Author's response to reviews

Title: Estimation of Cardiac Output and Pulmonary Vascular Resistance by Contrast Echocardiography Transit Time Measurement: a Prospective Pilot Study

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Editorial Board
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Dear Editors:

Thank you for the detailed review of our original research paper, MS: 2248814213859545, for publication in *Cardiovascular Ultrasound*. We especially appreciated the constructive advice and comments describing our research as “interesting”, “well-constructed”, and “an article of outstanding merit”. Thank you for inviting our paper for re-submission, and we are now pleased to present our paper, “Estimation of Cardiac Output and Pulmonary Vascular Resistance by Contrast Echocardiography Transit Time Measurement: a Prospective Pilot Study”, for your consideration.

The contribution of each author is detailed here:

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<th>Author</th>
<th>Conception &amp; Design</th>
<th>Data analysis &amp; interpretation</th>
<th>Manuscript drafting or revising</th>
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This paper is not under consideration elsewhere for publication; none of the paper’s contents have been previously published; and all authors have read and approved the manuscript. No author has relationships that may pose a conflict of interest with the submitted article.

As we have addressed all of the reviewers’ comments on the following pages, I hope that you will find our paper acceptable for publication. Thank you for your consideration of our research that we are excited to share with the ultrasound community.

Kind regards,

Brian G. Choi, MD, MBA, FACC
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Ref.: MS 2248814213859545
Response to Reviewer #1
We thank Reviewer #1 for the kind comments describing our paper as “interesting and well-conducted” and “an article of outstanding merit” and for the detailed constructive review. We have addressed Reviewer #1’s comments below.

1. My main concern regarding presented technique is the variability in measurement of the interval between full opacification of the right and left ventricle and the interval between the peak opacification of the right and left ventricle. I am afraid that the visual estimation of the moment of peak opacification may be highly subjective. The authors presented high inter-observer and intra-observer correlation, but I believe that presenting the absolute mean differences between the observers in these measurements is necessary to support the reproducibility of these measurements.

We shared the reviewer’s concern with variability in measurement, and debated whether peak opacification should be determined through image analysis (i.e., assessment of brightness within a region of interest). We were concerned that such a technique would discourage the practical use of this measure as echo reading workstations frequently do not have the same image analysis capabilities as traditional radiology workstations. However, we found that the visual frame-by-frame technique described in this paper appears highly reproducible, and per the reviewer’s recommendation, we have included the absolute mean differences of the observations in the Results section of the manuscript.

2. The authors observed that previously described echocardiographic methods for the determination of CO (Huntsman method) and PVR (Abbas and Haddad methods) did not correlate with RHC-determined values. I believe such findings should be discussed in the manuscript.

As per the Reviewer’s recommendation, the Discussion section has been expanded to discuss these alternative methods, and why these values may have failed to correlate as well as our proposed method. In addition, we have added additional references for the reader’s benefit to other papers that also highlight the limitations of the Huntsman, Abbas and Haddad methods.

3. The quantitative analysis of contrast enhancement in the ventricle might increase the objectivity of measuring the time to peak opacification of the cardiac chamber. I realize it was not the included in the methodology of this study, but this aspect should be discussed in the manuscript.

Although we considered quantitative image analysis, e.g., off-line analysis of image intensity, we elected to pursue a method that is more easily reproducible and can be performed on most cardiac PACS systems. The methodology section for the image analysis has been expanded per the reviewer’s request for better reproducibility. The reproducibility of this method was demonstrated through our inter- and intra-reader variability analysis.
Ref.: MS 2248814213859545
Response to Reviewer #2
We thank Reviewer #2 for the kind comments describing our paper as “well-written”, “very interesting” and “an article of importance” and for the detailed constructive review. We have addressed Reviewer #2’s comments below.

1. What do the authors mean by “peak LV/RV opacification” in opposition to “full opacification”, and how did they define those two different stages of opacification. This is not clear in the text or in figure 1. Please give more details.

Per the Reviewer’s suggestion, we have clarified the definitions in the methodology section.

2. Which formula (linear regression analysis) allowed to assess PVR? The authors explain that these values correlate, but how do they obtain a PVR value? This was explained for CO but not for PVR.

Per the Reviewer’s request, the linear regression analysis for PVR assessment has been added to the results section.

3. There is little explanation/hypothesis regarding why one interval rather than the other best reflects CO or PVR, and no clear practical summary of how to perform the measurements despite the difficulties the authors met during their study. Please develop.

Per the Reviewer’s suggestion, we have added to the Discussion section hypotheses to explain our results and added greater depth to the methodology section to enhance the reader’s ability to understand how the measurements were performed.

4. Also no mention of the poor performance of the standard echo measurements. Please develop.

As per the Reviewer’s recommendation, the Discussion section has been expanded to discuss these alternative methods, and why these values may have failed to correlate as well as our proposed method. In addition, we have added additional references for the reader’s benefit to other papers that also highlight the limitations of the Huntsman, Abbas and Haddad methods.

5. Regarding the contrast agent, there is no discussion regarding potential side effects. Please provide some information about safety of the contrast agent used.

Per the Reviewer’s recommendation, we have added to the Limitations section a discussion of the safety of the use of Definity.

6. Regarding the excluded patients, the authors refer to 5 patients who did not meet inclusion criteria, but in brackets 4+1+1 = 6). Please make the correction.

We thank the reviewer for alerting us to the unclear wording used. There were five patients that did not meet inclusion criteria, and one of these five patients met two exclusion criteria – both suspected tamponade and no right-heart catheterization. We have amended the confusing sentence in the revised manuscript.