Deliberate systemic hypotension to facilitate endovascular therapy of cerebral arteriovenous malformations: a computer modeling study

Erzhen Gao, Ph.D., William L. Young, M.D., John Pile-Spellman, M.D., Eugene Ornstein, M.D., Ph.D., and Qiyuan Ma, Ph.D.

Departments of Anesthesiology, Neurological Surgery, and Radiology, College of Physicians and Surgeons of Columbia University, New York, New York; and Department of Electrical Engineering, Columbia University, New York, New York

With the aid of a computer model, this investigation describes the relationship between mean arterial pressure (MAP) reduction and its effect on total arteriovenous malformation (AVM) shunt flow, feeding artery velocities, and cerebral blood flow in hypotensive, structurally normal vascular beds adjacent to the AVM nidus.

Simulations were performed for two feeding artery sizes (2 and 4 mm in diameter) and two AVM shunt flows (500 and 1000 ml/minute) with and without the presence of autoregulation in normal brain. Systemic arterial hypotension was simulated in a stepwise fashion by reducing aortic pressure from 100 to 10 mm Hg in 10-mm Hg steps. The percentage of MAP that resulted in a 50% reduction of shunt flow was calculated (%MAP reduction at half-maximal shunt flow).

As the MAP decreased, the shunt flow decreased in a nearly linear fashion; the cerebral blood flow remained constant in neighboring brain until the MAP dropped below 60 and 80 mm Hg for the medium and large AVMs, respectively. The %MAP reductions at half-maximal shunt flow for the medium and large AVMs were not significantly different from 50%: 44% and 47%, respectively. Results for 2 and 4 mm AVM feeding artery sizes were similar.

The decrease in both total shunt flow and flow velocity in feeding artery pedicles, potentially embolized by glue injection, were nearly linear with the institution of systemic hypotension. The presence or absence of autoregulation in normal brain, or different variations in the simulated angioarchitecture of the AVMs, did not affect this relationship in the model.

Key Words * cerebral blood flow * cerebrovascular regulation * circulatory models

Endovascular therapy of arteriovenous malformations (AVMs) is performed primarily as a preparatory adjunct to surgery.[10] Using various glues or other embolic materials, the blood supply to the fistula can be pared down, most commonly in several stages. As a preoperative adjunct, embolization is thought to facilitate operative removal of the AVM by several mechanisms. Embolization can eliminate deep vascular pedicles that might be difficult to control surgically and the excision of a lower flow nidus may be associated with reduced blood loss. There is a theoretical advantage in allowing the brain to adapt to
the complex circulatory changes that occur after shunt ablation, although this is a controversial and poorly understood area.[4]

Embolization of cerebral AVMs is becoming increasingly safe because of a variety of reasons. Improvements in catheter materials and endovascular techniques appear to be making inadvertent vessel occlusion, reflux of embolic materials, missed identification of normal branches, and uncontrolled antegrade or retrograde thrombosis less common.[10] The current challenge for improving embolization of AVMs is to make the treatment more effective. Total permanent obliteration of AVMs by endovascular techniques will require further developments in methodology.

Increasing the relative transit time through the arteriovenous fistulas in the AVM nidus can allow for more controlled deposition of embolic material, especially glues. Relative "flow arrest" may be achieved by pharmacological lowering of systemic arterial blood pressure, either in conjunction with a general anesthetic or light intravenous sedation in a patient.[13] The effect of lowering systemic arterial blood pressure on AVM shunt flow has not been rigorously studied. The objective of this investigation, based on a robust computer model,[2] was to describe the quantitative relationship between mean arterial pressure (MAP) reduction and its effect on total AVM shunt flow and feeding artery velocities and cerebral blood flow (CBF) in hypotensive, structurally normal vascular beds adjacent to the AVM nidus.

