Autonomic Neural Control of Dynamic Cerebral Autoregulation in Humans

Rong Zhang, PhD; Julie H. Zuckerman, RN; Kenichi Iwasaki, MD; Thad E. Wilson, PhD; Craig G. Crandall, PhD; Benjamin D. Levine, MD

Background—The purpose of the present study was to determine the role of autonomic neural control of dynamic cerebral autoregulation in humans.

Methods and Results—We measured arterial pressure and cerebral blood flow (CBF) velocity in 12 healthy subjects (aged 29±6 years) before and after ganglion blockade with trimethaphan. CBF velocity was measured in the middle cerebral artery using transcranial Doppler. The magnitude of spontaneous changes in mean blood pressure and CBF velocity were quantified by spectral analysis. The transfer function gain, phase, and coherence between these variables were estimated to quantify dynamic cerebral autoregulation. After ganglion blockade, systolic and pulse pressure decreased significantly by 13% and 26%, respectively. CBF velocity decreased by 6% (P<0.05). In the very low frequency range (0.02 to 0.07 Hz), mean blood pressure variability decreased significantly (by 82%), while CBF velocity variability persisted. Thus, transfer function gain increased by 81%. In addition, the phase lead of CBF velocity to arterial pressure diminished. These changes in transfer function gain and phase persisted despite restoration of arterial pressure by infusion of phenylephrine and normalization of mean blood pressure variability by oscillatory lower body negative pressure.

Conclusions—These data suggest that dynamic cerebral autoregulation is altered by ganglion blockade. We speculate that autonomic neural control of the cerebral circulation is tonically active and likely plays a significant role in the regulation of beat-to-beat CBF in humans. (Circulation. 2002;106:1814-1820.)

Key Words: blood flow ■ brain ■ nervous system, autonomic ■ ultrasonics

Cerebral vessels are richly innervated by both sympathetic and parasympathetic nerves. However, despite extensive study, the role of autonomic neural control of the cerebral circulation remains controversial. For example, in animal studies, neither electrical stimulation nor autonomic denervation has led to consistent changes in cerebral blood flow (CBF). Moreover, the effect of these interventions on the cerebral pressure-flow relationship and/or on cerebral vessel response to metabolic stimuli remains unclear. In addition, data in humans regarding neural control of the cerebral circulation are scarce, and the findings in animals may not apply because of substantial interspecies differences in the regulation of CBF.

These difficulties persist not only because of the complexity of the cerebral circulation, but also because of the limitations of technology for CBF measurement. CBF is heterogeneous both in time and in space. Different methods may assess different aspects of CBF. Recently, with the advent of transcranial Doppler technology for the measurement of CBF velocity with high-temporal resolution, and others have observed that in humans, CBF velocity in the middle cerebral artery (MCA) decreased substantially during lower body negative pressure (LBNP) and head-up tilt in the absence of systemic hypotension. These findings suggest the presence of cerebral vasoconstriction associated with the augmented sympathetic nerve activity during orthostatic stress.

In addition, in contrast to the traditional concept of cerebral autoregulation, which suggests that steady-state CBF remains relatively constant despite large changes in arterial pressure, we and others have found that beat-to-beat CBF velocity measured in the MCA in humans fluctuates spontaneously in response to dynamic changes in arterial pressure. If MCA diameter remains relatively constant, as has been shown by numerous studies, these changes in CBF velocity reflect changes in CBF. Thus, estimation of transfer function between these 2 variables may identify frequency-dependent properties of dynamic cerebral autoregulation.

This study was conducted to test directly the hypothesis that beat-to-beat CBF velocity, in response to dynamic changes in arterial pressure, is under tonic autonomic neural control in humans. For this purpose, we blocked both sym-
pathetic and parasympathetic nerve activity with an intravenous infusion of trimethaphan (ganglion blockade). We hypothesized that estimation of transfer function between changes in arterial pressure and CBF velocity would be altered by the removal of autonomic neural activity.

