Current Cardiology Reports (2019) 21: 136
https://doi.org/10.1007/s11886-019-1231-8

VALVULAR HEART DISEASE (TL KIEFER, SECTION EDITOR)

Mitral Valve Disease in Hypertrophic Cardiomyopathy: Evaluation and Management

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Published online: 31 October 2019

Abstract

Purpose of Review To discuss the critical role of the mitral valve (MV) in the pathophysiology of obstruction in hypertrophic cardiomyopathy (HCM), evaluation of the MV in HCM, the impact of MV characteristics on treatment in HCM, and management of the MV at the time of septal myectomy.

Recent Findings Multimodality imaging helps describe mitral abnormalities in HCM, though significant controversy persists on what to do with these abnormalities. In certain cases, intervention on the MV may be necessary, although outcomes may be worse in those who undergo mitral interventions.

Summary Thorough assessment of MV anatomy and function is paramount in evaluating a patient with HCM. Emphasis should be placed on thorough evaluation and description of mitral abnormalities in HCM. Given significant practice variation, future studies could compare MV practice differences across institutions and how these impact long-term outcomes.

Keywords Hypertrophic cardiomyopathy · Mitral valve · Systolic anterior motion · Myectomy

Introduction

In the 1950s and 1960s, hypertrophic cardiomyopathy (HCM) was initially described as left ventricular outflow tract (LVOT) obstruction absent of an anatomic cause [1–5]. It has subsequently been recognized that LVOT obstruction is dynamic, and moreover, that absence of a fixed obstruction does not translate to absence of an anatomic mechanism. Systolic anterior motion (SAM) and apposition of the mitral valve (MV) apparatus with the ventricular septum have now been established as the dynamic and anatomic cause of LVOT obstruction in HCM. Approximately one third of patients with HCM have resting obstruction, one third have provocable obstruction, and one third have no obstruction [6]. The key determinants of LVOT obstruction are vigorous ventricular contraction, hemodynamic loading conditions, abnormal chamber geometry with a small LVOT, and intrinsic abnormalities of the MV [7, 8]. This review will focus on MV anatomy in HCM, the mechanism of LVOT obstruction, evaluation of the MV with multimodality imaging, and discussion of MV management in HCM.

This article is part of the Topical Collection on *Valvular Heart Disease*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11886-019-1231-8) contains supplementary material, which is available to authorized users.

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Brief Review of Relevant Normal Mitral Valve Anatomy

Recognition of the dynamic nature of the MV throughout the cardiac cycle as well as with changes in hemodynamic loading conditions is central to understanding the integral role the MV plays in LVOT obstruction [9, 10]. The MV consists of the annulus fibrosus, leaflets, chordae tendinae, and papillary muscles (PM) [9–11]. The annulus fibrosus forms the collagenous framework for attachment of valve tissue at the atrioventricular orifices. The mitral annulus is saddle-shaped and the anteromedial aspect is in continuity with the left coronary cusp and a portion of the noncoronary cusp of the aortic valve [12]. The total surface area of the anterior and posterior mitral

leaflets is two times larger than the area at the mitral annulus in order to allow for optimal leaflet coaptation [12]. If the length of leaflet coaptation is too short relative to the size of the annulus, mitral regurgitation (MR) will occur [13]. The anterior leaflet is triangular shaped and nearly twice the length of the posterior leaflet [14]. The posterior leaflet has less mobility than the anterior leaflet [13]. Each half of the anterior and posterior mitral leaflet is connected to its corresponding PM by an extensive branching network of first- and second-order chordae tendinae [12]. The PMs are located at the junction of the apical and middle third of the left ventricle (LV) and project into the cavity toward the leaflet commissures. The positioning of the PMs in relation to the chordae, leaflets, and annulus is optimal for alignment of leaflet coaptation and prevention of regurgitation [10, 11]. The positioning of the PMs relative to each other provides posteriorly directed tension to prevent anterior motion of the mitral apparatus. This complex interplay of the different parts of the mitral apparatus allows it to adapt throughout the cardiac cycle and under different loading conditions for optimal valve function.

