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ORIGINAL ARTICLE

Acute exercise stress reveals cerebrovascular benefits associated with moderate gains in cardiorespiratory fitness

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Elevated cardiorespiratory fitness improves resting cerebral perfusion, although to what extent this is further amplified during acute exposure to exercise stress and the corresponding implications for cerebral oxygenation remain unknown. To examine this, we recruited 12 moderately active and 12 sedentary healthy males. Middle cerebral artery blood velocity (MCAv) and prefrontal cortical oxyhemoglobin (cO_2Hb) concentration were monitored continuously at rest and throughout an incremental cycling test to exhaustion. Despite a subtle elevation in the maximal oxygen uptake (active: 52 ± 9 ml/kg per minute versus sedentary: 33 ± 5 ml/kg per minute, $P < 0.05$), resting MCAv was not different between groups. However, more marked increases in both MCAv (+28 ± 13% versus +18 ± 6%, $P < 0.05$) and cO_2Hb (+5 ± 4% versus − 2 ± 3%, $P < 0.05$) were observed in the active group during the transition from low- to moderate-intensity exercise. Collectively, these findings indicate that the long-term benefits associated with moderate increase in physical activity are not observed in the resting state and only become apparent when the cerebrovasculature is challenged by acute exertional stress. This has important clinical implications when assessing the true extent of cerebrovascular adaptation.

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INTRODUCTION

Regular physical activity has the capacity to delay the longitudinal decline in cerebral perfusion during sedentary aging and thus reduce the risk of cognitive decline, dementia and stroke.[1] A corresponding improvement in cardiorespiratory fitness in the form of elevated maximal oxygen uptake ($\dot{V}O_{2max}$) has been associated with increased cerebral perfusion[2] and cerebrovascular reactivity to carbon dioxide detectable in the resting state.[3]

However, to what extent adaptation is further amplified in response to the cerebrovascular stress imposed by an acute bout of exercise remains unknown. Although acute exercise-induced increases in cerebral perfusion are typically accompanied by improved cortical oxygenation,[4] the corresponding relationships with physical activity and cardiorespiratory fitness in the setting of acute exercise stress has not previously been examined. This is surprising given that improved cerebral oxygenation is a likely mechanism underlying the cognitive benefits associated with regular physical activity.[5,6]

In a previous study by our group,[3] we identified that resting cerebral perfusion and cerebrovascular reactivity to carbon dioxide were both increased in direct proportion to $\dot{V}O_{2max}$ across the adult lifespan. To further extend these findings, we designed a comparative study to test the following hypotheses. First, a modest gain in aerobic fitness would be associated with a subtle improvement in resting cerebral perfusion, consistent with previous observations.[3] Second, the cerebrovascular stress imposed by acute exercise stress would amplify these baseline improvements in perfusion and from a functional perspective, translate into improved exercise-induced cerebral oxygenation.

MATERIALS AND METHODS

Participants

After ethics approval from the University of South Wales ethics committee and written informed consent, we recruited 12 active and 12 sedentary males matched for anthropometric characteristics (Table 1). By design, we recruited participants from an active group after completion of a self-report physical activity questionnaire.[3] They had engaged in 2 to 3 sessions of moderate recreational physical activity (football and general fitness activities) per week over the last 12 months. Likewise, we recruited a sedentary group based on the premise that they had not partaken in any form of scheduled physical activity over the adult lifespan.[3]

Procedures

All procedures were carried out in accordance with the Declaration of Helsinki.

Cerebral Hemodynamic Function

Middle cerebral artery blood flow velocity. The right middle cerebral artery blood velocity (MCAv) was insonated using a 2 MHz pulsed doppler ultrasound system (Multi-Dop X4, DWL Elektroniche Systeme, Singen, Germany).

Mean arterial blood pressure and heart rate. Beat-to-beat mean arterial blood pressure (MAP) and heart rate were monitored using finger photoplethysmography (Finometer PRO; Finapres Medical Systems, Amsterdam, The Netherlands).

Cerebral oxygenation. Left frontal cortical oxyhemoglobin (cO_2Hb) concentration was monitored by pulsed continuous wave (780 and 850 nm) near infrared spectroscopy (Oxymon MkIII, Artinis Medical Systems, Elst,

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Table 1. Participant demographics

	Sedentary (n = *12*)	*Active* (n = *12*)
Age (years)	24 ± 5	26 ± 7
Height (cm)	177 ± 6	180 ± 6
Weight (kg)	87 ± 13	79 ± 6
HR (bpm)	81 ± 10	68 ± 16†
PET_{CO2} (mmHg)	37 ± 4	37 ± 3
MCAv (cm/second)	63 ± 14	58 ± 11
MAP (mmHg)	98 ± 13	84 ± 13†
CVRi (mmHg/cm per second)	1.67 ± 0.52	1.52 ± 0.46
CVCi (cm/second per mmHg)	0.65 ± 0.20	0.72 ± 0.22

CVRi/CVCi cerebrovascular resistance/conductance indices; HR, resting heart rate; MAP, mean arterial pressure; MCAv, middle cerebral artery velocity; PET_{CO2}, end-tidal partial pressure of carbon dioxide. Values are means ± s.d. †$P < 0.05$ versus sedentary.

The Netherlands). Relative changes (to a normalized baseline, arbitrarily defined as 0 μmol/L) in cO_2Hb were derived using the modified Beer–Lambert law[7] and differential pathlength factors were calculated according to participant's age.[8]

Cardiorespiratory Fitness

Each participant was seated on an electronically braked semi-recumbent cycle ergometer (Corival, Lode, Groningen, The Netherlands) with the backrest maintained at 70°. The initial workload was set at 100 Watts (W) and increased by 25 W/minute until volitional exhaustion. Expired gas fractions including end-tidal partial pressure of carbon dioxide (PET_{CO2}) were measured via breath-by-breath online gas analysis (MedGraphics, Ultima Series, Gloucester, UK) and $\dot{V}O_{2max}$ was determined according to the established criteria.[3]

Data Acquisition and Analyzes

All cerebral hemodyamic recordings were averaged during the last 5 seconds of a 10-minute seated resting period and during the final 5 seconds of each incremental exercise stage including up to the point of volitional exhaustion. Beat-by-beat data were continuously sampled at 1 kHz using an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments, Oxford, UK) and stored on a personal computer for off-line analysis (Chart version 7.2.2, ADInstruments, Oxford, UK). Both the MAP and transcranial Doppler channels were 'time aligned' and CVR (cerebrovascular resistance) calculated as MAP/MCAv and CVCi (cerebrovascular conductance index) as MCAv/MAP.

Statistical Analysis

After pilot work, the present study was designed with 90% power at the $P < 0.05$ level to detect between-group differences in selected cerebral hemodynamic variables (notably exercise-induced differences in MCAv and cO_2Hb). Statistical analyses were performed using SPSS Statistics (v. 20, IBM, Chicago, IL, USA). After confirmation of distribution normality, between-group differences (rest) were analyzed using independent samples *t*-tests. A combination of 1- and 2-factor (group x intensity) repeated measures analysis of variance were used to assess within- and between-group differences (exercise) with appropriate Bonferroni-corrected *post hoc* comparisons. Significance was established at $P < 0.05$ and data expressed as mean ± s.d.

RESULTS

Power Calculations

Consistent with our original calculations, a retrospective power calculation confirmed an average value of >0.9 for all hemodynamic variables of primary interest.

Rest

Both heart rate and MAP were lower in the active group ($P < 0.05$ versus sedentary) whereas no differences were observed in MCAv, PET_{CO2}, CVRi and CVCi (Table 1).

Exercise

By design, the active group presented with a higher $\dot{V}O_{2max}$ (52 ± 9 ml/kg per minute versus sedentary: 33 ± 5 ml/kg per minute, $P < 0.05$) that was associated with a higher power output (335 ± 39 W versus 242 ± 36 W, $P < 0.05$). As a consequence, the duration of exercise was also extended in the active group (587 ± 85 seconds versus 358 ± 92 seconds, $P < 0.05$). Given that the bi-phasic response of cerebral blood flow during dynamic exercise is well established,[9] we chose to differentiate the MCAv kinetic into two phases (increased and decreased perfusion that tentatively reflect vasodilation and vasoconstriction, respectively) as illustrated in Figure 1A. A more pronounced elevation was observed in the active group during the increased MCAv phase (+28 ± 13% versus sedentary: +18 ± 6%, $P < 0.05$). However, both groups exhibited a similar reduction during the decreased MCAv phase (−15 ± 12% versus − 17 ± 8% $P > 0.05$). Similarly, there were no between-group differences in PET_{CO2} during either phase (Figure 1C). Although cO_2Hb did not change in the sedentary group, a progressive increase was observed in the active group (+11 ± 9% versus sedentary: − 2 ± 4%, $P < 0.05$) with a maximum value attained at 80% $\dot{V}O_{2max}$ (Figure 1B).

DISCUSSION

The major findings of the present study indicate that the cerebrovascular benefits associated with only modest gains in cardiorespiratory fitness were not detectable in the resting state and only became apparent upon exertion revealing improvements in both cerebral perfusion and oxygenation. This has important clinical implications in that investigators should be aware of the need to 'challenge' the cerebrovasculature through acute exercise stress to provide a more accurate assessment of the adaptive benefits associated with physical activity.

The lower resting MAP in the active group is consistent with findings reported by Banda *et al*[10] who demonstrated that even moderate levels of physical activity can (independently of other factors) reduce the risk of hypertension. In contrast, the fact that we failed to observe any evidence for improved cerebral hemodynamic function in the form of elevated perfusion and lower CVRi in the resting state would appear to contradict our recent findings[3] and those of others.[2] The most likely explanation for this is that the participants used in the present study, by design, were comparatively less aerobically conditioned compared with those involved in our previous study[3] ($\dot{V}O_{2max}$ of 52 ± 9 ml/kg per minute in the present study versus 62 ± 9 ml/kg per minute) which highlights the intriguing possibility that a threshold level of cardiorespiratory fitness needs to be exceeded before any adaptive benefits can be observed in the resting state. Based on both studies, we speculate that this threshold may be in the order of ≈55 to 60 ml/kg per minute. The fact that nitric oxide bioavailability is positively associated with aerobic fitness[11] could explain why the more aerobically conditioned participants employed in our previous study exhibited a higher resting MCAv in the resting state, whereas no differences were detectable in the moderately active participants in the present study.

In contrast and consistent with our original hypothesis, the cerebrovascular stress imposed by an acute exercise challenge facilitated detection of improved cerebrovascular function. Indeed, whereas MCAv increased at the same rate in both groups from low- to moderate-exercise intensity (20% to 65% $\dot{V}O_{2max}$), MCAv was elevated and maintained at a consistently higher level in the active group. In contrast, the magnitude of the decrease in MCAv beyond the ventilatory threshold was equivalent across groups during the transition from moderate to maximal exercise intensity. The elevation in cerebral perfusion was accompanied by a corresponding improvement in cortical cO_2Hb (Figure 1B). Even in the face of falling perfusion during the transition from

