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LETTERS TO THE EDITOR

The missing piece to solve the equation

TO THE EDITOR: We read with great pleasure the article by Berg et al.[1] (Berg P, Saalfeld S, Voß S, et al: A review on the reliability of hemodynamic modeling in intracranial aneurysms: why computational fluid dynamics alone cannot solve the equation. *Neurosurg Focus 47(1):*E15, July 2019). The authors provided a review of the main findings of computational fluid dynamics (CFD) simulations of intracranial aneurysms. Their work reviews state-of-the-art techniques to obtain credible hemodynamic predictions in the pathophysiology of cerebral aneurysms.

In the last few years, the field of hemodynamics has been bolstered by formidable research. Flow dynamics represents a key to understanding how vascular disease progresses. Thus, the CFD approach has come to be applied to neurovascular research.

Nevertheless, there is no universal consensus on which variables are most important in this area. For these reasons, Berg and colleagues decided to review the principal steps of the CFD techniques used to ascertain the hemodynamic predictors of intracranial aneurysmal disease. To this end, they divided the phases of this procedure into 3 stages: presimulation, simulation, and postsimulation. The importance of this article is underscored by the fact that, in each section, Berg et al. compared and contrasted the best studies in the literature and came up with recommendations for future studies that will employ CFD techniques.[1]

When they discuss how to conceptualize arterial vessel walls in the simulation phase, they offer some interesting considerations. Cebral and collaborators have suggested that the assumption that vessel walls are rigid is imprecise because the motion of an aneurysm can be visualized.[2] Additionally, Ghodsi et al. have encouraged the investigation of additional vessel wall data to better understand fluid-structure interactions, such as wall thickness or material model.[3] Moreover, Voß and colleagues indicate that considering wall thickness as a constant factor may be erroneous.[6] For these reasons, Berg and colleagues affirm that assuming vessel walls are nonrigid is only meaningful when precise wall data (e.g., local thickness, strength) are available.[1]

In addition, Berg and colleagues promote a systematic recommendation for the use of CFD techniques and underscore the value of an interdisciplinary collaboration among disciplines, such as morphometry, biomechanics, and histology.[1]

Here, regarding the promotion of interdisciplinary partnership, it is our pleasure to share with the scientific community our experience with the multidisciplinary nature of our research projects.

In 2017, our Neurosurgical Department began a collaboration with the Bio/NanoMechanics for the Medical Sciences Laboratory and the Engineering Department at the University of Palermo. Our work group endeavored to analyze ex vivo a range of cerebral arterial walls to speculate what happens when a mechanical force is applied to the intracranial arterial walls and investigate the relationship between flow dynamics and biomechanical wall responses.

Thus far, we have collected and tested 5 porcine cerebral arteries that were subjected to a displacement-controlled test using the T150 Nanotensile UTM (universal testing machine) from Agilent (Fig. 1).

We tested the engineering stress (σ)/engineering strain (ε) ratio. The σ/ε ratio represents a coefficient of proportionality described as Young's elastic modulus (or tensile modulus), which is a measure of the stiffness of an elastic material used to predict the elongation (or compression) of an object if stress were applied to it. Through the application of a longitudinal force, our biomechanical testing has shown that cerebral arteries do not have a constant Young's modulus; indeed, the data suggest a clear hyperelastic behavior, characterized by an increasing stiffness in response to the level of strain. Experimental data have been further reproduced by means of two hyperelastic mechanical models, namely the Yeoh model and the Fung model, in which the behavior of the tested basilar arteries has been well described.

In consideration of these results, we think that the role of the aneurysm wall's response during the application of force should not be considered irrelevant and pointless. Moreover, we recognize the validity of the role of the aneurysm wall's response thanks to a great number of experimental tests, in order to value biomechanical simulations.

Additionally, Parshin et al. have performed experiments to measure the wall stiffness of 3 aneurysms and assessed the mechanical properties of the tissue specimens.[5]

Our ongoing research will extend the experimental data obtained to produce accurate models. A force acting

