Role of Fluid Dynamics and Inflammation in Intracranial Aneurysm Formation

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The emergence of inflammation as a key mediator of aneurysmogenesis provides new opportunities to understand the processes underlying the development of intracranial aneurysms (IAs). Inflammation unifies the triptych influences of alterations in local flow, mechanical properties of the wall, and biochemical mediators and opens new avenues for building robust predictive tools. This review discusses the impact of the inflammatory cascade during the formation of IAs and its associated morphological, structural, and mechanical changes, especially in the setting of flow-induced endothelial dysfunction.

Overview of the Disease

IAs are dynamic but silent. Therefore, their true prevalence is not known and their first manifestation may be catastrophic. Mortality and morbidity are high; aneurysm rupture is sudden and has devastating side effects. Subarachnoid hemorrhage is a common consequence of IA rupture, which occurs in \( \approx 1 \) in 10,000\(^1\) in the general population, translating into \( \approx 30,000 \) new cases yearly, in the United States alone. Twelve percent of these patients die before receiving medical attention; 40% of hospitalized patients die within a month; and more than one third of survivors are left with permanent neurological deficits.\(^2\) Yet, aneurysm initiation, propagation, and rupture remain poorly defined, hindering optimal treatment.

Three options are available for management of unruptured IA: monitored follow-up, surgical clipping, or endovascular occlusion. Observation and monitoring assumes that there is a premonitory sign or critical dimensional threshold for destabilization and that there is adequate time for warning before catastrophic failure; however, neither may be true. The first clinical evidence of IA destabilization may be complete rupture, and it is not clear whether size alone or rate of dimensional change is determinant. Correlation of static anatomic images and clinical presentation with past experience is challenging and ambiguous. At the same time, surgical and endovascular interventions are not without significant complications. The International Study of Unruptured Intracranial Aneurysms\(^3\) recommends interventions when IAs exceed 7 mm in diameter, but sequential images are rarely obtained because of the burden imposed on the patient or the lax enforcement of periodic follow-ups. There is therefore little mechanistic insight for predicting the fate of an IA from first principles such as change in arterial dimensions and flow characteristics and a limited experiential data set for comparison. Clinical decisions are often made in the face of sparse data and comparison with incompletely applicable predicate lesions or clinical conditions, and treatment choices force a tradeoff between procedural risks and the probability of subarachnoid hemorrhage. It is imperative to understand the origin and physiology of IAs, particularly the emerging role of inflammation and interaction with mechanical and flow forces.

Mechanical and Flow Properties of IAs

Current understanding of the natural history of IAs, including growth, rupture, and to a lesser extent initiation, considers vascular wall mechanical properties key. Growth is considered to result from a combination of cell proliferation and wall distension, whereas rupture occurs when blood pressure–induced tension exceeds aneurysmal wall strength, a consequence of wall degeneration. In addition, quantitative values of mechanical properties are required for computational fluid dynamics (CFD) simulations.

The life span of an aneurysm can be divided into 3 separate stages: initiation, growth, and rupture. In each of these stages, blood flow plays an important role through the conversion of mechanical stimuli into biological signaling.\(^4,5\) The focal nature of lesions, preferentially located at bifurcations or sharp curves,\(^6\) supports the role of hemodynamics in IA biology. Flow is a central process in many of the components of aneurysm formation. Flow determines where inflammatory cells will adhere and how the endothelium and its endothelial cells will respond to local inflammation.\(^7-9\) The endothelium is the primary interfacial surface with flowing blood, and the endothelial cells are premier sensors of shear from above and strain from below.\(^10\) An intact endothelium and “normal” near-parabolic laminar flow ensure vascular homeostasis through the controlled secretion of an array of antithrombotic and anti-inflammatory factors. However, this fragile equilibrium can be thrown off-balance by external stimuli that alter flow and damage the vessel wall. The preponderance of IAs at bifurcations and segments with large curvature correlates with disturbed flow patterns characterized by large swings in shear stress. The focal nature of IA manifestation supports the role of flow as the driving force of inflammation. When applied...
to vascular aneurysms, we surmise that aneurysm-protective flows and wall states maintain vascular homeostasis throughout the cerebral tree despite the large number of circulating inflammatory cells, whereas aneurysm-prone waveforms are responsible for remodeling and inflammation. The initiation of IA is a complex interaction of mechanics, fluid dynamics, and biology. Alterations in shear stress may be required but are not sufficient to explain the pathogenesis of IAs. Instead, we regard anatomically driven flow disturbances in the cerebral vasculature as a trigger that acts on the substrate of genetic heterogeneity and superimposes on other environmental cues to affect the kinetics of the progression of the disease.

