Peer Review File

Article Information: https://dx.doi.org/10.21037/jtd-23-1727

Reviewer A

Thank you for allowing me the opportunity to review this paper about RV dysfunction after mitral valve surgery. I read the manuscript with interest. My comments are as follow:

1: Page 6 lines 197-198. Please add indications and contraindications of minimally invasive approach. For example, presence of concomitant tricuspid disease, severe LV/RV dysfunction, and severe pulmonary hypertension, the history of prior cardiac surgery, etc. Authors concluded that minimally invasive approach could contribute to decrease the risk of postoperative RV dysfunction. But without data on differences in preoperative characteristics between minimally invasive approach and conventional approach, it is difficult to give such conclusion. Patients with minimally invasive approach might have better hemodynamic etc preoperatively, which could be associated with better postoperative RV function.

Reply 1: We thank the reviewer for this comment. We partially agree with the reviewer in this regard. As the reviewer mentioned baseline characteristics might affect the incidence of RV-dysfunction. Even though, the following points should be considered: First of all, the surgical access is mainly surgeon depended, experienced surgeons tend to perform minimally access MV-surgery especially in isolated MV procedures or even when combined with TV-surgery. Second of all, other factors impact the surgical access are mainly other concomitant procedures, patients BSA and peripheral artery disease (PAD) etc. This however, did not play any role in patient selection and inclusion in this study as the main aim of the study is to evaluate the postoperative RV-function after MV-surgery and not the outcomes of the surgical access. Third, in this cohort, the main aim was to examine the RV performance after MV-Surgery, the cohort is quite small and the number of patients undergoing MIS was even smaller (only 26%), hence a baseline comparison might allow confusing misleading results which are not the purpose of the study. Therefor we performed a multivariate analysis to re-evaluate the results of the univariate analysis which is a prober statistical analysis in small cohorts. Finally, we concluded that these factors “seem” to influence the incidence of postoperative RV-dysfunction. Accordingly, the conclusion has been modified to avoid any misleading messaging.

Change: Page 6: lines 174-178 & Page 14: lines 414 - 421

2: Considering that residual mitral regurgitation (and postoperative trans-mitral valve pressure) or tricuspid regurgitation after surgery are very important factors associated with postoperative hemodynamic data and heart function, please add such data in tables.

Reply 2: We thank the reviewer for this comment. We added all the requested data to table 6A.

Change: Please check table 6A

3: Page 6 lines 198-199. Although the authors mentioned that anti-pulmonary hypertension use reduced incidence of postoperative RV dysfunction, the cohorts to whom anti-pulmonary hypertension agents seem to have higher rate of postoperative RV dysfunction compared with those who did not receive the agents in Figure 4. Could you add explanation?

Reply 3: We thank the reviewer for this comment. We believe the reading of the figure from

the side of the reviewer was not clear. The clustered bars in figure 4 is reporting a "cross tables" analysis (X&Y) that represents the usage of anti-pulmonary hypertension on the "x" aches and the incidence of RV dysfunction on the "y" aches. The figure shows a reduction in the incidence of RV dysfunction in patients received anti-pulmonary hypertension agents n=18 in comparison to patients, who did not receive an anti-pulmonary hypertension agents n=22 (as represented with the red bars). The reduction is statistically not significant, that's why we reported that the usage of anti-pulmonary hypertension agents tends to reduce the incidence of postoperative RV dysfunction, however, this did not reach statistical significance (p = 0.104). The reading of only one side of the figure might lead to a misleading interpretation.
Change 3: No changes. Please check figure 4.

