Multiscale three-dimensional surface reconstruction and surface roughness of porcine left anterior descending coronary arteries

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Article citation details
R. Soc. open sci. 6: 190915.
http://dx.doi.org/10.1098/rsos.190915

Review timeline
Original submission: 18 May 2019  
Revised submission: 2 August 2019  
Final acceptance: 7 August 2019  
Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Note: This manuscript was transferred from another Royal Society journal with peer review.

Review History

RSOS-190915.R0 (Original submission)

Review form: Reviewer 1

Is the manuscript scientifically sound in its present form?
No

Are the interpretations and conclusions justified by the results?
No

Is the language acceptable?
Yes

Do you have any ethical concerns with this paper?
No

Have you any concerns about statistical analyses in this paper?
No
Recommendation?
Reject

Comments to the Author(s)
I am not convinced by the rebuttal, mainly regarding the two main concerns expressed earlier.

1) the surface roughness of the endothelium is not relevant for stenting. Re-endothelialization is obviously important, but the luminal surface roughness is not relevant in this context. It is the attachment of the abluminal part of the endothelial cells that determine the re-endothelialization!

2) the artifacts that are induced by processing are not only chemical by nature, there is a strong mechanical component to it. The residual stresses in the wall will cause the artery to shrink, thus inducing the well known 'ridges'. How much this contributes to the observed results will remain unknown.

Review form: Reviewer 2

Is the manuscript scientifically sound in its present form?
Yes

Are the interpretations and conclusions justified by the results?
Yes

Is the language acceptable?
Yes

Do you have any ethical concerns with this paper?
No

Have you any concerns about statistical analyses in this paper?
No

Recommendation?
Accept as is

Comments to the Author(s)
I thank the authors for addressing my comments on the first submitted version of the manuscript.

Decision letter (RSOS-190915.R0)

26-Jun-2019

Dear Dr Burton,

The editors assigned to your paper (“Multiscale three-dimensional surface reconstruction and surface roughness of porcine left anterior descending coronary arteries”) have now received
comments from reviewers. We would like you to revise your paper in accordance with the referee and Associate Editor suggestions which can be found below (not including confidential reports to the Editor). Please note this decision does not guarantee eventual acceptance.

Please submit a copy of your revised paper before 19-Jul-2019. Please note that the revision deadline will expire at 00.00am on this date. If we do not hear from you within this time then it will be assumed that the paper has been withdrawn. In exceptional circumstances, extensions may be possible if agreed with the Editorial Office in advance. We do not allow multiple rounds of revision so we urge you to make every effort to fully address all of the comments at this stage. If deemed necessary by the Editors, your manuscript will be sent back to one or more of the original reviewers for assessment. If the original reviewers are not available, we may invite new reviewers.

To revise your manuscript, log into http://mc.manuscriptcentral.com/rsos and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision. Revise your manuscript and upload a new version through your Author Centre.

When submitting your revised manuscript, you must respond to the comments made by the referees and upload a file "Response to Referees" in "Section 6 - File Upload". Please use this to document how you have responded to the comments, and the adjustments you have made. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response.

In addition to addressing all of the reviewers' and editor's comments please also ensure that your revised manuscript contains the following sections as appropriate before the reference list:

- Ethics statement (if applicable)
  If your study uses humans or animals please include details of the ethical approval received, including the name of the committee that granted approval. For human studies please also detail whether informed consent was obtained. For field studies on animals please include details of all permissions, licences and/or approvals granted to carry out the fieldwork.

- Data accessibility
  It is a condition of publication that all supporting data are made available either as supplementary information or preferably in a suitable permanent repository. The data accessibility section should state where the article’s supporting data can be accessed. This section should also include details, where possible of where to access other relevant research materials such as statistical tools, protocols, software etc can be accessed. If the data have been deposited in an external repository this section should list the database, accession number and link to the DOI for all data from the article that have been made publicly available. Data sets that have been deposited in an external repository and have a DOI should also be appropriately cited in the manuscript and included in the reference list.

