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MRI Measures of Middle Cerebral Artery Diameter in Conscious Humans During Simulated Orthostasis

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Background and Purpose—The relationship between middle cerebral artery (MCA) flow velocity (CFV) and cerebral blood flow (CBF) is uncertain because of unknown vessel diameter response to physiological stimuli. The purpose of this study was to directly examine the effect of a simulated orthostatic stress (lower body negative pressure [LBNP]) as well as increased or decreased end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) on MCA diameter and CFV.

Methods—Twelve subjects participated in a CO_2 manipulation protocol and/or an LBNP protocol. In the CO_2 manipulation protocol, subjects breathed room air (normocapnia) or 6% inspired CO_2 (hypercapnia), or they hyperventilated to ≈ 25 mm Hg $P_{ET}CO_2$ (hypocapnia). In the LBNP protocol, subjects experienced 10 minutes each of -20 and -40 mm Hg lower body suction. CFV and diameter of the MCA were measured by transcranial Doppler and MRI, respectively, during the experimental protocols.

Results—Compared with normocapnia, hypercapnia produced increases in both $P_{ET}CO_2$ (from 36 ± 3 to 40 ± 4 mm Hg, $P < 0.05$) and CFV (from 63 ± 4 to 80 ± 6 cm/s, $P < 0.001$) but did not change MCA diameters (from 2.9 ± 0.3 to 2.8 ± 0.3 mm). Hypocapnia produced decreases in both $P_{ET}CO_2$ (24 ± 2 mm Hg, $P < 0.005$) and CFV (43 ± 7 cm/s, $P < 0.001$) compared with normocapnia, with no change in MCA diameters (from 2.9 ± 0.3 to 2.9 ± 0.4 mm). During -40 mm Hg LBNP, $P_{ET}CO_2$ was not changed, but CFV (55 ± 4 cm/s) was reduced from baseline (58 ± 4 cm/s, $P < 0.05$), with no change in MCA diameter.

Conclusions—Under the conditions of this study, changes in MCA diameter were not detected. Therefore, we conclude that relative changes in CFV were representative of changes in CBF during the physiological stimuli of moderate LBNP or changes in $P_{ET}CO_2$. (*Stroke*. 2000;31:1672-1678.)

Key Words: cerebral blood flow ■ hypotension, orthostatic ■ middle cerebral artery
■ ultrasonography, Doppler, transcranial

Ever since Aaslid et al¹ introduced transcranial Doppler (TCD) as a noninvasive method of determining beat-by-beat relative changes in cerebral flow velocity (CFV), many groups have adopted use of this technique to examine cerebrovascular control. The basic assumption with this methodology is that relative changes in CFV represent relative changes in cerebral blood flow (CBF) as long as there is no change in arterial diameter at the point of insonation. This assumption has been challenged,² and several groups have found poor correlations between changes in CFV and CBF during drug stimulation.³⁻⁷ This may have been due to drug-induced constriction or dilation of the middle cerebral artery (MCA), which may result in a change in CFV without any effect on CBF.⁴⁻⁷

In contrast, others have found good correlations between relative changes in CFV and CBF by using various techniques: xenon (¹³³Xe), single-photon emission computed tomography (SPECT), MRI, and direct Fick calculations from

the arterial to jugular venous oxygen difference under various stimuli.⁸⁻¹⁰

Giller et al¹¹ directly measured MCA external diameter during open craniotomy and found no change in the dimensions of this vessel during manipulations of end-tidal CO_2 . Similarly, cerebral angiography^{12,13} and MRI¹⁴ techniques have not detected changes in MCA diameter under various stimuli. However, the majority of these studies were performed on anesthetized patients,¹¹⁻¹³ in whom cerebrovascular response may have been compromised,^{15,16} or under a limited range of cerebral vasomotor stimuli.¹⁴

In animals, MCA dimensions appear to be sensitive to increased sympathetic outflow.¹⁷⁻¹⁹ However, large interspecies differences in the response of the various cerebral beds suggest caution in drawing conclusions about human cerebrovascular regulation from animal studies.²⁰

The only study to examine MCA diameters in conscious humans has been under hypocapnic conditions, in which no

