Effects of Local Reduction in Pressure on Endothelium-Dependent Responses of Cerebral Arterioles

Gary L. Baumbach, MD; Frank M. Faraci, PhD; Donald D. Heistad, MD

Background and Purpose  The goal of this study was to examine effects of local reductions in intravascular pressure and dP/dt on endothelium-dependent responses of cerebral arterioles in normotensive Wistar-Kyoto rats (WKY) and stroke-prone spontaneously hypertensive rats (SHRSP).

Methods  WKY and SHRSP underwent clipping of one carotid artery at 1 month of age. At 6 months of age, responses of pial arterioles were examined in vivo in anesthetized rats. Bilateral craniotomies were performed to expose pial arterioles in the sham-operated and clipped cerebral hemispheres. Pressure (servo-null) was measured in sham-operated and clipped pial arterioles, and arteriolar diameter was measured before and during suffusion with bradykinin, A23187, and nitroprusside.

Results  Carotid clipping normalized pial arteriolar pulse pressure but not mean pressure in SHRSP. Responses of sham-operated pial arterioles to bradykinin and A23187 were less in SHRSP than in WKY. Responses of sham-operated pial arterioles to nitroprusside were greater in SHRSP than in WKY. Carotid clipping in SHRSP normalized responses of pial arterioles to bradykinin but not A23187 and had no effect on responses to nitroprusside.

Conclusions  These findings suggest that elevated intravascular pressure per se may contribute to impairment of endothelium-dependent relaxation to at least some agonists in cerebral arterioles during chronic hypertension. Furthermore, the findings lead us to speculate that arteriolar pulse pressure may play a more important role than mean pressure in development of impaired endothelium dilation during chronic hypertension. (Stroke. 1994;25:1456-1462.)

Key Words  • bradykinin  • calcium  • cerebral blood flow  • hypertension  • rats

See Editorial Comment, page 1461

Chronic hypertension impairs endothelium-dependent relaxation of cerebral arterioles to a variety of agents including acetylcholine,1 adenosine diphosphate,2 bradykinin,3 and A23187.4 It is not clear, however, whether increases in intravascular pressure contribute directly to impairment of endothelium-dependent relaxation during chronic hypertension. Based on the effects of treatment with hydralazine, reserpine, and hydrochlorothiazide, Luschér et al4 suggested that increases in arterial pressure probably play an important role in attenuation of endothelium-dependent relaxation of aorta in Dahl salt-sensitive hypertensive rats. In contrast, the effects of treatment with an angiotensin-converting enzyme (ACE) inhibitor led Clozel et al5 to suggest that humoral and neural factors may contribute more importantly than increases in arterial pressure to impaired endothelium-dependent relaxation of aorta in spontaneously hypertensive rats (SHR).

The first goal of this study was to determine whether increases in intravascular pressure per se play an important role in impairment of endothelium-dependent dilatation of cerebral arterioles of stroke-prone spontan-
anesthetized with sodium pentobarbital (25 mg · kg⁻¹ body weight IP), and a clip was placed on the left common carotid artery. Clips with a gap size of 0.30 mm were made from 2-mm strips of silver sheet. The right carotid artery was exposed but not clipped. Because we could not exclude damage to sympathetic nerves by the carotid clip, the superior cervical ganglia were removed on both sides. All rats had pithos bilaterally.

About 5 months after carotid clipping, we measured local microvascular pressure and examined changes in diameter of first-order pial arterioles to endothelium-dependent and endothelium-independent agents. Animals were anesthetized with pentobarbital sodium (50 mg · kg⁻¹ body weight IP) and mechanically ventilated with room air supplemented with oxygen. Parasystolic muscle was induced with gal-lamine triethiodide (20 mg · kg⁻¹ IV). Because the animals were paralyzed, we evaluated them frequently for adequacy of anesthesia. Additional anesthesia was administered when pressure to a paw evoked a change in blood pressure or heart rate.

A catheter was inserted into a femoral vein for infusion of drugs and fluids. A catheter was inserted into a femoral artery to record systemic arterial pressure and obtain blood samples.

