The relationship between cardiac output and dynamic cerebral autoregulation in humans

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1School of Engineering and Informatics and 2National Centre for Biomedical Engineering Science, National University of Ireland Galway, Galway, Ireland; 3Integrative Cerebral Hemodynamics Laboratory, Beth Israel Deaconess Medical Center, Boston, Massachusetts; 4University College Dublin, Dublin, Ireland; and 5Department of Neurology, Harvard Medical School, Boston, Massachusetts

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Deegan BM, Devine ER, Geraghty MC, Jones E, ÓLaighin G, Serrador JM. The relationship between cardiac output and dynamic cerebral autoregulation in humans. J Appl Physiol 109: 1424–1431, 2010. First published August 5, 2010; doi:10.1152/japplphysiol.01262.2009.— Cerebral autoregulation adjusts cerebrovascular resistance in the face of changing perfusion pressures to maintain relatively constant flow. Results from several studies suggest that cardiac output may also play a role. We tested the hypothesis that cerebral blood flow would autoregulate independent of changes in cardiac output. Transient systemic hypotension was induced by thigh-cuff deflation in 19 healthy volunteers (7 women) in both supine and seated positions. Mean arterial pressure (Finapres), cerebral blood flow (transcranial Doppler) in the anterior (ACA) and middle cerebral artery (MCA), beat-by-beat cardiac output (echocardiography), and end-tidal PCO2 were measured. Autoregulation was assessed using the autoregulatory index (ARI) defined by Tiecks et al. (Tiecks FP, Lam AM, Aaslid R, Newell DW. Stroke 26: 1014–1019, 1995). Cerebral autoregulation was better in the supine position in both the ACA [supine ARI: 5.0 ± 0.21 (mean ± SE), seated ARI: 3.9 ± 0.4, P = 0.01] and MCA (supine ARI: 5.0 ± 0.2, seated ARI: 3.8 ± 0.3, P = 0.004). In contrast, cardiac output responses were not different between positions and did not correlate with cerebral blood flow ARIs. In addition, women had better autoregulation in the ACA (P = 0.046), but not the MCA, despite having the same cardiac output response. These data demonstrate cardiac output does not appear to affect the dynamic cerebral autoregulatory response to sudden hypotension in healthy controls, regardless of posture. These results also highlighted the importance of considering sex when studying cerebral autoregulation.

cerebral blood flow; echocardiography; transcranial Doppler

CEREBRAL AUTOREGULATION, an intrinsic mechanism of the cerebrovasculature, maintains cerebral blood flow relatively constant over a wide range of blood pressures (24). Autoregulation is essential in postural changes, since the assumption of the upright posture causes both a transient drop in mean arterial pressure (MAP), associated with a reduction in thoracic blood volume, as well as a reduction in cerebral perfusion pressure, due to the hydrostatic gradient. In both cases, cerebral blood flow must be maintained in the face of reduced pressure.

While the mechanisms underlying cerebral autoregulation are not completely understood, they most likely are dependent on the interplay between myogenic mechanisms, the influence of perivascular nerves, and the vascular endothelium (24). Previous work demonstrates that cerebral vessels actively dilate during a sudden pressure drop, causing a return of cerebral blood flow to baseline levels before pressure increases (1, 27). Previous work has considered vessel wall stretch as the input stimulus for this vasodilatory response (34). However, the results of a number of studies have suggested that cardiac output (CO) may play a role in determining cerebral blood flow (14, 31, 32, 36).

To date, the relationship between CO and cerebral blood flow remains unclear. For example, increases in CO resulted in increased cerebral blood flow without changing MAP during hypervolemia (19) and during muscle tensing while standing (31). In contrast, Brown et al. (4) showed that lower body negative pressure (LBNP) caused a reduction of ~44% in CO at −50 mmHg of LBNP, whereas middle cerebral artery (MCA) flow velocity only decreased by ~19%. There was also a 6-Torr drop in end-tidal PCO2. As cerebral blood flow velocity (CBFV) changes by ~2–3%/mmHg, it is likely that the observed reduction in CBFV was related to the reduction in end-tidal PCO2, rather than the drop in CO. Similarly, Levine et al. (16) showed that the drop in MCA flow velocity was approximately one-half the drop in CO, although the change in end-tidal PCO2 was not reported. In both fulminant hepatic failure patients (15) and head-injured patients (3), cerebral blood flow was correlated with arterial pressure and not CO.