MATERIALS AND METHODS

Design Overview

We simulated the effects of deliberate systemic hypotension on AVM shunt flow and CBF in brain adjacent to the AVM. Simulations were performed for two feeding vessel sizes and two AVM sizes; thus, four different AVMs were simulated. The two feeding artery sizes were wide (4 mm) and narrow (2 mm) in diameter. The two AVM sizes, medium and large, were defined by their total shunt flows, which were 500 and 1000 ml/minute, respectively. The numbers of feeding vessels in each case were determined by the flow velocity through the feeding arteries, as discussed below. Simulations were conducted using a previously described computer model.[2]

Computational Approach

We developed a comprehensive computer model of cerebral circulation, based on both hydrodynamics and electrical network analysis, to investigate the influences of AVMs on regional cerebral hemodynamics.[2] The basic model contains 114 normal compartments: 55 arteries, 37 veins, 20 microvessel groups (MVGs), one compartment representing systemic and extracranial vascular resistance, and one representing the heart. Each MVG, which represents the arteriolar bed, consists of 5000 microvessels. Cerebral blood flow autoregulation was simulated by a formula that determined the flow rate of the MVGs (arterioles) as a function of perfusion pressure. Elasticity was introduced to describe the compliance of each vessel. The flow rate was made a controlling factor for the regulation of the diameters of conductance vessels by calculating the shear stress on the vessel wall through a function in which shear stress caused flow-induced vessel dilation. The AVM models were constructed by adding an AVM compartment and its feeding arteries and draining veins. A diagram of the model is presented in Fig. 1 and a brief mathematical description of the model is provided in the Appendix.
Fig. 1. Schematic diagram showing the model of the intracranial blood vessel network. A wider line represents a compartment that contains a number of identical parallel vessels. The numbers indicate the nodes. Between the arteries and veins are 20 MVGs, each of which consists of 5000 microvessels. A narrower line between an MVG and a vein does not represent a compartment but indicates a connection between the compartments. See Methods and Appendix for details.

**Lower Limit of Autoregulation Shift**

Autoregulation was introduced into the model by using a mathematical function to determine the CBF (see Appendix). Clinical observations and model studies suggest that the lower limit of autoregulation (LLA) is shifted toward lower pressure in chronically hypotensive but structurally normal vascular beds adjacent to the AVM nidus.[7,14] To take into account this autoregulatory curve shift, we used the data reported by Young, et al.,[14] which suggested that vascular territories with a pressure of approximately 30 mm Hg in the midlevel conductance vessels still retained autoregulatory vasoconstriction in the distal arteriolar beds. Therefore, the LLA at the level of the arteriolar bed (corresponding to the MVG in the model) was approximately 25 mm Hg. Hence, the LLA of our model was shifted to 25 mm Hg by the following definition (see Appendix).

**Equation 1:**

\[ Q = \frac{W}{100} \times \frac{2\bar{P}}{50} - 0.2(2\bar{P} - 50)^2 \]

- if 0 mm Hg < \( \bar{P} < 22.5 \) mm Hg
- if 22.5 mm Hg < \( \bar{P} < 25 \) mm Hg
- if 25 mm Hg < \( \bar{P} < 100 \) mm Hg

Note that the upper limit of autoregulation should also be changed; however, it has not been included in
Equation 1 and does not affect the results in this study because we focus our discussion on hypotension.

**Constellation of AVM Feeding Arteries**

The schematic depiction of the angioarchitecture of feeding vessels, draining veins, and AVMs specific to the present simulation are shown in Fig. 2.

![Fig. 2. Schematic diagram showing the submodel for AVM shunting used in this study. The AVM (between nodes 90 and 91) was fed by two wide arteries with a diameter of 4 mm, which are represented by two compartments (between nodes 21 and 90 and between nodes 25 and 90). The parameters and the numbers of the vessels for all simulations are shown in Table 1.](image)

