Phenylephrine-Induced Hypertension Reduces Ischemia Following Middle Cerebral Artery Occlusion in Rats

John C. Drummond, MD, FRCP(C), Yong-Seok Oh, MD,
Daniel J. Cole, MD, and Harvey M. Shapiro, MD

We studied the influence of phenylephrine-induced hypertension on the area of ischemia during brief middle cerebral artery occlusion. Rats were anesthetized with 1.2 minimal alveolar concentration (MAC) isoflurane, and the middle cerebral artery was occluded via a subtemporal craniectomy. Immediately thereafter, in one group (n=9) arterial blood pressure was increased 30–35 mm Hg above the preocclusion level by intravenous infusion of phenylephrine. In a second, control, group (n=10) there was no manipulation of blood pressure. Local cerebral blood flow was determined autoradiographically 15 minutes after occlusion. The areas (expressed as a percentage of the total coronal cross-sectional area) in which local cerebral blood flow decreased to three ranges (0–6 ml/100 g/min [rapid neuronal death probable], 6–15 ml/100 g/min [delayed neuronal death probable], and 15–23 ml/100 g/min [electrophysiologic dysfunction with prolonged survival probable]) were measured. The areas in which local cerebral blood flow decreased to the two more severely ischemic ranges were smaller in the phenylephrine group than in the control group. For example, in the coronal section in the center of the middle cerebral artery distribution, local cerebral blood flow was 0–6 ml/100 g/min in 6.7±1.4% of the section in normotensive rats but was in that range in only 1.7±0.6% of the section during phenylephrine-induced hypertension (p<0.05). For the 6–15 ml/100 g/min range, the areas were 6.8±0.8% and 3.8±0.7%, respectively (p<0.05). For the 15–23 ml/100 g/min range, there were no differences between groups. In the nonischemic hemisphere, local cerebral blood flow in cortical and subcortical regions did not differ between groups. The data suggest that phenylephrine-induced hypertension can acutely improve local cerebral blood flow in an area of focal ischemia and, in addition, suggest that phenylephrine is not a cerebral vasoconstrictor in isoflurane-anesthetized rats. (Stroke 1989;20:1538–1544)
Anesthesia was induced with 4% isoflurane in oxygen. The trachea was intubated, and the lungs were ventilated to maintain normocarbia. Subsequently, and throughout the entire experiment, the rats received an inspired concentration of 2% isoflurane in 40% oxygen, the balance nitrogen. (Isoflurane minimal alveolar anesthetic concentration [MAC] for adult Sprague-Dawley rats as previously determined in our laboratory is 1.58%.

An inspired isoflurane concentration of 2% yields an end-tidal concentration of approximately 1.8% [1.2 MAC]). Rectal temperature was servo-controlled at 37°C. The femoral veins were cannulated to permit fluid and isotope administration. The rats received a maintenance infusion of normal saline at 6 ml/kg/hr throughout the study period.

A left subtemporal craniectomy was performed by the method of Tamura et al.8 The dura was opened to expose the MCA. A 15-minute equilibration period ensued during which normocapnia and normoxia were confirmed by blood gas analysis. The MCA was then occluded, using micro bipolar forceps under continuous saline irrigation, from proximal to the origin of the lenticulostriate branch to the level of the inferior cerebral vein.9 The rats were then assigned alternately to the control group or the phenylephrine group. In the latter, phenylephrine was infused to increase mean arterial blood pressure (MABP) to a level 30-35 mm Hg above that recorded immediately before MCAO. MABP was elevated gradually over 5 minutes and the maximum was limited to 140 mm Hg. MABP was held constant for 10 minutes before ICBF determination. In the control group, there was no manipulation of blood pressure and ICBF was determined 15 minutes after MCAO. MABP, arterial blood gases (Paco2, Pao2, and pH), and hematocrit were recorded before MCAO and immediately after ICBF determination.

ICBF was determined according to the method of Sakurada et al10; 100 μCi/kg of [14C]iodoantipyrine was infused over 46 seconds. During the infusion, 15–18 timed samples of arterial blood were collected on filter paper for the determination of carbon-14 concentrations. At time t=45 seconds, the rat was decapitated and the brain was rapidly removed and frozen. Coronal brain sections (20 μm) were placed on Kodak OM-1 film (Rochester, New York) with carbon-14 standards for 21 days. The autoradiographs were analyzed by an individual blinded as to the experimental course. For each rat, five standard coronal sections chosen to span the anteroposterior extent of the distribution of the MCA (Figure 1) were analyzed using a Drexel Dumas image processing system (Drexel University Image Processing Center, Philadelphia, Pennsylvania). Section 1 was 1.8 mm anterior to the anterior midline extent of the corpus callosum, Section 2 was at the anterior midline extent of the corpus callosum, Section 3 was at the junction of the anterior and middle thirds of the corpus callosum, Section 4 was at the junction of the middle and posterior thirds of the corpus callosum, and Section 5 was at the posterior midline extent of the corpus callosum. Sections 1–5 correspond to Plates 5, 11, 19, 27, and 36, respectively, of Palkovits and Brownstein.