Methods

Subjects
Twelve healthy subjects (9 men and 3 women) with a mean age of 29±6 years, height of 174±10 cm, and weight of 71±10 kg voluntarily participated in this study. No subject smoked or had known medical problems. Subjects were screened carefully with a medical history and a physical examination with 12-lead ECG. All subjects signed an informed consent form approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

Instrumentation
In 9 subjects, arterial pressure was measured noninvasively with finger photoplethysmography (Finapres). In 3 subjects, pressure was measured simultaneously with both a radial arterial catheter (Abbott Critical Care System) and the photoplethysmography methods ipsilaterally. The pressure transducer of the intra-arterial catheter was calibrated and zeroed to the subject’s midaxillary line during the experiments. The Finapres pressure transducer was also positioned at heart level. CBF velocity was measured continuously in the MCA using transcranial Doppler. A 2-MHz probe (Multiflow, DWL) was placed over the subject’s temporal window and fixed at a constant angle with a probe holder that was custom-made to fit each subject’s facial bone structure. The optimal signal was obtained according to standard techniques, with the Doppler sample volume adjusted to the proximal segment of the MCA. Heart rate was monitored by ECG. Respiratory excursions were monitored with a piezoelectric transducer (Pneumotrace, Morro Bay). End-tidal CO₂ (ETCO₂) was obtained via a nasal cannula by using a mass spectrometer (Marquette Electronics). In addition, arterial CO₂ and pH were measured in the 3 subjects with arterial catheters using a blood gas analyzer (Instrumentation Laboratory).

Protocol
All experiments were performed in the morning at least 2 hours after a light breakfast in a quiet, environmentally controlled laboratory with an ambient temperature of 25°C. The subjects refrained from heavy exercise and caffeinated or alcoholic beverages at least 24 hours before the tests. After at least 30 minutes of supine rest, 6 minutes of baseline data were collected during spontaneous breathing. Then, the subjects performed a Valsalva maneuver with an expiratory strain of 30 mmHg for 15 seconds with beat-to-beat monitoring of heart rate and arterial pressure. After the baseline Valsalva maneuver, infusion of trimethaphan (trimethaphan camsylate, Cambridge Laboratories) was begun at a low dose of 3 mg/min. Three minutes after the infusion, the Valsalva maneuver was repeated to evaluate both the heart rate and pressure responses. The infusion dose was increased incrementally by 1 mg/min until the heart rate response during the Valsalva maneuver was eliminated. The absence of heart rate response, plus the absence of phase II recovery and phase IV overshoot of arterial pressure during the Valsalva maneuver demonstrated the efficacy of ganglion blockade on both parasympathetic and sympathetic nerve activity.20,21 The ultimate infusion dose used for ganglion blockade was 6 to 7 mg/min for most subjects in the present study, which was similar to that used by others for total elimination of muscle sympathetic nerve activity in humans.22

Once complete blockade was achieved, the infusion of trimethaphan continued at this maximal dosage throughout the experiments. Six minutes of data were then collected after ganglion blockade. To determine whether the changes in the transfer function might be secondary to the drug-induced hypotension per se (inde-

### TABLE 1. Steady-State Hemodynamics Before and After Ganglion Blockade

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Blockade</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>65±4</td>
<td>88±4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>126±3</td>
<td>110±4</td>
<td>&lt;0.01</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>67±2</td>
<td>66±3</td>
<td>0.73</td>
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<tr>
<td>PPB, mm Hg</td>
<td>58±2</td>
<td>43±2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>85±2</td>
<td>80±3</td>
<td>0.17</td>
</tr>
<tr>
<td>CBF velocity, cm/s</td>
<td>64±4</td>
<td>60±3</td>
<td>0.02</td>
</tr>
<tr>
<td>ETCO₂, mm Hg</td>
<td>40±1</td>
<td>38±1</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Values are mean±SD. BP indicates blood pressure.

