AJNR

Reply:

C.M. Putman, P. Lylyk and J. Cebral

AJNR Am J Neuroradiol 2011, 32 (5) E98-E100
doi: https://doi.org/10.3174/ajnr.A2560
http://www.ajnr.org/content/32/5/E98

Reply:

We appreciate the opportunity to respond to criticisms of our article in the letter to the editor by Fiorella et al. The comments by Fiorella et al are emphatically presented, full of misrepresentations, and dismissive of our work. We find them insulting and offensive in their tone and attack on our scientific integrity. However, there are several interesting points raised by Fiorella et al that would benefit from discussion.

Fiorella et al are dismissive of computational fluid dynamics (CFD) approaches as complex mathematic constructs that are fantasies without connection to the real world. This opinion may be based on a misunderstanding of how our group used the method and our motivation in using the tool.

CFD is a method of designing scientific experiments in a controlled, safe, efficient, and cost-effective manner. Our study of the current group is not an attempt to perfectly reproduce the exact conditions of each of the patients presented but, in a scientific controlled manner, to explore the relationships among physical parameters. We are interested in the physiologic effects of placement of a flow diverter (FD) in these systems. Our approach is to use CFD to identify hypotheses that can be tested and confirmed with clinical data. If we have confused Fiorella et al or the reader on this, we are concerned and wish to make it perfectly clear that we have consistently advised care in generalizing our conclusions to patient care without further investigation. If the goal of Fiorella et al is to reinforce this notion, we completely agree.

In this long rambling attack, Fiorella et al caution the reader that our calculations must not be correct because the results do not conform to their experience. We firmly believe the calculations are correct for the conditions imposed in this series of experiments. The solver used for this work has been extensively validated in studies comparing with physiologic and imaging data and against commercially available solvers in both medical and nonmedical applications.[1-8] The solver and our CFD method have been specifically validated against in vitro data for pressure drops in arterial stenoses.[9] We are confident that the mathematic calculations are correct (we can provide the geometries necessary if others wish to perform their own simulations). They have been rechecked and tested in multiple simulations on these specific geometries. In addition, we have done extensive sensitivity analysis to evaluate the impact of changes of input assumptions on our method.[10-14]

However stated, Fiorella et al are correct in pointing out that the actual values presented are not accurate "measurements" of the values that could have been measured in these individual patients (if that was or could have been done). As stated above, Fiorella et al misunderstand the purpose of this series of experiments. To obtain accurate values, we would need the actual flow conditions in each patient. In that situation, we would not be doing a controlled experiment for this study group for the input and output flow conditions. In this study, we were controlling for everything other than geometry and the placement of an FD. For those conditions, we stand by the relationships we have identified and have proposed a possible mechanism for delayed rupture. Whether this is proved or not is up to further work by anyone interested.

As we stated in our article, there are always limitations to CFD modeling due to incomplete data on which assumptions are made. We have no direct physiologic measurements, so we used estimations that we think are representative of the physiologic range. Different input and output assumptions will yield significant changes in the magnitude of pressure drops but will not change the relationships between them. Our conclusions are based on the potential increase in intra-aneurysmal pressure in these specific situations, but the absolute values are very dependent on the exact flow rates in the treated arteries. Our estimated flow rates are based on data provided in the literature referenced in our article and yield pressure increases that we found only in the aneurysms that had delayed rupture. This observation leads us to recommend further study of this potential mechanism. We now advise the reader not to dismiss our work due to the criticisms of Fiorella et al.

However, what would a fair review of our data say about the assumptions made in these experiments? Fiorella et al asserted that our baseline pressures are "incorrect" and point out a conflict with "in/ex vivo" experimental data. Careful analysis of our data will show that the pressures are only in conflict in the analyses done on those patients with delayed rupture. The 4 cases successfully treated have pressure drops very similar to the 4–5 mm Hg drops championed by Fiorella et al. The calculations, geometric methods, assumptions, input, and outflow assumptions were appropriately held constant through the study group. If we had available patient-specific physiologic data, we agree that this could be applied to the simulations to improve the accuracy of the absolute values of the pressure changes. We had neither these data nor, for that matter, "dynamic angiographic data," as implied by Fiorella et al, to refine our assumptions and/or validate our predictions. As we clearly stated, we chose to hold flow conditions constant.