Mitral Valve Abnormalities in HCM

Abnormalities of the mitral apparatus are varied in HCM. In all patients with dynamic LVOT obstruction, the MV has some abnormality that allows for systolic anterior motion (SAM) of the mitral apparatus. Dynamic LVOT obstruction occurs as a result of SAM in the setting of vigorous ventricular contraction, abnormal chamber geometry, and/or alterations in ventricular loading (e.g., markedly decreased preload). In HCM, MV abnormalities may be present in any component of the mitral apparatus (Table 1 and Fig. 1). While numerous abnormalities of the MV have been described, the most common are abnormally large/elongated mitral leaflets (particularly the anterior leaflet) and anterior displacement of any part of the mitral apparatus [7, 14, 17–19, 37–42]. While less appreciated, there can be abnormalities in the size, shape, and angulation of the annulus [20, 21, 35]. Given the stressful hemodynamic loading conditions in HCM, mitral annular calcification may be seen [16•]. The leaflets may also have calcification in addition to being elongated as mentioned above. There are many other possible abnormalities of the leaflet including prolapse and clefts [15, 16•, 20, 22, 23, 29, 30]. Of note, while the anterior leaflet is often elongated, the posterior leaflet may be shortened or elongated [43•]. The chordae tendinae are often fibrinous, with abnormal attachments to the leaflets as well as ventricular walls [18, 32, 44]. Chordal rupture is a common complication of repetitive stress on the mitral apparatus [32, 33•]. Papillary muscles can have a number of morphologic abnormalities, including being shortened, elongated, or thickened. Papillary muscles may have abnormal attachments on the ventricular walls, or even directly to the mitral leaflets, as well as additional heads or accessory PMs [16•, 18, 21, 24, 34, 36, 38, 45–48]. The most common abnormality of the base of the PM is anterior and basal displacement of the anterolateral PM, while the most common abnormality of the head of the PM is direct attachment of the anterolateral PM to or near the A1 scallop of the anterior mitral leaflet [16•].

The true prevalence of mitral abnormalities in HCM is difficult to assess, as many abnormalities are poorly appreciated and often not documented. Moreover, patients frequently will have multiple MV abnormalities present. Supporting the observation that MV abnormalities are inherent to HCM, MV abnormalities have been documented in patients who carry a genetic mutation for HCM but have not manifested septal hypertrophy or LVOT obstruction [40]. While MV abnormalities vary widely among patients with HCM, it is important to emphasize that intrinsic MV disease necessitating MV repair or replacement at the time of myectomy is relatively uncommon, with a reported prevalence of 5% to 9% [33•, 43•]. At the time of myectomy, the most common indications for concomitant MV intervention are chordal rupture or leaflet prolapse without chordal rupture [33•]. Common non-invasive imaging examples of abnormalities of the mitral apparatus are shown in Fig. 1, underscoring the importance of carefully inspecting each aspect of the mitral valve including the annulus, leaflets, chordae, and PMs.

Table 1 Possible anatomic abnormalities of the mitral apparatus in HCM

	Annulus	Leaflets	Chordae tendinae	Papillary muscles
Morphology	• Typically large [15] • Annular calcification [16]	• Elongated anterior and/or posterior leaflets [10, 15–28] • Prolapse [29] • Clefts [30]	• Elongated or fibrotic/retracted [31] • Potential for rupture of elongated chordae [32]	• Hypertrophied • Elongated or shortened • Accessory PMs • Additional PM heads [16, 18, 21, 24, 33, 34]
Location	• Acute aorto-septal angulation, thus distorting the mitral annulus [35]	• Coaptation more apically or closer to septum [27]	• Abnormal attachments to mitral leaflets • Attachment to the ventricular walls (false chords) [17]	• PMs closer together, more anterior, medial, basal, or apical [24, 36] • Direct insertion to leaflet or fusion to the septum [34]

