Experimental Radiosurgery Simulations Using a Theoretical Model of Cerebral Arteriovenous Malformations

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Background and Purpose—A novel biomathematical arteriovenous malformation (AVM) model based on electric network analysis was used to investigate theoretically the potential role of intranidal hemodynamic perturbations in elevating the risk of rupture after simulated brain AVM radiosurgery.

Methods—The effects of radiation on 28 interconnected plexiform and fistulous AVM nidus vessels were simulated by predefined random or stepwise occlusion. Electric circuit analysis revealed the changes in intranidal flow, pressure, and risk of rupture at intervals of 3 months during a 3-year latency period after simulated partial/complete irradiation of the nidus using doses $<25$ and $\geq 25$ Gy. An expression for risk of rupture was derived on the basis of the functional distribution of the critical radii of component vessels. The theoretical effects of radiation were also tested on AVM nidus vessels with progressively increasing elastic modulus ($E$) and wall thickness during the latency period, simulating their eventual fibrosis.

Results—In an AVM with $E=5.0 \times 10^4$ dyne/cm$^2$, 4 (14.3%) of a total 28 sets of AVM radiosurgery simulations revealed theoretical nidus rupture (risk of rupture $\geq 100\%$). Three of these were associated with partial nidus coverage and 1 with complete treatment. All ruptures occurred after random occlusion of nidus vessels in AVMs receiving low-dose radiosurgery. Intranidal hemodynamic perturbations were observed in all cases of AVM rupture; the occlusion of a fistulous component resulted in intranidal rerouting of flow and escalation of the intravascular pressure in adjacent plexiform components. Risk of rupture was found to correlate with nidus vessel wall strength: a low $E$ of $1.9 \times 10^4$ dyne/cm$^2$ resulted in a 92.8% incidence of AVM rupture, whereas a higher $E$ of $7.0 \times 10^4$ dyne/cm$^2$ resulted in only a 3.6% incidence of AVM rupture. A dramatic reduction in rupture incidence was observed when increasing fibrosis of the nidus was modeled during the latency period.

Conclusions—It was found that the theoretical occurrence of AVM hemorrhage after radiosurgery was low, particularly when radiation-induced fibrosis of nidus vessels was considered. When rupture does occur, it would appear from a theoretical standpoint that the occlusion of intranidal fistulas or larger-caliber plexiform vessels could be a significant culprit in the generation of critical intranidal hemodynamic surges resulting in nidus rupture. The described AVM model should serve as a useful research tool for further theoretical investigations of cerebral AVM radiosurgery and its hemodynamic sequelae. (Stroke. 2000;31:2466-2477.)

Key Words: cerebral arteriovenous malformations ■ hemodynamics ■ intracerebral hemorrhage ■ models, theoretical ■ radiosurgery

Minimally invasive treatment with stereotaxic radiosurgery represents a useful adjuvant to conventional neurosurgery in selected patients with intracranial arteriovenous malformations (AVMs). Although radiosurgical techniques continue to evolve with advancing experience and technology, the risks of AVM rupture and ensuing neurological complications associated with postradiosurgery latency periods are still present and remain a concern.

Optimal stereotaxic radiosurgery would utilize the highest therapeutic radiation dose associated with the lowest incidence of possible complications. Radiation injury to the AVM vessels causes endothelial cell damage and proliferation, intimal and medial degeneration, and hyalin thickening, which leads to altered blood flow dynamics, hemostasis, and eventually thrombosis and obliteration of the AVM. Complete AVM obliteration is observed when blood flow through the AVM has ceased and all involved AVM nidus vessels have disappeared and is generally noted angiographically up to 3 years after radiosurgery. Thus, a latency period exists before complete obliteration, during which the irradiated nidus vessels begin to narrow, resulting in potentially dangerous intranidal hemodynamic disturbances that may predis-
pose to AVM rupture.\textsuperscript{3} It is during this latency period that some radiosurgeons consider the risk of AVM hemorrhage to remain elevated before falling to negligible levels, particularly for partially treated AVMs. Colombo et al\textsuperscript{3} reported in a study of 180 patients with radiosurgically treated intracranial AVMs that the bleeding risk for partially treated cases (ie, the entire nidus was not irradiated) was disturbingly high at 26\% per year, with the normal risk of rupture for untreated AVMs being approximately 3\% per year.\textsuperscript{2,3} Concern regarding the increased likelihood of hemorrhage after partial AVM radiosurgery has also been expressed by others.\textsuperscript{4,5} Deliberate partial radiosurgery may be adopted as a management strategy for some giant AVMs,\textsuperscript{6} and in some patients partial AVM radiosurgery occurs after inadvertent incomplete obliteration.\textsuperscript{7} The risk of hemorrhage in both categories of patients may be elevated and therefore remains worrisome. In addition to these observations for partially treated AVMs, preliminary experience from large\textsuperscript{8} and smaller\textsuperscript{9–11} clinical series is accumulating to indicate a possible increased propensity to rupture for some completely irradiated AVMs during postradiosurgery latency periods, regardless of selection or referral biases. By contrast, a recent study by Karlsson et al\textsuperscript{12} has demonstrated a protective effect of radiation on AVMs, as evidenced by an observed decrease in the incidence of AVM hemorrhage compared with the natural course. In an attempt to shed further light on these contradictory clinical observations, we provide in this preliminary report a theoretical analysis of the intranidal hemodynamic changes and some biophysical mechanisms that affect the risk of AVM nidus rupture after radiosurgery.