An arrangement of feeding arteries that feed an AVM is termed a "constellation." The AVMs in these simulations were fed by the anterior cerebral artery (ACA) and middle cerebral artery (MCA). We used two feeding compartments to simulate feeding vessels rising from the ACA and MCA, respectively: ACA feeding compartment (connecting nodes 21 and 90; see Appendix for description of nodes) and MCA feeding compartment (connecting nodes 25 and 90). The number of vessels in each compartment was determined by the total shunt flow and the diameter of the feeding vessel. Using data previously reported by Nornes and Grip,[8] the velocity of feeding vessel flow was calculated based on the assigned diameter.[8] We used flow velocities of 60 and 30 cm/second to estimate the number of vessels. Based on these assumptions, the large AVM was fed by 2 wide vessels (one in each compartment) or 18 narrow vessels (nine in each compartment), whereas a medium AVM was fed by one wide vessel (in the MCA feeding vessel compartment) or nine narrow vessels (four in the ACA compartment and five in the MCA compartment). A summary of diameters and numbers of feeding vessels for four simulations is shown in Table 1.
Near-field blood pressure was calculated in the proximal arteries of the capillary beds (represented by MVGs) that were directly adjacent to the AVM. Autoregulation, that is, active vasomotion of the adjacent normal circulatory beds, might influence the relationship between reduction of systemic pressure and total shunt flow. To estimate the magnitude of any such effects, autoregulation was abolished in the whole brain for this simulation (as a worst case scenario) using the large AVM fed by two wide vessels.

**Systemic Hypotension**

Systemic arterial hypotension was simulated in a stepwise fashion by reducing aortic pressure from 100 to 10 mm Hg in 10-mm Hg steps. Normotension was considered to be an MAP of 80 mm Hg. The total shunt blood flow and CBF of the brain adjacent to the AVM nidus were calculated at each step. Because our a priori assumption was that both total shunt flow and feeding artery velocity would decrease in a nonlinear fashion, we introduced a term to denote the percentage of MAP reduction that results in a 50% reduction of shunt flow: %MAP reduction at half-maximal shunt flow = (100 mm Hg - MAP)/100 mm Hg, where 100 mm Hg is the starting MAP.

<table>
<thead>
<tr>
<th>AVM Size</th>
<th>Feeding Artery Size</th>
<th>Vessel Diameter (mm)</th>
<th>No. of Vessels</th>
<th>Mean Velocity (cm/sec)*</th>
<th>Shunt Flow Rate (ml/min)</th>
<th>%MAP†</th>
<th>CBF in Adjacent Brain††</th>
</tr>
</thead>
<tbody>
<tr>
<td>large</td>
<td>wide</td>
<td>4</td>
<td>2</td>
<td>68</td>
<td>1000</td>
<td>53</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>narrow</td>
<td>2</td>
<td>18</td>
<td>30</td>
<td>1000</td>
<td>53</td>
<td>65</td>
</tr>
<tr>
<td>medium</td>
<td>wide</td>
<td>4</td>
<td>1</td>
<td>66</td>
<td>500</td>
<td>56</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>narrow</td>
<td>2</td>
<td>9</td>
<td>30</td>
<td>500</td>
<td>56</td>
<td>85</td>
</tr>
</tbody>
</table>

* Mean velocity = velocity of blood flow through the feeding vessels.
† %MAP reduction at half-maximal shunt flow (percentage of the initial maximum).
†† CBF in adjacent brain at %MAP reduction at half-maximal shunt flow (percentage of normotensive value).
Fig. 3. Graphs depicting the effects of reducing MAP on two AVMs with total shunt flows of 1000 ml/min and 500 ml/min, respectively. The AVMs were fed by wide arteries (see Table 1 and Fig. 2). As the MAP decreased, the shunt flow decreased in a nearly linear fashion, whereas CBF remained constant in neighboring regions until the MAP exhausted autoregulatory vasodilation at values of 60 and 80 mm Hg for the medium and large AVMs, respectively. The MAPs corresponding to %MAP reduction at half-maximal shunt flow, in which the shunt flow was reduced by 50% of normotension, are indicated by dashed lines. For a medium AVM %MAP reduction at half-maximal shunt flow = 44 (A), whereas the CBF of the adjacent brain was 85% of its normotensive value (B). For a large AVM %MAP at half-maximal shunt flow = 47 (A), whereas the CBF of the adjacent brain was 65% of its normotensive value (B). A baseline (normal) MAP of 80 mm Hg is indicated by a dotted line. The simulation results for narrow-feeder constellations were similar to those for wide-feeder constellations and are therefore not represented in the figure.