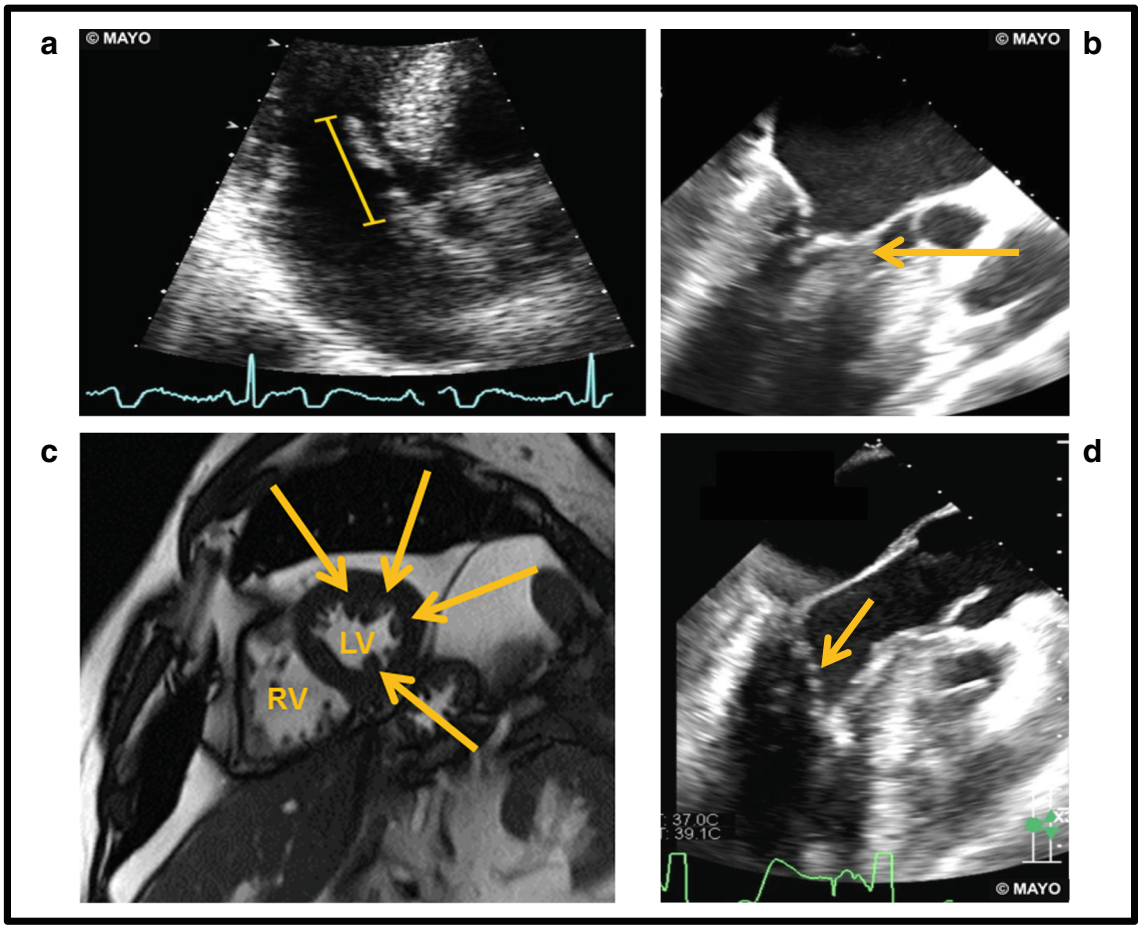

Fig. 1 Examples of mitral leaflet and papillary muscle abnormalities. **a** transthoracic echocardiogram in the apical long axis view shows an elongated anterior mitral leaflet (37.5 mm, indicated by *yellow measurement line*), resulting in abnormal coaptation and allowing systolic anterior motion of the MV to occur. **b** Transesophageal echocardiogram in the long axis view, off axis, demonstrating an anomalous PM (*yellow arrow*) attached directly to the ventricular surface of the anterior mitral leaflet. This anomalous PM was resected at time of myectomy. **c** Cardiac MRI in the short axis view, showing multiple PMs (*yellow arrows*) which contributed to generation of SAM. The more anterior PM had to be resected at time of myectomy. **d** Transesophageal echocardiogram in the long axis view, displaying an anomalous PM (*yellow arrow*) attached to the ventricular septum, causing midventricular obstruction. At time of myectomy, this PM was adherent to the septum and needed to be partially resected

Mechanism of LVOT Obstruction in Relation to the Mitral Valve

Dynamic LVOT obstruction is reliant upon the presence of MV abnormalities. This principle holds true for cases of dynamic LVOT obstruction in HCM as well as other disease states (e.g., hypertensive heart disease, cardiac amyloidosis, dehydration with hyperdynamic left ventricular systolic function). A historical perspective sheds insight into recognition of this relationship. Initially, HCM was thought of as a functional obstruction without an anatomic substrate. In the 1960s, angiographic studies demonstrated posteriorly directed MR in HCM, bringing to light the contributory role of the MV [49]. Further angiographic observations by Wigle and colleagues clarified the sequence of events that occur with LVOT obstruction: "eject, obstruct, leak," the latter referring to SAM-mediated MR (Video 1) [50]. More than half a century later, combined surgical and echocardiographic data have validated that MR in HCM is mostly due to SAM [43•]. Furthermore, while nearly all (97%) cases of posteriorly directed MR are due to SAM, the majority (83%) of cases of with jets that are not posteriorly directed MR are still due to SAM [43•].

