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Echocardiographic and clinical outcomes of patients undergoing septal myectomy plus anterior mitral leaflet extension for hypertrophic cardiomyopathy

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Septal myectomy is indicated in patients with obstructive hypertrophic cardiomyopathy (HCM) and intractable symptoms. Concomitant mitral valve (MV) surgery is performed for abnormalities contributing to systolic anterior motion (SAM), or for SAM-mediated mitral regurgitation (MR) with or without left ventricular outflow tract (LVOT) obstruction. One MV repair technique is anterior mitral leaflet extension (AMLE) utilizing bovine pericardium, stiffening the leaflet and enhancing coaptation posteriorly. Fifteen HCM patients who underwent combined myectomy-AMLE for LVOT obstruction or moderate-to-severe MR between 2009 and 2020 were analyzed using detailed echocardiography. The mean age was 56.6 years and 67% were female. The average peak systolic LVOT gradient and MR grade measured 73.4 mmHg and 2.3, respectively. Indications for myectomy-AMLE were LVOT obstruction and moderate-to-severe MR in 67%, MR only in 20%, and LVOT obstruction only in 13%. There was no mortality observed, and median follow-up was 1.2 years. Two patients had follow-up grade 1 mitral SAM, one of whom also had mild LVOT obstruction. No recurrent MR was observed in 93%, and mild MR in 7%. Compared with preoperative measures, there was a decrease in follow-up LV ejection fraction (68.2 vs 56.3%, $p = 0.02$) and maximal septal wall thickness (25.5 vs 21.3 mm, $p < 0.001$), and an increase in the end-diastolic diameter (21.9 vs 24.8 mm/m^2, $p = 0.04$). There was no change in global longitudinal strain (–12.1 vs –11.6%, $p = 0.73$) and peak LV twist (7.4 vs 7.3°, $p = 0.97$). In conclusion, myectomy-AMLE is a viable treatment option for carefully selected symptomatic HCM patients with LVOT obstruction or moderate-to-severe MR.

Keywords

HOCM; Hypertrophic cardiomyopathy; Mitral regurgitation; Mitral valve repair; Myectomy; Systolic anterior motion

1. Introduction

Approximately 70% of patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM) have left ventricular outflow tract (LVOT) obstruction due to systolic anterior motion (SAM) of the mitral valve (MV) [1]. SAM results from a complex interplay between LV hypertrophy, anatomic abnormalities of the MV apparatus, and flow vortices within the LV [2, 3]. During systolic ejection, the flow trajectory becomes aligned with the MV leaflet tips and results in anteriorly-directed drag forces towards the interventricular septum, and ultimately, outflow tract obstruction [4]. Septal reduction therapy, preferably via surgical myectomy, is indicated in patients with intractable symptoms [5, 6]. Concomitant MV surgery may be performed when there are structural abnormalities of the MV apparatus that contribute to SAM, or in the setting of significant SAM-mediated mitral regurgitation (MR) with or without LVOT obstruction.

One reparative approach that is applicable to these groups is anterior mitral leaflet extension (AMLE) utilizing harvested pericardium [7, 8]. This technique stiffens the anterior leaflet, and results in improved MV coaptation and shifting of the coaptation point posterolaterally, with a reduction in SAM [9]. When combined with septal myectomy, AMLE has been shown to be a safe and effective approach in patients with symptomatic obstructive HCM [10]. Our aim is to further describe the hemodynamic and clinical outcomes of this approach via detailed pre-operative and follow-up analyses of echocardiographic data.

2. Methods

2.1 Patient selection and definitions

In accordance with institutional regulations and the ethical guidelines of the 1975 declaration of Helsinki, the Mount Sinai Medical Center Institutional Review Board in Miami Beach, Florida approved the study protocol. We retrospectively analyzed the Echocardiography digital database and identified 15 patients with symptomatic HCM who underwent myectomy-AMLE between January 2009 and December 2020.

