Cerebral and myocardial blood flow responses to hypercapnia and hypoxia in humans

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—In humans, cerebrovascular responses to alterations in arterial Pcco2 and Pco2 are well documented. However, few studies have investigated human coronary vascular responses to alterations in blood gases. This study investigated the extent to which the cerebral and coronary vasculatures differ in their responses to euoxic hypercapnia and isocapnic hypoxia in healthy volunteers. Participants (n = 15) were tested at rest on two occasions. On the first visit, middle cerebral artery blood velocity (Vp) was assessed using transcranial Doppler ultrasound. On the second visit, coronary sinus blood flow (CSBF) was measured using cardiac MRI. For comparison with Vp, CSBF was normalized to the rate pressure product [an index of myocardial oxygen consumption; normalized (n)CSBF]. Both testing sessions began with 5 min of euoxic [end-tidal Pco2 (Peto2) = 88 Torr] isocapnia [end-tidal Pco2 (Petc02) = +1 Torr above resting values]. Petco2 was next held at 88 Torr, and Peto2 was increased to 40 and 45 Torr in 5-min increments. Participants were then returned to euoxic isocapnia for 5 min, after which Peto2 was decreased from 88 to 60, 52 and 45 Torr in 5-min decrements. Changes in Vp and nCSBF were normalized to isocapnic euoxic conditions and indexed against Petco2 and arterial oxyhemoglobin saturation. The Vp gain for euoxic hypercapnia (%/Torr) was significantly higher than nCSBF (P = 0.030). Conversely, the Vp gain for isocapnic hypoxia (%/desaturation) was not different from nCSBF (P = 0.518). These findings demonstrate, compared with coronary circulation, that the cerebral circulation is more sensitive to hypercapnia but similarly sensitive to hypoxia.

METHODS

Participants

Fifteen healthy volunteers (8 men, and 7 women) participated in this study. All participants were nonsmoking; had resided in Calgary, Alberta, Canada (altitude = 1,103 m) for at least 1 yr; and had no prolonged exposure to high altitude in the 6 mo before participating in the study. Female participants were not taking oral contraceptives and were tested in the late luteal to early follicular phases of their menstrual cycle. The mean ± SE age, height, weight, and body mass...
Experimental Design

Each participant was tested on two occasions. On the first visit, CBF, arterial hemoglobin oxygen saturation (SaO2), heart rate (HR), and blood pressure (BP) were measured during euoxic ischemia, euoxic hypercapnia, and isocapnic hypoxia while the participant was lying with their torso elevated from the horizontal plane. On the second visit, MBF, SaO2, HR, and BP were measured during identical bouts of euoxic ischemia, euoxic hypercapnia, and isocapnic hypoxia while each participant was lying supine within a cardiac MRI scanning system.

Instrumentation

CBF was assessed by measuring blood velocity through the middle cerebral artery (MCA) using a 2-MHz pulsed transcranial Doppler (TCD) ultrasound (PCDOP 842; SciMed, Bristol, UK), held in place by snug-fitting headgear (marc600, Spencer Technologies, Seattle, WA). SaO2 was measured using a pulse oximeter (3900p, Datex-Ohmeda, Madison, WI) on the left index finger, HR was measured using a three-lead ECG (Micromon 7142 B, Kontron Medical, Milton Keynes, UK), and BP was measured from the left middle finger using a pneumotachograph and differential pressure transducer (RSS-100 HR, Hans Rudolph, Kansas City, MO). MBF was measured using a clinical full-body 1.5 Tesla cardiac MRI system (MAGNETOM Avanto, Siemens Healthcare, Erlangen, DE) and two six-channel phased-array coils. One coil rested on the participant’s chest, and the other was placed below the spine. The Embolus detection was performed using an interleaved velocity-encoded fast-gradient echo cine sequence. Typical scan parameters were as follows: field of view of 138 × 340 mm, matrix size of 66 × 192, in-plane resolution of 2.1 × 1.8 mm, slice thickness of 5 mm, repetition-time-to-echo time ratio of 7.6/4.3 ms, flip angle of 25°, and seven lines per segment. To prevent movement artifacts within the images, the participant performed a breath hold throughout each scan, typically lasting ~14 s. An MR-compatible patient monitoring assembly (Magscreen C, Schiller Medical, Bussy-St.-Georges, France) was used to measure SaO2 with a pulse oximeter on the left index finger, HR via a three-lead ECG, and brachial artery BP via oscillographic measurement. A portable DEF system was used to control PETCO2 and PETO2 at desired levels by manually titrating CO2, O2, and nitrogen into the inspirate. Total gas flow to the participant was maintained at ~75 l/min. The DEF monitoring computer, mass spectrometer, and gas cylinders were placed in the MR control room with the inspired gas sampling capillary and gas delivery tubes passed from the control room to the participant via a small waveguide (~4.5 m).

