Mechanisms of Vasodilation of Cerebral Vessels Induced by the Potassium Channel Opener Nicorandil in Canine In Vivo Experiments

Tadahiko Ishiyama, MD; Shuji Dohi, MD; Hiroki Iida, MD; Shigeru Akamatsu, MD; Shuichiro Ohta, MD; Hiroyuki Shimonaka, MD

Background and Purpose Nicorandil, a potent antianginal agent characterized as a potassium channel opener, could produce cerebrovascular dilation in vitro studies. Our aim was to investigate the pharmacologic response to the topical application of nicorandil on the vasomotor tone of pial vessels in vivo. To elucidate its mechanism, we also studied the inhibitory action of methylene blue and glibenclamide against nicorandil-induced vasodilation.

Methods In 14 dogs prepared with a parietal cranial window, we administered five different concentrations of nicorandil solution (10^{-7}, 10^{-6}, 10^{-5}, and 10^{-3} mol/L) under the window and measured pial arteriolar and venular diameters. After pretreating pial vessels with either 10^{-2} mol/L methylene blue or 10^{-3} mol/L glibenclamide, we examined inhibitory action after the application of 10^{-3} mol/L nicorandil. In additional experiments with 9 dogs, we evaluated the effects of nitroglycerin and cromakalim on pial vessels in the absence or presence of 10^{-3} mol/L methylene blue and 10^{-3} mol/L glibenclamide, respectively.

Results Nicorandil produced significant, concentration-dependent dilation of pial vessels (P<.05). Methylene blue blocked nicorandil-induced dilation, whereas glibenclamide only attenuated such action of nicorandil. Nitroglycerin and cromakalim also produced a concentration-dependent increase in pial arteriolar and venular diameters (P<.05), and those effects were blocked in the presence of methylene blue or glibenclamide, respectively.

Conclusions Our in vivo study demonstrates that topical application of nicorandil dilates both pial arterioles and venules in a concentration-dependent manner and suggests that the mechanisms of such action are most likely due to both cyclic GMP-mediated vascular smooth muscle dilation and the regulation of K^+ flux. (Stroke. 1994;25:1644-1650.)

Key Words • microcirculation • nitroglycerin • dogs • potassium channels • vasodilation

Nicorandil belongs chemically to the nitrate group and was originally introduced as a coronary vasodilator. Another nitrate agent, nitroglycerin, causes endothelium-independent vasodilation in rat basilar arteries and produces a dose-related dilation of basilar and pial arterioles in vivo experiments. Nicorandil may also possess a cerebrovascular dilating action, but its pharmacologic effect is different from classic nitrates. Although nitroglycerin mainly dilates the capacitance vessels, nicorandil has been reported to dilate coronary arterioles. Resitive vessel dilators are more beneficial than conductive vessel dilators as cerebrovascular-dilating drugs. However, it has not been confirmed whether nicorandil dilates cerebral vessels.

The vascular effect of nicorandil is characterized by opening of the potassium channels of the smooth muscle cell membranes. A recent in vitro observation in smooth muscles of rabbit cerebral arteries suggests that K^+ channels located in cerebral arterial smooth muscles serve as a negative feedback pathway to control the degree of membrane depolarization and vasoconstriction. In a few in vitro experiments, nicorandil has been suggested to produce dilation on rat basilar arteries and dog basilar and cerebral arteries; however, the mechanism for its putative cerebral-vasodilating action has not been studied in vivo experiments. The endothelium-derived relaxing factor (EDRF) is involved generally in the regulation of systemic vasomotor tone and more specifically in the regulation of cerebral vascular activity.

To our knowledge, the effects of topical application of nicorandil on pial vessels have not been reported in vivo experiments. We investigated its effects on vasomotor tone of normal pial arterioles and venules in anesthetized dogs using the cranial window technique. To elucidate its mechanisms, we also evaluated the inhibitory effect of methylene blue and glibenclamide against nicorandil-induced vasodilation in the current in vivo model.

