Cerebrovascular Regulation During Transient Hypotension and Hypertension in Humans

Yu-Chieh Tzeng, Chris K. Willie, Greg Atkinson, Samuel J.E. Lucas, Aaron Wong, Philip N. Ainslie

Abstract—The cerebrovasculature dilates or constricts in response to acute blood pressure changes to stabilize cerebral blood flow across a range of blood pressures. It is unclear, however, whether such dynamic cerebral autoregulation (dCA) is equally effective in responding to falling versus rising blood pressure. In this study we applied a pharmacological approach to evaluate dCA gain to transient hypotension and hypertension and compared this method with 2 established indices of dCA that do not explicitly differentiate between dCA efficacy and falling versus rising blood pressure. Middle cerebral arterial velocity and blood pressure recordings were made in 26 healthy volunteers randomized to 2 protocols. In 10 subjects, dCA gain to transient hypotension induced with intravenous nitroprusside was compared with dCA gain to transient hypertension induced with intravenous phenylephrine. In 16 subjects, dCA gain to transient hypotension induced with intravenous nitroprusside was compared with the rate of regulation and autoregulatory index derived from transient hypotension induced with the thigh cuff deflation technique. dCA gain to transient hypotension induced with intravenous nitroprusside was unrelated to dCA gain to transient hypertension induced with intravenous phenylephrine (r=0.06; P=0.87) and was consistently greater than dCA gain to transient hypertension induced with intravenous phenylephrine (0.57±0.16 versus 0.31±0.20 cm/s per millimeter of mercury; P<0.01). However, dCA gain to transient hypotension induced with intravenous nitroprusside was inversely related to the rate of regulation (r=−0.52; P=0.037) and autoregulatory index (r=−0.66; P=0.005). These data indicate that, under our laboratory conditions, dCA appears to be inherently nonlinear with disparate efficacy against rising and falling blood pressure, and dCA gain derived from pharmacologically induced transient hypotension correlates with established nonpharmacological indices of dCA. (Hypertension. 2010;56:268-273.)

Key Words: brain circulation ▪ blood flow regulation ▪ blood pressure ▪ hemodynamics ▪ transcranial Doppler

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during hypertension, but not hypotension, we examined the hypothesis that dCA responds to rising blood pressure more effectively than to falling blood pressure in healthy humans. The second objective was to compare dCA, as determined using the Oxford method against the established rate of regulation (RoR) and autoregulatory index (ARI) indices derived from the thigh-cuff technique.

Methods

Subjects
Twenty-six healthy fasted subjects (21 men) were recruited to 2 study protocols (A, n=16; 5 women; B, n=10 men), which were approved by the Central Regional Ethics Committee and conformed to the standards set by the Declaration of Helsinki. The subjects’ mean age was 26 years (range: 20 to 33 years).

Measurements
The ECG, respiratory flow (Hans Rudolph Heated Pneumotach HR 800), noninvasive blood pressure (Finometer, TNO-TPD Biomedical Instrumentation), right middle cerebral artery flow velocity (MCAv; 2-MHz pulsed Doppler ultrasound, DWL Doppler), and end-tidal pCO2 (ETCO2) sampled from a leak-free mask (gas analyzer model CD-3A, AEI Technologies), were acquired at 1000 Hz via an analog-to-digital converter (Powerlab/16SP ML795, ADInstruments). The Doppler probe was secured with a headband device (Spencer Technologies) to maintain optimal insonation position. From the blood pressure and MCAv waveforms, we determined beat-to-beat mean arterial pressure (MAP) and MCAv values using custom written software in LabView 8.2 (National Instruments).

Protocol
All of the trained subjects were studied in the supine position. After an initial 10-minute stabilization period, baseline data were recorded for 5 minutes. Thereafter, subjects were randomized to 1 of 2 protocols, as described below.

Protocol A: Hypotension Versus Hypertension Comparison
Transient hypotension and hypertension were induced with intravenous bolus injections of sodium nitroprusside (150 to 300 µg) and phenylephrine hydrochloride (200 to 400 µg) in randomized order. For comparison against a more physiological (nonpharmacological) transient hypotensive stimulus, subjects also performed a sit-to-stand maneuver. This involved asking subjects to rapidly assume a standing posture 15 minutes after the completion of the final drug intervention.