TCD ultrasound was used for CBF measurements, and MRI was used to assess MBF because the MRI system was specifically dedicated for cardiac MRI applications and, therefore, did not have the capacity to assess CBF. TCD ultrasound was chosen to assess global CBF reactivity to hypercapnia and hypoxia because it has been shown to be comparable with global CBF responses measured using intravenous Xenon133 clearance (11, 17), positron emissions tomography (10), and pulsed arterial spin labeling MRI (48).

Protocol

CBF measurements. Following instrumentation, resting values of PETCO2 and PETO2 were determined while the participant breathed through a mouthpiece with their nose occluded for 10 min. After resting values were obtained, the participant was switched to breathing through the full-face respiratory mask connected to the DEF system. The protocol started with 5 min of euoxic ischemia (Bl1) where PETCO2 was maintained at +1 Torr above resting values and PETO2 was held at 88 Torr [mean PETO2 for the altitude (1,103 m) at which the laboratory is located]. After completion of Bl1, PETCO2 was increased to 40 (Hc1) and 45 (Hc2) Torr in 5-min increments, whereas PETO2 was maintained at 88 Torr. At the completion of Hc2, the participant was returned to isocapnic euoxia for 5 min (Bl2). PETO2 was next decreased from 88 to 60 (Hx1), 52 (Hx2) and 45 Torr (Hx3) every 5 min, while PETCO2 was maintained at +1 Torr above resting values. Five-minute stages were selected based on previously reported values of the time constants for CBF responses to hypercapnia (~45 s) and hypoxia (~80 s) (50). A representative figure of data collected during the testing protocol is shown in Fig. 1.

MBF measurements. The testing protocol was identical to that performed during CBF measurements, but the transition between euoxic hypercapnia and isocapnic hypoxia stages occurred over ~1 min because of the greater distance the gases needed to travel to reach the participant in the MRI. At each stage of the protocol, once PETCO2 and PETO2 achieved a steady state, the participant was maintained at this new level for an additional 4 min (i.e., total stage length was ~5 min). Images used to calculate MBF were acquired during the final minute of each stage. The dynamics of the MBF response to hypercapnia and hypoxia are not well documented, but 5-min stages appear to be of sufficient duration for the response to develop (39) with previous animal (12) and human studies (47) using similar hypercapnic and hypoxic stage durations.

Analyses

Indexes of CBF analyzed have been previously described (51, 52). They include the velocity associated with the maximal frequency of the Doppler shift (Vp, cm/s), the velocity related to the intensity-weighted mean frequency of the Doppler shift (Vint, cm/s), the total power of the Doppler spectrum (P; arbitrary units), and the flow index calculated as the product of P and Vint (PVint; arbitrary units). All indexes were averaged over each heart beat, and the mean of the last 15 s of each stage of the protocol was calculated. The last 15 s of each stage was used because it was of similar duration to the MRI scan...


Fig. 1. Representative data from one participant of the euoxic hypercapnia and isocapnic hypoxia protocol employed. PETCO₂, end-tidal partial pressure of CO₂; PETO₂, end-tidal partial pressure of O₂; V̇p, velocity associated with the maximal frequency of the Doppler shift; Bl.1, first euoxic isocapnic baseline period; Hc.1 to Hc.2, euoxic hypercapnia stages; Bl.2, second euoxic isocapnic baseline period; Hx.1 to Hx.3, isocapnic hypoxia stages.

