 24 in all groups (Table 2).

Neurovascular coupling
Compared to the control group, there was no change from Week 0 to Week 24 in the land-based (group*time interaction, P = 0.18) or water-based exercise group (P = 0.17, Figure 1). No difference was evident between the land and water-based groups (P = 0.97).
The MCAv hypercapnic reactivity did not differ between the groups (group*time interaction, P=0.87 and P=0.83, respectively, Figure 2), but the change in MCA CVC reactivity in the WW group was lower than that in the control group (P=0.04); with no difference evident between LW and control (P=0.13) or between the exercise groups (P=0.63). When the exercise groups were pooled, and the change in fitness [VO$_2$max previously published in (21)] was plotted against change in MCAv hypercapnic reactivity between Week 0 and 24, there was a significant negative correlation (P=0.003, Figure 3) indicating that greater improvement in cardiorespiratory fitness was associated with a decrease in cerebrovascular hypercapnic reactivity.

**Dynamic cerebral autoregulation**

As forced oscillations were performed at 10 secs on:10 secs off (20 sec cycle, 0.05 Hz), TFA outputs within the very low frequency range (0.02-0.07 Hz) are presented (Table 3). No difference was observed in gain in the land-based (group*time interaction, P=0.57) or water-based exercise group (P=0.32), when compared to the control group. Similarly, gain was not different between the exercise groups (P=0.13). While change in normalised gain across the intervention was not different between the control and land (P=0.37) or water group (P=0.21); there was a significant difference between the exercise groups, with the water-based exercise group showing a greater positive change (Table 3, P=0.03).

No change in phase was observed in the exercise conditions compared to the control group (Table 3), while coherence from Week 0 to 24 was not different in land or water-based conditions compared to the controls (P=0.38, P=0.72, respectively), and there was no difference between the exercise groups (P=0.59).
Discussion

This is the first supervised and centre-based exercise training study in healthy older individuals to assess multiple domains of cerebrovascular function. The novel use of water exercise allowed for an intensity-matched exercise condition to land walking, but with a greater increase in cardiovascular loading which previous experiments have shown to be associated with increased cerebral blood flow responses (16-18). Our results suggest that 6-months of exercise training did not modify resting cerebral perfusion or neurovascular coupling. Whilst one parameter associated with cerebral autoregulation improved and we observed an inverse correlation between changes in fitness and hypercapnic reactivity in the trained subjects, our data indicate that land and water based exercise training do not induce marked or systematic cerebrovascular adaptation in older healthy subjects.

We observed no change or group differences in resting intracranial velocities, a predictor of cardiovascular mortality (25). Some (26, 27), but not all (28, 29), previous cross-sectional studies have suggested that habitual exercise may prevent or slow the natural decline in resting cerebral perfusion, thereby modifying disease risk. However, cross-sectional studies to ascertain the impacts of exercise training are fraught (30), being compromised by myriad between-subjects differences and selection biases. Longitudinal studies provide a more valid way of ascertaining the effect of exercise training, but these are rare in the context of cerebrovascular assessment. Although lacking a control group, a recent study assessed the impact of a supervised 6 month aerobic training study in 206 healthy low-active middle-aged and older adults on cognition and selected metrics of cerebrovascular function, assessed via transcranial Doppler (5). Consistent with the current findings,
this study reported that resting intra-cranial velocities were unchanged. Similarly, while previous studies have reported visually evoked NVC responses are lower with ageing and in a myriad of pathologies (31, 32), this is the first study to investigate the longitudinal impact of supervised exercise training on NVC in older participants. Contrary to our hypothesis, we observed no changes in any group in NVC. A potential explanation for our finding may be that the relationship between neural stimulation and hyperemia is not linear and that it involves a myriad of different mechanism(s). It is known that the blood flow response is ~4-fold higher than the metabolic requirement (33).

