The Effect of Intravenous Dipyridamole on the Cerebral and Systemic Circulations of the Dog

David J. Boarini, M.D., Neal F. Kassell, M.D., Julie J. Olin, B.S.S., and James A. Sprowell, B.S.

SUMMARY In 7 dogs anesthetized with halothane and nitrous oxide, dipyridamole was administered in a loading dose of 1 mg/kg supplemented with 0.5 mg/kg every 30 minutes. Cardiovascular parameters and organ blood flows (using the radioactive microsphere technique) were measured before and at 30 minute intervals after each administration of dipyridamole, for a total of 105 minutes.

The administration of dipyridamole was associated with a 20% reduction in systemic arterial pressure, a 31% reduction in peripheral vascular resistance, and a 13% increase in cardiac index. Cerebrovascular resistance decreased 21%, but regional cerebral blood flow and metabolism were unchanged. Blood flow to the heart increased 355% in the right ventricle and 213% in the left ventricle. Blood flow to the jejunum decreased 52% while blood flow to the kidney and liver decreased slightly.

The circulatory effects of dipyridamole are probably related to its interference with the inactivation of endogenous adenosine. The differential effects of dipyridamole on organ flow are similar to those seen following the IV infusion of adenosine.

DIPYRIDAMOLE is a compound that is best known as an antiplatelet agent.8, 9, 25 It also has vasodilatory actions that are very marked on the coronary vessels, and less pronounced on the cerebral and peripheral circulation.5, 6, 10, 15, 24, 28 These properties suggest that dipyridamole may be a potentially useful agent in the management of patients in whom the cerebral circulation is compromised by thromboembolism or vasospasm following subarachnoid hemorrhage, particularly when the full anticoagulant effects of heparin are contraindicated. The purpose of this study was to document the cerebral and systemic circulatory effects of intravenous dipyridamole.

Materials and Methods

Seven mongrel dogs weighing approximately 17 kilograms (14.5–20 kg) were used for this study. Anesthesia was induced with 1% halothane and maintained with 0.5% halothane and nitrous oxide-oxygen (70:30). Muscular paralysis was achieved with pancuronium 0.5 to 0.7 mg per kilogram total, given in divided doses. Ventilation was controlled with a pump respirator. The animals were hyperventilated and CO2 added to the inspired gas mixture to maintain arterial PCO2 at approximately 40 torr. Temperature was maintained at 37º C. with a warming blanket.

Blood flow was determined six times in each dog using the radioactive microsphere technique with 15 ± 5 μm spheres labeled with 141Ce, 46Sc, 46Nb, 88Sr, 113Sn, and 153Gd. 5, 16, 21 The microspheres were injected into the left ventricle utilizing a pigtail catheter inserted through the femoral artery and positioned manometrically. Blood reference samples were drawn from the right femoral and brachial arteries. At the completion of the experiment the brain was removed and divided into cerebral hemisphere gray matter and mixed gray and white samples, caudate nuclei, corpus callosum, brain stem, and cerebellum. In addition, samples of the
cervical and thoracic spinal cord, temporalis and para-
spinous muscles, left and right ventricles of the heart,
and liver, stomach, jejunum, and kidneys were removed for blood flow determinations.

End tidal CO₂ was monitored continuously. Systemic arterial pressure was measured from a brachial artery. Central venous and pulmonary artery pressures were measured from a Swan-Ganz catheter inserted through a femoral vein. This catheter was also used to measure cardiac output with the thermodilution technique. Left ventricular pressure was measured with a pigtail catheter inserted retrogradely, through the femoral artery. Sagittal-sinus pressure was measured from a catheter placed in the anterior sagittal sinus and directed posteriorly. Heart rate was derived from the EKG. These physiological parameters were recorded on an 8 channel strip chart recorder. The electroencephalogram (EEG) was monitored from four muscle leads and recorded on an 8 channel electroencephalograph. Immediately prior to each blood flow determination, arterial blood gases, hematocrit, and oxygen and glucose content of sagittal sinus and arterial blood were determined. Serum potassium and sodium were measured prior to the first and after the last blood flow determinations.