A novel biomathematical model of intracranial AVMs based on electric network analysis has been developed\textsuperscript{13,14} and employed\textsuperscript{14} previously as an experimental tool capable of qualitative simulation of complex hemodynamics through a theoretical AVM nidus and of assessment of its risk of rupture before, during, and after therapy. In this preliminary study, we used this new biomathematical AVM model to simulate the hypothetical occlusive responses of nidus vessels to 2 levels of radiosurgical dosages and to investigate the resultant theoretical intranidal hemodynamic changes. In addition, we studied the intranidal stability during the latency period by theoretical quantification of the risk of nidus rupture at defined temporal intervals up to 3 years after treatment. The goals of this preliminary study were as follows: (1) to investigate the theoretical influence of radiation dosage, rate of AVM occlusion, extent of irradiated AVM volume (partial versus complete), and inherent strength of nidus vessels on the risk of nidus rupture after radiosurgery and (2) to examine theoretically whether intranidal hemodynamic perturbations occur after AVM radiosurgery and to what extent these may contribute to the elevation in risk of rupture during the latency period.

**Methods**

The details of this AVM model are described elsewhere,\textsuperscript{13–15} in Appendix 1, and in Figure 1.
AVM Model Simulations of Radiosurgery

The biomathematical AVM model was used to simulate the response of a theoretical intracranial AVM to radiosurgery with the application of 2 different hypothetical occlusion schemes to intranidal vessels. The occlusion schemes (ie, the schemes by which simulated vessels of an AVM nidus could theoretically undergo occlusion after irradiation) were based on 3 primary factors: mechanism of vessel occlusion, radiation dosage, and extent of irradiated AVM volume.

Although the underlying mechanisms of vessel occlusion in response to radiation are speculative, 2 mechanisms have been proposed in the literature16–18 and are applied individually to the AVM model simulations described herein. These 2 mechanisms of vessel occlusion are (1) stepwise circumferential vessel narrowing and eventual occlusion (and 2) random immediate total vessel occlusion. In the first mechanism, the radius of each nidus vessel within the irradiated AVM volume was reduced abruptly by a uniform percentage of the initial vessel radius at discrete time intervals after simulated radiosurgery. The quantitative percentage values depended on the radiation dosage and the time lapse after irradiation and will be discussed in detail below. The second mechanism of occlusion involves the total occlusion of nidus vessels randomly selected (using a random number generator) within the irradiated AVM volume according to the percentage of affected vessels dictated by the radiation dosage and time lapse after irradiation.

Both stepwise and random occlusion schemes were investigated in the biomathematical AVM model simulations according to 2 levels of radiation dosage (D): (1) D < 25 Gy and (2) D ≥ 25 Gy. The rate of occlusion is dependent strongly on the radiation dose delivered to the AVM volume, as evidenced by the data presented in Figure 4 of the report by Yamamoto et al.19 In that study, postradiation changes in angiographically determined nidus volumes were studied quantitatively in 22 AVM cases treated by gamma-unit radiosurgery. In the aforementioned Figure 4 of Reference 19, the percentage of occlusion was plotted for each dosage level at 1 year, 2 years, and 3 years. Significantly, it was the region within 6 months after irradiation at which the propensity of the nidus to hemorrhage reached its maximum before subsiding at later times. Using that information from the work of Yamamoto et al19 to determine quantitatively the rate of occlusion at points within each year, we recorded the exact data points from the aforementioned plots and fitted them to polynomial functions through interpolation. These functions for each radiation dose are given below:

\[ y = \frac{40 - 14(2 - x) - 1}{3} x \]  for D < 25 Gy

\[ y = 88 + 32(2 - x) - 1 \]  for D ≥ 25 Gy

where x is the time after radiosurgery and y is the percent occlusion. These functions are displayed graphically in Figure 2. Thus, for each dose, the percentage of nidus vessel occlusion was determined at 3-month intervals from 0 (time of AVM irradiation) to 3 years after irradiation. The resultant reduction in caliber of plexiform and fistulous vessels is seen in Figure 3. In this study, each simulated radiosurgery of the AVM model was executed with a theoretical dosimetry that simulates a hypothetical target dose distribution of 50 Gy, 90% isodose contour.3,20

Investigations of the effects of radiosurgery on irradiated AVM volume were performed through simulations of the occlusion schemes on the total nidus (complete treatment), the upper and lower halves of the nidus, and 4 quarters of the nidus (partial treatment). The upper and lower halves of the nidus were separated such that all 4 fistulous components were contained within the lower half of the nidus. Similarly, in the quarters of the nidus, the fistulous components were contained in the lower 2 quarters. For each of the simulations, particularly with the partially irradiated volumes, the radiosurgery occlusion schemes were applied only to the nidus vessels contained within the volume under investigation while keeping the remainder of the nidus vessels untreated, ie, patent.

