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Hypertrophic cardiomyopathy with dynamic obstruction and high left ventricular outflow gradients associated with paradoxical apical ballooning

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Background: Acute left ventricular (LV) apical ballooning with normal coronary angiography occurs rarely in obstructive hypertrophic cardiomyopathy (OHCM); it may be associated with severe hemodynamic instability.

Methods, Results: We searched for acute LV ballooning with apical hypokinesia/akinesia in databases of two HCM treatment programs. Diagnosis of OHCM was made by conventional criteria of LV hypertrophy in the absence of a clinical cause for hypertrophy and mitral-septal contact. Among 1519 patients, we observed acute LV ballooning in 13 (0.9%), associated with dynamic left ventricular outflow tract (LVOT) obstruction and high gradients, 92 ± 37 mm Hg, 10 female (77%), age 64 ± 7 years, LVEF 31.6 ± 10%. Septal hypertrophy was mild compared to that of the rest of our HCM cohort, 15 vs 20 mm ($P < 0.00001$). An elongated anterior mitral leaflet or anteriorly displaced papillary muscles occurred in 77%. Course was complicated by cardiogenic shock and heart failure in 5, and refractory heart failure in 1. High-dose beta-blockade was the mainstay of therapy. Three patients required urgent surgical relief of LVOT obstruction, 2 for refractory cardiogenic shock, and one for refractory heart failure. In the three patients, surgery immediately normalized refractory severe LV dysfunction, and immediately reversed cardiogenic shock and heart failure. All have normal LV systolic function at 45-month follow-up, and all have survived.

Conclusions: Acute LV apical ballooning, associated with high dynamic LVOT gradients, may punctuate the course of obstructive HCM. The syndrome is important to recognize on echocardiography because it may be associated with profound reversible LV decompensation.

KEYWORDS
hypertrophic cardiomyopathy, left ventricular outflow obstruction, left ventricular systolic dysfunction

1 | INTRODUCTION

Dynamic variation of gradient severity is characteristic of left ventricular outflow tract (LVOT) obstruction in hypertrophic cardiomyopathy (HCM).[1,2] Obstruction may be spontaneously labile. Gradients may be provocable by activities of daily life such as standing, eating, or exercise and are an important cause of symptoms and disability.[2] The systolic pressure gradients across the LVOT cause symptoms due to increased LV pressure and work, coronary hypoperfusion, supply demand ischemia,[3] an instantaneous drop in ejection velocities and flow caused by obstruction, mitral regurgitation, tension-mediated diastolic dysfunction, inability to increase cardiac output with exercise, and occasionally frank hypotension. Moreover, the cardiomyocytes of HCM patients often demonstrate genetically determined inefficient energy utilization, and consequent depletion of high-energy phosphate moieties.[4,5] Cardiomyocyte energy depletion, shown by phosphorus-31 cardiac magnetic resonance imaging, occurs in HCM patients irrespective of obstruction and is also present in genotype-positive, phenotype-negative patients before the development of hypertrophy.[6] Obstruction in HCM additionally exacerbates energy depletion by dint of the increased work. Similar reversible energy depletion occurs in aortic stenosis that can lead to systolic dysfunction.[7] In light of the adverse pathophysiology, it is not surprising that contractile impairment of varying severity occurs in some HCM patients with LVOT obstruction, even when the LV ejection fraction is normal or high. This systolic impairment is paradoxical because HCM is understood as a hyperdynamic condition, both of global LV function and at the granular sarcomeric level.

We have termed this phenomenon "dynamic systolic dysfunction due to LVOT obstruction."[4,8–13] It is most commonly manifest as a reversible mid-systolic drop in pulsed Doppler mid-LV ejection velocities and flow in patients with LVOT gradients >60 mm Hg; its characteristic spectral Doppler appearance has fostered the term the "lobster claw" abnormality.[8,9] This flow abnormality is caused by a premature termination of longitudinal LV contraction.[10,11]

We cared for two HCM patients with known latent obstruction who suddenly developed persistent systolic anterior motion (SAM) at rest with unrelenting high resting gradients. These two patients developed apical and mid-ventricular ballooning, refractory cardiogenic shock, and heart failure. They improved intra-operatively immediately after surgical relief of LV outflow obstruction.[12] Their dramatic clinical course led us to search our databases for other patients with apical ballooning in obstructive HCM.

2 | METHODS

This is a retrospective study of patients under our care who developed apical ballooning in the presence of obstructive HCM. We searched the comprehensive research databases of the HCM Programs of New York University Langone Health and Mount Sinai West Hospital (formerly Roosevelt Hospital) in New York for all patients with an episode of acute LV apical ballooning. The databases comprise patients who provided consent to use their clinical information for research purposes beginning in 1999. Follow-up is acquired yearly, either in the clinic or by scripted telephone interview. These longitudinal registries have been approved by the respective IRBs of the institutions. The two previously reported cases[12] are included in the present case series.

2.1 | Diagnoses of obstructive HCM and apical ballooning

Hypertrophic cardiomyopathy with latent obstruction was diagnosed if a patient had asymmetric hypertrophy (ASH) ≥ 13 mm in the absence of a clinical cause for the degree of hypertrophy observed, and no LVOT obstruction or <30 mm Hg gradient at rest, but who developed gradients ≥ 30 mm Hg due to SAM with mitral-septal contact provoked by Valsalva's maneuver, standing, or exercise. An episode of apical ballooning was diagnosed if a patient was hospitalized with an episode of acute cardiac symptoms and new ECG abnormalities associated with dilatation of the apical-mid-LV segments, along with hypokinesia/akinesia in those segments. Wall motion abnormalities extended past the distribution of a single coronary artery.

2.2 | Clinical characterization

Chronic HCM-related symptoms of exercise intolerance, dyspnea, angina, or syncope were tabulated as well as medications before the index admission. Details of the apical ballooning admission were recorded, including acute symptoms, initial ECG, laboratory values, echocardiogram, catheterization results, pharmacologic and other treatments, and outcome. Cardiogenic shock was diagnosed when there was prolonged hypotension systolic <80 mm Hg, cool extremities, and oliguria in the absence of any other cause of shock.

