Author's response to reviews

Title: Head to head comparisons of two modalities of perfusion adenosine stress echocardiography with simultaneous SPECT

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Author's response to reviews:

To the Editor

We hereby submit a revised version of the paper "Head to head comparisons of two modalities of perfusion adenosine stress echocardiography with simultaneous SPECT" for consideration. We have carefully read the comments by the reviewer and made changes accordingly, and present a point-by-point description of the changes made. We are prepared to make additional changes if deemed necessary. We now hope that you will find the paper suitable for publication in the Cardiovascular Ultrasound.

Best regards

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Point-to-point response to reviewer's comments
Reviewer 1;

1. Title: The title is too long and should be shortened

Response: The title has been shortened and now reads: “Head to head comparisons of two modalities of perfusion adenosine stress echocardiography with simultaneous SPECT”

2. Background: In the first paragraph authors state that exercise ECG is commonly used but has a low accuracy in low pre-test probability patients. This is somewhat confusing since low pre-test probability is the not the main indication for imaging techniques. Please change and state that in case of non-diagnostic exercise ECG, non-invasive imaging techniques are more accurate as indicated by stable angina guidelines (Fox et al, Eur Heart J 2003)

Response: We thank the reviewer for these comments and they have been incorporated into the revised manuscript. We now clearly state that non-invasive imaging techniques are not to be used as first-line of investigation, but to be used when exercise ECG are non-diagnostic or non-interpretable. One additional reference has been added to the revised manuscript (Sicare et al 2008).

3. Although this is an agreement study, authors try to assess the overall diagnostic accuracy of the combined evaluation of wall motion and perfusion abnormalities. This is the appropriate way to analyze stress echocardiography but still the results should be reanalyzed showing the additive value of perfusion over wall motion, if any. A) authors used a suboptimal stressor such as adenosine for the assessment of wall motion abnormalities. Please address; b) although perfusion defects appear earlier in the ischemic cascade they are unable to distinguish between macro-vascular and micro-vascular disease, whereas wall motion abnormalities are more specific of true ischemia. This is a major limitation of all perfusion techniques and wall motion analysis may overcome this limitation. Please discuss.

Response: We thank the reviewer for these comments and they have been incorporated into the revised manuscript. We address the fact that adenosine is an inadequate stressor concerning wall motion and the fact that we cannot separate perfusion defects caused by macro-vascular or by micro-vascular disease because coronary angiography was not available in these patients.

4. In line with the previous comment the use of wall motion analysis as a back-up to perfusion is questionable.

Response: The purposes of those analyses were to use all available data and
avoid non interpretable segments due to perfusion artefacts. It is correct that adenosine is an inadequate stressor concerning wall motion, and this is addressed in the revised manuscript.

5. All the accuracy results should be displayed in graph format
Response; A graph of accuracy has been added to the revised manuscript.

6. In the study limitations section of the manuscript please acknowledge the fact that this is an agreement study but not an accuracy study due to the lack of results on coronary angiography. It is not surprising that contrast and SPECT should exert the same diagnostic accuracy. Please address.
Response; Correct, we have made alteration in the revised manuscript and now state that this is an agreement study, not an accuracy study.

7. Authors address the safety issue of contrast in an appropriate way. However, costs and the real additive value has not been demonstrated
Response; Correct, we are not aware of any prospective randomised multicentre studies which have demonstrated cost effectiveness and real additive value of routine use of echo contrast in every patient that undergo stress echocardiography. This has been incorporated into the revised manuscript.

8. In the discussion section authors provide a very balanced view on contrast use, however it would be important to have their opinion on the clinical implications of these results.
Response; The implication of the findings in the present investigation is that different techniques of real-time myocardial perfusion echocardiography yield similar findings, thus data derived from different techniques for real-time myocardial perfusion echocardiography are reasonably interchangeable. This has been added to the revised manuscript.

9. Due to the nature of the journal it would be important to upload moving images (clips), since there is no space limit.
Response; This has been added to the revised manuscript.

Reviewer 2;
- This is another paper in which RTP stress echo accuracy is not validated versus coronary angiography but vs. myocardial perfusion scintigraphy. Therefore, it is a good concordance study between the two techniques. However, both techniques suffer from the same limitation: they are unable to distinguish between micro and macrovascular coronary disease. It is well known that SPECT
is able to detect perfusion abnormalities, which are not necessarily caused by epicardial coronary artery disease. The perfusion defects could be related to microvascular disease and do not cause obvious wall motion abnormalities. Considering this point, the Authors should better state the diagnostic endpoints of stress echocardiographic testing. In other words, do they consider positive for myocardial ischemia a stress test when stress-inducible perfusion deficit is found, even in absence of any new onset of wall-motion abnormality?

Response; Reviewer 1 also raised this question. We agree and we address in the revised manuscript the fact that we cannot separate perfusion defects caused by macro-vascular or by micro-vascular disease because coronary angiography was not available in these patients.

- It would be interesting make an head to head comparisons of the RTP stress echo with magnetic resonance stress testing, which is becoming widely accepted in clinical practice. Both techniques are able to evaluate at the same time perfusion and regional mechanical function

Response; We agree and we now mention this in the revised manuscript.

- When authors in table define the percentage of patients with heart failure: how was diagnosis made: symptoms and signs of heart failure or left ventricular dysfunction? Please, be more clear.

Response; Data in table 1 are clinical data extracted from patients records. The diagnosis of heart failure was made according to current guidelines, based on symptoms and signs of heart failure, as well as echocardiographic assessment. This has been clarified in the revised manuscript.

- Author report: “Normal findings at stress were not followed by a rest study”. Considering that 60% of patients show wall motion abnormality and perfusion defect at rest, normal findings at stress could be a sign of myocardial viability.

Response; Both American and European recommendations now recommend selective use of stress-only imaging when the stress images are normal. These additional references have been added to the revised manuscript;


Henzlova MJ, Cerqueira MD, Mahmari JJ, Yao SS. ASNC imaging guidelines

- There is still a number of methodological problems that currently hamper clinical application of RTP stress echo (for instance, off-line analysis, contrast agent costs, availability of dedicated software). Please comment.

Response: We agree and we have added a section about this issue in the revised manuscript. We now state in the discussion that there are several additional issues with RTP-ASE that needs to improve user-friendly dedicated software, need for off-line analysis and the additional cost of contrast agents.

- The Authors specify medications at time of testing in the table, but they should discuss the limitations of the stress test imaging, which is highly influenced by anti.anginal therapy.

Response: Correct, this has been clarified in the revised manuscript. We clearly state that patients who had cardiac medications, which could interfere with the stress test, were informed to have their medication interrupted prior to the stress test. The decision whether to interrupt the drug administration was at the discretion of the referring physician. This should however not be a major issue since this is an agreement study between two different perfusion modalities.