Protocol B: Pharmacological Versus Thigh-Cuff Comparison
Transient hypotension was induced with bolus injections of sodium nitroprusside (150 to 300 µg) and the rapid thigh-cuff technique in randomized order. All of the subjects were trained to breathe in time with visual breathing frequency to minimize changes in ventilatory pattern and to maintain ETCO2 at approximately their baseline levels via visual feedback from the gas analyzer output. All of the tests were spaced 15 minutes apart to allow for hemodynamic stabilization. Drug injections were conducted twice and further repeated if changes in MAP were inadequate (<10 mm Hg) or if ETCO2 levels increased significantly above or below (>2.5 mm Hg) baseline. Data from nitroprusside and phenylephrine trials were averaged for subsequent analysis.

Quantification of dCA
The dCA gain (G), determined separately for falling (nitroprusside, Gdown; sit-to-stand, Gk) and rising (phenylephrine, Gup) blood pressure, was quantified as the regression slope between MAP and MCAv where MAP was falling or rising in a linear fashion. Beat-by-beat values were averaged over 2 mm Hg bins to account for respiratory-related fluctuations. G values were reported without phase delays, because correlation coefficients were greatest when MAP and MCAv were calculated by dividing MAP. The MAP, MCAv, and CVCi values were determined relative to control values. Control data were taken as the mean of the 4 seconds immediately before thigh-cuff release. The RoR index was defined as

\[ \text{RoR} = \frac{\Delta \text{CVCi}/\Delta t}{\text{MAP}} \]

where \(\Delta \text{CVCi}/\Delta t\) is the slope of the linear regression between CVCi and time, and \(\text{MAP}\) is the difference between baseline MAP and the average MAP during the 1.0- to 3.5-second period after cuff release. Consistent with previous studies, the RoR was calculated using CVCi (flow-pressure) ratio between the cerebrovascular resistance index and (pressure/flow),4 because CVCi may better reflect regional vascular tone under situations where changes in tone lead to changes in flow.21 The dCA response to transient hypotension was also assessed using the ARI from Tieck et al.,20 defined as graded coefficients from 0 (absence of dCA) to 9 (strongest dCA). This involved applying a second-order linear differential equation, defined as follows:

\[
\frac{dP_n}{dt} = \frac{\text{MAP} - \text{MAP}_{\text{base}}}{\text{MAP}_{\text{base}} - \text{CCP}} \times_2 x_2 + \frac{(x_1 - 2D \times_2 x_1)}{f \cdot T} \\

x_1 = x_1 \times_1 + \frac{(dP_n - x_2)}{f \cdot T} \\

mV_a = \text{MCAv}_{\text{base}} \times (1 + \frac{dP_a}{k \cdot x_2})
\]

where \(dP_n\) is the normalized change in MAP relative to the control value (MAPbase) adjusted for the estimated critical closing pressure (CCP) of 12 mm Hg, \(x_2\), and \(x_1\) are state variables (equal to 0 at baseline), \(mV_a\) is modeled mean velocity, MCAvbase is baseline MCAv, \(f\) is the sampling frequency (10 Hz), and \(n\) is the sample number. The \(mV_a\) generated from 10 predefined combinations of parameters \(T\) (time constant), \(D\) (damping factor), and \(k\) (autoregulatory gain) that best fit (quadratic error: 30-second window) the actual MCAv recording was taken as an index of dCA.

Statistical Analysis
Data were assessed for normality and log transformed if there was evidence of nonnormality. All of the variables were reported as mean±SD. For the appraisal of the agreement between \(G\) and the RoR and ARI indices, Pearson’s product-moment correlation coefficients and least-squares regression analysis were used. Correlations between variables were compared using Steiger’s method.13 Because ARI is measured on a 0 to 9 discrete scale and is, therefore, borderline parametric in nature, this variable was also analyzed with an ordinal regression model.14 Specific a priori defined comparison of changes in ETCO\(_2\) during hypotension and hypertensions against baseline were conducted as planned using Student’s paired t test. Differences in dependent variables were assessed using 1-way repeated-measures ANOVA (Huynh-Feldt corrected). Post-hoc analyses were made with Student’s paired t test. Statistical significance was set at \(P<0.05\), and the Bonferroni correction was applied where appropriate to control for type I error associated with multiple testing. Analyses were conducted using SPSS 16.0.2 (SPSS Inc) and Statview 5 (SAS Institute).
Hypertension Versus Hypertension Comparison

