De Novo Cerebral Aneurysm Formation Associated With Proximal Stenosis

BACKGROUND: Hemodynamic insults—high wall shear stress (WSS) combined with high positive WSS gradient (WSSG)—have been proposed to link to cerebral aneurysm initiation. We report 4 cases of aneurysms with proximal stenosis, including 1 de novo aneurysm, that might be associated with hemodynamic insults caused by the proximal stenosis.

CLINICAL PRESENTATION: In 4 clinical cases, the diameter stenosis was 37% to 49% (mean, 42%) located 2.7 to 4.7 mm (mean, 3.7 mm) from the apex. We performed computational fluid dynamics simulations for 2 cases: a ruptured basilar terminus aneurysm with proximal stenosis (which had an angiogram taken 15 years previously that showed no aneurysm and no stenosis) and a cavernous carotid artery aneurysm with proximal stenosis. In both cases, the stenosis caused unphysiologically high WSS (>7 Pa) at the apex, nearly doubling the WSS and WSSG values. To investigate the relationship between stenosis and distal hemodynamic elevation, we created a series of T-shaped vascular models by varying the degree and location of stenosis. We found that stenosis >40% by diameter located within 10 mm from the apex caused unphysiologically high WSS and WSSG. All 4 clinical cases satisfied these conditions.

CONCLUSION: Proximal stenosis could produce high WSS and high positive WSSG at the apex, thus potentially inducing de novo aneurysm formation.

KEY WORDS: Aneurysm formation, Computational fluid dynamics simulations, De novo cerebral aneurysm, Hemodynamic insults, Proximal stenosis, Wall shear stress, Wall shear stress gradient
### TABLE. List of the 4 Cases of Aneurysms With Proximal Stenosis

<table>
<thead>
<tr>
<th>Case (Figure)</th>
<th>Age, y</th>
<th>Sex</th>
<th>Aneurysm Status</th>
<th>Location</th>
<th>Preaneurysm Image Available</th>
<th>CFD</th>
<th>Stenosis, %</th>
<th>Distance, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1A, 1B)</td>
<td>81</td>
<td>F</td>
<td>R</td>
<td>BT</td>
<td>Yes (−15 y)</td>
<td>Yes</td>
<td>38</td>
<td>4.7</td>
</tr>
<tr>
<td>2 (5A)</td>
<td>84</td>
<td>F</td>
<td>R</td>
<td>Cavernous ICA</td>
<td>No</td>
<td>Yes</td>
<td>37</td>
<td>3.5</td>
</tr>
<tr>
<td>3 (9C)</td>
<td>76</td>
<td>F</td>
<td>R</td>
<td>BT</td>
<td>No</td>
<td>No</td>
<td>43</td>
<td>2.7</td>
</tr>
<tr>
<td>4 (9D)</td>
<td>87</td>
<td>M</td>
<td>R</td>
<td>VA-PICA</td>
<td>No</td>
<td>No</td>
<td>49</td>
<td>3.7</td>
</tr>
</tbody>
</table>

*BT, basilar terminus; CFD, computational fluid dynamics; ICA, internal carotid artery; R, ruptured; VA-PICA, vertebral artery–posterior inferior cerebellar artery.

**FIGURE 1.** Case 1 is a ruptured basilar terminus aneurysm. A, an angiogram 15 years before the rupture shows no stenosis and no aneurysm. B, an angiogram at the time of the rupture shows the ruptured aneurysm with proximal stenosis (arrow). C through F, computational fluid dynamics simulation results for this case. There are 3 vascular models: the original geometry with no stenosis and no aneurysm (C and F), an intermediate geometry with stenosis and no aneurysm (D and G), and the final geometry with stenosis and the aneurysm (E and H). C through E, streamlines colored according to velocity magnitude at peak systole. F through H, cycle-averaged wall shear stress (WSS). Jet flow through the stenosis (arrow in D) produces evaluated WSS at the apex before aneurysm formation. Although the jet flow (arrow in E) is also present in the aneurysm model, WSS on the aneurysm dome is low (H).
PATIENTS AND METHODS