In the hemisphere ipsilateral to the MCAO, the ICBF analysis method employed was designed to identify the area of each section in which ICBF decreased to three predetermined ranges: 0–6, 6–15, and 15–23 ml/100 g/min. The area with ICBF in each range was expressed as a percentage of the cross-sectional area of the entire coronal section. The hemisphere contralateral to the MCAO was divided into cortical and subcortical regions (Figure 2), and the mean ICBF of each region was measured. For the purposes of this phase of the analysis, Section 1 was omitted because of the limited amount of subcortical structure present in this plane.

The data were analyzed using a t test for unpaired data. A probability value of <0.05 was considered significant. All data are presented as mean±SEM.

Results

Five of the 24 rats (two in the control and three in the phenylephrine group) were excluded for technical reasons prior to data analysis. MABP in the two groups was not different at the time of MCAO (control: 95±6 mm Hg; phenylephrine: 99±5 mm Hg). At the time of ICBF determination, there were no differences between groups in terms of Paco2, Pao2, pH, hematocrit, and rectal temperature (Table 1); by protocol design, MABP was significantly greater in the phenylephrine group than in the control group. The phenylephrine infusion rate required to achieve the MABP elevation was 16.1±1.4 μg/kg/min. MCAO resulted in an...
FIGURE 2. Schematic representation of location of regions of rat brain designated as “cortex” and “subcortex” for analysis of cerebral blood flow in hemisphere contralateral to occluded middle cerebral artery. This figure corresponds to Section 3 in Figure 1. Similar analyses were performed in Sections 2, 4, and 5.

 autoradiographically obvious area of ipsilateral ICBF reduction in the lateral and dorsolateral cortex and in the dorsal and lateral portions of the caudate-putamen.

In the hemisphere ipsilateral to the MCAO, the areas with ICBF in the two lower ranges were smaller in the phenylephrine group than in the control group (Table 2). For example, for Section 3 (at the center of the MCA distribution) 6.7±1.4% of the area had an ICBF within the 0–6 ml/100 g/min range in the control group; by contrast, in the phenylephrine group, only 1.7±0.6% of section had an ICBF within that range (p<0.05). This tendency was apparent in all five coronal sections (Table 2) and was significant for the two lower ranges in Sections 3 and 4. For the 15–23 ml/100 g/min range, there were no significant differences between groups in any section, nor was any trend evident.

In the hemisphere contralateral to the MCAO, the average ICBF for the cortical and subcortical regions of Sections 2–5 are presented in Table 3. There were no significant between-group differences for either region, but there was an apparent tendency for ICBF to be slightly greater in the subcortical than in the cortical region in both groups. This between-region difference was significant (paired t test) in Sections 2 and 4 in the control group and in Section 4 in the phenylephrine group. These differences are consistent with other reports of the effect of isoflurane on ICBF in normal rats.12

Discussion

The ICBF analysis technique we used allowed measurement of brain areas in which ICBF was within preselected ranges (0–6, 6–15, 15–23 ml/100 g/min), the boundaries of which have been identified as important physiologic thresholds. Astrup et al13 identified 6 ml/100 g/min as the cerebral blood flow (CBF) at which substantial release of intracellular K+ occurs in baboon cortex; it is likely that neuronal demise occurs rapidly when CBF is at or below this level. Astrup et al13 and Branston et al14 demonstrated that the somatosensory cortical evoked response in baboons is abolished at a CBF of 15 ml/100 g/min. Brain regions within CBF in the 6–15 ml/100 g/min range constitute the ischemic penumbra13 within which neurons are functionally inactive but temporarily viable, with the duration of viability dependent on the severity of blood flow reduction. At a CBF of 23 ml/100 g/min, the first evidence of electrophysiologic dysfunction is seen. Momma et al15 and Carter et al16 demonstrated impairment of the direct cortical response in cats at approximately this CBF. The zone with an ICBF in the 15–23 ml/100 g/min range is, in essence, an ischemic penumbra in which the energy supply falls just short of that required for normal electrophysiologic activity and in which neurons are functionally impaired but indefinitely viable. No similar studies of K+ release and/or electrophysiologic dysfunction have been performed in rats. However, investigations of ischemia performed in gerbils by Crockard et al17,18 suggest that despite differences in resting CBF in normal brain, these physiologic thresholds are similar in other rodents. These authors demonstrated that abnormalities of energy metabolites occurred only at a CBF of <20 ml/100 g/min, that adenosine triphosphate (ATP) was undetectable at a CBF of <10 ml/100 g/min,12 that edema formation was maximal at a CBF of 7 ml/100 g/min, suggesting complete membrane failure at that level.18 It is zones with ICBF in the two lower ranges (0–6 and 6–15 ml/100 g/min) that should be the target of therapeutic interventions because maneuvers that result in a reduction in the size of these zones might be expected to lead to a reduction in the extent of