So what is different between the 2 groups and the most important determinant of blood flow in these studies? It is the patient-specific geometry. The studies referenced by Fiorella et al are of arteries with simpler geometries (less irregularity, no aneurysms, stenoses, or extreme tortuosity, and so forth), so they are not readily comparable with the cases we studied. Furthermore, as should be well known to Fiorella et al, Poiseuille's Law can cause significant inaccuracies in complex anatomies and flow conditions, which is why the Navier-Stokes equations must be solved for situations as complex as we are studying. This is precisely what we are reporting, and we have clearly defined the conditions we used.

So, Fiorella et al are dismissing our calculations because they fall outside of their experience. Perhaps, no one should be surprised. We are presenting work that is outside of everyone's common experience. Coupling a cerebral aneurysm to vascular stenoses, complex tapering, and tortuous arteries has not been reported for these types of situations. In addition, cases that have a history of delayed hemorrhage following FD treatment are extremely uncommon. We are the first to report such an analysis. Perhaps, we should be surprised! Using "common sense" when considering possible failures related to an FD device, one would naturally consider abnormal and potentially negative changes to the hemodynamic environment that could be caused by affecting the flow in these patients with aneurysms. Logically, an unplanned elevation of the intra-aneurysmal pressure by the treatment came to mind. Somewhat surprising, to our knowledge, no data or discussions on this issue from those promoting this technology have been reported. Fiorella et al and other participants in the FD technology have not produced any experimental or computational data to alleviate this concern. We look forward to the release of this information for an appropriate peer review.

As correctly pointed out by Fiorella et al and discussed in the article, we did not model the distensibility of the artery. We do not agree (and for that matter never stated) "that using rigid walls can result in unrealistic pressure gradients across the domain." In fact, we only noted that there is an influence on pressure gradients, and we do

not agree with the characterization of the production of an unrealistic gradient. Fiorella et al did not calculate the expected impact of this assumption, roughly an overestimation of approximately 10% (estimated by considering the geometric change due to distensibility in a Poiseuille flow). They also did not comment on the implications of implanting an FD on the parent artery and aneurysmal compliance as well as the possibility that these diseased arteries may be stiffer. Common sense would suggest that these effects could make the rigid wall approximation even more realistic. This issue probably disserves further study. Again, in our opinion, neither of these will be large enough to alter our conclusions.

Fiorella et al have made a ridiculous but serious charge that we have twisted the data to "conform" to our preconceived assumption. We are quite insulted by this accusation and strongly confirm that this is absolutely false. We have no vested interest in promoting or attacking this technology. Our interest has been entirely related to advancing the understanding of the pathophysiology of cerebral aneurysm disease by the medical communities. Our interests are entirely misrepresented by the statements of Fiorella et al. The misguided comment of Fiorella et al may relate to an incomplete understanding of the handling of patient 2. Their charge that we have selectively applied certain assumptions to the treatment failure cases is objectively false. As stated above, assumptions have been held constant for all cases, and these data are reported. We did explore changing the hemodynamic conditions (and disclosed the reasoning for this) in patient 2. Both results were reported.

Perhaps one could erroneously come to the conclusion that we purposefully created an unrealistic condition to invoke a pressure increase if one fails to faithfully read and understand our article. If our reasoning is not clear, we again apologize. We reported the results with and without the assumption of "autoregulation" so that the reader can understand the context in which we see a possible clinical concern. We observed an increase in vascular resistance through the parent artery following placement of the FD, implying a reduction in overall parent artery blood flow. As we have reported, no increase in the intra-aneurysmal pressure was observed in our result. We agree that this aneurysm does not share the features we identified in the other 2 patients. From our experience with collateral circulation provided by the circle of Willis, this is the most likely result because distal demand could be met by compensatory flow from collateral circulation and a restoration to pretreatment flow rates would not be required.

However, we also considered the clinical situation in which no compensatory flow is possible (ie, isolated vascular territory with an absence or inadequate collateral circulation). Our argument is that in that situation, the flow rates would have to be maintained to meet the demand of the brain relying on this artery. We chose to model a range of flow rates up to the pretreatment rates to understand the potential effects. These we have reported, and we have tried to explain our hypothesis. We have not claimed that this has been clinically observed or was active in this particular case. We do not have a sufficient evaluation of the circle of Willis to make this determination. However, as flow rates increased in this particular patient, our calculations show that the intra-aneurysmal pressure increased. Pointing out this hypothesis could provide the incentive to measure systemic blood pressures or intra-arterial pressures so that determination of the clinical importance of this potential effect could be studied in the right clinical context.

