Cerebral autoregulation (CA) is a critical process for the maintenance of cerebral blood flow and oxygenation. Assessment of CA is frequently used for experimental research and in the diagnosis, monitoring, or prognosis of cerebrovascular disease; however, despite the extensive use and reference to static CA, a valid quantification of “normal” CA has not been clearly identified. While controlling for the influence of arterial PCO2, we provide the first clear examination of static CA in healthy humans over a wide range of blood pressure. In 11 healthy humans, beat-to-beat blood pressure (radial arterial), middle cerebral artery blood velocity (MCAv; transcranial Doppler ultrasound), end-tidal PCO2, and cerebral oxygenation (near infrared spectroscopy) were recorded continuously during pharmacological-induced changes in mean blood pressure. In a randomized order, steady-state decreases and increases in mean blood pressure (8 to 14 levels; range: ∼40 to ∼125 mm Hg) were achieved using intravenous infusions of sodium nitroprusside or phenylephrine, respectively. MCAvmean was altered by 0.82±0.35% per millimeter of mercury change in mean blood pressure (R²=0.82). Changes in cortical oxygenation index were inversely related to changes in mean blood pressure (slope=−0.18%/mm Hg; R²=0.60) and MCAvmean (slope=−0.26%/cm · s⁻¹; R²=0.54). There was a progressive increase in MCAv pulsatility with hypotension. These findings indicate that cerebral blood flow closely follows pharmacological-induced changes in blood pressure in otherwise healthy humans. Thus, a finite slope of the plateau region does not necessarily imply a defective CA. Moreover, with progressive hypotension and hypertension there are differential changes in cerebral oxygenation and MCAvmean. (Hypertension. 2010;55:698-705.)

Key Words: cerebral blood flow ■ blood pressure ■ cerebral oxygenation ■ cerebral autoregulation ■ pulsatility

Cerebral autoregulation (CA) adjusts cerebrovascular resistance to ensure that cerebral blood flow (CBF) levels are matched to metabolic needs; it is composed of 2 main components: static and dynamic.1 “Static CA” regulates CBF over gradual and progressive changes in cerebral perfusion pressure,2 whereas dynamic CA refers to the rapid regulation of CBF in response to changes in arterial blood pressure that occur across a few seconds (<5 s).3 Assessment of CA is used as a critical tool for diagnosis, monitoring, or prognosis of cerebrovascular disease. The use of static and dynamic CA has been extensively validated to show that it is a highly sensitive and reliable index of a threatened cerebral circulation.4

In 1959, Lassen5 established that CBF in humans is independent of changes in mean arterial blood pressure (MAP) within a range of ∼60 to 150 mm Hg; and this has become the traditionally accepted model for static CA (as illustrated in Figure 1). However, this so-called autoregulatory curve relating CBF and MAP was based on steady-state data points from a cohort of different subjects with and without pathology and included subjects premedicated with drugs now known to directly affect CBF regulation (as reviewed in Reference 4). Interestingly, Heistad and Kontos,6 in 1983, performed a more accurate reanalysis of Lassen’s5 data by excluding some of these problematic groups. This reanalysis showed that CBF decreased 2% to 7% per 10-mm Hg fall in MAP and increased 7% per 10-mm Hg rise in MAP, challenging the notion that CBF is invariant to changes in MAP across the autoregulatory range. Unfortunately, this report, which is often overlooked in the literature, still deals with an ensemble of data taken from different subjects. Therefore, the CA curve remains to be clearly shown within healthy volunteers.

Impaired static CA, with loss of the more-or-less zero-slope MAP versus CBF relationship, has been reported in ischemic stroke,7 in severe head injury,8 after cardiac arrest,9 and in patients with malignant hypertension.10 Although the majority of these studies did not include a healthy age group
Manipulations. Because changes in arterial PCO₂ have a hypotensive effect, reductions in arterial PCO₂ of 8-10 mm Hg (lower limit) or >150 mm Hg (upper limit).