It can be seen from the equation in Appendix 1, and as outlined in previous accounts of this model,14,15 that the risk of nidus rupture is also assumed to be dependent on the elastic modulus (E) and the thickness (t) of nidus vessels. The “typical” or average values assumed for these parameters in the present and previous studies are 5.0×10^4 dyne/cm^2 and 50 μm, respectively. In reality, our adopted value for t is a fair approximation, as evidenced by inspection of light microscopic sections of cerebral AVM tissue. On the other hand, the value for E is speculative but, at least, is derived through knowledge of values of E for normal venules (1.0×10^5 dyne/cm^2)21 and arteries (3.0 to 5.0×10^5 dyne/cm^2),22 as is available in the literature. Clearly, the value of E (and to a similar extent that of t) assigned to nidus vessels and used in calculating the risk of rupture after radiosurgery could have a significant/crucial influence on whether or not an AVM is found to rupture. Since the exact value of E for AVM nidus vessels is unknown, one might speculate that if a high value of E is assumed, then our calculations might yield low percentages of risk of rupture, and vice versa. For this reason, and to study precisely the influence of E on our results, all radiosurgical simulations were performed in the typical AVM model using the typical value of E at 5.0×10^4 dyne/cm^2; these were then repeated in models possessing values of E that varied at intervals within the range 1.9×10^4 to 8.0×10^4 dyne/cm^2. Note that the lower value of this range was chosen because the resultant AVM was found to have a baseline risk of rupture that remained <100% (ie, was unruptured in its natural state before radiosurgery). The use of any lower values of E would result in AVMs that were inherently too unstable/fragile (ie, with a risk of rupture ≥100%) prior to therapy.

An additional issue with regard to investigating the risk of rupture of AVMs after radiosurgery is the likelihood that values of E and t do not remain static but instead increase in value (as a result of the actual radiosurgery) during the latency period as the nidus vessel walls get stronger and thicker with time, leading eventually to oblitative fibrosis. Therefore, the 3 cases of rupture occurring in the irradiated zones of the typical AVM possessing an E of 5.0×10^4 dyne/cm^2 were subject to a separate reassessment of their risk of rupture as the value of E itself was gradually increased during the latency period, to ultimately approach the known value of E for thick sclerotic vessels, ie, 5.0 to 8.0×10^4 dyne/cm^2.23 Furthermore, by using the data on temporal change in vessel radius obtained from Figure 3 and by simplistically assuming that this caliber reduction could be a direct result of progressive increase in mural thickness, we
calculated the hypothetical temporal increases in $t$ for the 3 vessels exhibiting rupture within irradiated zones of the nidus (when only a static $t$ is assumed). These new progressively higher values of $t$ were, in turn, used in the equation in Appendix 1 to calculate the new values of risk of rupture for these 3 cases at 3-month intervals during the latency period.

**Results**

Results of the baseline AVM hemodynamics and risk of nidus rupture before simulated radiosurgery are presented in Appendix 2. A total of 364 AVM radiosurgery simulations were performed for the AVM assigned the typical value of $E$. The various permutations of factors (28 AVM cases at 13 time intervals) considered in arriving at this total number of simulations are outlined in Figure 4.

**Risk of Nidus Rupture After Radiosurgery of the Typical AVM**

Gradual trends in the transnidal and intranidal distribution of hemodynamics and corresponding risk of rupture were observed for almost all radiosurgery simulations over the temporal intervals after AVM irradiation. For the nidus vessels subjected to the random vascular occlusion scheme, immediate pronounced surges in the risk of rupture of vessels adjacent to the occluded vessels after irradiation were identified before reaching a plateau and subsequent drop to negligible values of risk of rupture. Similar patterns of surges in the risk of rupture for nidus vessels affected by the stepwise vascular occlusion scheme were noted. For all occluded nidus vessels, regardless of occlusion scheme, marked increases in the risk of rupture of adjoining nidus vessels were shown, indicating a corresponding shift in the hemodynamic burden originally accommodated by the occluded vessels.

For the typical AVM, definite nidus rupture was observed in a total of 4 of 28 theoretical AVM cases (14.3%) after simulated radiosurgery with simulations of $\leq 25$ Gy and random vascular occlusion (Table 1). Overall, 1 of 4 cases (25%) of total AVM irradiation, compared with 3 of 24 cases (12.5%) of partial AVM irradiation, resulted in nidus rupture. Figure 5A through 5D consists of schematic diagrams of the nidus network for the 4 cases of rupture, also displaying examples of either total or subtotal (half or quarter) irradiation of the nidus as performed in this study. Accompanying
Biomechanical Properties of Nidus Vessel Walls

The results of radiosurgery simulations in AVM models that possess varying values of \( E \) for nidus vessels are shown in Table 2. The following can be seen: (1) The weaker the nidus vessels (low \( E \)), the higher was the percentage of AVMs that ruptured after radiosurgery, and vice versa. At \( E=8.0 \times 10^4 \) dyne/cm\(^2\), none of the AVMs ruptured during the latency period. (2) The weaker the nidus vessels (low \( E \)), the higher was the proportion of ruptures that occurred with partial nidus irradiation, and the stronger the nidus vessels (high \( E \)), the higher was the proportion of ruptures that occurred with total nidus irradiation. However, the use of proportions or percentages in this instance may be misleading because, overall, there were far fewer simulations of total nidus irradiation. In fact, many more theoretical ruptures were observed after partial nidus irradiation, supporting to some extent knowledge of the dangers of this particular therapeutic strategy (deliberate or inadvertent). In AVMs composed of weak nidus vessels (low \( E \)), no difference was observed in the risk of rupture after either low-dose (<25 Gy) or high-dose (≥25 Gy) radiosurgery. Random vessel occlusion resulted in higher percentages of nidus rupture, presumably as a consequence of the associated sudden and complete shifts of hemodynamic forces into adjacent nidus vessels. By contrast, stepwise vessel occlusion was associated with lesser incidence of nidus rupture.