4: Page 6 line 208. I am not sure whether it can be said that prolonged ventilation time was an independent predictors of postoperative RV dysfunction, as this factor is 'postoperative' instead of 'preoperative' factor (I mean MV surgery was already done and some of patients already developed RV dysfunction due to surgery itself at the time of postoperative ventilation management). I understand there is relationship/association between prolonged ventilation and postoperative RV dysfunction, however, the cause and the effect might be reversed (RV dysfunction might have caused prolonged ventilation).
Reply 4: We thank the reviewer for this comment. We agree with the reviewer in this point if mechanical ventilation occurred after surgery. However, the ventilation time begins from the time of intubation until extubation and not from the time of admission to the ICU, so the mechanical ventilation per se was occurred before and during surgery and not after surgery. The term prolonged ventilation was captured after performing multivariate regression analysis were the OR (CI) define that the increased ventilation time as an independent factor for incidence of postoperative RV-dysfunction → 1.12 (0.996 – 1.258), P= 0.058. We added an explanation to the discussion text accordingly.
Change 4: Page 13, Lines 385 – 390. Please check table 7
****

Reviewer B
The paper under review explores the impact of mitral valve regurgitation (MR) surgery on right ventricular (RV) dysfunction. It delves into the assessment methods pre- and post-surgery, examining the incidence and potential predictors of RV dysfunction, particularly in the context of pulmonary arterial hypertension (PAH) and the type of surgery performed. While the study offers valuable insights into the field, several points warrant criticism and consideration.

1. There are numerous papers that have discussed both short term and long-term RV dysfunction after mitral valve surgery and the authors should cite.
Reply 1: We thank the reviewer for this comment. We already cited couple of papers and we cited some recent studies to the text.
Change 1: Page 3: lines 67-68 & Page 10: lines 300 - 308

2. The authors should provide the target cooling temperature for the bypass cases as well type and method of cardioplegia protection. Was left ventricular vent placed during bypass, also The

Major concerns relate to the P values on table 7 that do not hold acceptable statistical significance. As none of the P values are below 0.05; Therefore, highlighting the significant in bold is erroneous and misleading. The author's response is required.

Reply 2: We thank the reviewer for this comment. During mitral valve surgery the patients would be cooled down and aiming temperature would be 32° C. All patients received left ventricular venting via the left atrial structures (directly or via right superior pulmonary vein). All patients received antegrade cold crystalloid cardioplegia (Custodiol, Köhler Chemie, Alsbach Germany).

Based on the statistical methodology of multivariate regression analysis, all p values between 0.05 up to 0.1 are defined to be significant or tend to be significant values (*Cox DR. Regression models and life tables (with discussion). Journal of Royal Statistical Society B 1972; 34:187–220.*). In this case, the sample size and the incidence of any event (variables) would play an important role for the calculated p-value (the bigger the cohort the more significance the p-value). The multivariate regression analysis in the current study reported 2 parameters to be significant parameter and three parameters to tend for significance to influence the incidence of postoperative RV-dysfunction as mentioned in details within the results section. The bold highlighting was just to provide rapid check from the reader and not to cause any confusion, the bold highlight is now eliminated.

Change 2: Page 6 Line 178-185. Please check page 9: Line 270-282 and table 7.

3. Moreover, the study lacks a detailed discussion of potential confounding variables and their impact on the outcomes. Variables like comorbidities, other concurrent cardiac issues, or variations in surgical techniques could significantly influence RV function post-surgery. Failing to thoroughly address these confounders might weaken the study's conclusions and limit the applicability of the findings.

Reply 3: We thank the reviewer for this comment. We totally agree with the reviewer regarding this point. The regression analysis module was used in the current study to define variable that may impact incidence of the postoperative RV-dysfunction, however due to the small cohort size, we were not able to add all baseline and perioperative variables to the multivariate regression analysis which in turn would weaken the statistical analysis and might allow misleading results. This has been mentioned within the limitation section as recommended.

Change: Page 9: lines 270-282, Page 14: lines 414 -421 & 427-429.

4. Additionally, the discussion of the results lacks an in-depth exploration of the clinical implications and practical relevance of the findings. For example, while RV dysfunction is reduced, did that require more heart failure medication, re-admissions or hospital stay. Despite reporting statistical correlations between variables, the study could better elucidate the clinical significance of these correlations and their implications for patient care and prognosis.