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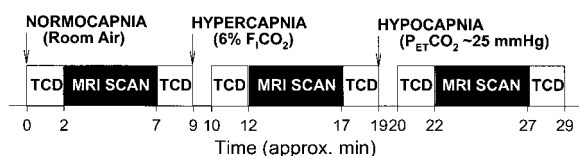
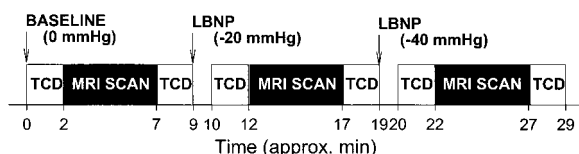
EXPERIMENT A: CO₂ MANIPULATION**EXPERIMENT B: LBNP CONDITION**

Figure 1. Schematic representation of 2 experimental protocols. MRI scans took ≈ 5 minutes depending on subject's HR. TCD collections lasted for 2 minutes before and after scan. Approximately 1 minute was provided between changing conditions for subjects to reach steady state.

change in MCA diameter was found.¹⁴ The role of increased arterial CO₂ or sympathetic tone on the dimensions of large cerebral arteries in conscious humans has not been reported. Therefore, the purpose of the present study was to directly measure MCA diameter by using MRI during changes in end-tidal CO₂ partial pressure (P_{ET}CO₂) and lower body negative pressure (LBNP). The latter was used to increase sympathetic outflow. To accomplish this objective, “black blood” magnetic resonance images (described in Subjects and Methods) of the intraluminal diameter of the MCA during hypocapnic, hypercapnic, and LBNP exposure were obtained. We tested the hypothesis that MCA diameters were stable during physiological manipulations of P_{ET}CO₂ and sympathetic stimulation.

Subjects and Methods

Subjects

Twelve subjects (7 women and 5 men), aged 20 to 29 years, gave informed consent to undergo the Ethics Review Board–approved protocol.

Experimental Protocols

Subjects participated in 1 or both of 2 experimental protocols. The experimental protocols were performed on separate days. After instrumentation, subjects remained supine for 10 minutes before data collection. Both protocols began with a 2-minute collection of CFV data, which was followed by the MRI scan (≈ 5 minutes) and then by another 2-minute collection of CFV data. This procedure was performed at each level of CO₂ and LBNP (Figure 1).

Experiment A: CO₂ Manipulation

Three of the women and 3 of the men participated in this protocol. To examine the effect of CO₂ on CBF and diameter of the MCA, 3 levels of P_{ET}CO₂ were maintained for 10 minutes so that CFV could be monitored before and after the scanning period. After the subject breathed room air (normocapnia), the inspired gas was switched to contain 6% CO₂ (hypercapnia). This is a typical clinical dose, and it allowed us to investigate the assumption that MCA diameter is not affected by this dose of inspired CO₂. After the hypercapnic period, the subject was asked to hyperventilate to a target P_{ET}CO₂ value of 25 mm Hg (hypocapnia). The subject was provided with visual feedback of the P_{ET}CO₂ level and the effectiveness of his/her breathing efforts.

Experiment B: LBNP

Five of the women and 3 of the men experienced the LBNP protocol. The purpose of this experiment was to evoke baroreflex-mediated increases in sympathetic discharge²¹ without modifying cerebral perfusion pressure and thus not eliciting autoregulatory contributions to changes in CFV and MCA diameter. The legs and pelvis were sealed inside a wooden box connected to an adjustable vacuum source to allow the development of negative pressure around their lower limbs. An adjustable foot plate was provided to ensure that the position of the subjects in the magnet would not change when vacuum was applied. Each subject experienced 0, -20, and -40 mm Hg negative pressure for 10 minutes each, allowing measures of CFV for 2 minutes before and after a 5-minute period of MRI scanning. P_{ET}CO₂ values were not controlled.

Data Acquisition

Inside the MRI unit, the P_{ET}CO₂ and respiratory rate (Normocap 200, Datex) were measured with the use of a 8.2-m catheter tube (1-mm ID) inserted into a sampling port in a face mask worn by the subject. Previous work has shown that this length of tube has little effect on the expired CO₂ profile.²² Blood pressure was measured every 1 to 2 minutes by an automated blood pressure–monitoring cuff (Dinamap, Critikon Inc) on the left arm. The respiratory and blood pressure monitors were located outside the MRI room. An important aspect of the present study was the close to simultaneous recordings of flow velocity and diameters during each condition. CFV was recorded for 2 minutes before and after each MRI scan in each condition.