The Table summarizes the hemodynamic changes in MAP and MCA\textsubscript{mean} after the nitroprusside and phenylephrine injections and after standing from a seated position. In all of the subjects, nitroprusside and standing induced a fall in MAP, and phenylephrine induced a rise in MAP (Figure 1). The time interval between the point at which MAP begins to change to the first local maximum change was 19±4 s for nitroprusside injection (P=0.10 versus phenylephrine), 11±1.2 s for standing (P<0.01 versus phenylephrine), and 23±6.9 s for phenylephrine injection. The magnitude of absolute MAP change was greater with standing but was similar between nitroprusside hypotension and phenylephrine hypertension. In contrast, the MCA\textsubscript{mean} rise with phenylephrine was significantly smaller than the MCA\textsubscript{mean} reduction with both nitroprusside injection and standing. Compared with baseline (39±3.7 mm Hg), average ETCO\textsubscript{2} did not differ during nitroprusside hypotension (40±4.1 mm Hg; P=0.80 versus baseline), stand hypotension (38±4.0 mm Hg; P=0.064 versus baseline), or phenylephrine hypertension (39±2.8 mm Hg; P=0.88 versus baseline).

Figure 2 shows the differences among G\textsubscript{down}, G\textsubscript{up}, and G\textsubscript{stand} for all of the subjects recruited to protocol B. With the exception of 2 individuals, both G\textsubscript{down} and G\textsubscript{stand} were consistently greater than G\textsubscript{up}. Across all of the subjects, the average G\textsubscript{down} (0.57±0.16 cm/s per mm Hg; r=0.93±0.089) was similar to G\textsubscript{stand} (0.58±0.15 cm/s per mm Hg; r=0.95±0.028), and both were substantially greater than G\textsubscript{up} (0.31±0.20 cm/s per mm Hg; r=0.72±0.22; ANOVA

Table. Summary of MAP and MCA\textsubscript{mean} Changes Relative to Baseline After Nitroprusside and Phenylephrine Injections and After Standing From a Sitting Position (n=10)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change Relative to Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>84±14</td>
</tr>
<tr>
<td>MCA\textsubscript{mean} cm/s</td>
<td>70±13</td>
</tr>
</tbody>
</table>

P values are for 1-way repeated-measures ANOVA.

*Data are statistically different from phenylephrine.

Results

Figure 1. Data from one subject with very prominent asymmetric hemodynamic responses to intravenous nitroprusside, phenylephrine, and standing from the seated position relative to baseline. Baseline is defined as the 10 s before a change in MAP. Nitroprusside (B)-induced hypotension and sit-to-stand (C) hypotension were accompanied by concurrent reductions in MCA\textsubscript{mean}. In contrast, phenylephrine (A)-induced hypertension was associated with negligible changes in MCA\textsubscript{mean} in this individual. The onset of hypotension and hypertension was associated with approximately linear increases and decreases in the CVC\textsubscript{i} index. G\textsubscript{down} (E; 0.61 cm/s per mm Hg) and G\textsubscript{stand} (F; 0.70 cm/s per mm Hg) were clearly different from G\textsubscript{up} (D; 0.11 cm/s per mm Hg). Horizontal bars denotes segments of data take for gain calculations.
Across all of the subjects, \( P < 0.01 \), consistent with greater dCA capacity against acute transient hypertension. There were no significant relationships between \( G_{up} \) and \( G_{down} \) \( (r = 0.06; P = 0.87) \) or between \( G_{up} \) and \( G_{stand} \) \( (r = 0.24; P = 0.50) \).

### Pharmacological Versus Thigh-Cuff Comparison

In contrast to nitroprusside injections, the thigh-cuff technique caused a sudden drop in MAP (20 ± 4.5 mm Hg) that returned to baseline over a variable time period (mean: 38 ± 6 s). Across all of the subjects, \( G_{down} \) was inversely related to both RoR \( (r = -0.52; P = 0.037) \) and ARI \( (r = -0.66; P = 0.005) \). There was no significant difference between these 2 correlation coefficients \( (P = 0.25) \), and the standardized estimates of the 2 regression slopes were similar \( (-0.5 \text{ to } -0.6) \). The relationship between \( G_{down} \) and ARI was also statistically significant \( (P = 0.006) \) when the ARI data were analyzed with repeated-measures ANOVA; \( P < 0.01 \). *Statistically different from \( G_{up} \).

