Author’s response to reviews

Title: Three dimensional intracardiac echocardiography and pulmonary embolism

Authors:

Konstantin Yastrebov (syastrebov@y7mail.com)

Laurencie Brunel (laurencie.brunel@sydney.edu.au)

Hugh S Paterson (patersonh@aol.com)

Zoe A Williams (zoe.williams@sydney.edu.au)

Paul G Bannon (paul.bannon@sydney.edu.au)

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Responses to the Reviewers:
Reviewer 1.
In my view the authors have addressed all the items I had raised and the paper is now ready for publication.

Thank you

Reviewer 2.
General
- Please check that references are provided for the different statements made throughout the text (i.e. "The tip of the ICE catheter is usually positioned within right heart chambers, although left atrial imaging is possible after atrial septal puncture (reference)."; "(...) available in narrow-angle (22°) and wide-angle (up to 50°) azimuthal elevation (reference)."; "(...) than the ICE catheter, incorporating a hemostatic valve and a side port (reference)."; "However, the technique is invasive, which increases the risk of iatrogenic complications (reference)."; "catheter, flushing of the sheath with a heparinised crystalloid solution following removal of the dilator and minimizing the time between vascular sheath placement and insertion of the ICE catheter (reference)."; "2D echocardiographic identification and comprehensive assessment of intracardiac thrombi can be inadequate due to the potential for two-dimensional planes missing or under-estimating complex three-dimensional long mobile structures (reference)."; "3D wide azimuthal ICE allows real-time display of the complete cardiac structures, even relatively close to the transducer (reference).".

Additional references 1-5 have been included where appropriate.

Abstract
- In order to improve clarity and readability, consider changing: "of cardiac anatomy and guidance of intracardiac procedures. It offers unique views with good spatial and temporal resolution."
To:
"of cardiac anatomy and guidance of intracardiac procedures, being able to provide unique views."

Changed

- Consider changing: "Complications arising from this highly invasive procedure and the value of 3D ICE in detection"
To:
"Complications arising from this invasive procedure and the value of 3D ICE in the detection"

Changed

- Consider changing: "We conducted a translational study of three-dimensional intracardiac echocardiography with"
To:
"We conducted a translational study of 3D ICE with"

Changed

- "to guide implantation of a left ventricular assist device (Impella CP®) in eight adult sheep."
In the article in reference 2 (Yastrebov K et al. Implantation of Impella CP® left ventricular assist device under the guidance of three-dimensional intracardiac echocardiography. Research Square preprint. DOI: 10.21203/rs.3.rs-23212/v1), an n of 7 sheep is presented; please review.

The Research Square manuscript pre-print have been revised and re-uploaded two days ago following a parallel review. One extra sheep and five Impella implantations have been added to the original numbers, amounting to the total of eight experimental animals. Version 2 of the pre-print has been referenced.

- Consider changing: "Insertion of 3D ICE catheter was accompanied by"
To:
"Insertion of the 3D ICE catheter was accompanied by"

Changed

Background
- "3D ICE catheters provide a 90° imaging sector and are commercially available in narrow-angle (22°) and wide-angle (up to 50°) azimuthal elevation."
As described in the general comments, please provide the reference for this statement (please note that this is a particularly important point, as to provide the reader - especially if not an expert on the use of ICE - with additional information).
Also, please review the data concerning if the 3D ICE catheter used in the present study is presently commercially available (if not, this should be highlighted in the Discussion).
References 4 and 5 have been included.

There is a notice on the global Siemens website: “The ACUSON AcuNav Volume ICE Catheter is no longer commercially available. Updates will be posted when available.” The Canadian Government website (https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/73363r-eng.php) posted an alert with product recall on the 16th of June 2020: “Reason: Siemens Healthineers has received reports of left atrial perforations and AV (atrioventricular node) block occurring while the Acuson Acunav Volume ICE catheter is enabling structural heart interventional procedures.” Atrial wall perforation is theoretically possible with any ICE catheter, and we are not aware of general world-wide recall of ICE catheters. We enquired with the representative from Siemens in Sydney and were verbally advised that there is “limited availability” of Acunav Volume ICE catheters in Australia via independent distributor. Due to the uncertainty regarding this catheter’s availability in different countries, the extent and the term of very recent recall, we decided not to comment on this issue.