### Table 1. Physiologic Data at Time of Local Cerebral Blood Flow Determination in Normotensive Control and Phenylephrine-Induced Hypertensive Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>PaCO₂ (mm Hg)</th>
<th>PaO₂ (mm Hg)</th>
<th>pH</th>
<th>Hematocrit (%)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>87±4</td>
<td>37±0.3</td>
<td>134±8</td>
<td>7.39±0.01</td>
<td>42±1</td>
<td>36.5±0.2</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>9</td>
<td>134±3*</td>
<td>38±0.8</td>
<td>125±8</td>
<td>7.40±0.01</td>
<td>44±1</td>
<td>36.9±0.1</td>
</tr>
</tbody>
</table>

Data are mean±SEM.
*p<0.0001 different from control by unpaired t test.
neuronal damage following a period of focal cerebral ischemia.

In our study, 15 minutes of phenoxyphrine-induced hypertension resulted in a decrease in the size of zones with ICBF in the 0–6 and 6–15 ml/100 g/min ranges occurring during MCAO in rats. There are two mechanisms by which this might have occurred: 1) a cerebral perfusion pressure (CPP)-dependent increase in CBF via collateral pathways; and/or 2) an intracerebral redistribution of CBF (a so-called inverse or Robin Hood steal) caused by a vasoconstrictor effect of phenylephrine in normal brain regions adjacent to the ischemic territory. The data do not support the latter mechanism. The ICBF values we obtained in the nonischemic hemisphere contralateral to the MCAO (Table 3) give no evidence that phenylephrine in the doses employed caused cerebral vasoconstriction. The data are therefore more consistent with the occurrence of a CPP-dependent augmentation of CBF via collateral pathways. However, the data cannot be construed as proof of the latter because an alternate, though unlikely, possibility persists. Specifically, it is possible that phenylephrine is in fact a cerebral vasoconstrictor and that the pattern of identical ICBF values seen in the contralateral hemisphere in the control and phenylephrine groups was the result of an isoflurane-induced impairment of autoregulation and a coincidentally opposite and equivalent vasoconstrictor effect of phenylephrine. This hypothesis further requires the assumption that a vasoconstrictor response does not occur in the physiologically impaired zones with ICBF in the 0–6 and 6–15 ml/100 g/min ranges. While most of the available data favor the notion that autoregulation is preserved during approximately 1.0 MAC isoflurane anesthesia, the information is scanty and the question should probably be viewed as unresolved.

The effect of phenylephrine on the cerebral circulation is similarly uncertain. Chikovani et al induced hypertension in halothane-anesthetized dogs using either phenylephrine or angiotensin. CBF increased with angiotensin administration but was unchanged with phenylephrine administration. Their results led these authors to suspect that halothane “disrupted” autoregulation and that phenylephrine, but not angiotensin, “restored” it. However, their results might also be interpreted as indicating that phenylephrine is a cerebral vasoconstrictor and that angiotensin is not. Waltz obtained similar results; he observed no increase in CBF during phenylephrine-induced hypertension in halothane-anesthetized cats. There is little additional information regarding phenylephrine. Data concerning the effects of other agents with potent α-adrenergic effects may be relevant; however, the reported information is inconsistent. Lluch et al and Oberdörster et al studied the effects of intracarotid infusions of norepinephrine in awake goats and in barbiturate-urethane–anesthetized dogs, respectively. Both teams of investigators concluded that norepinephrine was a cerebral vasoconstrictor. By contrast, Olesen performed a similar study in unanesthetized humans and concluded that norepinephrine had no effect. In the face of the foregoing, the possibility of counterbalancing effects of phenylephrine-induced vasoconstriction and isoflurane-induced impairment of autoregulation lacks firm support but cannot be excluded.