TCD Sonography

The CFV in the MCA was obtained with a 2-MHz pulsed flat TCD probe located over the temporal bone. The signal was range-gated to a depth of 45 to 60 mm to ensure insonation of the M1 segment of the MCA according to standard techniques. After the optimum signal was achieved, a hook-and-loop fastener (Velcro) headband with the probe attached was secured for the duration of the test, including MRI scans. The Doppler unit (Transpect TCD, Medasonics) was located outside the MRI room and attached to the probe with a 10-m cable that passed through the wave-guide port of the radiofrequency-shielded room. This potential violation of the radiofrequency-shielding integrity did not cause substantial artifact in the MR images.

MRI Studies

MRI examinations were performed on all subjects in a General Electric Signa Horizon EchoSpeed (version 5.5) 1.5-T clinical scanner (General Electric Medical Systems). Black blood magnetic resonance angiography was used to create a contrast between the MCA lumen and the surrounding tissue. In this technique, transverse slabs of tissue in the middle of the brain immediately adjacent to the imaging plane and containing the carotid arteries and the circle of Willis were chosen. These tissue sections, including the blood present therein, were presaturated with use of a slab-selective 90° radiofrequency pulse to produce a signal void from those tissues. When that signal-nulled blood then flowed into the MCA in the imaging plane, the blood within that lumen appeared black. Imaging of the plane of interest was accomplished with a 2D cardiac-gated fast spin echo pulse sequence by using a 5-mm slice thickness, a 12×12-cm field of view, and a 256×256 matrix, giving 0.47-mm square pixels. Other parameters of relevance were as follows: echo train length, 4; repetition time, 2 cardiac cycles; and effective echo time, 17 ms. Three oblique imaging planes were chosen to intersect with each MCA normally and through a straight section (Figure 2). Scanning sessions took ≈ 5 minutes, depending on the subject's heart rate (HR). During scanning sessions, the nonmetallic TCD probe was unplugged to ensure that there was no interference with the MRI images in the area of interest.

Four to 6 diameter images were obtained for each subject in each condition. The diameter measurements for each scan were determined manually by 5 independent observers who were blinded to subject or condition. Any images in which the vessel boundaries were not clearly defined because of subject motion or vessel

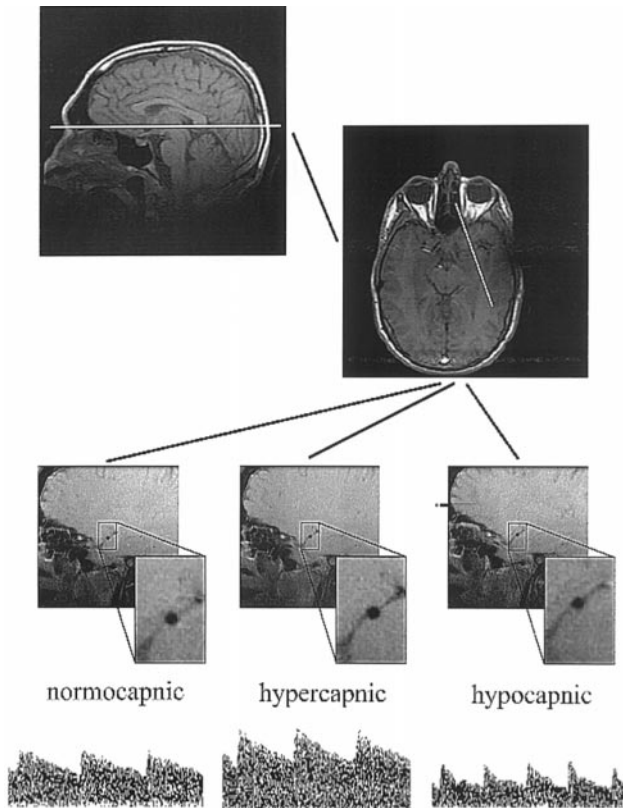


Figure 2. Sample MRI images used to obtain MCA diameters during 3 CO₂ conditions. Bottom tracings show TCD signal just before imaging during normocapnic (room air), hypercapnic (6% inspired CO₂), and hypocapnic (hyperventilation) conditions.

tortuosity were excluded from analysis. Mean values for each condition were obtained by averaging the values for each image from the 5 observers. CBF was then calculated as the product of CFV and vessel cross-sectional area. HR and blood pressure were monitored throughout the scans.