Blood applies pressure and wall shear stress (WSS) on the lumen (Figure 1); however, peak pressure alone is not enough to explain the initiation of IAs. The extra pressure applied to an IA from jet impingement is only \( \approx 1 \text{ mmHg}, 1\% \text{ to } 2\% \text{ of the peak pressure} \). In this review, we do not discuss the biological implications of pressure changes in IA formation. Other physical properties of the flow such as WSS or the gradient of WSS must play a role, similar to other cardiovascular diseases, for example, intimal hyperplasia. Cells of the vascular endothelium respond to flow, converting mechanical stimuli into biological processes. Thus, measuring or estimating the physical properties of the cerebral flow is critical to the study of IAs. However, the researcher’s toolbox is limited vis-à-vis in vivo measurements of flow. Phase-contrast magnetic resonance imaging (MRI) allows the measurement of pressure fields, but its spatial resolution and temporal resolution are too low to practically compute WSS. CFD can augment imaging and physiological data to provide a convenient way to quantify patient-specific flow parameters. The combination of sequential imaging and blood flow simulation can be used to track regions of growth. Over the years, CFD methods have gained in precision and power, enabling the progression from 2-dimensional idealized geometries to 3-dimensional patient-specific problems with nonrigid walls.

Flowing blood applies 2 types of stress on the vascular bed: pressure, which acts normal to the lumen and can affect the physiology of the endothelium and the tension of the smooth muscle cells (SMCs), and WSS or endothelial shear stress. WSS corresponds to the force per unit area applied by the blood in a direction tangential to the wall; it is also defined as the product of viscosity, the friction between layers of the

flow with different velocities, and shear rate. In general and when parabolic flow dominates, blood flow can be considered a series of parallel flow lines with a velocity that is maximal at the centerline and zero at the walls. The change in velocity follows inversely, maximum at the walls and zero at the centerline. Shear rate describes the rate by which the velocity changes as a distance from the wall. WSS and shear rate computed from the derivation of velocities throughout the fluid domain are particularly interesting in the study of vascular diseases because endothelial cells respond to variations in WSS, eliciting different phenotypes and biological processes.

Computational Fluid Dynamics

CFD emerged in the 1930s as a branch of fluid mechanics to solve problems too complex for analytic solutions. CFD is based on the strategic partition of a fluid domain into small elements, usually tetrahedrons or hexahedrons. The equations that define fluid mechanics in each element provide neighboring elements with boundary conditions for their equations of state and, when coupled, provide an integrated view of the fluid dynamics of the system. The quality of the results depends on many parameters, including the partitioning strategy and the number of elements used to divide the fluid domain (the mesh; Figure 2), the original boundary conditions, the algorithm used to solve the equations, and the time steps between each calculation, in the case of a time-dependent simulation. As discussed in detail later in this section, the geometry of the vasculature, the fluid boundary conditions, and the constitutive laws describing the vessel rigidity and blood collectively determine the degree of precision of the solution, and extra care should be taken to generate a solution that matches the level of understanding of the biological phenomenon studied.

Modeling of IA blood flow has helped confirm and explain the role of hemodynamics in the pathogenesis of IA, although
much needs to be done. Knowledge of the mechanical properties of IA is needed to circumvent the use of rigid boundaries in classic simulations, yet few of the relevant data are available. To date, no method can reliably measure the mechanical properties of the aneurysmal wall in vivo. Grasping the mechanical properties of cerebrovascular lesions ex vivo is equally challenging because of the imperative to manipulate small, highly anisotropic,\textsuperscript{18} fresh human tissue samples of limited availability. Preservation with fixation for later analysis is not an option because tissue mechanical properties are modified in the processing. Furthermore, although a map of sample thickness is necessary to translate a force into a stress, there is no valid method to map thickness in vivo, which varies in space, ranging from 16 to 500 µm in the unloaded state,\textsuperscript{19,20} and time during the progression of the disease.