These data highlight the fact that it remains unclear what role changes in CO play in regulation of cerebral blood flow. Furthermore, no data have directly measured beat-by-beat changes in CO and cerebral blood flow to determine the role CO changes may play in dynamic autoregulation. To address this issue, we directly measured beat-by-beat stroke volume (SV) and CO using echocardiography during dynamic changes in cerebral perfusion pressure. We hypothesized that dynamic cerebral blood flow autoregulation is independent of changes in CO.

METHODS

Ethical approval. All testing was conducted in the Integrative Cerebral Hemodynamics Laboratory at Beth Israel Deaconess Medical Center, Boston, Massachusetts. The study was reviewed by the Beth Israel Deaconess Medical Center institutional review board and followed institutional guidelines in accordance with ethical guidelines established in the Declaration of Helsinki (1964). All subjects gave their informed, written consent before their inclusion in the study.

Subjects. Twenty-four subjects (10 women, 14 men) participated in this study. All subjects were screened with a medical history to exclude acute medical conditions, and with an electrocardiogram for arrhythmias. Subjects with a history of cardiovascular disease were excluded from the study. Subjects were also evaluated to ensure adequate transcranial Doppler insonation windows for the MCA and anterior cerebral arteries (ACA).

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Cardiac index (CI) and stroke index (SI) were calculated by dividing heart rate (HR) by the stroke volume (SV). The SV was determined by dividing baseline recording, bilateral thigh cuffs were inflated to 200 mmHg (suprasystolic pressure). Occlusion was maintained for 2 min, followed by a rapid deflation, which caused a transient drop in blood pressure. Subjects were allowed at least 5-min rest between thigh-cuff tests. Thigh-cuff tests that resulted in a 10-mmHg or greater decrease in MAP were used for analysis. Drops in MAP < 10 mmHg were not considered a sufficient stimulus to elicit an appropriate autoregulatory response. For CO analysis, the best echocardiography image for each subject in the supine and seated positions was selected for analysis. Beat-by-beat SV was determined during the 15 s before inflation (baseline), the last 15 s of inflation, and the 25 s following deflation.

Data processing. MAP, CBFV, ECG, and CO2 data were displayed and digitized in real time at 500 Hz using commercially available data-acquisition software (Powerlab, ADInstruments). Beat-to-beat R-R interval, arterial blood pressure, and cerebral blood flow were determined from the R wave of the ECG and the maximum and minimum of the arterial or CBFV waveforms. Blood pressure, CBFV, and CO2 waveforms were resampled at 1 Hz using MATLAB (MathWorks, Natick, MA).

For supine vs. seated differences, MAP, HR, end-tidal PCO2, and CBFV and autoregulatory index (ARI) values are presented as the average of three thigh-cuff responses in both supine and seated positions. For CO analysis, CO data were obtained from the highest quality echocardiography recording for one thigh-cuff release in each position, and all data presented are taken from this thigh-cuff test. To compare responses in each position, percent changes in CBFV and CVR were calculated as the difference between deflated and inflated values and normalized to supine baseline levels. Individual percent changes were then averaged to obtain percent changes in CBFV for supine and seated tests. Mean values for baseline (15 s starting 20 s before inflation), pre-thigh-cuff release (last 15 s of inflation), and post-thigh-cuff release (2–10 s following deflation) for all recorded variables were calculated. ARI was calculated based on a second-order differential equation, as defined by Tiecks et al. (27).

Statistical analysis. Cerebral autoregulation was assessed using 2 × 2 repeated-measures ANOVA with position (supine, seated) as the within-subjects factor, and sex (male, female) as the between-subjects factor. All data were tested for normality using the Shapiro–Wilks test, and equivalent nonparametric tests were used for nonnormal data. P values reported are for normal data, unless otherwise indicated. Linear regression was used to compute the relationships between SV, CO, ARI, and CBFV. All statistical analyses were performed using SPSS version 15 for Windows.