Influence of Increasing Nidus Vessel Fibrosis on Risk of AVM Rupture

At present, there is no documentation in the literature of the rate at which nidus vessels change their mechanical properties during the latency period to eventually become fibrotic. Simplistically and speculatively, if it is assumed, for example, that the typical AVM might change its value of \( E \) from \( 5 \times 10^4 \) dyne/cm\(^2\) to that of \( 1 \times 10^5 \) dyne/cm\(^2\) (that of a fibrotic vessel) in a linear fashion, it can be seen from Figure 6 that the 3 cases of rupture that occurred within irradiated zones of the nidus originally at 6, 9, and 15 months after irradiation (when the value of \( E \) was assumed static) would all have considerably higher values of \( E \) at these specific times. From Table 2, it can be appreciated that no AVM ruptures at \( E=8.0 \times 10^4 \) dyne/cm\(^2\). These higher values of \( E \) due to progressive fibrosis would result in a 0% rate of rupture instead of the 14.3% previously obtained in the presence of a static \( E \). The use of this typical AVM as a single example of implementing the possible effects of additional fibrosis after irradiation shows that, in reality, all the figures obtained for percentages of rupture after radiosurgery (seen in Table 2) are likely to be artificially elevated. This assertion is further supported by the absence of rupture observed when increasing thickness of vessels during the latency period is also accounted for. Figure 7 exemplifies this in case 1, in which rupture occurs with a static \( t \) but the risk falls below the rupture threshold when increasing mural thickness and eventual luminal occlusion are modeled after simulated radiosurgery.

Discussion

The salient findings of this preliminary study are as follows: (1) The occurrence of theoretical AVM hemorrhage after simulated radiosurgery in this model is infrequent; this provides some indirect support for the likelihood that irradiation does not change or even lowers the propensity of AVMs to rupture, rather than actually increasing it. This appears to

<table>
<thead>
<tr>
<th>Vascular Occlusion Scheme</th>
<th>Dose</th>
<th>Extent of Nidus Rupture</th>
<th>Time, Vessel, and Location of Nidus Rupture</th>
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</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Case</td>
<td>Random</td>
<td>Stepwise</td>
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<tr>
<td>4</td>
<td>+</td>
<td>...</td>
<td>+</td>
</tr>
</tbody>
</table>

Q3 indicates lower left quadrant of the nidus; Q4, lower right quadrant of the nidus; Vessel, specific nidus vessel in AVM model; Location, nidus region: A, nidus region near the arterial feeders; and V, nidus region near the draining veins. Baseline (pretreatment) risk of rupture values for vessels 12, 14, 21, and 37 were 86.2%, 74.3%, 89.4%, and 91.1%, respectively. These values of risk of rupture rose to 100.3%, 102.7%, 103.9%, and 100.7%, respectively, during the radiosurgical latency period.
and it should be possible to establish this for specimens of AVM tissue as well. (3) As seen theoretically in this model, intranidal hemodynamic perturbations appear to play a significant role in the generation of hemorrhage when this occurs during the latency period. (4) As seen theoretically in this model, partial and/or low-dose radiosurgery are found to be of particular danger when treating AVMs. The implications of these findings are discussed below.

Biomathematical Modeling of AVM Radiosurgery

Models are necessary to achieve reproducibility, which is an essential component of scientific experimentation. The many advantages of biomathematical modeling and the rationale behind using this experimental approach have been described previously. Biomathematical models offer a way to theoretically understand AVM physiology under normal hemodynamic conditions and during various types and stages of therapy, particularly in a region of an AVM (the nidus) that is otherwise inaccessible to detailed investigations by any other current technique. The biomathematical modeling of AVM radiosurgery will always be limited by the lack of biological and biovariability traits and is therefore best used in combination with other experimental techniques, eg, recently developed animal models, and in concert may provide the potential to enhance dramatically our understanding of AVM radiosurgery and create a forum for research and exploration of new ideas. Generally, the results of biomathematical modeling are not intended to be extrapolated directly to the clinical setting but instead are to be used as a framework within which clinical phenomena can be better understood and possible implications suggested. The advantages and disadvantages of the specific AVM model used in this study have been discussed previously. In addition, the general principles and philosophical premises of modeling in biomedical research have been reviewed in detail recently by the authors; the present modeling study was conducted within a framework provided by these previously presented guidelines. Importantly, no quantitative extrapolation to a human AVM setting is possible with this model (at least, as presented in this preliminary study) in assessing the risk of hemorrhage after treatment; instead, a qualitative appreciation can be obtained for the ability of irradiation to induce hemodynamic and biomechanical alterations in the stability of the nidus vessels and to induce rupture.

A biomathematical model was used previously by Lo and colleagues to analyze the theoretical hemodynamic perturbations in and around abnormal AVM shunts in response to radiosurgery. This important work has provided some support and a theoretical basis to clinical observations that partial volume irradiation of AVMs may lead to transient increases in pressure gradients and a propensity to hemorrhage within persistent AVM shunts. In the present study we have expanded on this subject by performing a more detailed theoretical analysis of the hemodynamic changes and risks of vessel rupture within a much more complex and realistically simulated AVM nidus in a model based on electric network analysis.