Few published studies have reported the mechanical properties of IAs\textsuperscript{18,21–23}, those that do have generally reported uniaxial loading and reported a critical stress of 3.68 MPa. The reliability of CFD has been assessed by comparing simulation results with various forms of experimental measurements. Ford et al\textsuperscript{29} measured the velocity field of fluid mimicking blood flow in phantoms with particle image velocimetry and found good agreement with CFD predictions, although simulation tended to overestimate the velocity. Similarly, Hollnagel et al\textsuperscript{19} reported good qualitative agreement of CFD predictions with phase-contrast magnetic resonance angiography and laser Doppler velocimetry but quantitative differences with phase-contrast magnetic resonance angiography, especially in zones of complex flow. Virtual angiography was proposed as an indirect validation of CFD.\textsuperscript{31,32} Ford et al\textsuperscript{19} recorded the error between virtual and true angiograms in healthy patients, and despite decoupled flow and diffusion equations, the best-suited model yielded <10% error for 80% of the pixels in the sac.

Table 1. Summary of Experimental Results for the Properties of Intracranial Aneurysms

<table>
<thead>
<tr>
<th>Stress to Rupture, MPa</th>
<th>Comments</th>
<th>Scott et al\textsuperscript{21}</th>
<th>Steiger et al\textsuperscript{22}</th>
<th>Toth et al\textsuperscript{23}</th>
<th>MacDonald et al\textsuperscript{26}</th>
<th>Monson et al\textsuperscript{26}</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–3</td>
<td>Fresh and postmortem tissue</td>
<td>0.5–1.2</td>
<td>0.14–1.00</td>
<td>0.73–1.9</td>
<td>3.68</td>
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</tr>
</tbody>
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As noted, the overall relevance of CFD depends on the definition of the boundary conditions: the geometry describing the arterial wall, the inflow and outflow conditions, and the model used to describe the behavior of the blood. CFD is a tool, and one should not expect that the precision of the simulation will be greater than the precision of the input values or constitutive models. The CFD procedure to model IAs begins with the reconstruction of the lumen geometry obtained from a range of medical imaging modalities. The gold standard is 3-dimensional rotational angiography, which produces contrast...
maps of the brain and the vascular lumen. Angiography is often used in concert with iodine-based contrast agents that increase the quality and contrast of the images. Software is used to segment and stack together sequential images and then to clean and smooth the volume. The most delicate steps in setting up a CFD analysis are adequately meshing the fluid domain and prescribing the fluid boundary conditions. Figure 2 gives an example of a mesh used to compute physical properties in branches of the internal carotid artery of a patient with a sidewall middle cerebral artery aneurysm (IA not shown). The ideal mesh should be fine enough that increasing the number of elements does not affect the solution of the problem. Detailed procedures and information are available in the work by Bathe. The precision and relevance of the waveforms/flow rates imposed at inlets and outlets are the subject of debate. Options include phase-contrast MRI, Doppler, or intravascular ultrasound velocimetry. MRI gives the most precise information because it yields a map of velocities in a section of the artery, but it extends the diagnostic time and thus is not always available. Alternatively, one can compute the Womersley profiles at the inlet from the waveform of the flow rate, which correspond to the analytic solution of the specific waveform in a pipe. The cross section of the pipe is scaled to fit the size of the feeding artery.

Four major areas require definition to more completely understand the hemodynamics of IA. In decreasing order of sensitivity to modeling, they are the arterial geometry, fluid boundary conditions, rigid-wall assumption, and description of the physics of blood.

