Autonomic Neural Control of the Cerebral Vasculature
Acute Hypotension

Shigehiko Ogoh, PhD; R. Matthew Brothers, PhD; Wendy L. Eubank, MS; Peter B. Raven, PhD

Background and Purpose—The effect of antihypertensive drugs on autonomic neural control of the cerebral circulation remains unclear. This study was designed to compare middle cerebral artery mean blood velocity responses to acute hypotension with and without α1-adrenoreceptor blockade (Prazosin) in young, healthy humans.

Methods—Acute hypotension was induced nonpharmacologically in 6 healthy subjects (mean±SE; 28±2 years) by releasing bilateral thigh cuffs after 9 minutes of suprasystolic resting ischemia before and after an oral dose of Prazosin (1 mg/20 kg body weight).

Results—Prazosin had no effect on thigh cuff release-induced reductions in mean arterial pressure and middle cerebral artery mean blood velocity. However, Prazosin attenuated the amount of peripheral vasoconstriction through the arterial baroreflex as evidenced by a slower return of mean arterial pressure to baseline (P=0.03). Immediately after cuff release, cerebral vascular conductance index increased through cerebral autoregulation and returned to resting values as a result of an increased perfusion pressure mediated through arterial baroreflex mechanisms. The rate of regulation, an index of cerebral autoregulation, was attenuated with Prazosin (control versus Prazosin; rate of regulation=0.204±0.020 versus 0.006±0.053/s, P=0.037). In addition, as mean arterial pressure was returning to resting values, the rate of change in cerebral vascular conductance index was decreased with Prazosin (0.005±0.006/s) compared with control (0.025±0.005/s; P=0.010).

Conclusions—These data suggest that during recovery from acute hypotension, decreases in cerebral vascular conductance index were mediated by increases in arterial blood pressure and sympathetically mediated cerebral vasoconstriction.

Key Words: arterial blood pressure ■ middle cerebral artery blood velocity ■ sympathetic activity

Animal studies have shown that cerebral arteries are richly innervated with sympathetic nerve fibers.1,2 However, the role of autonomic neural control of the cerebral circulation remains controversial. The traditional thinking is that in the presence of normocapnia, changes in sympathetic tone appear to have limited effects on cerebral blood flow (CBF).3–5 Although sympathoexcitation has little effect on CBF during rest, several investigators have reported a direct effect of sympathoexcitation on CBF associated with pathophysiology.6–9

Hypertension is a major risk factor for the development of stroke and heart disease.10 In patients with hypertension, reductions in CBF and increases in cerebrovascular resistance have been reported.11,12 Although chronic hypertension appears to shift the lower limit of CBF autoregulation to higher pressures, cerebral autoregulation is notably impaired in patients with malignant hypertension.13 Antihypertensive drug-induced decreases in blood pressure reduce the risk of acquiring major cardiovascular or cerebrovascular diseases.11,14 In addition, previous studies have reported that antihypertensive drugs, ie, α1- and β1-adrenoreceptor blockers, angiotensin type I receptor blockers, and angiotensin-converting enzyme inhibitors, directly influence the vasculature in both the cerebral and skeletal muscle circulations7,15–17 and suggest that antihypertensive drugs may compromise CBF regulation. However, the effect of antihypertensive drugs on autonomic neural control of the cerebral circulation remains unclear.

Prazosin, the α1-adrenoreceptor blocker, does not influence CBF under resting conditions in individuals who are normotensive.17 However, in patients with hypertension, a small but significant increase in CBF along with a significant decrease in blood pressure was observed after Prazosin therapy.18 Previous animal studies17,19 demonstrated that cervical spinal cord stimulation augmented CBF with decreases in sympathetic nerve activity. Interestingly, Prazosin attenuates the cervical spinal cord stimulation-induced increases in CBF.17 These findings suggest that Prazosin-induced α1-adrenoreceptor blockade interferes with autonomic neural control of the cerebral circulation, especially during changes in sympathetic activity.