- Consider changing: "The risk associated with wide-bore sheath introducers used for"
To: "The presently described complication associated with wide-bore sheath introducers used for"

Changed

Case presentation
- "Sheep number three of eight developed the reported complication."
As described above (in the section concerning the Abstract), in the article in reference 2 (Yastrebov K et al. Implantation of Impella CP® left ventricular assist device under the guidance of three-dimensional intracardiac echocardiography. Research Square preprint. DOI: 10.21203/rs.3.rs-23212/v1) an n of 7 sheep is presented; please review.

The Research Square manuscript pre-print have been revised and re-uploaded following a parallel review. One extra sheep and five Impella implantations have been added to the original numbers, amounting to the total of eight experimental animals. Version 2 of the pre-print has been referenced.

- Consider changing: "A cut-down technique was used to expose left internal"
To: "A cut-down technique was used to expose the left internal"

Changed

- Consider changing: "An AcuNav Volume 12.5 Fr, 90 cm four-ways steerable intracardiac echocardiography catheter"
To: "An AcuNav Volume 12.5 Fr, 90 cm four-ways steerable ICE catheter"

Changed
"was inserted through the haemostatic valve of the vascular sheath introducer approximately 5 minutes following removal of the dilator during which time systemic heparinisation had not been administered until immediately prior to the ICE catheter insertion."

Please describe, at this point (and further briefly expanding in the Discussion) if this is the standard approach when using this ICE catheter. This is a particularly important point, especially given the translational nature of the present study, as illustrated in lines 199 to 206 of the Discussion.

Discussion has been expanded to reflect this point.

- Consider changing: "The diagnosis of pulmonary embolism and reactive pulmonary arterial vasoconstriction with"
  To:
  "The diagnosis of pulmonary embolism with"

Changed

- "Severe arterial hypotension and cardiac output reduction gradually improved with boluses of adrenaline, initiation of noradrenaline and a titrated dobutamine infusion."

Please comment whether changes in the anticoagulation protocol or the use of thrombolysis were considered at this point.

Extra information has been added: “Full systemic anticoagulation was achieved with administration of heparin. Thrombolysis was not considered in thoracotomised animal.”

Discussion
- Consider changing: "Its proximity to the cardiac structures creates unique imaging capabilities for assessment of"
  To:
  "Its proximity to the cardiac structures creates unique imaging capabilities for the assessment of"

Changed

- Consider changing: "However, the technique is highly invasive, which"
  To:
  "However, the technique is invasive, which"

Changed

- Consider changing: "Such complication has not been previously described."
  To:
  "To our knowledge, such complication has not been previously described."

Changed
- "Our report suggests that life-threatening pulmonary embolism should be considered among other diagnoses in patients undergoing ICE who develop sudden episodes of desaturation or significant haemodynamic compromise."

At this point, please briefly describe a limitation of the present report, in that no echocardiographic assessment of the study subject was undertaken prior to the ICE catheter insertion.

Acknowledged in the text

- "Sheep have a clotting time similar to humans [5], thus making our report highly applicable for human clinical practice."

As expertly discussed by the previous reviewer, this is an important point in the present report. As to provide the reader with further information on this topic, please consider also referencing the study: Foley SR et al. A comprehensive study of ovine haemostasis to assess suitability to model human coagulation. Thromb Res. 2014;134:468-73.

Referenced

- Consider changing: "This is the first report of clot-in transit being imaged with 3D ICE in the right heart chambers."
  To:
  "This is, to our knowledge, the first report of clot-in transit being imaged with 3D ICE in the right heart chambers."

Changed

- Consider changing: "3D wide azimuthal intracardiac echocardiography allows"
  To:
  "3D wide azimuthal ICE allows"

Changed

- As to provide a more focused point, consider changing: "capability of the contemporary 3D ICE to provide a uniquely detailed demonstration of the morphological and anatomical relationships between the clot and the cardiac structures, with high temporal resolution."
  To:
  "capability of contemporary 3D ICE to provide a uniquely detailed assessment of the morphological and anatomical relationships between the clot and the cardiac structures."

As you are aware, high temporal resolution is an important quality of modern 3D ICE for imaging clots in transit within cardiac chambers due to the highly mobile nature of these clots and frequently associated with PE tachycardia and so we would prefer to retain this point.

Conclusion
- Consider changing: "complication during intracardiac echocardiography resulting"
  To:
  "complication during ICE resulting"
Changed