Data Analysis

The analog CFV, HR, and P_{ET}CO₂ signals were sampled simultaneously at 10 kHz per channel by use of an 8-channel digital tape recorder (TEAC RD-111T, Teac Inc). Offline data analysis was performed with customized data analysis software.²³ The peak velocity envelope of the TCD waveform was used to represent the instantaneous blood flow velocity in the MCA. Beat-by-beat signals were displayed during analysis, and any artifacts were removed. Blood pressure data were recorded each minute throughout both experimental trials. CBF was calculated as the product of CFV and the vessel cross-sectional area by use of the MRI-derived diameter measures for that condition. HR was obtained from the CFV

waveforms. An estimate of regional cerebrovascular resistance (CVR_{est}) in the distribution of the MCA was calculated as $CVR_{est} = MAP/CFV$, where MAP is the mean arterial pressure.

Interobserver agreement was assessed with a Kendall coefficient of concordance (W) test, and a Friedman rank test was used to assess whether all diameter measures were considered to have come from the same population, regardless of observer.

The effect of P_{ET}CO₂ or LBNP on CFV and diameter was assessed by repeated-measures 2-way and 1-way ANOVA, respectively, with a Student-Newman-Keuls test for multiple comparisons. Data are presented as mean ± SEM, and levels of $P < 0.05$ are considered significant.

Results

We measured P_{ET}CO₂, HR, and MAP both before and after the MRI scanning period within each experimental phase to determine whether steady-state conditions were maintained during the MRI and transcranial Doppler measures. A significant tachycardia occurred during the first 2 minutes of hypocapnia ($P < 0.05$, Table 1). However, the variables with the greatest impact on CFV, namely, P_{ET}CO₂ and MAP, were maintained throughout each experimental phase. During LBNP, HR increased between the prescan and postscan periods ($P < 0.05$), but MAP was maintained (Table 2). In the LBNP conditions, there were no differences between the prescan and postscan values of CFV (Table 2); however, there was a significant increase in CFV during the postscan period of hypocapnia (Table 1). Together, these data indicate that CFV and MCA diameter measures were made under steady-state conditions.

Of the 270 images captured, 158 were considered suitable for analysis. Strong interobserver concordance was observed between diameter measures across all observers (Kendall $W = 0.74$). Also, the Friedman test was significant ($P < 0.001$), indicating that all diameter measures were drawn from the same population regardless of observer.

P_{ET}CO₂ Manipulations

Compared with normocapnia, P_{ET}CO₂ increased and decreased significantly during the hypercapnic and hypocapnic conditions, respectively ($P < 0.05$, Table 1). MFV was increased by 26% and decreased by 33% during hypercapnia and hypocapnia, respectively ($P < 0.001$, Figure 3). CVR_{est} increased by 49% ($P < 0.05$) during hypocapnia and decreased by 13% ($P < 0.05$) during hypercapnia. MCA diameters were not altered from normocapnia by either hypercapnia or hypocapnia (Figure 3). Examination of the individual responses indicated that 4 of 6 subjects showed minimal change

TABLE 1. Response to CO₂ Manipulation

Gas Condition	Scan	HR, bpm	MAP, mm Hg	P _{ET} CO ₂ , mm Hg	CFV, cm/s
Normocapnic	Pre	58.6 ± 3.3	84.3 ± 3.0	36.5 ± 1.0	63.5 ± 4.3
	Post	59.8 ± 2.4	83.6 ± 3.2	36.8 ± 0.5	63.1 ± 3.9
Hypercapnic	Pre	64.5 ± 3.7	86.2 ± 2.6	44.7 ± 1.0*	80.2 ± 6.0*
	Post	68.4 ± 6.0	89.9 ± 3.2	45.0 ± 0.9	79.7 ± 6.3
Hypocapnic	Pre	85.4 ± 5.0*	84.9 ± 2.8‡	23.8 ± 0.4*	40.1 ± 1.4*
	Post	62.6 ± 3.7†	89.4 ± 3.4	23.5 ± 0.2	45.5 ± 2.4†

Values are mean ± SEM. Changes in HR, MAP, P_{ET}CO₂, and CFV during CO₂ manipulation are shown.

