Renal Blood Flow in Acute Cerebral Ischemia in Spontaneously Hypertensive Rats: Effects of α- and β-Adrenergic Blockade

Hiroshi Yao, Seizo Sadoshima, Osamu Shiokawa, Kenichiro Fujii, and Masatoshi Fujishima

The influences of acute cerebral ischemia on renal hemodynamics were examined in spontaneously hypertensive rats in which cerebral ischemia was induced by bilateral carotid artery occlusion. Renal and cerebral blood flow were measured with a hydrogen clearance technique. Either phenoxybenzamine (0.5 mg/kg body wt) or propranolol (2 mg/kg) was given i.v. immediately after ischemia was induced to examine the drugs' effects on cerebral and renal hemodynamics. One hour after ischemia, cerebral blood flow was markedly reduced to 5, 3, and almost 0% of the preischemic value in the untreated, phenoxybenzamine-treated, and propranolol-treated rats, respectively. In contrast, renal blood flow at that time was decreased to 65, 88, and 67%, respectively. The calculated renal vascular resistance was similarly increased to 151% in the untreated and 136% in the propranolol-treated rats, but decreased to 82% in the phenoxybenzamine-treated rats. The present results indicate that in acute cerebral ischemia, renal blood flow was considerably decreased with concomitant increased renal vascular resistance, and that such reduction in renal blood flow was minimized by α-adrenergic blockade but not by β-blockade. It is concluded that activation of the α-adrenergic system in acute cerebral ischemia causes renal vasoconstriction. (Stroke 1987;18:629–633)

It is known that cerebrovascular disease not only leads to severe derangements of the cerebral circulation and metabolism, but also to undesirable dysfunctions of various extracranial organs. Cardiac arrhythmias, electrocardiographic changes, and myocardial necrosis are not uncommon, 1-3 acute gastric erosion or ulcer sometimes causes massive hemorrhage, 4-5 and pulmonary congestion and edema lead to respiratory distress. 6-7 Increased activity of the sympathetic nervous system is explained to be, in part, responsible for these extracranial changes.

Renal blood flow (RBF) is mainly regulated by intrinsic (autoregulation) and extrinsic factors (autonomic nervous system and humoral elements), 8-10 although the renal hemodynamics in acute cerebral ischemia are not fully understood. In this study, we measured renal cortical blood flow in spontaneously hypertensive rats (SHR) in which cerebral ischemia was produced by bilateral carotid occlusion (BCO). The purposes of this study were to observe whether cerebral ischemia affects the regulation of RBF and, if so, to examine whether sympathetic nerve activity influences its regulation.

Materials and Methods

Twenty-six male SHR aged 5-6 months, weighing 240-360 g, were used in this study. The rats were fed stock chow diet (Oriental Co., Japan) and tap water ad libitum. Under amobarbital anesthesia (100 mg/kg body wt i.p.), both femoral arteries were cannulated, one for continuous recording of systemic arterial blood pressure and heart rate, and the other for anaerobic sampling of blood for pH, P\text{O}_2, and P\text{CO}_2 determinations. A femoral vein was also cannulated for infusion of drugs. Both common carotid arteries were exposed through a ventral midline incision in the neck, separated from the vagosympathetic trunks carefully, and loosely encircled with sutures for later ligation. The rectal temperature was maintained close to 37°C by a heat lamp, and the rats breathed room air spontaneously throughout the experiment.

A hydrogen clearance technique was chosen for cerebral cortical blood flow (CBF) and RBF determinations. 11,12 Details of CBF measurement were described previously. 13 Briefly, the rat's head was fixed in a head holder, and a small burr hole was made on the skull 2 mm lateral to the bregma. A Teflon-coated platinum electrode, 200 \mu m in diameter, with a 1-mm portion at its tip uncoated and plated with platinum black, was placed stereotactically in the cerebral parietal cortex, 2 mm from the surface of the brain. The reference Ag-AgCl electrode was inserted under the skin. RBF was determined simultaneously in the same rat. After a longitudinal skin incision was made in the loin, the right kidney was exposed through the muscle layers. A fine platinum electrode, 80 \mu m in diameter, with a 1-mm portion at its tip uncoated, was put in the renal cortex, 2 mm from the surface of the kidney, through the renal capsule manually.

