Cerebral arteriovenous malformations, steal, and the hypertensive breakthrough threshold

An experimental study in rats


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An experiment was designed to investigate the effects of arteriovenous (AV) fistula occlusion on cerebral autoregulation. A right carotid-jugular fistula was created in 63 rats in such a way as to produce an intracranial AV fistula with a loop extension into the neck. The fistula was occluded after an 8-week interval with the rats under both normotension and metaraminol-induced hypertension, and evidence of blood-brain barrier disruption was investigated with an Evans blue dye technique. The results indicate that an intracranial AV fistula may cause cerebral steal which is responsible for a reduction in the threshold for hypertensive breakthrough following fistula occlusion.

Key Words: carotid-jugular fistula • arteriovenous malformation • cerebral steal • blood-brain barrier • rat

The "normal perfusion pressure breakthrough" hypothesis proposed by Spetzler, et al., offers a possible explanation for the hemorrhage or swelling that occurs in adjacent brain tissue shortly after reduction of flow through an arteriovenous (AV) malformation. The validity of this hypothesis may be questioned on clinical, experimental, and theoretical grounds. Alternative explanations for the phenomena cited in the literature as examples of "breakthrough" have not been rigorously excluded. Furthermore, the conclusions drawn from the limited early studies of this phenomenon may not be applicable to the clinical situation. Furthermore, the theoretical basis for a "resetting" of autoregulation (the cornerstone of the hypothesis) remains in doubt.

The aim of our present study was to create a model of a large AV fistula in an attempt to determine whether cerebral vasogenic edema occurs following occlusion of the fistula.

Materials and Methods

Sixty-three adult Wistar rats underwent general anesthesia with intraperitoneal pentobarbital sodium. Under magnification, the right internal jugular vein and the right carotid sheath were exposed. A carotid-jugular fistula was created as follows. The external carotid artery was ligated at its origin and the common carotid artery and internal jugular vein were ligated caudally in the neck. The common carotid artery and the internal jugular vein were divided above the caudal ligature, and an end-to-end anastomosis of the artery to the vein was performed with 10-0 nylon. This creates a functional intracranial AV fistula between the anterior circle of Willis and the right lateral sinus via a loop extension into the neck, composed of the internal carotid artery, distal common carotid artery, and the internal jugular vein. A functioning fistula was confirmed at angiography performed on four of the 63 rats at intervals of 1 day, 1 week, 3 weeks, and 6 weeks following the anastomosis.

After an interval of 8 weeks the animals were subjected to challenge of the blood-brain barrier (BBB) to protein as follows. Two ml/kg of a filtered 2% solution of Evans blue dye in 0.9% sodium chloride was injected intravenously 5 minutes before the anticipated BBB challenge by fistula occlusion or by induction of hyper-
tension with metaraminol infusion. This quantity of Evans blue dye binds almost completely to plasma albumin and will cross a disrupted BBB.5,23

At the time of the acute experiment the rats were anesthetized with intraperitoneal pentobarbital sodium (40 mg/kg) and allowed to breathe room air spontaneously. A laparotomy was performed and the aorta and inferior vena cava were cannulated to enable measurement of arterial blood gases, continuous recording of arterial blood pressure, and venous access for infusion of Evans blue dye and metaraminol.*

The fistula was explored and measured with a Zeiss microscope eye-piece graticule, and patency was assessed. The arterial and venous diameters were measured to determine whether the fistula was not patent, patent but smaller in diameter than at the time of anastomosis, patent and unchanged in diameter, or patent and increased in diameter.

The 50 animals with a right carotid-jugular fistula survived 8 weeks, and were divided into three experimental groups (see Table 1). Group 1 comprised 20 rats that underwent ligation of the fistula at normal blood pressure. Group 2 consisted of 14 rats that underwent fistula ligation and 5 minutes of hypertension with mean arterial blood pressure (MABP) maintained between 150 and 180 mm Hg by means of continuous metaraminol infusion titrated to the rat's MABP (average 20 μg/min). Group 3 included 13 rats that underwent hypertension for 5 minutes at an MABP between 150 and 180 mm Hg but did not undergo ligation of the fistula. A group of 16 control rats (Group 4) had no fistula placed, but underwent a similar procedure with metaraminol-induced hypertension only, with pressure controlled between 150 and 180 mm Hg for 5 minutes. The peak MABP maintained for 30 seconds was recorded in all four groups.