While angiographic studies have shown that SAM with leaflet-septal contact obstructs flow, echocardiographic investigations have clarified that SAM of the MV is what initiates the process of LVOT obstruction [25, 45, 51]. The first study to show this used electrocardiographic timing to correlate the left ventricular-aortic gradient with SAM-septal contact on M-mode [25]. The cause of LVOT obstruction was shown to be SAM by evaluating the timing of flow through the LVOT on continuous wave Doppler and correlating it with the timing of leaflet-septal contact on M-mode. This analysis demonstrated that flow acceleration across the LVOT did not occur until SAM occurred [52]. Furthermore, multiple studies have

shown that the duration of leaflet-septal contact correlates with the severity of LVOT obstruction [26, 53, 54].

If SAM results in LVOT obstruction in HCM, then the question must be posed: what is the underlying mechanism of SAM? In the 1980s, multiple studies demonstrated that SAM occurs early in systole [25, 27]. It was initially thought that a pressure differential between the LV cavity and the LVOT created a suction phenomenon on the mitral leaflets, bringing them toward the septum (referred to as the Venturi effect). Studies have since shown that the drag effect is the primary mechanism of SAM, as opposed to the Venturi effect (Fig. 2) [21, 52, 54, 55]. The drag effect refers to the mitral leaflets being pushed toward the septum, much like the sail of a sailboat being pushed by the wind. Drag effect occurs because of vigorous ventricular contraction, with blood flow directed along abnormal chamber geometry, displacing blood flow more posteriorly. This generates a different "angle of attack" as blood coming from the midventricular aspect of the posterior wall lifts the MV towards the septum. Anterior displacement of the mitral apparatus further contributes to the altered "angle of attack". While the anterior leaflet is more likely to be affected, the posterior can also be affected. A small LVOT increases the likelihood of SAM and LVOT obstruction [52]. In summary, SAM with subsequent LVOT obstruction is currently best explained by a combination of vigorous ventricular contraction, abnormal chamber geometry (small cavity, thick walls, small LVOT), and abnormal mitral leaflet coaptation [8].

Hemodynamic loading conditions that predispose to worsened obstruction include decreased preload, decreased afterload, and increased contractility. Perhaps less intuitive is the day-to-day and even beat-to-beat variability in obstruction severity, without apparent changes in activity or loading conditions [56, 57]. Approximately two-thirds of all patients with HCM will have dynamic LVOT obstruction: one-third with a gradient present at rest and another third with a gradient present only with provocation [6]. Invasive hemodynamic data has confirmed that LVOT obstruction can vary to such an extent that patients could be quantitatively reclassified (e.g., severe, less than severe) during a single cardiac catheterization in 50% of cases [56]. Given this degree of dynamic change in LVOT gradient, one can infer that SAM and the severity of MR also vary significantly.

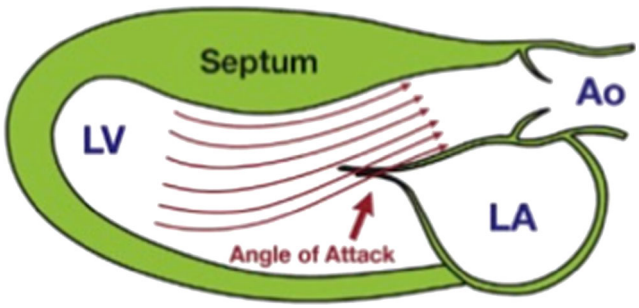

Fig. 2 Drag effect as the cause of SAM. A thickened septum displaces blood posteriorly during systole. This creates an "angle of attack" in which blood pushes against the mitral apparatus as it leaves the left ventricle, similar to a sail in the wind, resulting in MV SAM. SAM results in obstruction of blood flow through the LVOT. Ao = aorta, LA = left atrium, LV = left ventricle (reprinted from: Silbiger JJ. J Am Soc Echocardiogr. 2016;29(7):622–39, with permission from Elsevier) [21]

The aforementioned mechanism of obstruction is the prototypical model for LVOT obstruction in HCM. However, just as septal morphology and MV anatomy varies vastly between patients, there are many different mechanisms of obstruction in HCM, with some patients demonstrating more than one type of obstruction [58]. Midventricular obstruction can be due to septal contact with the mitral sub-valvular apparatus, cavity obliteration without mitral anomalies, or a combination of both. Dynamic obstruction is less frequently observed with the apical variant of HCM and mitral anomalies are not well characterized in this variant of HCM [59, 60]. Conversely, in patients without HCM that have dynamic LVOT obstruction, SAM is a common cause [44, 61]. In these patients, there is usually septal hypertrophy for another reason (e.g., hypertensive heart disease, cardiac amyloidosis) and some MV abnormality predisposing to the drag effect.