The cerebral metabolic rate for oxygen (CMRO₂) and glucose (CMRGGL) were estimated by multiplying the mean cerebral hemisphere flow by the difference between the oxygen or glucose content of the systemic arterial and sagittal sinus blood. Cerebral vascular resistance (CVR) was calculated by dividing the difference between mean systemic arterial pressure (MAP) and the sagittal sinus pressure (SSP) by the total brain blood flow. Peripheral vascular resistance (PVR) was calculated by dividing the systemic arterial pressure by the cardiac index (C.I.). The cardiac index was estimated by dividing the cardiac output (C.O.) by the animal's weight.

The animals were allowed to stabilize for approximately three hours after the induction of anesthesia, at which time two control measurements of blood flow were performed. After the control measurements dipyridamole was administered intravenously. Initially, a loading dose of 1 mg/kg was given over approximately five minutes and thereafter three supplemental doses of 0.5 mg/kg were given at 30 minute intervals. Blood flow determinations were made 15 minutes after each dose of dipyridamole. Control values were calculated by averaging the two control determinations. Data was analyzed using paired t-tests and values are expressed as mean ± standard error.

**Results**

Hematocrit, blood gases, temperature, and electrolytes showed no important changes during the experiment (table 1). Administration of dipyridamole resulted in an average reduction in mean arterial pressure of approximately 20%, associated with a decrease in peripheral vascular resistance of 31%. Heart rate did not change and there was a slight but statistically insignificant increase in cardiac index and a decrease in cardiac work (table 2, fig. 1). Central venous, pulmonary artery wedge, and left ventricular end diastolic pressure did not change. Dipyridamole had a marked influence on myocardial blood flow. The average increase in right ventricle flow was approximately 355% and in left ventricle flow was 213% (table 3, fig. 2).

No significant changes were noted in blood flow to the cerebral hemispheres, brain stem, cerebellum and cervical or thoracic spinal cord (fig. 3). Cerebral metabolic rates of oxygen and glucose were not influenced by dipyridamole, except that CMRO₂, following the initial dipyridamole dose increased slightly. Cerebrovascular resistance decreased approximately 21% (table 4, fig. 4).

There was no significant changes in blood flow to the stomach or temporalis muscle. However, blood flow to the jejunum increased approximately 52%, while flow to the liver and kidney decreased slightly (fig. 5).

**Discussion**

Dipyridamole has two major actions of current therapeutic interest. First, it is an antiplatelet drug that has been associated with reduced thrombotic events in a number of settings. There is some evidence that this action is through an inhibition of platelet adhesion and aggregation and a decrease in the availability of platelet factor 4. Secondly, dipyridamole produces vasodilation in most vascular beds, this effect being most pronounced in the coronary circulation. The mechanism of vasodilation has not been fully elu-