Once the limits of autoregulation are reached, cerebrovascular resistance over a wide range of perfusion pressures. (the so-called autoregulatory plateau) via changes in cerebrovascular resistance cannot correct for further changes in pressure, and the brain becomes "pressure passive," as represented by the linear portion of the curve <60 mm Hg (lower limit) or >150 mm Hg (upper limit).

for comparison, they indicated that CA was impaired because of the relatively high slope of the MAP versus CBF relationship. Moreover, in all studies, the confounding influence of arterial PCO₂ was not controlled for during blood pressure manipulations. Because changes in arterial PCO₂ have a profound independent effect on CBF, it not clear whether the changes in CBF were determined by the blood pressure, per se, or by concomitant changes in arterial PCO₂. This is an important consideration because, at least during orthostatic hypotension, reductions in arterial PCO₂ of 8-10 mm Hg account for 25% of the reduction in CBF velocity. Thus, despite the extensive use and reference to static CA, quantification of CA has not been clearly identified for human experimentation. In addition, near infrared spectroscopy (NIRS) for the monitoring of local cerebral oxygenation has been used in the clinical assessment of CA, in addition to the assessment of cerebral ischemia. The use of NIRS is attractive because it is noninvasive, does not require frequent calibration, is robust, and, unlike transcranial Doppler, the problem of a constant and precise location of the probes is of less of an issue. Recently, Brassard et al have published data on cerebral oxygenation responses using NIRS during norepinephrine-induced hypertension in healthy subjects. These authors reported that progressive increases in MAP resulted in elevations in cerebral oxygenation and reductions in CBF velocity. However, the use of norepinephrine to increase MAP confounds the hemodynamic responses in the cerebrovascular system because it is a vasoactive agent that alters CBF independent of its effect on MAP. Furthermore, because a decrease in arterial PCO₂ induces a 2% to 3% decline in CBF velocity per millimeter of mercury, the observed decline in CBF velocity was also likely influenced by the reported decrease in arterial PCO₂. Therefore, the main aim of this current study, while controlling for the influence of arterial PCO₂, was to provide the first clear examination of static CA in healthy humans over a wide range of blood pressures.

Methods

Subjects
Eleven healthy individuals (1 women, subject 1; Table), age 27±7 years, height 179±9 cm, weight 73±8 kg (mean±SD) were recruited to participate in the study, which was approved by the Central Regional Ethics Committee and conformed to the standards set by the Declaration of Helsinki. Subjects were informed of the experimental procedures and possible risks involved in the study, and written informed consent was obtained. Subjects were not taking any medication, all were nonsmokers, and none had any history of cardiovascular, cerebrovascular, or respiratory disease.

Table. Linear Regression Analyses of the Relationship Between the Change in Cerebral Blood Flow (MCAvmean) and Cortical Oxygenation (Cox) as a Function of Change in Blood Pressure (MAP) for Each Subject During Pharmacological-Induced Alterations in MAP