2.3 | Echocardiography

Echocardiograms were reviewed by one of two experienced HCM physicians (MS or BK). Detailed measurements were made from echocardiograms, during the ballooning episode, and before or after the episode, at a time when LV function was normal. If the patient had multiple echocardiograms performed on the ballooning admission, we selected the study with the highest CW Doppler LVOT gradient for measurement. We measured segmental LV wall thicknesses from 2D echocardiography as previously reported.[14] We measured mitral valve leaflet length as previously described and assessed abnormalities of the papillary muscles and chordae tendineae, both known associations with LVOT obstruction.[15–22] Mitral anterior leaflets were measured from the tip of the leaflet to the aortic annulus, including the intervalvular fibrosa. Based upon previous work, anterior leaflets measuring >30 mm (>16 mm/m^2) were characterized as abnormally long.[23–25] Papillary muscle and chordal abnormalities position the mitral valve anteriorly in the LV cavity, subjecting it to the drag of ejection flow.[21,22,26] Exercise echocardiography with standing and supine postexercise gradient acquisitions was performed when

indicated clinically as previously described.[1,2] Postprandial exercise echocardiography (SPEPP) was performed in two patients because the conventional treadmill stress echo showed postexercise SAM but gradients were not high enough to explain the patient's symptoms.[27] Mitral regurgitation was qualitatively assessed from grade 0–4. LV ejection fraction was calculated using Simpson's method. Coronary angiography was performed in every case on either the day of or the day after admission. LV ejection fraction was qualitatively estimated. Cine-angiographic mitral regurgitation was qualitatively assessed from grade 0 to 4.

Cardiac magnetic resonance imaging was performed when indicated, measuring wall thicknesses in the short-axis views, assessing for SAM and quantitative measurement of late gadolinium enhancement (LGE).

2.4 | Statistics

Comparison of means of independent groups was performed by unpaired Student's *t*-test.

3 | RESULTS

There were 13 HCM patients with an acute episode of apical ballooning, 0.9% of the 1519 HCM patients enrolled in our databases from 1999 to July 2017. All 13 patients had high CW Doppler LVOT gradients during their ballooning admission 92 ± 37 mm Hg; these were due to SAM, mitral-septal contact, and asymmetric septal hypertrophy.

3.1 | Clinical features of HCM

Table 1 summarizes the demographic, clinical, and HCM echocardiographic variables at a time when LV systolic function was normal. Patients were aged 62.8 ± 7 years when HCM was diagnosed. Ten (77%) were female. Eleven of the patients were white, one was black, and one Asian. Eight patients were diagnosed with HCM and latent obstruction a median of 24.5 (range 4–122 months) *before* their ballooning admission. Six patients had cardiac symptoms: dyspnea in 6, chest pain in 2, syncope in 2, and paroxysmal atrial fibrillation in 1; the remaining two patients were diagnosed because of a heart murmur. In five other patients, obstructive HCM was first diagnosed *at the time of* their ballooning event because of ASH and SAM. In these five patients, during recovery afterward, gradients subsided to <30 mm Hg and LV function normalized. But, 5 months later severe latent LVOT obstruction was definitively demonstrated by provocation of LV outflow gradients averaging 92 mm Hg (range 50–144) after Valsalva or exercise.

3.2 | Clinical presentation of apical ballooning event

Table 2 summarizes the clinical, echocardiographic, angiographic, and treatment variables of the ballooning admission. The patients were 64.3 ± 7 years when the ballooning event occurred. Ten patients (77%) had precipitants that appeared to provoke their ballooning episodes: overexertion in 3, a diarrheal illness in 2, dehydration in 3, and a funeral in 2.Symptoms that prompted the emergency room visit were dyspnea and typical chest pain in 5, dyspnea in 2, chest pain in 2, and syncope in 4. ECGs demonstrated ST segment elevations in 5, ST and T wave depressions in 2, T wave inversions in 2, and acute QT prolongation in 1. Three patients had LVH. Peak troponin I was 1.78 ± 0.97 ng/mL (normal < 0.04). Thus, clinical presentations in all cases met criteria for an acute coronary syndrome. On this basis, all patients underwent emergent coronary angiography shortly after presentation; no patient had significant narrowing.

TABLE 1 Clinical and echocardiographic variables in 13 patients with hypertrophic cardiomyopathy at time of normal LV systolic function

Variable	
Age at HCM Dx	62.8 ± 7
Gender (%F)	10/13
HCM symptoms before ballooning event[a]	6/13
Family history of HCM	4/13
Septal thickness (mm)	15.4 ± 2
Other segmental thickening	0/13
Resting LVOT gradient ≥30 mm Hg	0/13
Mild SAM	11/13
Latent provoked gradient ≥50 mm Hg	13/13
Provoked gradient (mm Hg)	115 ± 52
Mitral valve abnormality[b]	10/13
Pharmacologic Rx[c]	7/13

[a]Dyspnea 6, angina 2, syncope 2, paroxysmal atrial fibrillation 1.
[b]Elongated leaflets 5, anteriorly displaced papillary muscles 5 and thickened shortened chordae in one.
[c]Beta-blockade 2; beta-blockade and disopyramide 3; calcium channel blockade 2.

3.3 | Treatment of the ballooning episode

Acutely, twelve patients were treated with beta-blockade, 8 intravenously, in an attempt to reduce LVOT obstruction. The clinical course was complicated in seven patients (54%) who had persistent high degree obstruction. Five suffered both cardiogenic shock and heart failure, one had hypotension, and one had refractory heart failure. Five patients required IV phenylephrine for blood pressure support, and 2 were treated with an intra-aortic balloon pump (IABP). Two patients with acute refractory cardiogenic shock and heart failure underwent emergent surgery to abolish LVOT obstruction. In these 2 patients, arterial pH was 7.23 and 7.18, respectively, from metabolic acidosis immediately before they were taken to surgery. A third patient had acute and persistent refractory heart failure and underwent urgent surgery to relieve her unrelenting outflow obstruction. The individual clinical courses of the 13 patients are shown in Figure 1. Representative sequential echocardiograms from patients are shown in Figures 2–6.

TABLE 2 Clinical, echocardiographic, and catheterization variables of 13 patients at the time of their ballooning episode

Age at ballooning event (y)	64.3 ± 7
Provoking event identified[a]	10/13
Apical dilatation and apical/mid hypo or akinesia	13/13
Echo EF at ballooning (%)	31.6 ± 10
LVOTG at ballooning (mm Hg)	91.8 ± 37
Anterior septal thickness	15.2 ± 2
Echo Mitral Regurgitation	3.30 ± 0.8
Mitral structural abnormalities	10/13
Left atrial diameter	3.9 ± 0.5
Troponin (ng/mL)	1.78 ± 0.97
Cath EF (%)	27 ± 5
Coronary stenosis >50%	0/13
Cath LVOT gradient (mm Hg)[b]	46.3 ± 27
Cardiogenic shock and heart failure (%)	5
Refractory heart failure	1
Hypotension	1
IABP	2
IV Phenylephrine	5
Acute Rx beta blocker[c]	12/13
Emergent surgery to relieve LVOT obstruction	3
Overall surgery	4

[a]Overexertion 3, gastroenteritis 2, dehydration 3, funeral 2.
[b]Peak-to-peak gradient.
[c]Intravenous in 7.