RESULTS

Results for the four simulations are summarized in Table 1, which shows the feeding artery velocities predicted by the model during normotension (MAP 80 mm Hg) and the values of %MAP reduction at half-maximal shunt flow. The corresponding CBF in adjacent hypotensive brain regions is also given as a percentage of its normotensive value. The results for large-feeder AVMs were similar to those for small-feeder AVMs. The effects of reducing MAP on the total shunt flow and CBF of adjacent brain are illustrated in Fig. 3 for two different AVM shunt flows with wide arterial feeders (Table 1 and Fig. 2). As the MAP decreased, the shunt flow decreased in a nearly linear fashion. The CBF remained constant in neighboring regions until the MAP exhausted autoregulatory vasodilation at values of 60 and 80 mm Hg for the medium and large AVM, respectively. For a medium AVM, the %MAP reduction at half-maximal shunt flow was 44; the CBF in adjacent brain at this MAP was 85% of the normotensive
value. For a large AVM, the %MAP reduction at half-maximal shunt flow was 47; the CBF in adjacent brain at this reduced MAP was 65% of normotensive value. The effects of hypotension on near-field pressure are shown in Fig. 4. The near-field blood pressure decreased with the MAP and was higher for the medium AVM and narrow vessels than for the other three simulations, but was in the same (clinically comparable) range. The feeding vessel flow velocity decreased in a nearly linear fashion with the MAP (Fig. 4).

Fig. 4. Graphs depicting the effects of hypotension on near-field pressure (A) and vessel flow velocity (B). Near-field pressure was calculated for the region of brain directly adjacent to the AVM. Four simulations were computed for varying AVM size (large and medium AVMs) and vessel size (wide and narrow feeders). The near-field pressure decreased with the MAP, and was higher for medium AVMs and narrow vessels than for the other three simulations, but was in the same (clinically comparable) range. The vessel flow velocity decreased in a nearly linear fashion with decreasing MAP.

The effect of autoregulation on the relationship between the MAP and the total AVM shunt flow is shown in Fig. 5. The shunt flow was calculated for a large AVM fed by two wide vessels. When autoregulation was intact the shunt flow decreased slightly more as the MAP decreased; however, this difference might not be clinically notable.
DISCUSSION

This computer simulation demonstrates that the decrease in both the total AVM shunt flow and flow velocity in feeding artery pedicles potentially embolized by glue injection should decrease in a nearly linear fashion with progressive deliberate systemic hypotension. The presence or absence of autoregulation in normal brain, or different variations in the simulated angioarchitecture of the AVMs, did not affect this relationship in the model.

We introduced the term "%MAP reduction at half-maximal shunt flow" to describe the degree of deliberate hypotension necessary to decrease shunt flow by 50%. Such a term is useful for the description of a nonlinear relationship. However, the relationship between systemic arterial pressure and the total AVM shunt was nearly linear so this value was slightly lower than 50%. Therefore, estimation of shunt flow reduction should be possible by considering the MAP reduction. Further studies will have to determine whether the physical properties of injected embolization materials are similarly affected in a linear fashion by a reduction in shunt flow.

Systemic hypotension slows the flow through the AVM nidus and provides for a more controlled deposition of glues. As the pressure is lowered, serial contrast material injections administered under fluoroscopic guidance can be used to determine visually the optimum systemic pressure to slow the flow through the fistula. Clinically, we reduce systemic MAP to approximately 50 mm Hg, but greater or lesser degrees are selected based on the speed of the contrast material transit through the fistula.[12,13]

This subject has not been rigorously studied and it is not intuitively clear how the presence or absence of active vasomotion in normal vascular beds might affect the total shunt flow and feeding artery velocity. The nearly linear decrease in the total shunt flow observed in the present simulation of intact and
impaired autoregulation in adjacent normal brain suggests that there are minimal effects. Deliberate hypotension is used routinely not only for endovascular therapy but also for the operative removal of AVMs.[11] The potential disadvantage of using systemic hypotension to achieve partial flow arrest is that it might predispose to brain ischemia. Although never rigorously studied, in our experience it does not appear that deliberate systemic hypotension increases the morbidity of either embolization or surgery.[12] This might be explained as follows. The LLA appears to be shifted to the left in normal vascular territories rendered hypotensive by high proximal conductance vessel flow feeding the fistula. This adaptive shift to the left places the lower limit at a level considerably lower (25-30 mm Hg) than the lower limit postulated for normal brain (50 or 60 mm Hg).[14] The phenomenon of "cerebral steal" is invoked by many authors to explain focal neurological deficits in patients with AVMs, although as we have recently described, focal deficits are a rare presentation (< 10% of the time) and not necessarily associated with localized cerebral hypotension.[6] It is highly likely that local mass effects from the abnormal vessels of the AVM are more important than local "hemodynamic failure" in accounting for symptomatic focal neurological deficits unrelated to intracerebral hemorrhage.

