Aging blunts hyperventilation-induced hypocapnia and reduction in cerebral blood flow velocity during maximal exercise

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Abstract Cerebral blood flow (CBF) increases from rest to ~60% of peak oxygen uptake ($\text{VO}_{2\text{peak}}$) and thereafter decreases towards baseline due to hyperventilation-induced hypocapnia and subsequent cerebral vasoconstriction. It is unknown what happens to CBF in older adults (OA), who experience a decline in CBF at rest coupled with a blunted ventilatory response during $\text{VO}_{2\text{peak}}$. In 14 OA (71 ± 10 year) and 21 young controls (YA; 23 ± 4 years), we hypothesized

that OA would experience less hyperventilation-induced cerebral vasoconstriction and therefore an attenuated reduction in CBF at $\text{VO}_{2\text{peak}}$. Incremental exercise was performed on a cycle ergometer, whilst bilateral middle cerebral artery blood flow velocity (MCA V_{mean} ; transcranial Doppler ultrasound), heart rate (HR; ECG) and end-tidal PCO_2 (P_{ETCO_2}) were monitored continuously. Blood pressure (BP) was monitored intermittently. From rest to 50% of $\text{VO}_{2\text{peak}}$, despite greater elevations in BP in OA, the change in MCA V_{mean} was greater in YA compared to OA (28% vs. 15%, respectively; $P < 0.0005$). In the YA, at intensities $>70\%$ of $\text{VO}_{2\text{peak}}$, the hyperventilation-induced declines in both P_{ETCO_2} (14 mmHg (YA) vs. 4 mmHg (OA); $P < 0.05$) and MCA V_{mean} (–21% (YA) vs. –7% (OA); $P < 0.0005$) were greater in YA compared to OA. Our findings show (1), from rest-to-mild intensity exercise (50% $\text{VO}_{2\text{peak}}$), elevations in CBF are reduced in OA and (2) age-related declines in hyperventilation during maximal exercise result in less hypocapnic-induced cerebral vasoconstriction.

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Introduction

Studies have consistently demonstrated that cerebral blood flow (CBF) increases during mild-to-moderate exercise intensities (Jorgensen et al. 1992; Querido

and Sheel 2007; Pott et al. 1996; Hellstrom et al. 1996; Madsen et al. 1993; Ogoh et al. 2005b). This increase is reflected with a parallel increase in regional CBF, neuronal activity and metabolism (reviewed in Ogoh and Ainslie 2009). In contrast, at least in young healthy subjects, CBF declines towards baseline values (Moraine et al. 1993) when exercise intensity is $>60\%$ $\text{VO}_{2\text{peak}}$, regardless of the progressive increase in neuronal activity and metabolism. This reduction in CBF is attributed to increased cerebral vasoconstriction (Moraine et al. 1993; Hellstrom et al. 1996; Nybo and Rasmussen 2007) secondary to hyperventilatory-induced hypocapnia. This observation indicates that, during heavy exercise, CBF decreases despite progressive increases in cerebral metabolic demand (reviewed in Ogoh and Ainslie 2009). In contrast, this reduced CBF during heavy exercise lowers cerebral oxygenation and therefore may act as an independent influence on central fatigue.

With healthy aging, there is a progressive decline in CBF (approx: 28–50%) from 30 to 70 years of age (Yam et al. 2005; Ainslie et al. 2008; Fisher et al. 2008; Ogoh and Ainslie 2009). Such declines are caused by global cerebral atrophy without any disturbance in cerebral oxygen consumption (Ainslie et al. 2008; Buijs et al. 1998). However, in contrast to studies in young healthy subjects, the CBF response to exercise in older adults (OA) remains unclear. Only two studies have examined the influence of aging on CBF during *moderate* intensity exercise. Both studies reported elevations in CBF (6%, Fisher et al. 2008; 15%, Heckmann et al. 2003) during 15 min of steady-state cycling at 30–50% of heart rate reserve, in healthy middle-aged individuals (58 ± 5 years, Heckmann; 57 ± 7 years, Fisher) to younger controls (29 ± 5 and 24 ± 3 years, respectively). Whether the reduction in CBF at intensities greater than 60% $\text{VO}_{2\text{peak}}$ is altered with senescence (>65 years) or with increasing exercise intensity remains to be elucidated. Interestingly, pulmonary ventilation (V_E) during incremental exercise to exhaustion is attenuated in elderly (64 ± 3 years, V_E 90 ± 14 l/min) compared to younger males (24 ± 3 years, V_E 130 ± 23 l/min; Sidney and Shephard 1977).