The 2 simplistic approaches to occlusion of intranidal vessels used in this study have been used previously in...
TABLE 2. Summary of Results From Radiosurgical Simulations of Theoretical AVM Model When Nidus Vessels Are Assigned Different Values of Elastic Modulus

<table>
<thead>
<tr>
<th>Elastic Modulus of Nidus Vessels, dyne/cm²</th>
<th>Maximum Risk of Rupture Before Radiosurgery*</th>
<th>% Rupture Among All AVMs (n=28)</th>
<th>% Rupture Among Totally Irradiated AVMs (n=4)</th>
<th>% Rupture Among Partially Irradiated AVMs (n=24)</th>
<th>% Rupture With &lt;25 Gy Irradiation (n=14)</th>
<th>% Rupture With ≥25 Gy Irradiation (n=14)</th>
<th>% Rupture With Random Occlusion Scheme (n=14)</th>
<th>% Rupture With Stepwise Occlusion Scheme (n=14)</th>
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<td>1.9×10²</td>
<td>99.9</td>
<td>92.8</td>
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<td>92.8</td>
<td>92.8</td>
<td>100</td>
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<td>35.7</td>
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<td>92.1</td>
<td>21.4</td>
<td>25.0</td>
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<td>14.3</td>
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n indicates number of cases, as explained in Methods.

*The tabulated risk of rupture is a percentage figure, with a risk ≥100% denoting certain nidus rupture. To examine the effects of radiosurgery on AVM rupture, all AVM models used in our study possessed a pretherapy risk of rupture <100%. The maximum risk of rupture is that of the single intranidal vessel exhibiting the highest propensity to rupture. This value of risk of rupture sets the highest limit of risk of rupture for the entire nidus, because if 1 vessel ruptures then the entire nidus is deemed to have ruptured. Note that as the elastic modulus of nidus vessels increases, their inherent risk of rupture (before any treatment) decreases because of strengthening of their walls.

Theoretical modeling of radiosurgery. It is acknowledged, however, that random occlusion of vessels is the less likely of the 2 mechanisms to occur in vivo. In reality, a third more complex vessel occlusion mechanism would more likely replicate in vivo events within an AVM nidus after radiosurgery. This may be described as a “gradual” circumferential vessel occlusion scheme, in which intranidal vessels are reduced continuously and systematically in diameter as the time after irradiation increases. The difference between this and the stepwise mechanism arises by virtue of the latter’s inability to consider temporal/dynamic phenomena. The introduction of this gradual mechanism of occlusion would have increased greatly the complexity of our model simulations and the necessary mathematical calculations in this preliminary study. By adopting this third mechanism in future simulations, it may be possible for the model to account for the rate of increase in pressure gradients within nidus vessels and to study how a nidus responds to and accommodates dynamically the resultant hemodynamic surges after radiosurgery. We speculate that this may translate into even lower risks of nidus rupture than predicted by the results of the present study.

Risk of AVM Nidus Rupture

The results of the AVM model simulations demonstrate that as the nidus vessels becomes occluded after irradiation, the risk of rupture changes as the intranidal pressure redistributes itself to compensate for the radiosurgically induced occlusion. Generally, increases in risk of AVM nidus rupture were observed particularly in close proximity to the sites of ingress of arterial feeders and egress of draining veins. In the event of nidus rupture, those intranidal vessels adjacent to either the arterial feeders or draining veins were shown to exhibit an unsafe increase in the risk of rupture. The theoretical occurrence of more ruptured vessels at the boundaries of the nidus, as opposed to the center of the nidus, was interesting and due presumably to the already relatively high pretreatment intranidal vascular pressures found at the arterial end of the nidus and the already relatively high pretreatment risks of vessel rupture at the venous end of the nidus.

The observed lack of difference between the hemorrhage risks after optimal and suboptimal dosages in AVMs composed of inherently weak nidus vessels (low E) (Table 2) was presumably because in these vessels, any additional stresses after irradiation (regardless of dosage) might result in hemorrhage. Interestingly, this interpretation might hold true for a similarly encountered clinical observation by Lindquist in the radiosurgical management of some brain AVMs. On the other hand, our results suggest that in the majority of AVM models (with higher values of E), a lower dose was associated with higher percentages of nidus rupture in the latency period. This dependence of the obliterative process (and, therefore, AVM protection) on the delivery of an appropriate amount of radiation energy was demonstrated in previous clinical series to be of statistical significance.

The values for risk of AVM nidus rupture used in this study are not intended to duplicate figures that represent the annual risk of AVM hemorrhage as expressed commonly in clinical practice, such as the 3% annual hemorrhage rate for untreated...
AVMs. Nor are these values for risk of rupture intended to match other methods of assessing lifetime risk of AVM hemorrhage, such as that involving the multiplicative law of probability formula, which requires knowledge of the patient’s age and annual hemorrhage risk. Instead, the expression used in this study does not take into account age or time factors but provides results that are static and fixed at one time only, ie, at the time the intervening therapy or its effect takes place. This is another reason why the results of the model, although numerical in nature, can only be interpreted qualitatively with a view to appreciating the underlying or portrayed principles.

