significant parameter that has yet to be fully evaluated.² New technologies develop and evolve so as to both optimize their capabilities and expand the applications to which they may be applied. Such it was with x-rays, and such it is with CFD. New technologies are most often overvalued when first described; then, as they become disseminated, they sink below their true value, finally reaching a state of realistic value only when they have been widely tested and optimized. Potential applications of CFD have not been fully explored, optimization of computational techniques for assessing blood flow in and around IAs is ongoing, and the definition of the most meaningful output parameters are not at a stage where there can be any broad consensus. Thus, in our opinion, it is not realistic to make a value judgment regarding the ultimate value of CFDs, either as a means for investigating basic hemodynamic phenomena or as a tool that may be useful in a clinical environment.

Next Step and Closing Remarks

To us, it seems implausible to expect that, in isolation, CFD studies may reveal singular keys to important questions about a biologic process such as the initiation, growth, and rupture of IAs. It does, however, seem quite plausible that the results from CFD studies on large populations could provide great help in categorizing aneurysms according any number of hemodynamic parameters. Perhaps, then, these categories, when correlated with other factors known to be important in vascular health—such as collagen mutations, smoking, family history, and so on—and then if further combined with information specific to individual patients—such as age, sex, and perianeurysmal environment—could give insights that might prove useful in predicting the risk of aneurysm rupture. We fully realize that correlations do not represent causation; however, in our experiences, as well as in those of others, they sometimes offer very significant hints.^{3,4} As the ability to perform CFD in clinical environments on large numbers of patients increases, as more insight is gained into the regulation of arterial health (homeostasis) and remodeling, as more understanding is gained about the mechanics of the vascular wall, as the ability to image not only the vascular lumen but also the arterial wall increases, this additional information may send computational scientists back to broaden and refine their mathematic models, thereby leading to methods that would allow investigation and integration of other important and potentially clinically relevant parameters, such as collagen turnover, cross-linking, and so on (eg, fluid-structure-growth modeling).

Believing in the great potential for the integration of observations and measurements made by clinicians with simulations, calculations, and models made by scientists, we feel that this is a time to be optimistic and proactive in collaborations that unite and optimize our ability to define just what value CFD adds to the ability to mitigate the death and misery currently associated with IAs.

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EDITORIAL

Computational Fluid Dynamics in Aneurysm Research: Critical Reflections, Future Directions

Dr Kallmes’ provocative editorial “Point: CFD—Computational Fluid Dynamics or Confounding Factor Dissemination” raises a number of important questions about the status of aneurysm research.¹ It has served to initiate a public discourse between engineers and clinicians on the contributions of computational fluid dynamics (CFD) to this research field.² We would like to add to what we hope is an ongoing, informative, and productive dialogue.

The first article applying CFD to the field of aneurysm research appears to be that of Gonzalez et al in 1992.³ Despite the conclusion in this seminal article that “computer modeling can further our understanding of factors that determine the origin and progression of intracranial aneurysms,” it was more than 10 years before CFD took off as a tool for studying cerebral aneurysms. Indeed, in an advanced title search (TS) on the Web of Science for articles matching TS = (aneurysm AND [cerebral OR (cranial)]) AND TS = ([computational and fluid] OR [CFD]) came up with only 12 articles through 2004, increasing to 10 in 2006 alone, 19 in 2008, and 55 in 2011, with a total of 195 articles through 2011. In fact, the number of publications has grown nearly exponentially since 2002. Hence, it is certainly an appropriate time to step back as a community to reflect on where we are now and to consider where we would like to go.

In this Editorial, we focus on some of the questions raised by Dr Kallmes and comment on what we perceive as the most serious barriers to progress. While this complex and important subject clearly cannot be comprehensively addressed in a handful of editorials, we hope this initial dialogue will instigate a deeper analysis that will identify the most important technical limitations and highest priority avenues for future research.

Why Are There So Many Idealizations in CFD Studies?