Clinical Presentation

Four cases of aneurysms with proximal stenosis are summarized in the Table. Case 1 was a ruptured basilar terminus (BT) aneurysm with proximal stenosis (Figure 1B). An angiogram of the patient 15 years before the rupture showed no aneurysm and no stenosis (Figure 1A). In all 4 cases, the diameter stenosis was 37% to 49% (mean, 42%) and located at 2.7 to 4.7 mm (mean, 3.7 mm) from the apex. To measure the distance between the stenosis and the apex, we removed the aneurysms on the angiograms, hypothetically reconstructed the vessels before aneurysm initiation, and measured the distance from the stenosis to the apex. Although there are reports of de novo aneurysms associated with carotid artery occlusions,6,7 cases 1, 3, and 4 were vertebrobasilar aneurysms with no carotid artery occlusion or stenosis, and case 2 was an internal carotid artery (ICA) aneurysm with proximal stenosis. Only cases 1 and 2 had 3-D vascular images available; therefore, we performed CFD analysis only for these 2 patient-specific cases.

Patient-Specific Vascular Models for CFD Simulations

The 3-D aneurysm images in cases 1 and 2 were obtained by 3-D rotational angiography. Using the engineering design software 3-matic (Materialise NV, Leuven, Belgium), we reconstructed the patient-specific 3-D vascular models as previously described14-16. Small vessels such as the superior cerebellar arteries and anterior inferior cerebellar arteries were trimmed. In case 1, the end-point aneurysm model (Figure 1E and 1H) was directly reconstructed from the end-point 3-D angiogram (Figure 1B). Moreover, by referring to the angiogram taken 15 years ago (Figure 1A), we created 2 additional vascular models: the original bifurcation (Figure 1C and 1F) and an intermediate bifurcation with a proximal stenosis (Figure 1D and 1G). First, we removed the aneurysm from the end-point 3-D model to recover the shape of the bifurcation terminus shown on the angiogram 15 years previously but did not change the feeding vessel (Figure 1D and 1G). We then removed the stenosis so that the entire model corresponded to the vascular image obtained 15 years ago (Figure 1C and 1F). On these 2 re-created preaneurysm models, we defined a centerline on the top surface (Figure 2A and 2B). The centerline was selected among several parallel lines so that maximum WSS and WSSG on the line would be highest (data not shown).

We created additional vascular models of case 1 with artificial stenosis to examine the hemodynamic effects on the BT by different degrees of stenosis at different distances from the BT in the patient-specific model. The original stenosis was 38%. The stenosis was located 4.7 mm from the basilar tip (Figure 3C). We created artificial stenosis of 60% and 15% located 4.7 mm from the basilar tip and 30% located 10.0 mm from the BT, and we measured WSS and WSSG on the centerline (Figures 3 and 4).

FIGURE 2. In case 1, cycle-averaged wall shear stress (WSS) and WSS gradient (WSSG) before aneurysm formation are evaluated for the original model with no stenosis (A) and for the intermediate model with stenosis and no aneurysm (B). WSS and WSSG along the centerlines (A and B) are evaluated in C and D. C, maximum WSS on the centerline of the no-stenosis model is 3.8 Pa, which is within physiological levels (< 7 Pa). The regions with positive WSSG are defined as an acceleration zone. The regions with negative WSSG were defined as deceleration zones. D, maximum WSS on the centerline of the stenosis model is 8.5 Pa, which is unphysiologically high (> 7 Pa). WSSG is elevated nearly twice compared with the no-stenosis model.
In case 2 (Figure 5A), we applied the same procedures and created the end-point aneurysm model (Figure 5D and 5G), an intermediate model with stenosis but no aneurysm (Figure 5C and 5F), and an original model with no stenosis and no aneurysm (Figure 5B and 5E). We defined a centerline on the top surface among several parallel lines in the same fashion as in case 1 (Figure 6A and 6B). Two authors independently removed the aneurysm in the models of cases 1 and 2 to examine variability on WSS and WSSG magnitudes by the procedures of removal of the aneurysm.