Blood flow in the coronary sinus was used as a surrogate for MBF (5, 62) and calculated off-line using clinically validated cardiovascular MR analysis software (cmr42, CIRCLE Cardiovascular Imaging, Calgary, AB, Canada) with subpixel spatial resolution of the contours used for defining regions of interest used for flow measurements. A region of interest was drawn on the magnitude image of the flow sequence used to define the cross-sectional area of the coronary sinus (Fig. 2, A and B). The software automatically copies the region of interest contours to the corresponding velocity-encoded image (i.e., phase image; Fig. 2, C and D). Coronary sinus blood flow (CSBF; ml/min) was calculated from the cross-sectional area, velocity, and corresponding HR. Subsequently, individual CSBF values were normalized to the rate pressure product (RPP) as an index of myocardial oxygen consumption (MV̇O₂) (38, 70): nCSBF (ml·mmHg·heartbeat⁻¹); CSBF/RPP (Eq. 1), where nCSBF is the normalized CSBF, CSBF is the absolute CSBF (ml/min), and RPP is the RPP [systolic BP (SBP) × HR; mmHg·beats·min⁻¹]. Furthermore, cerebral and coronary sinus vascular conductance (CVĊV̇p and CVĊCSBF, respectively) were calculated by dividing V̇p and CSBF by mean arterial pressure (MAP).

CBF indexes of V̇p, V̇WM, and PV̇WM followed similar trends during euoxic hypercapnia and isocapnic hypoxia. Therefore, only V̇p is reported. Changes in V̇p, CSBF, nCSBF, CVĊV̇p, and CVĊCSBF at the two stages of euoxic hypercapnia and three stages of isocapnic hypoxia were normalized by indexing them against the prior baseline (i.e., Bl.1 for Hc.1 to Hc.2; Bl.2 for Hx.1 to Hx.3). The percent change (%Δ) in V̇p, CSBF, nCSBF, CVĊV̇p, and CVĊCSBF across the hypercapnic and hypoxic challenges was analyzed using a linear mixed model analysis of variance with repeated measures.

The gain of cerebral and CSBF and CVĊV̇p and CVĊCSBF to hypercapnia and hypoxia were calculated by fitting a linear regression through individual participant plots of %Δ V̇p, %Δ CSBF, %Δ nCSBF, %Δ CVĊV̇p, and %Δ CVĊCSBF versus PETCO₂ (Torr) and calculated O₂ saturation (56), respectively. The slope of each linear regression was taken as the gain of each response. Comparisons of cerebral and coronary circulation gains were performed using paired Student’s t-tests. There was no difference in cerebrovascular and coronary gains between sexes (P ≥ 0.058). As a result, reported values are the mean for all participants.

Finally, differences between experimental sessions for PETCO₂, PETO₂, pulmonary ventilation (V̇E), tidal volume (V̇T), breathing frequency (ḟR), HR, and arterial BP [SBP, diastolic BP (DBP), and MAP] were analyzed using a linear mixed model analysis of variance with repeated measures. All statistical analyses were performed in PASW Statistics (v. 17.0.2, SPSS, Chicago, IL). Alpha was set a priori at 0.05 and maintained by using the Sidak correction for post hoc comparisons. All results are presented as means ± SE.

RESULTS

Euvoxic Hypercapnia

Blood flow measurements. Euoxic hypercapnia resulted in significant increases in cerebral and CSBFs (P ≤ 0.014). Relative to Bl.1, V̇p was 51.3 ± 5.2% (P < 0.001), CSBF was 34.2 ± 4.6% (P < 0.001), and nCSBF was 17.1 ± 5.7% (P = 0.011) higher at Hc.2. Similarly, at Hc.2, CVĊV̇p was 39.4 ± 5.4% and CVĊCSBF was 26.97 ± 5.8% higher than values at Bl.1 (P < 0.001).

