Review Article

Systolic anterior motion of the mitral valve in hypertrophic cardiomyopathy: a narrative review

Sarah A. Guigui[1,2], Christian Torres[2], Esteban Escolar[2,3], Christos G. Mihos[1,2]

[1]Echocardiography Laboratory, Columbia University Division of Cardiology, Mount Sinai Heart Institute, Miami Beach, FL, USA; [2]Columbia University Division of Cardiology, Mount Sinai Heart Institute, Miami Beach, FL, USA; [3]Coronary Care Unit, Columbia University Division of Cardiology, Mount Sinai Heart Institute, Miami Beach, FL, USA

Contributions: (I) Conception and design: SA Guigui, CG Mihos; (II) Administrative support: E Escolar, CG Mihos; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Christos G. Mihos, DO. Director, Echocardiography Laboratory, Columbia University Division of Cardiology, Mount Sinai Heart Institute, 4300 Alton Road, De Hirsch Meyer Tower 1st Floor, Miami Beach, FL 33140, USA. Email: christos.mihos@msmc.com or drcmihos@gmail.com.

Background and Objective: The prevalence of hypertrophic cardiomyopathy (HCM) is estimated to be 1 in 200 to 500 individuals, with systolic anterior motion (SAM) of the mitral valve (MV) and left ventricular outflow tract (LVOT) obstruction present in 60% to 70%. In this narrative review, we aim to elucidate the pathophysiology of SAM-septal contact and LVOT obstruction in HCM by presenting a detailed review on the anatomy of the MV apparatus in HCM, examining the various existing theories pertaining to the SAM phenomenon as supported by cardiac imaging, and providing a critical assessment of management strategies for SAM in HCM.

Methods: A literature review was performed using PubMed, EMBASE, Ovid, and the Cochrane Library, of all scientific articles published through December 2021. A focus was placed on descriptive studies, reports correlating echocardiographic findings with pathologic diagnosis, and outcomes studies.

Key Content and Findings: The pathophysiology of SAM involves the complex interplay between HCM morphology, MV apparatus anatomic abnormalities, and labile hemodynamic derangements. Echocardiography and cardiac magnetic resonance (CMR) vector flow mapping have identified drag forces, as opposed to the "Venturi effect", as the main hydraulic forces responsible for SAM. The degree of mitral regurgitation with SAM is variable, and its severity is correlated with degree of LVOT obstruction and outcomes. First line therapy for the amelioration of SAM and LVOT obstruction is medical therapy with beta-blockers, non-dihydropyridine calcium-channel blockers, and disopyramide, in conjunction with lifestyle modifications. In refractory cases septal reduction therapy is performed, which may be combined with a 'resect-plicate-release' procedure, anterior mitral leaflet extension, surgical edge-to-edge MV repair, anterior mitral leaflet retention plasty, or secondary chordal cutting.

Conclusions: Recent scientific advances in the field of HCM have allowed for a maturation of our understanding of the SAM phenomenon. Cardiac imaging plays a critical role in its diagnosis, treatment, and surveillance, and in our ability to apply the appropriate therapeutic regimens. The increasing prevalence of HCM places an emphasis on continued basic and clinical research to further improve outcomes for this challenging population.

Keywords: Hypertrophic cardiomyopathy (HCM); left ventricular outflow tract obstruction; mitral valve regurgitation; systolic anterior motion (SAM)

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Introduction

The advent of cardiac ultrasound in the late 1960's, about a decade after the first descriptions of hypertrophic cardiomyopathy (HCM) and following initial work with angiography, allowed for the site of left ventricular outflow tract (LVOT) obstruction to be identified (1-3). Echocardiographic M-mode examination of 6 HCM patients diagnosed angiographically revealed that the anterior mitral valve leaflet (AML) was apposed to the interventricular septum for approximately 60% of the ejection phase, a phenomenon which has since been termed systolic anterior motion (SAM) of the mitral valve (MV). In that same study, the injection of methoxamine, a systemic vasoconstrictor, led to the disappearance of SAM (4).

Clinically ranging from a silent abnormality diagnosed by cardiac imaging to a dynamic LVOT obstruction with hemodynamic repercussions, SAM has been described in up to 95% of HCM patients (5-7). Approximately 60% to 70% of these patients have either resting or provocable LVOT obstruction (6). In order to fully elucidate the pathophysiology of the SAM-septal contact and LVOT obstruction in HCM, we first present a detailed and timely review on anatomy of the MV apparatus in HCM. Secondly, the various existing theories pertaining to the SAM phenomenon itself as supported by cardiac imaging is examined. Finally, we provide an overview on the medical and interventional management of SAM in HCM. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-182/rc).

Methods

A literature review was performed using PubMed, EMBASE, Ovid, and the Cochrane Library, of all scientific articles published through December 2021 (*Table 1*). The Boolean search terms used included: 'hypertrophic cardiomyopathy', 'left ventricular outflow tract obstruction', 'systolic anterior motion', 'SAM', 'mitral valve', 'septal myectomy', 'septal alcohol ablation', 'mitral valve surgery', 'mitral valve repair', 'mitral valve replacement', 'echocardiography', and 'cardiac magnetic resonance'. A focus was placed on descriptive studies, reports correlating echocardiographic findings with pathologic diagnosis, and outcomes studies. All authors conducted the literature search, and consensus was reached when three out of four authors agreed on all studies. Additionally, the echocardiography laboratory imaging archives at Columbia University Division of Cardiology, Mount Sinai Heart Institute (Miami Beach, FL, USA) were referenced.