HCM was defined by an LV wall thickness $\geq$15 mm in any myocardial segment, which was not explained by loading conditions or another cause of hypertrophy [5, 6]. The HCM phenotypes included upper septal hypertrophy (sigmoid septum) in 7 (47%) patients, reverse septal curve in 7 (47%), and neutral septum in 1 (6%). LVOT obstruction was defined as a

resting or provoked systolic gradient of at least 30 mmHg, as assessed by Doppler echocardiography [5, 6]. Patients were considered candidates for myectomy-AMLE if the following parameters were met: (1) history of obstructive HCM with a peak LVOT systolic gradient $\geq$50 mmHg and/or severe MR; (2) heart failure symptoms refractory to maximally-tolerated guideline-directed medical therapy; (3) moderate to severe (grades II or III) SAM of the mitral valve without evidence of organic disease precluding durable repair; and, (4) an end-diastolic MV coaptation point-interventricular septal (C-sept) distance $\leq$20 mm.

2.2 Echocardiography

All transthoracic echocardiograms were performed using a GE cardiovascular ultrasound system (General Electric Healthcare, Waukesha, WI, USA), with pre-operative echocardiograms performed within 1 month of surgery. The assessment of LV systolic function was performed using volumetric methods in accordance with the American Society of Echocardiography chamber quantification guidelines [11]. LV internal diameters were measured at end-systole and diastole, and mass was calculated and indexed to body surface area. Interventricular septum and posterior wall thickness were measured at end-diastole in the parasternal long axis and short-axis views [11, 12]. Cardiac mechanics were analyzed using the two-dimensional speckle tracking technique via the GE Echo PAC Q-Analysis software (General Electric Healthcare, Waukesha, WI, USA) according to the intersocietal consensus statement on cardiac mechanics quantitation [13]. Global longitudinal strain measurements were obtained in the apical four, three and two chamber views, and averaged. Peak systolic LV twist was obtained by subtracting LV basal rotation from apical rotation, using the manually calculated aortic valve closure time as a reference point for the end of systole.

Mitral and tricuspid regurgitation were graded in a multi-parametric manner according to American Society of Echocardiography native valvular regurgitation guidelines as trace/none (0), mild (1+), moderate (2+), moderate-to-severe (3+), or severe (4+) [14]. The vena contracta width was measured as the width of the narrowest portion of the MR jet as it exits the regurgitant orifice. The severity of mitral SAM was graded as mild (1, brief anterior motion without septal contact), moderate (2, brief septal contact), or severe (3, septal contact lasting $>$1/3rd of systole) [15]. The MV annulus anteroposterior diameter was measured in the parasternal long-axis view at end-systole. The C-sept distance was measured from the mitral leaflet coaptation point to the interventricular septum in a perpendicular fashion in the end-diastolic parasternal long axis view, as a descriptive variable of the extent of anterior shift in the position of the MV.

Right ventricular (RV) size was measured as the end-diastolic basal diameter, and systolic function was assessed by the tricuspid annular plane systolic excursion (TAPSE) [11]. The RV systolic pressure was estimated from the addition of the peak tricuspid regurgitant pressure gradient (using the modified Bernoulli equation) and the right atrial pressure, the latter which was estimated from the diameter of the inferior vena cava (IVC)and its collapsibility extent with inspiration [11]. Pulmonary hypertension was defined as an RV systolic pressure $>$35 mmHg. Left atrial anteroposterior diameter was measured in the parasternal long-axis view at end-systole.

2.3 Operative technique

The technique for AMLE has been previously described in detail [9, 16]. In brief, the anterior MV leaflet was detached from the valve commissures, which provided direct visualization and access of the interventricular septum. A transmitral extended Morrow procedure was utilized for septal myectomy and to increase the size of the LVOT. Thereafter, a pericardial patch was sized and fashioned to accommodate the defect created by the anterior leaflet detachment. The AMLE was performed using 5–0 Prolene suture to begin the patch anastomosis to the anterior mitral leaflet and was extended circumferentially around the annulus from commissure to commissure. Finally, sutures were placed through an annuloplasty ring which were tied down and transected (Figs. 1,2,3). A saline test confirmed adequate coaptation of the leaflets.