The main aim for the current study was to document the temporal changes in CBF during progressive exercise to exhaustion in both young and old individuals. Because of this apparent ‘blunting’ of maximal exercise ventilation with age, we hypothesized that OA would experience less hyperventilation-induced

cerebral vasoconstriction and therefore less reduction in CBF, at maximal exercise.

Method

Participants This study included 34 BMI-matched subjects (20 young males (YA; 23 ± 3 years, 24 ± 3 kg/m^2); 14 older males (OA; 71 ± 10 years, 25 ± 3 kg/m^2)), which was approved by the ethics boards of the Universities of British Columbia and Alberta. Subjects were informed of the purpose and risks of the study prior to providing written informed consent. Subjects were screened for overt cardiovascular or cerebrovascular disease by means of detailed medical history, chest auscultation and 12-lead ECG. Subjects were not taking any cardiovascular medications and all were non-smokers. All of the participants were recreationally active and typically engaged in low- (e.g. walking) to moderate- (e.g. jogging or cycling) intensity aerobic activities (2 to 3 days per week). None were highly trained athletes. Following successful screening, each subject underwent familiarisation of the laboratory and testing protocol before the initiation of a peak aerobic power ($\text{VO}_{2\text{peak}}$) test. During the familiarisation period, subjects were accustomed to the testing procedures (e.g. using the bike and optimizing comfort and related adjustments) and protocol (e.g. experience wearing the mouth piece, nose-clip and having the transcranial Doppler head-fixation device fitted).

Participants abstained from food and beverages containing alcohol and caffeine for 12 h prior to the testing. They were also instructed to arrive well hydrated by consuming 1 l of water during the evening prior and 0.5 l on the morning of testing. On arrival at the laboratory for the main session, participants voided their bladder prior to having height and body mass recorded. Following experimental setup, all participants remained upright on bike and rested for a 5-min baseline measurement.

Peak aerobic testing ($\text{VO}_{2\text{peak}}$) All participants were tested on an electrically braked cycle ergometer (Monark 894E, Varberg, Sweden) with the first stage beginning at 25 W (OA) and 50 W (YA). Workload was increased 25 W every 2 min until ventilatory threshold, after which workload increased by 25 W every minute until volitional exhaustion. Ventilatory

threshold was defined as having a respiratory exchange ratio (RER) ≥ 1.0 and a systematic rise in the ventilatory equivalent of O_2 (V_E/V_{O_2}), whilst the ventilatory equivalent of CO_2 remained constant or declined slightly (Wasserman 1987). Respiratory gas exchange, including end-tidal PCO_2 ($P_{ET}CO_2$), was measured by an online gas analyser (Vmax Encore VIASYS Healthcare Inc., Yorba Linda, CA, USA). To enable compatibility with the transcranial Doppler headpiece and probes, participants' gas exchange was assessed via the use of a light-weight mouthpiece fitted with a turbine and nose-clip. VO_{2peak} was determined from the highest value from a 20-s average. Criteria for reaching VO_{2peak} were a plateau in O_2 , RER above 1.15 and rating of perceived exertion (RPE; Borg 1970) equal to 20, or achievement of age-predicted maximal heart rate. Participants were familiarised with the Borg RPE scale and provided instructions on how to report their feelings of exertion prior to each exercise test; RPE was obtained randomly throughout the incremental test and immediately following exercise completion. All subjects reached VO_{2peak} by at least two of these criteria; there were no between group differences in RER or RPE.

MCA velocity, arterial BP and heart rate Middle cerebral artery blood flow velocity (MCA V_{mean}), systolic MCA (MCA V_S) and diastolic MCA (MCA V_D) were measured bilaterally, using a 2-MHz pulsed Doppler ultrasound system (Spencer Technologies, Seattle, WA, USA). The probes were adjusted over the temporal window of the MCA 1 cm distal to the MCA and anterior cerebral artery bifurcation; standardised search techniques were used to optimize signal quality, as recently described (Willie et al. 2011). The probes were fixed and held in place using a specialized headband fixation device (Marc 600, Spencer Technologies). Intermittent blood pressure (BP) was measured at each stage in the arm by electrophygmomanometry, with a microphone placed over the brachial artery and the Korotkoff sounds gated to ECG (SunTech Tango, SunTech Medicals, Morrisville, NC, USA). In a sub-group of OA ($n=3$) and YA ($n=3$), intra-radial arterial BP was also measured to confirm the automated BP. After local anaesthesia (1% lidocaine), a 20-gauge catheter (BD Insyte) was placed into the radial artery and attached to a pre-calibrated pressure transducer (Deltran II, Utah Medical Products Ltd) positioned at the level of