<table>
<thead>
<tr>
<th>Subject</th>
<th>MCAvmean, AbsOLUTE, cm · s⁻¹/mm Hg</th>
<th>Relative, %/mm Hg</th>
<th>Pearson Correlation (r)</th>
<th>P</th>
<th>Cox vs MAP, %/mm Hg</th>
<th>Pearson Correlation (r)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.78</td>
<td>0.86</td>
<td>0.99</td>
<td>&lt;0.01</td>
<td>-0.13</td>
<td>-0.71</td>
<td>0.11</td>
</tr>
<tr>
<td>2</td>
<td>0.38</td>
<td>0.70</td>
<td>0.93</td>
<td>&lt;0.01</td>
<td>-0.08</td>
<td>-0.76</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.32</td>
<td>0.51</td>
<td>0.59</td>
<td>&lt;0.01</td>
<td>-0.33</td>
<td>-0.85</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>4</td>
<td>0.20</td>
<td>0.50</td>
<td>0.94</td>
<td>&lt;0.01</td>
<td>-0.10</td>
<td>-0.95</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>5</td>
<td>0.43</td>
<td>0.62</td>
<td>0.97</td>
<td>&lt;0.01</td>
<td>-0.09</td>
<td>-0.87</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>6</td>
<td>0.75</td>
<td>0.83</td>
<td>0.88</td>
<td>&lt;0.01</td>
<td>-0.08</td>
<td>-0.74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>7</td>
<td>0.55</td>
<td>0.70</td>
<td>0.95</td>
<td>&lt;0.01</td>
<td>-0.24</td>
<td>-0.98</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>8</td>
<td>0.44</td>
<td>0.61</td>
<td>0.91</td>
<td>&lt;0.01</td>
<td>-0.03</td>
<td>-0.62</td>
<td>0.14</td>
</tr>
<tr>
<td>9</td>
<td>1.00</td>
<td>1.74</td>
<td>0.98</td>
<td>&lt;0.01</td>
<td>-0.33</td>
<td>-0.88</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>10</td>
<td>0.71</td>
<td>1.12</td>
<td>0.91</td>
<td>&lt;0.01</td>
<td>-0.40</td>
<td>-0.98</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>11</td>
<td>0.54</td>
<td>0.86</td>
<td>0.80</td>
<td>0.02</td>
<td>-0.16</td>
<td>-0.73</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean</td>
<td>0.55</td>
<td>0.82</td>
<td>0.89</td>
<td>(SD) 0.24</td>
<td>0.35</td>
<td>(SD) 0.11</td>
<td>(SD) 0.12</td>
</tr>
</tbody>
</table>
Experimental Design

After full familiarization (excluding cannulation) of each subject to the experimental protocol (>1 week previous), subjects arrived at the laboratory having abstained from caffeinated beverages for 12 hours and strenuous physical activity and alcohol for ≥24 hours before the day of the experiment.

Measurements of Arterial Blood Pressure, CBF Velocity, and Oxygenation

After local anesthesia (1% lidocaine), a 20-gauge catheter (BD Insite) was placed into the radial artery and attached to a pressure transducer (Deltran II, Utah Medical Products Ltd) positioned at the level of the right atrium in the midaxillary line for the measurement of beat-to-beat arterial blood pressure. After cannulation, subjects rested quietly in the supine position, breathing room air, for ≥20 minutes to allow the setup of monitoring equipment, which included calibration of this pressure transducer. Blood flow velocity in the right middle cerebral artery was measured using a 2-MHz pulsed Doppler ultrasound system (DVL Doppler) using search and fixation techniques described elsewhere. The use of transtraceral Doppler ultrasound for the noninvasive assessment of CBF during profound pharmacological-induced changes in MAP has been validated previously. Beat-to-beat arterial blood pressure and heart rate were also monitored using finger photoplethysmography (Finometer, TPD Biomedical Instrumentation) and ECG, respectively. For comparison, MAP/MCAvmean. However, CVCi (flow/pressure) was also calculated as CVCi = MCAvmean/MAP, because this index better reflects regional vascular tone under situations where changes in tone lead to changes in flow. As used previously, the Gosling pulsatility index for MCAv was calculated by: MCAv = MCAvmean − MCAvdiastolic/MCAvmean. Frontal cortical oxygenation was monitored noninvasively on the right side of the forehead using NIRS (NIRO-200, Hamamatsu Photonics KK). For details on this measure, please see the online Data Supplement (available at http://hyper.ahajournals.org). All of the data were acquired continuously at 200 Hz using an analog-to-digital converter (Powerlab/16SP ML795, ADInstruments) interfaced with a computer and were subsequently analyzed using commercially available software (Chart version 5.6, ADInstruments).

Measurements and Control of Respiratory Gas Exchange

Subjects were instructed to breathe at the same rate and depth during the drug infusions, and, if needed, to adjust their baseline tidal volume level to maintain end-tidal PCO2 close to baseline level. For details on this measure, please see the online Data Supplement.