The AMLE was performed using a glutaraldehyde-treated bovine pericardial patch in all patients. An MV annuloplasty ring was implanted in 13 (87%) patients, and included six 35-mm St. Jude Tailor rings (St. Paul, MN, USA), two 33-mm St. Jude Tailor rings, two 29-mm St. Jude Tailor rings, two 40-mm Medtronic 3D Profile rings (Minneapolis, MN, USA), and one 32-mm Medtronic Simulus ring. The size of the annuloplasty ring was based on the height of the anterior MV leaflet. Of note, 2 (13%) patients underwent AMLE without an annuloplasty ring. Additional procedures included bioprosthetic aortic valve replacement for aortic stenosis in 2 (13%) patients, and MAZE plus left atrial appendage ligation in 2 (13%).

2.4 Statistical methods

The variables are expressed as the mean $\pm$ 1 standard deviation, median and interquartile range, or as absolute number and percentage. A paired *t*-test was used to compare pre-operative and follow-up values of continuous data. A McNemar's chi-square test was performed to test the repeated measures of dichotomous variables. A two-tailed p-value $<$ 0.05 was considered statistically significant. The statistical analyses were conducted using Statistical Package for Social Sciences, version 21 (SPSS Inc, Chicago, IL, USA).

3. Results

3.1 Clinical characteristics

The mean age was 56.6 $\pm$ 18.3 years, 10 (67%) were female, and mean New York Heart Association functional class and median HCM-Risk score were 2.3 $\pm$ 0.8 and 2.5 (1.9–4.8), respectively. The most common symptoms were dysp-

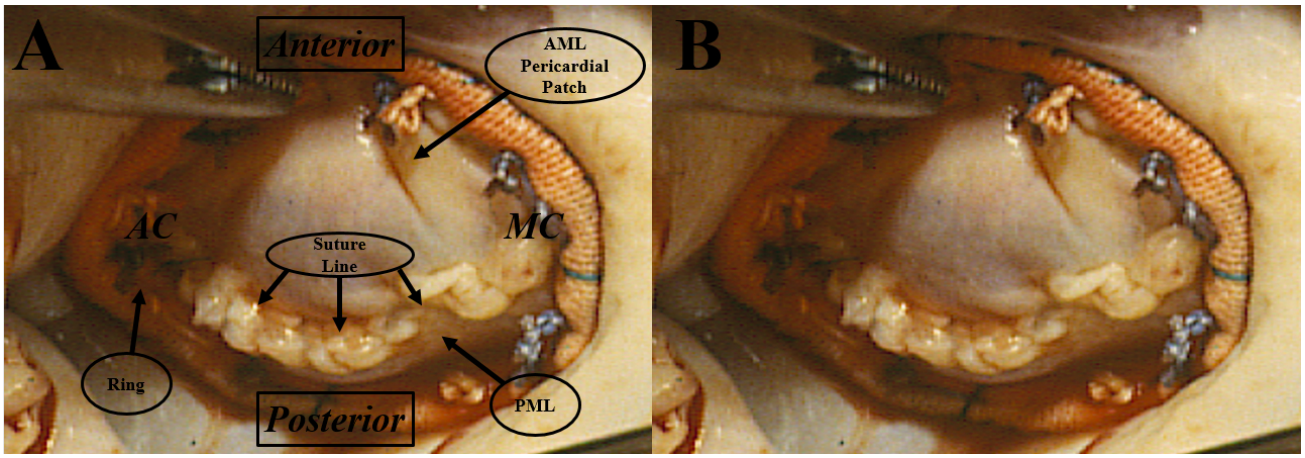

Fig. 1. Surgeon's Intra-Operative View of Anterior Mitral Leaflet Extension. (A) Annotated figure. AC, anterolateral commissure; AML, anterior mitral leaflet; MC, Posteromedial commissure; PML, posterior mitral leaflet. (B) Plain figure.