Results

Steady-State Hemodynamics
After ganglion blockade, systolic and pulse pressure decreased by 13% and 26%, respectively. Heart rate increased by 35% (Table 1). Beat-to-beat R-R variability was virtually abolished (from 49±5 ms at baseline to 5±1 ms after
blockade; \( P<0.001 \). Mean CBF velocity decreased by 6% (\( P<0.05 \)). ETCO\(_2\) also decreased by 2 mm Hg (Table 1). However, respiratory frequency remained unchanged (0.28±0.02 versus 0.27±0.02 Hz). In addition, arterial CO\(_2\) (42±2 versus 43±1 mm Hg) and pH (7.42±0.01 versus 7.4±0.01) measured in the 3 subjects with arterial catheters did not change, despite decreases in ETCO\(_2\). In these subjects, differences of 8 to 12 mm Hg in systolic pressure and 3 to 4 mm Hg in diastolic pressure were found between the measurements of radial and finger arterial pressure. However, the magnitude of reductions in arterial pressure after ganglion blockade was similar between the 2 methods (systolic: 11% by Finapres, 13% by catheter; pulse pressure: 22% by Finapres, 24% by catheter). In addition, a linear relationship for beat-to-beat changes in mean arterial pressure was observed between the 2 methods \( (R^2=0.94±0.02; \text{slope}=0.91±0.08; \text{intercept}=0±0 \text{ mm Hg}) \). These data confirm the validity of using finger photoplethysmography to measure changes in arterial pressure in the present study.23

Spectral and Transfer Function Analysis

Representative time series of beat-to-beat changes in mean arterial pressure and CBF velocity are shown in Figure 1. Group-averaged spectra are shown in Figure 2. After ganglion blockade, the spectral power of pressure variability decreased by 82% in the very low frequency range (Figure 2 and Table 2). In contrast, no significant change was observed in either CBF velocity or ETCO\(_2\) variability (Figure 2 and Table 2).

Consequently, transfer function gain increased substantially by 81% in the very low frequency range (Figure 3 and Table 2). The phase lead of changes in CBF velocity to arterial pressure was diminished, and coherence function tended to decrease after ganglion blockade \( (P=0.07) \) (Figure 3 and Table 2).

Application of oscillatory LBNP generated prominent changes in arterial pressure and CBF velocity simultaneously in the very low frequency range (Figures 4 and 5). This intervention restored the spectral power of pressure variability to the pretrimethaphan level (Figure 5). However, changes in transfer function gain and phase after ganglion blockade persisted, despite a trend toward increases in coherence function with oscillatory LBNP \( (P=0.08 \text{ compared with ganglion blockade; Figure 5}) \).

Finally, with phenylephrine infusion, mean arterial pressure increased in the 3 subjects (baseline, 85±3 mm Hg; trimethaphan, 79±1 mm Hg; phenylephrine, 90±3 mm Hg). The steady-state CBF velocity, which had been reduced during ganglion blockade, also increased commensurate with pressure (baseline, 68±0 cm/s; trimethaphan, 64±1 cm/s; phenylephrine, 71±1 cm/s). However, the augmented transfer function gain and the diminished phase after ganglion blockade remained unchanged (Figure 6).

Discussion

The primary new findings of this study are that with the removal of autonomic neural activity, transfer function gain between beat-to-beat changes in arterial pressure and CBF velocity increased (greater changes in CBF velocity for a given change in arterial pressure), and the phase lead of CBF velocity to arterial pressure was diminished. In addition, steady-state CBF velocity was reduced, associated with a reduction in arterial pressure. These data suggest altered dynamic and static cerebral autoregulation after ganglion blockade. We speculate that autonomic neural control of the cerebral circulation is tonically active and likely plays an important role in the beat-to-beat regulation of CBF in humans.
Neural Control of the Cerebral Circulation

Steady-State Autoregulation

Most studies in animals have found that baseline CBF did not change after autonomic denervation. Nevertheless, cerebral autoregulation may be altered. For example, CBF was reduced with stepwise reductions in arterial pressure after sympathetic and/or parasympathetic denervation in rats, suggesting impaired cerebral autoregulation. In addition, CBF decreased with sympathetic nerve stimulation in rats, dogs, and monkeys, and it increased with parasympathetic nerve stimulation in rats. These data suggest autonomic neural control of the cerebral circulation.