Cerebrovascular reactivity is impaired in clinical populations such as patients with Alzheimer’s disease (34) and, in some studies, this is predictive of stroke risk and cardiovascular-related mortality (35, 36). But it is unclear, based on extant literature, what effect exercise training has on cerebrovascular reactivity to CO₂ in humans. Previous studies that investigated the impact of lifelong activity and exercise training on CO₂ reactivity are equivocal, with increases (37, 38), decreases (27) and no change (28) reported. The discrepancy may be due to the different imaging techniques (MR vs. TCD) and/or distinct methodological approaches (breath holding vs. steady state vs. rebreathing, etc). We observed an inverse relationship between change in VO₂max and hypercapnic reactivity in participants who were randomized to the exercise interventions (Figure 3), whereby a greater change in VO₂max was associated with a lower hypercapnic reactivity. In a previous 6-month training study (5), there was a small but significant reduction in cerebrovascular resistance during hypercapnia. Somewhat in contrast, our current findings indicate that cerebrovascular reactivity declined in the WW group in comparison to controls, which is in keeping with a previous study that reported lower cerebrovascular reactivity in masters athletes compared to matched controls who were compared using 3T MRI (27). That study concluded that blood vessels in the athletes were less
responsive to hypercapnic-induced vasodilation and that this effect was spatially non-specific and present throughout the brain. The authors speculated that elevated CO₂ exposure as a result of repeated exercise may downregulate CO₂ 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 (27). We conclude that the current literature pertaining to exercise training and CO₂ reactivity are directionally uncertain; there is no clear consensus regarding training effects and reactivity in humans.

While cerebral autoregulation is impaired in clinical groups such as in people with diabetes (39), carotid and vertebral artery disease (40, 41) and ischaemic stroke (42), the majority of studies report that cerebral autoregulation is relatively well maintained across healthy ageing (43, 44). In this study, forced oscillations in blood pressure and MCAv were induced via lower body negative pressure to improve the reliability and validity of analyses via transfer function analysis (TFA). The TFA output gain represents the difference in amplitudes between the MCAv and blood pressure signals, while phase describes the temporal changes between the two signal inputs. We observed no change in gain or phase in either of the exercise groups compared to the control group. However, the decrease in normalised gain in the water exercise group from Week 0 to 24 was statistically significantly different compared to land exercise (P=0.03). This observation is consistent with previous studies that have revealed impaired cerebrovascular hemodynamics, indexed as an increase in autoregulatory gain, in intracerebral haemorrhage patients (45), elderly individuals with lower fractional anisotropy scores (46) and contact sport athletes (47). Our findings suggest that the ability to regulate CBF in the presence of changes in blood pressure improved following water-based exercise. While this finding warrants future confirmation, it may be related to the fact that the water-based exercise group were likely exposed to greater increases in BP during the exercise
bouts (compared to the land condition) as a consequence of blood volume redistribution and stroke volume changes (16, 17, 48, 49). This greater transmission of the haemodynamic stimulus to the brain during exercise may have led to a favourable counter-adaptation. It is important to note, however, that normalized gain was low at entry in the land-based exercise group and this could explain some of the difference with the water-based group. Furthermore, there were no differences in any other measures of cerebral autoregulation and we assessed autoregulation only at the very low frequency range. While acknowledging the poor interchangeability of metrics to index cerebral autoregulation in humans (50), future studies should specifically address the impacts of exercise training autoregulation using oscillations at both VLF and LF ranges.