**Measurement of Pial Arteriolar Pressure and Diameter**

Pressure and diameter were measured in first-order pial arterioles from both the right (sham-operated) and left (clipped) cerebral hemispheres using an open cranial window preparation that we have described in detail previously. We have shown previously that first-order pial arterioles in WKY and SHRSP correspond to the arteriolar segment immediately distal to the fourth-order branching point of the middle cerebral artery. After placing the animal in a head holder, the skull was exposed through a 1-cm incision in the skin, the skin edges were retracted with sutures, and ports were placed for inflow and outflow of artificial cerebrospinal fluid (CSF). A dam of dental acrylic was constructed along the exposed portion of the superior sagittal suture. Cerebrometanies were made over the parietal cortex of the left and right cerebral hemispheres with an air-cooled dental drill. The dura was incised to expose pial vessels. Cerebrometanies over exposed cerebrum were suffused continuously with artificial CSF, warmed to 37°C, and equilibrated with a gas mixture of 5% CO₂-95% N₂. The composition of the CSF was (in mmol/L): KCl 3.0, NaCl 131.9, CaCl₂ 1.5, NaH₂CO₃ 24.6, urea 6.7, and dextrose 3.7. The CSF sampled from the cistiotomy had a pH of 7.25±0.01 (mean±SE of mean), PCO₂ of 48±1 mm Hg, and PO₂ of 59±1 mm Hg.

Mean, systolic, and diastolic pressures and dP/dt were measured continuously in pial arterioles using a micropipette coupled to a servo-null pressure measuring system. Pial arteriolar pressure was calculated as pial arteriolar systolic minus diastolic pressure. The frequency response of the servo-null unit (model 5, Instruments for Physiology and Medicine, Inc) is DC to 30 Hz. Pipettes were sharpened to create a beveled tip of 2 to 4 μm, filled with 1.5 mol/L NaCl, and inserted into the lumen of a pial arteriole. To ensure consistency of quality and size of micropipette tips, pipettes were examined with a light microscope equipped with an ocular micrometer. Only pipettes with an inner-tip diameter of 2 to 4 μm and a smooth bevel were used for measuring pial arteriolar pressure. To ensure that pipette tips remained unobstructed while inserted in the vascular lumen, we added heparin to the hypertonic saline that was used to fill pipettes, closely monitored pipette resistance and bridge balance settings, and frequently checked the pipette tip using the intravitreal microscope. If any evidence of obstruction was detected, either visually or electrically, the pipette tip was reinserted, flushed with hypertonic saline, and reinserted in a different site in the same arteriole or a different arteriole.

Pial vessels were monitored through a Leitz microscope (NI 10× objective) connected to a closed-circuit video system with a final magnification of ×354. Pial arteriolar diameter was measured from videotapes using a Bioquant image analyzing system (R&M Biometrics, Inc). The precision of the Bioquant system is 0.4 to 0.6 μm.

**Experimental Protocol**

Cerebral vessels were superfused with artificial CSF for 30 minutes before testing responses of arterioles. We then examined the responses of first-order pial arterioles to the endothelium-dependent agents, bradykinin (10⁻², 10⁻³, and 10⁻⁴ mol/L) and the calcium ionophore, A23187 (10⁻⁴ and 10⁻³ mol/L). To determine if chronic hypertension and carotid clipping altered dilatation of cerebral arterioles to an agent that is not endothelium dependent, we examined responses of pial arterioles to nitroprusside (10⁻⁴ and 10⁻³ mol/L).

Bradykinin, A23187, and nitroprusside were purchased from Sigma Chemical Co. Drugs were mixed in artificial CSF and then superfused over the cerebral microcirculation. A23187 was dissolved in dimethylsulfoxide before mixing in artificial CSF. Application of vehicle did not affect arteriolar diameter. With the exception of A23187, the diameter of pial arterioles was measured immediately before application of agents and at intervals of 30 to 45 seconds for 5 minutes during application of agents. Steady-state responses to bradykinin and nitroprusside were reached within 1 to 2 minutes after application. Values obtained at steady state are reported in this study. Because increases in diameter of pial arterioles in response to A23187 are relatively slow, diameter of pial arterioles was measured after continuous superfusion with A23187 for 10 minutes.

**Statistical Analysis**

Comparison of interventions with control values obtained in the same animal was performed using a paired t test or a one-way ANOVA with a Tukey test. Results between separate groups of animals were compared with an unpaired t test, using the Bonferroni correction when multiple comparisons were made. A probability value of .05 was considered to be significant.