Hydrogen gas, 10% in room air, was administered under spontaneous breathing. At least 2 baseline CBF and RBF were measured at intervals of about 10 minutes. Then both carotid arteries were ligated tightly, and CBF and RBF were determined 5, 15, 30, and 60
Table 1. Arterial Acid–Base Parameters, Mean Arterial Blood Pressure, Heart Rate, Cerebral Blood Flow, and Renal Blood Flow Before and 60 Minutes After Bilateral Carotid Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Phenoxybenzamine</th>
<th>Propranolol</th>
<th>Distal occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 8</td>
<td>n = 6</td>
<td>n = 6</td>
<td>n = 6</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Pco₂ (mm Hg)</td>
<td>35.8 ± 1.1</td>
<td>16.7 ± 1.7</td>
<td>33.0 ± 1.0</td>
<td>14.4 ± 2.0</td>
</tr>
<tr>
<td>P0₂ (mm Hg)</td>
<td>83.3 ± 6.0</td>
<td>84.3 ± 4.2</td>
<td>92.0 ± 8.6</td>
<td>88.6 ± 5.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.45 ± 0.01</td>
<td>7.58 ± 0.02</td>
<td>7.45 ± 0.01</td>
<td>7.63 ± 0.04</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>198 ± 3</td>
<td>186 ± 2.7</td>
<td>189 ± 6</td>
<td>135 ± 14*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>371 ± 10</td>
<td>448 ± 17</td>
<td>372 ± 11</td>
<td>402 ± 21</td>
</tr>
<tr>
<td>CBF (ml/100 g/min)</td>
<td>49.9 ± 3.1</td>
<td>2.4 ± 2.4</td>
<td>48.4 ± 5.8</td>
<td>1.5 ± 1.5</td>
</tr>
<tr>
<td>RBF (ml/100 g/min)</td>
<td>275 ± 25</td>
<td>180 ± 21†</td>
<td>249 ± 39</td>
<td>218 ± 31</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Phenoxybenzamine (0.5 mg/kg) and propranolol (2 mg/kg) were given i.v. 1 minute after carotid occlusion. MABP, mean arterial blood pressure; HR, heart rate; CBF, cerebral blood flow; RBF, renal blood flow. *p < 0.02, †p < 0.01 vs. untreated, ‡p < 0.01 vs. before carotid occlusion.

Results

Table 1 summarizes the mean values for arterial acid–base parameters, MABP, HR, CBF, and RBF before and 60 minutes after BCO. There were no differences in physiologic parameters between untreated and the other 3 groups of rats before BCO. After BCO, the rats in all groups began to hyperventilate, resulting in decreased Pco₂ and increased pH. In the untreated and propranolol-treated groups, MABP rose to 231 and 225 mm Hg 5 minutes after BCO, followed by a gradual fall to 186 and 174 mm Hg, respectively, at 60 minutes after BCO (Figure 1). In the phenoxybenzamine-treated group, MABP rose less markedly to 206 mm Hg at 5 minutes and fell below the preischemic level, to 135 mm Hg at 60 minutes after BCO. In the distal occlusion group, MABP did not rise until 15 minutes after BCO, then rose to the same level as the untreated or propranolol-treated groups 30 and 60 minutes after BCO. HR rose gradually after occlusion in the untreated and phenoxybenzamine-treated groups, but remained unchanged in the propranolol-treated group throughout the experiment.

Five minutes after BCO, CBF in both the phenoxybenzamine- and propranolol-treated groups was greatly lowered, to < 10% of the resting value, while in the untreated group CBF was reduced to 34% (Figure 2). At 60 minutes after BCO, CBF was further reduced to

![Figure 1. Changes in mean arterial blood pressure (MABP) after bilateral common carotid or distal occlusion in untreated (●), phenoxybenzamine-treated (△), propranolol-treated (□), and distal occlusion (○) rats. *p < 0.05, ** p < 0.02, *** p < 0.01 vs. untreated rats. Bars represent SEM.](http://stroke.ahajournals.org/Downloaded from)
5, 3, and almost 0% of the resting value in untreated, phenoxybenzamine-, and propranolol-treated rats, respectively, but these differences were not significant.

RBF 60 minutes after BCO decreased significantly from 275 ± 25 to 180 ± 21 ml/100 g/min in untreated rats, from 240 ± 35 to 160 ± 22 ml/100 g/min in propranolol-treated rats, and from 252 ± 30 to 172 ± 30 ml/100 g/min in distal occlusion rats, while the decrease in RBF in phenoxybenzamine-treated rats was not statistically significant (Table 1). Figure 3 illustrates the percent changes in RBF after BCO. RBF in untreated and propranolol-treated rats showed a relatively steep reduction during the first 15 minutes and remained as low as 65-67% of the resting values. In the distal occlusion rats, RBF was less dramatically decreased at 30 minutes after carotid occlusion (not significant), and decreased to almost the same value as the untreated and propranolol-treated groups at 60 minutes after occlusion. In contrast, RBF in rats treated with phenoxybenzamine was less dramatically decreased, to 88% at 60 minutes after BCO. The changes in renal vascular resistance (RVR), calculated as MABP/RBF, were also markedly different between the phenoxybenzamine-treated and the other 3 groups (Figure 4). After an initial rise in RVR, the former group showed a gradual reduction to 82% of the baseline RVR at 60 minutes after BCO, whereas in the latter 3 groups RVR was sustained as high as 136–168% of baseline values.

