Author's response to reviews

Title: Influence of calcification on the mechanical stability of plaque in a three-dimensional carotid bifurcation model

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Author's response to reviews: see over
Authors’ Response to Reviewers’ Comments

Dear Editor,

We have accepted the reviews, and modified the manuscript based on all of the comments raised by Reviewer#1 and #2. Below are my responses to the reviewers’ comments that are highlighted in blue color. I would like to thank the reviewers for their effort in examining and suggesting improvements for this manuscript.

Regards,

Jiyuan Tu

(Corresponding Author)

Reviewer #1:

1. The methods should be more focused avoiding extensive description of prior works

Author’s response: It is worthwhile noting that the prior works are a necessity in this manuscript, and therefore, assist in giving the reader a comprehensive understanding of the current state-of-the-art modelling techniques and literature review.

Author’s action: However, we do understand that excessive description of these prior works lengthens the manuscript unnecessarily and therefore, we have truncated certain portions of the manuscript.

2. The results and discussion should be on separate sections. The greatest part of the conclusion should be moved to the discussion.

Author’s response: The manuscript requirements dictated by the BMC Cardiovascular Disorders journal states that the article is segregated into the 4 specific section titles: Background, Results and discussion, Conclusions, Methods, which we have formatted as according to the instructions.

3. The limitations of the study should be clearly addressed.

Author’s response: We have addressed the limitations of the study in Conclusion as follows:

   a) Assumption in the model that the microcalcifications are floating debris uniformly distributed in the lipid pool;
   b) Assumption that a continuous calcification structure along the curvature of the artery with a layer of lipid volume in between;
   c) Assumption of the configuration for the computational models based on observation of the histologic images of partially calcified plaque.
Reviewer #2:

MAJOR COMPULSORY REVISIONS

Comment 1: 2.2 Plaque rupture mechanics.

‘A two-dimensional modelling platform for calibrating the extent of plaque rupture based on mechanical parameters governing the atherosclerotic configuration.’ The authors should explain in more details or change the sentence since it is rather confusing and gives no specific data.

Author’s response: We apologise for the grammatical error.

Author’s action: The sentence is modified by adding “is” before the word “based” such that it becomes:

“A two-dimensional modelling platform for calibrating the extent of plaque rupture is based on mechanical parameters governing the atherosclerotic configuration.”

Comment 2: 2.2 Plaque rupture mechanics.

Please explain what you mean by patient-specific cases.

Author’s response: Patient-specific cases (modelling based on in-vivo medical image reconstruction of physiological arterial geometry) were previously investigated and our paper has performed an idealistic carotid bifurcation study to justify the modelling accuracy.

Author’s action: The sentence is modified as follows to improve the clarity of our 3D modelling work:

Three dimensional analyses have also been prepared to justify the accuracy of the results based on the plane analyses of patient-specific case studies that were previously investigated.

Comment 3: 2.2 Plaque Rupture Mechanics

You mention 65µm is the threshold for plaque rupture. However, in your experiments you talk about carotid arteries. There are recent data that suggest that TCFA in carotids is defined as cap thickness < 200µm.

Author’s response: The nature of plaque structural performance should be relatively independent of the lesion location and types of arteries under analysis (and also considering that the arteries do not deviate too much in terms of size). We select 65 µm as a safe threshold for plaque rupture in this study. This has been a standard value used in literature, but we do admit that variations in this specified value do exist. Furthermore, the plaque rupture mechanism and analysis will not be affected by the change of this threshold value.
Comment 4: 2.5.1 Geometry Reconstruction and Meshing

‘3D geometric model reconstruction based on realistic geometry which is used by (Tada et al., 2005) was performed for modelling of healthy carotid bifurcation (Fig 6).’ You state about healthy carotid bifurcation, nonetheless, in the actual figure 6 and its legend you talk about plaque in the bifurcation. There needs to be clarification.

Author’s response: We apologise for the mistake in conveying the meaning. Tada et al. developed the idealistic artery model and we have incorporated the plaque structure onto their idealistic artery model, which we have stated in the later part of the paragraph.

Author’s action: The sentence is modified as follows to improve the clarity of our sentence:

Tada et al. performed modelling of healthy carotid bifurcation based on an idealistic geometry.50

Comment 5: Conclusion.

Although you mention at the Conclusion some pitfalls of your experiments, I believe there should be a separate paragraph just for the limitations of your experiments, right before the Conclusion, stating in a more concise way the pitfalls, drawbacks and limitations of the experiments.