the right atrium in the mid-axillary line for the measurement of beat-to-beat arterial blood pressure. Data indicate that the automated BP system adequately reflected that of intra-arterial BP ($<8\%$ difference between automated and intra-arterial BP; $P=0.2$). Heart rate (HR) was monitored with R–R intervals from a three-lead ECG. All data were sampled continuously at 200 Hz using an analogue digital converter (Powerlab/16SP ML795; ADInstruments, Colorado Springs, CO, USA) interfaced with a computer. Data were later analysed using commercially available software (Chart version 7.1 ADInstruments). Cerebrovascular resistance was estimated as $MAP/MCA V_{mean}$.

Statistical and data analysis Data from determined levels (rest, 50%, 70%, 90% and VO_{2peak}) of each individual were averaged over the last minute of each stage. A mixed model ANOVA (SPSS version 17.0, SPSS Inc, Chicago, IL, USA) was used to assess the relationship between 'age' and concurrent exercise for each dependent variable. Pairwise comparisons (Bonferroni adjusted) were applied to further evaluate specific influences of significant main effects and interactions. Relationships between selected variables were determined by linear regression. Statistical significance was established at α -level of 0.05, and data are expressed as means ($\pm$ SD) or relative changes from baseline ($\%\pm$ SD). An important question in this study is how to correctly interpret changes in our dependant variables (e.g. $P_{ET}CO_2$, MCA V_{mean} , MAP, ventilation) in the young and old groups with disparate baseline flows or velocities. For example, because resting MCA V_{mean} in the OA is approximately half that of the YA, any increase in MCAv during exercise will manifest in a disproportionately large percent increase in the OA compared to YA. The converse argument is that the higher MCA V_{mean} in YA is likely to elicit a bigger absolute increase than compared with the OA. To account for these considerations, we present both absolute (Fig. 1; Table 2) and relative (Fig. 2) changes in our dependant variables and interpret our data in view of these considerations.

Results

Rest Resting systolic (SBP), diastolic (DBP), mean blood pressure (MAP) and cerebral vascular resistance (CVR) were higher in the OA compared to YA.

Fig. 1 Changes from rest to peak exercise intensity in the middle cerebral artery velocity mean ($MCA V_{mean}$; **a**), during a VO_2 peak test in young (black circles) and older (white circles) subjects. **b** Mean arterial pressure (MAP). **c** End-tidal CO_2 ($P_{ET}CO_2$). **d** Ventilation (V_E). * $P < 0.05$, significant difference between groups

Fig. 2 Relative changes from rest to peak exercise intensity in the middle cerebral artery velocity mean ($MCA V_{mean}$; **a**), during a VO_2 peak test in young (black circles) and older (white circles) subjects. **b** Mean arterial pressure (MAP). **c** End-tidal CO_2 ($P_{ET}CO_2$). **d** Ventilation (V_E). * $P < 0.05$, significant difference between groups

Although four OA fulfilled the criteria for hypertension (three subjects DBP >90 mmHg (92 ± 1 mmHg) and one subject SBP >140 mmHg (160 mmHg)), these subjects were not outliers for any of the cerebrovascular or respiratory variables. Moreover, upon reanalysis, removal of these subjects did not alter the principle statistical findings of the study; therefore, these subjects were included in the pooled analyses. As expected, resting MCA V_{mean} , MCA V_S and MCA V_D were higher in the YA compared with to OA (all P 's < 0.05; Table 1). There were no differences between right and left MCA V in either YA or OA; therefore, the average of the two sides was used for related analysis. No between group differences were found for anthropometric or gas exchange variables (Table 1).