The slopes of the linear regression between MAP and MCAvmean (\( G \)) after nitroprusside and phenylephrine injections were taken as indices of dCA gain to falling and rising blood pressure challenges. This approach is simplistic, as it assumes a linear systems response to blood pressure perturbation. However, the pharmacological method has clear advantage as a means of delineating dCA responses to rising and falling blood pressure across a wide pressure range, an important consideration given that dCA asymmetry cannot be reliably studied using conventional techniques, such as thigh-cuff deflation, which elicits only hypotension, or transfer function analysis of blood pressure and MCAvmean oscillations. Because the MAP changes induced with nitroprusside and phenylephrine both occur over \( \approx 20 \)-s intervals, they are well within the range \( (<0.07 \text{-Hz or } >14 \)-s cycles) in which CA is thought to be most effective. Therefore, the differences between \( G_{up} \) and \( G_{down} \) are unlikely to be attributable to the frequency-dependent efficacy of dCA. This finding provides the first clear evidence that asymmetrical dCA responses may indeed represent a fundamental property of CA in otherwise healthy humans.

### Assesment of dCA

The slopes of the linear regression between MAP and MCAvmean (\( G \)) after nitroprusside and phenylephrine injections were taken as indices of dCA gain to falling and rising blood pressure challenges. This approach is simplistic, as it assumes a linear systems response to blood pressure perturbation. However, the pharmacological method has clear advantage as a means of delineating dCA responses to rising and falling blood pressure across a wide pressure range, an important consideration given that dCA asymmetry cannot be reliably studied using conventional techniques, such as thigh-cuff deflation, which elicits only hypotension, or transfer function analysis of blood pressure and MCAvmean oscillations. Because the MAP changes induced with nitroprusside and phenylephrine both occur over \( \approx 20 \)-s intervals, they are well within the range \( (<0.07 \text{-Hz or } >14 \)-s cycles) in which CA is thought to be most effective. Therefore, the differences between \( G_{up} \) and \( G_{down} \) are unlikely to be attributable to the frequency-dependent efficacy of dCA. This finding provides the first clear evidence that asymmetrical dCA responses may indeed represent a fundamental property of CA in otherwise healthy humans.

## Discussion

### Main Findings

The 3 major new findings of this study are as follows: (1) across subjects, \( G_{down} \) and \( G_{stand} \) were consistently greater than \( G_{up} \); (2) both \( G_{down} \) and \( G_{stand} \) were unrelated to \( G_{up} \); and (3) dCA, as indexed by the RoR and ARI, showed an inverse relationship with \( G_{down} \). These findings indicate that dCA may be better adapted to compensating for rising than for falling blood pressure in humans. They also show that dCA responses to pharmacologically induced hypotension are correlated with established indices (RoR and ARI) of dCA.

### CBF Responses to Pharmacologically Induced Hypotension and Hypertension

Aaslid et al\(^8\) reported that dCA was more adept at compensating for transient hypertension than hypotension induced by cyclic inflation and deflation of thigh cuffs in head injury patients. Consequently, they hypothesized that this “asymmetry” may be a fundamental feature of CA. However, given there was no overt CA asymmetry in their control subjects, and the head injury cohort was artificially ventilated at hypocapnic levels (ETCO2 32 to 35 mm Hg), this extrapolation may have been misleading. For example, because hypocapnia causes cerebral arteriolar vasoconstriction and improves dCA,\(^8\) this alone may have explained why dCA was more effective in compensating for hypertension in the head-injury cohort.\(^8\) However, our findings that \( G_{down} \) and \( G_{stand} \) were both greater than \( G_{up} \) for the majority of subjects, that both \( G_{down} \) and \( G_{stand} \) were unrelated to \( G_{up} \), and that \( \Delta \text{MCAvmean} \) with rising blood pressure was less than \( \Delta \text{MCAvmean} \) with falling blood pressure despite similar \( \Delta \text{MAP} \) changes following phenylephrine and nitroprusside injections supports the hypothesis that the mechanisms underlying dCA are more effective in responding to acute transient hypertension than to hypotension.

The application of transfer function analysis has shown that dCA exhibits high pass filter characteristics consistent with more effective cerebrovascular control against blood pressure changes that occur slowly in the low (0.07 to 0.30 Hz) and very low (<0.07 Hz) frequency ranges.\(^8\) Because the MAP changes induced with nitroprusside and phenylephrine both occur over \( \approx 20 \)-s intervals, they are well within the range \( (<0.07 \text{-Hz or } >14 \)-s cycles) in which CA is thought to be most effective. Therefore, the differences between \( G_{up} \) and \( G_{down} \) are unlikely to be attributable to the frequency-dependent efficacy of dCA. This finding provides the first clear evidence that asymmetrical dCA responses may indeed represent a fundamental property of CA in otherwise healthy humans.

