Peer Review File
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Reviewer A

I found the manuscript engaging, thoughtful, and novel. I have the following constructive comments for consideration.

1. Line 60: HCM is described as a "disease characterized by unexplainable left ventricular hypertrophy". This statement is too vague in regards to our knowledge regarding HCM. As an introduction to the topic, mention of the genetic variability and pathologic changes (myofiber disarray, fibrosis, etc.) should be mentioned.

Reply 1:
We really appreciate your comment.
Hypertrophic cardiomyopathy (HCM) is a common genetic heart disease characterized by the presence of increased ventricular wall thickening, cardiomyocyte hypertrophy, disarrayed myofibers and interstitial fibrosis in the absence of hemodynamic stresses sufficient to account for the degree of hypertrophy and systemic diseases (1,2).
Changes:
We have revised this in the main document "Background" page 6 line 62-65 and "Discussion" page 12 line 208-210.

2. Line 67, line 196: Similar to comment #1, the authors mention that the "underlying mechanism" of SAM is not well defined. Citation #6 by Ro et al. published in JACC beautifully demonstrates pathophysiology of HCM-SAM using cardiac MR vector flow mapping, and a comprehensive review published recently in this very journal by Guigui et al. (J Thorac Dis. 2022 Jun;14(6):2309-2325) is recommended for discussion and inclusion.

Reply 2:
We really appreciate your advice.
Mitral regurgitation (MR) also contributes to symptoms (4) and, in HCM, may be mediated by systolic anterior motion (SAM) of the mitral valve, even in the absence of intrinsic mitral valve disease (4,5). The mechanism of SAM is being revealed by novel technologies such as vector flow mapping (4.6-9). However, its variable degree and clinical impact is still an unresolved issue.
Changes:
We have added this revision and reference in the main document. (page 6 lines 69-72 , reference number 9).
Reference 9
Guigui SA, Torres C, Escolar E, Mihos CG. Systolic anterior motion of the mitral valve in hypertrophic cardiomyopathy: A narrative review. Journal of thoracic disease. 2022;14:2309-2325

3. Line 71: The hypothesis of the study should be clearly mentioned in the "Objective" section.

Reply 3:
Thank you for your advice.
We hypothesized that specific mitral anatomical anomalies in obstructive HCM were associated with SAM-related MR and its severity. The present study aimed to (i) examine the impact of SAM-related MR and (ii) investigate the association between MR severity and clinical factors and mitral anatomical geometries by using the comprehensive imaging and intraoperative quantitative data.
Changes:
We have added this revision in the main document. (1.3 Objective section, page 6 lines 79-83).

4. Line 125: Is it fair to assume that no ring annuloplasty was used in any patients? What was the approach for myectomy? Transaortic? Mini-thoracotomy or sternotomy? Please describe the surgical technique in more detail.

Reply 4:
Thank you for your comment.
No ring annuloplasty was performed unless the patient had organic/intrinsic mitral disease. Transaortic approach thorough sternotomy was performed.
Approach for myectomy followed our previous publication (Ref 25 Septal Myectomy: How I Teach It. Nguyen SN, Blitzer D, Weiner S, Takayama H.Ann Thorac Surg (IF: 4.33; Q2). 2020 Sep;110(3):764-767. doi: 10.1016/j.athoracsur.2020.05.019. Epub 2020 Jun 6.).
Changes:

We have added this revision in the main document, (2.5 Septal Myectomy, page 9 lines 135-

136, Result section, page 10 line 166-168).

5. Line 129: In describing the septal myectomy, are the authors referencing the anterolateral or posteromedial papillary muscle (also known as the lateral or medial papillary muscles by some pathologists)? As stated in the manuscript, there is no anatomically defined 'posterolateral' papillary muscle.

Reply 5:
The definition of papillary muscle was determined according to a previous study (ref 23).
Changes
We have added this in the main document page 9 line 129-130.

6. Line 148: The authors state that 19 patients were excluded due to poor image quality or completely missing studies. In a small study, this is a very important form of attrition bias which represents an important confounder. At a minimum this should be mentioned as a study limitation.

Reply 6:
We really appreciate your thoughtful comment. According to your advice, we have added this in the limitation section.
Changes:
We have added this revision in the main document (4.2 Strengths and Limitations, page 13 lines 220-221).

7. Line 163: Post-operative echo was performed at a median of approximately 6 months, which provides early follow-up. Interpretation of the results should be tempered as there is no assessment on the possibility of late recurrent MR or adverse LV remodeling, particularly given that there is chordal resection being performed which may alter the LV spatial geometry (Circulation. 2004 Sep 14;110(11 Suppl 1):II115-22). It is recommended that this be discussed and also included as a study limitation.

Reply 7:
Thank you for your insight.
Abnormal chordal cutting could alter LV spatial geometry and impair LV function. As you have suggested, this could have influence on mitral valve geometry.
However, in patients with obstructive HCM, these potentially unfavorable effects are avoidable by the preserved or hyperdynamic systolic function and small LV cavity contributing SAM (26). We believe that this procedure is the effective therapy especially for patients with SAM and MR.