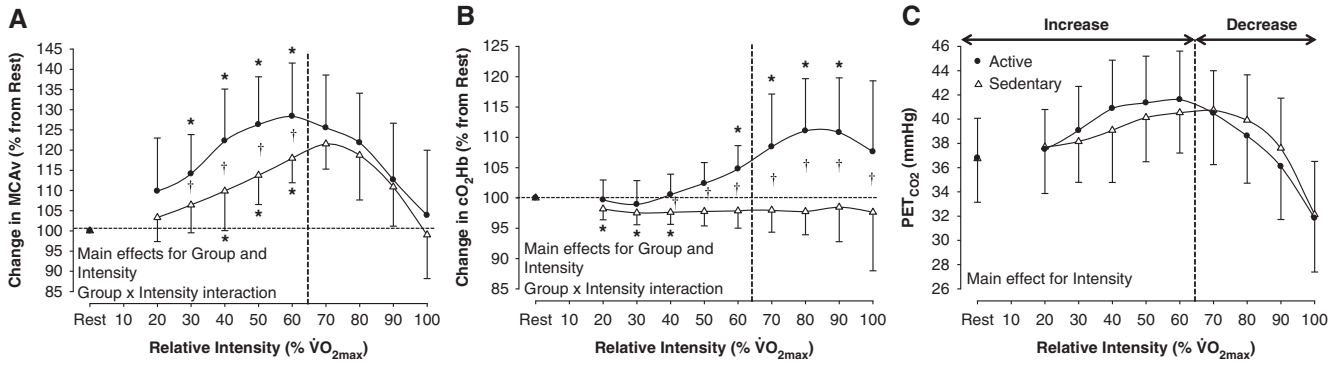

Figure 1. Relative (% from rest) changes in middle cerebral artery velocity (MCAv; (**A**)), cortical oxyhemoglobin concentration (cO_2Hb; (**B**)), and absolute values of end-tidal partial pressure of CO_2 (PET_{CO2}, (**C**)) as a function of relative exercise intensity from rest to maximum oxygen uptake ($\dot{V}O_{2max}$). Values are means ± s.d. $^*P < 0.05$ versus rest and $^\dagger P < 0.05$ versus sedentary.

moderate to high exercise intensity, cO_2Hb continued to rise highlighting the active brains' superior capacity to not only deliver but also extract oxygen at the extremes of physical exercise to maintain homeostasis. In contrast, cO_2Hb did not change throughout exercise in the sedentary group highlighting their apparent 'O_2 insensitivity'. In other words, as the intensity of exercise progressively increases, moderately active participants likely have the mitochondrial capacity to accommodate the increase in cerebral O_2 delivery confirmed by improved oxygenation, whereas the sedentary cannot (supply versus demand limitation).

Although beyond the scope of the present study, we did not explore the molecular mechanisms underlying the adaptive responses to regular physical activity that likely involve increased cardiac output, vascular bioavailability of nitric oxide, brain-derived neurotrophic factor, insulin-like growth factor and mitochondrial density.[3] However, what is apparent from these findings is that the observed improvements in cerebral perfusion and oxygenation cannot simply be ascribed to differences in the PET_{CO2} kinetic given that both the hyper and hypocapneic responses to exercise were comparable across groups. Likewise, whether these adaptations have the capacity to translate into improved cognitive function and stroke risk in later life, as previously suggested,[1] remain equally unclear and a topic for further investigation.

Analytical Considerations

It is important to emphasize that there are a number of methodological issues that warrant consideration. First, although providing excellent temporal resolution, transcranial Doppler ultrasonography assumes that the diameter of the MCA remains constant in response to the hyperventilation-induced reduction in PET_{CO2}. However, within the acute exercise setting, it is technically challenging to accurately insonate the MCAv and assess blood flow directly via Duplex ultrasound and/or MRI techniques. Second, finger photoplethysmography estimates MAP by filtering the arterial pressure waveform and becomes unreliable at workloads $>40\%$ $\dot{V}O_{2max}$.[12,13] Third, recent research has highlighted that prefrontal cortical oxygenation measured via near infrared spectroscopy may be overestimated owing to the increased forehead skin blood flow ($SkBF_{head}$) in response to the thermoregulatory stress associated with dynamic exercise.[14] To what extent this contributed towards elevated cortical oxygenation toward the higher exercise intensities is unknown. Nevertheless, it is noteworthy, that in the present study, oxygenation remained consistently elevated throughout exercise, even at the lower intensities, highlighting increased cerebral perfusion (and by consequence, oxygen delivery) as the predominant mechanism. Finally, it has to be noted that acute exercise stress is not the sole stimulus with the capacity to amplify the cerebrovascular adaptive benefits associated with long-term physical activity. Indeed, we have previously exposed participants to acute CO_2 and orthostatic stress to reveal subtle impairments in cerebral oxygenation after acute traumatic brain injury[15] that would otherwise be undetectable in the resting (unstressed) state. However, we were unable to perform these additional cerebrovascular stress tests in the present study owing to logistical constraints.

In conclusion, the present findings are the first to demonstrate that the cerebrovascular adaptive benefits associated with modest gains in cardiorespiratory fitness only become apparent when the cerebrovasculature is subject to acute exertional stress. Thus, an acute exercise challenge should be considered an integral component when assessing the true extent of cerebrovascular adaptation to subtle increases in physical activity.

DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest.

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