Therefore, the present study was designed to investigate the effect of the α1-adrenoreceptor blocker, Prazosin, on the
regulation of middle cerebral artery blood velocity and cerebral vascular conductance index during a hypotensive-induced reduction in cerebral perfusion pressure. To accomplish this, we used a mechanical noninvasive technique to induce cerebral hypoperfusion to test the hypothesis that Prazosin would impair cerebral autoregulation and arterial baroreflex mediated sympathetic regulation of CBF.

**Methods**

**Subjects**

Four men and 2 women (age, 28 ± 2 years; height, 177 ± 4 cm; weight, 77 ± 9 kg; mean ± SEM) volunteered to participate in the present protocol. All subjects were healthy; nonsmokers; free of known cerebral vascular, cardiovascular, and respiratory disease; and were not using prescription or over-the-counter medications. Before the study, all subjects provided written informed consent, were familiarized with all the testing protocols, and were asked to abstain from drinking alcohol and caffeine and to not exercise for the 24-hour time period before any scheduled experiments. All experimental procedures were approved by the Institutional Review Board at the University of North Texas Health Science Center (Institutional Review Board 2006-33) and were in accordance with the guidelines of the Declaration of Helsinki.

**Instrumentation**

A standard 4-lead electrocardiogram was used for heart rate monitoring. A catheter (1.1-mm inner diameter, 20-gauge) was inserted into the radial artery using sterile techniques under local anesthesia with approximately 2 mL of lidocaine and aseptic conditions and was connected to a pressure transducer (Maxxim Medical, Athens, Texas) positioned at the level of the heart. This catheter was used for assessment of beat-to-beat arterial blood pressure (ABP) and for arterial blood samples, which were obtained at each condition and stored in ice water until analyzed for arterial pCO2 (Paco2; Instrumentation Laboratory model #1735, Lexington, Mass.). Additionally, a venous catheter (1.2-mm inner diameter, 18-gauge) was inserted into the median antecubital vein and was used for bolus drug injections during the phenylephrine (PE) challenge protocol. Middle cerebral artery blood velocity was obtained by transcranial Doppler ultrasonography (Multidop X, DWL, Sipplingen, Germany). A 2-MHz Doppler probe was placed over the temporal window and fixed with an adjustable headband and adhesive ultrasonic gel (Tensive; Parker Laboratories, Orange, NJ).

**Protocol**

On the experimental day, all subjects came to the laboratory in the morning approximately 2 hours after a light breakfast. After they were instrumented, the subjects were seated in a semirecumbent position (approximately 45°) in a modified car seat and rested quietly for approximately 10 minutes before any testing began. Abrupt decreases in ABP were induced nonpharmacologically by releasing bilateral thigh cuffs after 9 minutes of suprasystolic (220 mm Hg) inflation. This ensured that all subjects were at the same point in the breathing cycle to minimize the effects of respiration on the comparison of responses between cuff release trials.

**Experimental Protocols**

**Control**

The control protocol started with a 5-minute baseline period, which was followed by inflation of the thigh cuffs for 9 minutes. Immediately after the 9 minutes of cuff inflation, the cuffs were deflated and measurements were continued for an additional 3 minutes. Cuff deflation was initiated at normal end expiration as observed from the subject’s diaphragmatic movement. This ensured that all subjects were at the same point in the breathing cycle to minimize the effects of respiration on the comparison of responses between cuff release trials.

**Intervention**

The same protocol used in the control protocol was repeated in the afternoon. The only difference between the 2 protocols was that the intervention (afternoon) protocol was performed at least 2 hours after oral ingestion of the α1-adrenoreceptor antagonist Prazosin (Mylan Pharmaceuticals, Morgantown, WV). The dose of Prazosin used was the usual clinical dose of 1 mg/20 kg of body weight. The 2-hour postgestion duration before beginning the intervention protocol was chosen because it has been previously demonstrated that peak Prazosin activity occurs approximately 2 hours postgestion.