Blood flow gains to hypercapnia are illustrated in Fig. 3A. The gains for V̇p and absolute CSBF were similar (P = 0.234), but V̇p had a significantly greater gain in response to hyper-
capnia compared with nCSBF ($P = 0.030$). Similarly, the CSBF gain was higher than the nCSBF gain ($P = 0.033$). Figure 4A shows the gains of CVC$_{Vp}$ and CVC$_{CSBF}$ in response to hypercapnia. The percent change in cardiovascular conductance per unit increase in PETCO$_2$ was not different between cerebral and coronary sinus circulations ($P = 0.292$).

**Ventilatory measurements.** Comparison of ventilatory parameters between cerebral (i.e., TCD) and CSBF (i.e., MRI) measurements revealed that there was a significant difference in PETCO$_2$ ($P = 0.003$; Table 1). Post hoc comparisons showed that PETCO$_2$ was significantly higher during TCD measurements at BL1 ($P = 0.003$). To correct for this difference in baseline PETCO$_2$, an exponential model was fitted to individual $V_{\dot{E}}$ versus PETCO$_2$ plots (33). The equation for the fitted model was then used to calculate individual $V_{\dot{E}}$ at the lower BL1 PETCO$_2$ during the MRI measurements. The gain of the $V_{\dot{E}}$ and CVC$_{Vp}$ responses to hypercapnia were then derived from the calculated $V_{\dot{E}}$.

PETO$_2$ was held constant at near-resting values during both the TCD and MRI experimental sessions ($P = 0.580$; Table 1). As euoxic hypercapnia progressed, the degree of hypercapnia-induced increase in $V_{\dot{E}}$ was significant ($P < 0.001$) and similar during the two experimental sessions ($P = 0.966$; Table 1). Within each session, the increased $V_{\dot{E}}$ resulted from an augmentation of both $V_T$ ($P < 0.001$) and $f_R$ ($P < 0.001$).

**Cardiovascular measurements.** HR and arterial BP both significantly increased with hypercapnia ($P \leq 0.001$; Table 1). Between the TCD and MRI experimental sessions, the increases in HR were similar ($P = 0.792$), there was no difference in SBP ($P = 0.523$), but DBP and MAP were higher during the MRI measurements ($P = 0.022$).

**Isoxiccapnic Hypoxia**

**Blood flow measurements.** At the end of Bl2, $V_{p}$ and CSBF were not significantly different from Bl1 values ($P \geq 0.334$). Middle cerebral artery blood velocity, CSBF, and nCSBF all increased with hypoxia ($P \leq 0.001$). At Hx3, $V_p$ was 28.9 $\pm$ 2.7$\%$ ($P < 0.001$), CSBF was 57.0 $\pm$ 7.7$\%$ ($P < 0.001$), and nCSBF was 38.6 $\pm$ 7.6$\%$ ($P < 0.001$) higher than the preceding baseline (i.e., Bl2). CVC$_{Vp}$ and CVC$_{CSBF}$ also increased with hypoxia ($P < 0.001$). By Hx3, CVC$_{Vp}$ and CVC$_{CSBF}$ were 16.7 $\pm$ 2.3$\%$ ($P < 0.001$) and 48.2 $\pm$ 7.4$\%$ ($P < 0.001$) higher than at Bl2, respectively.

Figure 3B illustrates the $V_p$, CSBF, and nCSBF gains to hypoxia. Overall, $V_p$ had a lower gain in response to decreases in calculated arterial oxyhemoglobin saturation than CSBF.
measurements, HR, SBP, and MAP were not different ($P \geq 0.088$), but DBP was significantly lower ($P = 0.015$) during $V_p$ assessment.

**DISCUSSION**

*Major Findings*

This is the first study to investigate cerebral and MBF responses to moderate euoxic hypercapnia and isocapnic hypoxia in young and healthy humans. Primary findings include the following: 1) hypercapnia elicits similar increases in total cerebral and MBF; 2) the cerebral vasculature is significantly more sensitive to increases in $\text{PETCO}_2$ after CSBF is normalized for the concurrent rise in $\text{MVO}_2$ with euoxic hypercapnia; and 3) CBF has a significantly lower gain than CSBF in response to hypoxia, but removing the influence of $\text{MVO}_2$ upon CSBF revealed that the cerebral and coronary circulations similarly respond to hypoxia.