Mild-to-moderate exercise (see Figs. 1 and 2) During mild (50% $\text{VO}_{2\text{peak}}$) to moderate (70% $\text{VO}_{2\text{peak}}$) exercise, both groups' MCA V_{mean} increased compared to rest, with peak MCA V_{mean} occurring around 70% $\text{VO}_{2\text{peak}}$ (28% YA and 15% OA vs. baseline; $P < 0.05$; Table 2). From rest to 50% of $\text{VO}_{2\text{peak}}$, the absolute and relative increase in MCA V_{mean} was greater in YA compared to OA ($P < 0.0005$); however, although the absolute increase from rest to 70% of $\text{VO}_{2\text{peak}}$ was higher in YA (Fig. 1), the relative increase did not quite reach significance ($P = 0.06$; Fig. 2). There was no change in MCA V_D in OA throughout exercise, whereas YA had a drop in MCA V_D at intensities >70% ($P < 0.05$). Throughout mild-to-moderate exercise, both groups had increases in HR between each subsequent workload, with greater HR increases in YA ($P < 0.05$). There was an increase in P_{ETCO_2} in both groups from rest-to-mild exercise intensity ($P < 0.001$). At intensities greater than 70% $\text{VO}_{2\text{peak}}$ (i.e. above ventilatory threshold) in both YA and OA, P_{ETCO_2} began to decline towards baseline values. As expected, V_E progressively increased ($P < 0.01$) with increasing workload in both groups, with greater absolute and relative elevations in the YA at intensities $\geq 50\%$ $\text{VO}_{2\text{peak}}$ ($P < 0.001$). Ventilatory threshold occurred at comparable relative intensities between young and old groups. Whilst DBP was maintained in both groups, the progressive increase in absolute SBP and MAP was greater in the OA throughout each stage of the $\text{VO}_{2\text{peak}}$ test ($P < 0.05$); however, when expressed in relative terms from baseline, the increase in MAP was comparable

Table 1 Participant characteristics

	Young adult ($N=20$) 18–32 years	Older adult ($N=14$) 53–83 years
Demographics		
Age (years)	22.7 ± 3.5	$70.6 \pm 10.2^*$
Height (cm)	179.0 ± 10.8	178.8 ± 8.0
Body mass (kg)	77.5 ± 8.7	78.6 ± 6.8
BMI (kg m^{-2})	24.3 ± 2.8	24.7 ± 2.8
$\text{VO}_{2\text{max}}$ ($\text{ml kg}^{-1} \text{ min}^{-1}$)	52.9 ± 3.5	$31.5 \pm 7.2^*$
Cardiovascular		
MAP (mmHg)	89.2 ± 5.6	$100.1 \pm 8.3^*$
SBP (mmHg)	117 ± 9.6	$133.5 \pm 17.6^*$
DBP (mmHg)	75.3 ± 7.6	$83.4 \pm 7.4^*$
HR (beats min^{-1})	78.2 ± 20.1	74.8 ± 7.5
Cerebrovascular		
MCA V_{mean} (cm s^{-1})	62.4 ± 11.0	$35.0 \pm 8.8^*$
MCA V_S (cm s^{-1})	110.4 ± 17.7	$56.4 \pm 11.5^*$
MCA V_D (cm s^{-1})	38.4 ± 10.0	$26.0 \pm 5.9^*$
CVR (mmHg cm s^{-1})	1.5 ± 0.3	$3.1 \pm 1.0^*$
Gas exchange		
P_{ETCO_2} (mmHg)	37.5 ± 3.4	34.7 ± 5.6
V_E ($\text{l min}^{-1} \text{ BTPS}$)	10.7 ± 3.0	13.1 ± 7.5

Values are mean $\pm$ SD

BMI body mass index, MAP mean arterial pressure, SBP systolic blood pressure, DBP diastolic blood pressure, MCA V_{mean} middle cerebral artery velocity, MCA V_S systolic middle cerebral artery velocity, MCA V_D diastolic middle cerebral artery velocity, CVR cerebral vascular resistance

* $P < 0.05$, significantly different from YA

between groups. There was no change in CVR between workloads in either group.

Peak VO_2 YA had a greater reduction in P_{ETCO_2} and MCA V_{mean} upon the cessation of exercise compared to OA (P_{ETCO_2} , -7 mmHg below baseline (YA) vs. $+2$ mmHg above baseline (OA) $P < 0.0005$; MCA V_{mean} , $2 \pm 18\%$ vs. $10 \pm 11\%$, respectively, $P < 0.0005$). In concurrence with the marked drop in P_{ETCO_2} in both groups, V_E reached maximum values at $\text{VO}_{2\text{peak}}$ (115 ± 2 l/min YA vs. 86 ± 44 l/min, Fig. 1; $P < 0.01$). Although increased minute V_E from 70% to $\text{VO}_{2\text{peak}}$ were smaller in OA (from ~ 45 to ~ 86 l/min) than YA (from ~ 73 to ~ 115 l/min), the relative (percent) changes tended to be greater in OA than

Table 2 Cardiorespiratory and cerebrovascular variables during the $VO_{2\text{peak}}$ test