While Dr Kallmes’ comments were directed specifically at CFD researchers, most of his questions are actually equally relevant to investigators using other tools to study aneurysms. For instance, if we ran the same hemodynamic studies in an experimental system, we would similarly need to question whether blood should be modeled as a single-phase liquid with constant viscosity, whether we have suitable inflow and out-

flow conditions, whether we have accurately reproduced the in vivo geometry, and whether we can neglect the motion of the vascular wall. In fact, these questions encumber all studies of large-artery hemodynamics, not just studies of cerebral aneurysms.⁴

Many modeling simplifications and errors arise from limitations in current clinical technology and patient treatment protocols. The reason CFD researchers use generic inflow and outflow boundary conditions is not simply because they are easier to implement but rather because patient-specific flow waveforms are generally unavailable. Model geometries are produced by using available imaging data and hence are limited by the resolution of the medical scanners. Furthermore, the relevance of lumen geometries of ruptured aneurysms may be lessened by thrombus formation or rapid changes in aneurysm geometry just before rupture. If wall motion is to be included in a study, either it is necessary to have clinical images of changes in wall position during the cardiac cycle, in which case wall motion can be prescribed,^{5,6} or the heterogeneous material properties and thicknesses of the aneurysm wall must be known, so wall motion can be predicted. This level of information is rarely available to CFD researchers.

The engineering community is aware of these shortcomings, and some effort has been made to assess the sensitivity of the hemodynamics in the aneurysm sac to parameter values for which we have limited information.^{4,7,8} A central challenge is that we have still not answered the question of which hemodynamic variables are of greatest importance in aneurysm stabilization or rupture, and hence should be the focus for sensitivity studies of this kind. For example, threshold values for time-averaged wall shear stress⁹ or the spatial wall shear stress gradient are important for wall degradation and remodeling, then sensitivity studies focused on qualitative flow features lose their relevance. Furthermore, the governing equations are highly nonlinear. Therefore, conclusions based on sensitivity studies in one geometry may be invalid for another geometry. More effort to evaluate and rank the importance of these idealizations in specific contexts, by using sophisticated mathematical tools, is clearly warranted.

Some modeling simplifications arise from technical challenges that are particular to CFD studies. For example, it is computationally taxing to model flow around individual coils packed into an aneurysm dome. Instead, the collection of coils is often idealized as a porous material.^{10,11} Validation of the CFD flow fields by using in vitro experimental models is of particular value in studies of this kind. The shear thinning viscosity of blood is largely due to the ability of erythrocytes to form a 3D microstructure that breaks down with increasing shear rates. Due to the high shear rates found in most arteries and the length of time necessary for the blood microstructure to form, it is reasonable to treat the blood viscosity as constant in most parts of the arterial system of healthy individuals.¹² If local wall shear stress and mass transport are of interest, this idealization may not be appropriate within the slow recirculating flows found in many saccular aneurysms. Modeling the formation and dissolution of these structures in aneurysms is beyond the scope of our current capabilities, though recent advances in multiphase modeling of blood are promising.¹³

Why Are There So Many Definitions for Wall Shear Stress?

Just as the velocity field within the aneurysm dome cannot be described by simply calculating a single Reynolds number, there is no single wall shear stress variable that can represent the time and space-dependent influence of blood dragging at the aneurysm wall. Rather, we need to speak of a wall shear stress “vector,” which is simply the viscous force vector per unit area of the aneurysm wall. Because the wall shear stress vector varies in both magnitude and direction across the aneurysm wall and throughout the cardiac cycle, there is no magic, unique, wall shear stress number. Indeed, even the magnitude of the wall shear stress vector, commonly referred to as WSS, is a function of time and spatial location. On the basis of earlier in vitro and in vivo studies of healthy and diseased vascular tissue, various hemodynamic parameters such as the time-averaged wall shear stress and the oscillatory shear index (OSI) were introduced in an attempt to replace this vector field with a scalar that represents chosen features. For example, the OSI attempts to quantify the changing direction of the wall shear stress vector over the cardiac cycle. When these initial choices failed to demonstrate value for predicting rupture risk, other variables were put forth. We observe the same scenario in attempts to use aneurysm sac geometry to predict rupture risk. There are similarly an unlimited number of variables that can be used to describe the aneurysm geometry. However, once the obvious choice (size) proved unsatisfactory, other choices such as aspect ratio and bottleneck factor were introduced.^{14–16}

Lack of uniformity in the definitions of physical parameters adds to the sense of unbounded indices in the literature and clouds our effort to make sense of data from diverse laboratories. This is not only true for hemodynamic parameters but also for geometric parameters. Aspect ratio and even parameters as seemingly unambiguous as aneurysm size and neck size are defined differently by various authors and sometimes even by the same author in different articles. As a community, we should try to standardize the definitions relevant to our field. At a minimum, journal editors should require authors to provide clearly stated definitions for these parameters as well as the details of their approximations in computational and experimental studies.