RESULTS

Baseline and demographic data for 19 subjects are shown in Table 1. Of the 24 subjects who were recruited for this study, 2 were not included for analysis because of poor MAP and CBFV data quality. Two subjects’ echocardiography video images were not of sufficient quality for analysis, and one subject withdrew consent before participation. Of the 19 remaining subjects, 11 subjects (6 men) performed supine and seated test, 7 (6 men) performed supine tests only, and 1 female subject performed the seated only. We were unable to acquire adequate echocardiography data for one subject while supine and one subject while seated. Therefore, we successfully gathered complete data for 17 subjects (11 men) in the supine position, and 11 subjects (6 men) in the seated position. Repeated-measures analysis showed that there was no effect of order on MAP drop, ARI response, or HR increase after thigh-cuff release.

CVRT. There was no significant difference between CVRT in the ACA and the MCA, and there was no effect of sex
(Table 1). Baseline supine flow velocity was higher for all subjects in the MCA than ACA (P < 0.001), and MCA flow was significantly higher in the women compared with the men (P < 0.001), while ACA flow did not differ significantly between sexes.

Thigh-cuff response. Figure 1 shows group mean averages for CBV, MAP, CO, HR, and end-tidal PCO₂ responses in the supine and seated position. Ten seconds of baseline data were taken from 20 s before thigh-cuff inflation (−140 to −130 s before deflation). ACA and MCA flow velocities are normalized to supine baseline (preinflation) levels. The cardiovascular response to thigh-cuff release is summarized in Table 2.

CO response. To determine whether or not SI or CI played a role in dynamic cerebral autoregulation, we performed regression analysis between the peak change in SI (ΔSI), CI (ΔCI), and ARI. ΔSI and ΔCI, respectively, were calculated as the difference between the highest SI and CI value 2–10 s post-thigh-cuff release and the average SI and CI in the last 15 s pre-thigh-cuff release.

As we only analyzed echocardiography for one thigh-cuff release per subject in the supine and seated positions, the ARI values in Fig. 2 are taken from the same thigh-cuff test. As two subjects had insufficient CBV data for ARI analysis during the corresponding thigh-cuff test, a total of 26 thigh-cuff tests (17 supine, 9 seated) are included for analysis. As can be seen in Fig. 2, there was no relationship between ΔSI or ΔCI and ARI (ΔSI vs. ACA ARI R²: supine = 0.031, seated = 0.020, combined = 0.041; MCA ARI R²: supine = 0.207, seated = 0.007, combined = 0.069; ΔCI vs. ACA ARI R²: supine = 0.002, seated = 0.004, combined = 0.025; MCA ARI R²: supine = 0.007, seated = 0.001, combined = 0.048).

Furthermore, we performed a median split on the subjects based on ΔCI (median: 0.92 l·min⁻¹·m⁻²), and compared cerebral blood flow responses between low ΔCI and high ΔCI groups. As can be seen in Fig. 3, despite the fact that the increase in CI was much higher in the high ΔCI group, there was no significant differences in cerebral blood flow response between the two groups (low ΔCI: ACA ARI = 5.17 ± 0.44, MCA ARI = 4.40 ± 0.50; high ΔCI: ACA ARI = 4.58 ± 0.51, MCA ARI = 4.23 ± 0.51).

We also divided the subjects based on the mean of their ACA and MCA ARI into low ARI and high ARI groups (Fig. 4). CI responses were virtually identical between low ARI and high ARI groups (low ARI peak ΔCI = 0.86 ± 0.12 l·min⁻¹·m⁻², high ARI peak ΔCI = 1.01 ± 0.15 l·min⁻¹·m⁻², P = 0.45), but the cerebral blood flow responses between the two groups were significantly different (low ARI: ACA = 3.8 ± 0.47, MCA = 3.3 ± 0.39; high ARI: ACA = 5.9 ± 0.22, MCA = 5.5 ± 1.31, P = 0.001). These results suggest that there is no relationship between beat-by-beat changes in CI and dynamic cerebral blood flow regulation.
Baseline, prerelease, and postrelease data