  If you wish to submit your supporting data or code to Dryad (http://datadryad.org/), or modify your current submission to dryad, please use the following link: http://datadryad.org/submit?journalID=RSOS&manu=RSOS-190915

- Competing interests
  Please declare any financial or non-financial competing interests, or state that you have no competing interests.
• Authors’ contributions
All submissions, other than those with a single author, must include an Authors’ Contributions section which individually lists the specific contribution of each author. The list of Authors should meet all of the following criteria; 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

All contributors who do not meet all of these criteria should be included in the acknowledgements.

We suggest the following format:
AB carried out the molecular lab work, participated in data analysis, carried out sequence alignments, participated in the design of the study and drafted the manuscript; CD carried out the statistical analyses; EF collected field data; GH conceived of the study, designed the study, coordinated the study and helped draft the manuscript. All authors gave final approval for publication.

• Acknowledgements
Please acknowledge anyone who contributed to the study but did not meet the authorship criteria.

• Funding statement
Please list the source of funding for each author.

Once again, thank you for submitting your manuscript to Royal Society Open Science and I look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Kind regards,

Lianne Parkhouse
Editorial Coordinator
Royal Society Open Science
openscience@royalsociety.org

on behalf of Dr Derek Abbott (Associate Editor) and R. Kerry Rowe (Subject Editor)
openscience@royalsociety.org

Associate Editor's comments (Dr Derek Abbott):

Comments to the Author:

Please add a new section to the paper called "Limitations of the Study" just before the conclusion section. In there please thoroughly discuss limitations, including but not limited to those raised by reviewers. The paper will be rejected if this is not carried out satisfactorily.

Reviewers' Comments to Author:

Reviewer: 1:

I am not convinced by the rebuttal, mainly regarding the two main concerns expressed earlier.
1) the surface roughness of the endothelium is not relevant for stenting. Re-endotheliazation is obviously important, but the luminal surface roughness is not relevant in this context. It is the attachment of the abluminal part of the endothelial cells that determine the re-endothelialization!

2) the artifacts that are induced by processing are not only chemical by nature, there is a strong mechanical component to it. The residual stresses in the wall will cause the artery to shrink, thus inducing the well known 'ridges'. How much this contributes to the observed results will remain unknown.

Reviewer: 2:

I thank the authors for addressing my comments on the first submitted version of the manuscript.

Author's Response to Decision Letter for (RSOS-190915.R0)

See Appendix A.

Decision letter (RSOS-190915.R1)

07-Aug-2019

Dear Dr Burton,

I am pleased to inform you that your manuscript entitled "Multiscale three-dimensional surface reconstruction and surface roughness of porcine left anterior descending coronary arteries" is now accepted for publication in Royal Society Open Science.

You can expect to receive a proof of your article in the near future. Please contact the editorial office (openscience_proofs@royalsociety.org and openscience@royalsociety.org) to let us know if you are likely to be away from e-mail contact. Due to rapid publication and an extremely tight schedule, if comments are not received, your paper may experience a delay in publication.

Royal Society Open Science operates under a continuous publication model (http://bit.ly/cpFAQ). Your article will be published straight into the next open issue and this will be the final version of the paper. As such, it can be cited immediately by other researchers. As the issue version of your paper will be the only version to be published I would advise you to check your proofs thoroughly as changes cannot be made once the paper is published.

On behalf of the Editors of Royal Society Open Science, we look forward to your continued contributions to the Journal.

Best regards,
Lianne Parkhouse
Editorial Coordinator
Royal Society Open Science
openscience@royalsociety.org
We would like to thank the reviewers and the editorial team for their time. We have addressed each point below and to aid this process have put reviewer’s comments in red and our responses in black. Within the manuscript, changes have been highlighted in yellow, including an address change for the corresponding author and the addition of a limitations section before the conclusion.