3.3.1 | Echocardiography

At the time of their ballooning admission, the basal anterior septal LV segment was thickened in the 13 patients, average 15.2 ± 2 mm. When LV cavity size and function were normal, it was 15.4 ± 2. The anterior septal thickening was less than that observed in the 1506 patients in our registries who did not have ballooning, 19.9 ± 6 mm, $P < 0.00001$. Wall thickening was absent or modest in the remaining segments. During the ballooning hospitalization, SAM with mitral-septal contact and resting LVOT gradients were noted all 13 patients, averaging 92 ± 37 mm Hg. In 10 of 13 patients, the initial echocardiogram, often obtained in the emergency department, showed the highest gradient of the ballooning admission. However, in three patients, higher resting gradients were documented later, associated with partial recovery of LV systolic function. LV ejection fraction was 32 ± 10% with apical dilation, and apical and mid-LV hypokinesia/akinesia. The basal LV segments were spared, evidencing normal, or hyperkinetic contraction. Mitral regurgitation grade was 3.3 ± 0.8, moderately severe on average.

3.4 | Low or absent gradients when LV function was normal

Both before and after their ballooning episodes, in the unprovoked state, no patient had a resting LVOT gradient ≥30 mm Hg. However, mild SAM was noted in 11 of 13 (85%) patients and 7 (54%) had mild resting gradients < 30 mm Hg. In the whole group, dynamic gradients provoked either before or after the ballooning episode by either Valsalva or exercise were 115 ± 52 mm Hg. In eight cases, stress echocardiography using treadmill exercise was performed at a time when LV systolic function was normal; for 2 of these cases, testing followed a moderately sized meal. No patient evidenced a resting systolic LVOT gradient ≥ 30 mm Hg. After stress, the peak LVOT gradients averaged 118 ± 44 mm Hg.

There were abnormalities of the mitral apparatus that contributed to SAM in 10 (77%) patients observed during ballooning episodes and also when the LV systolic function normalized. Findings included an elongated anterior leaflet in 5, and anterior displacement of the papillary muscles in 5 and thickened shortened chordae that anteriorly displaced the mitral valve in one. The mitral leaflet elongation observed in 4 HCM patients with latent obstruction and severe ballooning is shown in Figures 7–8. The obstructive HCM patient in Figure 7 developed cardiogenic shock 10 years after his initial obstructive HCM diagnosis. His anterior leaflet was particularly long, 38 mm (1.9 mm/m^2). This patient's pre- and postoperative echocardiograms are shown in Movies S1–S3. Another surgical case is shown in Movies S4–S5. This patient had refractory congestive heart failure; her severe LV dysfunction reversed to normal coming off cardiopulmonary bypass after septal myectomy. Figure 9 shows the ballooning episode of another patient. After normalization of LV function subsequent exercise echocardiogram showed a high provoked gradient. This patient also had an elongated anterior leaflet.

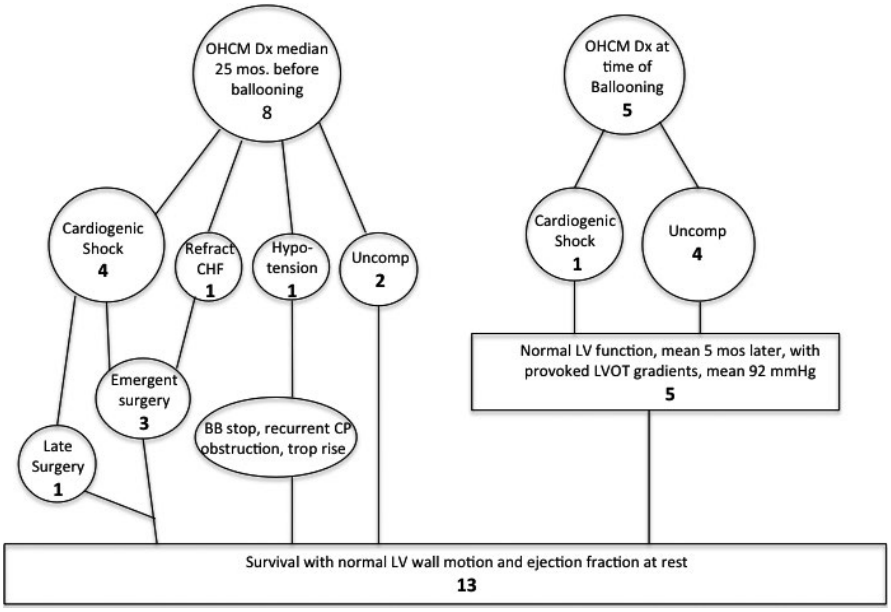

FIGURE 1 The individual clinical courses of the 13 patients. BB= beta blocker; CP = chest pain; Dx = diagnosis; Refract = refractory; trop = troponin; Uncomp = uncomplicated

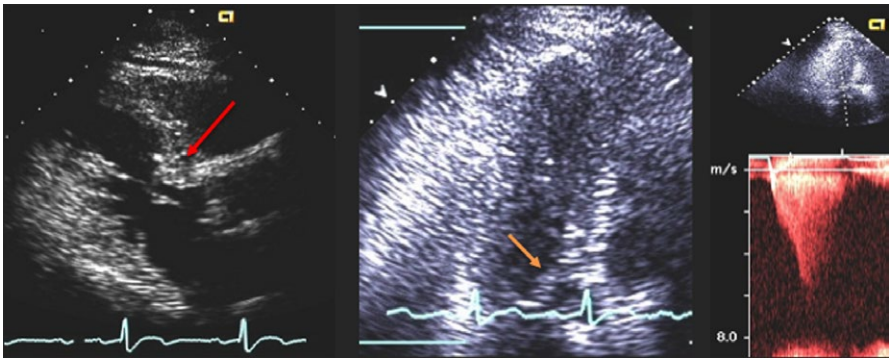

FIGURE 2 Sixty-seven-year-old male with hypertrophic cardiomyopathy (HCM) and provocable obstruction. Exercise echo at time of HCM diagnosis. LV function was normal at rest and hyperkinetic with exercise. Left frame: Parasternal long-axis view in end diastole. Mild basal anteroseptal hypertrophy, 17 mm (red arrow). Middle frame: Systolic postexercise apical 3-chamber view with systolic anterior motion and mitral-septal contact (orange arrow). Right frame: Postexercise CW Doppler: systolic left ventricular outflow tract gradient was 125 mm Hg