Reply 4. We thank the reviewer for this comment. The clinical implications drawn from our study findings emphasize the prevalence of RV dysfunction following MV surgery. Ensuring adequate intraoperative support for both LV and RV function is pivotal in preserving postoperative RV functionality. As such, meticulous preoperative preparation for these patients become imperative. Enhancing their clinical status by optimizing heart failure medication before surgery is crucial. Additionally, a thorough postoperative assessment of the RV is vital

to prevent any progression from dysfunction to outright RV failure. Long-term evaluations and prognosis regarding RV dysfunction subsequent to MV surgery warrant further comprehensive studies that delve into the extended functionality of the RV.
Change: Page 10: lines 300-308 & Page 12-13: lines 375- 403.

5. Finally, the study's conclusion suggests the need for further investigation with larger cohorts and longer follow-ups. While this recommendation is valid, the paper could have proposed specific directions for future research, highlighting key unanswered questions or potential avenues for more detailed exploration.
In summary, while the study offers insights into the impact of MR surgery on RV function, the paper is additional evidence of the collateral injury to the right ventricle following mitral valve surgery.
Reply 5: We thank the reviewer for this comment. We provide a protentional proposal for the future under investigation studies as recommended.
Change 5: Page 13, line 404 - 411
****

Reviewer C
The submitted manuscript appears very clear, informative and deals with a more or less unobserved topic. Despite this is a single centre study with limited number of patients the results are very interesting and comparable with many other centre experiences. Surprising the results and outcomes in MIMVS. I have no chance to recommend any changes, great paper!
Reply: We thank the reviewer for this comment. We have performed some changes based on comments from other reviewers and hope to have the chance to the glance the new version.
Change: Please check the revised manuscript.
****

Reviewer D
I am proud of reviewing the manuscript for journal of Thoracic Disease, in which the authors investigated right ventricular (RV) function in patients undergoing mitral valve repair. The reviewer congratulates the authors' excellent results of mitral valve repair, despite of high rate (9.8%) of re-exploration of bleeding. The authors clarified RV function using echocardiographic parameters of TAPSE, RV S', and FAC. The authors also described that minimally invasive surgery was an independent factor to prevent RV dysfunction after multivariate regression analysis, which was considered sceptical and be difficult to be explained, although the authors mentioned the possible cause could be less manipulations of the heart and a small wound area. Taken together, this manuscript is less impressive to this journal and should be submitted to more specific journals.

There are other points to be improved.
1. The authors adopted systolic pulmonary artery pressure (PAP) as an indicator of pulmonary hypertension (PH). However, according to ESC guideline, PH is defined as mean PAP ≧20mmHg. The authors should describe why systolic PAP was adopted?
Reply 1: We thank the reviewer for this comment. We totally agree with reviewer that

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) of ≥20mmHg as per the ESC guidelines, typically measured using pulmonary artery catheterization (PAC). In our study, we opted to use systolic pulmonary artery pressure (sPAP) to assess PH severity due to its common measurement via echocardiography, especially in cases of tricuspid valve regurgitation. The severity of PH holds significance in the EuroSCOREs, which provides easy and known classification of the severity of PH. During induction of anaesthesia, we meticulously measured the mPAS, sPAP and dPAP in every patient using PAC. Interestingly, while the sPAP values obtained via PAC were not significantly higher, they closely resembled the sPAP values measured via echocardiography.
Change: Page 5 & 6: lines 154-162.

2. The authors measured intraoperative PAP using Swan-Ganz catheter. What is the divergence between preoperative systolic PAP using echocardiography and intraoperative PAP?
Reply 2. We thank the reviewer for this comment. The mean systolic pulmonary artery pressure (sPAP) measured intraoperatively via transesophageal echocardiography was 38.7±10.5 mmHg, while the preoperative echocardiography recorded a mean sPAP of 35.6±15.7 mmHg. Notably, it is intriguing to note the higher mean sPAP values during the intraoperative phase, potentially influenced by various factors such as anesthesia, ventilation, volume status, and catecholamine intake.
Change 2: Page 6: lines 162-171.