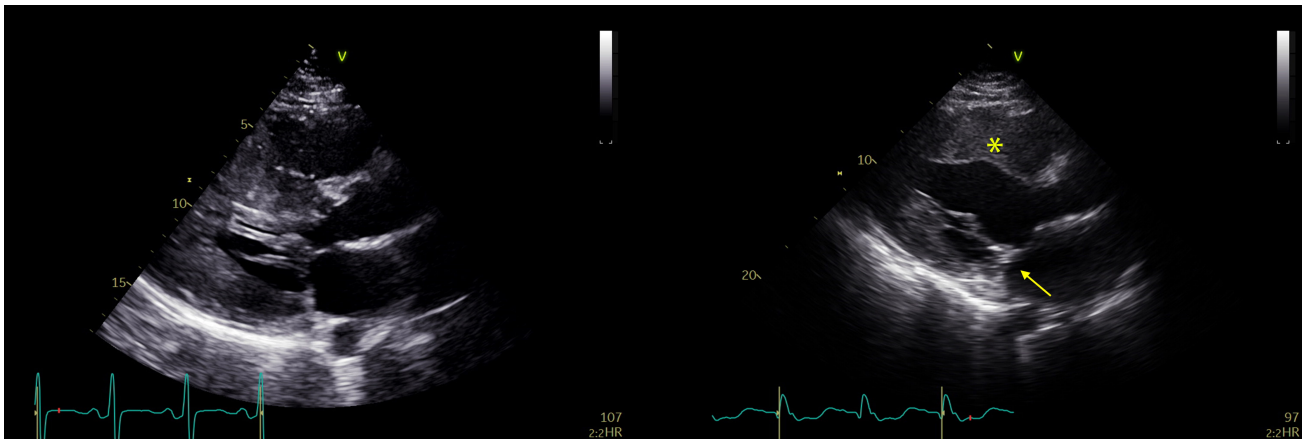

Fig. 2. Pre-operative and Follow-Up Echocardiography in A Patient Undergoing Septal Myectomy and Anterior Mitral Leaflet Extension. A transthoracic echocardiographic parasternal long-axis view shows marked asymmetric interventricular septal thickening and severe systolic anterior motion of the mitral valve (left panel). Follow-up echocardiography shows interventricular septal reduction (yellow asterisk) and posterolateral displacement of the mitral valve coaptation zone (yellow arrow) with relief of LVOT obstruction after septal myectomy and anterior mitral leaflet extension.