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Baseline, prerelease, and postrelease data</th>
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<tr>
<td></td>
<td>Baseline</td>
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<tr>
<td><strong>Supine</strong></td>
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<tr>
<td>ACA CBFV, %</td>
<td>100 ± 0</td>
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<tr>
<td>MCA CBFV, %</td>
<td>100 ± 0</td>
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<tr>
<td>MAP, mmHg</td>
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<tr>
<td>SI, ml/m²</td>
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<td>CI, 1·min⁻¹·m⁻²</td>
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<tr>
<td>HR, beats/min</td>
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<tr>
<td>Ejection fraction, %</td>
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<tr>
<td>TPR1, mmHg·ml⁻¹·s⁻¹·m⁻²</td>
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<td>End-tidal PCO₂, Torr</td>
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<td><strong>Seated</strong></td>
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<tr>
<td>ACA CBFV, %</td>
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<tr>
<td>MCA CBFV, %</td>
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<td>SI, ml/m²</td>
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<tr>
<td>CI, 1·min⁻¹·m⁻²</td>
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<tr>
<td>HR, beats/min</td>
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<tr>
<td>Ejection fraction, %</td>
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<tr>
<td>TPR1, mmHg·ml⁻¹·s⁻¹·m⁻²</td>
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<tr>
<td>End-tidal PCO₂, Torr</td>
<td>38.5 ± 0.8</td>
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Values are means ± SE for baseline (140–130 s before thigh-cuff inflation), prerelease (1–15 s before thigh-cuff release), and postrelease (2–10 s after thigh cuff release). Data are taken from subjects who completed both supine and seated testing (N = 11). Cardiac index (CI) and stroke index (SI) data are taken from one thigh-cuff release; all other variables are the average of three thigh-cuff releases. ACA CBFV and MCA CBFV are normalized values. MAP, mean arterial pressure; HR, heart rate; TPR1, total peripheral resistance index. Significant difference: *supine vs. seated, and †pre- or postrelease vs. baseline: P < 0.05.

Supine vs. seated thigh-cuff responses. We analyzed and compared the hemodynamic responses of the 11 subjects that had completed both supine and seated thigh-cuff testing. Cerebral autoregulation appeared to be less effective in the seated position in both the ACA (ΔARI = −1.3 ± 0.35, P < 0.001) and MCA (ΔARI = −1.2 ± 0.48, P = 0.015). When comparing the drop in cerebral flow following cuff deflation, flow drops were significantly greater during the seated vs. supine postrelease period in the ACA (−5.8 ± 2.2%, P = 0.011), but not in the MCA (−1.9 ± 1.6%, P = 0.233). CVR in both beds was lower while seated (ACA supine = 1.7 ± 0.13 mmHg·cm⁻¹·s⁻¹, seated = 1.44 ± 0.11 mmHg·cm⁻¹·s⁻¹, P = 0.15), but this difference only reached significance in the MCA.

Supine vs. seated. All data are taken from one thigh-cuff release per subject. Median ΔCI = +1.74 l/min. Values are means ± SE.

Supine vs. Seated.

Supine vs. seated. All data are taken from one thigh-cuff release per subject. Median ΔCI = +1.74 l/min. Values are means ± SE.
MAP also tended to reach lower values following cuff release when seated, although the mean decrease over 2–10 s was not significantly different ($P = 0.51$). The lower MAP values were not related to changes in CO (supine = 0.81 ± 0.22 l/min, seated = 0.80 ± 0.21 l/min, $P = 0.96$). In contrast, when comparing the change in HR during cuff inflation and post-cuff release, we found HRs were significantly higher when seated vs. supine (baseline = 93 ± 3.0 beats/min, $P = 0.003$, prerelease inflation = 4.9 ± 3.6 beats/min, $P = 0.17$, postrelease = 10.1 ± 3.4 beats/min, $P = 0.004$); however, the greater HRs were not great enough to result in a greater CO. Finally, the seated position had no effect on the decrease in CVR associated with cuff release and the associated drop in MAP ($\Delta$CVR supine = $-0.22 \pm 0.04$ mmHg·cm$^{-1}$·s$^{-1}$, seated = $-0.17 \pm 0.04$ mmHg·cm$^{-1}$·s$^{-1}$, $P = 0.28$; $\Delta$MCA CVR supine = $-0.15 \pm 0.02$ mmHg·cm$^{-1}$·s$^{-1}$, seated = $-0.16 \pm 0.02$ mmHg·cm$^{-1}$·s$^{-1}$, $P = 0.65$). End-tidal $P_{CO_2}$ was not significantly different between postures during thigh-cuff deflation and release.