Several clinical (eg, AVM hemorrhage within a year before radiosurgery and the patient’s age), morphological (eg, AVM size), and angioarchitectural (eg, the presence of aneurysms related to the AVM factors other than those examined in this study are thought to influence the risk of nidus rupture after radiosurgery as well. Our preliminary study was not intended to investigate all possible factors that could affect the risk of AVM hemorrhage during the latency period. Nevertheless, when possible, these additional influences will be examined in future studies. The results of this preliminary study show that, based on theoretical grounds, the risk of AVM nidus rupture is influenced by the extent of nidus volume undergoing irradiation and that perturbed hemodynamics resulting from occlusions of intranidal vessels represents a significant culprit among possible mechanisms of nidus rupture after radiosurgery.

Intranidal Hemodynamic Changes After AVM Radiosurgery

Several reports in the literature indicate the likelihood that incomplete AVM radiosurgery induces intranidal hemodynamic perturbations that ultimately contribute to hemorrhage during the latency period. The rationale for this hypothesis is indirect and relies on (1) generalized angiographic observations after AVM radiosurgery and (2) knowledge of intranidal hemodynamic changes consequent to other forms of partial AVM nidus occlusion (at embolotherapy) or resection (at surgery).

Angiographic changes in patients undergoing partial irradiation of AVMs and who have bled subsequently have been reported by Colombo. A high frequency of increase in blood flow rates through patent portions of AVMs, increased tortuosity of draining veins, and the appearance of aneurysms (all suggesting increased hemodynamic stresses) were recorded in these patients during the latency period. Therefore, with documentation of such changes consequent to radiosurgery, it has been speculated that partial thrombosis of the malformed nidus vessels may increase their outflow resistance, resulting in the creation of high-flow shunting within the remaining unoccluded portions of the nidus and predisposing it to rupture. Levy et al have suggested that this is a potential hazard of most treatments that obliterate only a portion of an AVM, occurring also with partial embolization or subtotal surgical resection of large AVMs.

The concept of intranidal surges in hazardous hemodynamics as a cause of nidus rupture during the latency period appears intuitively sound; however, this is not accepted universally because of the lack of concrete evidence to support it. One goal of this preliminary study was to attempt to investigate this controversial issue further. Our findings demonstrate, at least on theoretical grounds, that the generation of intranidal hemodynamic disturbances could represent a significant (perhaps, the main) cause of increased risk of AVM rupture when this occurs during the latency period after radiosurgery. Furthermore, the use of our novel theoretical model, which displays distinct intranidal components and simulates the presence of both fistulous and plexiform ves-

Figure 6. Schematic graph showing the hypothetical “linear” increase of elastic modulus (E) over time after radiosurgery. The y axis is presented as log (E) such that 4.7 is equal to log (5×10^4 dyne/cm^2) and 7.7 is equal to log (5×10^7 dyne/cm^2). Note the considerable increase in E approaching that of a fibrotic vessel toward the end of the latency period. The dotted line refers to the limit for E (8×10^4 dyne/cm^2) above which no rupture was observed in this study. Three AVM cases (at 6 months, 9 months, and 15 months) were shown previously to rupture within the irradiated zone of the nidus, as seen in Figure 5. By considering the effects of radiation-induced fibrosis, the lines drawn at these points in time now reveal the new values of E for these AVMs. It can be seen that all values of E have increased and now fall above the threshold for rupture. This demonstrates that, by factoring in the progressive strengthening of nidus vessel walls during the latency period, none of the 3 cases previously ruptured would exhibit rupture.

Figure 7. Graph depicting the temporal changes in the risk of rupture for the individual ruptured intranidal vessel (21) in case 1, used as an example to show how the risk of rupture falls below the threshold of 100% when radiosurgery-induced increasing thickness (t) of the nidus vessel is factored into the simulations.
els, has enabled for the first time the qualitative investigation and appreciation of these theoretical intranidal hemodynamic and biophysical events leading to rupture. Thus, in all simulated cases in which AVM rupture occurred, it was found that rupture in the implicated intranidal vessel was due to a connecting intranidal vessel becoming occluded totally, which causes a shift/escalation of the hemodynamic burden (the intravascular pressure) into an already weakened adjacent vessel, leading to its rupture.

As noted above, the presence of dangerous intranidal shifts in hemodynamic forces leading to AVM rupture after radiosurgery may be appreciated intuitively by some clinicians, but this is an idea not embraced by others. Three useful analogies in favor of this concept might be drawn through knowledge of hemodynamic events from other observations upstream, within, and downstream from an AVM: (1) It is well accepted that partial embolization of an AVM nidus raises the intravascular pressure within feeders situated proximal to the site of occlusion.37,38 (2) Viñuela et al39 have reported that intranidal rerouting of flow to plexiform portions of the nidus after abrupt endovascular obliteration of an intranidal fistula (ie, a scenario similar to that depicted by our simulations) may result in AVM rupture. (3) A previous study using this same AVM model has demonstrated a propensity of the nidus vessels to rupture consequent to simulated stenoses or occlusions more distally in the draining veins.14 It is not inconceivable for similar luminal narrowing and prestenotic buildup of hemodynamic forces to take place intranoidally. Therefore, such surges in intravascular pressures may occur (and the results of this study demonstrate this) in delicate nidus microvessels after irradiation; the rerouting of these pressure elevations may also occur on a microscopic level intranidally, and in some cases the buildup could lead to rises above the threshold for rupture. As also observed in a prior study pertaining to luminal narrowing more distally in the draining veins,14 that occurring within nidus vessels raises the risk of rupture to values >100% before a subsequent decline to values below the pretreatment state. Therefore, our theoretical hemodynamic observations possibly unravel the reason for another apparent “enigma,” as expressed by Lindquist,9 as to why radiosurgical obliteration of an AVM (with its known histological effects of progressive vessel wall thickening) does not simply (and only) decrease the hemorrhage risk before complete obliteration.