* $P < 0.001$ and ‡ $P < 0.05$ vs normocapnic (combined prescan and postscan values); † $P < 0.05$ vs prescan value.

TABLE 2. Response to LBNP Manipulation

LBNP Condition	Scan	HR, bpm	MAP, mm Hg	P _{ET} CO ₂ , mm Hg	CFV, cm/s
Baseline	Pre	65.5±3.1	85.1±2.1	35.9±1.0	57.9±4.1
	Post	64.7±3.0	83.2±2.0	36.1±1.3	57.7±4.4
−20 mm Hg	Pre	67.2±3.5	83.6±1.9	35.1±1.4	57.1±4.0
	Post	69.7±3.2*	83.3±2.2	34.7±1.3	56.8±3.9
−40 mm Hg	Pre	72.7±4.0†	82.0±1.8	35.0±0.9	55.2±3.8†
	Post	75.0±3.8*	83.2±2.2	33.8±1.3	55.1±3.7

Values are mean±SEM. Changes in HR, MAP, P_{ET}CO₂, and CFV during LBNP manipulation are shown. *P<0.05 vs prescan value; †P<0.05 vs baseline (combined prescan and postscan values).

across CO₂ conditions. In the other 2 subjects, the MCA diameter was increased (0.3 mm) in one and decreased (0.4 mm) in the other during hypocapnia, with no detectable change during hypercapnia.

LBNP Studies

P_{ET}CO₂ levels were constant during the LBNP protocol (Table 2). Compared with supine rest conditions, HR was increased during −40 mm Hg LBNP (P<0.05, Table 2). With −40 mm Hg LBNP, CFV decreased from 58±4 to 55±4 cm/s (P<0.01, Figure 4), and CVR_{est} was slightly but significantly increased by LBNP (Figure 4). No changes in MCA diameter were detected during LBNP (Figure 4). Individual subject data demonstrated no consistent change in diameters between supine rest and LBNP.

CFV Versus CBF

Because no change in MCA diameter was observed, the measured values for CFV and calculated CBF were highly correlated during the manipulations of P_{ET}CO₂ (r=0.94,

P<0.001) and LBNP (r=0.88, P<0.001). Similarly, the relative changes (ie, percent change) in CFV and CBF were closely related (r²=0.92, P<0.001) and not significantly different from the line of identity (Figure 5).

Discussion

The validity of relative changes in TCD CFV values as indicative of relative changes in CBF depends on whether the cerebral vessel diameters change. The unique feature of the present study was the ability to alternately collect CFV via Doppler and MCA dimensions via MRI in conscious humans. Therefore, the 2 indices of cerebrovascular control were measured under the same conditions in temporal proximity without pharmacological interventions. The present study demonstrates that MCA dimensions were stable under a wide range of P_{ET}CO₂ and simulated orthostatic stress. Therefore, it was concluded that in conscious humans, changes in CFV provide a valid index of changes in total MCA blood flow.

Our images of MCA diameter support the earlier findings of Giller et al,¹¹ who directly measured the MCA during

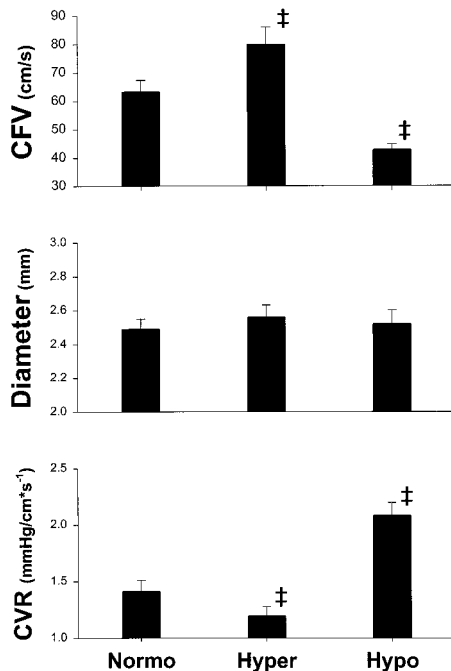


Figure 3. MCA CFV and diameter changes as well as values for CVR_{est} during normocapnic (Normo, room air), hypercapnic (Hyper, 6% inspired CO₂), and hypocapnic (Hypo, hyperventilation) conditions. Values are mean±SEM. ‡P<0.001 vs Normo.