After 5 minutes of hypertension and 10 minutes of Evans blue dye circulation, the rats were killed with an intravenous injection of barbiturate. The brain was removed and sectioned, and the pattern of Evans blue dye staining was assessed and recorded photographically.

Results

Of the 63 rats undergoing fistula formation, four underwent angiography via aortic cannulation and nine others died before the experiment was concluded. This left 50 rats with a fistula that completed the experiment. The overall patency rate of the fistula in these 50 rats was 94%, 81% of which had an increase in size of the constituent vessels of the fistula as compared to an initial average diameter of 0.8 mm for the internal carotid artery, 1.0 mm for the free end of the common carotid artery, and 1.3 mm for the internal jugular vein. Data for the experimental and control rats are summarized in Table 1.

<table>
<thead>
<tr>
<th>Group No.</th>
<th>No. of Rats</th>
<th>MABP Before Hypertension</th>
<th>30-sec Peak MABP</th>
<th>No. With Breakthrough</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>86 ± 10</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>102 ± 11</td>
<td>162 ± 5</td>
<td>11†</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>104 ± 16</td>
<td>166 ± 7</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>98 ± 12</td>
<td>166 ± 7</td>
<td>0</td>
</tr>
</tbody>
</table>

* For a description of animal groups see text. Mean arterial blood pressure (MABP) ± standard deviation is given in mm Hg. — = data not applicable.
† Significantly different results from other groups (see text).

Group 1

Twenty rats with a patent fistula were not subjected to blood pressure manipulation. The MABP of these animals prior to fistula occlusion ranged from 70 to 100 mm Hg (mean 86 mm Hg), and the PaCO₂ ranged from 46 to 57 mm Hg. In none of these rats did fistula occlusion lead to Evans blue dye staining of the brain.

Group 2

Fourteen rats with a patent fistula underwent occlusion of the fistula and moderate hypertension by metaraminol infusion with MABP maintained for 5 minutes between 150 and 180 mm Hg. In 12 of these rats the fistula increased in size and in two the fistula became smaller. The mean pre-hypertensive blood pressure was 102 mm Hg (range 85 to 120 mm Hg), and the mean 30-second hypertensive peak was 162 mm Hg (range 155 to 170 mm Hg). The PaCO₂ ranged from 44 to 55 mm Hg.

Eleven of the 14 Group 2 rats demonstrated Evans blue dye staining of the brain. Of the three with no staining, two had smaller-diameter fistulae at 8 weeks than they did initially. In all instances of dye breakthrough the right hemisphere (the side of the fistula) was the only hemisphere involved. The Evans blue dye uptake was petechial, involved the gray matter, and ranged from only a few cortical petechiae to widespread staining of the hemisphere (Fig. 1).

Group 3

Sixteen rats with a patent fistula underwent hypertension by metaraminol infusion with a 5-minute MABP maintained between 150 and 180 mm Hg. In 10 of these rats the diameter of the fistula had increased, in one it was unchanged, and in two rats the fistula was smaller. The mean pre-hypertensive blood pressure was 104 mm Hg (range 80 to 140 mm Hg), and the mean 30-second hypertensive peak was 166 mm Hg (range 155 to 175 mm Hg). The PaCO₂ ranged from 48 to 59 mm Hg. There was no Evans blue dye staining of any of the 13 brains in this group.

Group 4

The control group (Group 4) consisted of 13 rats

* Blood gas analyzer (ABL2) manufactured by Radiometer America Inc., Westlake, Ohio; pressure recorder manufactured by Sanborn Co., Waltham, Massachusetts.
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FIG. 1. Photograph of the right hemisphere of a rat brain demonstrating the typical petechial staining by Evans blue dye in cases of breakthrough.

with no previous fistula and three rats with occluded fistulae. The mean pre-hypertensive blood pressure was 98 mm Hg (range 75 to 125 mm Hg), and the mean 30-second hypertensive peak was 166 mm Hg (range 160 to 180 mm Hg). The PaCO2 ranged from 42 to 59 mm Hg. There was no Evans blue dye staining of any of the 16 brains in this group.

Statistical Correlation

When Evans blue dye uptake in the hypertensive group with fistula occlusion (Group 2) was compared to that in the group with hypertension and a patent fistula (Group 3) and to that in the group with hypertension and no fistula (Group 4), the difference was found to be highly significant (p < 0.00003 according to Fisher's exact probability chi-square test) (Table 1).