Materials and Methods We studied 23 dogs weighing between 6 and 10 kg. Experimental protocols were approved by our institutional animal care committee. All dogs were initially anesthetized with a bolus infusion of pentobarbital sodium (20 mg/kg) and then after maintained with a continuous intravenous infusion (2 mg/kg per hour). After tracheal intubation, each dog was mechanically ventilated with a positive-pressure respirator and received vecuronium intravenously for muscle paralysis. Tidal
volume and respiratory rate were adjusted to maintain PaCO₂ between 35 and 45 mm Hg, and supplemental oxygen was given to maintain PaO₂ between 90 and 120 mm Hg. The left femoral vein was cannulated to administer fluid and drugs. The left femoral artery was also cannulated to measure mean arterial pressure (MAP) continuously and to provide blood samples for analyzing arterial blood gas tensions, pH, and serum electrolytes. Rectal temperature was maintained between 36.5°C and 37.5°C by a water-circulating warming blanket.

A closed cranial window was used for visualization of the pial microcirculation. The scalp was retracted and temporal muscles were removed. A 2-cm-diameter hole was made in the parietal cortex. After the coagulation of dural vessels with a bipolar electrocoagulator, the dura was cut and retracted over the bone. A stainless steel ring with a glass coverslip was placed over the hole and secured with bone wax and dental acrylic. The space under the window was filled with artificial cerebrospinal fluid (aCSF), and four polyethylene catheters were inserted in the ring. One catheter was attached to a reservoir bottle containing aCSF to maintain a constant intracranial pressure of 7 mm H₂O. Two other catheters were used for infusion of aCSF or study drugs and the last one was for continuous monitoring of intracranial pressure. The volume below the window was between 0.5 and 1 mL. The composition of aCSF was Na⁺, 151 mEq/L; K⁺, 4 mEq/L; Ca²⁺, 3 mEq/L; Cl⁻, 110 mEq/L; and glucose, 100 mg/dL; pH was adjusted to 7.48, and the solution was bubbled with 5% CO₂ and air at 37.0°C.

Nicorandil was freshly dissolved in aCSF; five different concentrations (10⁻⁷, 10⁻⁹, 10⁻¹, 10⁻³, and 10⁻⁵ mol/L) were prepared and used for the current study. The diameters of three or four pial arterioles and venules were measured sequentially with different nicorandil concentrations by videomicrometer (Olympus Flovel model VM-20) attached to a microscope (model OMK-1, Olympus).

All in vivo experiments were carried out in the following manner. After 30 minutes of stabilization, pial arteriolar and venular diameters, MAP, heart rate, rectal temperature, arterial blood gas tensions, pH, and serum electrolytes were measured before and after topical application of the five different nicorandil concentrations into the cranial window in sequential stages in eight dogs. To establish the baseline volume size, the window was continuously flushed with aCSF at the rate of 0.5 to 1 mL/min for 60 minutes after each measurement. After 60 minutes from the last administration of nicorandil solution, the pial vascular diameter returned to control volume.

The effects of methylene blue and glibenclamide on pial vessels were evaluated against the action of topical 10⁻³ mol/L nicorandil solution in six dogs with the aforementioned experimental design. Methylene blue was dissolved in aCSF to make a 10⁻⁵ mol/L solution. After the completion of baseline measurements following topical use of 10⁻³ mol/L methylene blue, 10⁻⁴ mol/L nicorandil solution was applied and the measurements were repeated.

Glibenclamide was dissolved in 100% dimethyl sulfoxide (DMSO) and then diluted with aCSF to make a 10⁻⁷ mol/L solution. The DMSO concentration in the 10⁻⁵ mol/L glibenclamide solution was 0.1%. A similar experiment was repeated with either 0.1% DMSO or 10⁻⁵ mol/L glibenclamide alone followed by 10⁻⁷ mol/L nicorandil solution.

In additional experiments with nine dogs, we also examined the role of guanylate cyclase and K⁺ channels in mediating the pial vascular responses to nicorandil. After control measurements of pial vascular diameter and laboratory data, three different concentrations (10⁻⁷, 10⁻⁹, and 10⁻³ mol/L) of nitroglycerin, a classic nitrate, and cromakalim, an ATP-sensitive K⁺ channel opener, were administered under the window, and pial arteriolar and venular responses were evaluated. To elucidate the efficacy and specificity of blockade with methylene blue or glibenclamide, we evaluated the effects of preapplication of 10⁻⁵ mol/L methylene blue or 10⁻⁵ mol/L glibenclamide after the topical application of nitroglycerin or cromakalim, respectively. Cromakalim was dissolved in DMSO and diluted with aCSF.

