The biophysical role of hemodynamics in the pathogenesis of cerebral aneurysm formation and rupture

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The pathogenesis of intracranial aneurysms remains complex and multifactorial. While vascular, genetic, and epidemiological factors play a role, nascent aneurysm formation is believed to be induced by hemodynamic forces. Hemodynamic stresses and vascular insults lead to additional aneurysm and vessel remodeling. Advanced imaging techniques allow us to better define the roles of aneurysm and vessel morphology and hemodynamic parameters, such as wall shear stress, oscillatory shear index, and patterns of flow on aneurysm formation, growth, and rupture. While a complete understanding of the interplay between these hemodynamic variables remains elusive, the authors review the efforts that have been made over the past several decades in an attempt to elucidate the physical and biological interactions that govern aneurysm pathophysiology. Furthermore, the current clinical utility of hemodynamics in predicting aneurysm rupture is discussed.

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KEYWORDS cerebral aneurysm; hemodynamics; wall shear stress; computational fluid dynamics; vascular remodeling

Intracranial aneurysms (IAs) are acquired outpouchings of arteries that occur in 1%–2% of the population. Likely as a result of improved imaging modalities, the incidence of unruptured IAs has increased. Despite the estimated 1% annual risk of rupture, our ability to predict which aneurysms are best managed conservatively versus treated with either open or endovascular techniques is not without controversy. While aneurysm size and location are the main determinants in our decision-making process, there are a multitude of additional factors that are often considered.

Recently, considerable research has focused on the relationship between hemodynamic stressors and aneurysm pathogenesis. From a mathematical and biophysical standpoint, aneurysm morphology and evolution over time is highly complex due to the heterogeneous nature of fluid mechanics. Complicating matters even further is the living nature of blood vessels, i.e., mechanical stimuli are transduced into biological signals, triggering inflammatory cascades and, ultimately, a wide range of transcriptional and signaling changes that lead to vascular wall remodeling. The advent of computational and radiographic modeling has allowed for the study of hemodynamics within vessels and aneurysms. For this reason, cerebral aneurysm hemodynamics can serve as a tool in understanding the biophysical pathogenesis of IAs and has been used to evaluate aneurysm rupture risk.

In this article, we review the hemodynamic parameters related to aneurysm formation and rupture and the biophysical pathways that contribute to vascular remodeling. Additionally, we discuss the current state and utility of radiographic and computational modeling in predicting IA rupture in clinical practice.

Aneurysm Morphology

Aneurysm shape is believed to be an important predictor of subsequent rupture and may be characterized in sev-
eral ways. Ujjie et al.\textsuperscript{54} found that an aspect ratio (AR)—the ratio of aneurysm depth to aneurysm neck width—above 1.6 was a reliable predictor of aneurysm rupture. Nader-Sepahi et al.\textsuperscript{45} also found the AR to be a reliable predictor of rupture, but reported mean ARs of 2.70 and 1.80 for ruptured and unruptured aneurysms, respectively. However, Xiang et al.\textsuperscript{56} found that the AR was not significantly different between ruptured and unruptured groups, while Hassan et al.\textsuperscript{20} found sidewall, but not bifurcation, ruptured aneurysms to be strongly associated with AR exceeding 1.6.

The size ratio (SR) of an aneurysm, defined as the ratio between maximum aneurysm height and parent artery diameter, with rupture status has also been explored. Several investigators found strong correlations between greater SR and rupture status.\textsuperscript{51,56} In their systematic review and meta-analysis, Kleiengoog et al.\textsuperscript{33} identified irregular aneurysm shape, larger AR, larger SR, higher bottleneck factor (aneurysm width divided by the diameter of the neck), and aneurysm height-to-width ratio as morphological characteristics with strong levels of evidence for increased risk of rupture. Morphological characteristics with moderate levels of evidence for association with rupture included downward/inferior direction of the dome and volume-to-ostium ratio (ratio of the aneurysm volume to the area of the neck). They suggest that based on the available evidence, the risk factor of irregular shape has high predictive potential and should be considered in risk stratification of aneurysms in clinical practice.\textsuperscript{44}

### Computational Fluid Dynamics

Computational fluid dynamics (CFD) creates 3D models of fluid flow from patient CT angiography, MR angiography (MRA), 3D digital subtraction angiography, or 3D rotational angiography.\textsuperscript{65} Aneurysm and vessel characteristics, such as location, size, morphology, AR, and SR, can be used to calculate the wall tension, wall shear stress (WSS), and flow velocity to better estimate aneurysm rupture risk.\textsuperscript{2,3,5,8,9,28,42,54,56,62,65,66} The results thus far have been quite promising, as CFD has been successfully used to estimate these parameters and predict aneurysm rupture risk in many different studies.