The current trial is the first to conduct a 6-month supervised exercise intervention, with two separate exercise intervention groups (combined n=41) alongside a control group. We applied state-of-the-art and comprehensive approaches to cerebrovascular functional assessment (20), based on a broad spectrum of physiological stimuli, with dose-response paradigms applied. These study design strengths add robustness to our findings. Importantly, we recently published the cardiorespiratory fitness, body composition and peripheral vascular outcomes of this study, which revealed that our exercise interventions increased VO$_2$max, decreased fat mass, increased lean mass and improved brachial artery endothelium-mediated vasodilation (21-23). This unique set of outcomes in the same participants reconfirms the efficacy of our training interventions across a range of physiological and health outcomes. Our findings suggest that the peripheral vasculature may be more amenable to exercise-induced changes than the cerebral circulation. This may relate to the fact that the range in cerebral blood flow from a sedentary to the exercising state is considerably smaller than that in the peripheral vasculature, where blood flow and concomitant endothelial shear stress might increase ~20-50 fold beyond resting flow states (51). The inclusion of
the water-based exercise group that was exposed to higher increases in CBF suggests that there may be a threshold of blood flow and shear stress necessary to induce cerebrovascular adaptation.

This study has several limitations. Our assessment of cerebral blood flow using transcranial Doppler relies on the assumption that the diameter of the insonated vessels (MCAv, PCAv) did not change during the cerebrovascular assessments (NVC, CO2 reactivity, autoregulation), and was not different post-intervention. Exercise has been shown to induce structural remodelling of peripheral blood vessels in humans (7), but this has not been confirmed in the cerebral vasculature. Importantly, our inclusion of functional measures of the cerebral vasculature presented as relative change (CO2 reactivity and NVC) is less susceptible to this confounding factor. As cerebral metabolism and oxygen extraction is not measurable using TCD, we cannot rule out the possibility that exercise training improved cerebral metabolic efficiency or oxygen extraction. This would necessitate invasive experimental approaches which carry high risk in humans and are ethically challenging. It is also possible that our exercise intensity was not high enough to induce cerebrovascular change, however this seems unlikely given that peripheral vascular function, cardiorespiratory fitness and body composition were all improved in the exercise groups (21-23). Also, we cannot partition, in humans, the contribution of NO mediated function to cerebrovascular adaptation in this study. This would require infusion NO blockers pre and post training which would be ethically and logistically challenging in our experimental setting. As stated above, there are limitations in this study and the wider literature regarding metrics used to describe cerebral autoregulation. Future studies should use oscillations at both VLF and LF ranges. A final caveat of our study is that the participants were relatively healthy; we cannot extrapolate our findings to groups with more impaired a priori cerebrovascular function, such as vascular cognitive impairment, dementia or stroke patients.
In summary, this is the first study to employ a comprehensive array of cerebrovascular measures across a longer-term exercise training intervention, and to use the novel application of water immersion to augment cerebrovascular blood flow during exercise training. While exercise was not associated with systematic changes across multiple domains of cerebrovascular function, our data suggest that exercise may induce modest changes in autoregulation and CO₂ reactivity. These findings should encourage further studies of the longer term implications of exercise training on cerebrovascular health.
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Conflict of interest

None.

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and statement that results of the present study do not constitute endorsement by ACSM.
References


Figure legends

Figure 1
Visually evoked neurovascular coupling responses of the posterior cerebral artery (PCAv, %change from baseline) to a standardised chequerboard reversal stimulus at Week 0 and 24 in the control (closed), land (grey) and water (white) walking groups. No significant change was observed between or within the groups. Data are mean ± SE.

Figure 2
Hypercapnic reactivity slopes of the middle cerebral artery velocity (MCAv; A) and conductance (CVC; B) in response to inhalation of 3% and 6% CO₂ at Week 0 and 24 in the control, land and water walking groups. No significant change was observed between or within the groups for MCAv (A). * MCA CVC reactivity was significantly different in the water-based exercise compared to the control group, P<0.05. Data are mean ± SE.

Figure 3
Correlation between change in VO₂max (data from (21)) and MCAv reactivity linear regressions from Week 0 to 24 for the two exercise intervention groups. There was a significant negative correlation (R²=0.25, P=0.003), whereby a larger increase in fitness was associated with a lower MCAv hypercapnic reactivity. When analysed separately, both land (light circles) and water (dark squares) walking groups showed negative correlations: Land R² = 0.278, P=0.030; Water R² = 0.233, P=0.058.