Discussion

Normal mitral valve apparatus anatomy

The normal MV apparatus is a complex structure comprised of the anterior and posterior leaflets, fibromuscular annulus, chordae tendinae, lateral and medial papillary muscles, and subtending left ventricular (LV) myocardium. The valvular tissue attaches circumferentially to the fibromuscular mitral annulus, which is saddle-shaped and dynamic in motion (8,9). The anterior leaflet is longer (18–24 mm) and semicircular in shape, while the posterior leaflet is shorter (11–14 mm) but encompasses a larger surface area. The free edges of the posterior leaflet are indented and create distinct scallops which are named P1 (lateral), P2 (central), and P3 (medial); while no distinct scallops are present on the anterior leaflet, it is customary to divide the tissue visually into counterpart scallops to allow for anatomic description. The chordae tendinae originate from both papillary muscles and serve to prevent leaflet eversion (10). Primary (marginal) chordae insert into the leaflet free edges, superior to which a ridge demarcates the leaflet coaptation zone. Secondary (basal) chordae attach to the anterior leaflet rough zone and posterior leaflet body, while some patients may also display tertiary chordae from the posterobasal LV myocardium directly into the posterior leaflet (11). The two papillary muscles arise from the distal third of the ventricular myocardium and are oriented beneath the correspondingly named valvular commissures (12). The lateral papillary muscle most commonly exhibits a single head, while the medial displays two separate heads. The spatial orientation and dynamic function of the papillary muscles serves to balance the closing-tethering forces on the MV leaflets, and their tensile vectors maintain a posteriorly directed coaptation point away from the LVOT.

Anatomic basis for SAM in HCM

The cardiac anatomy in HCM is characterized by: (I) marked thickening of the interventricular septum; (II) narrowing of the LVOT; and (III) abnormalities of the MV apparatus and papillary muscle orientation (*Table 2*; *Figure 1*) (13,14). This results in significant overlap between the LV inflow and outflow tracts resulting in hemodynamic

Table 1 Search strategy summary

Variable	Search details
Date of search	12/1/2021–12/31/2021
Databases searched	PubMed, EMBASE, Ovid, Cochrane Library
Search items used	'hypertrophic cardiomyopathy', 'left ventricular outflow tract obstruction', 'systolic anterior motion', 'SAM', 'mitral valve', 'septal myectomy', 'septal alcohol ablation', 'mitral valve surgery', 'mitral valve repair', 'mitral valve replacement', 'echocardiography', 'cardiac magnetic resonance'
Timeframe of studies	1/1/1958–12/31/2021
Inclusion and exclusion criteria	Focus placed on descriptive studies, reports correlating echocardiographic findings with pathologic diagnosis, and outcomes studies. No exclusion criteria.
Selection process	All authors conducted the literature search. Consensus was reached by at least two of three authors on all studies

SAM, systolic anterior motion.

Table 2 Common abnormalities of the mitral valve apparatus in hypertrophic cardiomyopathy

Mitral valve structure	Common abnormalities
Valvular	Elongated mitral valve leaflets (both anterior and posterior)
	Increased mitral tenting volume
	Increased distance from coaptation point to anterior leaflet tip ("residual leaflet")
	Smaller coaptation-septal distance (C-sept distance)
	Papillary muscle hypertrophy
Papillary muscles	Increased number of papillary muscles
	Displacement and abnormal papillary muscle insertion
	Shorter interpapillary muscle distance
Chordal apparatus	Shortened and fibrotic chordae tendinae

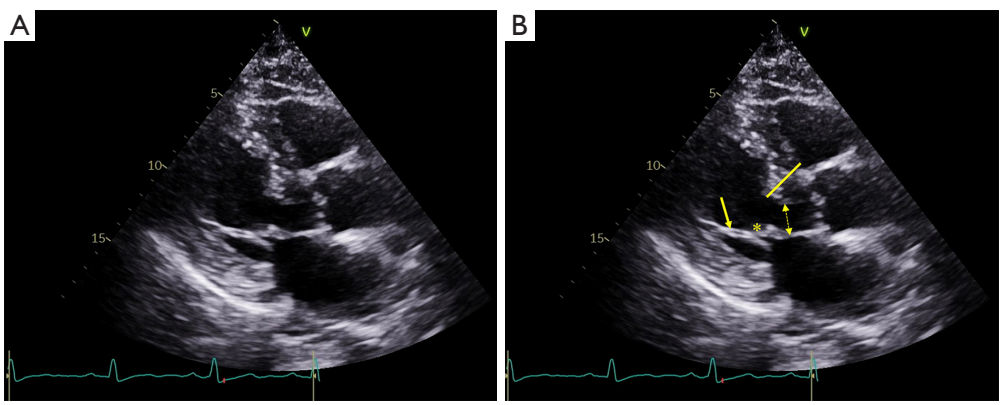

Figure 1 Asymmetric interventricular septal thickening in hypertrophic cardiomyopathy. (A) A parasternal long-axis view at end-diastole; note the sigmoid septum morphology; (B) the solid line measures the maximum thickness of the basal interventricular septum at 20 mm, the double arrowhead highlights left ventricular outflow tract narrowing, the asterisk highlights a thickened mitral valve with an anteriorly-displaced coaptation point, and the single arrowhead points to short and fibrotic chordae tendinae.

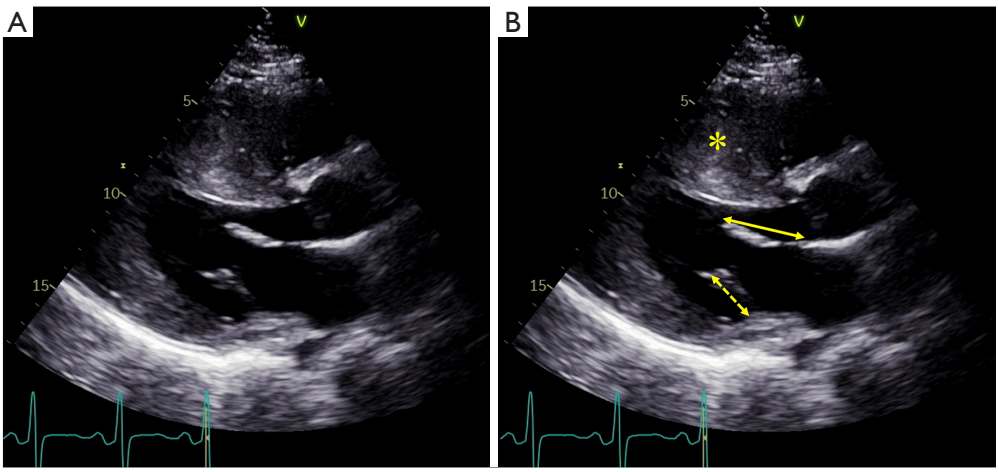

Figure 2 Elongated mitral valve leaflets in hypertrophic cardiomyopathy. (A) A mid-diastolic parasternal long-axis view; (B) the double-headed arrow highlights an elongated anterior mitral leaflet measuring 28 mm, the double-headed dashed arrow highlights an elongated posterior mitral valve leaflet measuring 16 mm, and the asterisk highlights a markedly thickened interventricular septum measuring 30 mm with a reverse curve morphology.

derangements and obstruction. When comparing the MV and ventricular geometry between HCM patients with SAM and normal subjects, it reveals a significantly shorter MV leaflet coaptation-septal distance (C-sept) (12±4 *vs.* 21±3 mm, P<0.001) and inter-papillary muscle distance (13±5 *vs.* 18±4, P=0.02), as well as a larger MV tenting volume indexed to body surface area (2.1±1 *vs.* 0.5±0.3 mL/m^2, P<0.001) (15). The MV coaptation point is on average 9 mm from the AML tip versus within 3 mm from the leaflet tip in HCM versus normal patients (16).