### Table 1 Blood Gases, Chemistry, and Temperature

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Loading dose</th>
<th>Supplement #1</th>
<th>Supplement #2</th>
<th>Supplement #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>44 ± 4</td>
<td>43 ± 4</td>
<td>41 ± 4</td>
<td>41 ± 4</td>
<td>41 ± 4</td>
</tr>
<tr>
<td>pH</td>
<td>7.32 ± 0.02</td>
<td>7.31 ± 0.01†</td>
<td>7.29 ± 0.2†</td>
<td>7.29 ± 0.02†</td>
<td>7.29 ± 0.02†</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>40.5 ± 0.3</td>
<td>39.4 ± 0.7</td>
<td>39.9 ± 0.4</td>
<td>39.7 ± 0.5</td>
<td>40.9 ± 0.5</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.1 ± 0.3</td>
<td>37.0 ± 0.3</td>
<td>36.9 ± 0.2</td>
<td>36.8 ± 0.2</td>
<td>36.7 ± 0.2</td>
</tr>
<tr>
<td>Na⁺ (mg%)</td>
<td>149 ± 2</td>
<td></td>
<td>150 ± 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl⁻ (mg%)</td>
<td>95 ± 1</td>
<td></td>
<td>97 ± 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺ (mg%)</td>
<td>3.8 ± 0.1</td>
<td></td>
<td>5.0 ± 0.1†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p ≤ 0.05, †p ≤ 0.01.
TABLE 2  Cardiovascular Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Loading dose</th>
<th>Supplement #1</th>
<th>Supplement #2</th>
<th>Supplement #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>147 ± 6</td>
<td>137 ± 5</td>
<td>142 ± 3</td>
<td>146 ± 4</td>
<td>148 ± 4</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>99 ± 5</td>
<td>73 ± 7†</td>
<td>79 ± 7†</td>
<td>82 ± 7*</td>
<td>84 ± 8*</td>
</tr>
<tr>
<td>C.I. (L/Kg/min)</td>
<td>0.14 ± 0.02</td>
<td>0.15 ± 0.02</td>
<td>0.16 ± 0.02</td>
<td>0.16 ± 0.02</td>
<td>0.16 ± 0.02</td>
</tr>
<tr>
<td>C.W. ((MAP - LVEDP) \times SV) x 1.33 x 10^{-3}]</td>
<td>1.9 ± 0.4</td>
<td>1.8 ± 0.3</td>
<td>1.7 ± 0.4</td>
<td>1.7 ± 0.3</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>PVR \times 10^2 ((MAP - CVP) / C.I.)</td>
<td>7.3 ± 1.2</td>
<td>5.0 ± 1.0†</td>
<td>5.0 ± 0.9†</td>
<td>5.0 ± 0.7†</td>
<td>5.3 ± 0.8†</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>11 ± 1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>9 ± 1</td>
<td>8 ± 1</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
<td>10 ± 1</td>
<td>11 ± 1</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>SSP (mmHg)</td>
<td>7 ± 1</td>
<td>7 ± 1</td>
<td>7 ± 1</td>
<td>7 ± 1</td>
<td>7 ± 1</td>
</tr>
</tbody>
</table>

*p ≤ 0.05, †p ≤ 0.01.

MAP = mean arterial pressure; C.I. = cardiac index; C.W. = cardiac work; PVR = peripheral vascular resistance; PAWP = pulmonary artery wedge pressure; CVP = central venous pressure; LVEDP = left ventricular end diastolic pressure; SSP = sagittal sinus pressure.

which is itself an extremely potent vasodilator. 6, 10 Other possible mechanisms by which dipyridamole dilates vessels include 1) a direct relaxant effect on vascular smooth muscle, 2) inhibition of adenosine deaminase, and 3) phosphodiesterase inhibition and subsequent interaction with prostaglandins to increase cyclic AMP. 4, 7, 22

The most common clinical uses of dipyridamole relate to its antithrombotic actions and include prevention of cerebral thromboembolism, myocardial infarction, embolism from cardiac valve prostheses and deep vein thrombosis. 1, 7, 27 For these purposes the drug is administered orally on a chronic basis. In addition, dipyridamole is being used parenterally to increase myocardial blood flow during radioisotope imaging of the heart. 2, 3, 12-14 While the profound coronary vasodilator properties of dipyridamole have also led to its use in the treatment of angina pectoris and in attempts to reduce damage from acute myocardial infarction, the results in these areas have so far been disappoint-

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Cardiovascular parameters in seven anesthetized dogs given intermittent dipyridamole. Only the mean arterial pressure and peripheral vascular resistance showed statistically significant changes.