T-Shaped Bifurcation Models With Proximal Stenosis for CFD Simulations

To further clarify the relationship between hemodynamic stresses at a bifurcation apex and the degree and location of a proximal stenosis, we conducted a parametric study using idealized vascular models. We created 11 idealized T-shaped bifurcation vascular models to simulate the basilar bifurcation with different degrees of stenosis at different proximal distances from the BT using the 3-matic software. The diameters of the vessels were all 3 mm. Four of these models are shown in Figure 7. Six models had a fixed 50% diameter stenosis at different locations (3.5, 4.5, 6.5, 9, 11.5, and 16.5 mm) from the apex. Five models had stenosis located at a fixed distance of 6.5 mm with degree of stenosis increasing from 30% to 70% with 10% intervals. We defined a centerline on the top surface of the basilar artery (arrows) can be seen in G and H.

CFD Simulations

We performed CFD simulations in patient models (cases 1 and 2) in a manner similar to that described previously.14,17,18 The fluid domains
RESULTS

Patient-Specific Vascular Models

In case 1, a jet flow associated with the proximal stenosis was obvious in the end-point model (Figure 1E). In the intermediate, preaneurysm model, the proximal stenosis caused strong jet flow impingement at the BT (Figure 1D), resulting in high WSS on the top surface of the vessel (Figure 1G). WSSG on the centerline of the top surface was calculated from the cycle-averaged WSS on the centerline (Figure 2). As defined by Metaxa et al., the region of increasing WSS along the flow direction corresponds to positive WSSG and is called the acceleration zone; the region of decreasing WSS corresponds to negative WSSG and is called the deceleration zone. In both preaneurysm models, WSS was low at the impingement site, was elevated in the adjacent acceleration zone, and then decreased further downstream (Figure 2C and 2D). The increase of WSS in the acceleration zone corresponded to positive WSSG values. The maximum WSS and WSSG in the acceleration zones were 3.8 Pa and 3.4 Pa/mm, respectively, in the original preaneurysm model and 8.5 Pa and 6.3 Pa/mm in the stenosis preaneurysm model. The maximum WSS and WSSG were roughly doubled as a result of the stenosis.

In patient-specific vascular models of case 1 with artificial stenosis, although jet flow was observed in all 4 patient-specific stenosis models (Figure 3B and 3E), high WSS on the top surface was observed in only 2 stenosis models (Figure 3G and 3H), which had moderate to severe stenosis close to the BT. The maximum WSS and maximum WSSG were measured in the models with different degrees of stenosis located 4.7 mm from the BT (Figure 4). There were positive correlations between the degree of stenosis and WSS and between the degree of stenosis and WSSG. WSS achieved an unphysiologically high level of 7 Pa, when stenosis was elevated by approximately 30% (Figure 4). In the model with 30% stenosis at 10.0 mm from the BT, the maximum WSS and WSSG in the acceleration zones were 4.6 Pa and 4.2 Pa/mm, respectively. This demonstrated that stenosis close to the BT was necessary to produce high WSS and high positive WSSG.

In case 2, proximal stenosis caused jet flow (Figure 5C), which resulted in focally high WSS on the surface of the distal vessel (Figure 6B). The maximum WSS and WSSG in the acceleration zones were 5.6 Pa and 5.5 Pa/mm, respectively, in the original preaneurysm model and 9.9 Pa and 7.7 Pa/mm in the stenosis preaneurysm model (Figure 6C and 6D). The maximum WSS was again almost doubled and the maximum WSSG increased by a factor of 1.4 because of the stenosis. It should be noted that we measured cycle-averaged WSS. The maximum WSS magnitudes at peak systole in the stenosis preaneurysm models were even higher: 19.8 Pa in case 1 and 20.6 Pa in case 2.