Owing to this unique configuration, the MV in HCM has been termed the "nightcap mitral valve" as it extends into the LV cavity and its coaptation point lies above the plane of the mitral annulus (17). Excess MV leaflet tissue often extends past the coaptation zone and is termed "residual leaflet", resulting in increased leaflet length and area. This residual MV tissue typically makes the first contact with the septum, and intraventricular hemodynamics in the setting of HCM geometric abnormalities keep the obstructing MV leaflet in the LVOT (18). An examination of 94 MV specimens from HCM patients by Klues and colleagues revealed a significantly increased MV leaflet area compared with controls (12.9±3.7 *vs.* 8.7±2.0 cm^2, P<0.001), mainly driven by increased AML length (*Figure 2*) (19). The generally accepted normal values for MV leaflet length by echocardiography are 18 to 24 mm for the AML, and 11 to 14 mm for the posterior mitral leaflet (20).

A cardiac magnetic resonance (CMR) study of 172 HCM patients and 15 HCM gene positive/phenotype negative patients detailed the elongation of the MV leaflets (21). The AML length was 26±5 mm and significantly greater than in control subjects (19±5 mm, P<0.001). The length of the posterior mitral leaflet was also significantly greater than that of the controls measuring 14±4 *vs.* 10±3 mm, respectively (P<0.001). Keeping in mind the differences in measurement techniques between CMR and echocardiography, MV leaflet elongation in HCM patients compared with controls has also been documented by transesophageal echocardiography: 31±4 *vs.* 22±3 mm for the AML, and 20±2 *vs.* 15±3 mm for the posterior mitral leaflet (P<0.00001 for both) (16). These structural MV leaflet abnormalities are typically noted in 60% to 70% of HCM patients (19). While a ratio of leaflet length to transverse LVOT diameter >2 has been found to correlate with LVOT obstruction, no relationship has been established between the absolute MV leaflet length and New York Heart Association (NYHA) functional class, severity of mitral regurgitation (MR), maximal LV wall thickness, or the presence of late gadolinium enhancement, so that absolute leaflet length does not seem to be a marker of severity of the disease (22,23).

Papillary muscle hypertrophy, defined as an end-diastolic short-axis thickness of >11 mm on echocardiography, is another anatomical abnormality observed in over 50% of HCM hearts (24,25). CMR characterization of HCM patients has also shown a significant increase in papillary

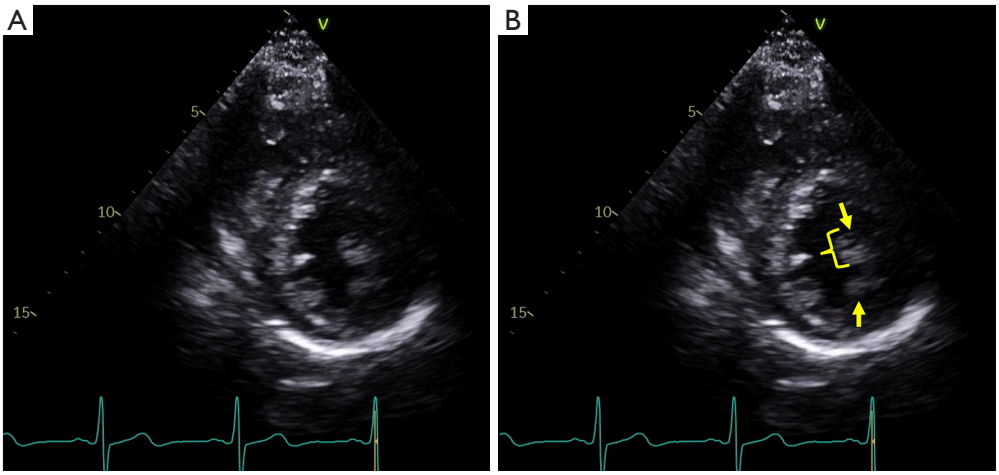

Figure 3 Papillary muscle abnormalities in hypertrophic cardiomyopathy. (A) An end-diastolic parasternal short-axis view; (B) the arrows point to a bifid anterolateral papillary muscle, with the bracket highlighting a hypertrophied anterior head measuring 13 mm in thickness.

muscle number (2.5 *vs.* 2.1, P<0.001) and mass as compared with controls (26). In fact, bifid papillary muscles or accessory papillary muscles are frequently identified on imaging (*Figure 3*). Papillary muscles may also be displaced anteriorly and towards the base, causing an overlap of the LV inflow and outflow, or they may be displaced apically (27). Alternatively, they may fuse with the ventricular septum or to the LV free wall, or may be oriented inwards towards the LV centroid reducing intrapapillary muscle distance and thus creating chordal slack, which in turn may promote SAM. A particularly pathologic variant is insertion of an anomalous papillary muscle directly into the AML causing SAM and LVOT obstruction (28). A type 1 abnormality is characterized by direct insertion of the anomalous papillary muscle into the AML mid-body without chordal attachments; type II has a direct insertion into the AML mid-body with chordal attachments to the leaflet free edge; and, type III has a direct insertion with or without short fibrotic chordae into the AML free edge (29). Papillary muscle abnormalities have been associated with a higher resting LVOT gradient independent of septal thickness or resting heart rate, and are capable of generating SAM in HCM *in vitro* models with no septal hypertrophy; these abnormalities can be expected in up to 20% of patients (26,27,30).

