A Model Study of Why Some Intracranial Aneurysms Thrombose but Others Rupture

MARGOT R. ROACH, M.D., PH.D.

SUMMARY A perspex model of a dog aortic trifurcation was machined to scale and perfused with steady flow from a constant pressure reservoir. The tail artery was plugged to produce a flow model of an intracranial saccular aneurysm. At all flow rates, no flow occurred beyond 2.5 tube diameters of the tail artery downstream from the mouth of the aneurysm. This was assumed to explain why large aneurysms thrombose. Measurements of velocity fluctuations were made with a hot film anemometer and recorded on tape. Frequency analysis showed that the peak frequency was a function of flow rate, and suggested that eddies were shed from the origin of the aneurysm. This was presumed to be an artifact due to sharp entrance produced by machining the perspex. The total energy at any one point in the aneurysm was independent of the size of the aneurysm but increased with flow rate. The maximum fluctuations were comparable in the center and in the sides of the aneurysm, but were less on the top and bottom of it (assuming the central plane was in the plane of the trifurcation). This difference presumably would be less if the aneurysm were spherical rather than cylindrical.

MOST INTRACRANIAL saccular aneurysms rupture and the patients present with symptoms of subarachnoid hemorrhage. However, a few go on to become giant aneurysms (i.e. greater than 2.5 cm diameter), and present as space-occupying lesions. From my earlier analysis, which assumed that all of the wall of the aneurysm came from the tissue at the apex of the artery, we would predict that all aneurysms should rupture eventually. Ferguson discussed this in more detail. Thus, when the stress (force/unit area) in the wall exceeds the breaking strength of collagen, or about 10^9 dynes/cm^2, the aneurysm should rupture.

In spite of this apparently logical argument of why all aneurysms should rupture, some do not. The exact incidence of these giant aneurysms, which are almost always thrombosed, is unknown. Many of them have atheromatous changes in their walls. In preliminary studies, we developed a flow model for studying these aneurysms by tying the tail artery of the dog. As shown in figure 1, the aorta trifurcates, and intimal cushions at the origin of the tail artery narrow the entrance to that vessel. It runs for six to eight tube diameters (T.D.) before bifurcating, and so a large variety of "aneurysms" can be created by tying it in different regions. We found that short aneurysms (< 1 T.D.) were unaltered after 2 weeks, medium-sized aneurysms (2-2.5 T.D.) ruptured, and long ones (> 4 T.D.) thrombosed. The wall of the tail artery (TA) obviously is thicker than the wall of the aneurysm, so this is a better model to study flow than to study rupture. We suspected that the thrombosis was caused by stasis, and decided to pursue this in the model experiments described here.

Methods

A model of the dog trifurcation region was drilled in a solid perspex block by an expert machinist. As shown in table 1, the areas of the aorta and branches were scaled, as were the angles, to fit the mean values obtained from measurements of the dog vessels studied previously. The junction itself was not an exact replica, and we were unable to obtain exact data on the way the aorta trifurcated. Thus the entrance to the branches was sharp and the top and bottom part of the aortic wall ended blindly, as shown in figure 2. The implications of this will be discussed below.

The test section (above) was then attached to machined tubes of the same internal diameter, and perfused with steady flow from a constant head tank of the sort described previously by Bellhouse and Bellhouse for testing artificial heart valves. Each branch emptied into a dump tank, and the resistance of each could be altered as desired with screw clamps. The aneurysm was created by putting a plunger sealed with an O-ring in the central (tail artery) branch. A small hole in the center allowed insertion of a hot film anemometer, designed by Clark, which was less than 1 mm in diameter. The temperature of the water was kept constant to within ± 0.05°C, as is required for valid recordings with a hot film anemometer.

Initially, dye studies were done, and photographs taken, to show the type of flow patterns as the flow rate and aneurysm length were varied independently. Then velocity tracings were obtained, using the calibrated Disa anemometer with linearizer. The circuit diagram is shown in figure 3. The flow rate in the aorta was varied between 1.5 and 6.4 L/min. This gave Reynolds numbers of 750 to 3200.

Because we were uncertain how the turbulent energy was transferred to the wall, two types of analysis were done on the velocity trace:

(a) The total energy at all frequencies was integrated electrically, and analyzed as a function of both flow rate and of position in the aneurysm.

(b) The taped signal was played through a Muirhead D489-GM Wave Analyzer as shown in figure 3, and was then analyzed to determine if the flow was truly turbulent (i.e. random) or some complex type of nonlaminar flow. All recordings were done at a tape speed of 1/16 RPM and played back at 15 RPM in order to analyze for low frequencies.
Finally, the effects of probe position were assessed to determine if one should expect uniform flow patterns and so an equal chance of damage in all parts of the aneurysm. Because the aneurysm is planar rather than spherical (see figure 2), we predicted that the top and bottom of the aneurysm would have different flows from those which occurred at the right and left sides of the aneurysm (i.e., adjacent to the iliacs).

**Results**

Initially, studies were done with flow in all branches, and with Evans blue dye, or ink, injected into the aorta proximal to the test section. The results are shown in figure 4, and described in the legend. The flow is fully developed or laminar in the aorta, and enters all branches undisturbed unless it is reflected from the top and bottom surfaces as shown in figure 2.

<table>
<thead>
<tr>
<th>Diameter of Aneurysm Models</th>
<th>Dog trifurcation (cm)</th>
<th>Plastic model (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trunk (Aorta)</td>
<td>0.60 - 1.45</td>
<td>2.54</td>
</tr>
<tr>
<td>Tail Artery/Aorta</td>
<td>41.8 ± 1.2%</td>
<td>43%</td>
</tr>
<tr>
<td>Right Iliac/Aorta</td>
<td>40.2 ± 2.1%</td>
<td>40%</td>
</tr>
<tr>
<td>Angle TA-RI</td>
<td>32°</td>
<td>32°</td>
</tr>
<tr>
<td>Left Iliac/Aorta</td>
<td>47.2 ± 3.5%</td>
<td>48%</td>
</tr>
<tr>
<td>Angle TA-LI</td>
<td>29°</td>
<td>29°</td>
</tr>
</tbody>
</table>

The patterns were comparable at all flow rates until eddies (fig. 5) or turbulence developed.

Figure 5 shows the variation in patterns seen when the TA was blocked. With short aneurysms (A), the dye entered and left the aneurysm rapidly, and appeared to have little effect on flow in the branch. With longer aneurysms (B and C), the dye is reflected from the end (B), or becomes turbulent (C). These are the ones most prone to rupture. With longer aneurysms (D–F), the dye does not reach the end (D), except by diffusion (E), and then clears slowly (F). Thus, the flow at the distal end of these long aneurysms is quite stagnant, and we believe this is why they are prone to thrombosis. The stagnant zone starts at 2–2.5 T.D. downstream from the mouth. This is the size of aneurysm we found to thrombose in the dog.

Our visual observations were then confirmed by passing an anemometer into the aneurysm through the probe. The results were observed on the oscilloscope, read on the voltmeter, and recorded on tape (fig. 3). First we analyzed the total energy in the aneurysm by rectifying and then integrating the recordings from the tape. The results are shown in figure 6. Note that at any one position, the energy in all sizes of aneurysms was comparable. The maximum energy occurred near the mouth of the aneurysm (1 T.D. from its entrance), and had reached zero by 2.5 T.D. from the mouth. This is the size of aneurysm we found to thrombose in the dog.
WHY SOME ANEURYSMS THROMBOSE/Raich

FIGURE 4. Photographs of dye injections in the model with the tail artery open. In A, the fully developed flow profile is seen in the aorta. This enters the tail artery (B) and iliac (C) undisturbed. However, dye that hits the junction of the TA and iliac (D) is split and goes down each branch. The apparent distortion (C) is in fact a visual artefact due to refraction of the perspex. Flow in all cases is from top to bottom.

the entrance. At all positions, the energy increased roughly linearly as a function of flow rate.