There was some interobserver variability in aneurysm virtual removal by 2 independent observers, resulting in different preaneurysmal flow fields, but this difference did not change the main result. For case 1, the maximum WSS values in the acceleration zones were 8.5 and 7.9 Pa and WSSG values were 6.3
and 5.9 Pa/mm in the stenosis preaneurysm model. In case 2, they were 9.9 vs 11.2 Pa and 7.7 vs 8.7 Pa/mm. These 6% to 13% differences did not affect the result that stenosis increased the maximum WSS and the maximum WSSG by a factor of approximately 1.4 to 2.2 in both cases.

**T-Shaped Bifurcation Models With Proximal Stenosis**

In the 6 models with a 50% diameter stenosis at a varying distance from the apex, the maximum WSS and WSSG increased when stenosis distance decreased (Figure 8A). The increase was especially drastic when the stenosis was < 10 mm, when the magnitude of WSS became unphysiologically high (> 7 Pa). In the 5 models with a varying degree of stenosis located at a fixed 6.5-mm distance, the maximum WSS and WSSG increased when the degree of stenosis was increased (Figure 8B). Especially, when the degree of stenosis exceeded approximately 40%, the maximum WSS and WSSG increased rapidly and the magnitude of WSS became unphysiologically high (> 7 Pa).

**FIGURE 5.** A, case 2 is a cavernous carotid artery aneurysm with proximal stenosis (arrow). B through G, computational fluid dynamics simulation results are shown. There are 3 vascular models: the original geometry with no stenosis and no aneurysm (B and E), an intermediate geometry with stenosis and no aneurysm (C and F), and the final geometry with stenosis and the aneurysm (D and G). B through D, streamlines colored according to velocity magnitude at peak systole. E through G, cycle-averaged wall shear stress. Jet flow through the stenosis is observed (arrows in C and D). WSS, wall shear stress.
DISCUSSION

De Novo Aneurysms

Six large-scale studies (> 60 patients) reported annual incidences of de novo aneurysm formation ranging from 0.3% to 1.8%.8-13 To the best of our knowledge, there was only 1 case report of a de novo aneurysm associated with proximal stenosis.22 In that report, a right ICA-posterior communicating artery de novo aneurysm was found 11 years after the diagnosis of ipsilateral stenosis of the supraclinoid ICA. Without detailed flow analysis using CFD, these authors postulated that the stenosis weakened the ICA flow, causing a stronger reversal flow from the posterior communicating artery, thereby giving rise to collision, turbulence, and WSS fluctuations that led to the formation of a de novo aneurysm. Their explanation was different from our detailed flow analysis results. Rather than flow reversal, we have consistently found that the proximal stenosis produces a jet flow that impinges on the distal apex to raise the WSS and WSSG, and this effect intensifies as the degree of stenosis increases and the stenosis moves closer to the apex.

Therapeutic carotid occlusion is known to cause a compensatory flow increase in the contralateral arteries. The resulting increased hemodynamic stress may result in the formation of de novo aneurysms on the contralateral side.6 In a rabbit model, bilateral carotid artery ligation causes initiation of de novo aneurysms at the BT.1,23,24 In our clinical cases, cases 1, 3, and 4 are vertebrobasilar artery aneurysms with no carotid artery occlusion or stenosis, and case 2 is an ICA aneurysm with proximal stenosis. Therefore, the formation of these 4 aneurysms was not associated with occlusion or stenosis of other vessels but potentially associated with proximal stenosis of the feeding artery.

CFD and Experimental Study on Aneurysm Initiation

Several reports have described that high WSS combined with high positive WSSG is associated with the initiation of de novo aneurysms, as shown by CFD studies, animal experiments, and in vitro experiments.1-3,25 Kulcsár et al3 showed that high WSS and high positive WSSG were associated with de novo aneurysms in 3 patients, which had no proximal stenosis. What types of situation will produce high WSS and high positive WSSG in humans? Carotid occlusion produces high WSS and high positive WSSG at the BT in rabbits1 and may be associated with aneurysm initiation in humans.5 Besides carotid occlusion, we have demonstrated that proximal stenosis can produce high WSS and high positive WSSG.