What Are the Main Impediments to Correlating Hemodynamics and Aneurysm Rupture?

Aneurysm rupture occurs when the tissue stress exceeds the tissue strength. Hence, it would be desirable if we could accurately determine the stress and strength distributions in an aneurysm wall for a given clinical case. However, significant challenge remains with this objective because the only information that we can reliably obtain from clinical imaging modalities is the geometry of the aneurysm (eg, it is currently not possible to obtain information on tissue composition, thickness, and structure that is required for accurate structural analyses). Conversely, CFD offers a method to use this geometric data to assess a single aspect of the biomechanical state of an aneurysm. However, while rigid-walled CFD analyses provide an estimate of the intrasaccular hemodynamics, an inherent limitation is that they provide no information about stresses within the aneurysm wall.

Our lack of understanding of the mechanobiology of the wall under prolonged pathologic hemodynamic loading found in the aneurysm dome is perhaps the most important impediment to our effort to use hemodynamics to predict aneurysm rupture. In this regard, we emphasize that an implicit underlying assumption in all CFD studies attempting to link wall shear stress variables to aneurysm rupture is that the vascular cells responsible for sensing the hemodynamic loads exist within the aneurysm sac. However, this assumption is often invalid—that is, the endothelial lining was found to be absent in 50% of the fundi resected after microsurgical clipping from 66 human aneurysms.¹⁷ While in the absence of these cells, the intra-aneurysmal flow may continue to impact factors such as thrombus formation and mass transport to and from the wall, the role of hemodynamics on the mechanobiology of the arterial wall will clearly be altered; thus, the wall shear stress will no longer play the same role. Second, even when endothelial cells are present, given that they are in a continual state of turnover, it is important to understand whether they are pre-programmed with a homeostatic level of WSS or if they learn this information from their local mechanical environment. The fact that aneurysms can remain stable in size for a decade or more¹⁸ is suggestive of the latter or at least that a direct relationship between the hemodynamic environment and aneurysm enlargement/rupture may not always exist.

How Has CFD Contributed to Our Assessment of Cerebral Aneurysms?

As clearly discussed by Cebal and Meng,² while modeling of any kind is inherently an idealization of the full complex system, it provides a tool for exploring hypotheses and potentially reducing the number of variables and enabling the ranking of modeling limitations. CFD research on cerebral aneurysms has provided us with tremendous insights regarding the variability of flow within the aneurysm dome and has illustrated some of the challenges and complexities we face in attempting to further our understanding of the relationship between flow and aneurysm inception, enlargement, and wall rupture. Furthermore, at this point in time, CFD provides the best tool for estimating the in vivo wall shear stress vector in human aneurysms as well as in animal models of saccular aneurysms.^{19–21} Localized results of this kind are essential for evaluating the influence of local hemodynamics on the structure and biologic content of the aneurysm wall.

Future Directions

We agree with the authors of the previous editorials^{1,2} that a more comprehensive approach to assessing rupture potential is needed. However, we would argue that it is not sufficient to merely increase our data bases of intrasaccular flow fields and enlist statisticians to make sense of the results. We need to recognize that the role of the hemodynamics will change at different stages of this disease and hence there is a pressing need to obtain additional data from resected tissue, animal models, and clinical studies of aneurysm growth with time.

We cannot emphasize strongly enough that the hemodynamics of the arterial wall and the biology of the arterial wall are not mutually exclusive: Aneurysm rupture is likely governed by the mechanobiology of the aneurysm wall—that is, the interaction of the mechanics with the biology. Moreover,

wall shear stress is not the only mechanical stimulus at work that influences the mechanobiology of the arterial wall. Cyclic stretching affects the functionality and structural arrangement of endothelial,²² vascular smooth muscle,²³ and fibroblast cells.²⁴ Clearly, in aneurysm walls that are hypocellular,¹⁷ the process of collagen turnover in the wall will be altered. This in turn will alter the mechanical stiffness of the wall and hence the cyclic stretch experienced by the tissue. The impact of these effects on the mechanobiology of the wall and thus aneurysm evolution remains an open question. Novel Fluid-Solid-Growth models of cerebral aneurysm evolution,^{25,26} which combine fluid and solid mechanics analyses of the vascular wall with descriptions of the kinetics of biologic growth and remodeling, provide a more general framework to explore aneurysm evolution and test hypotheses related to aneurysm inception, enlargement, stabilization, and rupture.