CFD has been used to further investigate the theories of high and low shear stress and aneurysm rupture risk. Castro et al.\textsuperscript{9} created models of 26 anterior communicating artery aneurysms and found significant associations between elevated maximum intraaneurysmal WSS and a clinical history of previous rupture. They observed this association in later studies examining 42 aneurysms at other locations.\textsuperscript{7} Cebral et al.\textsuperscript{12} analyzed hemodynamic environments in 210 cerebral aneurysms using image-based CFD; they found ruptured aneurysms were more likely to have larger maximum WSS (MWSS). However, other investigations have observed conflicting findings. Xiang et al.\textsuperscript{56} analyzed 119 aneurysms based on 3D angiographic images. They found lower MWSS and WSS in ruptured aneurysms compared to unruptured aneurysms. Shojima et al.\textsuperscript{55} created 20 models of middle cerebral artery vessels with aneurysms from angiography studies, and demonstrated the average WSS of the aneurysm was significantly lower than that of the vessel. Additionally, WSS at the tip of the ruptured aneurysms was markedly low. Other studies also found that aneurysm growth and rupture were more likely to occur in regions of abnormally low WSS,\textsuperscript{3,21,32,43,51,58} suggesting that low, rather than high, WSS is associated with aneurysm growth and rupture.

Differences in model assumptions or algorithmic approaches may result in different predicted aneurysm rupture risk scores from the same data.\textsuperscript{29,30} While CFD model predictions have been validated in many different studies,\textsuperscript{1,2,4,9} the results suggest that CFD models will likely become more accurate over time as more data sets are assembled. Complex models integrating multiple different parameters could also further improve CFD model predictions. Further studies in larger patient cohorts are necessary to determine how CFD can be optimized to supplement clinical decision-making as current models are associated with uncertainty and may take hours to days to compute.\textsuperscript{58}

### Hemodynamic Parameters

#### Aneurysm Initiation: WSS

The effect of arterial WSS on aneurysm pathogenesis has been the subject of extensive study. Shear stress is composed of the tangential, frictional forces that exist between blood and the stationary vessel wall (Fig. 1).\textsuperscript{53} The relative difference in velocity between two parallel objects creates a shear stress. The shear stress becomes proportional to the velocity gradients between the two objects. As a derivative, the WSS gradient (WSSG) is defined as the spatial derivative of WSS along the direction of flow. It can be thought of as the change in WSS along the length of the vessel.\textsuperscript{15} In response to physiological levels of shear stress, endothelial cells assume a quiescent and atheroprotective gene expression profile characterized by resistance to inflammation, apoptosis, and oxidative stress. Low levels of shear stress promote atherosclerosis by inducing inflammation and an atherogenic phenotype.\textsuperscript{37,45,59,63} When discussing the pathophysiology of IAs, it is important to distinguish aneurysm initiation and growth as two separate entities with distinct hemodynamic and inflammatory mechanisms involved.

WSS is an important parameter in animal aneurysm formation models. Gao et al.\textsuperscript{22} identified high WSS as an important factor in aneurysm formation in a rabbit model. Dramatic increases in basilar artery (BA) flow rate (105%–900%) and nascent aneurysm formation at the BA bifurcation were found following common carotid artery ligation. Histologically, the nascent aneurysms were characterized by a bulging and thinned tunica media as well as loss of the internal elastic lamina (IEL). The extent of aneurysm sac formation was related to the degree of BA flow-rate increase. High WSS and WSSG were implicated in vessel remodeling and eventual aneurysm formation, with the authors theorizing that endothelial cells at bifurcation apices became dysfunctional under sustained abnormal hemodynamic conditions. Other studies utilizing animal models reported similar findings.\textsuperscript{1,4,14,23,35,39,41,54} A systematic review and meta-analysis conducted by Can and Du\textsuperscript{6} found a high positive correlation between elevated WSS and location of aneurysm formation. While a significant association of

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high WSSG with aneurysm formation was not found, they found that sidewall and bifurcation aneurysms were impacted differently by these hemodynamic factors.

**Enlargement and Rupture: Low- and High-Stress Theories**

Although aneurysm formation has been clearly linked to regions of high WSS, the impact of the hemodynamic environment on aneurysm enlargement and rupture is less certain. Conflicting studies have found both high and low WSS to be related to aneurysm growth and eventual rupture.