An important subgroup within HCM are the genotype positive-phenotype negative patients, which is also referred to as "pre-clinical" HCM (21,31,32). In these patients LV wall thickness and geometry are commonly normal. However, they are characterized by abnormalities in the MV apparatus anatomy when compared with non-affected individuals, including longer anterior MV leaflets (17.1±0.4 *vs.* 16±0.4 mm/m^2, P=0.006), thicker posterior leaflets (1.79±0.008 *vs.* 1.62±0.007 cm, P=0.06), and decreased papillary muscle separation (31.1±0.7 *vs.* 34.2±0.9 mm, P=0.007) (33). Additionally, the prevalence of SAM is also significantly increased in "pre-clinical" HCM (15.2% *vs.* 1.6%, P=0.006). These abnormalities are more severe in overt genotype and phenotype-positive HCM, which makes a high index of suspicion and comprehensive imaging assessment paramount in identifying these patients for proper risk stratification and treatment.

Mechanical forces responsible for SAM in HCM

Early theories attributed SAM to a Venturi effect whereby narrowing of the LVOT from septal hypertrophy leads to blood flow acceleration due to decreased cross-sectional area, resulting in displacement of the MV leaflets towards the interventricular septum and LVOT via a "suction" force (34). However, timing of SAM has shown that this phenomenon starts even before the onset of systole, when the velocities in the LVOT are still low (35). The technique of vector flow mapping, which combines color Doppler data and speckle tracking analysis, allows for the creation of velocity vectors to characterize the flow of blood inside vascular structures. When applied to HCM hearts, it has shown that in the majority of obstructive HCM, late diastolic mitral inflow creates a posterior vortex pushing the MV leaflets anteriorly, even before the onset of systole (36).

This phenomenon has been termed diastolic anterior motion of the MV, which acts as a precursor to SAM. The protruding septum is also responsible for redirecting early, low-velocity systolic flow below to the MV, displacing it anteriorly. It thus appears that in both cases of vortical SAM and ejection SAM, drag forces, as opposed to the Venturi effect, are the main hydraulic forces at play (*Figure 4*).

SAM and mitral regurgitation

The degree of MR with SAM is variable, and its severity is correlated with degree of LVOT obstruction, symptomatology, and clinical outcomes (37,38). It typically occurs from poor coaptation of the mitral leaflets which results from the posterior leaflet not being able to move anteriorly with the AML, either because it is too short or because it is not mobile enough (39). Note, however, that primary or degenerative changes of the MV are also common in HCM. These include restrictive or tethered leaflets (70%), de-generative and calcific changes (31%), myxomatous disease (20%), and restrictive chordae (19%) (40). Mitral annular calcification is observed in 19% to 46% of HCM patients with variable degrees of severity (41,42). Annular calcification, particularly when significant posteriorly, decreases the distance between the anterior MV leaflet and coaptation point to the interventricular septum, and displaces the valve apparatus anterior towards the LVOT. When compared to HCM patients without annular calcification, those with the pathology have a greater prevalence of SAM (84% *vs.* 64%, P<0.001) and LVOT obstruction (81% *vs.* 58%, P<0.001), and a 46% increased risk of death (P=0.01). Finally, the differentiation between MR secondary to SAM and primary MR is primordial for appropriate management. In order to differentiate the two, the jet direction may be helpful, whereby a posteriorly directed jet usually points to SAM as the etiology of the MR versus a central or anteriorly directed jet which usually indicates primary MV disease (43,44) (*Figure 5*).

Diagnosis of SAM in HCM

Echocardiography is the modality of choice for diagnosis of HCM and SAM. Care should be taken to evaluate the LV wall thickness, MV leaflet length, and papillary muscle anatomy and orientation (45,46). The maximal interventricular septal and posterior wall thickness is assessed in the parasternal long axis view at end-diastole; maximal apical thickness may be assessed in the parasternal short axis view, or in the apical views, and is enhanced by the use of myocardial contrast. Given their perpendicular orientation to the ultrasound beam, MV leaflet length is also best assessed at mid-diastole in the parasternal long axis orientation. Assessment of the morphology of HCM is also important, as a sigmoid-shaped or reverse curve interventricular septum is more likely to be found in obstructive phenotypes than a neutral hypertrophic septum or apical HCM (47). Color flow Doppler reveals turbulence at the site of SAM-septal contact (*Figure 5*). SAM severity can be graded as follows: mild for brief SAM without septal contact; moderate for SAM with septal contact lasting <1/3 of the systolic period; and, severe for SAM with septal contact lasting >1/3 of the systolic period (48) (*Figure 6*). Pulse wave Doppler interrogation at the site of the obstruction should reveal a characteristic "lobster claw" pattern, with a late-peaking signal generally indicating a peak pressure gradient of at least 30 mmHg (49).

CMR is a critical complementary imaging modality in the detailed assessment of HCM and structural abnormalities of the MV apparatus. It provides superior spatial resolution, tomographic imaging and reconstruction of the heart, and a sharp contrast between the myocardium and blood pool which allows for accurate LV wall thickness measurement and assessment of HCM morphology (50,51). Additionally, CMR has furthered our understanding of HCM-associated papillary muscle abnormalities, and thus provides important insights into the optimal surgical or percutaneous treatments for individual patients (52,53). Limitations to the use of CMR include lack of widespread availability, cost, patient factors such as age, body habitus, and claustrophobia, and certain medical contraindications.