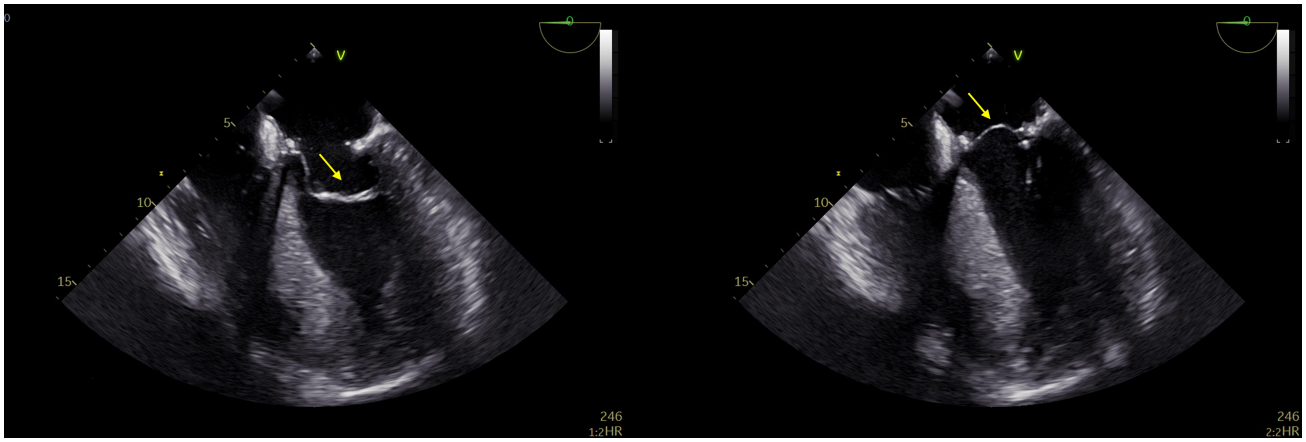

Fig. 3. Transesophageal Echocardiography Status Post Septal Myectomy and Anterior Mitral Leaflet Extension. Mid-esophageal four-chamber echocardiographic view showing the anterior mitral leaflet extension patch (yellow arrow) in diastole (left panel) and systole (right panel). A mitral valve ring annuloplasty has also been implanted.

Table 1. Clinical characteristics of patients undergoing septal myectomy plus anterior mitral leaflet extension for hypertrophic cardiomyopathy.

Variable	N = 15
Age (years)	56.6 ± 18.3
Body surface area (m^2)	1.93 ± 0.24
Female	10 (67%)
Systolic blood pressure (mmHg)	129 ± 15.5
Diastolic blood pressure (mmHg)	76 ± 10.1
Heart rate (bpm)	70.9 ± 12.1
Estimated glomerular filtration rate (mL/min/1.73 m^2)	97.1 ± 34.6
Family history of Hypertrophic Cardiomyopathy	0
Symptoms	
Angina	6 (40%)
Syncope	3 (20%)
Dyspnea	11 (73%)
Palpitations	3 (20%)
Co-morbidities	
Non-sustained ventricular tachycardia	3 (20%)
Left bundle branch block	6 (40%)
Hypertension	8 (53%)
Diabetes mellitus	2 (13%)
Atrial fibrillation	2 (13%)
Medications	
Aspirin	10 (67%)
Amiodarone	2 (13%)
Loop diuretic	5 (33%)
Beta-blocker	11 (73%)
Disopyramide	1 (7%)
Warfarin	2 (13%)
Implantable cardioverter defibrillator	5 (33%)
New York Heart Association functional class	2.3 ± 0.8
HCM risk-SCD score	2.5 (1.9–4.8)

Variables presented as mean ± standard deviation, median (interquartile range), or number (percentage).
SCD, sudden cardiac death.

nea (73%) and angina (40%). Beta-blockers were utilized by 73%, and disopyramide by 7% of patients; no patient was prescribed a calcium channel blocker (Table 1).

3.2 Surgical indications and pathology

The primary indication for myectomy-AMLE was symptomatic drug-refractory LVOT obstruction and moderate to severe MR in 10 patients (67%), severe MR only in 3 (20%), and LVOT obstruction only in 2 (13%). All patients had SAM of the mitral valve with a mean SAM grade of 2.7 ± 0.5, an end-diastolic C-sept distance of 16.5 ± 3.1 mm, and anteroposterior mitral annular diameter of 33.3 ± 5.7 mm. The average peak systolic LVOT pressure gradient measured 73.4 ± 20.1 mmHg. The mean MR grade was 2.3 ± 0.9, which was reflected by a vena contracta width of 0.43 ± 0.09 cm. Papillary muscle abnormalities included hypertrophy in 8 (53%) patients, anterolateral muscle elongation in 2 (13%), and posteromedial muscle elongation in 1 (6%).

3.3 Follow-up and clinical outcomes

Median length of clinical and echocardiographic follow-up was 1.2 (0.2–5.2) years. There was no in-hospital mortality. Post-operatively there was 1 (6%) emergent re-operative bioprosthetic MV replacement for atrio-ventricular groove disruption, and 1 (6%) case of new-onset atrial fibrillation. During follow-up there were 2 (13%) patients who had heart failure re-hospitalizations. There were no cases of cerebrovascular accident, myocardial infarction, sudden death, or all-cause mortality.

3.4 Echocardiographic follow-up analyses of cardiac function, geometry, and mechanics

Echocardiographic follow-up was 100% complete. Two (13%) patients had evidence of mild grade 1 mitral SAM; 1 with LVOT obstruction and a peak systolic gradient of 36 mmHg (decreased from an 89-mmHg preoperative gradient), and 1 without residual obstruction. Of the 14 patients with successful myectomy-AMLE, no recurrent MR was observed in 13 (93%) patients, and mild MR was present in 1 (7%). All patients had a mean transmitral gradient measuring $\leq$5 mmHg.

When compared with baseline preoperative measures, there was a significant decrease in the follow-up LV ejection fraction (68.2 vs 56.3%, $p = 0.02$) and maximal interventricular septal wall thickness (25.5 vs 21.3 mm, $p < 0.001$), and an increase in the end-diastolic (21.9 vs 24.8 mm/m^2, $p = 0.04$) and end-systolic (12.1 vs 17.5 mm/m^2, $p = 0.002$) diameter indices. There was no change in LV mechanics as assessed by the global longitudinal strain (–12.1 vs –11.6%, $p = 0.73$) and peak LV twist (7.4 vs 7.3°, $p = 0.97$), or in left atrial size or incidence of pulmonary hypertension. In assessment of the right heart, there was an increase in the follow-up mean RV basal diameter (31.7 vs 35.5 mm, $p = 0.02$) and a decrease in the tricuspid annular plane systolic excursion (21.8 vs 13.9 mm, $p < 0.001$) (Table 2).

4. Discussion

In the present study of selected patients with HCM and LVOT obstruction or moderate-to-severe MR, a myectomy-AMLE was safely performed with no mortality and a durable MV repair at 1-year follow-up. A successful reduction in the maximal interventricular septal wall thickness and stable LV mechanics were also observed at last echocardiographic assessment. Notable events included one emergent re-operative MV replacement for atrio-ventricular groove disruption, owing to the technical complexity of myectomy-AMLE, and two heart failure re-hospitalizations as a result of progressive HCM. Importantly, no patient experienced sudden cardiac death.

The mechanisms resulting in LVOT obstruction and MR in HCM are centered on anatomic, geometric, and hemodynamic abnormalities of the LV cavity and MV apparatus including: (1) marked thickening, most commonly in an asymmetric morphology, of the interventricular septum; (2) SAM of the mitral valve; and, (3) a narrowed LVOT [1, 2, 17]. The

Table 2. Baseline versus follow-up echocardiography in patients undergoing septal myectomy plus anterior mitral leaflet extension for hypertrophic cardiomyopathy.