	MCA V_{mean} (cm s^{-1})	MCA V_S (cm s^{-1})	MCA V_D (cm s^{-1})	CVR (mmHg cm s^{-1})	MAP (mmHg)	SBP (mmHg)	DBP (mmHg)	$P_{\text{ET}}\text{CO}_2$ (mmHg)	$\dot{V}_E$ (l/min)	HR (bpm)	Workload (W)
Rest											
YA	62.4±11.0	110±17.7	38.4±10	1.5±0.3	89.2±5.6	117.1±9.6	75.3±7.6	37.5±3.4	10.8±3.0	78.1±20.1	N/A
OA	35.0±8.8*	56.4±11.4*	26±5.4*	3.1±1.0*	100.1±8.3*	133.5±17.6*	83.4±7.4*	34.7±5.6	13.1±7.5	74.8±7.5	N/A
50% $VO_{2\text{peak}}$											
YA	78.8±11.7**	150±21.8**	43.1±9**	1.3±0.2**	97.6±5.6**	142.3±8.7**	75.5±7.1**	45.5±4.0**	49.3±14.3**	122.3±20.5**	188.1±38.4
OA	40.7±13.2***	69±18.4***	28.1±9.1*	3.0±1.1*	110.8±8.7***	166.6±17.4***	82.9±8.2*	40.5±4.5***	30.4±9.5***	96.2±9.5***	87.9±24.6*
70% $VO_{2\text{peak}}$											
YA	79.4±12.2	156.1±18.8**	41.8±9.2	1.4±0.3**	104.6±5.9**	164±10.6**	75.4±6.5**	45.2±4.0	72.6±14.5**	150.7±28.7**	248.8±40.7
OA	42.2±12.7*	72.5±16.8*	29.1±8.8*	3.1±1.2*	119.1±8.9***	193±15.8***	82.1±8.7*	41.0±4.6*	44.9±17.8***	117±16.0***	128.6±34.1*
90% $VO_{2\text{peak}}$											
YA	71±9.2**	145.3±17.7**	33.6±8.4**	1.6±0.3**	110±6.7**	181±10.1**	74.7±6.9**	38.1±4.4**	102.4±22.6**	168.7±30.5**	296.4±44.2
OA	41.4±11.6*	71.9±15.3*	28.3±8.0	3.4±1.3*	127.3±7.4***	213.3±16***	84.3±8*	39.3±6.0**	64.9±31.6***	135.0±18.0***	168.9±47.5*
Peak VO_2											
YA	62.1±8.7**	135.3±19.5**	25.5±7.4**	1.8±.3	112.4±7.8**	191.7±12.3**	74±7.5**	30.8±4.7**	115.1±25.4**	169.4±45.2	326.2±47.7
OA	38.7±10.6***	68±14.4***	25.9±7.4**	3.7±1.3*	130±11.2*	223±16***	83.4±13*	36.6±6.2***	86.2±44.1***	144.0±15.6***	192.4±63.0*

All values are means±SD

MCA V_{mean} middle cerebral artery velocity, MCA V_S systolic middle cerebral artery velocity, MCA V_D diastolic middle cerebral artery velocity, C/R cerebral vascular resistance, MAP mean arterial pressure, SBP systolic blood pressure, DBP diastolic blood pressure, $P_{\text{ET}}\text{CO}_2$ end-tidal CO_2 * $P<0.05$, significant difference from YA; ** $P<0.05$, significant difference from preceding workload

YA (Fig. 2; $P=0.1$). From 70% $\text{VO}_{2\text{peak}}$ until cessation of exercise, there was a selective reduction in MCA V_{D} in YA (Table 2; $P<0.05$) but not OA. The values of MCA V_{D} at $\text{VO}_{2\text{peak}}$ were -30% YA vs. -1% OA from baseline ($P<0.0005$). Although absolute elevations in MCA V_{S} were greater in YA ($P<0.0005$), MCA V_{S} was not reduced in either groups at $\text{VO}_{2\text{peak}}$. In OA, absolute MAP, SBP and DBP were elevated ($P<0.05$) in comparison to YA at peak; however, the relative changes in these variables were comparable (Fig. 2). CVR remained stable at peak exercise for both groups. From 70% to $\text{VO}_{2\text{peak}}$, the correlation between the reductions in P_{ETCO_2} with the reductions in MCA V_{mean} were comparable between the YA and OA ($R^2=0.24$; $P<0.05$ vs. $R^2=0.25$; both $P<0.05$). Consistent with this finding, there were no between age differences in the slope of the MCA V_{mean} to P_{ETCO_2} relationship at this time point (0.72 ± 0.33 cm/s/mmHg (YA) vs. 0.63 ± 0.49 cm/s/mmHg (OA); $P=0.54$). To lesser extent, a weak but significant correlation was also observed between the V_{E} and CBF responses from 70% to $\text{VO}_{2\text{peak}}$ ($R^2=0.1$ in OA vs. $R^2=0.13$ in YA).