**Phenylephrine Infusion Challenge**

The validity of these results requires that the dose of Prazosin was capable of significantly inhibiting the pressor effects of α1-adrenoreceptor agonists during the afternoon protocol. Therefore, in the morning after catheterization (before any drug conditions), each subject received an intravenous bolus dose of 1.0 µg/kg body weight of the specific α1-adrenoreceptor agonist PE.21 This exact same bolus dose of PE was injected at 2 hours post-Prazosin ingestion and immediately before the afternoon intervention protocol. PE was diluted with physiological saline to yield a bolus dose equal to 1.0 µg/20 kg of body weight. The dose of PE was chosen because it has been demonstrated to evoke an increase in mean arterial pressure (MAP) of approximately 15 to 20 mm Hg.22 During the 2 PE infusion protocols, MAP was recorded and used to identify the degree of α1-adrenoreceptor receptor blockade.

**Data Analysis**

All data were sampled continuously at 1 kHz using an analog-to-digital converter interfaced with a computer. Beat-to-beat MAP and mean middle cerebral artery blood velocity (MCA Vmean) were obtained from each waveform. The cerebrovascular conductance index (CVCi) was calculated by dividing MCA Vmean by MAP and was used as an estimate of changes in cerebrovascular conductance. The derived CVCi during acute hypotension is not directly related to steady-state cerebrovascular conductance because changes in the vascular compliance and resistance affect CBF during dynamic regulation. Control values of MAP, MCA Vmean, and CVCi were defined by calculating their means during the 4 seconds immediately before the thigh cuff release. Changes in MAP, MCA Vmean, and CVCi during cuff release and recovery from cuff release were determined relative to their concomitant control values.

During the cuff release protocol, the ABP decreased abruptly and remained at a low nadir for a limited time (6 to 8 seconds). At the end of the nadir of the ABP, the arterial baroreflex gradually restored ABP toward the control value. In the present study, we identify the measurements made during the time after deflation that were unaffected by the arterial baroreflex correction of the ABP as “Phase I.” The time period starting from 1 second after the end of the nadir of ABP was identified as the onset of the arterial baroreflex control of ABP and its effect on CVCi and was designated as “Phase II” (see Figure 1).

During Phase I at time 1.0 to 3.5 seconds, the rate of the change in CVCi is directly related to cerebral autoregulation without arterial baroreflex regulation.22 The rate of regulation (RoR) is calculated as an index of cerebral autoregulation.

\[
\text{RoR} = \left( \frac{\Delta \text{CVCi}}{\Delta T} \right) / \Delta \text{MAP}
\]

where ΔCVCi/ΔT is the slope of the linear regression between CVCi and time (T) and ΔMAP was calculated by subtracting control MAP from averaged MAP during Phase I.

One second after the onset of the arterial baroreflex correction of the nadir of the hypotensive ABP (ie, the beginning of Phase II) through the fourth second of Phase II, the rate of the change in CVCi is related to cerebral autoregulation and arterial baroreflex sympathetic activation. During Phase II, the slope of the linear regression between MAP and T (ΔMAP/ΔT), MCA Vmean, and T (ΔMCA Vmean/ΔT), and CVCi and T (ΔCVCi/ΔT) were calculated to identify the effect of an increase in sympathetic activity on the cerebral vasculature. In addition, the ratio between ΔMAP/ΔT and Δ MCA Vmean/ΔT was calculated to identify the effect of perfusion pressure on MCA Vmean (ie, cerebral autoregulation) during Phase II.
Figure 1. Representative normalized beat-to-beat data of continuous recordings of MAP, MCA \( V_{\text{mean}} \), and CVCi during thigh cuff release with (right panel) and without Prazosin (left panel) in 2 individual subjects. The thigh cuffs were released at time 0. Straight lines through data were determined by linear regression analysis in Phase I (1 to 3.5 seconds after cuff release) and II (1 second after the start of increasing ABP). All data are shown in normalized units relative to control prerelease values obtained during -4 to 0 seconds. Upper panel, In this subject, Prazosin impaired the recovery of middle cerebral artery blood velocity (Phase II) despite no change in the recovery of MAP, whereas middle cerebral artery blood velocity returned to baseline quickly and was well maintained in Phase II without Prazosin. Lower panel, In this subject, Prazosin caused an increase in middle cerebral artery blood velocity over the control value during recovery (Phase II) despite slow MAP recovery.
Results