3. The authors should describe definition of PH in Method, although Table 1 showed no PH, moderate PH, and severe PH.
Reply 3: We thank the reviewer for this comment. Prior to surgery, we did not employ a pulmonary artery catheter (PAC) in the patient. Consequently, we relied on the EuroSCORE classification of pulmonary hypertension (PH) and categorized the patients into three groups, as delineated in Table 1: those without systolic PH, those with moderate systolic PH (31-55 mmHg), and those with severe PH (> 55 mmHg
Changes: Page 6: lines 162-166.

4. The authors administered Iloprost or NO or Tadalafil to 34.7% of patients. The authors should describe inclusion criteria of administration of these drugs.
Reply 4: We thank the reviewer for this comment. Patients exhibiting preoperative or intraoperative right ventricular (RV) dysfunction alongside an increase in intraoperative systolic pulmonary artery pressure (sPAP) measured by pulmonary artery catheterization (PAC) were administered Iloprost. Those experiencing a decline in oxygenation postoperatively received additional Nitric Oxide (NO) therapy. Moreover, individuals who sustained elevated systolic PAP measured by PAC despite Iloprost administration postoperatively were provided with Tadalafil.
Change 4: Page 8: lines 245-250.
****

Reviewer E
This article evaluates right heart function after mitral valvuloplasty and demonstrates the utility

of 3D echo evaluation, MICS surgery, and the importance of perioperative PH management.

1) What do you think is the mechanism by which MICS surgery preserves postoperative right heart function?
Reply 1: We thank the reviewer for his comment. In this study minimal invasive MV repair seems to reduce the incidence of RV dysfunction despite a longer bypass time. This could be attributed to less manipulations of the heart and the small wound area of the heart.
Change 1: Page 12: lines 375-378.

2) Is there any difference in background between patients undergoing MICS surgery and those undergoing midline incision?
Reply 2: We thank the reviewer for this comment. We basically did not perform any statistical analysis to confirm this as mentioned to the first reviewer. The study cohort is small and the number of patients undergoing MICS is even smaller and this might allow misleading interpretation of the results. Additionally, the aim of the study was to evaluated to the RV performance after MV-surgery and not to evaluate outcomes of the which surgical access.
Change 2: No Change

3) Table 1 includes 9.8% of patients with COPD. Does this have any effect on postoperative right heart function after MVP?
Reply 3: We thank the reviewer for this comment. As mentioned in Table 1 Nine patients (9.8%) had COPD classified as GOLD I – II, indicating that the COPD stage was not severe among these individuals. Their ventilation time was not prolonged, and it had no significant impact on postoperative RV function when compared to patients without COPD.
Change 3: Page 7 & 8: lines 217-220.
4) Please state the indications for using NO or tadalafil. I believe tadalafil is indicated for pulmonary hypertension without high PCWP.
Reply 4: We thank the reviewer for this comment. Patients exhibiting preoperative or intraoperative right ventricular (RV) dysfunction alongside an increase in intraoperative systolic pulmonary artery pressure (sPAP) measured by pulmonary artery catheterization (PAC) were administered Iloprost. Those experiencing a decline in oxygenation postoperatively received additional Nitric Oxide (NO) therapy. Moreover, individuals who sustained elevated systolic PAP measured by PAC despite Iloprost administration postoperatively were provided with Tadalafil.
Change 4: Page 8: lines 245-250.

5) Please state why prolonged ventilation time contributes to postoperative right heart failure
Reply 5: We thank the reviewer for this comment. The multivariate regression analysis identified increased mechanical ventilation time to correlate with the development of postoperative right heart failure. This might be attributed to the potential association between the incidence of perioperative atelectasis and increased pressure overload on the right ventricle.
Change 5: Page 13: lines 385-390.

6) What is the definition of RV dysfunction in this paper?