Fiorella et al are skeptical of the resistance increase imposed by the placement of the FD in patient 2 and argue that our calculations must be wrong because of the values obtained. The absolute values of the resistance are related to the flow conditions and pressure gradients imposed. We are certain that Fiorella et al have faithfully provided numbers as accurate as possible, but they have not made it clear that they are not repeating our calculations for our specific cases and flow conditions. They have simply applied their own physiologic "guesses" (to use their words) to achieve numbers that they believe. We are most concerned about the relationships that are involved. It is not difficult to understand why the FD is actually a higher resistance system compared with the pretreatment state in patient 2. Simply the cross-sectional area of the arterial system is dramatically reduced (ie, the aneurysm is no longer used as a flow path). Basic hemodynamic principles seem to quite clearly indicate that this would cause an increase in resistance. The actual values obtained are dependent on the flow conditions imposed.

Similarly, Fiorella et al have characterized the posttreatment changes in pressure gradient in patient 1 as defying basic hemodynamic principles. This appears to be a bit of an overstatement because basic hemodynamic principles predict a pressure gradient across a stenosis. So, Fiorella et al appear to mean not this but that they cannot agree that the magnitudes of changes we report are understandable for what they define as a "mild stenosis." With the limited images we provided, we doubt they are in a position to accurately assess the geometry of the stenosis. The treating physicians of this patient (Drs Lylyk and Ceratto), independent of this study, reported this value that we relay as an approximation and do not put it forth as a scientific analysis of the actual geometry. Regardless, the geometry we used is obtained from the 3D rotational angiography data obtained by Dr Lylyk and his team at the time of treatment. The calculations we made are faithful to the input geometry we presented. Navier-Stokes equations yielded the result presented.

Fiorella et al again approximate the pressure gradient on the basis of simplified geometry in 3 independent components to achieve a result significantly lower than that obtained by the more appropriate Navier-Stokes equations and the accurate anatomy. This again neglects the complex change in flow and wall shear stress and their effects on inertia and pressure differentials. They cite a 15% drop in viscous pressure in a tapered artery of >6 cm compared with the Poiseuille value. The tapering evident in patient 3 is well in excess of 33% and is a nonsymmetric change in diameter. Because flow patterns are not laminar, making any comparison with the case in patient 3 is problematic. Certainly, a better understanding of why the Navier-Stokes equations gave the reported result will be important in solving this discrepancy.

Rather than consider other possible explanations, Fiorella et al have dismissed the results as impossible and concluded that for this reason, the calculations are erroneous. They seem not to consider the complexity of the situation and all the changes that treatment has imposed on the system. In addition to opening the stenosis, placement of the FD made a significant change in the aneurysmal and downstream environment. The flow into the aneurysm is dramatically reduced; this reduction has the effect of reducing the wall shear stress and the dissipation of the kinetic energy of the flow in the aneurysm. With further analysis, it should be possible to understand why Navier-Stokes would predict this change. Scientifically, we believe it is important to understand this result but cannot support the dismissive attitude put forth by Fiorella et al. As stated earlier, this issue has not been studied and conventional "experience" likely is misleading.

Within this discussion, Fiorella et al go on to misrepresent our

statements and then sarcastically criticize. We did not state that the endovascular specialist would predict a 20-mm Hg pressure change by opening the stenosis. We simply said that the basic hemodynamic principle of a pressure gradient being formed at a stenosis is commonly understood by those familiar with endovascular treatment. As Fiorella et al should well know, opening of stenoses has been cautioned in a variety of clinical situations in the cerebrovasculature, including ischemic disease and aneurysms because of the propagation of increased pressure into the distal pathology by the amelioration of the stenosis. This is hardly new to an experienced endovascular specialist. We do not believe the dismissive and derogatory statements of Fiorella et al are justified.

We have suggested a potential adverse mechanism that could lead to posttreatment ruptures. Fiorella et al suggest ignoring this possibility, while our suggestion has been and continues to be to further study this possibility to determine if it actually takes place in some aneurysms. If so, clinicians could be in a position to formulate possible preventive measures to save patients from these devastating complications. Fiorella et al have characterized CFD as "mathematic calculations that are at best physiologic guesses." They are entitled to their opinion, but we do not find their arguments to be particularly compelling on a theoretic basis, unsubstantiated by any appropriate scientific analysis of these specific cases or any independent experimental work, dismissive without a balanced assessment of the complex interrelations in these systems, and offensive in erroneously assigning unethical and unscientific motives to our work. We do agree and have attempted to clearly relay our caution in applying these results to clinical treatments. We are not in agreement that these issues should be dismissed and believe that our data are a reasonable justification for studying these mechanisms. Because we have no vested interest in the results, we welcome ultimate settlement of this dispute with sufficient scientific methods regardless of what may be the ultimate result.