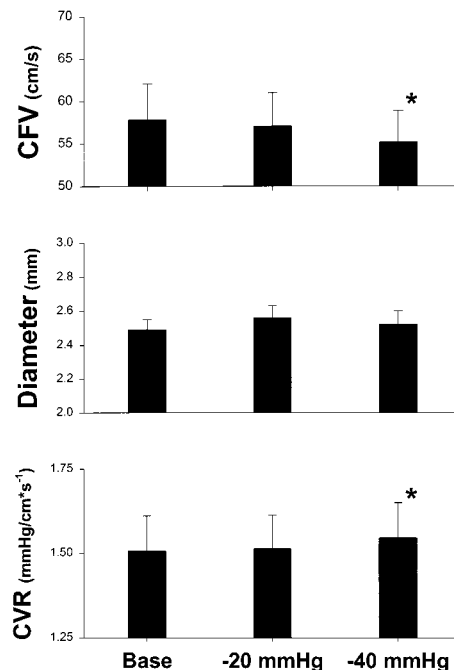


Figure 4. MCA CFV and diameter changes as well as values for CVR_{est} during various levels of LBNP. Values are mean±SEM. *P<0.05 vs baseline (base).

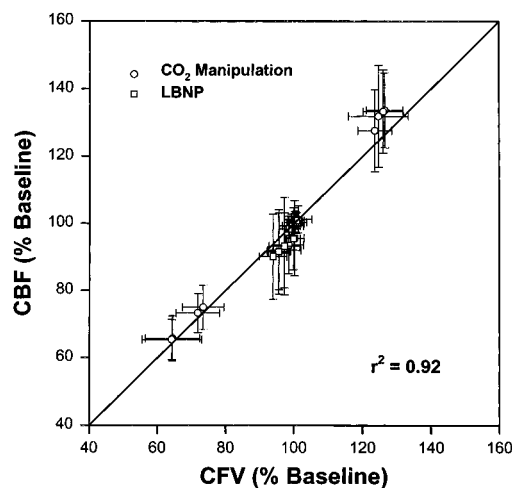


Figure 5. Comparison of relative changes in CFV and CBF from baseline during both experiments. Regression lines for CO₂ manipulation and LBNP were not significantly different from line of identity. Value of r^2 displayed is for all data in combination. Values are 1-minute mean \pm SD.

craniotomy. Several additional studies have failed to detect the effects of $P_{ET}CO_2$ on MCA dimensions by use of angiography.^{12,13} Therefore, the bulk of evidence suggests that changes in cerebrovascular resistance caused by changes in arterial CO₂ occur downstream from the MCA M1 segment.^{16,24} In contrast, Valdeuzza et al²⁵ reported a dilation of the MCA with hypercapnia in conscious humans. This observation was made by comparing the change in MCA inflow velocity with the contralateral sphenoparietal sinus outflow velocity. However, it is not known whether differential drainage from other cerebral vascular beds and/or whether venous sinus volumes remained constant in their study.²⁵

There is controversy regarding sympathetic vasoconstrictor effects on cerebral vasculature. Sympathetic innervation of cerebral arteries has been found to be greatest in the basal arteries (ie, MCA and anterior cerebral artery).¹⁷ In rabbits and cats, sympathetic activation caused increased cerebral vascular resistance in the large cerebral arteries.²⁶ To examine autonomic cerebrovascular control in humans, investigators have used models that ablate or augment sympathetic activity. Increases in ipsilateral MCA flow velocity have been observed after stellate ganglion blockade,²⁷ suggesting tonic sympathetic tone in MCA vessels at rest. However, sympathetic blockade did not alter vertebral artery flow or diameter.²⁸ Stimulation of T₂ and T₃ sympathetic ganglia during surgery caused marked increases in CFV,²⁹ which could have been due to vasoconstriction at the vessel of insonation or increases in CBF. Concurrent increases in MAP during stimulation may have augmented CBF through vessels with impaired autoregulation secondary to anesthetic effects on cerebrovascular control,^{30,31} resulting in increased CBF and CFV. Direct infusions of norepinephrine in both anesthetized³² and conscious³³ patients have not affected CFV, but cerebral vascular resistance was increased, possibly because of the myogenic constriction after the increase in systemic MAP.