The reconstruction of the arterial geometry is crucial because real images rarely delineate a clean border between tissue and blood; thus, image segmentation and smoothing are left to the judgment of the operator. This is all the more important because such considerations freeze the geometry, affecting subsequent results. Fluid boundary conditions include evaluation of the flow inlets and outlets. Classically, inlets are set to drive the simulation by specifying the velocity or flow rate in a cross section, whereas outlets ensure the continuity of the flow through setting of the exit pressure. Controversy remains about whether these data should be measured from the same patient or can be measured in different patients and scaled and about the degree of precision required. Ideally, phase-contrast MRI at the inlet and pressure measurements at the outlet in the same patient should be used for maximal precision. Differences in spatial averages of WSS values derived from an archetypal volumetric flow rate waveform compared with patient-specific data might be as high as 30%. The sample size of this study was 6 cases, and overall results with archetypal waveforms overestimated mean WSS by ±15%. However, phase-contrast MRI is not a panacea; it is highly dependent on the parameters specified for acquisition, and the range of velocities that can be tracked is limited. Thus, heterogeneous flows have larger uncertainty and may require extrapolation of the velocity distribution near the wall. Fortunately, the characteristics of the flow change as it develops in the vasculature, decreasing its dependence on the boundary condition away from the inlet; consequently, it is key to keep enough length before the region of interest. Aneurysms often rupture during a spike of heart rate, for example, during physical activity. As a result, it was suggested that simulation be carried out at higher volumetric flow rates, which was shown to modify the flow patterns and WSS values.

Many neurosurgeons have reported the cyclic expansion of the IA cavity throughout the cardiac cycle and inhomogeneity in the thickness of the IA wall. If detected by human eye, the change in geometry should be sufficient to affect computed characteristics of flow, yet classic assumptions and boundary conditions may have interfered with modeling such deformations. Significant deformation was indeed detected in model systems configured with elastic boundaries. Rigid boundaries overestimate shear stress in IA and by definition dampen deformation. These results are interesting as proof of concept of fluid structure interaction in IAs but require validation because they rely on uncertain wall mechanics data and arbitrary choice of IA thickness. Fluid structure interaction simulations couple CFD (fluids) and solid (wall and perianeurysmal structures) interactions.

Blood parameters are similarly fraught with assumption dependence. Blood is a viscous fluid, described with classic newtonian physics, but more appropriately considered with more complex models. Carreau-Yasuda or Casson approximations offer a more general framework, allowing viscosity to vary with the shear rate. Rheological effects can be important, depending on the geometry. Newtonian models can degrade the results of the simulation whereas Casson models do not significantly burden computational cost.

The trend in CFD is to bring additional physiological relevance and complexity to the models and boundary conditions, in particular, to circumvent the rigid wall assumption. Fluid structure interaction takes into account a model of deformation of the wall to constantly iterate on the mechanical model of the artery to make the geometry current as pulses of flow induce the dilation of the vasculature. The challenges that remain are to obtain more precise and appropriate experimental data on the mechanics and patient-specific topology of the wall to drive the models proposed.

Thus, assessment of flow is essential to understanding the initiation, development, and rupture of IAs. CFD is a valuable tool because of the dearth of adequate in vivo imaging that can reliably measure flow parameters such as WSS, but as a sensitive tool, it requires careful selection of boundary conditions. The precision of CFD should match the level of understanding required. General mechanistic processes such as mechano-transduction need only low precision and averages because they seek to reach global conclusions. Case-specific problems such as rupture are in contrast highly dependent on the level of details (Figure 3). We believe that careful CFD analysis is valuable and will be best used to further characterize the mechanism that lead to IA initiation and enlargement in vitro.