Pharmacological-Induced Alterations in MAP

Steady-state testing of CA was achieved by stepwise lowering and increasing of MAP in ~10-mm Hg increments via intravenous infusion of sodium nitroprusside and phenylephrine hydrochloride (for details on this measure please see the online Data Supplement). Each step was held relatively constant for 30 to 90 s. The drug order was randomly assigned, and subjects rested for >10 minutes between drug interventions to ensure adequate washout and return to baseline MAP. Throughout the test protocol, the online intra-arterial blood pressure and ECG waveform morphology were closely monitored. Studies were terminated if cardiac effects associated with either drug infusion were identified on the ECG or if subjects developed symptoms or signs of intolerance. Therefore, although we aimed for 6 to 7 steps of pressure change, either side of baseline within each subject, this was not achieved in all of the individuals.

Calculations

Static CA was calculated using linear regression to calculate the slope, correlation coefficient (r) and determination (R²), and significance value between MCAv and MAP. With this method, if the slope is = 0, it can be assumed that the linear regression coincides with the plateau region of a normal autoregulatory curve. If the slope is significantly positive, this can either represent the linear portion of the curve below its lower limit (Figure 1) or the central region of the curve when autoregulation is impaired (eg, >0.5% to 3.0% increase in MCAv per millimeter of mercury change in MAP or when r>0.52).

Statistical Analysis

Data were analyzed using SPSS (version 15, SPSS Inc). A repeated-measures design was used with changes in dependent variables compared with the preceding baseline. To enable comparisons with other studies and to reduce interindividual variability unrelated to the experimental manipulation, dependent variables of interest were analyzed as a linear function of change in MAP, with comparison of slopes between hypotension and hypertension undertaken using a paired-sample t test. Average change in MCAv and CVR within each 10-mm Hg step in MAP from baseline was used to show the average group changes for these dependent variables across the range of MAP (Figure 2). Pearson correlations were used to examine the relationships between the change in MAP with MCAvmean and cortical oxygenation for each subject (Table). For the pooled data, within-subject correlation coefficients using a multiple regression were used to examine the change in MAP with MCAvmean and cortical oxygenation, using the method described by Bland and Altman (Figure 3). All of the group data are expressed as mean ± SD. Significance was established at an α level of P<0.05.

Results

On average, although tidal volume and breathing frequency were maintained, MCAvmean changed 0.82 ± 0.35% per millimeter of mercury change in MAP (Table). There was no difference between the slopes for hypotension and hypertension for MCAvmean versus MAP and cortical oxygenation versus MAP (all P>0.05); therefore, these data were pooled across the range of MAP for each subject (Table). On the basis of the pooled group data (117 measurement points, excluding baselines), the relative changes in MCAvmean CVR and CVCi are illustrated in Figure 2. Compared with baseline, the relative and absolute change in MCAvmean were positively related (slope = 0.82% · mm Hg⁻¹, R² = 0.82 and slope = 0.55 cm · s⁻¹ · mm Hg⁻¹, R² = 0.77, respectively) to the change in MAP (both P<0.01; Figure 3B). Changes in cortical oxygenation were inversely related to changes in MAP (slope = −0.18% · mm Hg⁻¹, R² = 0.60, Figure 3A) and MCAvmean (slope = −0.26% · cm · s⁻¹, R² = 0.54; Figure 3C). Hypotension caused a larger fall in MCAvmean than in MCAvmean, whereas during hypertension they increased similarly (Figure 2A); these differences are reflected by the differential MCAv pulsatility responses between hypotension and hypertension (Figure 2C).

Discussion

This is the first study to report the systemic changes in MCAv and cerebral oxygenation over a wide range of pharmacologically induced alterations in MAP in otherwise healthy
The major new findings are as follows: (1) there is a relative “pressure-passive” relationship in otherwise healthy humans during pharmacological-induced changes in MAP; (2) progressive hypotension and hypertension were associated with differential changes in cerebral oxygenation and MCAvmean; and (3) during hypotension, but not hypertension, despite a preferential decrease in MCAvdiastolic, MCAvsystolic was well maintained, that is, pulsatility of MCAv was elevated. Collectively, our findings indicate that CBF and oxygenation are not independent of changes in blood pressure; therefore, a paradigm shift in the concept of CA is required. Before we discuss the theoretical and physiological implications of our findings, several methodological aspects of the study require comment.