Author’s response: The manuscript requirements dictated by the BMC Cardiovascular Disorders journal states that the article is segregated into the following section titles: Background, Results and discussion, Conclusions, Methods, which we have formatted as according to the instructions. Therefore, we have included our limitations (2 paragraphs, 254 words) into the Conclusion section, which can be clearly read within the Conclusion.

Comment 6: 2.4 Designs of plaque models

How did you decide to fix your experimental models? What influenced you to put: Fibrous tissue (# = 5%), lipid (# = 20%) and calcium (# = 75%)?

Author’s response: We arbitrary assume the configuration of the experimental models such that Fibrous tissue (=5%), lipid (=20%) and calcium (=75%) based on observation of the histologic images of partially calcified plaque. It represents one particular stage of calcified plaque development. The nature of analysis would remain the same even though this configuration is changed at a later stage of the development.

Comment 7: Figure 8

You mention at Fig 8 that you achieved 107mmHg blood pressure. So, all experiments were performed in this blood pressure? Are there results for higher or lower blood pressure?

Author’s response: We utilise the peak pressure (107 mmHg) to evaluate the plaque rupture risk as this is the maximum index. There will be no higher pressure. Lower pressures
would not cause the maximum danger condition for the plaque rupture and will not deem important for analysis in this paper.

Comment 8: Figure 10

You state in Fig 10 that you use varying fibrous cap thickness dfc, however from the values there is only a dfc of 0.05mm. Could you please clarify?

**Author’s response:** We apologise for the mistake in our caption. It should be a specific value of 0.05 mm, and not a variable value.

**Author’s action:** We have changed the word from “varying” to “specific”.

Comment 9:

What prompt you to use constant lipid pool ($E_{lp} = 1$ kPa) and fixed thickness (0.35 mm)?

**Author’s response:** Our work was extended from the study by Loree et al. and Holzapfel et al., which they have stated a constant lipid pool ($E_{lp} = 1$ kPa) and fixed thickness (0.35 mm). Therefore, we can safely assume that this value was reasonable.

**MINOR ESSENTIAL REVISIONS**

Comment 1: 1. Background.

IVUS is an invasive imaging modality and has several limitations for detection of plaque morphology. Certainly it cannot be used for vulnerable plaque detection. However, it can be used in the form of VH.

**Author’s response:** Intravascular ultrasound (IVUS) was well known for non-invasive detection of plaque morphology and composition (calcified versus non-calcified atherosclerotic plaques), which we can utilise to determine the plaque composition prior to the computational modelling to determine plaque vulnerability.


I think there is a mix-up with numbering the paragraphs of the entire chapter 2. For instance, you begin with 2.1 Plaque Composite Model, then 2.2 Plaque Rupture Mechanics, then it follows 2.4 Design of Plaque Models, then there is 2.6 2D Finite Element Method Validation, then comes 2.5 3D Computational Fluid Dynamics Modelling.

**Author’s action:** We have corrected the numbering error in our manuscript.
Comment 3: 2.5.1 Geometry Reconstruction and Meshing

You talk about ‘inner carotid artery’. I believe the right term is internal carotid artery.

**Author’s action:** We have corrected the error in terminology.

Comment 4: 3.3.1 2D Structural Analysis

‘Highest plague vulnerability’. It is plaque.

**Author’s action:** We have corrected the typo error in our manuscript.

Comment 5: 3.4.2 3D Fluid-Structural Analysis

You mention Fig 12. I believe it would be Figure 14. Please also specify what is 14A and 14B in the text.

**Author’s action:** We have corrected the typo error in our manuscript. We have also specified 14A and 14B in the text now.

Comment 6: 4. Conclusion

‘Non-invasive imaging not only identify flow-limiting vascular stenosis, but also to detect calcified and non-calcified plaque, measure atherosclerotic plaque burden and its response to treatment, and to differentiate stable plaques from those which tend to rupture.’ Please correct the grammar in order to achieve a better understanding.

**Author’s action:** We have modified the sentence as follows:

“Not only can non- or less-invasive imaging identify flow-limiting coronary stenosis, but it can also to detect plaque components, measure atherosclerotic plaque burden and its response to treatment, and to differentiate stable plaques from those that are prone to rupture.”

Comment 7:

Did you perform both 2D and 3D experiments in your lab? How many times each? Did you achieve significant reproducibility of your results?

**Author’s response:** The simulation models were performed by computational fluid dynamics and finite element analysis, which are coupled together to produce the fluid structure interaction that governs the Blood-Vessel-Plaque Simulation. Therefore, reproducibility of computational modelling and fluid dynamic simulation is not an issue unless we perform clinical experiments.