Pial vessels were divided into two groups on the basis of initial diameter—greater than 200 μm or less than 200 μm. All physiological variables; concentration-dependent effects of nicorandil, nitroglycerin, or cromakalim; and inhibitory effects of methylene blue or glibenclamide for nicorandil-, nitroglycerin-, or cromakalim-induced pial vascular dilation were examined via one-way ANOVA and Scheffé's F test for post hoc comparison. Comparison between absolute values for pial arteriolar or venular diameter was made using a paired t test. A value of P<.05 was considered statistically significant. Values are represented as mean±SEM.

**Results**

MAP, heart rate, body temperature, arterial blood gas tensions, pH, and serum electrolytes did not change significantly in the first experiment with five different nicorandil concentrations (Table 1).

Nicorandil produced significant pial arteriolar and venular dilations (Table 2). Concentration-dependent dilations in large and small arterioles and large venules between two stepwise concentration differences (P<.05, Fig 1) were also detected. In small pial venules, a concentration-related increase in diameter was detected at the lower concentration but not at higher concentrations (P<.05). The percent increase in diameter was more prominent in small arterioles at concentrations of 10⁻⁴ (P<.05), 10⁻³ (P<.001), and 10⁻² mol/L (P<.01, Fig 1A). There was no significant percent change in diameter between large and small venules (Fig 1B).

Methylene blue, DMSO, and glibenclamide had no effect on pial vascular diameter (Table 3). Methylene blue inhibited 10⁻³ mol/L nicorandil-mediated pial arteriolar (large, P<.005; small, P<.001) and venular (large, P<.0005; small, P<.05) dilations (Fig 2). There was no significant difference in percent change in diameter with topical application of 10⁻³ mol/L nicorandil.
TABLE 2. Effects of Nicorandil on Pial Arterioles and Venules

<table>
<thead>
<tr>
<th>Concentration, mol/L</th>
<th>10^-7</th>
<th>10^-6</th>
<th>10^-5</th>
<th>10^-4</th>
<th>10^-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large arterioles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>346.23±28.06</td>
<td>348.06±29.41</td>
<td>340.75±26.94</td>
<td>343.86±30.86</td>
<td>342.48±31.08</td>
</tr>
<tr>
<td>After</td>
<td>347.39±28.60</td>
<td>357.49±31.78</td>
<td>361.80±27.57†</td>
<td>386.44±30.46†</td>
<td>416.66±34.70†</td>
</tr>
<tr>
<td>Small arterioles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>144.39±7.1</td>
<td>144.01±6.42</td>
<td>146.71±7.03</td>
<td>141.68±8.18</td>
<td>142.84±7.84</td>
</tr>
<tr>
<td>After</td>
<td>145.43±7.03</td>
<td>154.45±7.21†</td>
<td>168.81±8.05†</td>
<td>176.44±9.28†</td>
<td>190.44±10.02†</td>
</tr>
<tr>
<td>Large venules</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>263.60±23.57</td>
<td>260.46±26.86</td>
<td>265.97±21.03</td>
<td>268.34±30.94</td>
<td>270.38±30.62</td>
</tr>
<tr>
<td>After</td>
<td>263.59±23.73</td>
<td>265.45±26.38</td>
<td>284.80±21.07†</td>
<td>296.79±32.93†</td>
<td>307.35±31.60†</td>
</tr>
<tr>
<td>Small venules</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>157.31±7.85</td>
<td>159.80±9.19</td>
<td>164.11±7.98</td>
<td>161.36±8.06†</td>
<td>168.02±9.12*</td>
</tr>
<tr>
<td>After</td>
<td>156.06±8.47</td>
<td>168.02±9.12*</td>
<td>187.55±9.06†</td>
<td>188.26±9.35+</td>
<td>193.91±9.6‡</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *P<.05, †P<.005, +P<.0001 compared with corresponding control.