The use of model simulations in future studies may be helpful in determining optimum approaches to achieving flow arrest for endovascular therapy and to designing the applications of newer embolic materials.

Acknowledgments

The authors wish to thank Joyce Ouchi for assistance in preparation of the manuscript. The authors gratefully acknowledge the support and contributions of the other members of the Columbia University AVM study project.

Click here to view Appendix.

References


Manuscript received April 15, 1997.

Accepted in final form May 9, 1997.

This work was supported in part by NIH Grants RO1-NS27713 and RO1-NS34949 and by a Clinical Scholar Grant from the International Anesthesia Research Society to Dr. Young.

Corresponding author: William L. Young, M.D., Columbia University, College of Physicians & Surgeons, 622 West 168th Street, Presbyterian Hospital 5-Center, New York, New York 10032. email: WLY1@columbia.edu.
APPENDIX

The structure of the basic model is the blood vessel network shown in Fig. 1. The element used in the model is a group of identical vessels or a "compartment." The geometric and structural parameters of the vessel network in this model, such as radius, length, elastic coefficient of a blood vessel, and the number of vessels in a compartment, as well as the position of its two ends within the model, are listed in Tables 1 and 2 of one of our previously published papers.[2] To simulate the arteriolar resistance beds, we introduced MVGs as special compartments. The model contains 20 MVGs, each consisting of 5000 parallel small vessels that are 0.1 mm in diameter. As shown in Fig. 1, six of the 20 MVGs are perfused by the ACA, 10 by the MCA, and the remaining four are perfused by the posterior cerebral artery. They are symmetrically distributed in the left and right hemispheres. Assuming a brain weight of 1500 g, each MVG feeds a brain tissue weight of 75 g.

It has been observed clinically that a conductance blood vessel will dilate if there is additional blood flow through the vessel. Although the mechanisms of vessel dilation remain unclear, shear stress on the vessel wall is one possible mediator of dilation.[1,5] In this model, whenever the mean shear stress is greater than 10 times normal, the vessel dilates to adjust so that shear stress is equal to up to 10 times the normal value.

Poiseuille's formula was used for single-vessel hemodynamics:[3]

\[ Q = \frac{\pi r^4}{8\eta L} \Delta P, \]

where \( Q \) is the flow rate through the vessel, \( \Delta P \) is the pressure drop across the vessel, \( r \) is the inner radius, \( L \) is the length, and \( \eta \) is the blood viscosity (\( \eta = 3.5 \text{ centipoise} \)). If the internal pressure of the vessel is \( P \), the relationship between \( r \) and \( P \) can be approximated as:

\[ r = r(0)(1 + mP), \]

where \( r(0) \) is the vessel radius at \( P = 0 \), \( m \) is the elastic coefficient of the vessel:[9]

\[ m = \frac{r(0)}{Eh}, \]

where \( E \) is the elastic modulus and \( h \) is the thickness.

For the inclusion of autoregulation, the precapillary arterioles (embedded in the MVGs) are assumed to regulate flow as a function of the mean perfusion pressure (pressure drop across the MVG):

\[ Q = \frac{W}{100} \times \begin{cases} \frac{\bar{P}}{50 - 0.2(\bar{P} - 50)^2} & \text{if } 0 \text{ mm Hg} < \bar{P} < 45 \text{ mm Hg} \\ \frac{50}{50} & \text{if } 45 \text{ mm Hg} < \bar{P} < 50 \text{ mm Hg} \\ \frac{50 + 0.2(\bar{P} - 150)^2}{\bar{P} - 100} & \text{if } 50 \text{ mm Hg} < \bar{P} < 150 \text{ mm Hg} \\ \text{if } \bar{P} > 150 \text{ mm Hg} \end{cases} \]
Here, $W$ is the weight of tissue perfused by one MVG and $P$ is the mean perfusion pressure averaged over a recent, short period of time.