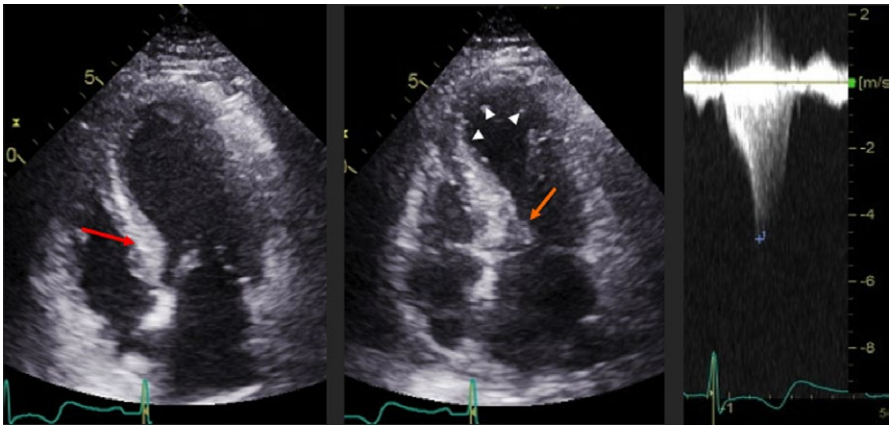

FIGURE 3 Same patient as Figure 2. Four years later after exercising vigorously on a hot summer day, he was admitted with severe chest pain and dyspnea. Left frame: Diastolic 2-D apical 4-chamber view performed on admission. Red arrow indicates the mild septal bulge. Middle frame: Systolic frame shows systolic anterior motion (SAM) of the mitral valve (orange arrow) and apical akinesis (white arrowheads). Right frame: CW Doppler with resting left ventricular outflow tract gradient of 85 mm Hg. Thus, this patient with known hypertrophic cardiomyopathy and latent obstruction and normal LV systolic function (figure 1) presented 4 y later with apical ballooning (Figure 2). This paper proposes that the ballooning is due to the sudden obstruction at rest, and unrelenting high LVOT gradients

3.4.1 | Cardiac catheterization

Coronary angiograms were either completely normal or showed mild luminal irregularities. No patient had a coronary stenosis >50%. The peak-to-peak catheter LV intraventricular pressure gradient was measured in 10 patients and was 47 ± 26 mm Hg. LV cineangiography was performed in 6 patients; visually estimated ejection fraction averaged 27 ± 5%, and mitral regurgitation averaged grade 2.8 ± 1.7.

3.4.2 | Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed as clinically indicated on 8 of 13 patients. In two it was performed before LV segmental systolic function had normalized. Thickening was localized to the anterior septum and averaged 15.1 ± 2.1 mm. Six patients had mild SAM with acceleration of flow in the outflow tract. Two patients had LGE encompassing 4 and 5% of the LV mass.

3.4.3 | Follow-up

Patients were followed-up for a median of 45 months after the diagnosis of HCM. Nine patients were treated with oral beta-blockade, two with beta-blockade and disopyramide, and 2 with warfarin. No patient who had not received surgery was treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blockade. The one patient who could not take beta-blockade because of a drug-related rash had a second episode of severe chest pain 11 months later, associated with a 100 mm Hg LVOT gradient due to SAM, and a troponin rise to 2.3 ng/mL. LV wall motion was normal at that time. She was treated with IV metoprolol with resolution of symptoms and gradient, but the beta blocker was again discontinued due to drug rash. She remains limited. In the 13 patients at follow-up, NYHA class was 1.9 ± 0.7. All had normal LV systolic function, and no patient evidenced a resting LVOT gradient ≥30 mm Hg. Three patients continue to have moderate dyspnea after mild exertion due to latent obstruction. No patient expired.

4 | DISCUSSION

An episode of LV apical ballooning prompted urgent admission and coronary angiography in 13 HCM patients with dynamic obstruction. The ballooning event was associated with high LVOT gradients, 92 ± 37 mm Hg. HCM was diagnosed by conventional criteria: (a) asymmetric hypertrophy in the absence of clinical cause for the hypertrophy; and (b) LVOT obstruction due to SAM, with mitral-septal contact provoked by Valsalva's maneuver or exercise. All patients demonstrated severe LVOT obstruction during the acute episode of apical ballooning with gradients averaging 92 mm Hg. Eight patients had latent obstruction diagnosed median 25 months before their ballooning episodes, while five had their obstructive HCM diagnosis made during the course of their acute ballooning admission, and definitively confirmed later, after their ventricular function had normalized, by the demonstration of high latent gradients with physiologic provocation.

Three-quarters of these patients were elderly women. Presentation mimicked an acute coronary syndrome with sudden-onset cardiac symptoms, ischemic ECG abnormalities, and modest troponin elevations for the degree of wall motion abnormality. Their echocardiograms showed only a modest degree of isolated basal anterior septal thickening averaging 15.2 mm. Echocardiographic LVEF averaged 32% with apical dilatation, and apical and mid-LV akinesia or hypokinesia with normal or increased basilar contraction.LV cineangiograms corroborated the echocardiographic LV findings; coronary angiograms showed no significant coronary stenosis.

Of note, despite treatment with IV beta blockade and fluids, 5 patients developed cardiogenic shock, and one developed refractory heart failure and one patient developed hypotension during the ballooning hospitalization; 5 required IV phenylephrine for blood pressure support and two patients underwent IABP. Two other patients, previously reported, are included in this series[12]; they developed refractory cardiogenic shock and profound heart failure despite intravenous beta blockade, liters of intravenous fluid and intravenous phenylephrine. They were taken to the operating room in extremis for relief of their LV outflow obstruction; within 2 hours of abolition of their LV gradients systolic function had dramatically improved. A third patient with refractory heart failure had urgent surgery for relief of obstruction; her LV severe systolic dysfunction reversed immediately after surgical relief of obstruction at termination of cardiopulmonary bypass.

Thus, LVOT obstruction occurring in patients with modest asymmetric hypertrophy is a treatable cause of cardiogenic shock; the importance of echocardiographic identification of the etiology cannot be overstated. Beta blockade, IV fluids, and pure alpha-adrenergic agonist therapy with phenylephrine are appropriate. Inotropes like dobutamine and dopamine, and vasodilators like nitrates are contraindicated and potentially catastrophic in effect.

4.1 | Dynamic systolic dysfunction in obstructive HCM

A spectrum of dynamic systolic dysfunction with varying severity has been demonstrated in obstructive HCM patients even in patients with normal or high ejection fractions.[4,8–13] In patients with LVOT gradients ≥60 mm Hg, there is a ubiquitous mid-systolic drop in Doppler velocities and flow of LV ejection that can be demonstrated with pulsed Doppler interrogation of the LV cavity before entry into the LVOT.[8–11,13] Others demonstrated a mid-systolic drop in descending aortic velocities.[28] The drop in LV ejection velocities explains some of the well-recognized clinical features of HCM, including the biphasic carotid pulse and mid-systolic closure of the aortic valve. Conklin and colleagues showed an exacerbation of the reduction in forward flow after administration of dobutamine.[9] The mid-systolic drop in velocities and its spectral appearance may vary from patient to patient and from hour to hour depending on the severity of the outflow