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Myocardial blood flows as measured by radioactive microspheres in seven anesthetized dogs given intravenous dipyridamole.
Table 3  Organ Blood Flows

<table>
<thead>
<tr>
<th>Blood flow (ml/100gm/min)</th>
<th>Control</th>
<th>Loading dose</th>
<th>Supplement #1</th>
<th>Supplement #2</th>
<th>Supplement #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle</td>
<td>91 ± 17</td>
<td>261 ± 84</td>
<td>243 ± 85*</td>
<td>365 ± 139*</td>
<td>269 ± 72*</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>75 ± 20</td>
<td>317 ± 98*</td>
<td>310 ± 124</td>
<td>429 ± 158*</td>
<td>308 ± 91*</td>
</tr>
<tr>
<td>Hemispheres</td>
<td>114 ± 9</td>
<td>119 ± 9</td>
<td>95 ± 9</td>
<td>114 ± 15</td>
<td>93 ± 9</td>
</tr>
<tr>
<td>Brainstem</td>
<td>61 ± 7</td>
<td>76 ± 8</td>
<td>66 ± 7</td>
<td>79 ± 8</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>77 ± 7</td>
<td>87 ± 8</td>
<td>76 ± 7</td>
<td>92 ± 10</td>
<td>76 ± 7</td>
</tr>
<tr>
<td>Cervical spinal cord</td>
<td>30 ± 2</td>
<td>35 ± 4</td>
<td>32 ± 5</td>
<td>36 ± 5</td>
<td>43 ± 10</td>
</tr>
<tr>
<td>Stomach</td>
<td>39 ± 8</td>
<td>29 ± 6</td>
<td>39 ± 8</td>
<td>48 ± 10</td>
<td>46 ± 17</td>
</tr>
<tr>
<td>Jejunum</td>
<td>59 ± 9</td>
<td>90 ± 21</td>
<td>81 ± 9</td>
<td>100 ± 9</td>
<td>85 ± 11*</td>
</tr>
<tr>
<td>Kidney</td>
<td>484 ± 28</td>
<td>471 ± 50</td>
<td>446 ± 37</td>
<td>496 ± 52</td>
<td>405 ± 41*</td>
</tr>
<tr>
<td>Liver</td>
<td>4 ± 1</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>2 ± 1*</td>
<td>2 ± 1</td>
</tr>
</tbody>
</table>

* p ≤ 0.05, † p ≤ 0.01.

Table 4  Cerebral Vascular Resistance and Metabolism

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Loading dose</th>
<th>Supplement #1</th>
<th>Supplement #2</th>
<th>Supplement #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVR (MAP - SSP) / CBF</td>
<td>0.89 ± 0.08</td>
<td>0.58 ± 0.04†</td>
<td>0.71 ± 0.06</td>
<td>0.75 ± 0.12</td>
<td>0.77 ± 0.10</td>
</tr>
<tr>
<td>CMRO2 (ML O2/100gm/min)</td>
<td>3.5 ± 0.4</td>
<td>4.9 ± 0.8*</td>
<td>3.5 ± 0.5</td>
<td>4.8 ± 0.7</td>
<td>3.8 ± 0.6</td>
</tr>
<tr>
<td>CMRGL (mg/100gm/min)</td>
<td>19.7 ± 4.2</td>
<td>23.2 ± 2.5</td>
<td>21.4 ± 4.7</td>
<td>32.1 ± 8.4</td>
<td>17.9 ± 2.6</td>
</tr>
</tbody>
</table>

* p ≤ 0.05, † p ≤ 0.01.

CVR = cerebral vascular resistance; CMRO2 = cerebral metabolic rate of oxygen; CMRGL = cerebral metabolic rate of glucose; MAP = mean arterial pressure; SSP = sagittal sinus pressure; CBF = cerebral blood flow.

Some of these various trials have involved modulating the effect of dipyridamole with synergists such as aspirin or antagonists including theophylline. As previously noted, dipyridamole is currently being used in certain centers in an attempt to prevent cerebral thromboembolism, although its effectiveness in this regard has not been proven. The cerebral vasodilatory and antithrombotic properties of dipyridamole make it a theoretically attractive agent for preventing infarction in situations where the cerebral circulation has been acutely compromised but the full anticoagulant effect of heparin is contraindicated such as in patients with vasospasm from ruptured intracranial aneurysm. However, the cerebral and systemic circulatory effects of high dose IV dipyridamole administered over several hours have not been fully documented. The dose of dipyridamole used in this study is similar to that used clinically for increasing myocardial flow. In anesthetized animals this intravenous dose causes a mild reduction in systemic arterial pressure. In unanesthetized patients, however, IV dipyridamole has only rarely resulted in hypotension, since the decreased peripheral vascular resistance is compensated for by an increase in cardiac output.