**Effects of sex on response.** Women had significantly higher ARI values in the ACA than men (Fig. 5, Table 1), in both supine and seated tests ($P = 0.036$, Mann-Whitney U-test), but similar values in the MCA ($P = 0.92$, Mann-Whitney U-test). Assumption of the seated position resulted in a reduction in ARI values in both the ACA and MCA for both sexes. Consistent with ARI values, decreases in ACA flow were significantly greater in men than women when seated (women: $-9.2 \pm 2.2\%$, men: $-15.7 \pm 1.9\%$, $P < 0.05$); however, they were similar when supine (women: $-5.8 \pm 2.0\%$, men: $-6.9 \pm 1.4\%$). While flow drops were similar, women were able to maintain similar flow drops to men, despite a greater drop in MAP (supine: women $\Delta$MAP = 22.9 ± 1.5 mmHg, men $\Delta$MAP = 18.3 ± 1.1 mmHg, $P = 0.014$; upright: women $\Delta$MAP = 27.2 ± 2.1 mmHg, men $\Delta$MAP = 20.9 ± 1.2 mmHg, $P = 0.011$), suggesting improved autoregulation. In contrast, in the MCA, where ARI values were similar, there were no sex differences in MCA flow changes between seated and supine (supine: women = 6.5 ± 1.6%, men = 5.0 ± 1.2%; seated: women = 8.8 ± 1.7%, men = 8.7 ± 1.5%).

There were no sex differences in HR baseline levels or response to thigh-cuff release. While women had significantly lower SV (supine: women = 53.4 ± 4.4 ml, men = 74.7 ± 3.6 ml, $P < 0.001$), changes following cuff release were not significantly different between sexes. This same pattern was true for CO. Female subjects had lower baseline supine end-tidal $P_{CO_2}$ levels (women = 37.4 ± 0.5 Torr, men = 41.3 ± 0.5 Torr, $P < 0.001$). This pattern of greater hypocapnia was true during cuff inflation and release in women. However, end-tidal $P_{CO_2}$ did not change significantly pre- and post-thigh-cuff release in men or women (women: prerelease = 36.2 ± 0.6 Torr, postrelease = 35.6 ± 0.7 Torr, $P = 0.29$; men: prerelease = 40.7 ± 0.6 Torr, postrelease = 40.9 ± 0.7 Torr, $P = 0.23$). CVR was higher in men before and after thigh-cuff release in the ACA (prerelease: women: 1.55 ± 0.48 mmHg·cm$^{-1}$·s$^{-1}$, men: 1.82 ± 0.91 mmHg·cm$^{-1}$·s$^{-1}$, $P = 0.16$; postrelease: women: 1.44 ± 0.51 mmHg·cm$^{-1}$·s$^{-1}$, men: 1.80 ± 0.94 mmHg·cm$^{-1}$·s$^{-1}$, $P = 0.058$), and in the MCA (prerelease: women: 1.04 ± 0.29 mmHg·cm$^{-1}$·s$^{-1}$, men: 1.19 ± 0.32 mmHg·cm$^{-1}$·s$^{-1}$, $P = 0.025$; postrelease: women: 0.96 ± 0.30 mmHg·cm$^{-1}$·s$^{-1}$, men: 1.12 ± 0.29 mmHg·cm$^{-1}$·s$^{-1}$, $P = 0.011$).

**DISCUSSION**

This study provides three main findings: 1) beat-by-beat changes in CO and SV do not correspond with dynamic changes in CBFV following thigh-cuff release; 2) cerebral autoregulation is less effective in the seated posture; and 3) women have better autoregulation in the ACA than men, but similar autoregulation in the MCA. To our knowledge, this is the first study to directly measure beat-by-beat changes in CO during dynamic cerebral autoregulation. Our results suggest there is no relationship between CO and dynamic cerebral autoregulation in healthy subjects during supine or seated thigh-cuff testing.