Reply 6: We thank the reviewer for this comment. .RV-function and dimensions were assessed according to the American Society of Echocardiography (ASE) guidelines for assessment of the right heart in adults. RV-function was assessed using tricuspid annular plane excursion (TAPSE), RV systolic prime (S') and fractional area change (FAC) with abnormal levels considered as less than 16 mm, 10 cm/s and 35%, respectively. In the current study RV-dysfunction was defined when at least two of these three echocardiographic indices were significantly reduced according to the ASE guidelines.
Change 6: Page 4: lines 116- 120 & Page 5: lines 129-130.

7) The values of TAPSE and RV S' in Table 2 and Table 6A are different from the text.
Reply 7: We thank the reviewer for this comment. There was a typing mistake in table 2 and 6A. The correct values for TAPSE and RV S´ were reported within table 6B and within the text as the reviewer notice. Therefore, we did correct the values in tables 2 and 6A.
Change 7: Please check table 2 and table 6A.
****

Reviewer F
I would like to point out some observations on the study methodology and interpretation of results.
1) The authors include various etiologies of mitral valve disease in the study, but I believe that endocarditis cases (9.8% of the study population, that required emergency surgery) should be exclude, because it would be optimal to have a homogeneous population (for example only degenerative mitral valve disease).
Reply 1: We thank the Reviewer for this comment. It is right that 9.8% of the patients were presented with endocarditis, but the result of the disease was a MV regurgitation. We think the exclusion of these patients will further reduce the number of the cohort and hence weaken the power of the study. Therefore, we would exclude endocarditis from future studies addressing this point to avoid inhomogeneity.
Change: No changes.

2) Only 6 patients had a preoperative RV dysfunction and only 10 patients had a preoperative PAH. During follow-up (3 months after surgery) a postoperative RV dysfunction was reported in 41 patients and 46.9% of the patients developed RV-dysfunction even if they initially presented without PAH. These data could be influenced by short term follow up: three months are too short of a period. Intraoperative myocardial ischemia, pericardial disruption, cardiopulmonary bypass and aortic cross clamp timing could be the real explanation of these results.
Reply 2: We thank the Reviewer for this comment. We totally agree with the reviewer. The postoperative RV dysfunction seems to be multifactorial and influenced by different issues. However, all factors mentioned by the Reviewer could play a role in developing RV dysfunction immediately after surgery. Therefore, we performed a multivariate regression analysis to defined predictors of RV-dysfunction as reported in table 7. Even though, we still need more investigation with larger cohort and to perform a long-term follow up to provide the proper answer for this question. We mentioned this within the limitation section of the study.

Change: Page 13: lines 381-403 & Page 14: lines 414-421

3) What are the selection criteria to minimal invasive surgery in authors' center? In the study emerges that minimal invasive surgical procedure significantly reduced the incidence of the postoperative RV dysfunction, but the authors don't explain if the subgroup patients that underwent minimally invasive surgery had a preoperative good RV function or not. Moreover, they do not explain which kind of minimally invasive surgery is performed in the authors' center (by mini-thoracotomy or mini-sternotomy).

Reply 3: We thank the reviewer for this comment. Similar question was raised by reviewer A. Please check the first reply on reviewer A comment.

Change 3: Page 6: lines 174-178.

4) The paper does not clarify what are the causes of 30-day mortality (3.3%).

Reply 4: We thank the reviewer for this comment. The cause of the 30-day mortality was attributed to multiorgan failure resulting from sepsis due to mitral valve endocarditis.

Change 4: Page 8: lines 237-239.

5) The authors failed to clarify another point: do all their patients undergo right-side heart catheterization after induction of anesthesia with a pulmonary arterial catheter, or this was instead done only for this study?

Reply 5: We thank the Reviewer for this comment. In our department, it is standard operating procedure (SOP) for all patients undergoing mitral valve surgery to receive a pulmonary artery catheter (PAC) following the induction of anesthesia.

Change 5: Page 5: lines 140-142.