Iatrogenic hypertension has long been considered a potential adjunct to the management of focal cerebral ischemia. Hypertension is a generally accepted part of the management of vascular accidents occurring during interventional neuroradiology and of vasospasm. However, with respect to the latter, the relative contributions made by MABP elevation and by the hemodilution that is commonly induced simultaneously are not well defined. Reviews of the therapy of neurologic stroke mention the possible advantages of induced hypertension. However, there have been no controlled trials, and only one author clearly recommends the practice. Yatsu recommends that

---

**Table 2. Area of Rat Coronal Brain Sections Ipsilateral to Middle Cerebral Artery Occlusion Within Cerebral Blood Flow Specified in Normotensive Control and Phenylephrine-Induced Hypertensive Groups**

<table>
<thead>
<tr>
<th>Cerebral blood flow range (ml/100 g/min)</th>
<th>Control</th>
<th>Phenylephrine</th>
<th>Control</th>
<th>Phenylephrine</th>
<th>Control</th>
<th>Phenylephrine</th>
<th>Control</th>
<th>Phenylephrine</th>
<th>Control</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6</td>
<td>1.6±1.0</td>
<td>0.01±0.01</td>
<td>4.0±1.2</td>
<td>1.7±0.8</td>
<td>6.7±1.4</td>
<td>1.7±0.6*</td>
<td>2.2±0.8</td>
<td>0.3±0.1*</td>
<td>0.4±0.4</td>
<td>0.1±0.1</td>
</tr>
<tr>
<td>6–15</td>
<td>3.3±1.2</td>
<td>0.7±0.3</td>
<td>7.2±1.2</td>
<td>5.2±1.0</td>
<td>6.8±0.8</td>
<td>3.8±0.7*</td>
<td>4.4±0.8</td>
<td>2.1±0.6*</td>
<td>1.6±0.7</td>
<td>0.8±0.5</td>
</tr>
<tr>
<td>15–23</td>
<td>1.8±0.3</td>
<td>1.5±0.3</td>
<td>3.8±0.5</td>
<td>4.2±0.6</td>
<td>3.5±0.3</td>
<td>3.6±0.6</td>
<td>3.1±0.6</td>
<td>1.9±0.3</td>
<td>0.7±0.2</td>
<td>1.4±1.0</td>
</tr>
</tbody>
</table>

Data are mean±SEM ml/100 g/min. See Figure 1 for location of sections. n=10 for control, n=9 for phenylephrine.

* p<0.05 different from control by unpaired t-test.

---

**Table 3. Cortical and Subcortical Local Cerebral Blood Flow in Rat Coronal Brain Sections Ipsilateral to Middle Cerebral Artery Occlusion in Normotensive Control and Phenylephrine-Induced Hypertensive Groups**

<table>
<thead>
<tr>
<th>Section</th>
<th>Control</th>
<th>Phenylephrine</th>
<th>Control</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>169±7</td>
<td>166±9</td>
<td>175±9</td>
<td>182±11</td>
</tr>
<tr>
<td>Subcortical</td>
<td>172±10</td>
<td>169±10</td>
<td>181±11</td>
<td>171±8</td>
</tr>
<tr>
<td>4</td>
<td>166±7</td>
<td>174±12</td>
<td>176±10</td>
<td>174±9</td>
</tr>
<tr>
<td>5</td>
<td>160±7</td>
<td>158±11</td>
<td>214±12</td>
<td>187±7</td>
</tr>
</tbody>
</table>

Data are mean±SEM ml/100 g/min. See Figure 1 for location of sections. n=10 for control, n=9 for phenylephrine. No significant differences between groups.
MABP be elevated 10–20 mm Hg with norepinephrine or dopamine; he did not specify the duration of the therapy. Only one animal investigation has attempted to evaluate the effect of induced hypertension on neurologic outcome in the setting of acute stroke. Michenfelder and Milde used various pressors in an attempt to maintain a 20% elevation of MABP for 48 hours after MCAO in monkeys; these authors abandoned their attempts because of cardiopulmonary failure. Various laboratory investigations have evaluated induced hypertension using outcome measures other than gross neurologic function. Hope et al performed MCAO in baboons and observed improvements in evoked responses, regional cerebral blood flow (rCBF), and extracellular K+ concentration after inducing hypertension with metaraminol. Olsen instituted angiotensin-induced hypertension in humans 72 hours after the onset of stroke. In some patients in whom peri-infarct rCBF was initially very low, he observed an improvement in rCBF; however, in other patients hyperemia already present at the time of the initial rCBF study was increased by hypertension. He attributed the hyperemia to disintegration of the original embolus and postulated that in these circumstances, induced hypertension could worsen edema or result in conversion to hemorrhagic infarction. Brawley et al measured CBF in the ischemic territory distal to a MCAO in dogs and observed increases during the intravenous infusion of both norepinephrine and phenylephrine. Waltz, who measured cortical CBF during MABP manipulation in halothane-anesthetized cats following MCAO, found that hypertension induced with phenylephrine was usually ineffective at increasing CBF. The reasons for the differences in the CBF response to hypertension in the study of Waltz as opposed to the response seen in our study and those of Hope et al., Olsen, and Brawley et al. are obscure. Nonetheless, the bulk of the available data suggest that induced hypertension can serve to increase ICBF in brain regions that are poorly perfused immediately following occlusion of large cerebral vessels.