The tape, which had been recorded at 1-7½ RPM, was then played through the sound analyzer at 15 RPM. This allowed us to analyze frequencies down to about 2.5 Hz. Figure 7 shows that at any one flow rate, the spectrum produced was the same for all sizes of aneurysms at any one position in the aneurysm. The absolute values varied with flow rate (fig. 8), but the results were comparable otherwise. The peak frequency increased as a function of flow rate.

Finally, we assessed the effect of the probe position around the aneurysm. As noted above, these aneurysms are not spherical. Recordings at the top and bottom were comparable but different from those on the right and left. Figure 9 shows typical results. Note that there are at least fluctuations at the top center. The fluctuations were comparable on the top and bottom but different there from in the center of the aneurysm or on the sides. This was true for all flow rates, and for all sizes of aneurysms. Note that in figure 5(A), the dye which has entered the aneurysm is flowing back along the sides of the aneurysm to enter the branches.

Discussion

Any model is only as good as the assumptions made to create it. The parameters which should be considered can be divided into two; a) those due to the wall — primarily the elastic behavior which we have described previously and the endothelial lining which has not been investigated and, b) those due to the flow which include the geometry of the system, the Reynolds number for steady flow, and the Strouhl number or alpha parameter for pulsatile flow.

Both my dog tail artery model5 and the perspex model described here are poor models for the wall factors in human intracranial aneurysms. We found4 that the aneurysms were much less distensible than the

FIGURE 5. Effect of aneurysm size on flow in the aneurysm. (For details, see text).

FIGURE 6. Total energy (arbitrary units) as a function of aortic flow for four plug positions. Recordings were done at 1, 1.5, 2, and 2.5 T.D. The last were too small to measure. (For details, see text).
AMPLITUDE (mV)

PROBE AT 1.0 TD

FREQUENCY (Hz)

FLOW 6.4 L/min

PLUG AT 1.5 TD

2.5 TD

3.5 TD

4.5 TD

PROBE AT 0.5 TD

FIGURE 7. Frequency analysis of velocity fluctuations at two probe positions for four different lengths of aneurysm. As in Fig. 6, the maximum fluctuations were near the mouth (0.5 T.D.), but the frequency spectrum at any one location was the same for all aneurysms.

cerebral arteries from which they arose. This may be an important factor biologically since Ferguson found that the pressure inside the aneurysm was the same as the pressure in the arteries. Thus, the size of the arteries may change more between systole and diastole than does the aneurysm. We have unpublished data which shows that the tail artery of the dog is more distensible than the iliac arteries. Thus, the relative size of the aneurysm may increase more than that of the arteries. By contrast, the geometry of the perspex model remains fixed. The endothelium is important for thrombosis, but plays no role in the elastic behavior. Thus, both of our models are inadequate to assess the effect of the wall on whether intracranial aneurysms will rupture or thrombose.

Flow may be steady or pulsatile, and laminar or non-laminar. The latter includes turbulence and eddy shedding as well as the skewed velocity profile seen in the aortic arch and near bifurcations. The factors which determine which type of flow will occur include the geometry, the distance from the entrance to the system (the inlet length), the Reynolds number, Re (where Re = $\frac{\rho vD}{\eta}$ where $\rho$ is density, $\eta$ viscosity, $v$ mean velocity and D the diameter), the Strouhal number ($St = f.R/\nu$ where $f$ is the frequency and $R$ the radius), and the alpha-parameter ($\alpha = R(\omega p/\eta)$) where $\omega$ is the angular frequency. The three parameters are all related as $\alpha^2 = \pi Re St$. The factor which is most difficult to model is the geometry. Most human intracranial aneurysms are roughly spherical, but the necks vary enormously, and there may be blebs on the surface. The dog tail artery is cylindrical rather than spherical, there may be a small neck if intimal cushions are present, but usually they are not, and the end may be puckered by the ligature used to create the aneurysm. The perspex model had sharp edges at the entrance, is even more cylindrical than the tail artery, and has no neck. Its chief flaw is probably the sharp entrance (fig. 2) which almost certainly explains the eddy shedding seen in figures 7 and

spherical, but the necks vary enormously, and there may be blebs on the surface. The dog tail artery is cylindrical rather than spherical, there may be a small neck if intimal cushions are present, but usually they are not, and the end may be puckered by the ligature used to create the aneurysm. The perspex model had sharp edges at the entrance, is even more cylindrical than the tail artery, and has no neck. Its chief flaw is probably the sharp entrance (fig. 2) which almost certainly explains the eddy shedding seen in figures 7 and

FIGURE 8. Frequency analysis of velocity fluctuations for one position of one size of aneurysm. Note that the peak frequency increases as the flow rate increases.

