Title: New Method for Retrospective Study of Hemodynamic Changes before and after Aneurysm Formation in Patients with Ruptured or Unruptured Aneurysms

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Author's response to reviews: see over
Dear Editors

Thank you for your review of our manuscript (MS1547047250979416; BMC Neurology). We appreciate the concerns and suggestions provided by the reviewers, and have revised our manuscript in accordance with these suggestions. Our point-by-point responses are provided below. Text that has been added or modified from the original text is shown in red font in the revised manuscript. Most importantly, the manuscript has been edited by a very experienced medical editor whose first language is English.

Sincerely yours,

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Response to comments from Professor Wen-Guo Cui

(1) Major Compulsory Revisions

1. Detailed description of computational fluid dynamics analysis should be reduced and simplified, as the BMC Neurology is a neurological journal and most of the readers are neurologists.

Response: We have moved detailed information regarding hemodynamic conditions into a Supplementary Data file.

2. Conclusion of this study should be rewrite as the main of this study was to compare hemodynamic changes between a runptured and unruptured aneurysm.

Response: We have rewritten the conclusion (as shown below) on page 3 and 16 of the revised manuscript.

“Hemodynamic analyses in patients with ruptured or unruptured aneurysms employing methods to simulate the situation before and after aneurysm formation using the vessel surface repair method are feasible, economical, and simple. Our preliminary results indicated that the arterial wall was subjected to elevated WSS, WSSG and blood-flow velocity before aneurysm generation. However, more complicated flow patterns (often with an inflow jet or narrowed impaction zone) were more likely to be observed in ruptured aneurysms.”

3. Remove the aneurysm sac from parent artery was only partial simulate a status before aneurysm generation, from geometric and hemodynamic aspects, but aneurysm formation may involve many complicated mechanisms, the authors should discuss limitations of this technique.

Response: We have detailed the study limitations in the Discussion section of the
revised manuscript on page 15:

“The main deficiency of this study was that all comparisons were made based on hemodynamic analyses. However, the occurrence, development or rupture of aneurysms (especially brain aneurysms) is dependent upon genetics, degeneration of the arterial wall, hemodynamics, age, sex, smoking history, hypertension and atherosclerosis. [5, 23, 24] The second limitation was that we selected only two typical posterior communicating aneurysms for analyses. Future studies to include more aneurysm samples at different locations and multifactorial analyses should be conducted to better understand the generation or rupture of brain aneurysms.”

Also, the relevant references have been added.


(2) Minor Essential Revisions

1. Geometric comparison discussion should be reduced, since only two human models comparison could be meaningless. More importantly, the main focus of this study was hemodynamic analysis comparison as you have stated in your title.

Response: We have edited the discussion of the geometric comparison to make it more focused on hemodynamic findings in the revised manuscript.

2. Figure 6 and 7 could be merged to reduce the figure number.
Response: The original Figures 6 and 7 have been merged (Figure 5 in the revised manuscript).
Responses to comments from Professor Jian He

In this study, the authors compared hemodynamic changes before and after formation of brain aneurysms between a ruptured and unruptured Pcom aneurysm patient. They have found that using a vessel surface repair method to retrospectively study hemodynamic characteristics before and after aneurysm formation is feasible, economical, and simple. I have only a few small concerns which need to be addressed.

(1) Major Compulsory Revisions

None

(2) Minor Essential Revisions

1. In the abstract, a conclusion statement of the hemodynamic characteristics between ruptured and unruptured aneurysm should be added.

Response: We have rewritten the conclusion section in the Abstract on page 3 of the revised manuscript:

“These data suggest that hemodynamic analyses in patients with ruptured or unruptured aneurysms using the vessel surface repair method are feasible, economical, and simple. Our preliminary results indicated that the arterial wall was subjected to elevated WSS, WSSG and blood-flow velocity before aneurysm generation. However, more complicated flow patterns (often with an inflow jet or narrowed impaction zone) were more likely to be observed in ruptured aneurysms.”

2. The discussion is too long and should be reduced and more focused.

Response: We have rewritten the Discussion to make it more focused on hemodynamic findings in the revised manuscript.

3. Hemodynamics is one of the most important factors but not the only factor causing brain aneurysm rupture, other possible factors such as arterial wall degeneration, high
blood pressure should also be briefly discussed.

**Response:** We have added the relevant content in the Discussion section on page 13:
“This is because decreased WSS is likely to induce degeneration or an inflammation reaction in the aneurysm wall, which can potentially involve increased: infiltration of inflammatory cells; activity of matrix metalloproteinases (MMPs); protein synthesis in the extracellular matrix; apoptosis of smooth muscle cells.[17]”

We have also added relevant content on page 14:
“However, besides patterns of blood flow and WSS, degeneration of the extracellular matrix in the arterial wall by upregulation of MMP2 and MMP9 or infiltration of macrophages also have important synergistic effects with hemodynamic status if an aneurysm develops or ruptures.[19, 20]”

Lastly, we have also added a limitation statement of this study on page 15:
“The main deficiency of this study was that all comparisons were made based on hemodynamic analyses. However, the occurrence, development or rupture of aneurysms (especially brain aneurysms) is dependent upon genetics, degeneration of the arterial wall, hemodynamics, age, sex, smoking history, hypertension and artherosclerosis. [5, 23, 24] The second limitation was that we selected only two typical posterior communicating aneurysms for analyses. Future studies to include more aneurysm samples at different locations and multifactorial analyses should be conducted to better understand the generation or rupture of brain aneurysms.”

Also, the related references have been added:

5. Norman PE, Powell JT: **Site Specificity of Aneurysmal Disease.** *Circulation* 2010;121(4);560-568.

17. Shojima M, Oshima M, Takagi K, Torii R, Hayakawa M, Katada K, Morita A,
Kirino T: Magnitude and Role of Wall Shear Stress on Cerebral Aneurysm Computational Fluid Dynamic Study of 20 Middle Cerebral Artery Aneurysms. 


4. Figure 5 should be canceled because in Figure 2-B and Figure 3-B, an inflow jet has already been observed in the ruptured aneurysm and not observed in the unruptured aneurysm.

**Response:** We have deleted Figure 5 in the revised manuscript.

5. Despite well writing, this manuscript still needs some language corrections before
being published.

**Response:** The manuscript has been edited by a very experienced medical editor whose first language is English according to your advice.