![Figure 2. Cerebral hemodynamic responses to sodium nitroprusside and phenylephrine. Averaged changes in cerebral blood flow (MCAvmean; A), cerebral vascular resistance and conductance (CVR/CVC; B), and MCAv pulsatility index (MCAvsystolic/MCAvmean; C) of 11 subjects during alterations in MAP induced by sodium nitroprusside and phenylephrine. These data show a pressure-passive relationship for CBF across a wide range of blood pressure, despite directional changes in CVR in an attempt to regulate CBF.](http://hyper.ahajournals.org/)

![Figure 3. Pooled data (117 points) of absolute changes from baseline for cortical oxygenation (A) and cerebral blood flow (MCAvmean; B) as a function of change in MAP from baseline (millimeters of mercury), and relationship between absolute changes in MCAvmean and cortical oxygenation (C) during pharmacological-induced changes in blood pressure.](http://hyper.ahajournals.org/)
Methodological Considerations

There are two main technological considerations that merit clarification. First, changes in MCAv reflect changes in flow, provided MCA diameter remains constant; therefore, an important consideration is whether the pharmacological agents used to manipulate MAP could interfere with the CA adjustments via direct vasodilatory (ie, sodium nitroprusside) or vasoconstrictive (ie, phenylephrine) effects on the MCA or cerebral resistance vessels. Direct observations made during craniotomy have revealed that sodium nitroprusside does not affect the vessel diameter of the MCA. In addition, constancy of MCA diameter has been demonstrated for a range of blood pressures. Both human and animal studies indicate that phenylephrine has no relevant vasoconstrictive of cerebral vasculature. Furthermore, intravenous infusion of phenylephrine increases arterial pressure acutely but is unlikely to have a direct effect on the cerebral blood vessels, because it does not pass the blood–brain barrier, and the density of $\alpha_1$-adrenoreceptors in the cerebral blood vessels is likely to be low in humans. It is acknowledged that a disruption of the blood–brain barrier can occur with hypertension. However, the evidence for this is largely from animal studies that have induced extreme levels of hypertension (eg, MAP > 180 mm Hg) that scarcely resemble the conditions of this study. Admittedly, a change in the vascular resistance of the smaller arterioles in the cerebral vasculature may have occurred during our drug infusions; however, any effect of sodium nitroprusside on downstream (distal) vascular resistance should be one of augmenting CBF, not inhibiting it. Likewise, any $\alpha$ agonist activity with phenylephrine would reduce CBF rather than increase it. Therefore, in the current study, we consider that changes in MCAv were proportional to those in blood flow; any direct effect of sodium nitroprusside or phenylephrine on downstream vascular resistance would actually favor the plateau phenomenon of CA rather than the pressure-passive relationship observed in the current study. Second, the advantages and limitations of NIRS have been well described and validated against multiple experimental and imaging modalities.

Comparison With Previous Studies

The origin of the autoregulation curve is usually attributed to Lassen in 1990. What is not commonly appreciated is that Lassen plotted the results from multiple studies on a single graph and interpolated the data points to show a plateau region that appeared perfectly flat, suggesting that CBF was held constant for changes in MAP in the range $\approx 60$ to 150 mm Hg. Collectively, these 2 studies have been cited $> 1500$ times, with Lassen’s review cited $> 1000$ times alone. However, this so-called autoregulatory curve between CBF and MAP was based on steady-state CBF data points from a cohort of different subjects with and without pathology and included subjects premedicated with drugs now known to directly affect CBF regulation (as reviewed in Reference 4). An important, yet often overlooked, reanalysis of the data presented by Lassen was published by Heistad and Kontos in 1983, which, with the exclusion of some of these problematic groups, reported a 2% to 7% decrease in CBF per 10-mm Hg fall in MAP and a 7% increase in CBF per 10-mm Hg rise in MAP. Even so, the diagrammatic representation that these authors use to illustrate the relationship between CBF and perfusion pressure still shows a plateau-like portion in the curve, and, surprisingly, Heistad in a later publication suggested that, “CBF is regulated at or near control levels over a wide range of systemic pressure” (p 10). In comparison, our data indicate that CBF is regulated at or near control levels over a wide range of systemic pressure across both hypotension and hypertension. Therefore, our findings indicate an even more marked positive slope of the MAP-CBF relationship, using dynamic measurement technology (ie, transcranial Doppler) compared with that described by Heistad and Kontos from studies using the classic steady state Kety-Schmidt method and, importantly, for the first time, this was observed within the same individuals. It should also be noted that these previous studies did not provide information on the serial changes in CBF over a wide range of blood pressure and did not control for the confounding influence of $\mathrm{PACO}_2$. At least during orthostatic-induced hypotension, reductions in arterial $\mathrm{PCO}_2$ of $\approx 8$ mm Hg account for $\approx 25$% of the reduction in CBF velocity; therefore, if comparable changes occurred during the pharmacological-induced hypotension, it is conceivable that our findings are an underestimation of what would occur during uncontrolled, nonexperimental situations. Thus, this is further evidence that the plateau region of the CA curve is not valid for healthy subjects.