The Biology of IA Remodeling

A simple analysis of the thicknesses shows that aneurysm expansion is dynamic: cells or collagen must be produced throughout the growth of the lesion (Figure 4 and Table 2). The observation of the thickness of aneurysmal walls of various sizes and morphologies rules out theories suggesting that aneurysms grow only through a rearrangement of mass in the wall as a result of tension. In effect, the average thickness reported for IAs is inconsistent with values predicted by simple
distention of the wall. Aneurysmal growth must have an associated addition of mass from either cell proliferation or collagen production. Consider an idealized aneurysm model built from a sphere of radius $r_1$ intersecting a cylinder of radius $r_2$, so that the size of neck in the direction of the axis of the cylinder is $n$. If the aneurysm balloons out from a bent disk of diameter $n$ without a change in arterial wall density, then conservation of mass should allow us to approximate the thickness of the aneurysm, $t_{\text{aneurysm}}$, as a function of the average thickness of the arterial wall, $t_{\text{artery}}$, and the ratio of arterial and aneurysmal surface areas $S_{\text{artery}}$ and $S_{\text{aneurysm}}$. This ratio can be approximated in the case of pure distention in terms of the radius of the aneurysm, $r_2$, and diameter of the neck of the aneurysm, $n$:

$$t_{\text{aneurysm}} = t_{\text{artery}} \frac{S_{\text{artery}}}{S_{\text{aneurysm}}} = t_{\text{artery}} \frac{\Pi \left( \frac{n}{2} \right)^2}{4\Pi r_2^2} = \left( \frac{n}{4r_2} \right)^2$$

The calculated aneurysm thicknesses computed for pure distention for an artery 300 $\mu$m thick with an aneurysm arising from a 4- to 6-mm neck that balloons to a sphere 5 to 8 mm in radius (Table 2) should then be 8 to 12 $\mu$m. This value, however, is far lower than the average thickness observed in aneurysmal specimens (16–500 $\mu$m), implying that distention alone likely is not responsible and that there must be additional sources of cell gain or extracellular matrix accumulation. Inflammation is increasingly perceived as central to these remodeling events.

Evidence of Inflammation

The inflammation cascade is critical to the pathogenesis of cardiovascular diseases. All IAs show evidence of intense inflammatory remodeling, including the presence of monocytes, macrophages, mast cells, and T lymphocytes, and complement activation. Gene expression analysis of IA specimens corroborates the prevalence of inflammation through the upregulation of multiple proinflammatory genes, highlighting the critical role of antigen-presenting cells. A discussion of the genetic dependence of IA is beyond the scope of this review but can be found elsewhere.

Potential Mechanisms of Flow-Driven Inflammation

The endothelial monolayer is the center of command of vascular health. Its endothelial cells are the first line of exposure to
Residing at the privileged vantage point at the frontier between vessel and blood on one side and smooth muscle from the opposing side, the endothelium is ideally suited to orchestrate the sensing of complex forces and flows, surveillance of circulating elements, and right of passage and defense of the vessel against these entities. Changes in endothelial connectivity, endothelial cell shape, and cytoskeleton are followed by dynamic alterations to the secretome of the cell and, with that, regulation of state and environment. For example, under laminar flow, endothelial cells become spindoidal and align with the flow but lose a preferential orientation and turn cuboidal under disturbed or turbulent flow as a result of F-actin reorganization. Although the former inhibit thrombosis, leukocyte adhesion, smooth muscle proliferation, and vasoconstriction, the latter phenotype promotes these processes.

The transmission of force to the cell is carried out through intracellular tension created by the contraction of cytoskeletal filaments influenced by flow via the anchorage of the cell membrane to the substrate, or neighboring cells. Intracellular forces act on the conformation of intracellular proteins to modify the physiology of the cell. Consequently, the extracellular milieu, including the mechanical properties of the substrate, indirectly influences the cell biology through this mechanism. During the initiation of aneurysms, the luminal surface of the vessel becomes irregular and often damaged, even denuded, a probable consequence of disturbed hemodynamic stress. The topology of the changing vessel in turn modifies the local hemodynamic environment that loops around to command intracellular forces and cellular biology. This dynamic actuation of the flow-force elicits changing biochemical signaling throughout the pathogenesis of IAs. If intense hemodynamic stress seems to be incriminated over the course of initiation, low atheroprofane-like shear stress dominates in the cavity during progression, which might explain why >40% of unruptured IAs present intimal hyperplasia.