**Relationship between CO and dynamic cerebral autoregulation.** Our finding that changes in CO did not affect ARI is supported by the results of Guo et al. (8), who performed thigh-cuff testing during resting conditions and during LBPN up to $-40$ mmHg. Their results showed that, after thigh-cuff release, the magnitude of MCA CBFV drop, the time to nadir, and time to recovery to baseline levels were not significantly affected by LBPN-induced systemic hypovolemia. Ogoh et al. (22) evaluated the influence of CO variability on beat-to-beat MCA CBFV during exercise and found that cardiac-arterial baroreflex function does not influence dynamic control of MCA CBFV, even when the ability of exercise-induced increase in CO is reduced by cardiac $\beta_1$-adrenergic blockade. In contrast, in a recent study by Ogoh et al. (23), the authors stated that dynamic CA is impaired at time 1–3.5 s post-thigh-cuff release when complete autonomic blockade reduced the tachycardic response to pressure drops. This would suggest that the dynamic CBFV response to pressure change reflects an integrated response between the baroreflex-mediated changes in CO and dynamic adjustments in CVR. However, recent work by the
same authors (30) showed an inverse relationship between baroreflex sensitivity and dynamic cerebral autoregulation during thigh-cuff release. If the baroreflex-mediated increase in CO affected the CBFV response in an additive fashion with changes during cycling exercise are correlated with MCA flow velocity.

In atrial fibrillation patients, it has been reported that CO changes during cycling exercise are correlated with MCA flow velocity ($r^2 = 0.55, P < 0.01$) (11). However, greater increases in flow velocity in the patients during cycling were again related to increases in both CO and MAP. In septic patients, common carotid blood flow was related to CI, independent of MAP, arterial PCO2, or PO2; however, the effect of sepsis on arterial reactivity was not examined (26). In addition, the external vs. internal carotid blood flow in the response remains unclear. Thus previous data demonstrating changes in CO and cerebral blood flow have also demonstrated concurrent changes in arterial pressure, making it difficult to interpret the cause of cerebral blood flow changes.

One possible explanation for these findings is that, without adequate CO, static autoregulation is impaired, and thus blood pressure changes result in associated cerebral blood flow changes. However, if this were the case, then we would expect that, when CO was high before β-blockade, there would be no associated change in CBF because of static autoregulation. However, in fact, there was an increase in CBF that was attenuated by reducing CO, suggesting a direct effect of CO on CBF.

Do CO changes affect cerebral blood flow independent of cerebral autoregulation? For CO to have a direct effect on CBF, independent of autoregulation, changes in CO should cause changes in CBF without any associated change in MAP. Thus autoregulation is not activated, and the CBF change is related to CO changes. Support for this comes from Van Lieshout et al. (31), who reported that leg muscle tensing during standing increased central venous pressure, CO, and MCA cerebral blood flow, with no significant effect on blood pressure in healthy subjects. Similarly, increases in CO by saline infusion caused increased cerebral blood flow without changing MAP during hypervolemia (19). Ogoh et al. (20) examined the relationship between CO and cerebral blood flow during reduced (LBNP) and increased (albumin infusion) CO levels at rest and exercise. Their data demonstrated a linear relationship between CO and cerebral blood flow during rest and exercise with no concurrent changes in arterial PCO2 or MAP.

In contrast, studies examining cerebral blood flow and CO during LBNP have found that significant decreases in CO did not produce changes in cerebral blood flow (4, 16). In addition, skin cooling, which does not affect CO, increases MAP during tilt and improves cerebral blood flow (36). These data suggest that CO plays a minimal role in cerebral blood flow changes in healthy subjects.

Examination of patient populations shows similar results. Changes in CO in fulminant hepatic liver failure did not affect cerebral blood flow (15). Eicke et al. (6) found no association between internal carotid artery blood flow and CO in cardiac patients with a wide range of CO levels. Bouma and Muijzelaar (3) found no relationship between CO and cerebral blood flow in head-injured patients. Thus data in patient populations have also found a limited role for CO.

Immink et al. (13) performed head upright tilt testing with and without end-tidal PCO2 clamped at the supine level. Their results showed that the end-tidal PCO2 contribution to the postural reduction in MCA CBFV is transient, and that, after 2 min in the upright position, there was no difference in the postural drop in MCA CBFV between spontaneous breathing and clamped end-tidal PCO2 conditions. The authors suggest that the postural reduction in MCA CBFV is due to the postural reduction in CO. However, during the tilt, CO response was unchanged by end-tidal PCO2 clamping during the first minute of head-up tilt, but MCA CBFV was higher. This would suggest that there is not a direct relationship between CO and CBFV.