Discussion

The three novel findings of this study are: (1) From rest-to-mild exercise (50% $\text{VO}_{2\text{peak}}$), the elevations in CBF were reduced in OA compared with YA; (2) age-related declines in hyperventilation during maximal exercise were associated with less hypocapnic-induced cerebral vasoconstriction and (3) the ability of the cerebrovascular to maintain a near constant MCA V_{mean} despite marked exercise-induced hypertension is preserved with healthy aging.

CBF during mild-to-moderate intensity exercise: influence of age

Despite no disturbances to total cerebral oxygen consumption with healthy aging, there is a progressive decline in CBF (approximately 28–50%) from 30 to 70 years of age (Yam et al. 2005; Ainslie et al. 2008; Fisher et al. 2008; Ogoh and Ainslie 2009) that is associated with global cerebral atrophy (Ainslie et al. 2008; Buijs et al. 1998). In contrast to healthy YA, as mentioned, only two studies (Fisher et al. 2008; Heckmann et al. 2003) have examined CBF in middle-aged OA during mild-to-moderate exercise.

Both of these studies reported significant and comparable increases in MCA V_{mean} during steady-state exercise in both ‘middle’-aged older and younger subjects. However, for the first time, our data demonstrate that the relative and absolute increase in MCA V_{mean} is lower in OA compared with YA from rest-to-mild exercise (50% $\text{VO}_{2\text{peak}}$). Apart from this difference from rest-to-mild intensity exercise, there was a comparable *relative* increase in MCA V_{mean} (Fig. 2) in the OA and YA, from mild-to-moderate intensity exercise. The rise in MCA V_{mean} was supported by concurrent changes in P_{ETCO_2} (at 50% and 70% $\text{VO}_{2\text{peak}}$) and elevations in MAP (at 50%, 70%, 90% and $\text{VO}_{2\text{peak}}$). Our experimental design precludes explicit elucidation of the mechanisms responsible for the smaller MCA V_{mean} increase from rest-to-mild exercise in OA. Assuming comparable cerebrovascular responses to P_{ETCO_2} and MAP (see below), given the close association of MCA V_{mean} with both P_{ETCO_2} (at 50% and 70% $\text{VO}_{2\text{peak}}$) and MAP (at 50%, 70%, 90% and $\text{VO}_{2\text{peak}}$) in both groups, neither MAP nor P_{ETCO_2} would seem logical variables to explain the age-related differences. Thus, the major factor that may underpin this differential change in MCA V_{mean} is likely due to age-related differences in exercise-induced neuronal activity and related metabolism escalation.

Absence of age-related hypocapnic-induced cerebral vasoconstriction at maximal exercise

Ventilation rates at maximal intensity exercise in elderly subjects (64 ± 3 years) were substantially lower in relation to the younger controls (24 ± 3 years; Sidney and Shephard 1977). Based on this report, we anticipated and confirmed that OA exhibited ‘blunted’ hyperventilatory responses that were associated with less hypocapnia and a consequent attenuation of CBF at the same relative maximal intensity ($-6\pm5\%$ vs. $-21\pm9\%$ Δ from the peak MCA V_{mean} at 70% of $\text{VO}_{2\text{peak}}$). We confirmed our hypothesis that, likely due to an attenuated hyperventilatory response, OA were less hypocapnic at maximal exercise, which resulted in less of a reduction in MCA V_{mean} compared to YA, respectively ($-6\pm5\%$ vs. $-21\pm9\%$ Δ from the peak MCA V_{mean} at 70% of $\text{VO}_{2\text{peak}}$). The reason OA are less able than YA to elevate ventilation is not clear, but may be a result of a myriad of alterations such as reduced lung and chest wall compliance (Mittman