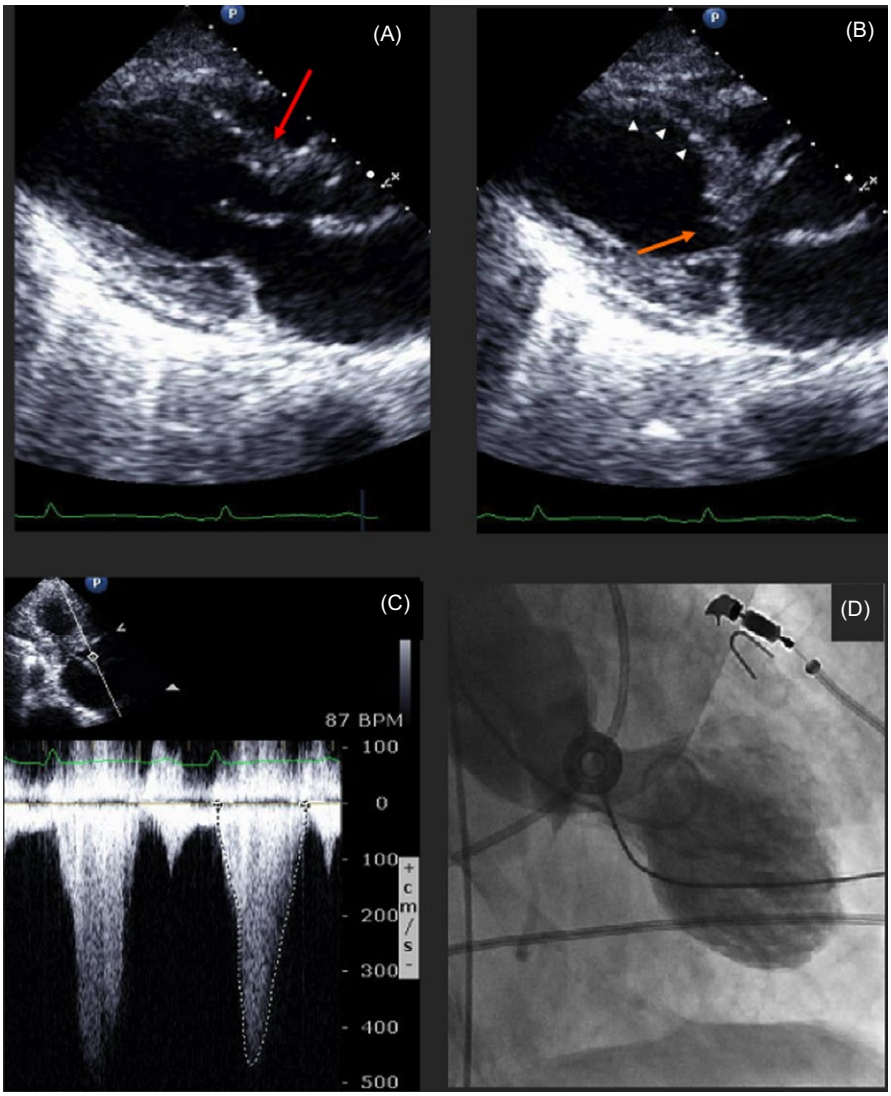

FIGURE 4 Ballooning event of 66-year-old female with known hypertrophic cardiomyopathy and systolic anterior motion (SAM) but not previously known to obstruct presented acutely with chest pressure, shortness of breath and syncope. Frame A and B: Parasternal long-axis view in diastole (A) and systole (B). The frames demonstrate the septal bulge (red arrow), SAM with mitral-septal contact (orange arrow), and akinetic anteroseptum (white arrowheads). Panel C, CW Doppler with resting left ventricular outflow tract gradient of 88 mm Hg. Panel D, Systolic LV cine-angiographic frame on admission with apical and mid-LV ballooning

gradient, and the capability of the LV to overcome the obstruction. However, the timing of the nadir always moves in precise lockstep with the peak velocity of the CW Doppler across the outflow tract and hence coincides with peak LV afterload.[8,11] Tissue Doppler imaging records a mid-systolic drop in systolic myocardial velocities due to obstruction and premature termination of septal contraction. Both the mid-systolic drop in ejection velocities and the drop in tissue Doppler contraction velocities are reversed and normalized upon abolition of obstruction.[10,11] This demonstrates that the mid-systolic drop is not merely a flow phenomenon; rather, it is due to myocardial dysfunction. It is an instantaneous failure of the ventricle to overcome obstruction.

Narrowing of the intramyocardial penetrating arterioles is a frequent observation in HCM patients, as is provocable ischemia in watershed areas. Ischemia may be worsened by afterload, exercise, or catecholamine surges such as that seen in takotsubo syndrome.[3] A mid-systolic drop in ejection velocities can also be seen when chronic mid-LV obstruction causes apical aneurysms due to complete mid-LV obstruction of ejection flow.[13,29,30] Such patients often have characteristic Doppler echocardiographic findings including a mid-systolic drop in apical PW ejection velocities (almost to zero), a LV mid-systolic Doppler signal void on the CW Doppler spectral tracing due to complete cessation of flow out of the apex, and paradoxical diastolic flow of trapped blood out of the LV apex.[30] A stepwise pathologic cascade to apical aneurysm has been described; the etiology is chronic afterload-mismatch and supply demand ischemia from obstruction.[30,31] Intimal and medial hyperplasia causing narrowing of the intramural penetrating arteries and jeopardizing flow reserve is an important co-contributor.[32] Afterload mismatch is caused by the extremely high impedance to flow from the mid-LV obstruction, and inherent inefficiency of sarcomeric energy utilization due to the cardiomyopathy of the mutated cardiomyocytes.[4] The same pathophysiologic factors are acting in mid-LV obstruction as in acute ballooning, albeit in ballooning the process is acute and due to LVOT obstruction. The slow development of apical aneurysms adds to the plausibility of the acute development of ballooning; they are both part of the spectrum of dynamic systolic dysfunction due to afterload and ischemia in HCM, differing in their rate of deterioration and capacity for resolution.