It remains unclear why previous studies investigating the effects of CO on cerebral flow have reported conflicting results. One possibility is that CO and cerebral blood flow are only related when autoregulation is impaired. In our work, we found no relationship between ARI and/or CO response, suggesting that autoregulatory state was not important; however, all of our subjects demonstrated intact autoregulation. Consistent with this, previous work in head-injured patients found there was no relationship between CO and cerebral blood flow, regardless of impairment of autoregulation (3). In contrast, studies in animal models have shown that monkeys with focal cerebral ischemia show changes in cerebral blood flow related to CO changes in the ischemic regions, with impaired autoregulation, but not the nonischemic areas (29). Thus previous data in humans, as opposed to animals, suggest that impaired autoregulation does not result in a dependence of cerebral blood flow on CO changes.

Effect of posture on dynamic cerebral autoregulation. Our second finding is that autoregulatory responses were worse in the seated position in both the ACA and MCA. One possible reason could be that the hydrostatic gradient when seated causes a reduction in cerebral perfusion pressure. To compensate for this drop, cerebral vessels dilate, reducing CVR. Consistent with this theory, our subjects had lower CVR in the seated position both before and following cuff release. Aaslid et al. (1) have shown that the rate of cerebral autoregulation is dependent on vascular tone, and that the autoregulatory response rate was slower when cerebral vessels were dilated. We have also previously shown that transfer function gain was...
higher in subjects with low CVR, suggesting that autoregulation is impaired when cerebral vessels are dilated (25). Thus our subjects likely had dilated cerebral vessels while seated and thus a slower autoregulatory response resulting in lower ARI.

Another possible explanation is that a rightward shift in the cerebral autoregulatory curve causes the pressure drop following cuff release to fall below the lower limits of autoregulation, where cerebral blood flow passively follows MAP. It has been suggested that sympathoexcitation causes a rightward shift in the autoregulatory curve (8, 24, 37). Since our subjects demonstrated a greater HR when seated, this would suggest increased sympathetic activity. However, increased sympathetic tone would theoretically cause constriction in cerebral vessels, increasing CVR. In contrast, we observed a reduction in CVR during seated testing, implying dilation of cerebral vessels. Zhang and Levine (37) reported that autonomic blockade did not prevent the reduction in CBFV during LBNP, suggesting that sympathetic activity does not play an obligatory role in reducing cerebral blood flow. We, therefore, believe that the impaired autoregulation observed in seated thigh-cuff testing is a result of the cerebral vasodilation associated with reduced cerebral perfusion pressure, due to the hydrostatic gradient, resulting in a reduction in the autoregulatory response rate.

Sex differences in regional dynamic autoregulatory response. Finally, we found significant sex differences in autoregulatory responses in the two cerebral arterial beds measured. Female subjects had higher ARI values in the ACA than the male subjects, but similar values in the MCA. The female subjects in this study did have lower baseline end-tidal PCO$_2$ levels. Hypocapnia has been shown to cause improved autoregulatory response (1) and may partially explain the sex-based autoregulatory findings in this study. However, CVR was higher in men than in women during thigh-cuff testing. It is, therefore, unlikely that the sex differences in autoregulation were related to hypocapnia. Also, hypocapnia would not explain the regional autoregulatory differences between ACA and MCA. Previous work suggests that women have significantly greater global cerebral blood flow than men (9). In recent data, there were no differences in MCA and basilar artery autoregulation in young children (4–8 yr) (28), but better autoregulation in the basilar artery and impaired autoregulation in the MCA in young females (10–16 yr) (33). Consistent with this, Wang et al. (35) found that adult women had higher MCA transfer function gains when supine, suggesting impaired autoregulation. It remains unclear why our data conflict with previous data. These data highlight the need for future work to examine sex differences in various cerebral arterial beds to better understand the underlying autoregulatory differences.

Conclusion. In summary, dynamic cerebral autoregulatory responses to sudden pressure changes in healthy subjects appear not to be associated with changes in CO. It also appears that cerebral autoregulation is less effective during seated thigh-cuff testing, suggesting dilation of cerebral vessels to compensate for reduced cerebral perfusion pressure in the seated posture. Finally, women had better autoregulation in the ACA than male subjects, whereas there was no significant difference in autoregulation in the MCA.

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DISCLOSURES

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