The concept that the plateau region has a slope of zero has had considerable influence on the static assessment of CA in physiological and clinical studies. Our findings clearly show that, at least in healthy humans, the slope between CBF and MAP is relatively linear (Table; compare Figure 1 with Figure 2). This finding is consistent with the view shared by a number of authors who are also cognizant of the limitations of Lassen’s original analysis. Moreover, consistent with our findings, mathematical models also indicate that perfect CA (ie, flat plateau) would require feedback gains much greater than those normally observed in biological systems. Our data provide evidence that a finite slope of the plateau region does not necessarily imply defective autoregulation.

We found that the degree of relative change in MCAv after change in MAP is 0.82% per millimeter of mercury change in MAP. The key question arises: how do these changes compare with those reported in pathological studies, which are suggested to represent “impairment” in CA? Previously, using transcranial Doppler, values between 0.5% and 3.0% per millimeter of mercury change in MAP have been proposed as thresholds for an impaired autoregulation (reviewed in Reference 4). More recently, in patients with malignant hypertension, the slope of reduction in MCAv with MAP was shown to be smaller with labetalol than with sodium nitroprusside (0.45% versus 0.78% cm$^{-1}$ mm Hg$^{-1}$). Unfortunately, data for a control group were not reported. Impaired CA, with loss of the more-or-less zero-slope MAP-MCAv relationship, has also been reported in ischemic stroke, in severe head injury, after cardiac arrest, and in patients with malignant hypertension. The same
comparison exists with investigators performing linear regression analysis, adopting the correlation coefficient ($r$) as a measure of CA.$^{13,47}$ Although the majority of these studies did not include a healthy age group for comparison, they nevertheless concluded that CA was impaired because of the relatively high correlation coefficient of the MAP versus CBF relationship. The findings of the present study, on the basis of otherwise healthy humans, indicate that neither a high linear regression slope nor a correlation coefficient between alterations in CBF with MAP necessarily imply a defective CA.

The data in the Table illustrate the presence of between-individual variability for the CA response in our healthy participants. Maintenance of adequate cerebral perfusion during normal physiological challenges, such as assumption of upright posture from a supine, squatting, or sitting position, requires the integrated control of CBF and systemic blood pressure via CA and the arterial baroreflex.$^{48}$ In our experimental design, we effectively override the input from one of these components (ie, the baroreflex) by pharmacologically maintaining an increased or decreased MAP. Although speculative, it would seem possible that some of the variation in the CA response between participants could be explained by between-individual variability in the CA-baroreflex relationship; that is, those with a greater input from the baroreflex under “normal conditions” would show the greater reductions in CA in this experimental setting. Our future work is aimed at examining the fundamental relationships between baroreflex and CA.