Changes:
We have added this in the Strengths and Limitations section in page 13 line 224-228.
Reference 26
Rodriguez F, Langer F, Harrington KB, Tibayan FA, Zasio MK, Cheng A, et al. Importance of mitral valve second-order chordae for left ventricular geometry, wall thickening mechanics, and global systolic function. Circulation. 2004;110:Ii115-122

8. Line 174: Spearman's correlation coefficient was used to assess between MR severity and echocardiographic measures. This simply provides the correlative linear strength between the variables selected and does not imply causation. It is recommended that these relationships be more carefully described rather than as "association". Did the authors consider multivariate linear regression modeling to assess independent associations between the variables? This would certainly strengthen the manuscript.

Reply 8:
Thank you for your suggestion.
According to your advice, we performed multivariate analysis for the determinants associated with MR grade.
Multivariate linear regression analysis has demonstrated that tenting area was the only significant parameter among preoperative TTE and 3DCT (Table S2).

The preoperative TTE and 3DCT parameters with P-value <0.05 on univariate analyses, were entered into a multivariate linear regression model to determine the independent importance of each parameter.
Please note that we could not put the length of anterior mitral leaflet together due to collinearity with tenting area. We did not also include the presence of abnormal chordae because this parameter is not a preoperative parameter and had significant correlation with tenting area.

Multivariate linear regression of determinants associated with MR grade (Table S2)

Variables	Adjusted R^2=0.65)	
	β	p value
Tenting area, cm^2	1.48	<0.001
LA volume index, mL/m^2	0.006	0.28
E wave velocity, cm/s	0.003	0.57

β standard regression coefficient;

Changes:
We have added them in the main document (Statistical Analysis, page 10 lines 152-154, 3.3 Correlations Between MR Severity and Other Parameters in page 12, lines 196-198 and Table S2).

9. Line 182: "LV mass index" is mentioned twice.

Reply 9:
We really appreciate your comments. According to reviewer B's comment # 6, we have removed this sentence.
Changes:
We have removed this sentence.

10. Table 1: Three patients had coronary artery disease. Please describe the extent of CAD, and if these patients required revascularization.

Reply 10:

Coronary artery disease was defined as ≥1 coronary arteries with ≥50% stenosis. In our cohort, all three patients who had history of CAD have never required revascularization at the time of septal myectomy.
Change:
We have added them in Table 1.

11. Table 1: No patients in either group had strokes or VSDs, yet the comparison p-value is reported as 0.73. Is this correct?

Reply 11.
Thank you for your insight.
Fisher's exact test was used to compare the group differences if the case count was less than five in each cell.
As we have addressed reviewer B's comment 5, we moved the postoperative outcome from Table 1 to the main document.
To avoid confusion for the readers, we have also excluded the P value in the main document.
Change:
We have added them in the main document (Results section, page 10 lines 168-171).

Reviewer B

In my view, the essential points are as follows on this topic:
(1) In patients with HCM, MR is often associated with such condition.
(2) It is known that the anatomy of the mitral valve itself is often unusual (such as having additional thick second chordae or having the second chord implanted directly on the leaflet).
(3) SAM often occurs in HCM due to both mitral valve anatomy abnormality and septal thickening. SAM itself contributes to the LVOT obstruction and to the MR.
It is this trifecta (HCM, SAM and MR) that the authors are exploring, like many others before them.

Comment 1 - Throughout the whole manuscript the core problem is unclear and confusing.
The best exemple of this confusion is stated in the "methods" portion of the abstract - "we reviewed 34 consecutive patients who underwent septal myectomy with SAM". This was not understandable to me.
I believe the authors meant to pose the following question: "out of 34 patients with HCM and SAM, we compared patients with and without prep >=moderate MR in order to identify pre-op anatomical characteristics and post-op outcomes"?
It is only while reading the figures that I finally understood the whole point of the manuscript.
I think the initial question must be restated otherwise it is not understandable to the readership.
As such, I suggest that the abstract be rewritten.

Reply 1:
We really appreciate your thoughtful comments.
The abstract has been rewritten as follows:

Background: Systolic anterior motion (SAM) of the mitral valve can result in mitral regurgitation (MR) and adverse outcomes in patients with obstructive hypertrophic cardiomyopathy (HCM). However, the mechanism and characteristics of MR severity mediated by SAM are unresolved. This study aimed to elucidate the anatomic and hemodynamic

associations of MR and the impact of septal myectomy on changes in MR severity in patients with HCM.

***Methods*:** We retrospectively reviewed patients who underwent septal myectomy with SAM and interpretable imaging between 2017–2022. Significant MR was defined as moderate or more MR. The mitral valve, papillary muscle, and left ventricular geometry were quantitatively evaluated via echocardiography and cardiac computed tomography.

