Neurosurgical Forum 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. Cerebral 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.

Lara Brunasso, MD

Enrico Lo Bue, MD

AOUP "Paolo Giaccone," Palermo, Italy

Massimiliano Zingales, PhD

ATeN-Center, University of Palermo, Palermo, Italy

Domenico G. Iacopino, MD, PhD

Francesca Graziano, MD, PhD

AOUP "Paolo Giaccone," Palermo, Italy

References

1. Berg P, Saalfeld S, Voß S, Beuing O, Janiga G: 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, 2019
2. Cebal JR, Detmer F, Chung BJ, Choque-Velasquez J, Rezai B, Lehto H, et al: Local hemodynamic conditions associated with focal changes in the intracranial aneurysm wall. **AJNR Am J Neuroradiol** 40:510–516, 2019
3. Ghodsi SR, Esfahanian V, Ghodsi SM: Modeling requirements for computer simulation of cerebral aneurysm. **J Comput Med** 2014:653845, 2014
4. Graziano F, Russo VM, Wang W, Khismatullin D, Ulm AJ: 3D computational fluid dynamics of a treated vertebrobasilar giant aneurysm: a multistage analysis. **AJNR Am J Neuroradiol** 34:1387–1394, 2013
5. Parshin DV, Kuianova IO, Yunoshev AS, Ovsyannikov KS, Dubovov AV: On the mechanics of cerebral aneurysms: experimental research and numerical simulation. **J Phys Conf Ser** 894:012071, 2017
6. Voß S, Glaßer S, Hoffmann T, Beuing O, Weigand S, Jachau K, et al: Fluid-structure simulations of a ruptured intracranial aneurysm: constant versus patient-specific wall thickness. **Comput Math Methods Med** 2016:9854539, 2016
7. Wang W, Graziano F, Russo V, Ulm AJ, De Kee D, Khismatullin DB: Giant intracranial aneurysm embolization with a yield stress fluid material: insights from CFD analysis. **Biorheology** 50:99–114, 2013

Disclosures

The authors report no conflict of interest.

Correspondence

Francesca Graziano: francesca.graziano03@unipa.it.

INCLUDE WHEN CITING

DOI: 10.3171/2019.9.FOCUS19573.

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, Cebal 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.

Philipp Berg, PhD

Sylvia Saalfeld, PhD

Samuel Voß, MSc

University of Magdeburg, Germany

Oliver Beuing, MD

Belal Neyazi, MD

University Hospital Magdeburg, Germany

Leonid Goubergrits, PhD

Charité–Universitätsmedizin Berlin, Germany

Gábor Janiga, PhD

University of Magdeburg, Germany

References

1. Cebal JR, Detmer F, Chung BJ, Choque-Velasquez J, Rezaei B, Lehto H, et al: Local hemodynamic conditions associated with focal changes in the intracranial aneurysm wall. **AJNR Am J Neuroradiol** **40**:510–516, 2019
2. Frösen J, Cebal J, Robertson AM, Aoki T: Flow-induced, inflammation-mediated arterial wall remodeling in the formation and progression of intracranial aneurysms. **Neurosurg Focus** **47**(1):E21, 2019
3. Gounis MJ, Ughi GJ, Marosfoi M, Lopes DK, Fiorella D, Bezerra HG, et al: Intravascular optical coherence tomography for neurointerventional surgery. **Stroke** **50**:218–223, 2019
4. Hartmann K, Stein KP, Neyazi B, Sandalcioğlu IE: Aneurysm architecture: first in vivo imaging of human cerebral aneurysms with extravascular optical coherence tomography. **Cerebrovasc Dis** **48**:26–31, 2019
5. Khan MO, Steinman DA, Valen-Sendstad K: Non-Newtonian versus numerical rheology: practical impact of shear-thinning on the prediction of stable and unstable flows in intracranial aneurysms. **Int J Numer Method Biomed Eng** **33**:e2836, 2017
6. Meng H, Tutino VM, Xiang J, Siddiqui A: High WSS or low WSS? Complex interactions of hemodynamics with intracranial aneurysm initiation, growth, and rupture: toward a unifying hypothesis. **AJNR Am J Neuroradiol** **35**:1254–1262, 2014
7. Ngoepe MN, Frangi AF, Byrne JV, Ventikos Y: Thrombosis in cerebral aneurysms and the computational modeling thereof: a review. **Front Physiol** **9**:306, 2018
8. Robertson AM, Duan X, Aziz KM, Hill MR, Watkins SC, Cebal JR: Diversity in the strength and structure of unruptured cerebral aneurysms. **Ann Biomed Eng** **43**:1502–1515, 2015
9. Thompson JW, Elwardany O, McCarthy DJ, Sheinberg DL, Alvarez CM, Nada A, et al: In vivo cerebral aneurysm models. **Neurosurg Focus** **47**(1):E20, 2019
10. Weigand S, Saalfeld S, Hoffmann T, Eppler E, Kalinski T, Jachau K, et al: Suitability of intravascular imaging for assessment of cerebrovascular diseases. **Neuroradiology** **61**:1093–1101, 2019

INCLUDE WHEN CITING

DOI: 10.3171/2019.10.FOCUS19743.

©AANS 2020, except where prohibited by US copyright law