To date, only two studies have compared CBF and MBF responses to hypercapnia and no study has compared the responses of the two vascular beds to hypoxia. Hoffman et al. (31), employing a hyperoxic-hypercapnic challenge in dogs, found CBF and MBF increased a similar degree when there

**Ventilatory measurements.** When compared with the CSBF assessment in the MRI, $\text{PETCO}_2$ was $2.2 \pm 4.4$ Torr higher during $V_p$ measurements using TCD ($P = 0.002$; Table 1). Conversely, $\text{PETO}_2$ was similar between experimental sessions ($P = 0.455$). In both sessions, the hypoxia-induced increase in $V_p$ ($P < 0.001$) resulted from a higher $V_T$ ($P < 0.001$), whereas $f_R$ did not change across the isocapnic hypoxia protocol ($P = 0.972$).

**Cardiovascular measurements.** With the increasing severity of hypoxia HR, the measurements of SBP, DBP, and MAP all increased concurrently ($P < 0.001$). Between TCD and MRI

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Fig. 3. Mean gains for the cerebral and myocardial circulations with increases in $\text{PETCO}_2$ (%/Torr; A) and decreases in $\text{PETO}_2$ (%/desaturation; B). $V_p$, peak blood velocity through the middle cerebral artery; nCSBF, normalized CSBF. Error bars represent means ± SE. *$P \leq 0.05$, significant difference.

Fig. 4. Individual and mean gains for cerebral vascular conductance (CVC$_{\theta P}$) and coronary sinus vascular conductance (CVC$_{\text{CSBF}}$) to hypercapnia (%/Torr; A) and hypoxia (%/desaturation; B). $P$ values, for comparison of CVC$_{\theta P}$ and CVC$_{\text{CSBF}}$ gains in response to hypercapnia and hypoxia, respectively. Error bars represent means ± SE.
was no change in cerebral O₂ consumption or MVₐO₂. However, mean PaO₂ during the CBF and MBF measurements was 137 and 160 Torr, respectively. As hyperoxia exerts an independent, opposing effect to hypercapnia on CBF (37, 49) and MBF (8, 22), the differences in PaO₂ between the two blood flow measurements precludes direct comparisons between the cerebral and coronary circulations. In the only previous human study, Yokoyama et al. (70) compared CBF and MBF responses to hypercapnia in elderly, healthy men. They also reported similar increases in CBF and MBF with mild hypercapnia (+3 Torr), but MV₂O₂ also increased during the hypercapnic challenge. Normalizing MBF to the MV₂O₂ (nMBF) revealed that the increase in MBF resulted from the indirect influence of hypercapnia on MV₂O₂ and not the increased PaCO₂ directly.

The CBF and MBF hypercapnic gains in the present study are similar to those observed by Hoffman et al. (31) but lower than those reported by Yokoyama et al. (70). Furthermore, the reported nMBF gain during hypercapnia of ~1%/Torr is opposite to the ~1%/Torr observed by Yokoyama et al. (70). Regrettably, experimental differences between the three studies limit the inferences that can be made from these comparisons. First, PaO₂ was not similar between studies. We used euvolic hypercapnia to remove the influence of changes in PaO₂ on CBF, MBF, and nMBF, whereas Hoffman et al. (31) (see above) used hyperoxic (30% O₂) hypercapnia and Yokoyama et al. (70) did not report PaO₂. Consequently, Hoffman et al. (31) likely underestimated CBF and MBF because of the imposed hyperoxia (8, 22, 37, 49), and the true stimulus employed by Yokoyama et al. (70) is unknown. Second, a +3-Torr increase in PETCO₂ (70) may have been insufficient to increase MBF above that required for myocardial metabolic demand. In the present study, PETCO₂ was increased by ~9 Torr from resting levels, resulting in an ~18% increase in nMBF. These opposing results may be the consequence of a PaCO₂ threshold for increases in MBF (61), age-related differences between participants in the two studies (45), or the use of hyperoxic hypercapnia by Yokoyama et al. (70).