The MAP responses to PE challenge pre- and post-Prazosin ingestion are illustrated in the Table. During control rest, PE yielded an increase in MAP of 14.5±0.4 mm Hg. Two hours post-Prazosin ingestion (ie, immediately before the start of the afternoon’s intervention protocol), the same dose of PE yielded an increase in MAP of 3.5±0.2 mm Hg (76±2% blockade). This identifies a significant functional blockade of α1-adrenoceptors during the afternoon intervention protocol. However, during the resting period all hemodynamic variables; heart rate, MAP, MCA Vmean, CVCi, and PaCO2, were unchanged by the oral ingestion of Prazosin.

Phase I (1 to 3.5 seconds after thigh cuff release)

The release of the thigh cuffs elicited an acute decrease in ABP (Figure 1). Changes in MAP were −30.1±2.6% and −33.8±3.1% without and with Prazosin, respectively. These decreases in ABP were sufficient to evoke a transient decrease in MCA Vmean and a marked cerebral autoregulatory response. Although the initial response to the decrease in ABP was a transient decrease in the MCA Vmean, the cerebral autoregulatory response gradually corrected the CVCi to prehypotensive values within 3.5 seconds of Phase I, thus preventing further decreases in MCA Vmean (Figure 1). Therefore, the return of MCA Vmean to the baseline velocity was much faster than that of ABP.

The RoR was calculated from the change in CVCi in Phase I (1 to 3.5 seconds) for each subject (Figure 2). The increase in CVCi was attenuated by Prazosin; thus, the RoR was significantly higher in the control condition compared with Prazosin (0.212±0.041 versus 0.089±0.050/s, P=0.021).

Although there was no significant difference in the thigh cuff release-induced decrease in absolute MCA Vmean between the control and Prazosin conditions (Table), the percent change in MCA Vmean with Prazosin was significantly larger (−35.1±3.2%) compared with the control condition (−26.8±2.4%; P=0.020).

Phase II (1 to 4 seconds after the start of increasing arterial blood pressure)

There was no significant difference in the MAP response to the thigh cuff release in Phase I between control and Prazosin conditions (−27±3 versus −28±2 mm Hg, P=0.666 and −30.1±2.6 versus −33.8±3.1, P=0.210; Table). However, the arterial baroreflex correction of the hypotensive ABP during Phase II was significantly decreased by Prazosin (0.025±0.005 to 0.009±0.005/s, P=0.030; see Figures 1 and 3).

Interestingly, the contribution of sympathetic activation on the return of ABP in Phase II was variable for each subject as evidenced by the variable effect of Prazosin on the rate of return of MAP compared with its respective control condition (Figure 3). In contrast, there was no significant difference in
the rate of return of MCA $V_{\text{mean}}$ between control and Prazosin conditions (0.007±0.007 versus 0.007±0.003/s, $P=0.948$; see Figures 1 and 4). However, in Phase II during the control condition, MCA $V_{\text{mean}}$ was maintained constant, whereas Prazosin elicited a variable MCA $V_{\text{mean}}$ response during Phase II (Figure 4). In addition, CVCi remained high and did not return to baseline values during the Prazosin condition. In contrast, the CVCi in the control condition returned to baseline values during Phase II (Figure 5). Therefore, the rate of return of MAP and MCA $V_{\text{mean}}$ during the Prazosin condition was significantly different from the control (0.179±0.169 versus 1.756±0.518, $P=0.023$; Figure 6).