In conscious humans, sympathetic activation during exercise increased CFV,^{34,35} whereas cold pressor tests both increased^{36,37} and decreased³⁸ CFV. Postexercise muscle ischemia did not change CFV.³⁴ It is difficult to interpret these results because MAP and sympathetic outflow increase concurrently. Thus, there may have been a baroreflex-mediated attenuation of sympathetic outflow.

To examine sympathetic effects on CFV without concurrent changes in MAP, we examined MCA diameters during LBNP, which has been used as a stimulus for baroreflex-mediated increases in peripheral sympathetic outflow.²¹ Lambert et al³⁹ demonstrated that increased spillover of norepinephrine from subcortical brain regions in healthy humans at rest was correlated with increased muscle sympathetic nerve activity, suggesting that cerebral and peripheral sympathetic activity increase similarly. In the present study, a 5% decrease in CFV was observed during -40 mm Hg LBNP, with no change in MAP. This reduction in CFV was less than the 15% to 22% reduction observed previously⁴⁰ but similar to the $\approx 4\%$ decrease in nonfainters at -40 mm Hg.⁴¹ The difference in values was likely due to different protocols with varying levels of LBNP and time of exposure in the different studies. Regardless, in the present study, this level of sympathetic stimulation that resulted in a small increase in cerebral vascular resistance did not alter the MCA diameters, suggesting that in humans, sympathetic effects on cerebrovascular control occur in vessels downstream from the MCA.

Accuracy of MRI

Our values of 2.51 ± 0.20 mm for the women and 2.54 ± 0.25 mm for the men are similar to the reported diameters from angiography of 3.05 ± 0.39 mm for women and 3.35 ± 0.43 mm for men.⁴² Our smaller values are in agreement with the finding that black blood images may underestimate the intraluminal diameters by a mean of 0.6 mm compared with conventional angiography in the aorta.⁴³ Magnetic resonance angiography has proven effective in detecting stenosis,^{44,45} with black blood imaging allowing for improved imaging of both vessel walls^{46,47} and complex geometry.⁴⁸

Although it is still unclear what the resolution of this imaging technique is, we believe that the resolution for the present study was greater than the single pixel size of 0.47 mm because of the interlacing of images. With this black blood technique, inaccuracy in diameter measurements could be accentuated by laminar flow and flow-related enhancement, pulsatility, and interobserver error. Although these factors may have affected the response of any single case, our data analysis approach served to reduce this variation. First, 5 independent measures of each image were determined and found not to be statistically different from each other. Furthermore, averaging of these multiple measures for each subject under each condition reduced the random error by a factor of \sqrt{n} . Second, we observed a very strong correlation between each subject's percent CFV and the corresponding percent CBF calculated from each individual's diameter and CFV value for each condition (see Figure 5). If individual diameter changes were large or inconsistent, then the correlation between CFV and CBF would be expected to be less

than that observed. The use of these analysis methods should have improved our ability to detect significant changes in MCA diameter.

Furthermore, if we assume that the changes in MFV were due solely to diameter changes and thus flow stayed constant, a dilation of 0.17 to 0.64 mm would have been necessary across subjects to account for the decrease in MFV of 32% during hypocapnia in the present study. Similarly, the MCA would have had to constrict by 0.41 to 0.64 mm across subjects to account for the increase in MFV during hypercapnia if total MCA flow had been maintained. Changes in MCA diameter on this order of magnitude should have been detectable, had they occurred.

Summary

The present data support the concept that in humans, moderate increases in sympathetic outflow by baroreflex disengagement or chemoreflex activation do not alter MCA diameter. With the lack of change in MCA diameter, changes in CFV closely follow changes in CBF. Thus, these data suggest that in conscious healthy humans, relative changes in CFV are a good reflection of changes in CBF. However, the effects of greater sympathetic activation or disease states on the velocity/flow relationship requires further study.

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