**Results**

**Control Conditions**

Diameter of sham-operated pial arterioles was significantly less in SHRSP than in WKY (Table). Carotid clipping did not significantly alter diameter in either group of rats. Carotid clipping reduced systolic and diastolic pressure, mean pressure, and pulse pressure in pial arterioles in both groups of rats (Table). Systolic, diastolic, and mean pressures were significantly greater in pial arterioles ipsilateral to the carotid clip in SHRSP than in WKY. Pulse pressure, on the other hand, was not significantly different in pial arterioles ipsilateral to the clip in the two groups. Thus, carotid clipping
Baseline Measurements in Sham and Clipped Pial Arterioles of Wistar-Kyoto Rats and Stroke-Prone Spontaneously Hypertensive Rats

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<tr>
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<th>WKY</th>
<th>SHRSP</th>
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<tr>
<td></td>
<td>Sham</td>
<td>Clipped</td>
</tr>
<tr>
<td>Systemic arterial mean pressure, mm Hg</td>
<td>117±3</td>
<td>181±4*</td>
</tr>
<tr>
<td>Pial arteriolar pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>82±3</td>
<td>63±2*</td>
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<tr>
<td>Diastolic pressure</td>
<td>60±2</td>
<td>49±2*</td>
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<tr>
<td>Mean pressure</td>
<td>67±2</td>
<td>54±2*</td>
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<tr>
<td>Pulse pressure</td>
<td>22±2</td>
<td>14±1*</td>
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<tr>
<td>Pial arteriolar dP/dt, mm Hg/s</td>
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<tr>
<td>Systolic peak dP/dt</td>
<td>601±56</td>
<td>307±22*</td>
</tr>
<tr>
<td>Diastolic peak dP/dt</td>
<td>-203±18</td>
<td>-124±10*</td>
</tr>
<tr>
<td>Pial arteriolar diameter, μm</td>
<td>46±2</td>
<td>48±2</td>
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Arterial blood gases

<table>
<thead>
<tr>
<th></th>
<th>WKY</th>
<th>SHRSP</th>
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<tr>
<td></td>
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<tr>
<td>Pco₂, mm Hg</td>
<td>36±1</td>
<td>37±1</td>
</tr>
<tr>
<td>pH</td>
<td>7.37±0.01</td>
<td>7.37±0.01</td>
</tr>
<tr>
<td>Po₂, mm Hg</td>
<td>114±11</td>
<td>120±8</td>
</tr>
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WKY indicates Wistar-Kyoto rats; SHRSP, stroke-prone spontaneously hypertensive rats. Values are mean±SE in 15 WKY and 14 SHRSP.

*P<.05 vs sham-operated arterioles in WKY; †P<.05 vs sham-operated arterioles in SHRSP; ‡P<.05 vs clipped arterioles in WKY.

reduced pulse pressure more effectively than systolic, diastolic, or mean pressure in pial arterioles of SHRSP.

Systolic and diastolic dP/dt in sham-operated pial arterioles were not significantly different in WKY and SHRSP (Table). Carotid clipping reduced systolic and diastolic dP/dt to similar levels in the two groups. The findings suggest that, in contrast to pulse pressure, dP/dt is not increased in pial arterioles of SHRSP and that carotid clipping reduces arteriolar dP/dt as effectively in WKY as in SHRSP.

Responses to Bradykinin and A23187

Bradykinin produced dilatation of sham-operated pial arterioles in WKY and SHRSP, and responses to the middle and high doses of bradykinin were impaired in SHRSP (Fig 1). Carotid clipping in WKY did not significantly alter responses of pial arterioles to bradykinin. In contrast, clipping in SHRSP significantly increased responses of pial arterioles to the highest dose of bradykinin. Furthermore, vasodilator responses to bradykinin after clipping were similar in WKY and SHRSP (Fig 1). Thus, after carotid clipping, endothelium-dependent dilatation of pial arterioles in SHRSP to bradykinin was normal.