Nicorandil reduced the dilatation of small pial arterioles (P<.05) and venules (P<.05) induced by 10^-3 mol/L nicorandil (Fig 2). MAP, heart rate, body temperature, arterial blood gas tensions, pH, and serum electrolytes did not change before and after topical methylene blue, glibenclamide, or DMSO (Table 4).

Topical application of nitroglycerin caused a concentration-dependent increase in diameter in small pial arterioles and large and small venules (P<.05; Table 5, Fig 3). Methylene blue inhibited pial arteriolar (small, P<.005) and venular (large, P<.005; small, P<.0001) dilation mediated with 10^-3 mol/L nitroglycerin, but glibenclamide did not affect the nitroglycerin-induced dilation (Fig 4).

A concentration-dependent vasodilation in pial arterioles and venules (P<.05) was observed after topical application of cromakalim (Table 6, Fig 5). The vasodilation induced by cromakalim was attenuated in the presence of glibenclamide (large arterioles, F<.005; small arterioles, P<.005; large venules, P<.005) but not in the presence of methylene blue (Fig 6).

Discussion

The results of the present in vivo study demonstrate that the topical application of nicorandil dissolved in aCSF dilates pial arterioles and venules in a concentration-dependent manner and that vasodilative responses

**TABLE 3. Effects of Methylene Blue, Dimethyl Sulfoxide, or Glibenclamide on Pial Arterioles and Venules**

<table>
<thead>
<tr>
<th></th>
<th>Methylene Blue</th>
<th>DMSO</th>
<th>Glibenclamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large arterioles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>321.58±30.74</td>
<td>323.88±30.59</td>
<td>325.04±31.34</td>
</tr>
<tr>
<td>After</td>
<td>318.86±29.87</td>
<td>323.88±29.52</td>
<td>325.04±31.34</td>
</tr>
<tr>
<td>Small arterioles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>168.65±5.91</td>
<td>166.04±5.23</td>
<td>169.15±5.56</td>
</tr>
<tr>
<td>After</td>
<td>165.67±6.47</td>
<td>160.45±6.76</td>
<td>164.18±5.56</td>
</tr>
<tr>
<td>Large venules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>278.61±19.79</td>
<td>274.88±19.13</td>
<td>278.99±20.30</td>
</tr>
<tr>
<td>After</td>
<td>278.61±19.86</td>
<td>273.63±19.39</td>
<td>280.13±20.22</td>
</tr>
<tr>
<td>Small venules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>174.13±6.29</td>
<td>171.64±6.39</td>
<td>170.15±7.61</td>
</tr>
<tr>
<td>After</td>
<td>169.15±6.29</td>
<td>174.13±6.29</td>
<td>170.15±7.61</td>
</tr>
</tbody>
</table>

DMSO indicates dimethyl sulfoxide. Topically applied methylene blue, DMSO, and glibenclamide had no effect on pial vascular diameter. Values are mean±SEM.
Fig 2. Bar graphs show effects of methylene blue or glibenclamide on nicorandil-induced dilation of pial arterioles (A) or venules (B). Methylene blue inhibited nicorandil-induced pial arteriolar and venular dilation. Glibenclamide attenuated the dilation of small pial arterioles and large and small venules induced by nicorandil. Values are mean±SEM. Black bars indicate 10⁻⁵ mol/L nicorandil; hatched bars, 10⁻⁴ mol/L methylene blue plus 10⁻⁵ mol/L nicorandil; and shaded bars, 10⁻⁵ mol/L glibenclamide plus 10⁻⁵ mol/L nicorandil. *P<.05, †P<.005, ‡P<.001, §P<.0005 compared with corresponding 10⁻⁵ mol/L nicorandil.

to nicorandil are more prominent in small arterioles. Since nicorandil-induced dilation of pial arterioles and venules was inhibited by methylene blue and attenuated by glibenclamide, mechanisms of such action are most likely caused by both cyclic GMP-mediated vascular smooth muscle dilation and the regulation of K⁺ flux. We also observed that topical application of nitroglycerin, a classic nitrate, and cromakalim, an ATP-sensitive K⁺ channel opener, caused a concentration-dependent dilation in canine pial arterioles and venules and that each dilation was blocked with topically applied methylene blue or glibenclamide. In addition, the presence of methylene blue and glibenclamide did not affect pial vasodilation induced by cromakalim and nitroglycerin, respectively. These data obtained from the present in vivo study allow us to conclude that the mechanisms of action of nicorandil on pial vessels are specifically mediated by cyclic GMP and a K⁺ channel opener.