This apparent conflict has led to the creation of two schools of thought: the high- and low-stress theories. In both theories, the hemodynamic environment within the aneurysm interacts with the cellular elements of the aneurysm wall resulting in further weakening. The differences, however, revolve around the mechanisms responsible for the wall weakening. The high-stress theory asserts that elevation of maximum WSS causes endothelial injury and initiates processes of wall remodeling and degeneration. Vascular endothelium exposed to elevated MWSS overexpresses nitric oxide (NO), leading to abnormally low arterial tone and apoptosis of wall-embedded smooth-muscle cells (SMCs). Conversely, the low-stress theory states that stagnation of blood within the aneurysm leads to red blood cell aggregation and buildup of platelets and leukocytes. These changes cause intimal damage and inflammatory cell infiltration of the vessel wall, leading to wall degeneration and a reduced ability to withstand physiological hemodynamic forces.

Meng et al. proposed that low WSS (as well as high oscillatory shear index [OSI]) leads to a proinflammatory endothelial cell phenotype and increased inflammatory cell infiltration, matrix metalloproteinase (MMP) production, SMC proliferation and migration, and thrombus formation. In contrast, high WSS combined with a positive WSSG resulted in endothelial cell damage and turnover, MMP production by mural cells, extracellular matrix (ECM) degradation, thinning of the media, and apoptosis of SMCs and fibroblasts. They classified these distinct responses as mural cell–mediated and inflammatory cell–mediated destructive remodeling pathways, each of which may drive aneurysm rupture under different hemodynamic conditions and in different aneurysm phenotypes. The mural cell–mediated pathway associated with high WSS could be associated with the growth and rupture of small or secondary bleb aneurysm phenotypes, while the inflammatory-mediated pathway may be responsible for the growth and rupture of large, atherosclerotic, and thrombotic IA phenotypes.

In contrast to Meng et al., a study comparing in vivo flow conditions with the histology of human IAs suggested the exact opposite association between WSS and aneurysm wall degeneration and rupture. Using the degree of CD45-positive and CD68-positive cells as a marker of leukocyte and macrophage expression, respectively, Cebral et al. found that conditions of high WSS were associated with higher levels of inflammation. However, low WSS conditions displayed negative CD45 immunostaining, and were instead associated with loss of mural cells. Immuno-}

**Oscillatory Shear Index**

The OSI is a variable that provides a measure of the changes in the direction of the shear forces during the cardiac cycle. Shearing forces are tangential forces that are parallel to the direction of blood flow. Areas where the direction of the WSS vector changes frequency through-
out the cardiac cycle (e.g., areas of flow recirculation or reversed flow) will have high OSI values. OSI measures temporal, rather than spatial, variation in flow direction. If the direction of flow at a given point is maintained throughout the cardiac cycle in an aneurysm with several different directions of flow, the OSI will be low at that point. Temporal variations in blood flow can be illustrated by the vortices of blood flow that are created and disappear throughout the cardiac cycle (Fig. 2).5

Given the importance of aneurysm geometry and parent vessel characteristics to intraaneurysmal hemodynamics,60 OSI may reflect aneurysm and parent-vessel morphological features. Low WSS is often accompanied by oscillatory flow, which may enhance atherogenesis, promote inflammation, and lead to intimal wall thickening.54,66 Although a number of studies have identified high OSI in ruptured aneurysms, Can and Du6 found that ruptured aneurysms did not have significantly different pooled OSI compared with unruptured aneurysms in a systematic review and meta-analysis. While Zhou et al.69 found a higher OSI in ruptured aneurysms, this finding did not reach statistical significance in their review. Oscillatory flow may be a contributing factor to adverse vascular remodeling that precedes aneurysm rupture, but its exact role in predicting aneurysm rupture remains uncertain.

Flow Patterns

Flow patterns within the aneurysm sac may also influence risk of rupture. Blood flow in singular and consistent patterns would be considered simple, while complex flow patterns are characterized by multiple areas of recirculation that may persist or temporarily exist throughout the cardiac cycle.54 Byrne et al.5 found that ruptured aneurysms had more complex and unstable flow patterns than unruptured aneurysms. Additionally, spatial complexity was more strongly associated with rupture than temporal stability. Xiang et al.67 found that most ruptured aneurysms exhibited complex flow with multiple vortices, while most unruptured aneurysms demonstrated simple flow patterns with a single vortex. Other reports have also associated rupture with complex flow patterns.21 However, Kleinloog et al.33 concluded that complex flow patterns had a low level of evidence for association with rupture in their systematic review. When the vascular wall can no longer tolerate hemodynamic stress, it ultimately leads to either aneurysm rupture or stabilization.

