Counterpoint: Realizing the Clinical Utility of Computational Fluid Dynamics ––Closing the Gap

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EDITORIAL

Counterpoint: Realizing the Clinical Utility of Computational Fluid Dynamics—Closing the Gap

With great interest, we read the stimulating editorial by Dr Kallmes, who raises important questions regarding the potential utility of computational fluid dynamics (CFD) in guiding neurointerventional and neurosurgical treatment of cerebral aneurysms. We believe that Dr Kallmes' opinion is representative of that of most avant-garde clinicians who have collaborated with computational scientists or engineering researchers. These clinicians not only appreciate the aesthetic and intuitive aspects of CFD simulations but also recognize their enormous potential for providing objective, quantitative, and mechanism-based parameters to stratify aneurysm rupture risk and help aneurysm management. Recently clinical journals such as the *American Journal of Neuroradiology* have seen an increasing number of articles about CFD. It is sobering to reflect on where we are and where we should be heading.

Dr Kallmes' main points are the following: 1) CFD involves assumptions that might make results questionable; 2) a large number of hemodynamic parameters have surfaced in recent publications, which are confusing and confounding; 3) to change the current situation of isolated groups working on a small number of cases, cross-disciplinary collaboration on a large amount of clinical data is required to realize the clinical utility of CFD; and 4) CFD researchers need to close the gaps in information and address the conflicting information and confounding variables. These are excellent points (despite a few minor misconceptions), with which we emphatically agree.

We wish to express our thoughts in response to Dr Kallmes' points. CFD holds great promise for revealing aneurysm pathophysiology and for becoming a tool that the neurointerventionalists could expect to use routinely someday to assess patients' aneurysm rupture risk and to guide treatment. However, an aneurysm is a complex problem. To make CFD work for clinical practice, computational scientists/engineers and clinicians have to work much closer together. We are fully on board with Dr Kallmes in his call for multidisciplinary collaboration to build a large clinical data base for CFD and to realize its clinical utility.

How Much Detail Should Clinicians Know about CFD and Its Assumptions?

Dr Kallmes raises an important question about whether clinicians need to know the details of CFD computations. We are of the opinion that though clinicians do not need to understand all the details of how CFD calculations are performed, just as they do not know all the details about the medical imaging equipment they use, it is very important that they at least understand the approximations, assumptions, and limitations of these techniques, just as they do with medical imaging systems.

Dr Kallmes mentions some typical approximations made in most CFD studies, apparently implying that because of these, the CFD methodology is inaccurate and unreliable. CFD has played an indispensible role in almost every aspect of technology that we enjoy in modern life, including aircraft design, food processing, and weather forecasting. Its technology is sound and its efficiency is increasing. To make the computational problem tractable, approximations and assumptions are inevitable. In fact, approximation is the way of modeling, whether it is numeric or physical. Some of these mentioned assumptions and approximations are not exclusive to CFD modeling. For instance, experimental in vitro flow models have similar limitations regarding flow conditions and geometry reconstruction, while animal models and in vivo flow measurements introduce a whole universe of other assumptions and limitations.

The decision of whether to accept certain approximations and simplifications is a trade-off between accuracy and cost and sometimes feasibility. What is important in our opinion is to understand the effects of these approximations and to understand what to expect from the computational, experimental, or animal models. These effects can be and some have been studied through sensitivity analyses to understand their relative importance. For instance, vascular wall motion can be considered a second-order effect compared with the variability of the physiologic flow conditions.[1] Computational models are particularly well-suited to perform this kind of analysis because they allow us to explore the effect of different factors independently.

Why There Are a Large Number of Parameters Published

Dr Kallmes expressed his concern over the growing number of hemodynamic factors being proposed as potential indicators of aneurysm rupture risk, leading him to wonder if CFD is "confounding factor dissemination." We understand that this situation is frustrating for clinicians, who, being initially excited by CFD as the aesthetically pleasing "color for doctors," are led to hope that this powerful simulation tool will soon help save patients' lives.

We think that the growing number of proposed parameters principally stems from the complexity of aneurysm rupture mechanisms and the scarce knowledge we have about them. Furthermore, the growing number of proposed parameters and conflicting results indicate that we are still in an exploration phase. Some divergence during this phase in the search for understand-

ing of a complex problem is not only unavoidable but also healthy. The list of proposed parameters is also growing because CFD comes in handy to test hypotheses (to some extent, because CFD can only reveal correlation, not causation).