Vasodilator effects of nicorandil in the coronary artery have been well established, but little is known about the effect of nicorandil on the cerebral vascular circulation. Nitrates, when topically applied, induce endothelium-independent vasodilation in basilar⁴ and cerebralarteries. Pinacidil and cromakalim as K⁺ channel openers have been reported to elicit vasodilation in in vitro experiments.¹⁴-¹⁶ Since the vascular effects of nicorandil are based on its action as a nitrate

and as a K⁺ channel opener, we suspected that nicorandil may also possess cerebrovascular dilating action. The present in vivo study confirms the fact that nicorandil dilates large and small pial arterioles and venules, with the greatest effect on small pial arterioles. Several studies¹⁷-¹⁸ have noted the correlation between blood flow and vessel diameter in the brain stem and peripheral microcirculation. Theoretically, nicorandil may have a clinical value, improving cerebral blood flow through its vasodilator effect.

Alteration in arterial diameter may modulate changes in blood flow. The present results demonstrate that a concentration-dependent increase in small pial arteriolar diameter was observed with a higher concentration of nicorandil, but no increase was detected in small pial venules within the concentration range studied. Because of its nitrate moiety in chemical structure, nicorandil has been suggested to cause a sustained dilation of both venous capitative and arterial resistance vessels.¹⁹ In the present acute in vivo experiments in dogs anesthetized with pentobarbital, which has been known to decrease cerebral blood flow associated with a decrease in cerebral oxygen consumption, it is possible that the basal anesthetic state might affect the cere-

### Table 4. Physiological Measurements During Topical Application of Methylene Blue, Glibenclamide, Dimethyl Sulfoxide, and Subsequent Nicorandil

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MAP, mmHg</th>
<th>HR, bpm</th>
<th>BT, °C</th>
<th>pH</th>
<th>PacO₂, mmHg</th>
<th>PacO₂, mmHg</th>
<th>Na, mEq/L</th>
<th>K, mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>117±2</td>
<td>131±6</td>
<td>37.0±0.1</td>
<td>7.35±0.01</td>
<td>39.6±1.1</td>
<td>110.7±8.0</td>
<td>147.1±1.1</td>
<td>3.33±0.21</td>
</tr>
<tr>
<td>MB+NC</td>
<td>112±4</td>
<td>127±9</td>
<td>37.0±0.1</td>
<td>7.36±0.01</td>
<td>38.8±1.3</td>
<td>113.8±7.7</td>
<td>143.7±1.5</td>
<td>3.69±0.11</td>
</tr>
<tr>
<td>GC+NC</td>
<td>118±4</td>
<td>121±10</td>
<td>37.0±0.1</td>
<td>7.37±0.01</td>
<td>38.5±1.0</td>
<td>109.8±8.1</td>
<td>143.5±2.4</td>
<td>3.75±0.21</td>
</tr>
<tr>
<td>DMSO+NC</td>
<td>116±4</td>
<td>119±10</td>
<td>36.9±0.2</td>
<td>7.36±0.01</td>
<td>39.5±1.4</td>
<td>112.4±8.5</td>
<td>145.2±2.3</td>
<td>3.65±0.18</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial blood pressure; HR, heart rate; BT, body temperature; NC, topical application of 10⁻⁵ mol/L nicorandil solution; MB+NC, topical application of 10⁻⁵ mol/L methylene blue and subsequent 10⁻⁵ mol/L nicorandil; GC+NC, topical application of 10⁻⁵ mol/L glibenclamide and subsequent 10⁻⁵ mol/L nicorandil; and DMSO+NC, topical application of 10⁻³ mol/L dimethyl sulfoxide and subsequent 10⁻⁵ mol/L nicorandil. Values are mean±SEM.
brovascular tone in both arterioles and venules. Although pentobarbital has been shown not to affect cerebrovascular tone in isolated dog experiments,¹⁰ we cannot exclude the possibility that nicorandil may work equivalently on pial arterioles and venules directly.