Hemodynamics and Vascular Remodeling

Abnormal hemodynamics serves as a trigger for vascular remodeling and the biochemical mechanisms that persist following the inciting stressor. Arterial remodeling is an adaptive process that attempts to return high or low WSS back to a physiological baseline of 15–20 dynes/cm².25 Vascular remodeling is characterized by vascular SMC (VSMC) apoptosis and migration, degradation of the ECM, and inflammation causing local dilation and thinning.
ning of the vessel wall (Fig. 4). Additionally, the biological interactions of flow and vessel wall remodeling that initiate aneurysm formation is a distinct process from the growth and rupture of an already formed aneurysm.

In the presence of hemodynamic stressors, flow-dependent NO release inhibits the proliferation of VSMCs and can initiate apoptosis by activating caspase 3. This results in pyknosis, karyorrhexis, and cell death. In addition, physical stretch on the vessel wall can induce apoptosis by activation of the tumor suppressor p53. Primarily found in the medial layer, VSMC migration is a normal response in the setting of vascular injury. Hemodynamic stimuli may alter migratory signals such as amines, peptide growth factors, cytokines, and ECM components, such that migration contributes to vessel wall thinning. Migration of VSMCs is in the direction of the intima, with a subsequent phenotypic reprogramming mediated by tumor necrosis factor–alpha (TNF-α) and Kruppel-like transcription factor 4. VSMCs gain the ability to express genes related to upregulation of proinflammatory molecules including MMPs, monocyte chemoattractant protein–1 (MCP-1), vascular cell adhesion molecule–1 (VCAM-1), and interleukin (IL). Within the intimal layer, these cells can proliferate and synthesize new matrix and fibrous tissue, resulting in the process known as intimal hyperplasia. Normally a part of the wound-healing process, decellularized areas characterized by loss of mural cells, matrix breakdown, and hyalinization resembling fibrinoid necrosis have been detected in rupture-prone aneurysms.

The disappearance of the IEL is among the first histological changes observed during aneurysmal growth, leaving the adventitia as the only layer resisting transmural...
blood pressure. ECM proteins continue to become compromised with MMPs degrading structural proteins such as collagens, elastin, proteoglycans, laminin, and fibronectin. MMP activity is further upregulated by flow-dependent NO release through posttranslational modification. Specifically, overexpression of MMP-1, -2, and -9 has been identified in aneurysm walls with MMP-2 and -9 being found at higher levels in ruptured aneurysms. Chronic proteolytic injury by collagenases is further enhanced by the downregulation of antiapoptotic genes.19

Monocytes are among the first cell types to respond to hemodynamic endothelial damage, infiltrating the site of injury and differentiating into macrophages that secrete cytokines and proteinases. MCP-1, TNF-α, and stromal cell-derived factor-1 (SDF-1; also known as CXCL12) are among the cytokines released by macrophages. SDF-1/CXCL12 functions to recruit endothelial progenitor cells and induce angiogenesis and further inflammatory cell migration and infiltration.27 Macrophages also contribute to further ECM degradation by secreting MMPs. CD163-positive, the primary macrophage found in IAs, expresses a specific receptor that is a member of the scavenger receptor cysteine-rich superfamily.16 These macrophages function to bind hemoglobin:haptoglobin complexes and are triggered by high levels of oxidative stress contributing to their role in IA wall degeneration and rupture.16,19 Macrophage infiltration has also been correlated with intracellular lipid accumulation and apolipoproteins, including ApoA-I50 and ApoB100.18

A difference in atherosclerotic lesions is evident between small and large aneurysms. In small aneurysms, atherosclerotic lesions are characterized by diffuse intimal thickening with predominantly VSMCs and minimal macrophages and lymphocytes. In contrast, larger aneurysms have more advanced atherosclerotic lesions with macrophages as the primary cellular infiltrate.34 Interestingly, Frøsen et al.18 noted that acquired antibodies against oxidized lipids within the vasculature served a protective role, with lower levels of oxidized low-density lipoprotein-reactive immunoglobulin G (IgG) antibodies associated with a history of IA rupture.