Because of difficulties with methods, studies in humans regarding neural control of the cerebral circulation are extremely sparse and findings are controversial. For example, stellate ganglion blockade and sympathectomy in patients with palmar hyperhidrosis increased CBF and CBF velocity in the MCA. Moreover, in patients with autonomic failure, CBF increased prominently in response to increases in arterial pressure, suggesting an obligatory role of autonomic neural control for intact cerebral autoregulation. Conversely, stellate ganglion blockade did not change vertebral CBF in patients with headache. Recently, we and others have shown that during LBNP, head-up tilt, and cold pressor tests, all of which enhance sympathetic nerve activity, CBF velocity decreased in the absence of systemic hypotension. These data suggest the presence of cerebral vasoconstriction, associated with the augmented sympathetic activity.

This study extends these previous observations by showing that CBF velocity was reduced slightly but significantly after ganglion blockade. Furthermore, this reduction in CBF velocity was associated with a reduction in arterial pressure that, in the absence of ganglion blockade, would not be expected to be of sufficient magnitude to reduce CBF given intact autoregulation. In addition, we observed that reduced CBF velocity after ganglion blockade could be restored by phenylephrine infusion, which restored arterial pressure. These data provide further evidence that that steady-state cerebral autoregulation in humans may be altered by ganglion blockade.

However, because the change in CBF velocity after ganglion blockade was relatively small (6%) and occurred simultaneously with a reduction in ETCO₂, the possibility...
cannot be excluded that the reduction in CBF velocity might be induced by the reduction in ETCO$_2$. However, directly measured arterial CO$_2$ and pH in a subgroup of subjects in the present study did not change after ganglion blockade. Thus, the observed reduction in ETCO$_2$ may reflect an altered ventilation/perfusion relationship of the lung and an exaggerated difference between the ETCO$_2$ and arterial CO$_2$ rather than a physiologically significant hypocapnia after ganglion blockade.

It is also possible that a small dilation of the MCA after ganglion blockade could lead to a small decrease in CBF velocity, as measured by Doppler. However, other investigators have demonstrated a close relationship between the changes in CBF velocity by Doppler and changes in CBF using single-photon emission computed tomography after ganglion blockade, thus providing further validation of using Doppler techniques under these circumstances.

Dynamic Autoregulation

In dynamic situations, animal studies suggest that CBF responds briskly to transient changes in arterial pressure, and stimulation of sympathetic nerves attenuates the magnitude of changes in CBF in cats. However, with sustained sympathetic activation, a “vasomotor escape” phenomenon may occur, suggesting that neural control of the cerebral circulation may be more effective under dynamic than under steady-state conditions. In the present study, CBF velocity variability at the very low frequencies persisted while pressure variability was reduced after ganglion blockade. Thus, transfer function gain, which reflects the magnitude of the relationship between these variables, increased substantially, while the phase lead of CBF velocity to pressure was diminished. These data document for the first time that removal of autonomic neural activity alters the beat-to-beat pressure-flow velocity relationship in humans.

In previous studies, estimation of transfer function gain has been used to quantify the buffering effects of the cerebrovascular bed on oscillations in CBF velocity induced by changes in arterial pressure. In addition, estimation of phase has been used to reflect the temporal relationship between these variables. Under clinical conditions of cerebral subarachnoid hemorrhage or hypercapnia, transfer function gain increased and phase diminished, suggesting impaired dynamic cerebral autoregulation. Thus, the changes in transfer function gain and phase observed in the present study suggest impairment of dynamic cerebral autoregulation with the removal of autonomic neural activity.

Interestingly, although transfer function gain increased and phase decreased at the very low frequencies, they remained unchanged at higher frequencies. Thus, the frequency-dependent nature of dynamic autoregulation was abolished by...
ganglion blockade (Figure 3), suggesting that the cerebral circulation was unable to buffer even slow changes in arterial pressure. In addition, these data suggest that after ganglion blockade, changes in CBF velocity likely depended solely on the magnitude of pressure, independent of the rate of change in pressure (the latter being the primary regulatory mechanism when the autonomic nervous system is intact).15