Activation of guanylate cyclase and the consequent increase in the amount of cyclic GMP are considered to be the mechanism of action of nitrates. Nicorandil also relaxes vascular smooth muscles by stimulating the synthesis of cyclic GMP. Twenty-one Since methylene blue blocks guanylate cyclase, we applied methylene blue to determine whether guanylate cyclase interferes with the nicorandil-induced pial vasodilation and found that methylene blue did not affect pial vascular diameter. Other investigators have reported that methylene blue per se did not change baseline arteriolar diameter and that methylene blue did not affect topical applied nitrovasodilators; therefore, guanylate cyclase could not be affected by topical methylene blue. Twenty-two Twenty-three These data also indicate that methylene blue cannot penetrate into smooth muscle in small arterioles but rather generates a hydroxyl radical that inhibits EDRF. Contrary to these reports, the present result demonstrated that topical applied nitroglycerin-induced pial arteriolar or venular dilation was attenuated in the presence of methylene blue. Nicorandil has been established to dilate blood vessels without activating EDRF²⁴ and to release a second messenger, distinct from EDRF, that then activated guanylate cyclase and subsequently elevated cyclic GMP. Twenty-five Furthermore, topically applied methylene blue was reported to inhibit production of cyclic GMP through blockade of guanylate cyclase.²⁶ We interpret these results to mean that methylene blue blocked the vasodilative response in pial vessels elicited by nicorandil and that the mechanism of the vasoactive effects of nicorandil may in part depend on cyclic GMP-mediated second messenger systems.

ATP-sensitive K⁺ channels are involved in a dilative action of resistance arteries in response to vasodilative agents.²⁷ Using dispersed cerebral arterial smooth muscle cells, Bonnet et al.²⁸ demonstrated that outward K⁺ current resulted in cerebrovascular dilation. In vitro
Membrane hyperpolarization elicited by a K⁺ channel opener may antagonize cerebral vasospasm after subarachnoid hemorrhage. Furthermore, ATP-sensitive K⁺ channels in the brain are known to be associated with the release of γ-aminobutyric acid (GABA). Inhibition of GABA-ergic inhibitory control after transient brain ischemia leads to delayed neuronal death, and ATP-sensitive K⁺ channels are proposed to play a significant role in posts ischemic delayed neuronal death. Since downregulation of ATP-sensitive K⁺ channels induced by brain ischemia exerts adverse effects on the brain, nicorandil may be beneficial for cerebral vasospasm after subarachnoid hemorrhage and may protect the brain from ischemia.

In conclusion, topical application of nicorandil dilates both pial arteriolar and venular vessels in a concentration-dependent manner. Nicorandil is a cerebrovascular dilator. The mechanisms of vasodilative response caused by nicorandil are involved in cyclic GMP–mediated second messenger systems, and regulations of K⁺ flux also play an important role in the action of nicorandil on small pial arteriolar and venular dilation.

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In this interesting article the authors examined the effects of nicorandil on the pial microcirculation of the dog. They examined responses in both arteries and veins, and they demonstrated that topical application of nicorandil dilates both pial arteries and veins in a dose-dependent manner. The authors also demonstrated that, since nicorandil-induced dilation of both pial arteries and veins was inhibited by methylene blue and attenuated by glibenclamide, the mechanism of action of nicorandil is most likely due to both cyclic GMP-mediated vascular smooth muscle dilation and the regulation of K+ flux. The new and interesting aspect of this manuscript is that this is the first time that topical applications of nicorandil have been examined on pial vessels in vivo experiments in which both arteries and veins have been examined simultaneously in the same experimental preparation by the same investigators. In addition, the authors demonstrated that the mechanism involved in nicorandil vasodilation via cyclic GMP and/or in part the regulation of K+ flux appear similar in both arteries and veins. Little work in the past has been done with pial veins, and this article makes an interesting contribution along those lines.

Richard J. Traystman, PhD
Anesthesiology/Critical Care Medicine
The Johns Hopkins Medical University
Baltimore, Md
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T Ishiyama, S Dohi, H Iida, S Akamatsu, S Ohta and H Shimonaka

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