Discussion

By comparing changes in cerebral vascular conductance during the early phase (Phase I) and late phase (Phase II) of the recovery response to a transient hypotension with and without $\alpha_1$-adrenergic blockade using Prazosin, we have identified an important functional role of sympathetic vasoconstriction in the regulation of CBF. These findings are in contrast to a number of investigations, which indicate little or no effect of sympathetic activation on the regulation of CBF.3–5 The different conclusions of the present study compared with the previous studies are probably related to the different experimental designs and analyses. The present study evaluated dynamic cerebrovascular responses to transient perturbations of ABP, whereas the previous investigations evaluated the cerebrovascular responses to changes in ABP during steady-state hemodynamic conditions.

Phase I: Cerebral Autoregulation

In the present study, we examined the CBF response to an acute hypotensive stimulus during Phase I, ie, the time before any possibility of an arterial baroreflex-mediated restoration of ABP.22 Prazosin significantly decreased the RoR of the cerebral vascular conductance by cerebral autoregulation to resting values (see Figure 2). In addition, Prazosin blockad centuated the decrease in MCA $V_{\text{mean}}$ during the acute hypotensive stimuli. These results suggest that cerebral autoregulation was impaired by $\alpha_1$-adrenoreceptor blockade and suggests that sympathetic vasoconstriction affects cerebral autoregulation. This finding is in accord with previous studies.23–24 Morita et al23 reported in rats that CBF was...
decreased with stepwise reductions in ABP after sympathetic denervation, indicating impaired cerebral autoregulation. Moreover, Zhang et al. analyzed transfer function gain, phase, and coherence between MAP and CBF in humans before and after ganglion blockade with trimethaphan. The findings indicated an increased gain and diminished phase after ganglion blockade, suggesting that dynamic cerebral autoregulation was impaired by the removal of autonomic neural activity.

Cerebral autoregulation of CBF has been demonstrated to be primarily mediated by myogenic and metabolic mechanisms. However, Aaslid et al. have reported that cerebral autoregulation was also affected by the basal vascular tone. They demonstrated that there was a highly significant relationship between Paco2 and cerebral autoregulation and confirmed a previous report in which Paco2 was found to strongly influence the vascular tone of cerebral vascular smooth muscle and resultant changes in CBF. Recently, it has been demonstrated that the autonomic nervous system does have a controlling influence on cerebral vasculature tone. D’Aleye et al. demonstrated that direct electric stimulation of the stellate ganglion in dogs reduced CBF even during profound hypercapnic-mediated vasodilation. In addition, Jordan et al. demonstrated that sympathetic nerve activation attenuated the CO2-induced increase in CBF. Moreover, sympathetic activation decreased PaCO2 by causing hyperventilation; thus, it can indirectly increase cerebrovascular tone.

In the present study, the oral ingestion of the α1-adrenergic-blocking drug, Prazosin, during rest did not directly increase MCA Vmean (Table). However, it has been reported that medications that induce vasodilation tend to cause mild changes in vascular tone; therefore, it was possible that after Prazosin ingestion, cerebral autoregulatory mechanisms compensated for the decreases in vascular tone and maintained CBF constant. In contrast, previous studies using direct stimulation of sympathetic nerves in rats, cats, and primates demonstrated that cerebral vasoconstriction occurred in response to sympathetic nerve activation. Furthermore, parasympathetic nerve stimulation resulted in cerebral vasodilation in rats. These findings suggest that the autonomic nervous system regulates the cerebral circulation through altering the vascular tone of the cerebral smooth muscle. In addition, although baseline CBF was not altered after removal of autonomic neural activity in humans, cerebral autoregulation was impaired.