Concerning hypoxia, the CBF gain reported in the present study (Fig. 3B) is within the typical range for independently assessed CBF responses in humans (3, 10, 59). We observed a lower MBF gain to hypoxia than that reported in the only published human study performed (47). This is most likely the result of differences in MBF measurement techniques between the two studies. We measured CSBF across a full cardiac cycle as a surrogate of MBF, whereas Momen et al. (47) measured arterial blood velocity through the left anterior descending artery during diastole. Finally, the nMBF gain to hypoxia reported is similar to that previously measured in dogs when MV₂O₂ changes during hypoxia are controlled (30).

**Physiological Considerations**

The present study was performed at an altitude of ~1,103 m above sea level. All participants had lived at ~1,103 m for at least 1 yr and were considered to be fully acclimatized to the altitude at which the study was performed. Acute exposure of a sea level resident to this altitude (i.e., minutes to hours) would result in a minimal increase in cerebral and coronary blood flow, but with prolonged exposure (i.e., hours to weeks) CBF and MBF would return toward baseline sea level values where it is maintained for the long term (13, 66).

To properly compare CBF and MBF responses to euvolic hypercapnia and isocapnic hypoxia, alterations in cerebral and MVO₂ needed to be considered. Although still controversial (69), there is substantial evidence showing that, at rest, the cerebral metabolic rate of O₂ consumption (CMRO₂) is not
influenced by either hypercapnia or hypoxia (7, 15, 16, 21, 31, 34, 37, 57, 58). In three recent studies using comparable hypercapnic challenges to that used within the present study, two out of the three reported no significant change in CMRO2 (15, 34, 67). The study reporting a change in CMRO2 observed a ~13% decrease with inhalation of 5% CO2-21% O2-74% N2 (67). With respect to hypoxia, calculating CMRO2 using the Fick principle, Bailey et al. (7) reported no change in CMRO2 with exposure to an inspired fraction of O2 of 12.9% O2. In contrast, Xu et al. (68) reported a 25% increase in CMRO2 with an inspired fraction of O2 of 13.5%. These contradictory findings are likely due to experimental differences. Bailey et al. (7) calculated CMRO2 by measuring CBF using the Kety-Schmidt technique and measuring arterial and venous oxyhemoglobin levels from blood samples drawn from the radial artery and jugular vein, whereas Xu et al. (68) measured all variables (i.e., CBF and arterial and venous oxyhemoglobin levels) with MRI. As there is no clear consensus and substantial evidence indicating the CMRO2 is not influenced by moderate levels of hypercapnia and hypoxia, the assumption was made that CMRO2 remained stable throughout the hypercapnic and hypoxic protocols. Thus the observed increases in CBF were taken as hypercapnia and hypoxia mediated and not the result of altered metabolic demand of neuronal tissues. In contrast, as MV˙O2 is linearly related to HR (38) and MBF is linearly related to MV˙O2 (20), a portion of the MBF responses observed would have been metabolically driven as a result of the increased HR during the euoxic hypercapnia and isocapnic hypoxia challenges (Table 1). For a more appropriate comparison with CBF, MBF was normalized to the RPP as an indirect measure of MV˙O2. A comparison of the more analogous blood flow measures of CBF and nMBF revealed that the cerebral vasculature has a greater gain in response to hypercapnia, whereas the cerebral and myocardial vasculatures have similar gains in response to hypoxia.