The calcium ionophore A23187 produced dilatation of pial arterioles in WKY and had minimal effects on diameter in SHRSP (Fig 2). Responses of pial arterioles to A23187 were not altered by carotid clipping in either group of rats. Thus, impaired endothelium-dependent dilatation to A23187 in pial arterioles of SHRSP was not normalized by carotid clipping.

Responses to Nitroprusside

Nitroprusside produced dilatation of pial arterioles in WKY and SHRSP (Fig 3). Responses of pial arterioles to nitroprusside were significantly greater in SHRSP than in WKY. Carotid clipping did not alter responses of pial arterioles to nitroprusside in either group of rats. These findings indicate that carotid clipping did not produce nonspecific improvement of cerebral arteriolar dilatation in SHRSP.

Discussion

There are three new findings in this study. First, carotid clipping restores dilator responses of pial arterioles in SHRSP to bradykinin. This finding suggests that intravascular pressure per se may contribute to impairment of endothelium-dependent relaxation in cerebral arterioles during chronic hypertension. Second, in contrast to responses to bradykinin, carotid clipping does not restore responses of pial arterioles in
are mean±SEM. *P<.05 vs sham-operated arterioles in WKY rats.

Values are mean±SEM. *P<.05 vs sham-operated arterioles in WKY rats; †P<.05 vs sham-operated arterioles in SHRSP.

SHRSP to A23187. Third, restoration of responses in pial arterioles of SHRSP to bradykinin was accompanied by normalization of pulse pressure but not systolic, diastolic, or mean pressure or arteriolar dp/dt. This finding suggests that pulse pressure may play a more important role than other components of arterial pressure or dp/dt in the development of impaired endothelium dilatation during chronic hypertension.

Consideration of Methods

The goal of carotid clipping was to lower intravascular pressure in pial arterioles of one cerebral hemisphere while maintaining the same conditions in both hemispheres with respect to neural and humoral regulation of cerebral blood vessels. Because there may be an interaction between sympathetic nerves and endothelium-dependent relaxation and because of the close proximity of the internal carotid artery and sympathetic nerves, we were concerned that the carotid clip, or fibrosis induced by the clip, might damage sympathetic nerves and thus alter endothelium-dependent responses of pial arterioles independently of reductions in pial arteriolar pressure. To ensure that pial arterioles in both cerebral hemispheres were exposed to the same level of sympathetic input during the interval between placement of the carotid clip and examination of arteriolar responses, we removed the superior cervical ganglia on both sides at the time the clip was placed.

Another goal of this study was to examine effects of carotid clipping on agents that produce endothelium-dependent dilatation of cerebral arterioles by different mechanisms. Both bradykinin and A23187 produce endothelium-dependent dilatation in cerebral arterioles. The rationale for using bradykinin was that responses to bradykinin are receptor dependent and mediated by oxygen radicals. Responses to A23187, on the other hand, are receptor independent and may be mediated in part by prostaglandin I₂. Dilator responses of cerebral arterioles to both bradykinin and A23187 are impaired in SHRSP.

In relation to the agonists that were used in this study, neither bradykinin nor A23187 appear to evoke endothelium-dependent dilatation of pial arterioles through release of the classic nitric oxide–type endothelium-derived relaxing factor (EDRF). This distinction is important because endothelium-dependent agonists that release nitric oxide may behave differently than bradykinin or A23187 in response to carotid clipping.

Several agents that release EDRF also can release an endothelium-derived contracting factor, particularly in SHR. Synthesis of one type of endothelium-derived contracting factor is inhibited by indomethacin. We therefore considered the possibility that impairment of cerebral vascular responses to bradykinin by elevated intravascular pressure in SHR might be related to corelease of an endothelium-derived contracting factor through the cyclooxygenase pathway. Because indomethacin inhibits the normal cerebral vasodilatation in response to bradykinin and A23187 in rats, however, we were unable to test this possibility.