Referee 1:

1) the surface roughness of the endothelium is not relevant for stenting. Re-endotheliazation is obviously important, but the luminal surface roughness is not relevant in this context. It is the attachment of the abluminal part of the endothelial cells that determine the re-endothelialization!

The focus of this current study is not re-endothelialization following the use of a medical device. The focus is to provide a first quantitative assessment of the multiscale properties of surface roughness. The authors suggest that such measurements may have applications to enable the next generation of medical devices to be manufactured so as to be bio-inspired; this might be tissue engineered replacement constructs (which intend to fully mimic the replaced artery) or this might be a more standard stent where its surface better mimics the roughness characteristics of the native artery. There might even be future applications to assess disease (as has been shown other tissues, e.g. osteoarthritis and cartilage surface roughness). However, we do not state that improved surface roughness would alter re-endothelialization in the manuscript. To avoid any misinterpretation, by association or otherwise, we have now also limited direct reference to neointimal hyperplasia in the abstract (lines 3-4) and on pg. 12 line 17. Additionally, a limitations section has been included in the manuscript. The limitation in regards to the scope of the findings has been clarified, as shown below:

Finally, it should be noted that this study makes no comment on the effect of a bio-inspired multi-scale surface on re-endothelialisation [41] or neointimal hyperplasia [42-43]. Re-endothelialisation is primarily driven by the abluminal attachment which falls outside the scope of this investigation. Instead, in this study we suggest that, firstly, the multi-scale surface roughness of coronary arteries should be considered for bio-inspired, next generation, replacement materials (either tissue engineered or as a medical device) so as to replicate the native system. Secondly, that multi-scale surface roughness can be used as a quantitative measure for comparison for such replacement materials.

2) the artifacts that are induced by processing are not only chemical by nature, there is a strong mechanical component to it. The residual stresses in the wall will cause the artery to shrink, thus inducing the well known ‘ridges’. How much this contributes to the observed results will remain unkown.

Tissue preparation and chemical processing may have altered the stress state of the tissue as compared to its in vivo state. It is possible that residual stresses may alter some of the measurements reported. To deal with this, firstly, the effects of chemical processing have been assessed. Returning excised ex vivo tissue to its innate stress state (which in itself is a dynamic phenomena) is a limitation of this study, and of any study where in vivo measurements cannot be made. However, the authors believe that this limitation highlights the advantage of performing multi-scale analysis because micro- and nano-scale analysis is less likely be prone to such bias than macro-scale measurements. Hence, small segments of tissue were analysed in this study, with
analysis is reported across a range of magnification. For clarification, a limitations section has been included within the manuscript, with the relevant section shown below:

As discussed above, the effect of chemical processing is likely to affect the surface roughness of coronary arteries [4]. Using a correction factor in this study, it was possible to calculate the outer limits of surface roughness and the results of this study support a multiscale trend. Further, this study highlights the importance of using the same microscopy preparation protocols to allow comparison of the endothelial surface. Subsequently, assessing like-for-like magnifications using different microscopy types, with differences noted between scale of magnification.

Residual stresses, induced during excision, preparation and processing of the tissue, could result in the macro-scale ‘ridges’ visible in the walls of the arteries. It is unclear as to what extent these ridges affect the final trends and results, and it is noted that other studies have noted their presence too [37]. However, this potential limitation highlights an additional benefit of performing measurements over multiple scales as it is unlikely that any bias introduced by macro-scale ridges would alter measurements at the micro- and nano-scale. Further, by focusing scans on a small area of the specimen any larger scale change in the tissue structure are reduced. Therefore, the trends obtained, and quantitative range of surface roughness reported, are expected to be representative of the roughness of porcine coronary arteries. The full extent of this limitations, though, will only be known through \textit{in vivo} and \textit{in situ} assessment multi-scale roughness, which is not currently feasible.