![FIGURE 6. In case 2, wall shear stress (WSS) and WSS gradient (WSSG) before aneurysm formation are evaluated for the original model with no stenosis (A) and for the intermediate model with stenosis and no aneurysm (B). WSS and WSSG along the centerlines (A and B) are evaluated in (C and D). C, maximum WSS on the centerline of the no-stenosis model is 5.6 Pa, which is within physiological levels (< 7 Pa). The regions with positive WSSG are defined as an acceleration zone. The regions with negative WSSG were defined as deceleration zones. D, maximum WSS on the centerline of the stenosis model is 9.9 Pa, which is unphysiologically high (> 7 Pa). WSSG is also elevated because of the stenosis.](image-url)
Measurements using different modalities show that WSS ranges from 1 to 7 Pa in the arterial vascular network. Therefore, we determine > 7 Pa as unphysiologically high WSS in this study. In cases 1 and 2, we demonstrate that WSS near the impingement zones not only increased at >7 Pa but also roughly doubled because of stenosis. Therefore, it is possible that in these cases, the proximal stenosis, which presumably developed before the aneurysm formation, produced unphysiologically high WSS combined with high positive WSSG and led to the initiation of aneurysms.

The parametric study of the T-shaped bifurcation models demonstrates that > 40% diameter stenosis located < 10 mm from the apex could cause unphysiologically high WSS combined with high positive WSSG, which might be associated with the initiation of aneurysms. All the clinical cases in this study roughly satisfied these stenosis conditions (Table and Figures 1B, 5A, and 9). Although their degree of stenosis was moderate (37%-49%), the location of stenosis was very close to the apex (2.7-4.7 mm). Thus, in these 4 cases, the close location of stenosis from the apex might have been the predominant factor to cause high WSS and high positive WSSG at the aneurysm initiation site.

Case 1 is the only one with an angiogram before aneurysm formation. There is 15-year duration between 2 angiograms, which is a very large time frame. Many other factors might have contributed to the aneurysm development. However, the patient-specific and parametric CFD studies support our hypothesis that the formation of proximal stenosis has potentially caused the aneurysm initiation in case 1. The remaining 3 cases were not proven to be de novo, which weakens our hypothesis that proximal stenosis caused aneurysm formation. However, the results of the parametric study support our hypothesis for the remaining 3 cases. In summary, we appreciate that we have studied different sets of

![Figure 7](image-url)

**FIGURE 7.** Results of computational fluid dynamics simulations of T-shaped bifurcation vascular models with varying degrees and locations of stenosis. **A**, bifurcation model without stenosis. **B** through **D**, 3 representative stenosis models from a total of 11 models (6 models with varying distance of stenosis and 5 models with varying degree of stenosis). The degree of diameter stenosis is 30% or 50%. The distance of the stenosis from the bifurcation apex is 6.5 or 11.5 mm. **A** through **D**, streamlines colored according to velocity at peak systole. **E** through **H**, cycle-averaged wall shear stress (WSS) in each model corresponding to **A** through **D**. Although a 50% stenosis causes strong jet flow (**B** and **D**), it causes high WSS at the apex only when it is located close to the apex (**F**).
data and that we could not prove that, in any case, aneurysms were formed after stenosis formation. We could still put forth the hypothesis that proximal stenosis could lead to aneurysm formation on the basis of the 4 cases and the parametric studies.

Other parameters, eg, the aneurysm formation indicator \(^{26}\) and gradient oscillatory number, \(^{27}\) have been also proposed in the literature as hemodynamic parameters of aneurysm initiation sites. In our study, we have not examined aneurysm formation indicator or gradient oscillatory number. Although WSS and WSSG have been studied in animal and in vitro experiments and CFD studies, aneurysm formation indicator and gradient oscillatory number have been studied only in CFD simulations with no experimental evidence. \(^{26-28}\) In this regard, we consider that WSS and WSSG should be examined first, although we do not deny aneurysm formation indicator or gradient oscillatory number as a potential parameter of initiation sites of aneurysms.