Lassen established cerebral autoregulatory range of MAP in humans to be on average from 60 to 150 mm Hg. In the present study, Prazosin tended to decrease MAP (Table). If Prazosin were to have decreased MAP to a pressure below the lower blood pressure limit (60 mm Hg) of cerebral autoregulation, we would have expected to have observed impaired cerebral autoregulation. However, the individual MAPs with and without Prazosin in all subjects (78 to 102 mm Hg) remained within their cerebral autoregulatory range. In addition, during the control period, Prazosin did not significantly decrease MCA Vmean, suggesting that static cerebral autoregulation was well maintained. Moreover, the differences in profound hypercapnic-mediated vasodilation. In addition, Jordan et al. demonstrated that sympathetic nerve activation attenuated the CO2-induced increase in CBF. Moreover, sympathetic activation decreased PaCO2 by causing hyperventilation; thus, it can indirectly increase cerebrovascular tone.

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Prazosin-induced changes in MAP did not influence the RoR response, indicating that the Prazosin blockade of the α1-adrenergic receptor and its corresponding change in MAP was not a limitation to our interpretation of the data. However, during the cuff release hypotension challenges, the minimum MAP was close to the lower blood pressure limit of cerebral autoregulation in both conditions. In addition, the minimum MAP in the Prazosin condition was lower than control (57 ± 4 mm Hg with Prazosin compared with 64 ± 4 mm Hg during the control; P = 0.125). It has been shown that maximal or near-maximal dilatation at the arteriolar bed that occurs at cerebral autoregulation threshold alters the autoregulatory response. Therefore, it is possible that the greater vasodilation that occurred during the Prazosin condition may have been a factor in the observed impaired RoR response.

**Phase II: Cerebral Autoregulation and Arterial Baroreflex Control of the Cerebral Vasculature**

To identify arterial baroreflex-mediated increases in sympathetic activity in response to the cuff release-induced hypotension, we analyzed the CBF response to changes in ABP in Phase II from the first to the fourth second of responses recorded from the start of increases in ABP after the nadir in ABP (see Figure 1). We observed no significant difference in the decrease of MAP in response to the thigh cuff release between control and Prazosin conditions (P = 0.666; Table); however, in Phase II, Prazosin significantly (P = 0.030) decreased the rate of return of MAP (Figures 1 and 3). These findings clearly demonstrate that increased sympathetic activity through arterial baroreflex disengagement was an important mechanism for the return of ABP to baseline values after acute hypotension. It should be noted that the contribution of sympathetic activation to the degree of the ABP correction in Phase II was variable among the individual subjects. This variability in the baroreflex correction appeared to be related to the differences in the correction rate of the MAP in the Prazosin condition compared with the control condition (see Figure 3).

In contrast to the changes in ABP during Phase II, there was no significant difference in the rate of return of MCA $V_{\text{mean}}$ with and without Prazosin (Figure 4). The change in MCA $V_{\text{mean}}$ observed during the control condition is consistent with a previous report. Because the intrinsic cerebral autoregulatory mechanisms correct changes in CBF faster than those of the arterial baroreflex-mediated regulation of ABP, the MCA $V_{\text{mean}}$ returned to baseline values before the arterial baroreflex-mediated corrections of ABP were completed.

Importantly, during the control condition, MCA $V_{\text{mean}}$ was well maintained around its baseline value (1.0) in Phase II despite increased ABP (Figure 4). This phenomenon is clearly related to the autonomic nervous system, because Prazosin varied the MCA $V_{\text{mean}}$ response. During the Prazosin condition in Phase II, the MCA $V_{\text{mean}}$ of some subjects continued to increase above baseline values, whereas the MCA $V_{\text{mean}}$ of other subjects was lower than their baseline value (Figure 4). These MCA $V_{\text{mean}}$ responses are related to the change in CVCi in Phase II. The recovery CVCi remained high and did not return to baseline during the Prazosin condition in Phase II; in contrast, the high CVCi returned to baseline during Phase II of the control condition (Figure 5). These findings suggest that, in contrast to the control condition, Prazosin maintained cerebral vasodilation in the Phase II period of recovery. In addition, the ratio of the return rate of MAP and MCA $V_{\text{mean}}$ was significantly higher during the Prazosin condition than in the control condition ($P = 0.023$; Figure 6). These findings indicate that in the Prazosin condition, the effect of perfusion pressure on MCA $V_{\text{mean}}$ was much higher than the control.