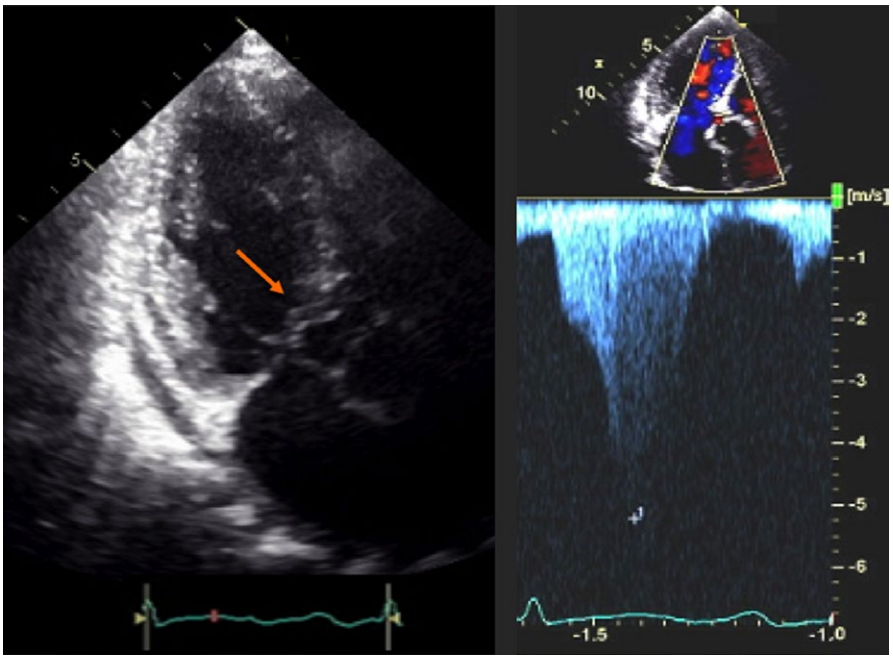

FIGURE 5 Same patient as Figure 4. After the ballooning hospitalization LV function normalized and there was no left ventricular outflow tract (LVOT) gradient. Eleven months after the ballooning hospitalization, she was readmitted with severe chest pain and dyspnea after walking up subway stairs. On this occasion, there was normal LV systolic wall motion. Left frame: Two dimensional systolic apical 3-chamber view on admission, LVEF was 65% with normal wall motion. There is systolic anterior motion with mitral-septal contact (orange arrow). Right frame: CW Doppler with resting LVOT gradient of 100 mm Hg

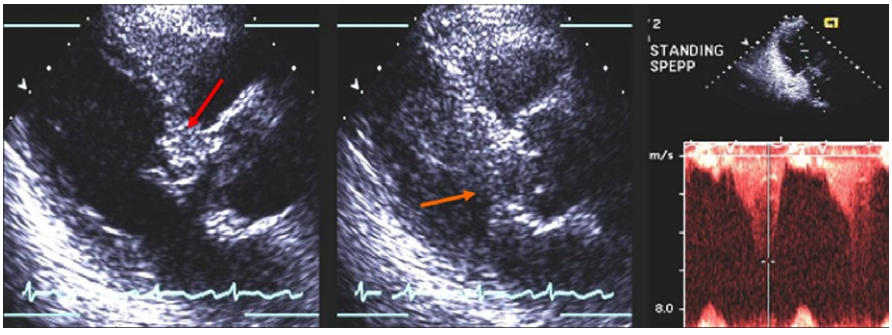

FIGURE 6 Same patient as Figures 4, 5. After discharge, intermittent exercise-related chest pain and dyspnea recurred. LV function at rest was normal and hyperkinetic after exercise. There was no obstruction at rest. Stress treadmill echocardiogram after eating (SPEPP) was performed to provoke gradient. Left frame: parasternal long-axis view in diastole. Middle frame: systolic anterior motion (SAM) of the mitral valve with mitral-septal contact. Right frame: Three-chamber view CW Doppler with a peak postexercise systolic gradient of 120 mm Hg. SPEPP = standing postexercise postprandial echocardiogram. Thus, this patient with known hypertrophic cardiomyopathy and SAM presented suddenly with an episode of apical ballooning and severe obstruction (Figure 4); subsequently, after LV function had recovered, she had another episode of severe symptoms associated with severe obstruction at rest, but normal LV function (Figure 5). After recovery from this episode, an exercise echocardiogram reproduced severe latent obstruction (Figure 6)

Previously we have reported two patients with latent LVOT obstruction in whom apical and mid-LV dilatation and severe hypokinesia developed after LVOT obstruction became severe and unrelenting.[12] Their downward spiral and cardiogenic shock was not relieved until they had surgical relief of their LVOT obstruction. Movies S1–S3 show the pre- and postoperative echocardiogram on one of these patients. Movies S4–S5 show the normalization of LV function in the operating room of a patient after surgical septal myectomy performed for refractory congestive heart failure.

4.1.1 | Previous reports

Left ventricular ballooning has been reported previously in isolated cases in HCM patients[33–37] but has not been mentioned as a possible complication of HCM in published reviews.[38,39] To our knowledge, the 13 patients reported here represent the largest case series of patients with these associated problems. The paucity of prior reports could stem from the uncommon occurrence, mild ASH, or because HCM publications tend to originate from centralized outpatient HCM clinics. Ballooning admissions may first be seen in the emergency departments of community hospitals.

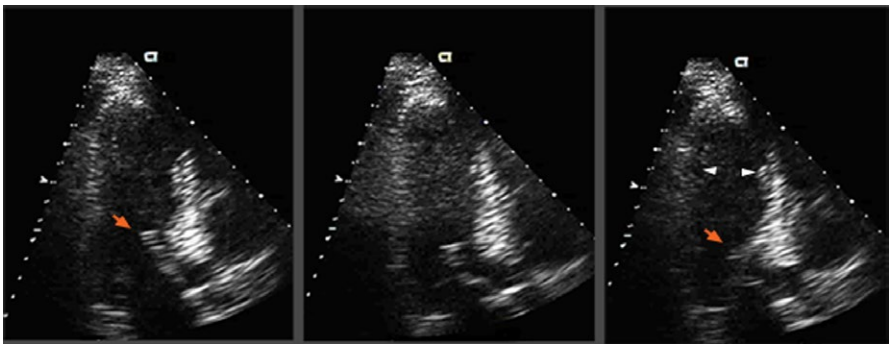

FIGURE 7 Mitral elongation in male patient with hypertrophic cardiomyopathy (HCM) and latent obstruction. He presented 10 years after his obstructive HCM diagnosis, at age 70 with apical ballooning and cardiogenic shock. These frames were acquired during his ballooning admission. Left: Diastolic frame showing the very elongated mitral anterior leaflet, 38 mm (19 mm/m^2). The orange arrow points to the anterior mitral leaflet. Middle: Moment of systolic coaptation showing "nightcap" mitral valve that protrudes into the LV cavity.[16] Right: mitral-septal contact (orange arrow). Left ventricular outflow tract gradient was 90 mm Hg. Akinetic anterior septal and posterior walls are seen (white arrowheads). Movies S1–S3 show preoperative and postoperative echocardiograms of this individual. Wall motion abnormalities normalized immediately after relief of LVOT obstruction after completion of cardiopulmonary bypass

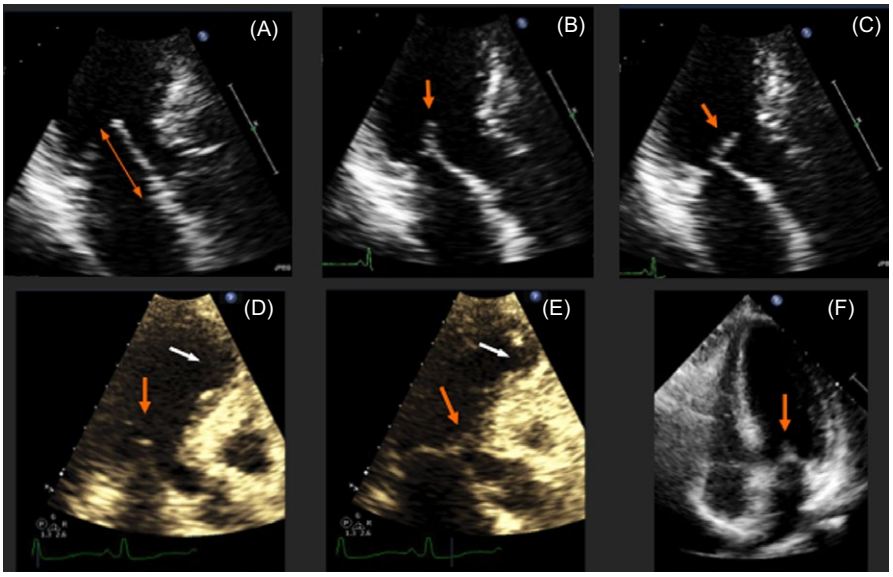

FIGURE 8 Three patients with mitral valve elongation mild septal hypertrophy and an episode of apical ballooning. Top 3 frames (A–C) show diastolic and systolic 3-chamber frames from the same patient at a time when LV systolic function was normal. A, Diastolic frame showing anterior mitral valve leaflet elongation 34 mm, 20 mm/m^2(elongated >16 mm/m^2).[23–25] B, Moment of coaptation. Protruding mitral anterior leaflet is shown by orange arrow. This pattern has been termed a "nightcap" mitral valve because of its characteristic appearance.[16,46] C, Early systole showing systolic anterior motion (SAM) of the mitral valve with the residual leaflet. There was no mitral-septal contact and no left ventricular outflow tract (LVOT) gradient. Such SAM can be a clue that LVOT obstruction is the cause of apical ballooning. Gradient was provoked by exercise echocardiography. Bottom, D–E, show systolic frames in another patient at the time of apical ballooning. D, "Nightcap," protruding mitral leaflet at the moment of coaptation (orange arrow). Elongated anterior leaflet length in this patient was 34 mm, 19.5 mm/m^2. E, Later in systole. SAM of the mitral valve and mitral-septal contact. The white arrows in frames D and E show the ballooning akinetic apical septum. F:Apical 4-chamber view in another patient. Protruding mitral valve at the moment of coaptation

4.2 | Variation in gradient during the ballooning admission

Temporal variation in the severity of LVOT obstruction is characteristic, as it depends upon dynamic changes in loading conditions and LV contractility. An abrupt drop in LV contractility decreases the hydrodynamic force on the mitral valve, decreasing the tendency for SAM and thereby reducing LVOT obstruction and gradient. This is the mechanism whereby negative inotropes decrease obstruction.[40,41] Thus, it would be anticipated that a severe insult to LV systolic function would decrease the originally high LVOT gradient. Conversely, recovery of LV systolic function would be expected to result in an increase in gradient. An increase in LVOT gradient observed in three of our patients during their ballooning episode followed this pattern.

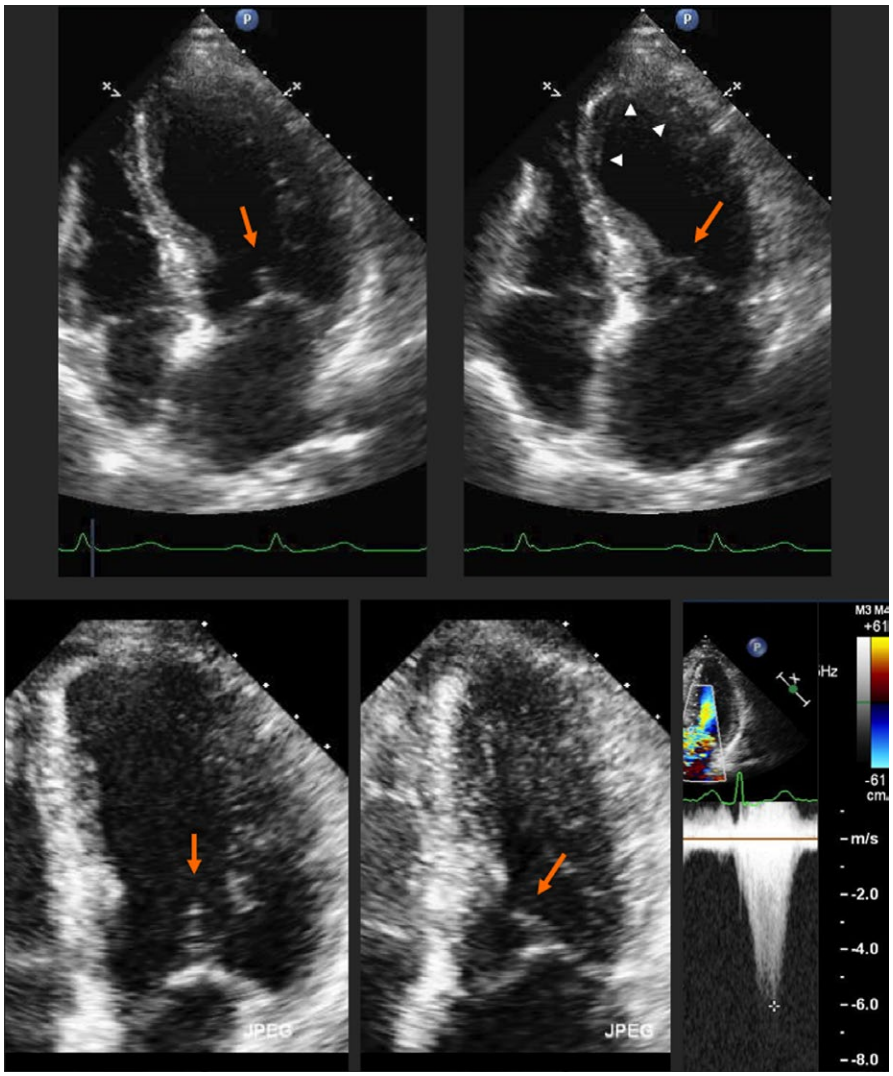

FIGURE 9 Another patient with mitral valve elongation, mild septal hypertrophy, and an episode of apical ballooning; there was subsequent provocation of high left ventricular outflow tract (LVOT) gradient after exercise. Top pair: Apical 4-chamber views during the apical ballooning admission. Protruding elongated mitral valve leaflets are shown with orange arrows. Mitral anterior leaflet in diastole measured 37 mm, 19 mm/m^2. The arrowheads indicate the severely hypokinetic apex. Bottom panels: Apical 4-chamber views and CW Doppler after peak exercise, at a time later when resting LV function was normal. Elongated protruding mitral leaflets are shown with orange arrows. Note that LV systolic function after stress is hyperkinetic and substantially better than in the frame above. Systolic anterior motion is shown and peak Doppler LVOT gradient was 144 mm Hg

4.3 | Is apical ballooning caused by HCM and sudden unrelenting obstruction, or caused by coincident Takotsubo syndrome?