et al. 1965; Turner et al. 1968), respiratory muscle fatigue (Chen and Kuo 1989) and chemosensitivity (Kronenberg and Drage 1973; Peterson et al. 1981). We found that the relationship between reductions in $P_{ET}CO_2$ at maximal exercise with the reductions in MCA V_{mean} was comparable between the YA and the OA ($R^2=0.24$ vs. $R^2=0.25$). Consistent with this finding, when $P_{ET}CO_2$ is prevented from falling at maximal exercise (via end-tidal clamping), MCA V_{mean} continues to increase to values 26% higher than control values when $P_{ET}CO_2$ is allowed to fall normally (Olin et al. 2010). Furthermore, this study also demonstrates that whilst $P_{ET}CO_2$ is a key regulator, it is not the only variable exerting an influence on MCA V_{mean} . Of interest, we did observe a weak but significant correlation between the V_E and CBF responses to exercise ($R^2=0.1$ in OA vs. $R^2=0.13$ in YA). The absence of strength of this relationship is not unexpected, however, given (1) that CBF is influenced by $PaCO_2$ and not V_E and (2) that alveolar (or arterial) PCO_2 is more tightly influenced by alveolar ventilation than pulmonary ventilation (i.e. alveolar $PCO_2=VCO_2/\text{alveolar ventilation}$). Further studies are needed to accurately measure dead-space (to enable calculation of alveolar ventilation) as well and related alterations in lung and chest wall compliance.

Maintained CBF during exercise with aging:
influence of blood pressure

During cycling exercise, MAP and SBP increase, combined with a slight decrease or no change in DBP (Rowell 1993; Ogoh et al. 2005b). In the present study, both YA and OA increased MAP and SBP (Table 2, $P<0.001$) at each workload until the cessation of exercise. Although the relative increase in BP was comparable, OA had higher absolute MAP, SBP and DBP relative to YA throughout exercise; these age-related changes are likely related to increased sympathetic nervous activity (Fagius and Wallin 1993), decreases in systemic arterial compliance (Fleg 1986) and cardiac baroreceptor sensitivity (Gribbin et al. 1971) and increased vascular resistance (Franklin et al. 1997).

Rapid changes in systemic blood pressure, as occurs during exercise, presents a substantial challenge to the cerebrovasculature. Although we did not measure cerebral autoregulation (CA; i.e. the ability of the brain to regulate CBF relatively independent of

changes in BP (Panerai et al. 1999; Brys et al. 2003; Paulson et al. 1990)), CA is maintained during mild-to-moderate exercise in YA (Ogoh et al. 2005a), at rest in OA (reviewed in van Beek et al. 2008) and during mild exercise in middle-aged OA (Ogoh et al. 2005a; Fisher et al. 2008). Some additional insight into CA may be provided from consideration of cerebrovascular resistance or conductance (Table 1). As expected, CVR was higher in the OA at rest; however, during exercise, CVR was maintained in both age groups. Whilst these findings may be supportive of effective CA with aging, we acknowledge that calculation of CVR is complicated by unknown values of intracranial and venous pressures. During our resting conditions, it is likely that the major determinant of cerebral perfusion pressure was MAP (Ainslie and Tzeng 2010). Although the calculation of CVR in the upright position has been used extensively in previous studies, we acknowledge that MAP cannot be relied on to reflect cerebral perfusion pressure under all circumstances, especially in the upright posture. The effects of exercise on creating large changes in intrathoracic pressure, intracranial/venous pressures and/or potentially cerebral blood volume may all additionally affect cerebral perfusion pressure. Nevertheless, regardless of methodological and physiological considerations of using CVR, the novel findings of this study are that, despite marked age-related differences in BP throughout the progressive exercise challenge (e.g. MAP=129 mmHg (OA) vs. 112 mmHg (YA) at VO_{2peak}), MCA V_{mean} remained significantly lower in OA at each stage. It appears that, at least with healthy aging, the brain is extremely effective at protecting itself from damage due to over-perfusion. Consistent with this idea, recent findings from both animal (Cassaglia et al. 2009) and humans (Tzeng et al. 2010) indicate that CA may be more adept at compensating for transient hypertension than for hypotension.

Implications

First, as mentioned above, that the older brain can maintain (relative) CBF with exercise is a novel and noteworthy finding. Whilst speculative, these age-related changes could serve to protect from blood–brain barrier ‘breakthrough’ and over-perfusion (from the exercise-induced hypertension) and help aid the maintenance of cerebral oxygenation at maximal exercise (from declines in CBF at maximal exercise). The extent

to which these changes reflect a central (i.e. CNS) adaptation with aging or are merely a consequence of age-related changes in a respiratory capacity warrants future investigation.