Additionally, there is a need to be more resourceful and creative in our use of clinical data—for example, combining data from multiple imaging modalities to improve the accuracy of segmented aneurysm geometry. The recent application of methods of data assimilation to computational hemodynamics provides a promising approach for improving the reliability and accuracy of CFD studies using clinical data.⁵

Dr Kallmes has raised timely and important questions for the field and has begun a beneficial and much needed exchange between clinicians and engineers. There is an irrefutable need to continue this frank dialogue in other forums, such as special sessions in conferences.²⁷ Such dialogues provide an opportunity for self-assessment as well as an opportunity to lay out plans for the community to work together. We would put the responsibility on all of us, not just CFD researchers, to “do more work to close the gaps in information and address the conflicting information and confounding variables.”¹

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EDITORIAL

Back to the Tower of Babel: Comparing Outcomes from Aneurysm Trials

Most therapies within the field of interventional neuroradiology have a lack of robust evidence. While several schemas describing the various tiers of “evidence” exist, most reserve the term “level 1 evidence” for that obtained in the context of randomized controlled trials (RCTs). Some scales

reserve level 1 for therapies vetted in multiple RCTs and then subjected to formal meta-analysis.

During the past several years, numerous RCTs have been performed comparing bare platinum coils with “modified coils,” including the HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS),¹ the Cerecyte Coil Trial (CCT),^{2–4} and the Matrix and Platinum Science (MAPS) trial.⁵ These relatively large studies with clearly defined, prospective end points would seem perfectly aligned to provide our field with this latter type of level 1 evidence, especially if pooled data were analyzed in a formal meta-analysis. Alas, the design and reporting of these studies likely will render it difficult or impossible to carry out such an analysis.

Questioning the Research Questions

Each of the 3 modified coil RCTs mentioned above compared the efficacy of new technologies (modified coils) with a similar control group (bare platinum coils) in the treatment of the same disease (ruptured and unruptured intracranial aneurysms). The most relevant question to be answered in these well-conducted RCTs is “What were the primary outcomes of the trials and were there any differences in outcomes between the treatment and control groups?” When examining the results of CCT, HELPS, and MAPS, we would expect that the primary outcomes of the studies were the same or at least similar. Disappointingly, however, this was not the case (Table).

In HELPS,¹ the primary outcome was composite in nature, meaning that either one or another outcome would define success or failure. The first portion of this composite end point was defined as a “major angiographic recurrence” at 18 months. This recurrence was considered as an aneurysm that could “theoretically” be re-treated. The second portion of this composite end point was related to deaths and morbidity that resulted in failure to obtain follow-up. Major angiographic recurrence did not necessarily mean that an aneurysm was re-treated; indeed, actual re-treatment rates were approximately one-tenth of the “theoretically re-treatable” rates in both groups. In HELPS, the primary outcome rate was met in 36% in the control group and 29% in the modified coil group ($P = .13$). The rate of procedure-related morbidity and mortality resulting in no angiographic follow-up between the 2 groups was minimal and nonsignificant between both groups; and as such, the imaging findings represented the major driver of outcomes. The rate of “major angiographic recurrence” was slightly lower in the HydroCoil group than the control group, 24% versus 34%, respectively ($P = .049$). Overall, the re-treatment rate for both groups was 3% with no statistical significance. Notably, HELPS did demonstrate a difference in composite outcome for ruptured intracranial aneurysms treated with HydroCoil over bare platinum coils.

In MAPS,⁵ the primary end point was “target aneurysm recurrence” (TAR) at 12 months. This composite outcome was target aneurysm re-intervention rates, aneurysm re-bleeding, or death from unknown cause. Outcomes for the primary end point were similar between groups (14.6% for control, 13.3% for treatment). The re-intervention rate for both groups was approximately 10%, and rupture and death rates were similarly very low. Angiographic occlusion rates, a