Humoral immune response has also been shown to be active in aneurysm walls in the form of complement component and antibody (immunoglobulin M [IgM] and IgG) deposition.39 Significant amounts of C3d accumulation have been observed in aneurysms, suggesting that a more chronic inflammatory state may be involved. Activation of the classic pathway with an alternative pathway amplification has also been implicated, causing the release of chemokines that further facilitate the recruitment of macrophages and T cells. Membrane attack complexes are rarely observed on the cell surface; instead, they are found within the matrix and cellular debris of degraded regions. This suggests complement activation may occur as a reaction to necrosis, rather than the cause of it.39

Predicting Aneurysm Rupture With Hemodynamics

MRI

Advances in MRI development and technology show significant promise for predicting aneurysm rupture risk. Four-dimensional flow MRI, also known as 3D time-resolved phase-contrast MRI, quantifies blood flow in three dimensions and can be used to estimate WSS, SR, and inflow hemodynamics much faster than traditional CFD, although 4D MRI often underestimates WSS.21,25 Contrast permeability across aneurysm walls as measured by dynamic contrast-enhanced MRI has been found to be predictive of aneurysm rupture risk independent of aneurysm size.62 Seven-tesla MRI has been used to measure wall thickness, which was found to be inversely related to WSS.2

The presence of atherosclerotic plaques in IAs has been extensively studied.18,34,50 Hybrid of opposite-contrast MRA is a combination of time-of-flight and flow-sensitive black-blood MRA that can be used to visualize atherosclerotic plaques along aneurysm walls.38 Even in the absence of visible atherosclerotic changes such as fatty streaks, the accumulation of oxidized lipids is associated with wall inflammation.34

Wall enhancement and microhemorrhage identification have also been explored as a tool for predicting aneurysm rupture.49 MRI with 3D turbo spin-echo sequences with motion-sensitized driven equilibrium can be used to detect aneurysm wall enhancement. While ruptured aneurysms are more often associated with aneurysm wall enhancement, it is still unclear whether aneurysm wall enhancement in unruptured aneurysms is suggestive of increased rupture risk.46 Circumferential aneurysm wall enhancement detected by 3T gadolinium-enhanced high-resolution MRI has been found to be associated with symptomatic aneurysms compared to asymptomatic aneurysms, although its ability to predict aneurysm rupture has not yet been studied.29

Quantitative susceptibility mapping mapping localized paramagnetic metals such as ferric iron and was used to detect microhemorrhages in a case report.47 T2-weighted gradient-recalled echo sequence MRI was used to detect cerebral microbleeds in a large study of 1847 patients and found to be associated with an increased risk of aneurysm rupture.68 While further research is needed to evaluate the usefulness of these methodologies in clinical practice, several hemodynamic parameters may predict aneurysm formation or rupture, summarized in Table 1.

Conclusions

As imaging studies and computational modeling continue to improve, understanding of the hemodynamic role in cerebral aneurysm formation, growth, and rupture will increase. While WSS is implicated in aneurysm initiation, its role in aneurysm growth and rupture remains controversial, with studies showing contrasting results. Other hemodynamic parameters may be involved in aneurysm pathogenesis, although they are much less studied than WSS. It appears that the cumulative effect of these hemodynamic stressors triggers an array of inflammatory and signaling cascades that ultimately results in vessel wall thinning, dilation, and rupture. With respect to imaging, current advances in MRI techniques and CFD provide a promising modality for predicting aneurysm rupture in patients, although a more integrative approach that incorpo-
rates vascular, genetic, and epidemiological risk factors of aneurysm rupture is needed to be a truly predictive model with clinical utility.

References


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### TABLE 1. Summary of flow and imaging parameters and their associated risk with aneurysm rupture or formation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Association</th>
<th>Risk</th>
</tr>
</thead>
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<tr>
<td>Aneurysm wall contrast permeability</td>
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</tr>
<tr>
<td>Aneurysm wall enhancement</td>
<td></td>
<td>Possibly increased</td>
</tr>
<tr>
<td>AR</td>
<td>Aneurysm rupture</td>
<td>Unclear</td>
</tr>
<tr>
<td>Atherosclerotic plaques</td>
<td>Aneurysm rupture</td>
<td>Unclear</td>
</tr>
<tr>
<td>Bottleneck factor</td>
<td>Aneurysm rupture</td>
<td>Increased</td>
</tr>
<tr>
<td>Complex flow patterns</td>
<td>Aneurysm rupture</td>
<td>Increased</td>
</tr>
<tr>
<td>Height-to-width ratio</td>
<td>Aneurysm rupture</td>
<td>Increased</td>
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<td>Irregular aneurysm shape</td>
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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Park, Soldozy. Acquisition of data: Soldozy, Elsarrag, Chatrath, Costello. Drafting the article: Soldozy, Elsarrag, Chatrath. Critically revising the article: Park, Soldozy, Norat, Elsarrag, Chatrath, Costello, Kalani. Reviewed submitted version of manuscript: Park, Soldozy, Norat, Elsarrag, Chatrath, Costello, Sokolowski, Tvrdik. Approved the final version of the manuscript on behalf of all authors: Park. Administrative/technical/material support: Park, Norat. Study supervision: Park, Kalani.

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