In this study the intravenous administration of dipyridamole reduced mean arterial pressure approximately 20%. This occurred as a result of a decrease in peripheral vascular resistance since cardiac output was unaffected. As reported previously, there was a very large increase in both right and left ventricular...
Cerebral blood flow remained constant, and there was decrease in cerebral vascular resistance equivalent to the reduction in mean arterial pressure. Whether the cerebral vasodilation was purely a manifestation of autoregulation or was in part related to the direct effect of dipyridamole on the cerebral vasculature cannot be answered from this data. Intracarotid adenosine has been shown in at least one study to increase CBF. There were no important changes in renal, hepatic, or gastric blood flow. However, there was a significant increase in flow to the jejunum. This differential effect of dipyridamole may be largely related to differing adenosine receptors in various vascular beds. A similar pattern has been seen in response to intravenous adenosine.

While there has been little investigation into the differential effects of intravenous dipyridamole on various organ systems in man, the cardiovascular effects appear to be similar to those we observed in the anesthetized dog. However, it is known that the decrease in blood pressure seen in the awake patient is less severe than that seen in our experimental preparation. Anesthesia has a major effect on the cardiovascular responses to intravenous dipyridamole. Accordingly, it must be emphasized that our observations in anesthetized dogs cannot be directly extrapolated to awake humans.

It appears that intravenous dipyridamole does not produce any adverse hemodynamic changes that would preclude its use in the management of patients whose cerebral circulation has been compromised, either by vasospasm after subarachnoid hemorrhage or thromboembolism. However its effectiveness in these situations remains to be proven.

References
4. Amer MS, Keighbaum WE: Cyclic nucleotide phosphodiesterases: properties, activators, inhibitors, structure-activity relationships, and possible role in drug development. J Pharm Sciences 64: 1-37, 1975
10. Feinberg H, Levitsky S, et al: Effect of dipyridamole on ischemia-
Experimental Air Embolism of the Brain: An Analysis of the Technique in the Rat

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SUMMARY Air embolization of the brain produces cerebral ischemia that can be focal and reversible. The method has previously been hampered by (1) lack of selective arterial injection of the embolus, (2) disruption of local hemodynamic relationships by ligation of major arterial channels, (3) excessive volume of the air embolus, and (4) uncontrolled bubble size. To minimize these factors, a technique was devised in which a fine catheter was advanced through a branch of the external carotid artery into the brain. The catheter was ligated at its distal end, allowing the catheter to be removed. For example, a common practice has been to ligate the external carotid artery before or after injection of air, which may result in a drop in cerebral blood flow and to attenuate electrical activity. As a result, the embolus of air is diverted from the internal carotid artery into the ipsilateral cerebral hemisphere for seconds to a couple of minutes. The duration of ischemia varied from region to region, and it tended to be prolonged by arterial hypotension. In the nonembolized hemisphere, CBF never declined abruptly (indicating no cross-over of air) although electrical activity was suppressed in two-thirds of the animals.

INJECTION OF AIR into the arterial vasculature of the brain is a convenient technique for producing focal and potentially reversible ischemia in animals. Many investigators have used the method through the years but under widely varying experimental conditions (table 1). Perusal of these reports reveals one or more methodological limitations in many of the animal models. First, the site of the arterial injection has at times lacked selectivity.8,12 As a result, the embolus of air distributes itself randomly into two or more major arteries, including those supplying noncerebral tissues, and the full volume of air may thus fail to reach the brain. Second, hemodynamic relationships between adjacent arterial territories have been needlessly disturbed during catheterization or puncture of the artery to be injected. For example, a common practice has been to ligate the external carotid artery before or after injection of air. Ligations of this type lead to alterations of flow through anastomotic channels that may cause a drop in the perfusion pressure in the tissue supplied by the ligated artery. It is, therefore, not surprising that blood is diverted from the internal carotid artery into the

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