In our model, consisting of $N_c$ compartments, the $j$th compartment contains $n_j$ identical vessels that have a uniform radius $r_j(0)$ at $P = 0$, and a length $L_j$. Two or more compartments meet at a junction called a node. Each node has a unique number that is given in Fig. 1. The $N_n$ is used to represent the total number of nodes in the model. According to Equation A1, the flow through compartment $j$ is:

$$Q_{j\text{k}-\text{k}'} = \frac{\pi r_{j\text{k}-\text{k}'}^4 n_{j\text{k}-\text{k}'}}{8 r_{j\text{k}-\text{k}'} L_{j\text{k}-\text{k}'}} (P_k - P_{k'})$$

where $r_{j\text{k}-\text{k}'}$ is the mean radius of the vessel connecting nodes $k$ and $k'$, and $P_k$ and $P_{k'}$ are the pressures at nodes $k$ and $k'$; $n_{j\text{k}-\text{k}'}$ is the number of vessels in the compartment, and $Q_{j\text{k}-\text{k}'}$ is the flow rate from node $k$ to $k'$ and $Q_{k'\text{k}} = -Q_{k\text{k}'}$. According to the law of conservation of mass, a system of $N_n$ node equations may be written for the sum of the blood flowing into node $k$, representing the blood imagined to accumulate within these nodes:

$$\Delta V_k = \Delta t \sum_{k'} Q_{k'\text{k}}(t) \quad (k = 1, 2, \ldots, N_n)$$

where $k'$ is the range of vessels entering or leaving node $k$, $\Delta t$ is a small time interval, and $V_k$ is the effective volume of node $k$. The volume of each vessel is assumed to be completely filled with blood, half the volume being associated with each node so that:

$$V_k = \frac{\pi}{2} \sum_{k'} 2k' L_k r_{k'\text{k}} k n_{k'\text{k}} k$$

In Equations A5 and A6, $k'$ varies over all compartments connected to node $k$. Substituting Equations A2 and A6 into Equation A5:

$$\Delta t \sum_{k'} Q_{k'\text{k}}(t) = \pi \sum_{k'} n_{k'\text{k}}^2 \left(1 + n_{k'\text{k}} P_k\right) L_{k'\text{k}} k \frac{dP_k}{dt} n_{k'\text{k}} k \quad (k = 1, 2, \ldots, N_n)$$

where $\Delta r_{k'\text{k}}$ is the change of $r_{k'\text{k}}$ from $t$ to $t + \Delta t$, and $\Delta r_{k'\text{k}} \ll r_{k'\text{k}}$. In Equation A7 the following approximation is also used:

$$\Delta x = \Delta t \frac{\partial x}{\partial P} \frac{dP}{dt}$$

We use a series of distinct points in time to represent the change of time: $t = \{t_i\}$, where $t_i < t_{i+1}$, $(i = 0, 1, 2, \ldots)$ and $t_{i+1} - t_i = \Delta t$. The $\Delta Q$ refers to the increase of flow $Q$ during the time interval from $t_i$ to $t_{i+1}$. Similarly, $\Delta P$ stands for the increase in pressure $P$. Substituting $t_i$ and $t_i + \Delta t$ into Equation A7, respectively, we obtain two equations. Subtracting these two equations yields,
From Equation A4, we see that $Q_{kk'} (k, k' = 0,1,\ldots,N_n)$ depends on $P_k, P_{k'}$ ($k, k' = 0,1,\ldots,N_n$). Starting with a proper set of initial conditions, Equation A8 can be solved.

As a special case, the heart not only has the common vascular properties of other vessels but it also serves as a driving pressure source. The systemic pressure and heart rate are changeable in the model, but a baseline MAP of 80 mm Hg and heart rate of 60 beats/minute were assumed for the present study. To reduce aortic pressure for simulation of systemic arterial hypotension, the heart output pressure was reduced.

$$\sum_{k'} \delta Q_{kk'} (t) = \pi \frac{\delta P_k}{\delta t} \sum_{k'} m_k r_{kk}(0)(1 + m_k' k P_k) L_k k k'$$

\[ (k = 1,2,\ldots,N_n) \]