The data from the present investigation strongly suggest that in humans sympathetic neural control of the cerebral vasculature provides dynamic functional control of CBF during acute hypotension. In animal models, the response of the cerebral vasculature to changes in sympathetic nerve activity during hypertension has been demonstrated to protect the blood–brain barrier from disruption. Furthermore, direct stimulation of the stellate ganglion and the superior cervical ganglion produced marked vasoconstriction in the normotensive primate. In addition, the data of the present study identify that arterial baroreflex regulation of systemic ABP during hypotension works in consort with cerebral autoregulation to return CBF to baseline values.

**Clinical Implications**

Chronic untreated hypertension increases one’s risk for stroke. In general, when diuretic or angiotensin inhibition therapy fails or becomes accommodated, additional antihypertensive drug-induced therapy using α1-adrenergic receptor inhibition is used to decrease the risk of acquiring major cardiovascular diseases and stroke. In the present study, a single dose of the antihypertensive drug, Prazosin, impaired the normal regulation of CBF during acute hypotension. This finding suggests that during α1-adrenoceptor blockade, there could potentially be hyperperfusion of the brain after a transient hypertensive stimuli, which may result in a breakdown of the blood–brain barrier. However, the present study only investigated healthy subjects. Patients with hypertension usually have high sympathetic nerve activity and increases in cerebrovascular resistance. In addition, patients with hypertension chronically using antihypertensive therapy may respond differently than the healthy subjects used in these experiments.

**Limitations**

Potential limitations of the present study should be considered. Transcranial Doppler is widely used to detect acute changes in cerebral perfusion. However, transcranial Doppler measures CBF velocity in the MCA rather than CBF. Blood velocity reflects blood flow only if the diameter of the insonated blood vessel remains constant. However, the middle cerebral artery diameter changes little with acute hemodynamic perturbations such as those elicited during the thigh cuff release protocol. In addition, during conditions in
which increases in sympathetic activity are manifest, the middle cerebral artery diameter remains relatively constant. 40 Therefore, we assumed that because the steady-state measures of the middle cerebral artery blood velocity reflected the steady-state measures of the CBF, the transcranial Doppler measures of the transient changes in MCA Vmean reflected the transient changes in CBF. 22,39–41

Recently, Ainslie et al 52 demonstrated that cerebral autoregulation exhibited a diurnal rhythm in which cerebral autoregulation was lowest in the morning and highest in the afternoon. In the present study, the protocol required a period of 2 hours postgestation of Prazosin to establish maximum efficacy. These 2 hours were incorporated between morning and afternoon in an experimental session and required that we incorporate an order effect into the experimental design. Because the decrease in cerebral autoregulation through α1-adrenoceptor blockade was observed in the afternoon protocol, the presence of a normal diurnal rhythm in cerebral autoregulation would further support the conclusions of the present study. In contrast to the previous investigations in which more than one thigh deflation test was used to analyze RoR for each condition, 22 the present study incorporated only one thigh cuff deflation-induced hypotensive challenge during control and Prazosin conditions. Although the repeatability of the data was unclear, we suggest that the conclusions drawn from the data would be unchanged, even if we had identified a variability in the response across repeated challenges because of the large difference in the RoR between the 2 conditions, ie, the RoR of Phase I without drug was 2.5 times more than that with Prazosin.

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Disclosures
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