Variable	N = 14	N = 14	*p*-value
Left ventricle			
Ejection fraction (%)	68.2 ± 11.1	56.3 ± 9.9	0.02
Maximal interventricular septal thickness (mm)	25.5 ± 5.5	21.3 ± 4.9	<0.001
Maximal posterior wall thickness (mm)	12.3 ± 4.2	12 ± 2.9	0.56
Internal diastolic diameter (mm)	41.7 ± 6.4	47.8 ± 7.9	0.03
Internal diastolic diameter index (mm/m^2)	21.9 ± 4.2	24.8 ± 3.7	0.04
Internal systolic diameter (mm)	25.3 ± 5.5	33.8 ± 6.8	0.001
Internal systolic diameter index (mm/m^2)	12.1 ± 4.5	17.5 ± 2.6	0.002
Mass	377 ± 176.7	372.5 ± 155.7	0.89
Mass index (g/m^2)	191.6 ± 76	189.5 ± 66.6	0.9
Relative wall thickness	0.63 ± 0.26	0.51 ± 0.14	0.07
Global longitudinal strain (%)[a]	−12.1 ± 3.7	−11.6 ± 4.1	0.73
Peak twist (°)[b]	7.4 ± 2.9	7.3 ± 6.6	0.97
Obstructive hypertrophic cardiomyopathy	12 (80%)	1 (6%)	<0.001
Left atrium			
Left atrial diameter (mm)	44.7 ± 7.3	47.9 ± 9.8	0.18
Left atrial diameter index (mm/m^2)	23.1 ± 4.7	24.9 ± 5	0.16
Right ventricle			
Basal diameter (mm)	31.7 ± 6.3	35.5 ± 5.2	0.02
Tricuspid annular plane systolic excursion (mm)	21.8 ± 4.8	13.9 ± 2.5	<0.001
Pulmonary hypertension	7 (47%)	4 (27%)	0.26
Secondary/functional tricuspid regurgitation	5 (33%)	4 (27%)	1

Variables presented as mean ± standard deviation, or number (percentage).

Analysis performed in 14 patients with successful myectomy-AMLE.

[a] Available in 8 patients. [b] Available in 7 patients.

° = Degrees.

MV leaflets are often elongated and lax, and as was observed in the present study, abnormal papillary muscle anatomy and function are also common [18]. Together this anatomy results in overlap of the LV inflow and outflow tracts, and anterior displacement of the MV coaptation point towards the interventricular septum. This was exhibited in the present cohort as a substantially decreased end-diastolic MV C-sept distance which is a quantitative marker of LVOT obstruction and SAM risk [19].

In this setting, early systolic flow generates drag forces on the posterior aspect of the MV leaflets at a high angle, initiating leaflet SAM and LVOT obstruction [1–4]. The hydraulic forces and pressure difference at the site of MV-septal contact perpetuate the hemodynamic derangement, and disturbed MV leaflet coaptation becomes largely responsible for ensuing SAM-related MR [20]. Myectomy-AMLE is an effective surgical approach in this population as it addresses both the LV inflow and outflow pathology. Extended septal myectomy results in a larger LVOT, streamlined systolic flow, and an improved spatial relationship between the LV and MV apparatus [21–23]. The AMLE decreases SAM by stiffening the base and mid-body of the anterior MV leaflet, pushing the coaptation point posterolaterally, and increasing chordal tensor forces [7–10].

A prior study by Vriesendorp and colleagues reported on 98 patients with obstructive HCM who underwent myectomy-AMLE [10]. At a mean follow-up of 8 years, 88% patients were alive, 6% patients required MV reoperation, 3% had sudden cardiac death, and 3% progressed to end-stage heart failure. There was a significant decrease in the interventricular septal wall thickness, a durable reduction in MR grade, and an increase in the LV end-diastolic diameter, which are associated with LV reverse remodeling after myectomy [21, 24, 25]. Similar findings were observed in the present study, and strain imaging suggested stable LV global longitudinal motion and twist mechanics at 1-year follow-up. This latter finding is intriguing, as impaired strain or progressive dysfunction are consistently regarded as robust markers of adverse clinical outcomes in patients with HCM [26].

An important finding in the present cohort was the development of RV remodeling and impaired systolic function at follow-up, which was expressed as an increase in the basal diameter of the RV and a decrease in the TAPSE. Development of RV failure may occur in up to 25% of cardiac operations, and is associated with a marked increase in mortality [27–29]. Prior data has established strong links between RV ischemia and oxidative stress, loss of pericardial constraint, and impaired interventricular septal contractile mechanics as etiologies of post-operative RV remodeling and dysfunction

[27, 30]. A high clinical index of suspicion and serial imaging assessment of the right heart is advised for all HCM patients. When feasible this should include RV free wall strain, which is a useful marker of global and regional RV function and performance. In patients with HCM, RV free wall strain is a sensitive marker of subclinical RV dysfunction and improves risk stratification when interpreted with LV global longitudinal strain and filling pressure [31].