Results: Out Of 34 patients, two groups were identified: those with preoperative significant MR (n=16) and those without significant MR (n=18). Patients with significant preoperative MR exhibited worse heart failure symptoms at baseline than those without. Following myectomy, these patients showed higher residual left ventricular outflow tract gradients at rest and with provocative measures than those without preoperative MR. Multivariate regression analysis revealed a significant association between the tenting area and MR severity. Additionally, the chordal cutting procedure alleviated the tenting area (2.1 [1.8–2.6] cm^2 vs. 1.4 [1.2–1.6] cm^2) compared to those without it.

***Conclusions*:** Our preliminary data suggested that chordal cutting with septal myectomy was associated with an improvement in the tenting area, contributing to MR severity. This procedure may serve as an effective therapy for patients with SAM and significant MR.

Changes:

We have revised the abstract.

Comment 2 - The tenting area is the only pre-operative anatomical parameter that is different between patients with or without >= moderate MR? Please comment.

Reply 2:

Thank you for your suggestion.

On preoperative TTE, patients with MR had a significantly larger LA volume index (P=0.04), tenting area (P<0.001), and E wave velocity (P=0.004) than those without MR.

Changes:

We have added this in the Results section, page 11 line 189-191.

Comment 3 - Chordal cutting was performed in 80% of HCM+SAM+MR+ patients versus 40% in HCM+SAM+MR- patients (table 1). Chordal cutting was performed in 7 patients with no or mild MR and it was not performed in 3 patients with moderate and sever MR (table S2). Can you explain why and when chordal cutting was performed? It seems that one of the conclusions of the manuscript could be “a systematic approach with secondary chordal cutting helps to promote good post-op outcomes regardless of the pre-op MR quantification”? Can you please comment on that?

Reply 3:

Thank you for your comments.

In this study, the abnormal chordae were found even in patients without significant MR. The characteristic of HCM is not only LV hypertrophy but shortened and fibrotic chordae. We resected abnormal chordae whenever we found them at the time of septal myectomy. As we have demonstrated in Figure 4 B and D (previous Figure S2), the recovery of tenting area and

AML ratio were observed in patients even without significant MR. Therefore, improvement of mitral geometry could be caused by the chordal cutting procedure without being influenced by change of MR severity.
However, the abnormal versus normal secondary chordae was determined at the surgeons' discretion, while the mitral subvalvular apparatus was directly and carefully examined. The number of study population is limited. Our preliminary data suggested chordal cutting with septal myectomy was associated with improvement of mitral geometry, contributing to SAM-related MR severity.
Further larger prospective studies are required.

Changes:
We have added these revisions and revised the conclusion section. (Discussion, Page 13 Lines 229–234 and Conclusion, Page 15 Lines 275-279).

Comment 4 -a) There are very few concomitant surgeries for this population. In many publications, the rate of additional surgery is higher for such population (Alfieri, mitral valve replacement, tricuspid annuloplasty, AVR).
Additional surgeries could be displayed more clearly in table 1 (this information should not be hidden).
b) Further, you seem to suggest that secondary chordal cutting results in alleviating MR in most cases for the HCM+SAM+MR+ patient population. If that is what you think, you should state this as a major conclusion.

Reply 4:
a) We really appreciate your insightful comments.
We excluded the patients with intrinsic/organic mitral valve disease because the etiology is totally different between those with and without /intrinsic/ organic valve diseases.
As we have commented in reviewer A's #4 comment, no ring annuloplasty and replacement were performed unless the patient had organic/intrinsic mitral disease.

b) We agree with your suggestion.
When performing septal myectomy, chordal cutting procedure may be particularly useful for patients with SAM and significant MR.
Change:
According to your suggestion, we have added supplementary explanation in Results section, page 10 lines 166-168; Conclusion, page 15 lines 275-279 and "Key note" in page 5.

Comment 5 - table 1 is too big.

Reply 5:
According to your advice, we have revised Table 1 and moved the postoperative parameters to main document.
Changes:
We have changed the main document, Results in page 10 lines 170-176 and revised Table 1.

Comment 6 - Figure 4. I find that Spearman's correlation is too difficult to understand.

Reply 6:

Thank you for your thoughtful comments. We have deleted Figure 4 and Table 4 to clarify the manuscript.

Changes:

We have deleted them.

Comment 7 - In conclusion, you state "The presence of abnormal secondary chordae … was significantly associated with MR severity". If you do not compare a population with or without abnormal secondary chordae, you cannot make such statement. Additionally, secondary chordae were cut in both MR+ and MR- populations, so the conclusion is hard to make.

Reply 7

We appreciate your advice.

According to your advice, we have changed the conclusions.

Changes

We have revised our conclusion, page 15 lines 275-279.

Reviewer C

The submitted paper appears clear, informative and is from high clinical relevance. Of course the number of patients is limited but the mechanism of SAM in HCM is challenging. In our experience we have not seen very much patients with tethering of the anterior leaflet due to abnormal secondary chords. But I totally agree that the main focus is the reduction of MR severity.

Reply 1

The authors thank the reviewer for the time and careful attention in reviewing this manuscript.

Changes

None for this comment.