Author's response to reviews

Title: Mitral Valve Analysis Adding a Virtual Semi-Transparent Annulus Plane for Improved Visualization of Prolapsing Segments

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Version: 3
Date: 13 May 2015

Author's response to reviews: see over
Dear
Editor Rosa Sicari,

We are grateful to receive our manuscript back peer reviewed and having the opportunity to submit the revised version of our manuscript, we have carefully addressed all the comments from the reviewers and hope the revised manuscript will be accepted for publication.

We would like to thank the reviewers for important and relevant comments to our manuscript “Mitral Valve Analysis Adding a virtual Semi-Transparent Annulus Plane for Improved Visualization of Prolapsing Segments”. We have made a revision of the paper based on the reviewer’s comments and suggestions.

Reviewer 1:

**Reg. Comment on the sample size of patients included.**
We agree that the sample size (10 patients) was small and have therefore added another 30 patients with degenerative mitral valve disease from our database. The sensitivity/specificity and accuracy/precision for both observers has been recalculated (page 10, table 3).

**Reg. Background and rationale of adding a virtual annulus plane.** Rationale of adding a virtual annulus plane to the method described in previous work (Beitnes et al. Int J Cardiovasc Imaging 2015;31:323-8).
The rationale of adding a virtual annulus plane is that it may further enhance diagnostic accuracy of mitral valve disease for less experienced echocardiographers, especially prolapses involving anterior leaflet, and furthermore, identify residual prolapses perioperatively, thus avoiding repair failures. In the previous work the two observers were experienced experts in echocardiography and the very good accuracy and precision may reflect that. In the present study, only one observer was experienced, and the other observer was a novice with limited echocardiographic experience. It turns out that their diagnostic accuracy was very similar and comparable with the former study. However, the study was not designed to allow for any comparism with conventional methods (2D/3D TEE), and therefore we can only speculate that use of 3D VSAP was of incremental help for non-experts. This study is first of all a proof of concept study, aiming to demonstrate that we were able to generate a virtual annulus plane in every patient and the potential of the method in demonstrating the prolapsing segments
crossing the annulus plane (Figure 8 and 9). We have added the rationale of using 3D VSAP in the manuscript (Background, page 5, para 2).

**Reg. Methods and how the virtual plane was created.**

We have added a figure that shows how the plane was created (Figure 2). Furthermore, a more comprehensive explanation is added in Methods, page 6, para 2. We typically used 20-25 points to generate the 3D virtual plane. The time frame used in systole for 3D VSAP analysis was chosen by scrolling frame by frame until the prolapse was most prominent by visual assessment (Methods, Echocardiography, page 8, para 2).

**Reg. Results.**

1. **Bland-Altman plot in phantom study.**

We have added two figures (Figures 6 and 7) showing Bland-Altman plots for non-planar angle measurements and the calculated AL-PM/AP ratio.

2. **Selection bias and limited statistical power due to low sample size of patients.**

We have added 30 patients with degenerative mitral valve disease in order to avoid selection bias and limited statistical power.

3. **Patients’ characteristics.**

A total of 6 patients (of 40) were diagnosed with Barlow disease.

4. **Incremental diagnostic value of the method.**

We recognize that comparison with 2D and 3D TEE may demonstrate the incremental diagnostic value of the method. As former pointed out, this study is first of all a proof of concept study, aiming to demonstrate that we were able to generate a virtual annulus plane and the potential of the method in demonstrating the prolapsing segments crossing the annulus plane (Figure 8 and 9). The method still needs refinement with even better detection of mitral annulus, improved saddle shape configuration as well as tracking algorithms that allow for movement of the annulus plane throughout the cardiac cycle. Furthermore, as stated in the text, with the present technique, we were not able to analyze 3D VSAP derived from 3D TEE recordings. This will be solved in the near future. When these challenges are solved, the method should be tested systematically including 3D VSAP from 3D TEE with the present methods used for mitral valve analysis as suggested by the reviewer.
5. Quantitative measurements of mitral annulus.

The mitral annulus diameter (MAD) derived from 2D parasternal long axis view (antero-posterior diameter) has been reported in Table 2.

Discussion.

We have expanded the discussion of the advantages and clinical implications of the 3D VSAP method (Discussion, page 11 and 12, para 2 and 3).
Reviewer 2:

1. **Reg. Major Compulsory Revisions. Sample size.**
   We agree that the sample size (10 patients) was small and have therefore added additional 30 patients with degenerative mitral valve disease from our database. The sensitivity/specificity and accuracy/precision for both observers has been recalculated (page 10, Table 3).

2. **Reg. Title of the manuscript ("improved visualization")**
   We agree that the title may be misleading and did not compare the findings with conventional methods applied today (2D/3D TEE). The title has therefore been modified to: “Mitral Valve Analysis Adding a Virtual Semi-Transparent Annulus Plane for Detection of Prolapsing Segments”.

3. **Reg. Agreement between 3D VSAP and direct measurements.**
   We have added two figures (Figures 6 and 7) showing Bland-Altman plots for non-planar angle measurements and the calculated AL-PM/AP ratio. With the present method, we were not able to measure absolute values of diameters, and therefore only reported the ratio. This will be implemented in the next version of the analysis tool.

4. **Reg. Agreement between observers. Kappa values.**
   This is an important comment and we have added the Kappa value in the paper (Results, patient study page 11, para 1).

5. **Reg. Statistical section. Normality of variables.**
   For the phantom study, there was no normal distribution. We have added to the statistical section all statistical tests used in the study.

**Minor Essential Revisions**
6. Reg. Equation and r value in the legend of fig 3 and 4
We have added the equation and r value in the legend of fig 4 and 5.

7. Reg. Error in regression coefficient reported in the text
We are sorry that the regression coefficient showed in figure 4 was different from value reported in the text (0.07776). The value is replaced with 0.7776 that is the correct number (page 10, para 1).

8. Reg. Regression coefficient in fig. 4
The scatter plot with regression line in fig. 5 demonstrates one out layer (1.53, 1.21) that causes the lower regression value (r = 0.65). We have added a Bland-Altman plot (fig 7) that also demonstrates this out layer (more than 2 SD from the mean value). The other values are very close to the mean value and systematic bias is only 0.03.

9. Reg. Reference of recent feasibility paper
Thank you. We have updated the reference (References, page 15, reference 16) and added a new one (References, page 15, reference 18).

The 2D and 3D data were not recorded by any of the two observers and they had no knowledge of the findings from these recordings. A third person copied the 3D full volume data sets from the image server and the recordings were labeled without any clinical information.

Discretionary Revisions

11. Non-planar angle analysis in patients
This is a well taken comment and theoretically the same concept can be applied to patients as was used in phantoms. However, in patients, we have no gold standard, and therefore decided not to perform these measurements.