While the majority of patients with symptomatic HCM can be successfully treated with an extended Morrow's procedure (septal myectomy), it is estimated that approximately 15% have MV abnormalities that may predispose to persistent post-operative LVOT obstruction [32]. In this group MV and subvalvular intervention should be carefully considered. Higher risk features include anterior MV leaflet elongation measuring >30 mm, prominent and centrally displaced papillary muscles, a narrow C-sept distance measuring <20 mm at end-diastole, and moderate to severe SAM [33]. The latter two criteria are proposed to select appropriate candidates for a safe and effective myectomy-AMLE. Multi-modality imaging allows for planning with regards to the site of myectomy, and helps identify additional pathology that may need to be addressed [34]. Pre-implantation treatment of the pericardial patch with glutaraldehyde promotes stiffening and improves handling, however, there is a risk of accelerated patch calcification, retraction, and recurrent MR [35–38]. Additional risk factors for AMLE failure include systemic inflammatory disorders, advanced age, chronic kidney disease, and abnormal calcium metabolism [38–40]. In their presence an alternative MV surgical strategy should be considered.

There are important limitations to the present study. Firstly, the sample size was small and focused on a specific patient population with HCM, and the study was retrospective in nature. These factors impart an important selection bias. Secondly, the present cohort was considered low-risk after multi-disciplinary heart team assessment. This was supported by the clinical risk factor profile and a median HCM risk-SCD score of 2.5. Thus, these results should not be applied to high-risk HCM patients. Thirdly, the bovine pericardium utilized was not standardized and included patches from three different manufacturers. Additionally, there were several different annuloplasty rings implanted, while in two patients no ring was used. Despite similar pericardial patch preparations, and data suggesting minimal inter-class differences between annuloplasty rings, these factors introduce important performance bias confounding [41]. Fourthly, measures of LV strain and twist mechanics were not available in all patients and should be interpreted cautiously. Additionally, RV function was assessed solely by TAPSE which reflects longitudinal ventricular contraction. While TAPSE is a robust surrogate of RV performance, it does not detail regional RV motion and mechanics. Fifthly, due to non-uniform imaging for fully quantitative assessment of MR, the vena contracta width was used as the semi-quantitative surrogate of severity. However, both the preferred proximal isovelocity surface area method and measurement of the vena contracta width have important limitations, including single-frame assessment, beat-to-beat variability, and regurgitant jet ecentricity, which can impact assessment of MR severity. Finally, published data regarding myectomy-AMLE remain limited, and there is a substantial learning curve as with all MV repair techniques. Further reporting of outcomes and longer-term follow-up analyses are needed for a more definitive assessment of safety and repair durability.

5. Conclusions

In conclusion, myectomy-AMLE is a viable surgical treatment option for carefully selected symptomatic HCM patients with LVOT obstruction or moderate-to-severe MR. Myectomy-AMLE may be safely performed and addresses both the LV inflow and outflow pathology. Further reporting of outcomes and follow-up analyses are awaited.

Author contributions

RF: Conceived the study, collected the data, wrote the manuscript; FN: Performed the analysis, wrote the manuscript; SAG: Collected the data, performed the analysis, wrote the manuscript; SAH: Performed the analysis, wrote the manuscript; CGM: Conceived the study, collected the data, performed the analysis, wrote the manuscript. All authors read, made changes and approved the final version of the manuscript.

Ethics approval and consent to participate

The institutional IRB determined that the specified criteria for the waiver of authorization and waiver of informed consent were met. The Federalwide Assurance Number is FWA00000176.

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Conflict of interest

The authors declare no conflict of interest. FM and CGM are our Guest Editors, and given their role as Guest Editors, had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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