A potential concern in relation to methodology is that the pH of artificial CSF used in this study to suffuse pial arterioles was lower (pH = 7.25±0.01) than the pH of samples of CSF obtained from cisterna magna in unanesthetized rats (pH = 7.36 to 7.40). Although it was comparable to the pH of perivascular CSF in cats and lower than the pH of artificial CSF in our previous studies. We considered the possibility that low pH in CSF might have reduced the responses to dilator stimuli in this study. In a previous study, however, in which the pH of the CSF used to suffuse pial arterioles was 7.32, we found that suffusion with bradykinin (3×10⁻⁷ mol/L) and nitroglycerin (10⁻⁵ mol/L) resulted in about 30% and 25% dilatation of pial arterioles in WKY, respectively. In this study, suffusion with bradykinin (10⁻⁶ mol/L) and nitroprusside (10⁻³ mol/L) resulted in similar amounts of pial arteriolar dilatation in WKY (about 25% with both bradykinin and nitroprusside), even though artificial CSF used to suffuse arterioles had a lower pH (7.25). These findings suggest that a small reduction in pH of CSF may not significantly attenuate responses of pial arterioles to endothelium-dependent or endothelium-independent stimuli.

Consideration of Previous Studies

Previous studies have focused on the effects of antihypertensive treatment on endothelium-dependent relaxation in aorta. Lüscher et al. found that treatment with hydralazine in combination with reserpine and hydrochlorothiazide prevents or reverses impaired endothelium-dependent responses to acetylcholine and adenosine.
diphosphoglycerate in aorta of Dahl salt-sensitive hypertensive rats. In a similar study, Nigro et al. found that treatment with hydralazine alone restores responses to acetylcholine in aorta of SHR. Although a direct effect of treatment on endothelium-dependent dilatation could not be ruled out in either of these studies, Lüscher et al. concluded that normalization of endothelium-dependent relaxation in aorta of Dahl salt-sensitive rats by antihypertensive treatment was likely related to pressure-lowering effects rather than direct effects of antihypertensive agents on endothelium.

Other studies, however, suggest that the effects of antihypertensive treatment on endothelium-dependent dilatation may not be related primarily to effects on arterial pressure. Treatment with an inhibitor of ACE, but not hydralazine, reversed impaired responses to acetylcholine in aortic rings of SHR. Furthermore, the ACE inhibitor reversed impairment of endothelium-dependent relaxation in SHR after only 4 days of treatment, even though it did not lower blood pressure in that time as effectively as hydralazine. In addition, treatment with subpressor doses of captopril potentiated endothelium-dependent relaxation in aorta of normotensive Sprague-Dawley rats. Based on previous studies, therefore, the contribution of increased pressure to impairment of endothelium-dependent relaxation is not clear.

In contrast to previous studies, we used a nonpharmacologic method to examine the effects of antihypertensive treatment. Because neurohumoral factors were the same on the sham-operated and clipped sides of the brain, the findings that responses of pial arterioles to bradykinin were normalized in SHRSP by carotid clipping suggests that increases in arteriolar pressure are an important factor in impairment of endothelium-dependent dilatation in cerebral arterioles during chronic hypertension.

We have considered mechanisms by which carotid clipping normalized responses to bradykinin in pial arterioles of SHRSP, even though it failed to normalize pial arteriolar systolic, diastolic, or mean pressure. Carotid clipping reduced pulse pressure more effectively than systolic, diastolic, and mean pressure in pial arterioles of SHRSP. We suggested previously that hypertrophy in cerebral arterioles of SHRSP may be related to increases in pulse pressure rather than increases in mean, systolic, or diastolic pressure. The findings in this study suggest that impairment of endothelium-dependent responses in cerebral arterioles of SHRSP, as well as development of vascular hypertrophy, may be related to increases in pulse pressure. An alternative possibility is that impairment of responses of pial arterioles to bradykinin does not occur until pial arteriolar pressure is increased above a critical threshold that is lower than pressures normally found in pial arterioles of SHRSP but higher than pressures normally found in pial arterioles of WKY. Thus, even though pial arteriolar systolic, diastolic, and mean pressures were not normalized by carotid clipping in SHRSP, these parameters may have been reduced sufficiently to produce normalization of pial arteriolar responses to bradykinin in SHRSP.

In contrast to effects in SHRSP, carotid clipping in WKY did not alter responses of pial arterioles to bradykinin, despite reduction of pial arteriolar pulse pressure in WKY as well as in SHRSP. This finding suggests that endothelium-dependent responses to bradykinin may remain stable within a fairly broad range of arteriolar pressure and only become impaired at high levels of pressure. Another interpretation of the finding is that there is not a linear relation between the magnitude of pial arteriolar pulse pressure and the magnitude of pial arteriolar response to bradykinin.