EFFECT OF PROBE POSITION

PLUG AT 2.5 TD

PROBE AT 0.5 TD

FREQUENCY (Hz)

FLOW 2.1 L/min

FIGURE 9. The effect of probe position with respect to the plane of the trifurcation. Flow was most stagnant on the top and bottom of the aneurysm and was comparable in the center and on the sides.
8. Characteristically, this frequency increases with flow rate as we found happened in our model (fig. 8).

The most important observation in this study is probably the presence of the stagnant zone in the distal part of the aneurysm. This is present regardless of the flow rate. Since it developed about 2–2.5 T.D. from the entrance, which was the critical length beyond which thrombosis occurred in our dog tail artery experiments, it seems reasonable to conclude that stagnant flow is an important factor in the initiation of thrombosis in the tail artery aneurysm. The crucial question, and one for which we have no answer, is whether the geometry of the neck and of the sac of the intracranial aneurysm play an important role in determining the size of the stagnant zone.

Ferguson found that the flow in most human intracranial aneurysms was turbulent as the recorded bruits had a wide frequency spectrum. In this study, the flow was found to be more characteristic of eddy shedding. Smith et al. found good evidence that turbulence increased the risk of thrombus formation, presumably because the turbulence alters the behavior of the endothelial cells. Since turbulence will dissipate more energy than eddy shedding, presumably the critical length beyond which stasis occurs may be shorter for the spherical aneurysm with turbulence than for our model with eddy shedding, although this has not been proved.

Ferguson speculated that turbulence was an important factor in the growth of human intracranial aneurysms but not in their initiation. I showed previously that turbulence was an essential factor in the development of a poststenotic dilation, but the changes in elastic behavior of these are quite different from that of aneurysms. We also found that specific frequencies were required to produce the dilation. Since we do not know the resonant frequency of human intracranial aneurysms, we cannot say if the frequencies present in turbulence, or those with eddy-shedding, are more apt to make the wall resonant. If resonance does occur, the wall will vibrate more vigorously and so is stretched more. This could greatly increase its chance of rupture.

Drake and Vanderlinden showed that cerebral aneurysms grow if they are clipped incompletely. They did not show if this was due to altered flow because the neck was different, or simply due to natural progression of the disease.

Most giant aneurysms have significant amounts of thrombus in them. If this develops before they become so large, the thrombus may damp out the damaging effects of pressure and flow and so prevent rupture. Elastin fragments early in the course of development of an aneurysm and so could expose more collagen to initiate thrombus formation. Turbulence might aggravate this. Conversely, if the geometry of the neck and sac were such that the aneurysm could become very large before it ruptures, then the size of the aneurysm alone might initiate thrombus formation either by producing stagnant flow and/or by stretching the endothelium. More detailed studies of the factors associated with thrombosis in human aneurysms are required to determine which factor is more important.

Acknowledgments

This work was done while on Sabbatical to the Department of Engineering at Oxford. Dr. B. Belhouse provided space and funds (British M.R.C.) but was away during my tenure there. Dr. Colin Clark helped with the instrumentation and interpretation of the data, and Mr. Colin Curi provided much technical help. My travel was paid by a Schering Travel Award from the Canadian Society for Clinical Investigation, and extra costs were provided by the Ontario Heart Foundation. I am grateful to all of them.

References

A model study of why some intracranial aneurysms thrombose but others rupture.

M R Roach

*Stroke*. 1978;9:583-587
doi: 10.1161/01.STR.9.6.583

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/9/6/583

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/