**Discussion**

The dysfunction of extracranial organs associated with stroke has been investigated clinically. Cardiac arrhythmias with giant negative T are often observed in patients with subarachnoid hemorrhage, focal or sometimes transmural necrosis of the myocardium is reported on postmortem examination,1 neurogenic pul-
monary edema with hemorrhage causes respiratory distress with low $P_{O_2}$ and is often misdiagnosed as bronchopneumonia.6,7 Gastric lesions are frequent and the mortality is high especially in patients with acute ulcer, multiple erosions, and petechiae.4,5 All these extracranial lesions are considered to result from the increased sympathetic outflow in acute stroke, although less attention has been paid to the derangement of RBF and its mechanism.

We have previously reported that bilateral carotid artery occlusion in SHR reduces supratentorial CBF to < 10 ml/100 g/min13 and develops large cerebral infarctions identical to those in humans histologically14 and biochemically.15 In the present study, CBF to the cerebral cortex 60 minutes after BCO was 2.4 ml/100 gmin in control SHR and 1.5 or actually 0 in phenoxybenzamine- or propranolol-treated rats, indicating that the cerebrum was exposed to severe ischemic insult in our model. Under such conditions, RBF was reduced to 72% of the resting value 30 minutes after BCO and to 65% at 60 minutes. RBF and RVR in the distal occlusion group were essentially the same as in the untreated group, indicating that the effect of the baroreflex on RBF during cerebral ischemia was minimal in our BCO model and that the reduction in RBF was primarily caused by cerebral ischemia. Although the effect of hypocapnia on RBF was not examined in this study, the previous examination by Norman et al16 indicated that variations in $P_{CO_2}$ of < 20 mm Hg have little effect on RBF. We assume, therefore, that the $P_{CO_2}$ levels in this study may not affect the renal vascular responses during cerebral ischemia.

The kidney constitutes only 0.5% of body weight although it receives 20% of the cardiac output. It is widely accepted that two major factors contribute to regulate RBF: autoregulation and neurogenic or other humoral factors. The autoregulatory range in normotension is 70–160 mm Hg MABP. In hypertention, the range may be shifted to a higher blood pressure. Since RBF was decreased despite raised MABP in this study, the reduced RBF during cerebral ischemia could not be explained simply by disturbance of RBF autoregulation but rather requires some other mechanism.

In a resting, stable condition, there is little sympathetic vasoconstrictor tone in the kidneys.10 In severe hypoxia, hypercapnia,8,16 hemorrhagic shock, or exercise,17,18 however, a neurogenic mechanism causes renal vasoconstriction and reduces RBF. Furthermore, noradrenaline infusion or renal nerve stimulation decreases RBF, indicating that neurogenic vasoconstriction could exceed autoregulatory control of the myogenic mechanism in some conditions.19 During swimming, RBF in dogs was reduced to about 62% of the resting value, although the dogs’ blood pressure was increased 43%.17,18 Phenoxybenzamine abolished such RBF reduction, indicating that enhanced sympathetic activity induced by stress constricts renal blood vessels, increases RVR, and reduces RBF.

In the acute stage of stroke, circulating catecholamines, as an index of sympathetic activity, are also reported to be elevated. Myers et al17 found that plasma norepinephrine concentration in patients with cerebral infarction was significantly increased to 433.2 ± 33.9 pg/ml in contrast to 282.1 ± 19.8 pg/ml in control subjects, and suggested that the high plasma norepinephrine could produce the cardiac abnormalities in stroke patients. To examine the possibility of neural influences on RBF in acute cerebral ischemia, $\alpha$- or $\beta$-adrenergic blocking agents were infused after carotid occlusion in this study. Compared with the untreated group, $\beta$-blockade with propranolol had little effect on changes in RBF and RVR, while $\alpha$-blockade with phenoxybenzamine significantly minimized such changes, indicating that $\alpha$-adrenergic activation plays an important or essential role in renal vasoconstriction in acute cerebral ischemia. However, whether such sympathetic activation is mediated by increases in renal sympathetic nerve discharge or in circulating catecholamines is not clear from the present study. Further study is needed to clarify the relation of renal hemodynamics to kidney function in acute stroke.

It is concluded that in acute cerebral ischemia in SHR, RBF is decreased with a concomitant increase in RVR, which is mediated by $\alpha$-adrenergic activity.

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References

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