Treatment options

While initial medical management of SAM in HCM includes beta or calcium-channel blockade, volume loading and avoidance of afterload reduction, definitive treatment for refractory symptomatic patients is surgical or percutaneous (45,46). Initially thought to be only present among those with obstructive HCM, SAM has now been described in other entities, which includes post-mitral and aortic valve surgical interventions and hyperdynamic states irrespective of LV hypertrophy (54-56). As previously discussed, anterior displacement of the MV is not only related to dragging forces across the septum but also to abnormalities of the MV apparatus, including increased mitral leaflet area, length, and laxity,

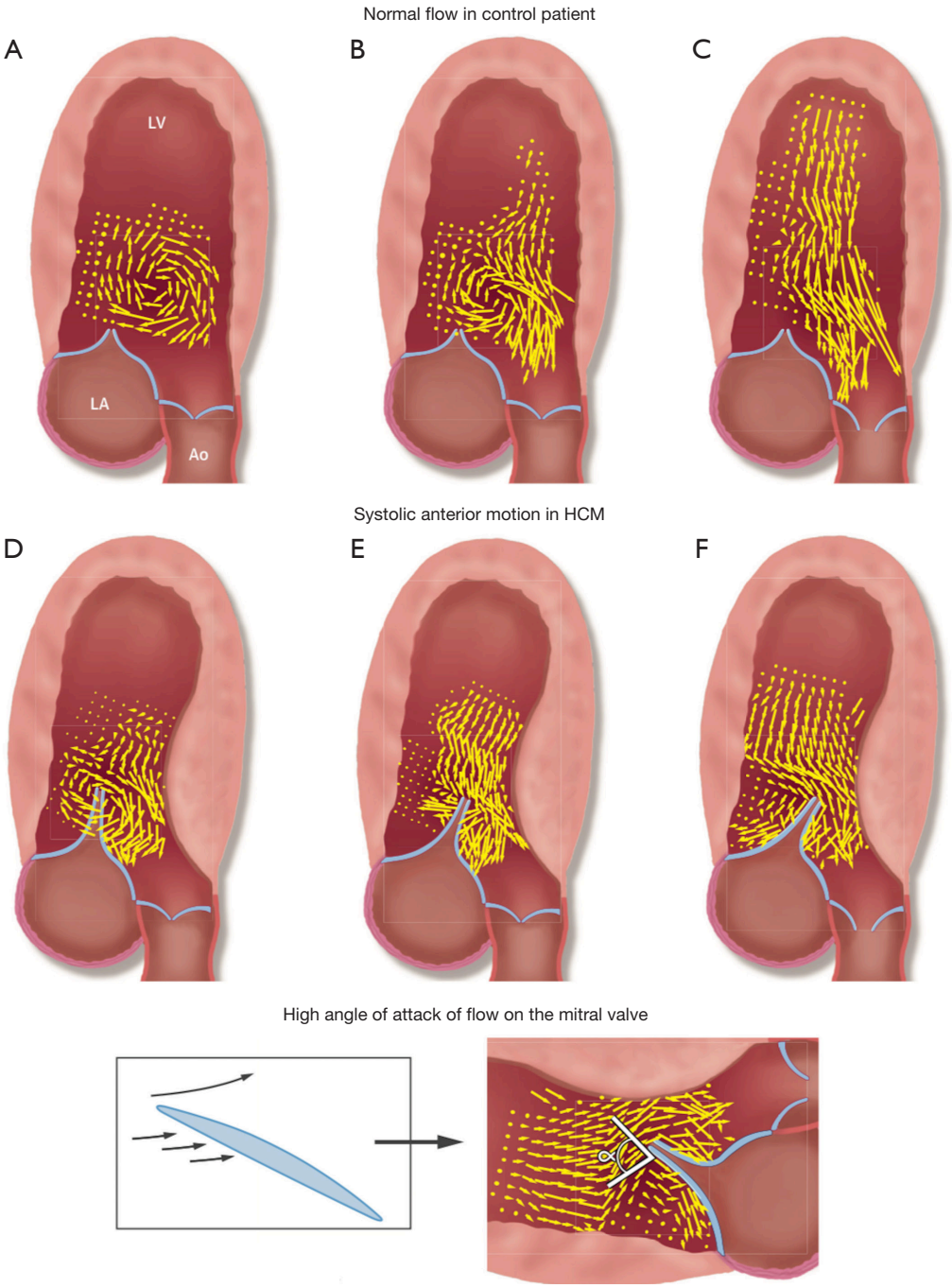

Figure 4 Depiction of systolic anterior motion of the mitral valve by vector flow mapping in hypertrophic cardiomyopathy. In a normal patient (top panel), there is progression from an early systolic isovolumic vortex to an organized ejection flow in the LVOT without evidence of interaction with the mitral valve (A-C). In a patient with obstructive hypertrophic cardiomyopathy and elongated mitral valve leaflets (middle panel), the isovolumic vortex initiates SAM of the mitral valve by pushing on the posterior surface of the mitral valve and positioning it in the LVOT (D,E). Alternatively, SAM is initiated in the early ejection phase (F), whereby flow is first deflected posteriorly by the bulging septum and then pushes on the posterior mitral valve leaflet surface, as it courses from a posterior to an anterior direction. In the bottom panel, the high angle of attack of flow on the mitral valve makes drag, and not lift, the predominant physical force leading to SAM. Reproduced with permission from Ro *et al.* (36). LV, left ventricle; LA, left atrium; Ao, aorta; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; SAM, systolic anterior motion.

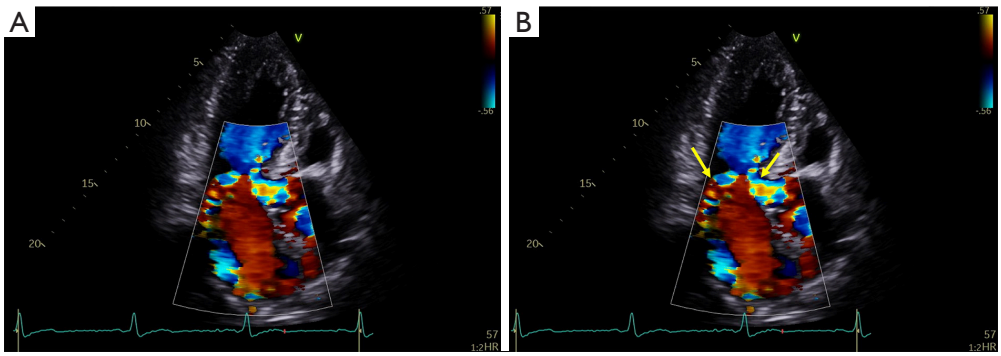

Figure 5 Color Doppler assessment at late systole of left ventricular outflow tract obstruction and mitral regurgitation in obstructive hypertrophic cardiomyopathy. (A) An apical 3-chamber view with color Doppler assessment; (B) the left arrow points to eccentric posteriorly-directed mitral regurgitation secondary to systolic anterior motion of the mitral valve; note the 'Coanda' effect of the regurgitant jet. The right arrow points to flow acceleration and turbulence in the left ventricular outflow tract as systolic obstruction occurs.

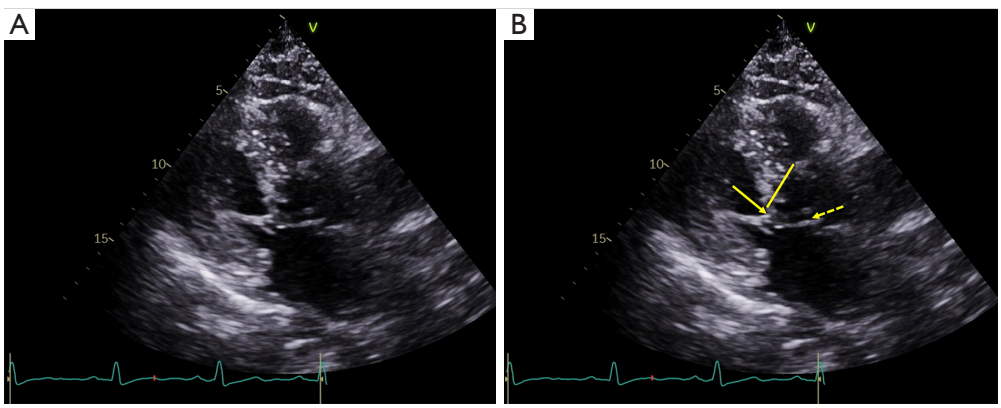

Figure 6 Severe SAM of the mitral valve. (A) A late-systolic parasternal long-axis view of severe mitral valve SAM in a patient with hypertrophic cardiomyopathy and discrete upper septal thickening (sigmoid septum morphology); (B) findings in panel B include marked basal septal systolic thickening (solid line), SAM with anterior mitral leaflet-septal contact (solid arrow), and systolic obliteration of the left ventricular outflow tract (dashed arrow). SAM, systolic anterior motion.

as well as anterior displacement of the papillary muscles and chordal abnormalities (7,44,57-60). Therefore, while septal reduction therapy is fundamental in the treatment of LVOT obstruction as it increases the size of the LVOT and the distance to the AML, a global approach considering the MV and papillary muscle geometry should be considered to avoid residual SAM, outflow obstruction or mitral regurgitation (*Table 3*) (45,46).

Septal reduction therapy

Septal myectomy (Morrow procedure) is the most widely used and accepted surgical procedure in patients with obstructive HCM resistant to medical therapy. Using a transaortic or transmitral approach, a resection of the basal portion of the interventricular septum is performed, thereby increasing the size of LVOT and eliminating the forces leading to SAM (61). For patients with more extensive septal thickening, the myectomy is extended to the mid-ventricular level distal to the point of AML-septal contact (Modified Morrow procedure) (62). In experienced HCM centers of excellence, myectomy is performed with an operative mortality <1%, effectively reduces septal thickness and LVOT gradient, improves functional status, and is associated with mid-to-long term survival equivalent to that of the general population (63,64).

In patients at high or prohibitive surgical risk, or in preference to surgical intervention, a percutaneous alcohol

Table 3 Surgical techniques for the management of systolic anterior motion of the mitral valve and left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

Technique	Procedure	Mechanism	Results	Caveats
Septal myectomy (Morrow procedure)	Classic: basal IVS resection OR Modified: extended resection to AML-septal contact point	LVOT widening; ↓SAM-generating forces	↓ LVOT gradients; ↓ SAM by 50–80%; Long-term survival equivalent to general population	VSD; AVB; Persistent LVOTO
Percutaneous septal alcohol ablation	96% EtOh injected in 1st septal perforator of LAD	Creation of basal septal myocardial infarction; ↓SAM-generating forces	↓ LVOT gradients; ↓ SAM by 50%	AVB; Persistent LVOTO; RV infarction
Resect-plicate-release	(I) 'Resect': extended SM; (II) 'Plicate': horizontal mid-body AML suture; AND/OR (III) 'Release': mobilization of abnormal PM	LVOT widening; ↓ SAM-generating forces; Stiffening of the AML; Posterior positioning of the PM	↓ LVOT gradients; ↓ SAM by 70–80%; ↓ MR	Caveats of SM; Technical complexity
Anterior mitral leaflet extension (MLE)	(I) Classic or extended SM; (II) Sewing of a pericardial patch to the central portion of the AML	LVOT widening; ↓ SAM-generating forces; Stiffening of the AML; Posterior displacement of the MV coaptation point	↓ LVOT gradients; Improved NYHA class symptoms; ↓ Residual SAM; ↓ MR	Caveats of SM; Pericardial patch failure; Recurrent MR; Careful patient selection
Surgical edge-to-edge repair	(I) Classic or extended SM; (II) Edge-to-edge suture of the A2-P2 MV scallops	LVOT widening; ↓ SAM-generating forces; ↓ MV leaflet motion	↓ LVOT gradients; Improved NYHA class symptoms; No SAM; No significant MR	Caveats of SM; No use of annuloplasty ring requires careful patient selection; Iaotrogenic MV stenosis
Anterior mitral leaflet retention plasty	(I) Classic or extended SM; (II) Medial and lateral AML sutured to the posterior annulus	LVOT widening; ↓ SAM-generating forces; Stretches central portion of the AML to prevent SAM	↓ LVOT gradients; ↑ Functional status; No SAM	Caveats of SM; Small study size; Contraindicated with PM abnormalities
Secondary chordal cutting	(I) Classic or extended SM; (II) Surgical transection of secondary AML strut chords	LVOT widening; ↓ SAM-generating forces; Relief of AML tethering toward LVOT	↓ LVOT gradients; ↑ Functional status; ↓ MR	Caveats of SM; Adverse LV remodeling; Careful patient selection
Transcatheter edge-to-edge mitral valve repair	Transcatheter edge-to-edge repair of the mitral valve in poor surgical candidates	↓ MV leaflet motion; Anchored MV coaptation point	↓ LVOT gradients; ↓ MR severity; No SAM	Small case series; Minimal follow-up

AML, anterior mitral leaflet; AVB, atrioventricular block; EtOh, ethanol; IVS, interventricular septum; LAD, left anterior descending coronary artery; LV, left ventricle; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MLE, mitral leaflet extension; MR, mitral regurgitation; MV, mitral valve; NYHA, New York Heart Association; PM, papillary muscle; RV, right ventricle; SAM, systolic anterior motion; SM, septal myectomy; VSD, ventricular septal defect. ↑: increased; ↓: decreased.

septal ablation can be performed. The procedure involves injection of small amount of 96% ethanol into the first septal perforator of the left anterior descending coronary artery, effectively causing a basal myocardial infarction and subsequent remodeling of the LVOT (65). When comparing the overall outcomes of septal myectomy and ablation, there is no difference in reported survival; however, patients undergoing myectomy have a greater reduction in LVOT gradient and less need for repeat intervention (66). Detailed registry data have shown that when stratified by 65 years of age, those <65 have superior outcomes with septal myectomy. Patients >65 years old have at least equivalent outcomes with either approach, and thus a less invasive alcohol ablation in this group is reasonable (67).