Evaluation of the Mitral Valve in HCM

Transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and cardiac magnetic resonance imaging (CMR) are valuable and validated in assessing the MV in HCM. TTE is the cornerstone diagnostic tool in HCM given that it is readily accessible, noninvasive, allows assessment of hemodynamics, and has excellent capability to visualize LV hypertrophy and MV abnormalities [62, 63]. TTE depicts SAM readily, with M-mode offering the highest temporal resolution and 2D and 3D echocardiography providing additional information regarding the mitral configuration and surrounding structures. In addition, a particular strength of TTE is the ability to assess the MV dynamically with provocation such as during Valsalva maneuver, during administration of pharmacotherapies (e.g., amyl nitrite, isoproterenol), with postural changes (such as repetitive squat-to-stand maneuver), or with exercise [6]. Because of these many features, TTE remains the imaging test of choice to screen for HCM in family members.

TTE continues to be the primary imaging modality to characterize and quantify MR in patients with and without HCM. TEE has strengths in clarifying anatomy and mechanism of MR, with better 2D and 3D imaging of the annulus and leaflets. On TTE and TEE, it is important to utilize off axis imaging planes in order to visualize abnormal structures and attachments of the mitral sub-valvular apparatus. CMR also offers excellent assessment of the sub-valvular apparatus. In particular, CMR has clear advantage in depicting abnormal morphology and location of PMs [31, 34]. While cardiac

computed tomography (CT) is not as well established for MV assessment in HCM, it has been shown to reliably measure leaflet lengths and also assess PM displacement [48].

In order to appropriately manage HCM, the etiology of MR must be thoroughly evaluated. A posteriorly directed jet has a positive predictive value of 94.9% on TTE and 97.1% on intraoperative TEE for SAM-mediated MR [43•]. Further evaluation must be performed for alternative etiologies of MR if the jet is not posteriorly directed, including consideration of TEE (Fig. 3). Alternative mechanisms of MR include other MV abnormalities common in HCM (e.g., abnormal attachment between leaflets and sub-valvular apparatus, MV prolapse) or degenerative valve disease (such as a flail segment) that can be present in any patient. Importantly, MR due entirely to SAM will alleviate with relief of LVOT obstruction.

Intraoperative TEE is recommended for all patients with HCM undergoing structural intervention, as it allows real-time assessment of pre-operative anatomy, hemodynamics, and mechanism of MR. Intraoperative TEE, compared with preoperative TTE, identifies new findings in one out of five patients with HCM [28, 64, 65]. These findings can significantly impact operative planning and outcomes.

Management of the Mitral Valve in HCM

In HCM patients with dynamic LVOT obstruction, initial treatment should focus on lifestyle modifications, such as avoidance of dehydration, and elimination of pharmacotherapies that worsen LVOT obstruction, most commonly diuretics and afterload reducing agents [62]. In symptomatic patients, beta blockers and non-dihydropyridine calcium channel blockers should be initiated [62]. In the majority of patients, these therapies are sufficient to relieve symptoms of dynamic LVOT obstruction.

In HCM patients with obstruction and symptoms refractory to medical management, septal reduction therapy via surgical myectomy or septal ablation is recommended [62]. The decision between septal ablation and surgical myectomy is influenced by multiple variables including patient comorbidities as well as the experience of the performing providers [66]. In addition, guidelines recommend surgery for patients with intrinsic MV disease [62, 67]. When MR is entirely due to SAM, it can be significantly decreased with myectomy alone, even if severe pre-operatively [33•, 68–70]. For the minority of HCM patients with non-SAM-mediated MR, there is ample data showing the superiority of valve repair over valve replacement [33•, 42, 71]. A surgical approach is also preferred if there are anomalies of the MV apparatus contributing to LVOT obstruction. In patients who have undergone myectomy performed by an experienced surgeon, the need for repeat myectomy is rare [72]. When repeat myectomy is required, the most commonly observed scenario is incomplete resection during the initial myectomy; however, a significant proportion of these patients also have anomalous PM that were not addressed at the time of surgery and contribute to residual obstruction [54]. Release and debulking are often employed for anteriorly displaced PMs in addition to excision of muscular connections between the PM head and left ventricular free wall. These observations further emphasize the importance of recognizing MV anomalies via detailed non-invasive imaging among patients with HCM to increase the likelihood of procedural success.

