**Author’s response to reviews**

**Title:** Evaluation Using a 4D Imaging Tool Before and After Pulmonary Valve Replacement in a Patient with Tetralogy of Fallot; What Is the Optimal Timing of Re-operation?

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Comments:

We would like to thank the Editors and Reviewers for their comments on our manuscript, including their very useful suggestions for improvement. We have endeavored to respond to their comment and suggestions, and we believe that we have adequately modified the revised manuscript to address their concerns.

Responses to all queries are highlighted in red in the revised manuscript.

(1) Responses to Reviewer #1
We very much appreciate your valuable comments and suggestions. According to your comments, we have revised the manuscript as follows.

Reviewer #1:

Takigami et al. reported that the 4D MRI imaging can clearly evaluate pulmonary regurgitation, right ventricular (RV) volume and flow energy loss (FEL) in a patient with post-operative TOF. They conclude that 4D imaging was useful in the decision of re-operation in this patient. The 4D MRI imaging and evaluation for RV dysfunction is quite impressive, however, I have some questions.

Concern 1: What was the operation method of TOF in her two years old? VSD closure and RVOTR by RA incision?

Response 1:

We greatly appreciate your comment. Unfortunately, we apologize that we can’t answer this question because she underwent the operation in other hospital 52 years ago and there is no surgical record about it. We guess that the surgery was performed in the way you mentioned.

Concern 2: What was this wide tachyarrhythmia? VT, rapid atrial fib or atrial flutter? Sinus rhythm was also CRBBB? How long was QRS duration in sinus rhythm? QRS duration was improved after re-operation?

Response 2:

We apologize for confusing you. We are convinced that this tachyarrhythmia was atrial flutter because the electrophysiological study showed an intact anterior internodal pathway and a slow pathway just through the outside of the right atriotomy line scar, which is supposed to cause a re-entry circuit (Fig. 3). Sinus rhythm was also CRBBB and QRS duration in sinus rhythm was 199 msec. QRS duration didn’t change after the procedure.

Concern 3: Is there any possibility that RV dysfunction was caused by tachycardia-induced cardiomyopathy? Did she have impaired LV dysfunction?

Response 3:
We assume that the deterioration of RV was mainly caused by severe PR. However, her LV ejection fraction was also slightly reduced (48%). Tachycardia-induced cardiomyopathy might have adversely affected both left ventricular function and right ventricular function.

Concern 4: The authors mentioned that RFCA for atrial flutter in this patient might have been effective to improve RV dysfunction. Did you have a choice of RFCA before PVR, or trans-catheter pulmonary valve replacement (TPVR)?

Response 4:

In the first section of Case presentation, she underwent atrial flutter ablation (cavo-tricuspid isthmus block line) when she was 50 and 51 years old. However, her atrial flutter was continued. We judged the operation combined with PVR and ablation was more effective than catheter procedure alone to treat both atrial flutter and pulmonary regurgitation, resulting in the RV improvement.

Concern 5: RV size and FEL had decreased remarkably, which contributed RV reverse remodeling (P10, L3).

The authors described the re-operation method in this patient was PVR, MAZE, and plication of RA. In contrast, some reports showed RV volume and dysfunction did not improve only PVR in patients with post-operative TOF. Is there any possibility that repeated tachyarrhythmia was mainly contributed RV remodeling in this patient? Or did she have any residual lesion, such as TR?

Response 5:

In this case, we performed only PVR and RA maze. As you mentioned, it is reported that surgery that is too late cannot improve RV function. In this case, repeated tachyarrhythmia might have partially contributed to the RV remodeling. However, we guess that the deterioration of RV was mainly caused by severe PR. Her RVEDVI was 169.54ml/m2 that was borderline considering the PVR in the guideline. From the RV volume, the timing of PVR was not too late. Moreover, her flow energy loss was very high that suggest the overload of RV. After PVR and RA Maze, the remarkable volume- and energy-overload of RV was decreased, and RV size would be remodeled.

Concern 6: In evaluation of RV function and RV remodeling, what is the superiority of MRI imaging to echocardiography to decide the optimal timing of re-operation?
Response 6:

Thank you for your valuable comment. We think MRI imaging has more excellent reproducibility. Furthermore, some study suggested MRI is more accurate than echocardiography in assessing the severity of MR (1), and regurgitant volume by CMR was more predictive of outcomes than by TTE in subjects with AR (2). Considering to evaluating of pulmonary valve, it seems to be more difficult to measure pulmonary regurgitant volume correctly by echocardiograph. And more, flow energy loss can detect the overload of RV early. We believe that 4D MRI is more effective tool to evaluate right heart system and to decide optimal timing of the operation.

We added about the superiority of MRI imaging to echocardiography in the discussion of revised our manuscript.

(2) Responses to Reviewer #3

We very much appreciate your valuable comments and suggestions. According to your comments, we have revised the manuscript as follows.

Reviewer #3:

Timing of operation for pulmonary artery stenosis after operation of TOF is controversial. The authors evaluated RV energy loss using a 4D imaging tool of cardiac MRI, and reported a case in which energy loss was decreased after operation of PS.

There were some comments from the reviewer to improve the understanding of this paper.

Concern 1: Although evaluation of RV function using echocardiography is difficult because of its anatomical shape, echo data of RV function such as TAPSE, s' of TV, FAC, and RV strain would be informative for doctors who don't have the 4D imaging tool.

Response 1:

Thank you for your valuable comment. I agree with your comment. However, we don't know obvious cut off value of RV function by echocardiographic parameter in adult congenital heart disease. We think MRI imaging has more excellent reproducibility. Furthermore, some study suggested MRI is more accurate than echocardiography in assessing the severity of MR (1), and regurgitant volume by CMR was more predictive of outcomes than by TTE in subjects with AR
(2). Considering to evaluating of pulmonary valve, it seems to be more difficult to measure pulmonary regurgitant volume correctly by echocardiograph. And more, flow energy loss can detect the overload of RV early. We believe that 4D MRI is more effective tool to evaluate right heart system and to decide optimal timing of the operation.

We added about the superiority of MRI imaging to echocardiography in the discussion of revised our manuscript.

Concern 2: Which was the most important factor to reduce energy loss of RV?

Response 2:

Thank you for your question. In this case, the energy loss was obvious in the phase both of early systole and diastole at the pulmonary valve position, indicating that the energy loss was mainly produced by severe PR and relative PS. We think PVR contributed most to energy loss reduction.

Concern 3: The reader will not know normal value and cut off to operate of energy loss.

Response 3:

We measured energy loss about normal volunteers in their thirties. The average of right heart system was about 1.0 mW. Now, we ready to publish about tThe normal value of energy loss is now in preparation for publication. On the other hand, Wwe have not found the optimal cutoff value for surgery yet and are trying to investigate.

Reference:
