

## Peer Review File

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### Reviewer A:

The manuscript demonstrates the larger area of tricuspid valve than that of mitral valve in healthy controls and patients with SMR (secondary mitral regurgitation) by CCTA (cardiac computed tomographic angiography). Furthermore, strong correlation between IC (intercommissural distance) of MVA (mitral valve annulus) and SI (superio-inferior distance) of TVA (tricuspid valve annulus), and between perimeter of MVA and TVA were observed in control subjects. These indexes will become indicator of TVA dilation which is the target of treatment at mitral valve operation. Thus, this manuscript includes new knowledge, but some improvements are required. Especially, numbering of figures must be confirmed carefully.

We thank the reviewer for thoroughly reviewing the manuscript and providing vital suggestions for improving it.

### Major comments

Comment 1: The method is close to the reference No.6 and 25. In those articles, trigones were determined and seem the important factor in the method. Also, Figure 2 in this manuscript shows the trace of trigones. On the other hand, the reference No.16 did not determine trigones in CMR (cardiovascular magnetic resonance) study. Documentation about methodology with and without the trigones might make better understanding of this study.

Reply 1: We have now clarified this in the methods section. We did include the trigones in our segmentation to fully represent the 3D shape of the mitral annulus, as shown in Figure 2.

Changes in the text 1: "The method for segmentation of the annulus was performed as previously described for the MVA after identifying the trigones (6,25), but with the inclusion of the anterior MVA horn (Figure 2) to represent the 3D saddle shape of the annulus fully." (see Page 7, lines 15-18).

Comment 2: The relation between TVA diameter in the reference No.19 and TVA SI distance in this study is not certain. From the mean +/- SD value in Table 4, it is difficult to imagine whether there were subjects who meet the operation criteria of over 70 mm of TVA diameter. Of course, 70 mm was measured during operation from the anteroseptal commissure to the anteroposterior commissure, and it could not become same indicator in this study. However, the usage of value in this CCTA study as predictor must be important to decrease operation time or determination of operative procedure. Please document about the relation of TVA diameter during the operation and the results of this manuscript.

Reply 2: We agree with the reviewer that the diameter measured by Dreyfus et al. is from the

anteroseptal commissure to the anteroposterior commissure. However, we measured differently in this study to allow for better characterization of the measurements by CT. We have added the following paragraph in the discussion.

Changes in the text 2: "It is noteworthy that our CCTA TVA measurements do not precisely reflect the anteroseptal to the anteroposterior commissural distance reported by Dreyfus et al. This distance is likely to be closer to the SI distance in our study but is not exactly the same. Future studies will be needed to correlate surgical and CCTA measurements." (Page 13, lines 19-22).

Comment 3: Limitation in this study includes the different ratio of patients with TR. In PMR group, only one patient had grade 2+ TR(tricuspid regurgitation) in 50 subjects (2%). But SMR group, 7 patients had grade 2+ TR in 25 subjects (28%). The larger TVA area in SMR than PMR might depend on this ratio. Additional explanation about this difference of ratio is required.

Reply 3: This is an excellent observation, and we have now performed a sensitivity analysis, excluding patients with 2+ TR. The results are shown in supplementary tables 1 and 2. Results are consistent with the original analysis, including these patients. We have included this in the discussion.

Changes in the text 3: "These changes remained significant even after excluding patients with 2+ TR (supplemental Tables 1 and 2)" (Page 13 Lines 5-6).

Comment 4: Figure 3(Figure: CDT-20-903-FIG3-9462.jpg) on Page 36 must be Figure 4, and Figure 4(Figure: CDT-20-903-FIG4-4702.jpg) on Page 37 must be Figure 3, by the manuscript in the section of Results and Figure legends.

Reply 4: Thanks for the careful review of figures and references. This has been corrected in the revised manuscript.

Comment 5: Figure 5(Figure: CDT-20-903-FIG5-2375.jpg on Page 38)(also the legend) is Figure 6. And, Figure 6(Figure: CDT-20-903-FIG6-9796.jpg on Page 39)(the legend too) is Figure 5.

Reply 5: Thanks for the careful review of figures and references. This has been corrected. We are sorry for missing these errors.

Comment 6: Table 2, Figure 3(Page 36) and Figure 5(Page 38) must be constructed with the data of Table 3 and 4. It is understandable to make comparison between MVA and TVA, new Figure or Table were required other than Table 3 and 4. Table 2 provides the result of statistical analysis. However, Figure 3(Page 36) is not including additional information (There is no statistical results in Figure 3).

Figure 5(Page 38) is illustrated figure with main results of this manuscript, and the Title of this figure should contain the term "summary".

Reply 6: We fully agree. As recommended, we have rearranged the figures' order, removed figure 4 (erroneously labeled as figure 3) as it does not provide additional information, and updated the title of figure 5 (previously numbered as figure 6) in the revised manuscript.

Comment 7: In the illustration of MVA in Figure 5(Page 38), IC length is shorter than SL length. However, the results showed that IC is longer than SL.

Reply 7: We have revised Figure 5 to portray the results correctly.

Comment 8: IC/SL and SI/AS ratios of Mitral Valve is  $1.17 \pm 0.10$  in Table 2, and it is  $1.16 \pm 0.11$  in Table 3. The difference was very small, but the data must be same.

Reply 8: We agree with this comment. The error occurred in rounding. Both should be  $1.16 \pm 0.11$  and have been corrected (see Table 2 and Table 3).

### **Minor comments**

Comment 1: Introduction - 1st Paragraph, line 7:"TV" needs full spelling before abbreviation.

Reply 1: Thank you for this comment. We have made this change.