It remains controversial whether HCM patients with SAM-mediated MR undergoing surgical myectomy benefit from specific interventions on the MV. Because abnormal structure begets abnormal function, it may seem logical to directly intervene on the MV when the MV is severely abnormal (e.g., leaflet plication for large

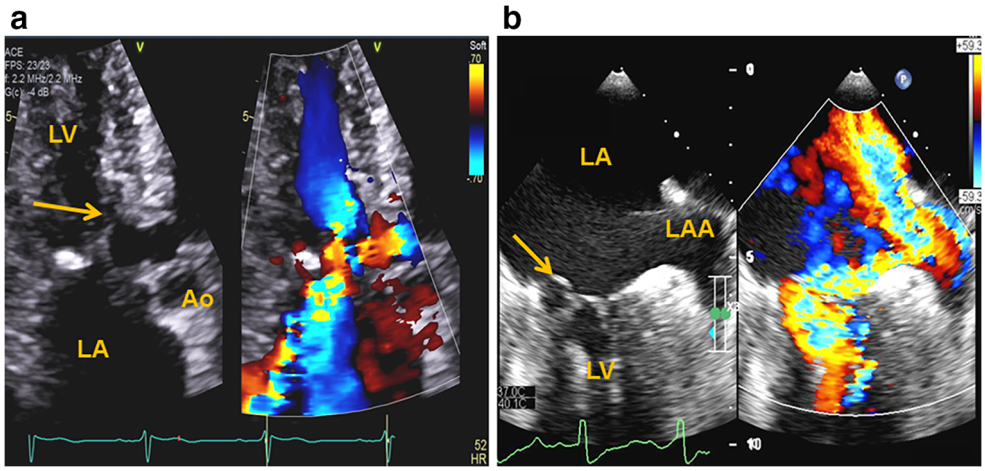

Fig. 3 Jets of mitral regurgitation. **a** TTE in the apical long axis view, demonstrating a posteriorly directed MR jet, indicating that the etiology of MR is secondary to MV SAM (*yellow arrow*). **b** TEE in the 2 chamber view, showing an anteriorly directed MR jet due to a flail chord (*yellow arrow*). Given the etiology of MR, MV repair was performed at the time of myectomy. Ao = aorta; LA = left atrium; LAA = left atrial appendage; LV = left ventricle

leaflets). However, central to the development of SAM is the drag effect, which is largely driven by abnormal chamber geometry and small LVOT size. Extended septal myectomy beyond the area of SAM-septal contact largely negates the drag effect and in the majority of patients abolishes SAM, even in the presence of elongated mitral leaflets, abnormal chordal attachments, and/or abnormal PMs (Fig. 4) [73]. Recently, a national retrospective cohort study showed that intervention on the MV is less common at specialized centers [74•] and MV interventions were associated with increased length of stay and increased hospital mortality [74•, 75]. However, there is significant practice variability with regards to MV interventions at high volume centers and there have not been head-to-head comparisons of outcomes between institutions [16•, 46, 69, 76, 77•]. Although selection bias likely contributes to the observed differences in surgical outcomes, it is important to tailor the surgical approach to each patient's unique anatomy. Some experts advocate primary MV interventions when SAM is present without significant septal hypertrophy [16•], whereas myectomy alone is often the preferred strategy in the absence of intrinsic valve disease on preoperative imaging. A large retrospective study demonstrated that only 2.1% of patients in the latter group required additional MV intervention when utilizing intraoperative TEE [52]. Importantly, long-term outcomes were similar regardless of the need for an additional cardiopulmonary bypass run.

Several small studies have investigated transcatheter MV plication (MitraClip) to reduce SAM and LVOT obstruction [41•, 78, 79]. Although these studies were limited by size and adequate follow-up, transcatheter MV plication is a potential therapeutic option in symptomatic HCM patients who are not surgical candidates and/or do not have optimal coronary (septal perforator) anatomy for alcohol septal ablation.