The similar gains between CVCVP and CVCCSBF with hypercapnia (Fig. 4A) corroborate the finding that the cerebral circulation had a greater blood flow response to hypercapnia. Contrarily, the greater gain of CVCCSBF to hypoxia (Fig. 4B) demonstrated the coronary circulation to be more responsive for a given decrease in oxyhemoglobin saturation. It is interesting to note that these differences between the cerebral and coronary circulations were observed despite implications of parallel underlying blood flow regulatory mechanisms (24, 28). Metabolites such as nitric oxide, adenosine, cAMP, and prostaglandins (18, 49), as well as ATP-dependent potassium channels, have been associated with vasodilation within both the cerebral and coronary vasculatures. Nitric oxide is an important regulator of the hypercapnia-induced, but not hypoxia-induced, increase in CBF. Thus the greater gain of the CBF response to hypercapnia may be a potential result of differences in the regulatory role of nitric oxide within the cerebral and coronary circulations. The greater CBF gain in response to euoxic hypercapnia may also be an effect of cerebral vasodilation occurring in vessels smaller than 0.57 mm (19) that vigorously respond to hypercapnia (65) and extracellular pH changes (26) via local myogenic mechanisms (40). Other mechanisms may include differences in sympathetic control of the two vasculatures (2, 18), as well as physical and functional differences in endothelium and smooth muscle cells within the two vascular beds (29). Overall, the specific mechanisms underlying the observed differences between CBF and MBF responses to euvic hypercapnia and isocapnic hypoxia require further investigations.

Limitations

CBF measurements. TCD ultrasound was used to measure blood velocity in the MCA and is reflective of blood flow only if the cross-sectional area of the insonated artery remains stable. The cross-sectional area of the MCA has been shown to change minimally with hypercapnia, hypoxia, and changes in BP (25, 51, 55). As a result, TCD velocity-derived indexes of blood flow (VP, V皿WM, and PV皿WM) have been shown to provide reasonable estimates of actual blood flow through the MCA. Furthermore, the TCD system used in the present study provides a continuous output of the P, which provides an index of relative changes in the cross-sectional area of the insonated artery-vasodilation increasing and vasoconstriction decreasing the total power signal (1, 6, 27). In our study, VP, V皿WM, and PV皿WM followed similar trends and P was stable throughout the hypercapnic and hypoxic protocols. Thus the changes in blood velocity observed represent changes in CBF.

CBF responses to hypercapnia and hypoxia are heterogeneous within different brain regions (10, 48), particularly in response to hypoxia (48). Accordingly, it is important to note that TCD-assessed blood velocity through the MCA is representative of global CBF, as the two MCAs provide ~80% of total brain perfusion (23). Global CBF responses measured using TCD have been shown to be comparable with global CBF responses measured using intravenous Xenon133 clearance (11, 17), positron emissions tomography, (10, 14), and pulsed arterial spin-labeling MRI (48).

MBF measurements. CSBF was used as a surrogate for MBF. Since 96% of coronary arterial inflow returns to the right atrium via the coronary sinus (32), CSBF is a good indicator of MBF (36, 54, 62) and is comparable with total flow through both the left anterior descending and circumflex arteries (43). Finally, MBF was normalized to changes in MV˙O2 using the RPP (RPP = HR X SBP). While an indirect index, the RPP is highly correlated with MV˙O2 (r = 0.90), is a better reflection of MV˙O2 than only HR (38), and is a useful tool when direct calculation of MV˙O2 is unavailable.

Clinical Significance

CBF responses to an increase in Paco2 or decrease in Paco2 in healthy humans are well established (9, 13), and cerebrovascular reactivity tests are sometimes clinically employed to assess a patient’s risk of stroke (44, 46), where a lower CBF response compared with healthy individuals is suggestive of an increased risk of stroke. Conversely, human coronary blood flow responses to hypercapnia and hypoxia are not well defined because studies have been primarily limited to animal models. Therefore, this study provides a novel insight into human coronary vascular responses to alterations in arterial blood gases and may play a role in helping develop new vascular reactivity tests to hypercapnia and hypoxia for the assessment of coronary vascular and brain health and for early detection of vascular disease.
Summary

This is the first direct comparison of cerebral and coronary blood flow responses to moderate hypercapnia and hypoxia within young, healthy human volunteers. CBF is significantly more sensitive to hypercapnia than MBF but similarly sensitive to hypoxia when changes in metabolic demand are considered. The consideration of vascular tone revealed the coronary circulation has a greater capacity for increasing vascular conductance than the cerebral circulation during hypoxia, but not hypercapnia.

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BRAIN AND MYOCARDIAL BLOOD FLOW RESPONSES TO O2 AND CO2

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DISCLOSURES

No disclosures.

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