**Limitations**

Our study is based on a small number of cases, namely 4 clinical presentations with 2 of them studied by CFD, combined with parametric studies using the patient-specific and idealized T-shaped vascular models. We cannot prove that the aneurysms in our cases were formed after the formation of stenosis owing to a lack of serial images. Aneurysm initiation is extremely elusive, and there is a dearth of knowledge about it. Although we hypothesize that stenosis was formed before aneurysm initiation, the opposite is also possible. However, hemodynamically and mechanistically, stenosis inducing the aneurysm is the more likely scenario. Many changes to the vessel geometry might have happened during the 15 years in case 1. Hence, our way of removing the aneurysm does not recover the previous geometry, but the exercise serves the purpose of proposing an interesting hypothesis, which is supported by previous experimental work and the present CFD study.

In the CFD studies, we simplified several properties such as the viscoelasticity of the vessel wall and the nonnewtonian property of the blood for technical reasons. Although the main hemodynamic features are thought to be preserved, \(^{29-31}\) these simplifications may cause differences between the results of CFD simulation and the in vivo state. Specifically, the present CFD study has the following limitations. First, inlet conditions were not patient specific. Karmonik et al\(^{32}\) demonstrated that, for accurate calculations of WSS parameters, patient-specific information on physiological flow may be necessary. Second, we reconstructed the 3-D images with no aneurysm or no stenosis by removing aneurysms or stenosis from the 3-D images with the aneurysms. The reconstructed 3-D

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**FIGURE 8.** Dependence of hemodynamic stress at the basilar terminus (BT) on the proximal stenosis in the T-shaped bifurcation vascular models. **A,** maximum wall shear stress (WSS) and WSS gradient (WSSG) at the BT vs distance of stenosis from the apex, with fixed 50% diameter stenosis. Within 10 mm from the apex, the maximum WSS and WSSG increase drastically when the distance is shortened. **B,** maximum WSS and WSSG at the BT vs degree of stenosis at a fixed 6.5-mm distance from the apex. When the stenosis is > 40%, the maximum WSS and WSSG increase sharply with increasing degree of stenosis.

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**FIGURE 9.** A, case 3 is a basilar terminus aneurysm with proximal stenosis (arrow). **B,** case 4 is a vertebral artery-posterior inferior cerebellar artery aneurysm with proximal stenosis (arrow).
images do not completely represent the real geometry. This may have slightly affected the CFD results. Third, we used a single patient-specific and idealized T-shaped vascular models for the parametric study. The shape of bifurcation in patients is usually not as simple as T-shaped models, although the bifurcation shape of the patient in case 1 was close to T-shaped. In particular, bifurcation angles differ in each case. Differences in bifurcation shape may have caused different hemodynamics. However, our conclusion holds at least for T-shaped bifurcation and may be applicable to other shapes because a proximal stenosis can produce jet flow to causes high WSS and high positive WSSG on the apex, regardless of the shapes of surrounding vessels.

CONCLUSION

We experienced 4 cases of aneurysms with proximal stenosis. From our CFD results, we propose that proximal stenosis might cause unphysiologically high WSS combined with high positive WSSG at the apex, leading to de novo aneurysm initiation. It is thus hypothesized that 1 class of aneurysms may be initiated by this mechanism whereby moderate stenosis closely located to a bifurcation apex can lead to aneurysm initiation.

Disclosures

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REFERENCES


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This article presents an interesting piece of research providing a concrete link between clinical findings and a thorough explanation exploiting computational fluid dynamics in realistic and idealized geometries in an elegant way. The further insights provided here to previous work by Meng et al. and Metaxa et al. might be seen as a “real-life” example of hemodynamic alterations leading to aneurysm initiation and growth. The considerably large time span of 15 years between scans leads us to think that other features might have caused aneurysm development and growth. Still, there is no reason to believe that stenosis proximal to bifurcations is not the real cause. In fact, the different flow features observed in previously research, namely unphysiologically high wall shear stress and high positive wall shear stress gradient, were also present in these cases and reproduced in idealized geometries as observed and pointed out by the authors. The study of flow in a larger number of cases presenting stenosis proximal to bifurcations might lead to more solid conclusions in the future.

Ignacio Larrabide
Barcelona, Spain