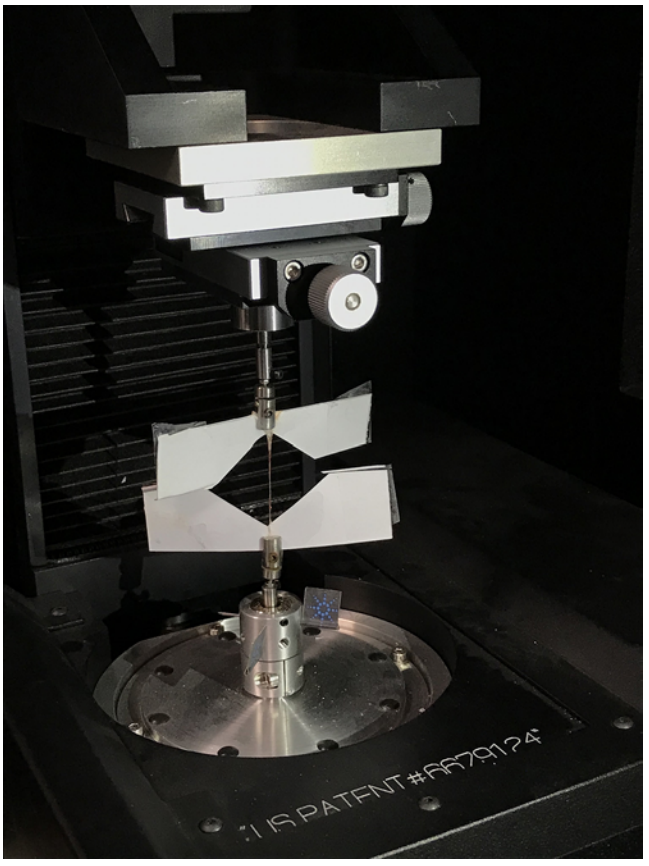

FIG. 1. Photograph of the T150 Nanotensile UTM, a universal testing machine from Agilent. The sample is placed on a standard template in order to facilitate the sample's positioning on the machine grips. All testing that we performed was done inside an isolated cabinet on an antivibration table.

on the entire circumference should be tested, and dynamic simulations of the in vivo aneurysmal environment should be performed. In fact, we are also beginning a new collaboration with the Department of Forensic Medicine at the University of Palermo, collecting human intracranial arteries in order to expand our studies of human vessels.

The CFD simulations have gone too far to predict the effects of endovascular embolization on the intraaneurysmal environment. Endovascular treatment determines intraaneurysmal biorheological blood changes, and this cannot be ignored.[4,7] In their CFD simulation analysis Berg et al. made the following recommendation: "As shear rates in the circle of Willis are high enough to avoid agglomeration effects, the assumption of blood as a Newtonian fluid is acceptable." Nevertheless, the rheological properties of blood cell deformation can result in considerable biomechanical changes; blood clots that form inside the aneurysm are composed of viscous-elastic materials that are less deformable than blood itself but can still be deformed under intrasaccular flow stress. It would seem, in the interest of a comprehensive analysis of a patient-specific aneurysm environment, that blood clots in CFD simulations should not be approximated as solid structures. Further studies should be encouraged in order to explore this interesting field.

There is no question about the crucial role that CFD plays in the study of cerebral aneurysm disease, but none of the biological interactions can be left to chance if we want to solve the equation and identify a real aneurysm-related scenario in order to select the most appropriate and safe treatment option that will produce optimal patient-specific long-term benefits.

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Disclosures

The authors report no conflict of interest.

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Response

We are grateful for the letter by Brunasso and colleagues and appreciate the exchange of experiences.

On the Role of Intracranial Aneurysm Walls

The presentation of intracranial aneurysms is extremely heterogeneous, ranging from thin-walled, translucent an-

eurysms to aneurysms with a thick, atherosclerotic wall.[6] Several studies have tried to classify aneurysms by measuring their mechanical properties and wall thicknesses.[8] Furthermore, the structures of the aneurysm dome and the parent vessel have been examined in vivo using extravascular optical coherence tomography (OCT).[4]

Nevertheless, reasonable doubts exist as to whether we can identify generalizable material properties and wall thickness models that are capable of accounting for individual representations. Fluid-structure-interaction simulations are technically feasible, even without individual parameters, but the added value is questionable until now. Additionally, they might imply an increased accuracy of the computational results, which is not ensured by the underlying models.

In order to better understand the mechanisms of aneurysm formation and rupture, animal aneurysm models have been proposed.[9] However, we emphasize the importance of *human* aneurysm specimen.[10] Furthermore, we think that additional research is needed regarding patient-specific intravascular vessel wall imaging, and Gounis et al.[3] have highlighted the capabilities of neurovascular OCT. Additionally, knowledge about the diseased aneurysm wall is increasingly gained via tissue extraction and extensive histological analysis. The recent review by Frösen et al.[2] illustrated models available for flow-induced aneurysm formation, inflammation-mediated growth, and remodeling. Finally, the major task will be the fusion of recent techniques used in large patient cohorts that will enable substantial and statically sound conclusions. Here, Cebral et al.[1] are pioneers, as they combined neurosurgery, image-based blood flow simulations, and histological evaluation.

On the Role of Intraaneurysmal Blood Rheology

Because properties such as shear thinning, yield stress, viscoelasticity, and thixotropy are individually pronounced, they complicate the model formulation and related parameter assessment. Regarding CFD, either a Newtonian flow is assumed (due to high strain rates), or non-Newtonian models with partly generalized model parameters are applied. However, recent findings indicate that rheology has second-order effects when compared to patient-specific lumen and flow conditions.[5]

When it comes to the modeling of clot and thrombus formation, purely CFD-based methods become inadequate, and coupling with biochemical reactions is required.[7] One must keep in mind that (clinically applicable) image-based blood flow simulations are macroscopic approaches following the assumptions of mass and continuity conservation. Hence, conceptual limitations with respect to spatial and temporal resolution exist, hampering the exact description of blood and associated pathological phenomena.

Therefore, the application of a mesoscopic modeling (e.g., based on the Lattice Boltzmann method) in combination with an improved parameter individualization could be beneficial in future investigations.

In summary, we believe that patient-specific knowledge about aneurysm walls is not *the* missing piece but rather *a* missing piece to solve the equation. We are convinced that only the intelligent combination of fluid dynamics, structural mechanics, and biological markers can draw a complete picture of the individual state. Hence, we encourage active collaboration among experienced research groups so that their knowledge can be merged and we can move toward an improved understanding of this complex and severe neurovascular disease.

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