Based on our previous finding that responses of pial arterioles to nitroglycerin were similar in SHRSP and WKY, we anticipated that responses of pial arterioles to nitroprusside in this study also would be similar in the groups. Instead, responses to nitroprusside were increased in SHRSP. A possible explanation for this finding is that production or release of EDRF by pial arteriolar endothelium may be less in SHRSP than in WKY, in which case levels of cyclic GMP in pial arteriolar smooth muscle would be expected to be lower in SHRSP. A reduction in cyclic guanosine monophosphate levels might lead to upregulation of guanylate cyclase activity in response to nitroprusside and thus to an increase in dilator responses of pial arterioles. Another possibility is that vasoconstrictor tone is greater in SHRSP than in WKY, which in turn might augment vasodilator responses in SHRSP.

**Functional Implications**

We have found that carotid clipping normalizes pulse pressure, but not other components of pressure or dP/dt, in cerebral arterioles of SHRSP and at the same time prevents impairment of dilator responses to bradykinin. In contrast, clipping does not prevent impairment of responses to A23187 in cerebral arterioles of SHRSP. These findings may have important functional implications in relation to mechanisms of impaired endothelium-dependent responses in chronic hypertension.

First, this study provides evidence for the possibility that increases in pulse pressure may modulate vascular responses and that modulation of vascular responses by pulse pressure may be mediated by vascular endothelium. This possibility was proposed by Hutcheson and Griffith, who found that acute increases in amplitude of pulse pressure augment phenylephrine-induced constriction of aorta in vitro. The finding that Nω-nitro-L-arginine methyl ester (a nitric oxide synthase inhibitor) completely abolished the response to increased pulse pressure suggests that augmentation of phenylephrine-induced constriction by increases in pulse pressure may be related to suppression of EDRF release. The findings in the present study suggest that chronic as well as acute increases in pulse pressure may modulate release of EDRF and thus alter vascular responses to endothelium-dependent agents. It is important to acknowledge that the experimental models in this study and a previous study do not permit one to distinguish between effects of pulsatile flow and pulsatile pressure on endothelium-dependent responses. It is possible, therefore, that modulation of endothelium-dependent responses during chronic hypertension results from increases in the pulsatile component of flow and not pressure.

Second, findings in relation to calcium ionophore imply that effects of increased pressure are not generalized to all endothelium-dependent agents. Endothelium-dependent relaxation by calcium ionophore is re-
ceptore dependent and, at least in the case of cerebral arterioles, appears to be partially cyclooxygenase dependent. Endothelium-dependent relaxation in response to bradykinin, on the other hand, is receptor dependent and appears to be mediated by oxygen radicals. Thus, the finding that carotid clipping normalizes responses to bradykinin but not to A23187 in pial arterioles of SHRSP suggests that increases in pressure during chronic hypertension may interfere specifically with receptor-mediated responses by cerebral endothelium.

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References

Editorial Comment
In this article Dr Baumbach and colleagues present evidence that increased pulse pressure in some way impairs endothelial function. They suggest that this is the cause of impaired endothelial function of pial arterioles in stroke-prone spontaneously hypertensive rats (SHRSP). It is interesting that of the two endothelium-dependent dilators, calcium ionophore and bradykinin, only the latter was influenced by decreasing the pulse pressure in SHRSP. Because dilution by bradykinin is mediated by receptors on the endothelium and ionophore works directly within the endothelial cell, it may be that increased pulse pressure alters the endothelial receptors for bradykinin. The term "endothelium-derived relaxing factor" (EDRF) is used without qualification throughout the paper. The reader must keep in mind that "classic" EDRF is not tested here. As the authors acknowledge, bradykinin and ionophore have different endothelium-derived mediators, ie, dilators released from the endothelium. Neither mediator is the "classic" EDRF released by acetylcholine (ACH). This EDRF (EDRFAC) is produced from arginine and in pial arterioles either contains or releases nitric oxide. The authors acknowledge that they have not tested the effect of pulse pressure on the response to ACH. They state that dilution produced by ACH is impaired in cerebral arte-
Effects of local reduction in pressure on endothelium-dependent responses of cerebral arterioles.
G L Baumbach, F M Faraci and D D Heistad

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