Changes in the text 1: "tricuspid valve (TV)" (see 1<sup>st</sup> paragraph line 8 of introduction)

Comment 2: Methods, Study Population - 1st Paragraph, line 8:"CT" needs full spelling before abbreviation.

Reply 2: Thank you for this comment. We have made this change.

Changes in the text 2: "computed tomography (CT)" (see 1<sup>st</sup> paragraph line 13 of Methods, Study Population)

Comment 3: Methods, Cardiac CT data acquisition - 1st Paragraph, line 5: "and SMR patients, and to the pelvis for PMR patients." and the radiation dose in Table 1 are not related (radiation dose of SMR is more than PMR).

Reply 3: Thank you for this comment. The radiation dose in SMR was higher despite the larger window of acquisition in PMR, given that SMR patients had a retrospective multiphase acquisition throughout the cardiac cycle without dose modulation. In contrast, PMR patients had a single phase prospective acquisition.

Changes in the text 3: "SMR patients had a retrospective multiphase acquisition throughout the

cardiac cycle without dose modulation. In contrast, PMR patients had a single phase prospective acquisition." (Page 27 Lines 3-4 Table 1)

Comment 4: Methods, CT Data analysis - 2nd Paragraph, last sentence: does "The atrial areas were measured on a reconstructed 4-chamber view" mean that the data of area was measured as projected area and not as 3D area?

Reply 4: This is accurate that the measurement of the LA area was the projected area and not measured as 3D area. This is now clarified in the manuscript.

Changes in the text 4: "The atrial areas were measured as a projected area on a reconstructed 4-chamber view" (Page 8 Line 9-10).

Comment 5: Methods, Echocardiographic Data - 1st paragraph, line 1: "cardiac CTA" could be "CCTA".

Reply 5: Thank you for this comment. We have made this change.

Changes in the text 5: "CCTA" (see Methods, Echocardiographic Data – page 8, line 12).

Comment 6: Methods, Statistical analysis - 1st Paragraph, line 2: "(25<sup>th</sup>, 75<sup>th</sup> percentile)" both "th" should be superscript.

Reply 6: We have made this change.

Changes in the text 6: "25<sup>th</sup>, 75<sup>th</sup> percentile" (see Methods, Statistical analysis – page 8, line 22).

Comment 7: Usually, insertion of the number of Table or Figure in brackets are not in Title or subtitle.

- a. MVA dimensions in PMR and SMR patients (Table3, Figure 4A) Title: Both of Figure 4A (as Figure 3 on Page 36) and Figure 4B are including the data about MVA dimensions in PMR and SMR patients.
- b. TVA dimensions in PMR and SMR patients (Table4, Figure 4B)Title: Both of Figure 4A (as Figure 3 on Page 36) and Figure 4B are including the data about TVA dimensions in PMR and SMR patients.

Reply 7a/b: Thank you for your suggestion. We have added table/figure headings into the text. Regarding figures 4A and figure 4B, we agree with the reviewer that they visually represent the same data as Tables 3 and 4, respectively. We have thus removed this figure to avoid redundancy.

Comment 8: Discussion, MVA and TVA changes in both PMR and SMR (Figure 6); Title:

"(Figure 6)" should be moved from the Title to the text.

Reply 8: We have made the appropriate changes.

Comment 9: Discussion, 1st paragraph, line 5:"TR(<=2)" may be TR(>=3+).

Reply 9: We have made this change.

Changes in the text 9: (>=3+)" (Page 13, Line 5).

Comment 10: References - No.15 and No.36 are same article(guideline) in different journals.

Reply 10: Thank you for this observation. We have removed number 36.

#### **Reviewer B:**

I would like to congratulate the authors on their work for evaluating the tricuspid valve which can be a major cause of comorbidity in patients with mitral valve disease. This work needs to be continue and have a better understanding of TV changes and time for intervention in patients with MV disease.

Thank you very much for thoroughly reviewing the manuscript, providing vital suggestions for improving the manuscript, and for the enthusiasm for our findings. We agree and aim to further explore these important points in our future research.

#### **Reviewer C:**

Thank you very much for thoroughly reviewing the manuscript and providing vital suggestions for improving the manuscript.

Comment 1: Page 8, Second line - We adopted SI and AS as better anatomic ....

Reply 1: Thank you for your comment. We have made this change.

Changes in the text 1: "as" (see Page 8, Line 7).

Comment 2: Replace word echo with TTE (add abbreviation at the beginning of paper) or add echo as an abbreviation for echocardiogram at beginning.

Reply 2: Thank you for the comment. We have made the following changes.

Changes in the text 2:

Echo has been replaced by “echocardiogram” throughout the manuscript.

Comment 3: Page 11 Section title: Predictor of indexed TVA area: The LVEF, Indexed LVEDV, RVSP, and presence of dysfunction showed moderate (add correlation).

Reply 3: Thank you for your comments. We have added the word correlation.

Changes in the Text: "correlation" (see Page 11 Line 12).

Comment 4: Atrial fibrillation is known to cause RA and LA dilation (and possibly annulation dilation); there was a difference in prevalence between the 3 groups. Was this adjusted for in the statistical analysis?

Reply 4: This is an excellent observation, and we have now performed a sensitivity analysis, excluding patients with atrial fibrillation. The results are shown in supplemental Tables 3 and 4 in the supplement. Results are consistent with the original analysis. We have included the following in the discussion.

Changes in the text 4: "These changes remained significant even after excluding patients with 2+ TR (supplemental Tables 1 and 2) and patients with atrial fibrillation (supplemental Tables 3 and 4)." (Page 13 Line 6-7)