Regional Differences in MCAv and Cerebral Oxygenation

An unexpected finding was that, whereas MCAv$_{\text{mean}}$ was progressively reduced with hypotension, cerebral oxygenation was elevated (Figure 3C). Our correlative ($R^2$) data identify that the relationship between cerebral oxygenation and MAP explains 60% of the variance and that between cerebral oxygenation and MCAv$_{\text{mean}}$ explains 54% of the variance. With hypertension, the opposite response occurred; that is, the elevations in CBF were associated with marked elevations in MCAv$_{\text{mean}}$ and significant reduction in cortical oxygenation (Figure 3A and 3B). Moreover, with progressive hypertension, the relationship between MCAv$_{\text{mean}}$ and cerebral oxygenation appears reduced (Figure 3C). The extent to which these findings are explained by the pressure and flow-sensitive changes of simple extracranial-intracranial collaterals or changes in sympathetic nerve activity distal to the MCA warrants future study. Regardless of the mechanism(s), which cannot be determined from our data, the reduction in cerebral oxygenation during hypertension is particularly noteworthy, because it was reduced by $\sim14\%$ during the higher range of MAP (Figure 3A); this reduction approximates the $\sim13\%$ estimated in a recent study as the "threshold" for cerebral ischemia.$^{13}$ The clinical relevance of these findings is that, with progressive hypertension, there may be a selective risk of severe cerebral ischemia to the intracranial regions over that of the extracranial regions, especially in those where CBF might already be compromised (eg, carotid artery stenosis and aortic stenosis). The possibility that discreet regions of the brain may respond differently during hypertension, to an extent of local ischemia, warrants further confirmation with functional magnetic resonance that also measures the balance between deoxyhemoglobin and oxyhemoglobin to evaluate the regional distribution of CBF and oxygenation. As mentioned, because NIRS is noninvasive, does not require frequent calibration, is robust, and avoids the issues of probe movement, the advantage for using NIRS for clinical monitoring, including assessment of CA,$^{12}$ is potentially immense. However, on the basis of the findings of the current study, it would seem necessary to express caution in using NIRS to monitor CA, because it likely reflects very different alterations in cerebral perfusion.

Static Versus Dynamic CA

Static measurements evaluate the overall efficiency of the autoregulatory action, that is, the change in CBF in response to the manipulation of MAP, but they do not address the time in which this change in CBF is achieved (ie, its “latency”). Nevertheless, a close relationship has been reported between both dynamic and static measurements of CA.$^{1}$ More recently, an elegant study has identified that changes in CBF due to steady-state (static) CA modulate the dynamic pressure-flow relationship of the cerebral circulation.$^{19}$ Despite observing a similar pattern for the CBF responses to that seen in the current study (Figure 2B), Zhang et al$^{19}$ did not observe the same change in CBF with 3 of the 4 steady-state increases in MAP. Nevertheless, their final pharmacologically induced elevation in MAP, which was within the so-called autoregulatory “plateau” ($112\, \text{mm Hg}$), was associated with an increase in CBF. Therefore, Zhang et al$^{19}$ findings lend additional support to our observations of a pressure-passive regulation of CBF.

Differential Changes in CBF Velocity Pulsatility During Hypotension

A relevant and novel observation in the present study was that, despite hypertension but not hypertension, despite a preferential decrease in MCAv$_{\text{diastolic}}$, MCAv$_{\text{systolic}}$ was relatively well maintained, that is, pulsatility of MCAv was elevated (Figure 2C). Although the etiology of the differential changes in pulsatility with hypotension are not known, elevations in pulsatility have been interpreted as a compensatory response that is associated with CBF preservation despite falling perfusion pressure by promoting pulsatile flow.$^{49}$ It has also been suggested, at least in patients with head injury, that pulsatile flow requires less energy expenditure to maintain forward flow.$^{47}$ At least in the animal model, this compensatory mechanism maintains CBF until further dilation and fall in MCAv$_{\text{diastolic}}$ is exhausted; once that point is surpassed, CBF diminishes rapidly.$^{49}$ The preferential declines in MCAv$_{\text{diastolic}}$ and maintained MCAv$_{\text{systolic}}$ are consistent with the changes that occur during profound hypotension at the point of syncope.$^{1,10}$ Some consider this increase in MCAv pulsatility to be indicative of a paradoxical increase in cerebrovascular resistance before syncope.$^{21,24}$ Others note that MCAv$_{\text{mean}}$ decreases much less than does
MAP, implying that dynamic cerebral autoregulatory mechanisms are intact and functioning at syncope.50