The complex nature of the interaction of hemodynamics and aneurysm progression and rupture is highlighted by apparently conflicting associations of what Dr Kallmes has dubbed the "bad actor," the wall shear stress (WSS), which is the frictional force of blood that could drive vascular remodeling via endothelial cell sensing. It is the most commonly explored potential hemodynamic marker of increased rupture risk. However, there have been CFD studies that found high and concentrated WSS being associated with rupture, exemplified by 1 of the authors (Cebral),[2,3] whereas other studies found low WSS being associated with rupture, exemplified by the work of another author (Meng).[4] Which one is correct? We think both could be correct because of the heterogeneity of aneurysms and possible mechanistic pathways. The high WSS pathway could be working through a destructive remodeling process akin to aneurysm initiation[5] in aneurysms in which an inflow jet impinges at the aneurysm wall, while the low WSS pathway could be mediated by inflammation facilitated by sluggish flow in large and complex-shaped aneurysms. Without being tested by large studies, such issues will remain unsettled.

CFD researchers have explored different variations of WSS definition, motivated by different hypotheses about the hemodynamic conditions driving the progression of cerebral aneurysms toward rupture. For example, time-averaged WSS reflects the common hypothesis that long-term exposure to abnormal WSS predisposes the wall to weakening and rupture. Oscillatory shear index reflects the hypothesis that directional variations of shear stress on endothelial cells during the cardiac cycle could induce a pathologic response (as shown in atherogenesis). Ideally, such hypotheses should be tested on animal models.

However, there are no experimental models that provide the whole natural history of aneurysms including rupture; the only animal model that allows exploration of the relationship between hemodynamic stresses and aneurysm pathophysiology is the aneurysm-initiation model in the rabbit basilar terminus.[5,6] CFD offers an excellent alternative for testing hypotheses statistically by correlating hemodynamic variables and aneurysm rupture by using clinical data. Correlation does not imply causation, but different causative mechanisms lead to different correlations that can be tested by combining hemodynamic models (computational or not) and clinical data.

Many studies have also related geometric characteristics of aneurysms to rupture (see for example the work of Raghavan et al.[7]) As with the CFD variables, many geometric measures have been proposed such as size, aspect ratio, size ratio, undulation index, nonsphericity index, and volume-to-ostium ratio. Each variable definition has been motivated by the attempt to capture a particular geometric characteristic that is thought to be associated to higher aneurysm risk. The distinctive aspect of CFD-based research is that CFD allow us to formulate mechanistic hypotheses about the process of aneurysm evolution and test them with clinical data.

How to Close the Gap

The current problem is that different CFD researchers are working on small numbers of cases that are inherently skewed. The numbers of cases reported in CFD-based studies have increased from approximately 20 per study in 2004[8] to approximately 210 in 2011.[3] Although these numbers are quite large from the computational modeling side, they are still too small to yield strong statistical results. Furthermore, these studies are based on single-center single-population data, which make the results not entirely objective and generalizable. In these points, we are in complete agreement with Dr Kallmes.

It is frustrating not only to Dr Kallmes but also to us that new hemodynamic parameters for rupture that have been examined in a few isolated aneurysms continue to show up in publications. Understanding this occurrence requires an appreciation of what excites the engineering researchers. It is natural for us, the researchers, to explore different facets and depths of a problem and to come up with new ideas and new tools and to be rewarded intellectually (including publications), but we must remember our responsibility of providing clinically pertinent information that will help improve clinical practice and health care. Therefore, the candidate parameters postulated to predict rupture must be followed up with testing based on large data bases.

We fully agree that we need to close the gaps in information and address the conflicting information and confounding variables. We believe, and here we are again in agreement with Dr Kallmes, that the current confusion and sometimes apparently inconsistent results can be resolved by conducting studies based on large multicenter and multipopulation data by using a unified and standardized modeling approach and definitions of variables to obtain strong and objective statistical results. Furthermore, multivariate statistical analyses such as the one by Xiang et al,[4] can help us identify the set of variables that best explains aneurysm rupture in a statistical sense. This strategy can also help us understand possible inter-relationships between different variables that may be associated with different underlying mechanisms and distill the best predictors of rupture.

To help make this happen, we need to facilitate the clinical use of computational tools by making them more user-friendly, streamlined, and efficient. The availability of such tools that combine medical imaging and computational modeling would not only accelerate the rate of building large databases but also enable clinicians to gain first-hand experience with hemodynamics modeling, develop intuition from the rich quantitative and visualization data, and provide sorely needed constructive feedback and guidance to researchers. These tools could eventually evolve, leading to incorporation of solid knowledge about conditions that predict aneurysm rupture into a quantitative rupture-risk-assessment system integrated into clinical workflow. Meanwhile, we believe much can be learned from ongoing but well-guided computational experiments based on CFD models.

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