Although quantitative extrapolation to the setting of human AVMs is not possible, the results of theoretical simulations using our biomathematical AVM model suggest and allow the qualitative appreciation of these intranidal hemodynamic perturbations. Moreover, the model simulations have demonstrated a difference in hemodynamic consequences to irradiation of the plexiform vis-à-vis the fistulous intranidal vessels. Occlusion of a fistulous component leads to greater hemodynamic shifts to adjacent vessels, and consequent increased risk of rupture, than for occlusion of plexiform components. This is similar to the mechanism speculated on by Viñuela et al39 (as mentioned above) for rupture after endovascular embolization of AVMs. In our simulations, this occurred in all cases demonstrating nidus rupture. This hazardous rise in risk of rupture occurs regardless of the extent of nidus radiosurgery, ie, this danger is present theoretically for total as well as subtotal irradiation of a nidus, although in our simulations, an increased risk of rupture for completely irradiated AVMs that results in a risk >100% was quite infrequent.

In clinical practice, large multifistulous AVMs are not considered optimal lesions for radiosurgical treatment40 or are first subjected to embolization (or even surgical resection in some cases) before radiosurgery for the purpose of volume reduction (down to the optimal <3 cm in size).11 With regard to treatment of large AVMs (which commonly contain fistulas), Pollock et al41 state that “unlike embolization before microsurgical resection, in which flow reduction is the goal, volume reduction is the goal of preradiosurgical embolization.” The results of this theoretical study are at variance with this assertion because if an intranidal fistula is present within an AVM of optimal size for radiosurgery (however uncommonly), then it may still predispose the nidus to rupture because of the induction of critical intranidal hemodynamic perturbations. Therefore, 2 clinically relevant ramifications to the results of this study are as follows: (1) the procurement of objective hemodynamic data and detailed angiomorphological information would be desirable in the evaluation of AVMs before their radiosurgical treatment; and (2) preradiosurgical embolotherapy should be regarded as (and efforts be made toward making it) a flow-reductive as well as a volume-reductive technique. Toward both aims, it may be desirable to perform superselective angiography on AVMs, at least those that show subjectively a suspiciously high flow (intimating, perhaps, the presence of a fistula/s) when delineated by less selective angiograms. It has been demonstrated previously that superselective angiography is of paramount importance in the accurate delineation of intranidal AVM angioarchitecture.41 This may also be accompanied by more objective hemodynamic characterization of AVMs through intravascular pressure measurements, and/or Doppler ultrasound, and/or MR angiography, with a view to establishing the presence of an intranidal fistula. For instance, the discovery of a transcatheter mean arterial feeder pressure >40 mm Hg below the mean systemic blood pressure is in itself highly indicative of the presence of a downstream intranidal fistula.42 Once a fistula is discovered after superselective angiography and hemodynamic assessment, it may be necessary to occlude it endovascularly (eg, under systemic hypotension, to reduce the possibility of rupture during the procedure43) before radiosurgery. It is speculated that future adoption of these measures may allow a more precise and objective means of selecting/screening those AVMs that are hemodynamically amenable to safe and effective radiosurgical treatment and may perhaps help in reducing the hemorrhage rates in those AVMs that are partially irradiated or those that are completely irradiated (such as some larger AVMs or those in older patients8). In addition, the future procurement of accurate hemodynamic data from human AVMs before and during the radiosurgical latency period may help considerably in further understanding and analysis of the basic mechanisms revealed by this preliminary theoretical study and in the promotion of newer and potentially...
more useful and safer strategies for radiosurgical treatment of AVMs.

In conclusion, this preliminary theoretical study supports the general consensus that radiosurgery does not increase the risk of rupture in AVMs and, if anything, may have a "protective" effect, as suggested by the Stockholm group. In the few cases in which rupture was observed, it was found that a larger number occurred after subtotal and low-dose radiosurgery, supporting theoretically the clinical observation that these are dangerous strategies. The radiosurgical occlusion of intranidal fistulas or larger-caliber plexiform vessels appears to be a major culprit in the generation of dangerous intranidal hemodynamic surges that lead to critical elevations in the risk of nidus rupture. Future studies directed at the detailed histometric and biomechanical characterization of human nidus vessels are required to further advance our understanding of cerebral AVMs, both before and after their radiosurgical treatment. The described novel AVM model should serve as a useful research tool for further theoretical studies of radiosurgical strategies (eg, we are currently studying the theoretical effects on the AVM nidus of dose inhomogeneity due to multiple isocenter irradiation) and in investigating the hemodynamic sequelae of treatment.

**Appendix 1**

**Biomathematical AVM Model**

The AVM theoretical electric network, nestled within a simulated circulatory network of the head and neck, consisted of 4 arterial feeders (AFs), 2 draining veins (DVs), and a nidus angioarchitecture with a randomly distributed array of 28 interconnected plexiform and fistulous components, as shown in Figure 1. Twenty-four of the nidus vessels were plexiform, and 4 nidus vessels were fistulous. Two AFs (AF1 and AF2) were considered major feeders, while AF3 and AF4 (a simulated transdural supply) were minor feeders. Both DVs drained into the simulated intracranial venous sinuses.