Discussion

It has been suggested that chronically ischemic areas of brain adjacent to a cerebral AV malformation may be especially vulnerable to edema and the kinetic energy of blood flow. This "breakthrough" phenomenon is said to occur at normal perfusion pressure and is thought to be a significant contributing factor to morbidity in the surgical treatment of cerebral AV malformations. Moreover, based on this theory, therapeutic intervention has been proposed to combat this complication. On theoretical grounds, it has been claimed that occlusion of the AV shunt leads to a transfer of kinetic energy of blood flow to potential energy in the form of increased pressure. Thus, it has been likened to hypertensive breakthrough in which an increase of systemic arterial blood pressure of more than 90 mm Hg will bring about damage to the BBB. However, Nornes and Grip were unable to demonstrate an increase in pressure beyond 40 mm Hg after abolition of an AV shunt, and it is not known whether this pressure increase is transmitted to the capillary bed. Support for this hypothesis of normal perfusion pressure breakthrough comes from a single experimental study by Spetzler and his associates. Clinical evidence is adduced from a series of case studies and a combined series incidence of 3%. It was our view that there was inadequate experimental and clinical evidence to support this concept; hence, we undertook the present study.

Twenty-four cases of hemodynamic disturbance attributed to this proposed mechanism have been documented. Also, there has been one case of presumed BBB breakthrough at normal perfusion pressure following carotid endarterectomy for a tight carotid stenosis: the patient suffered a perioperative myocardial infarction. In this case and in the 24 cases cited in Table 2, other possible mechanisms of hemodynamic disturbance were not satisfactorily excluded. Such mechanisms include premature ligation of major draining veins, occlusion of feeding arteries, unrecognized partial resection of the AV malformation with subsequent rupture of the remnant, reduction of flow in a capacious venous system with resulting venous thrombosis and its sequelae, and coincident pathology such as aneurysm rupture.

The experimental model designed by Spetzler, et al., to test the "normal perfusion pressure breakthrough" hypothesis suffers from two major deficiencies. First, there was failure to produce breakthrough edema or hemorrhage; second, incorporation of the external carotid circulation invalidates conclusions regarding changes in cerebral autoregulation. The fistula design was developed from the one first described in 1949, which was subsequently refined by Gurdjian, et al., and Scott, et al. The modified design called for an end-to-end anastomosis between the common carotid artery and the internal jugular vein such that flow was retrograde in the distal common carotid artery and anterograde in the jugular vein. However, no mention was made of ligation of the external carotid artery, which may be presumed to have contributed a continuous flow of unknown volume through the fistula. Five of 30 experimental animals in their study exhibited marked dilatation of the feeding system after 6 weeks, and this was associated with diminished CO2 reactivity and autoregulation with both an open and closed fistula. In addition, there was an increase in flow in the contralateral common carotid artery with the fistula closed. There was, however, no measurement of the actual cerebral blood flow changes nor any demonstration of BBB disruption to support the concept proposed clinically. Therefore, in summary, the failure to measure cerebral blood flow, the inclusion of the external carotid circulation in the fistula, and the absence of demon-
**TABLE 2**