Of note, SAM may persist in variable degrees of severity post-myectomy in 20 to 50% of patients (68,69). This is influenced by the aforementioned MV apparatus abnormalities inherent to the disease and can result in

recurrent symptomatic LVOT obstruction (70). Higher risk features for residual LVOT obstruction include anterior MV leaflet elongation measuring >30 mm, a narrow end-diastolic coaptation point-septal (C-sept) distance measuring <20 mm at end-diastole, moderate to severe SAM, and prominent centrally displaced papillary muscles; these markers identify patients in whom MV intervention with or without myectomy may be considered (17,47,71). The application of MV surgical intervention also becomes particularly useful in patients with less severe septal hypertrophy, defined as a thickness less than 18 mm, in whom standard myectomy increases the risk for creation of a ventricular septal defect (72,73). Finally, choosing a percutaneous approach to treatment of LVOT obstruction does not allow any MV abnormalities to be addressed. Thus, careful assessment of the cause of SAM and LVOT obstruction is of paramount importance to ensure accurate risk stratification and procedure selection.

Resect-plicate-release procedure

The primary component of the 'Resect-Plicate-Release' procedure is the extended septal myectomy ('resect') (74,75). In patients with an elongated and lax anterior MV leaflet, a horizontal suture is placed at the leaflet mid-body to 'plicate', shorten, and stiffen the tissues in order to prevent SAM. For an elongated or anterior displaced anterolateral papillary muscle, 'release' of the basal portion of the muscle and abnormal muscular attachments to the anterolateral LV wall allow for its posterior movement away from the LVOT. Halpern and colleagues reported on 77 obstructive HCM patients who underwent myectomy as part of a 'Resect-Plicate-Release' procedure; 50 patients underwent AML plication, and 50 underwent anterolateral papillary muscle release (76). At a mean follow-up of 9 months, there was a reduction in LVOT gradient (107 *vs.* 10 mmHg), MR grade (1.8 *vs.* 1.2), and presence of SAM (100% *vs.* 22%), a decrease in AML length in patients undergoing plication, and an increase in the C-sept distance after anterolateral papillary muscle release (P<0.01 for all). Pre-operative echocardiography is used to apply the procedural tenets as follows: (I) 'Plicate-Release', with possible limited myectomy, for septal thickness ≤18 mm and AML length >30 mm; (II) 'Resect-Plicate-Release' for septal thickness >18 mm and AML length >30 mm; and (III) 'Resect-Release' for septal thickness >18 mm and AML ≤30 mm. The surgical expertise required and procedural learning curve are the most limiting aspects of this technique.

Anterior mitral leaflet extension

Introduced in 1991, AML extension consists of sewing a harvested glutaraldehyde-treated pericardial patch to the basal or central portion of the leaflet (77). This area is considered the region where inward bending and protrusion of the leaflet into the LVOT occurs (57,78). By stiffening the base and mid-body of the AML, the technique effectively decreases SAM, reestablishes a posterolateral coaptation point away from the LVOT, and increases chordal tensor forces (79-82). Vriesendorp and colleagues reported on 98 obstructive HCM patients who underwent combined myectomy and AML extension (82). At a mean follow-up of 8 years, there were significant reductions in LVOT gradient (93 *vs.* 9 mmHg), MR grade (2 *vs.* 0.5), SAM grade (2.4 *vs.* 0.1), and New York Heart Association functional class (2.8 *vs.* 1.3) (P<0.001 for all), with a 15-year cumulative survival rate (83%) comparable to an age and sex-matched cohort (85%) as well as a non-obstructive HCM cohort (83%). In a smaller study of 15 patients treated with myectomy and AML extension, 93% had no recurrent MR, and global longitudinal strain mechanics and LV twist were preserved, at 1-year follow-up (83). Across the two studies 7 (6%) patients required reoperation for recurrent MR, patch failure, or persistent LVOT obstruction. Risk factors for pericardial patch calcification, retraction, and failure include advanced age, chronic kidney disease, abnormal calcium metabolism, and systemic inflammatory disorders (77,84,85). This predisposes to MV repair failure and recurrent MR, and thus, careful patient selection for this technique is advised (77,85,86).

Surgical edge-to-edge repair

The Alfieri technique, or surgical edge-to-edge repair, was introduced in the 1990s as an MV repair option for patients with primary or secondary MR. It is performed by suture approximation of the A2 and P2 scallops of the anterior and posterior leaflets, creating a double-orifice MV and anchoring the coaptation point to prevent SAM (87). Benefits include the ability to perform via a transaortic approach which obviates the need for an atriotomy, a short operative time, and decreased surgical trauma (87-89). In a pooled analysis of 6 studies and 158 HCM patients who underwent septal myectomy and edge-to-edge MV repair, there was a significant reduction in LVOT gradient (82 *vs.* 16 mmHg), moderate or greater MR (84% *vs.* 5%), and presence of SAM (96% *vs.* 0%) at 2.8-year follow-

up (P<0.001 for all). Survival at follow-up was 97%, re-operative MV surgery was required in 2%, and 97% were in New York Heart Association Function class I or II (90). Given the lack of an implanted MV annuloplasty ring with this approach, preserved MV annular mechanics and anatomy, and minimal leaflet and annular calcification are important for a durable edge-to-edge repair (89,91).