However, several important issues regarding the estimation of transfer function in the present study must be highlighted. First, the changes in transfer function gain and phase occurred coincident with a marked reduction in arterial pressure variability after ganglion blockade. On the basis of the presence of known nonlinearities in the cerebral circulation,16,35,36 the changes in the transfer function gain might be induced simply by the reduction of pressure variability. This consideration is particularly relevant because the coherence function between these variables was < 0.5 in the very low frequency range before blockade and was further reduced after ganglion blockade. To shed light on this issue, we applied oscillatory LBNP to regenerate arterial pressure variability at the very low frequencies. We found that oscillatory LBNP provoked prominent changes in both arterial pressure and CBF velocity. Most importantly, we found that although pressure variability was restored to the pretreatment level associated with increases in coherence function, the augmented transfer function gain and diminished phase persisted. Thus, it seems that the changes in transfer function gain and phase after ganglion blockade were not induced solely by the reduction in arterial pressure variability. Nevertheless, nonlinearities of the cerebral circulation might have contributed to the low coherence between the changes in pressure and CBF velocity at the very low frequencies.11 However, the optimal techniques for accurate quantification of these nonlinearities has yet to be determined.16,36

Second, because arterial pressure was reduced after ganglion blockade, hypotension per se may have modulated cerebrovascular tone via myogenic and/or endothelium-dependent mechanism(s)14 and thus affected the estimation of the transfer function. To elucidate this issue, we restored the reduced arterial pressure with phenylephrine infusion. Interestingly, this intervention did not affect the estimates of transfer function gain and phase after ganglion blockade, suggesting that they were not influenced significantly by the degree of reduction in arterial pressure observed in the present study.

Finally, we must acknowledge the potential effects of diminished R-R variability after ganglion blockade on the estimation of the transfer function. R-R variability may contribute to changes in CBF velocity independent of its effects on arterial pressure variability.37 Thus, estimation of the transfer function between the changes in pressure and CBF velocity may be confounded by the changes in R-R variability. However, we have considered that changes in mean CBF velocity in the MCA, and presumably changes in blood flow, are determined primarily by the driving force of mean arterial pressure. Thus, estimation of transfer function in the present study may not be affected significantly by the changes in R-R variability per se.

### Study Limitations

The fundamental limitation of the present study is that we measured CBF velocity in the MCA using transcranial Doppler rather than CBF. Changes in CBF velocity reflect changes in CBF only if the MCA diameter remains constant. Numerous studies have shown that MCA diameter in humans remains relatively constant under a variety of hemodynamic conditions.18,19,38 Therefore, we assumed that beat-to-beat changes in CBF velocity in the present study reflected primarily changes in blood flow. Moreover, we measured arterial pressure in the finger and radial artery rather than directly in the MCA for reasons of subject safety. Although arterial pressure waveforms in the finger or in the radial artery may be significantly different from those in the MCA because of pressure wave reflections, beat-to-beat changes in mean arterial pressure measured in the finger or in the radial artery likely reflect changes in mean pressure in the MCA in the supine position.39 Finally, studies in animals suggest that both sympathetic and parasympathetic nervous systems and their interactions likely play a role in the control of the cerebral circulation.40 Thus, because ganglion blockade blocks both pathways, changes in the transfer function gain and phase observed in the present study should be interpreted judiciously regarding the relative contribution of sympathetic and parasympathetic neural control of dynamic cerebral autoregulation in humans. We suspect, but cannot prove, that beat-to-beat fluctuations in sympathetic nerve activity may modulate cerebrovascular resistance and thus contribute to the changes in transfer function gain and phase observed in the present study.

In summary, we addressed a fundamental question as to whether autonomic neural activity controls dynamic CBF regulation in humans. We found that after ganglion blockade, transfer function gain between beat-to-beat changes in arterial pressure and CBF velocity increased and phase lead of CBF velocity to arterial pressure diminished at the very low frequencies <0.07Hz. In addition, steady-state CBF velocity decreased, associated with a reduction in arterial pressure. These findings suggest that both dynamic and static cerebral autoregulation are altered by the removal of autonomic neural activity. We speculate that tonic autonomic neural control of the cerebral circulation likely plays an important role in beat-to-beat CBF regulation in humans.

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