Several mechanosensors—ion channels, integrins, cell adhesion molecules, G-protein–coupled receptors, and other cellular organelles—have been identified at the apical and basal surfaces of the endothelium and can lead to activation of inflammation mediators such as the master regulator nuclear factor-kB, which is active in experimental IAs, or potent anti-inflammatory factors like Krüppel-like factor-2, depending on the waveform applied to the cells. Further details on endothelial flow-mediated mechanotransduction are summarized in an exhaustive review by Davies.

Flow-mediated endothelial dysfunction and the subsequent modulation of SMCs to a synthetic phenotype reinforce the belief that inflammation is at the heart of the IA genesis. The contractile phenotype contributes to the inflammation across many vascular diseases by generating a proinflammatory and proremodeling milieu, which in turn sustains and amplifies endothelial dysfunction and the recruitment of immune cells. This also applies to IAs, beginning with the reduction of the contractile apparatus of the cell such as α-actin, changes in differentiation regulatory mechanisms, and the expression of transcriptions factors mediating inflammation, for example, p47phox and Ets-1. During the development of aneurysmal lesions, SMCs of the media progressively transition from a quiescent contractile to a pathophysiologic synthetic phenotype, as observed on histological sections of human samples, and express proinflammatory cytokines and matrix metalloproteinases. These proteases can degrade the extracellular matrix and participate in the regulation of inflammation, and they are believed to contribute to the remodeling of IA lesions through the breakdown of the cellular substrate, ultimately achieving weakening of the vascular wall.

The media of diseased cerebral arteries gets thinner as the disease progresses and forms the aneurysmal cavity. This process occurs collectively through the degeneration or apoptosis of SMCs, the inhibition of proliferation of SMCs, and the inhibition of collagen production and processing by SMCs, which was observed in rat models of IAs. However, the predominant driving force for the remodeling of the media is unknown.

Inflammation builds up through the synergistic combination of leukocyte chemoattraction, activation, adhesion, and transmigration into the arterial wall. Monocyte chemoattractant protein-1 and interleukin-8 are expressed in human and experimental IAs, and vascular cell adhesion molecule-1 is expressed in the IA walls of human and rat model but not in control arteries. Monocyte chemoattractant protein-1 knockout rats were 6 times less likely to develop IAs or to have a ruptured internal elastic lamina than wild-type rats at 5 months and had almost 10 times fewer macrophages infiltrates. Leukocyte invasion is fostered by the secretion of 2 potent proinflammatory cytokines, tumor necrosis factor-α and interleukin-1, that are abundantly expressed in human aneurysmal wall and that activate and increase the permeability of the endothelium. Upon transmigration in the arterial intima, some monocytes mature and acquire the phenotype of macrophages (Figure 5). These latter cells secrete proteins that modify the vascular morphology. In particular, the balance of matrix metalloproteinases and their tissue inhibitors, as well as the cathepsins and cystatin C, tightly regulates the morphology of the extracellular matrix. In aneurysmal lesions, the expression pattern of these proteins diverges from that of healthy arteries. This imbalance is likely linked to the disruption of the internal elastic lamina and thinning of the wall, which cause the loss of mechanical properties. The quasi-disappearance of the medial layer is still an unanswered question. Several plausible hypotheses, biomechanical and biochemical, were proposed, but the reality might be a combination of processes. Matrix degradation, for example, can lead to anoikis. The tumor necrosis factor-α/tumor necrosis factor-α receptor type 1–associated death domain/caspase-3, 6, 7 is a known pathway for apoptosis for endothelial cells and SMCs, relevant in our context. Alternative proposed mechanisms include the inhibition of collagen production or processing. It is noteworthy that remodeling of the wall
might begin before the trafficking of immune cells because aneurysm-prone flows may not allow firm adhesion of inflammatory cells because of the intensity of the fluid forces.