Anterior mitral leaflet retention plasty

Retention plasty of the AML involves the suturing the medial and lateral AML segments to the fibrous posterior annulus using pericardial pledgets; this prevents displacement of the valvular and subvalvular apparatus anteriorly towards the septum by stretching taut the central portion of the AML (92). Delmo Walter and colleagues performed myectomy combined with AML retention plasty on 57 HCM patients with LVOT obstruction and moderate to severe MR (93). At a long-term follow-up of 17 years, there was a marked reduction in the LVOT gradient (99 *vs.* 9 mmHg), trivial MR was reported in 87%, and SAM was abolished in all patients (P<0.01 for all). Freedom from reoperation and cumulative survival rate were 92.9% and 91.2%, respectively. The primary selection criteria for AML retention plasty include marked septal thickening, elongated and lax AML, and persistent intraoperative LVOT obstruction or SAM after myectomy. Abnormalities of the papillary muscles, such as direct insertion in the AML, are a contraindication; the technical complexity and learning curve of the technique are also notable.

Secondary chordal cutting

Secondary order chordae of the MV, also known as 'strut' chordae, are defined as those which insert beyond the free edge and rough zone of the AML into the mid-body of the leaflet (20). In HCM these chordae may be fibrotic, thickened, or shortened, and in these instances contribute to SAM by tethering the AML anteriorly towards the LVOT. Ferrazzi and colleagues reported on 39 HCM patients who underwent a limited myectomy for mild to moderate septal hypertrophy (septal thickness ≤19 mm) and concomitant secondary chordal surgical transection ('cutting') (94). There was no operative mortality, and at a follow-up of 24 months there were significant reductions in LVOT gradient (82 *vs.* 9 mmHg), moderate or greater MR (56% *vs.* 16%), and New York Heart Association III or IV symptoms (82% *vs.* 0%) (P<0.001 for all), with no required reoperations. In a small randomized trial of 48 HCM patients undergoing myectomy comparing additional secondary chordal cutting with edge-to-edge MV repair, late survival was similar (100% *vs.* 96%, P=0.32), no patients had severe recurrent MR, required reoperation, or had NYHA class III or IV symptoms, and LVOT gradient (17 *vs.* 20 mmHg, P=0.33) was similar at follow-up (95). The main concern of chordal cutting is the perturbations it may cause in LV systolic and diastolic function, papillary muscle mechanics, ventricular torsion, and global remodeling (96).

MV replacement

Replacement of the MV for relief of LVOT obstruction and SAM is strongly discouraged by HCM experts and societal treatment guidelines, with the exception of co-existent MV disease prohibiting valve repair (i.e., rheumatic heart disease, radiation-induced valvulitis, severe annular calcification, infective endocarditis) (45,46,97). When compared to MV repair, replacement is associated with higher perioperative morbidity, left ventricular remodeling and dysfunction, and a predisposition for prosthesis-related complications (98). In patients undergoing septal myectomy, MV replacement is associated with a 12-fold increase in operative mortality, and a markedly attenuated 10-year survival when compared with patients undergoing MV repair (55.2% *vs.* 80%, P<0.001) (99,100). An important caveat to note is that the poor outcomes of MV replacement also reflect a generally older and sicker population as compared with those who undergo repair.

Transcatheter edge-to-edge MV repair

Transcatheter edge-to-edge MV repair has become an important treatment option for higher-risk patients with moderate-to-severe primary and secondary MR (101,102). Although not currently approved for patients with HCM, small studies have shown promising evidence. A pooled analysis of 4 studies presented the outcomes of 15 HCM patients who were treated with an edge-to-edge repair using the MitraClip device (Abbott Laboratories, Abbott Park, IL, USA) and were considered poor surgical candidates (103). Treatment resulted in elimination of SAM in all patients, decreased LVOT gradient (75 *vs.* 11 mmHg), reduction in MR severity, and an improvement in functional capacity. The need for further research in larger groups of patients with long-term follow-up is required before adoption of this technique can be considered.

Summary

The pathophysiology of SAM involves the complex interplay between HCM morphology, MV apparatus anatomic abnormalities, and the labile hemodynamic derangements that characterize each individual patient. SAM is a near universal finding in obstructive HCM patients and its amelioration is a primary goal of medical and interventional therapy. Per the American Heart Association and European Society of Cardiology guidelines recommendations, the initial step in this population is treatment with non-vasodilating beta-blockers, non-dihydropyridine calcium channel blockers, and/or disopyramide (Class I, LOE B-C) (45,46). Mavacamten, a myosin adenosine triphosphatase inhibitor which decreases systolic contraction, stabilizes myosin super-relaxed state, and improves diastolic myocardial relaxation, has also been developed for patients with symptomatic obstructive HCM (104). The EXPLORER-HCM trial of 251 symptomatic HCM patients on maximally-tolerated medical therapy showed that compared with placebo, more patients randomized to Mavacamten achieved a clinical response (30% *vs.* 17%, P=0.0005) and were in New York Heart Association functional class I (27% *vs.* 1%, 95% CI: 18.3–34.8%) at 30-week follow-up (105). Nevertheless, Mavacamten is not yet approved for clinical use, and further study is warranted given its side effect profile including LV systolic dysfunction, ventricular tachyarrhythmias, and QTc prolongation.

In patients with refractory obstruction and persistent symptoms, septal reduction therapy should be considered at HCM centers of excellence (Class I, LOE B). In these circumstances surgical septal myectomy is preferred, particularly in younger patients, while percutaneous alcohol septal ablation is a reasonable alternative in higher-risk individuals, advanced age, or patient preference. Finally, MV surgery is generally reserved for patients with mild to moderate septal hypertrophy, intrinsic MV disease, papillary muscle abnormalities, or abnormal leaflet morphology. The choice of reparative technique must be individualized for each patient. It is imperative to note that a class III (LOE B) recommendation is given to the use of MV replacement as the primary treatment for LVOT obstruction.

In conclusion, recent scientific advances in the field of HCM have allowed for a maturation of our understanding of the SAM phenomenon. Cardiac imaging plays a critical role in its diagnosis, treatment, and surveillance, and in our ability to apply the appropriate therapeutic regimens—whether that be medical, surgical, or percutaneous intervention. The increasing prevalence of HCM places an emphasis on continued basic and clinical research to further improve outcomes for this challenging population.

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