*Summary of 24 cases in the literature purporting to be examples of circulatory breakthrough*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Description of Fistula</th>
<th>Operative Procedure</th>
<th>Complications</th>
<th>Outcome*</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49, F</td>
<td>large</td>
<td>excision</td>
<td>swelling</td>
<td>died</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>very large</td>
<td></td>
<td></td>
<td>swelling</td>
<td>died</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>large</td>
<td></td>
<td></td>
<td>hemiplegia</td>
<td>alive</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>huge</td>
<td>excision</td>
<td>swelling</td>
<td>died</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>large</td>
<td></td>
<td>ruptured aneurysm</td>
<td>died</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>extensive</td>
<td>embolization</td>
<td>hemiparesis</td>
<td>died</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>large shunt</td>
<td>feeder occlusion</td>
<td>hemorrhage</td>
<td>died</td>
<td>19</td>
</tr>
<tr>
<td>8</td>
<td>18, F</td>
<td>large</td>
<td>feeder occlusion</td>
<td>hemorrhage</td>
<td>alive</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>48, F</td>
<td>large</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>63, F</td>
<td>large</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>37, M</td>
<td>550 ml/min†</td>
<td>“feeder occlusion”</td>
<td>swelling</td>
<td>alive</td>
<td>21</td>
</tr>
<tr>
<td>12</td>
<td>22, M</td>
<td>33 ml/min†</td>
<td>“feeder occlusion”</td>
<td>swelling</td>
<td>alive</td>
<td>21</td>
</tr>
<tr>
<td>13</td>
<td>35, M</td>
<td>190 ml/min†</td>
<td>“feeder occlusion”</td>
<td>swelling</td>
<td>alive</td>
<td>21</td>
</tr>
<tr>
<td>14</td>
<td>12, M</td>
<td></td>
<td>excision</td>
<td></td>
<td>well</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>9, M</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>16</td>
<td>48, M</td>
<td>large</td>
<td>excision</td>
<td>hemorrhage</td>
<td>well</td>
<td>8</td>
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<tr>
<td>17</td>
<td>43, M</td>
<td>large</td>
<td>excision</td>
<td>hemorrhage</td>
<td>poor</td>
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<tr>
<td>18</td>
<td>29, F</td>
<td>4-6 cm‡</td>
<td>embolization, feeder ligation, excision</td>
<td>hemorrhage</td>
<td>poor</td>
<td>8</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>4-6 cm‡</td>
<td>excision</td>
<td>hemorrhage</td>
<td>poor</td>
<td>16</td>
</tr>
<tr>
<td>20</td>
<td>35, F</td>
<td>4-6 cm‡</td>
<td>feeder occlusion</td>
<td>hemorrhage</td>
<td>poor</td>
<td>16</td>
</tr>
<tr>
<td>21</td>
<td>50, M</td>
<td>4-6 cm‡</td>
<td>embolization, excision</td>
<td>hemorrhage</td>
<td>died</td>
<td>16</td>
</tr>
<tr>
<td>22</td>
<td>21, F</td>
<td>diffuse</td>
<td>embolization</td>
<td>swelling</td>
<td>died</td>
<td>26</td>
</tr>
<tr>
<td>23</td>
<td>14, M</td>
<td>giant</td>
<td>embolization, feeder occlusion, excision</td>
<td>hemorrhage</td>
<td>well</td>
<td>26</td>
</tr>
<tr>
<td>24</td>
<td>60, F</td>
<td>large</td>
<td>embolization, excision</td>
<td>hemorrhage</td>
<td>died</td>
<td>26</td>
</tr>
</tbody>
</table>

*Well = no or minimal neurological deficits; poor = major incapacity; alive = alive but insufficient information to categorize.
† Calculated flow in main feeder artery.
‡ Maximum angiographic diameter in mid-arterial phase.

Possible BBB disruption casts doubt on the study by Spetzler, et al.,25 as an experimental basis for the normal perfusion pressure breakthrough hypothesis.

In the present experimental model, retrograde flow was established in both the internal carotid artery and the internal jugular vein. In addition, only the end result of BBB perturbation was measured by identifying loss of the barrier for plasma albumin.6,7,23 This was tested at normotension and at a level of hypertension below the threshold of hypertensive breakthrough identified by other authors.10,13—15,22 In our study, BBB disruption occurred reproducibly at moderate hypertension below this established threshold but did not occur under normotension nor in control animals. This disruption was limited to the hemisphere presumably previously deprived of blood by the fistula. While the concept of regional “steal” associated with a cerebral AV fistula remains controversial,1,18,28 it seems reasonable to postulate that such a steal is the basis for the abnormal vascular response that follows occlusion of the fistula. Because the fistula itself was remote and the increase in venous pressure was evenly distributed between both hemispheres, there is no other apparent explanation for the reduced breakthrough threshold that followed rapid occlusion of the fistula.

Why such a breakthrough did not occur at normotension remains unclear. Factors such as the volume of flow through the fistula and the duration of the fistula’s existence may be of significance. More detailed observations of the variations in blood flow and cerebral metabolism during the period of patency of the fistula and after occlusion will be necessary to extend this analysis of the observed phenomenon. Also, attempts to evaluate the importance of the length of time during which the fistula is open should be made. Much work remains to be done, therefore, to clarify the hemodynamic effects attendant upon occlusion of a long-standing cerebral AV fistula.

Conclusions

A sudden reduction of blood flow through an intracranial AV malformation is associated with a significant reduction in the threshold for hypertensive breakthrough. The proposed explanation is that, with obliteration of the shunt, the rapid reversal of the cerebral “steal” may lead to BBB breakdown in those regions of the brain previously affected by “steal.”

The therapeutic implication of obliterating cerebral AV malformations is that perioperative hypertension must be avoided, and that in patients at greater risk (that is, those with significant cerebral steal), a progressive reduction in the fistula, and hence a slow reversal of steal, may avoid the potentially catastrophic complication of breakthrough.

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References


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