It is our supposition that the favorable redistribution of ICBF occurred because of the effect of increased CPP in a pressure-passive region. In rats, isoflurane in the concentrations employed (1.2 MAC) has been shown to have little effect on CBF. Note that it is possible that the concurrent administration of drugs with cerebral vasoconstrictor or vasodilator effects might modify the influence of phenylephrine-induced hypertension. For instance, a pressor agent that caused cerebral vasodilation (e.g., dopamine at some concentrations) might in theory cause an adverse intracerebral redistribution of ICBF if vasodilation occurred in normal brain adjacent to an already maximally dilated ischemic area. During focal cerebral ischemia, both favorable and unfavorable ICBF redistribution phenomena have been reported during the administration of cerebral vasoconstrictors (barbiturates) and cerebral vasodilators (carbon dioxide), respectively. Accordingly, the cerebral vascular effects of all agents employed during induced hypertension may influence the effectiveness of a given therapy in improving CBF.

In our study, hypertension was established rapidly after the onset of ischemia, as might occur in the operating room environment (during aneurysm surgery or carotid endarterectomy) or during interventional radiology. This is in contrast to the circumstances of many stroke victims in whom delays before access to high-level care are common. However, the development of thrombolytic therapies may encourage rapid triage systems that might result in a population of acute stroke victims who are candidates for short-term supportive therapy until thrombolysis can be accomplished. It must be highlighted that the reports of Michenfelder and Milde and Olsen point to the possibility that therapies that are beneficial when used quickly and briefly may be hazardous when applied for longer periods or when initiated after a delay. The potential for cardiovascular dysfunction in the face of prolonged hypertension and the possibility of causing hyperemia, edema, and even hemorrhage in the event of delayed recanalization of the obstructed vessel make it unreasonable to extrapolate our results to justify either prolonged or delayed induction of hypertension. With regard to edema formation, it seems likely that the risk will be less when hypertension is used for short periods early in the course of the ischemic episode. Unlike the circumstances that prevail following head injury or freeze lesions, there is a considerable delay after an episode of hypoxia/ischemia before there is sufficient opening of the blood–brain barrier to permit the passage of albumin or other large molecules.

We used ICBF as an end point. However, an improvement in CBF is not a certain correlate of improved neuronal outcome, and there cannot be absolute assurance that the potential for neuronal survival was improved in brain regions in which ICBF rose above the threshold for rapid membrane failure (e.g., <6 ml/100 g/min). Nonetheless, it is generally accepted that, during normothermia, short periods of profound CBF reduction (e.g., <6 ml/100 g/min) will result in rapid neuronal death. Accordingly, it seems reasonable to conclude that, after the 15 minutes of ischemia, the minimum number of neurons doomed to succumb was smaller in the group with phenylephrine-induced hypertension.

In summary, our results indicate that phenylephrine-induced hypertension initiated immediately after MCAO in rats reduces the extent of brain regions in which ICBF is at or below levels that might result in neuronal death. Our results are therefore consistent with a potential benefit of iatrogenic hypertension as a supportive measure during brief episodes of focal cerebral ischemia.
Acknowledgments

The authors gratefully acknowledge the technical contributions of Laura Breen, AHT, and Robin Giamela, BS.

References

11. Palkovits M, Brownstein MJ: Cerebrovascular contributions of Laura Breen, AHT, and Robin Giamela, BS.
32. Michenfelder JD, Milde JH: Failure of prolonged hypocapnia, hypothermia or hypertension to favorably alter acute stroke in primates. Stroke 1977;8:87–91

42. Langford KH, Vitek JJ, Zeiger E: Migration of detachable mini balloon from the ICA causing occlusion of the MCA. J Neurosurg 1983;58:430–434


KEY WORDS • phenylephrine • cerebral ischemia • cerebral blood flow • rats
Phenylephrine-induced hypertension reduces ischemia following middle cerebral artery occlusion in rats.

J C Drummond, Y S Oh, D J Cole and H M Shapiro

Stroke. 1989;20:1538-1544
doi: 10.1161/01.STR.20.11.1538

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/20/11/1538

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/