References

1. Cebral JR, Yim PJ, Löhner R, et al. **Blood flow modeling in carotid arteries using computational fluid dynamics and magnetic resonance imaging.** *Acad Radiol* 2002;9:1286–99
2. Cebral JR, Castro MA, Satoh T, et al. **Evaluation of image-based CFD models of cerebral aneurysms using MRI.** In: *Proceedings of the International Workshop on Flow and Motion 2004,* Zurich, Switzerland. July 11–13, 2004, pp. 11–13
3. Cebral JR, Putman CM, Pergolizzi R, et al. **Multi-modality image-based models of carotid artery hemodynamics**. In: *Proceedings of the International Society for Optics and Photonic. Medical Imaging Meeting,* San Diego, California. February 14–19, 2004;5369:529–38
4. He X, Venugopal P, Cebral JR, et al. **Reproducibility of brain hemodynamic simulations: an inter-solver comparison**. In: *Proceedings of the International Society for Optics and Photonics Medical Imaging Meeting: Physiology, Function, and Structure from Medical Images,* San Diego, California. February 12, 2006;6143–17
5. Cebral JR, Pergolizzi R, Putman CM. **Computational fluid dynamics modeling of intracranial aneurysms: qualitative comparison with cerebral angiography.** *Acad Radiol* 2007;14:804–13
6. Radaelli A, Ausburger l, Cebral JR, et al. **Reproducibility of haemodynamical simulations in a subject-specific stented aneurysm model: a report on the Virtual Intracranial Stenting Challenge 2007.** *J Biomech* 2008;41:2069–81. Epub 2008 Jun 25
7. Cebral JR, Putman CM, Alley MT, et al. **Hemodynamics in normal cerebral arteries: qualitative comparison of 4D phase-contrast magnetic resonance and image-based computational fluid dynamics.** *J Eng Math* 2009;64:367–78
8. Raschi M, Mut F, Löhner R, et AL. **Computational and experimental hemodynamic analysis of an intracranial aneurysm**. In: *Proceedings of the IX Argentinian Congress on Computational Mechanics and XXXI Iberian-Latin-American Congress on Computational Methods in Engineering*, Buenos Aires, Argentina. November 15–18, 2010
9. Yim PJ, Cebral JR, Weaver A, et al. **Estimation of the differential pressure at renal artery stenoses.** *Magn Reson Med* 2004;51:969–77
10. Cebral JR, Castro MA, Appanaboyina S, et al. **Efficient pipeline for image-based patient-specific analysis of cerebral aneurysm hemodynamics: technique and sensitivity**. *IEEE Trans Med Imaging* 2005;24:457–67
11. Castro MA, Putman CM, Cebral JR. **Computational fluid dynamics modeling of intracranial aneurysms: effects of parent artery segmentation on intra-aneurysmal hemodynamics.** *AJNR AM J Neuroradiol* 2006;27:1703–09
12. Castro MA, Putman CM, Cebral JR. **Patient-specific computational fluid dynamics modeling of anterior communicating artery aneurysms: a study of the sensitivity of intra-aneurysmal flow patterns to flow conditions in the carotid arteries.** *AJNR Am J Neuroradiol* 2006;27:2061–68
13. Dempere-Marco L, Oubel E, Castro M, et al. **CFD analysis incorporating the influence of wall motion: application to intracranial aneurysms.** *Med Image Comput Comput Assist Interv* 2006;9:438–45
14. Sforza D, Löhner R, Putman CM, et al. **Hemodynamic analysis of intracranial aneurysms with moving parent arteries: basilar tip aneurysms.** *Int J Num Meth Biomed Eng* 2010;26:1219–27

C.M. Putman
Interventional Neuroradiology
Inova Fairfax Hospital
Fairfax, Virginia
P. Lylyk
Interventional Neuroradiology
Clinica Sagrada Familia
Buenos Aires, Argentina
J. Cebral
Center for Computational Fluid Dynamics
George Mason University
Fairfax, Virginia

DOI 10.3174/ajnr.A2560