The pressure values implemented into the radiosurgical simulations were as follows: mean systemic blood pressure, 74 mm Hg; mean AF pressure (for major AFs), 47 mm Hg; mean AF pressure (for minor AFs), 50 mm Hg; mean DV pressure, 17 mm Hg; and mean central venous pressure, 5 mm Hg. All the above values (and those of the nidus vessel elastic modulus $E$ and wall thickness $t$, used in calculating the risk of nidus vessel rupture) were considered for the purpose of this study to be "typical" or average ones. A separate parameter optimization study to further characterize the functioning of this AVM model had revealed that the adoption of all the aforementioned values results in an acceptable representation of a typical high-flow large intracranial AVM on the basis of its total volumetric blood flow and its baseline risk of rupture.

With the use of an electric analogy of Ohm’s law, flow rate was determined on the basis of Poiseuille’s law given the aforementioned pressures and resistance of each nidus vessel. To determine the hemodynamic quantities within each vessel of the vascular array during each simulation, network analysis of the loops and nodes constituting the AVM model circuit was performed to yield 41 linear equations corresponding to the 41 vessels and distinct values of volumetric flow rate. The 41 derived linear equations were solved simultaneously by expanding Poiseuille’s formula into matrix form.

The matrices corresponding to pressure and resistance were created with the use of a spreadsheet application (Microsoft Excel) and transported to an advanced mathematical computation program (Mathematica, Champaign, Ill) for solution of the flow rate values for all 41 vessels. Once the volumetric flow rate was determined for each simulation, it was then possible to calculate the risk of rupture for each nidus vessel.

**Risk of Nidus Rupture**

The highly tortuous, structurally weak intranidal vessels subjected to the continual impingement of large hemodynamic forces make AVMs highly susceptible to hemorrhage. The precise location or region of rupture is extremely difficult to observe angiographically and to detect histologically and remains a source of speculation in the study of AVMs. It is believed commonly that, based on the biomechanical properties of the intranidal vessels, rupture occurs when the cumulative hemodynamic stresses of the vessel wall exceed its elastic modulus. An expression for the risk of rupture has been derived previously on the basis of the functional distribution of the critical radius over a range of intravascular pressures experienced by a cylindrical vessel during a normal cardiac cycle and is given as follows:

$$\text{Risk} = \int_{P_{\text{min}}}^{P_{\text{max}}} \frac{[E/t/P] \, dP}{P_{\text{exp}} - P_{\text{min}}}$$

where $P_{\text{min}}$ and $P_{\text{max}}$ are the central venous pressure and the “maximum intranidal pressure,” respectively, $P_{\text{exp}}$ is the pressure of the nidus vessel determined at simulation, $E$ is the elastic modulus of the nidus vessel wall, and $t$ is nidus vessel wall thickness. The expression given above represents the normalized probability or risk of rupture and is multiplied by 100% to present the results as a percentage of risk of rupture. The denominator or normalization constant is the integrated distribution of critical radii for the maximum possible transmural pressure gradient. It can be seen that, on a qualitative basis, as the intravascular pressure of the nidus vessels increases exponentially and reaches that of the maximum intranidal pressure, the risk of rupture approaches 100%, implying certain rupture. Conversely, for intravascular pressures closer to that of central venous pressure, the risk of rupture decreases accordingly. Of particular importance to this study is whether these values of risk of rupture for individual nidus vessels equal or surpass the 100% limit. Should this occur for any nidus vessel, ie, the probability becomes that of certain rupture, the whole AVM nidus is deemed to have ruptured. The maximum extent to which the risk of rupture rises to $>100\%$ is theoretically of no significance; it is merely the occurrence of rupture (ie, the risk being $\geq100\%$) that is of paramount importance.

**Appendix 2**

**Baseline AVM Hemodynamics and Risk of Nidus Rupture**

The simulated total volumetric blood flow through the normal AVM model before any treatment was 814 mL/min, akin to values of flow through large intracranial AVMs. The intranidal flow rate varied from an average of 31.3 mL/min for the plexiform vessels and a substantially increased flow rate with an average of 617 mL/min within the intranidal fistula. For the "typical" AVM (with $E=5.0 \times 10^6$ dyne/cm$^2$), the risk of rupture for individual AVM vessels within the nidus before radiosurgery ranged from 4.4% to 91.2%.

**References**


The authors use a biomathematical model to evaluate the factors involved in an intracranial AVM rupture after a radiosurgery. This model uses electric network analysis whereby various anatomic characteristics of AVM are represented by a circuit analog. The most important factor in determining the validity of a biomathematical model is its ability to duplicate the real physiological situation.

One significant limitation of this model is the assumption made by the authors that a nidal vessel occlusion occurs by either of the 2 mechanisms: what they refer to as a stepwise occlusion and a random occlusion. In reality, as correctly pointed out by the authors, the nidal vessel occlusion after radiosurgery is more likely to be gradual and continuous. Thus, a sudden change in an intranidal flow hemodynamics is unlikely to be the main cause of AVM rupture. The authors, however, should be commended for their innovative approach in evaluating the different variables involved with the AVM rupture after a radiosurgical treatment.

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Experimental Radiosurgery Simulations Using a Theoretical Model of Cerebral Arteriovenous Malformations
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