The current study shows that the established RoR and ARI indices calculated from transient hypotension induced by deflating thigh cuffs were equally correlated to \( G_{down} \) derived from nitroprusside injections, suggesting that these indices likely reflect common components of dCA during transient hypotension. However, both RoR and ARI were only moderately related to the \( G_{down} \) index, indicating that the indices...
Potential Mechanisms

Animal data indicate that perivascular cerebral sympathetic nerves are activated during acute hypertension but not hypotension. This raises the possibility that selective cerebral vasoregulation (secondary to perivascular cerebral sympathetic nerve activation) may partly explain dCA asymmetry. Consistent with this hypothesis, transfer function gain and coherence between MCAvmean and MAP oscillations induced with oscillatory lower body negative pressure increases after \( \alpha \)-adrenergic blockade. Although potentially confounded by unexplained hypocapnia, the rise in coherence, which may be interpreted as an increase in linearity between MAP and MCAvmean relations, might be attributable to the loss of dCA asymmetry. Given that human pial arteries are sparsely innervated and are insensitive to topical noradrenaline, it is also possible that dCA asymmetry may relate to differences in intrinsic myogenic responses to hypotension versus hypertension. Finally, animal studies have identified collagen fibers and smooth muscle cells at the entrance of the bridging veins to the cerebral venous sinuses. These histological structures might be part of a venous cuff mechanism that is actively involved in cerebral venous outflow and, therefore, intracranial blood volume regulation. Although the relative importance of this putative mechanism in humans is unclear, we cannot exclude the possibility that venous outflow control contributes to the dCA asymmetry that we have observed.

Perspectives

Effective counterregulation against transient hypertension may reflect an evolutionary adaptation protecting the brain from transient blood pressure surges, such as those normally encountered during rapid eye movement sleep and exercise or those associated with labile hypertension, autonomic dysreflexia, and baroreflex failure. It is, therefore, conceivable that the loss of dCA asymmetry may increase hemorrhagic stroke risk. In addition, there is strong evidence that pharmacological testing of arterial baroreflex sensitivity is a powerful risk stratification tool for cardiac death. With emerging evidence suggesting that baroreflex dysfunction also independently modulates outcomes from acute hemorrhagic stroke, methods that can unobtrusively gauge both baroreflex sensitivity and dCA gain would be desirable. Because the \( G_{down} \) metric is correlated with both RoR and ARI scores, the potential use of the pharmacological approach as a combined measure of baroreflex and dCA function should be studied further.

Methodological Considerations

Two methodological considerations warrant discussion. First, changes in MCAv reflect changes in CBF only if the MCA diameter is constant. Previous studies have shown that intra-arterial phenylephrine (\( \alpha \)-adrenoceptor agonist) does not cause any relevant MCA vasoconstriction. Likewise, nitroprusside administered during craniotomy in humans did not affect MCA vessel diameter. Therefore, it seems reasonable to assume that changes in MCAv measured via transcranial Doppler ultrasound were proportional to changes in CBF. Second, the drugs used to manipulate blood pressure may have exerted unquantifiable effects on dCA responses by directly altering cerebrovascular resistance downstream from the MCA. However, direct confounding related to nitroprusside seems unlikely given that mechanoregulation of CBF occurs independent of NO-mediated pathways. Likewise, direct confounding because of phenylephrine is unlikely, because the intact blood-brain barrier normally prevents intravascular catecholamines (as opposed to catecholamines released from perivascular sympathetic nerves) from binding to \( \alpha \)-adrenoceptors of cerebral arterioles. Although there is evidence that raised intravascular pressure may compromise the integrity of the blood-brain barrier resulting in “leak through” of intravascular catecholamines, the evidence for this is based on animals studies conducted under conditions that are vastly different from those of the current study, that is, prolonged (hours) periods of extreme hypertension (e.g., MAP >180 mm Hg). We acknowledge that new developments in functional MRI will likely provide invaluable insight into how asymmetrical dCA may influence CBF to discrete regions of the brain.

Conclusions

The current study documents an asymmetrical dCA response that is relatively more effective at guarding the brain from transient hypertension than hypotension. Our results also
shows that dCA, as indexed by $G_{\text{down}}$, is positively related to the RoR and ARI index derived from the classical thigh-cuff deflation technique.

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**Disclosures**

None.

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