Perspectives
The concept that the plateau region has a slope of 0 has had considerable influence on the static assessment of CA in physiological and pathophysiological investigations. Routine evaluation of CA in health and disease requires objective and reliable indices that can provide a continuous measure of vasomotor control of CBF in the presence of fluctuations in MAP. Although both the slope and linear regression indices are well-established parameters for this purpose, previous studies have not adequately considered what constitutes the normal response. Such studies have incorrectly assumed that the plateau response is a robust experimentally tested observation. Our data clearly show that, in healthy humans, the normal slope between CBF and MAP is relatively linear. The 2 major implications of our findings are that, in contrast to the innumerable reports in the literature, a finite slope of the plateau region does not necessarily imply a defective CA, and CBF and oxygenation are not independent of changes in blood pressure; therefore, a paradigm shift in the concept of CA is required.

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None.

References


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Influence of Changes in Blood Pressure on Cerebral Perfusion and Oxygenation


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Short title: Blood pressure and cerebral perfusion

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**Measurements of cerebral oxygenation**
The methodology of this system has been described previously.\textsuperscript{1} In brief, although it is not possible to distinguish between them, this method measures the balance of oxygen supply and oxygen demand directly at a capillary level in the cerebral cortical tissue.\textsuperscript{2} The optodes were housed in an optically dense plastic holder secured on the skin with tape to minimize extraneous light, and local oxygenation was measured every one second throughout the experiment. Cerebral oxygenation measured by NIRS may also be influenced by changes in cerebral blood flow, cerebral metabolism, arterial saturation and hematocrit.\textsuperscript{3} However, in the present study, because of an adequate cardiac output (data not shown) and no alterations in blood volume, it is unlikely that either arterial saturation or hematocrit was altered. Likewise, our subjects were awake with no visual or audio distractions so we consider changes in cerebral metabolic rate unlikely to influence our findings.

**Measurements and control of respiratory gas exchange**
Subjects breathed through a leak-free respiratory mask (Hans-Rudolph 8980, Kansas City, MO, USA) attached to a one-way non-rebreathing valve (Hans-Rudolph 2700, Kansas City, MO, USA). Inspiratory flow was measured using a heated pneumotach (Hans-Rudolph HR800, Kansas City, MO, USA). End-tidal CO\textsubscript{2} (P\textsubscript{ET}CO\textsubscript{2}) and O\textsubscript{2} (P\textsubscript{ET}O\textsubscript{2}) were sampled from the leak-free mask and measured by a gas analyzer (model CD-3A, AEI Technologies, Pittsburgh, PA). Ventilation (flow, tidal volume, frequency) and gas values were displayed in real time during testing (PowerLab, ADI Instruments, Colorado Springs, CO, USA). Subjects’ baseline P\textsubscript{ET}CO\textsubscript{2} was recorded and they were instructed to breathe at the same rate and depth during the drug infusions, and, if needed, adjust their baseline tidal volume level in order to maintain P\textsubscript{ET}CO\textsubscript{2} close to baseline level.

**Pharmacological-induced alterations in mean arterial blood pressure**
Steady-state testing of CA was achieved by stepwise lowering and increasing of MAP in ~10 mm Hg increments; with each step held relatively constant for 30-90 s. Intravenous sodium nitroprusside infusions were commenced initially at a low rate (0.3 mcg/kg/min) and individually titrated upwards every 2 minutes until the desired blood pressure level was achieved, or when the pre-defined maximum MAP reduction below baseline (>40 mm Hg) or infusion rate (10 mcg/kg/min) had been reached. Similarly, intravenous phenylephrine hydrochloride infusions were commenced at a low rate (0.2 ug/kg/min) and individually titrated upwards every 2 minutes until the desired blood pressure level was achieved, or when the pre-defined maximum MAP rise above baseline (>60 mm Hg) had been reached.

References:
\begin{enumerate}
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\item Kurth CD, Uher B. Cerebral hemoglobin and optical pathlength influence near-infrared spectroscopy measurement of cerebral oxygen saturation. \textit{Anesth Analg.} 1997;84:1297-1305.
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