Conclusion

The MV plays a critical role in dynamic LVOT obstruction. A combination of vigorous ventricular contraction, abnormal chamber geometry with a small LVOT, and abnormal mitral leaflet coaptation accounts for the mechanism of dynamic obstruction in the majority of patients. The most common MV

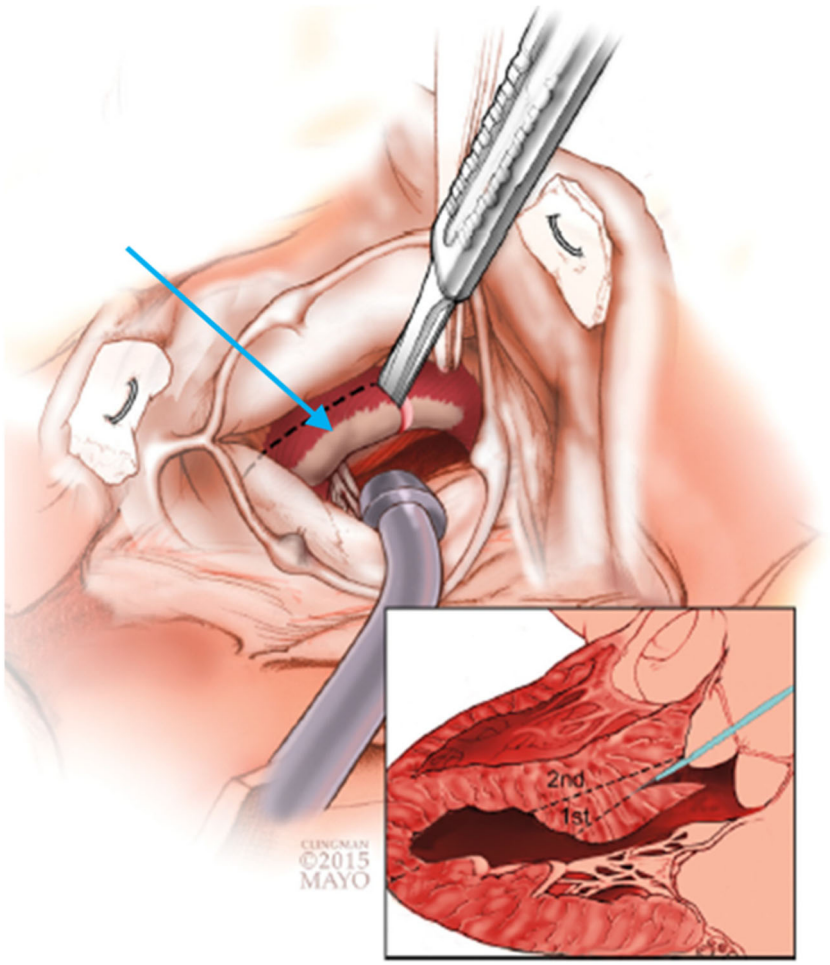

Fig. 4 Transaortic extended septal myectomy. Following aortic incision, the ventricular septum is viewed via retraction of the aortic cusps. The ventricular septum demonstrates a focal change within the LVOT (*blue arrow* pointing to the area shown in white, commonly referred to as a contact lesion) secondary to SAM and dynamic LVOT obstruction. On the inlay image in the bottom right, excising the contact lesion is labeled as the "1st" excision. Extending the myectomy deep to this lesion (labeled as the "2nd" excision) significantly improves procedural success, by reducing the potential for obstruction to occur deep to the initial resection and by altering the anatomy which promotes the drag effect (reprinted from: Nishimura RA, et al. Circulation Research. 2017;121(7):771–83, with permission from Wolters Kluwer Health Inc.) [8]

abnormalities are elongated mitral leaflets and anterior displacement of the mitral apparatus. Multi-modality imaging allows recognition of these and other MV abnormalities and can directly impact the therapeutic strategy. While practice patterns of MV intervention at the time of myectomy vary widely, it remains clear that thorough preoperative imaging assessment of the MV and surgical expertise are critical when approaching the highly variable mitral anatomy associated with HCM.

Compliance with Ethical Standards

Conflict of Interest Charles Jain, Darrell B. Newman, and Jeffrey B. Geske deny any conflicts of interest regarding this subject matter.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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