Comparison With Other Vascular Aneurysms

All vessels can become aneurysmal; therefore, deformation is part of the minimization of wall stress. The Laplace law dictates that wall stress in spherical coordinates is half of the stress in cylindrical systems, and as a result, all vessels under stress will naturally seek a new spherical set point. Therefore, the means by which aneurysms form in different vascular beds not unexpectedly share common features but also are unique. Aortic abdominal aneurysms (AAA) are common lesions of the aorta characterized by a focal increase in the diameter of the vessel exceeding half of its original size. Like IAs, they remain silent until catastrophic rupture and have a poor prognosis. AAAs were previously thought to originate from the progression of atherosclerosis, but novel hypotheses advocate distinct causes and pathogenesis. AAAs and IAs share many features, including the same risks factors and inflammation biology, but their origins, which remain under debate, may be separate. Some key histopathological traits are shared such as remodeling and degradation of the wall through imbalance of proteases and their inhibitors or the loss of medial elastin and SMCs. Both types of aneurysms may be local manifestations of a systemic condition because patients with AAA present biomechanical alterations in vessels distant from the AAA, whereas 15% to 35% of people with aneurysms have multiple ones. The canonical cocktail of inflammatory mediators and the presence of the same immune cell infiltrates also contribute to the development of both diseases. However, these similarities may only underline the universality of the mechanisms of inflammation.

Besides their similarities, important differences are noted such as the fusiform laminted AAA shape versus the quasi-spheroid IA shape. Critical questions on whether leukocyte trafficking occurs from the same vascular beds in AAAs and IAs remain unanswered at this time, and their answers would shed light on the filiation of these lesions. Does inflammation proceed through the vasa vasorum or the intima in AAAs? No clear answer has emerged for IAs, although morphological evidence supports intimal trafficking.

Inflammation Guiding Modeling

Understanding the kinetics of matrix degradation and remodeling in aneurysmal lesions can help predict IA fate. The need for innovations in simulation stems from the inability of current models to bridge the gap between physics and medicine or to help plan current intervention. The failure of current strategies arises often from decoupled analysis, which focuses...
solely on flow and lesion morphology to address a problem inherently translational. Neither flow patterns nor specific intensities of the physical parameters can be consistently associated with a state of the disease. As aneurysms evolve over years, in vivo correlations are by definition restricted to be quasi-static—only a handful of lesions are sufficiently documented throughout their life span to serve CFD analyses—whereas stabilization and catastrophic progression are dynamic processes. Thus, predictive tools should take this time dependency into account. Future directions in modeling aneurysms include integrating constitutive laws of mechanics and mechanotransduction. The introduction of fluid structure interaction is a first step that opens the possibility of gauging the maturity of the lesion, comparing patient-specific stress states with the ultimate stress of IAs and intact cerebral vascular beds. However, identifying the advancement of disease within the spectrum healthy to rupture is insufficient to estimate whether lesions will stabilize or fail catastrophically. Early stages of aneurysm expansion, for example, flow-driven phenotypic modulation of the endothelium in aneurysm-prone regions, are critical and deserve further investigation. Once remodeling of the wall begins, the loss of mechanical strength imposes ballooning out of the involved area, which coincides with a drastic reduction in WSS, eliciting a cascade of events that promote IA further. Future modeling must account for all of these effects with sufficient precision and time scale to account for the kinetics of flow alteration.

Conclusions

IAs are silent killers. Hidden from view, they remain occult before they strike, and first symptoms are often fatal. This silence has muted investigative ardor and clinical insight, and mechanistic insight lags medical significance. General aspects of vascular biology, coupled with specific elements of the cerebral circulation, can add greater insight into the nature, diagnosis, and potential intervention for these lesions. Advances in the understanding of the inflammatory cascade and vascular remodeling and improvements in mathematical modeling techniques to compute patient-specific flow open the possibility of designing new therapies individualized to specific patients. As we seek to use numeric simulation to guide clinical intervention, we will need to bridge a still-significant gap between the precision of definition of the physical parameters and the biological events. Research in the field must explain the role of inflammatory cells in the initiation and propagation of the aneurysmal wall and, most important, the coupling of these inflammatory processes with hemodynamic stress. As we define inflammation with greater precision, we can also begin to assign specific flow patterns and physical boundary conditions to aneurysms of different shapes, forms, morphologies, and positions. It is time to expand our knowledge of the effects of aneurysm-prone flow patterns on the biochemical remodeling of the wall by combining experimental techniques of vascular biology, molecular biology, and computational data.

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None.

References


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