Second, changes in CBF have important implications on the regulation of brain tissue pH and consequently on respiratory control and potentially dyspnea (reviewed in Ainslie and Duffin 2009). For example, changes in CBF that are not matched with changes in cerebral metabolism can affect the degree of CO₂ washout and therefore brain tissue pH. The latter has an important influence on ventilatory control at the level of the central chemoreceptors (i.e. if CBF is elevated, it leads to greater degree of CO₂ washout and may act to reduce the ventilatory drive; Ainslie and Duffin 2009). However, in view of the current findings of a maintained (rather than elevated) MCA V_{mean} during exercise in OA, this would seem an unlikely mechanism to explain the age-related changes in the ventilatory patterns during exercise. Although we did not measure the degree of dyspnea in our study and acknowledge that this may have played a role in reducing ventilation in OA at maximal exercise, age-related changes in MCA V_{mean} would also seem an unlikely mechanism dyspnea.

Third, cognitive function is closely associated with CBF and brain atrophy, and a reduction in either may precipitate the age-related decline in cognitive function (Poels et al. 2008). The association between brain volume and CBF has been reported in individuals with either mild cognitive impairment or mild Alzheimer disease (Luckhaus et al. 2010). In this context, if CBF was further blunted or abolished during exercise in OA, this may conceivably lead to a vicious cycle of reduced cerebral perfusion, cerebral atrophy and metabolic demand. Thus, despite the progression of cerebral atrophy with healthy aging (Buijs et al. 1998; Ainslie et al. 2008), the capability of CBF to meet the metabolic demands imposed during moderate-to-high intensity exercise is maintained with aging. How these responses may be hindered with pathologies such as cognitive impairment or mild Alzheimer disease would be a noteworthy future question.

Methodological considerations

Transcranial Doppler ultrasound Whilst caution should to be taken when interpreting absolute CBF values from transcranial Doppler technology, previous

reports indicate that MCA V_{mean} is a reliable index of global CBF both at rest and during exercise (reviewed in Ogoh and Ainslie 2009). Importantly, the current data are consistent with others that have reported age-related differences in MCA V_{mean} (Buijs et al. 1998; Ainslie et al. 2008), and the progressive decline in CBF from the age of 30 to 70 years has been confirmed repeatedly using a variety of imaging techniques (Kashimada et al. 1994, 1995; Buijs et al. 1998; Scheel et al. 2000; Beason-Held et al. 2007; Stoquart-ElSankari et al. 2007).

Cross-sectional study design Our study design was cross-sectional. Thus, we cannot exclude the influence of selective participation and cohort differences accounting for some of the age effects we have observed here. We selected healthy older (and younger) participants for this study; therefore, the findings of the present study can only be inferred to this group. Nevertheless, our findings do provide the first detailed documentation of the cerebrovascular responses to exercise in aging and serve as a point of reference for comparison against changes with elderly patients with pathology. Moreover, we intentionally matched BMI between the two distinct age groups; thus, it would seem unlikely that our findings were caused simply by age-related ‘size’ differences in lung volumes.

End-tidal vs. arterial PCO₂ and cerebrovascular reactivity Our findings are based on the assumption that P_{ET}CO₂ reflects arterial-PCO₂ and that the cerebrovascular responsiveness to CO₂ during exercise is not altered with aging. During exercise and related hypercapnia, P_{ET}CO₂ may slightly overestimate arterial PCO₂ (Jones et al. 1979; Peebles et al. 2007). Although this is a relevant consideration, we feel that this is unlikely to affect our findings since we used otherwise healthy subjects and we know of no evidence to indicate that end-tidal to arterial PCO₂ gradients may be altered with aging. Unlike hypercapnia, P_{ET}CO₂ is a better reflection of arterial PCO₂ during hypocapnia (Peebles et al. 2007; Thomas et al. 2009). Although cerebrovascular response to both hypocapnia and hypercapnia is enhanced during exercise (Ogoh et al. 2008), it is unknown whether this response is altered with aging. However, unpublished findings from our laboratory indicate that, at least up until 60% of peak VO₂, there are no age-related differences in cerebrovascular reac-

tivity to CO₂ during exercise. Although we do not know if this response is altered at higher intensities of exercise, our current findings of comparable slopes between the reductions in P_{ET}CO₂ with MCA $\dot{V}_{\text{mean}}$ from 70% to peak VO₂ would indicate an absence of an age-related difference.

Conclusion

Despite excess exercise-induced hypertension with aging, the brain can regulate CBF at normal levels. Moreover, age-related declines in hyperventilation during maximal exercise result in less hypocapnic-induced cerebral vasoconstriction. Collectively, although the mechanisms are unclear, maintenance of CBF during exercise with aging would seem an advantageous response.

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