Could the patients have two conditions, by coincidence? Takotsubo syndrome (TTS) is an acute, reversible LV systolic dysfunction of unknown cause, oftentimes triggered by a stressful event occurring most often in postmenopausal women. We notice that our patients have a similar demographic and clinical presentation as do patients with TTS. Patients present with symptoms similar to an acute coronary syndrome but there is no significant angiographic coronary artery disease. The mechanism of LV systolic dysfunction in TTS is a subject of active investigation.[42,43] Although SAM and LVOT obstruction have been observed in TTS, it has not been considered of pathogenic significance. Instead, SAM in TTS is considered to result from narrowing of the LV base and the resultant development of Venturi forces in the LVOT.

We think it is unlikely that our patients have two coincident conditions, HCM and TTS, to explain both their chronic HCM illness and their acute ballooning for the following reasons:

1. For our 13 patients, high provocable gradients due to SAM, and the morphologic predispositions to SAM of HCM were present temporally *remote* from the ballooning episode, at a time when the LV systolic function was normal. All the patients had asymmetric septal hypertrophy and latent LVOT obstruction due to SAM before and/or after the acute episode. In this regard, in 10 of 13 our patients, we found abnormalities of the mitral valve that previously have been associated with obstructive HCM. It has increasingly been appreciated that mitral abnormalities predispose to obstruction in HCM patients with only mild degrees of hypertrophy, as in the present series.[15–20,24,26] Thus, mitral-septal contact was shown by provocation to be *inherent to their HCM* with latent obstruction, and not from their ballooning, per se.
2. Two patients with known previous HCM and latent obstruction suddenly developed unrelenting high resting LVOT gradients and apical ballooning, refractory cardiogenic shock, and heart failure and did not respond to fluids, high dose IV beta blockers, or phenylephrine. However, their severe LV dysfunction, shock, and heart failure normalized within 2 hours of surgically

abolishing LVOT obstruction.[12] A third patient recently developed refractory heart failure and severe LV dysfunction due to high LVOT gradients. Coming off cardiopulmonary bypass her LV systolic function immediately normalized after surgical relief of obstruction. The immediate improvement would not be expected if there was an independent cause of these patients' LV dysfunction, that is, TTS.

3. It has been hypothesized that the SAM observed in TTS might be due to compensatory hyperkinesia of the basal LV, leading to narrowing of the base, high LVOT velocities at that locus, and SAM by a Venturi mechanism. Thus, it has been hypothesized that the SAM of TTS is due to the TTS itself. However, current thinking and the preponderance of evidence about SAM in HCM is that it is caused by flow drag, the pushing force of flow.[21,25,44] As ejection flow sweeps around the bulging septum, it catches the mitral valve from behind and pushes it into the septum, rather than pulled by a Venturi mechanism. LVOT velocities are low in obstructive HCM when SAM begins, precluding Venturi forces as a mechanism.[21,44] Thus, in our 13 patients, the SAM is inherent to their well-documented HCM with latent obstruction and not attributable to coincident TTS.
4. As summarized here, obstruction in HCM patients causes dynamic systolic contractile dysfunction even in patients with normal or high ejection fraction; this is reversible upon relief of SAM.[8–13] There is no compelling need to posit another neurohumoral mechanism. Thus, our principal hypothesis is that the reversible apical ballooning was caused by LVOT obstruction, afterload-mismatch and supply demand ischemia, not as a result of a separate process. HCM has been described as the "great masquerader" in cardiology.[45] In the 13 cases described herein, we posit that obstructive HCM has taken on another guise, that of the perpetrator of acute dilatation and severe systolic dysfunction of the apical and mid-LV myocardial segments.

4.4 | Why these HCM patients? Why ballooning now?

The sudden development of persistent resting obstruction in the elderly has been repeatedly reported even in patients with isolated septal thickening[38,39] by dint of a drop in preload or afterload, or increased contractility, or conceivably additional slack in their mitral valves or additional septal thickening. Latent obstruction can explosively escalate into persistent obstruction because of the amplifying nature of obstruction. The mitral valve is swept further into the septum by the pressure gradient itself; obstruction breeds more obstruction.[44] Any drop in stroke volume causes a reflex enhancement in contractility and gradient. Our 13 patients had a particular phenotype of HCM; except for the septal bulge seen in all, wall thickening was absent or modest in the remaining segments. The modest hypertrophy throughout the remainder of the LV may limit its ability to compensate for the sudden increase in wall stress associated with high LV systolic pressures, and not as well as if there were a wider distribution of hypertrophy. More widespread LV hypertrophy, as is often present in the vast majority of younger HCM patients, might have normalized wall stress and mitigated the apical ballooning. Thus, the sudden development of persistent high gradients may be particularly detrimental to the systolic function of these ventricles with only modest hypertrophy, and therefore unprepared to perform in the face of an abrupt increase in afterload. Supporting this concept was the immediate restoration of normal systolic function after the surgical removal of obstruction.

4.5 | When is surgical intervention indicated?

We have considered disopyramide in these patients but have not administered it out of concern that it might reduce already severely compromised LV function. However, it might be considered in a patient with severe obstruction and heart failure who could not be operated because of comorbidity. Intra-aortic balloon pumping might improve tissue perfusion, but it decreases afterload which might increase obstruction; thus, we have generally avoided this modality. Emergent surgical relief of obstruction should be considered when shock with poor tissue perfusion or pulmonary congestion persist despite high-dose intravenous beta blockade, copious intravenous fluids, and intravenous phenylephrine. Surgery should especially be considered when there is progressive metabolic acidosis, oliguria, or requirement for continued intubation and respiratory support. The specific surgical strategy for relief of left ventricular outflow obstruction should depend on local expertise and practice.[12,20,26,46] We believe that the paramount consideration is avoiding a second pump run because of incomplete abolition of obstruction; one should avoid imposing additional ischemia on an already compromised left ventricle.[12]

4.6 | Previously reported subsets of takotsubo patients

This was not a study of the cause of ballooning in takotsubo syndrome. In the literature, there are takotsubo case reports that bear on this case series and its discussion,[47–51] including that 25% of takotsubo patients may have septal hypertrophy and LVOT gradients, and the observation that LVOT gradients may only emerge in the recovery stage when LV function is recovering. However, the patients in the current report had much higher resting LVOT gradients, mean 92 mm Hg, compared with the previous takotsubo report where gradients were mean 34 mm Hg, occurring only in the 25% with obstruction.[47] In the present report, mitral abnormalities were common in the HCM patients with ballooning, but this has not been noted previously. While the patients with gradients reported by El Mahmoud et al had a greater NYHA functional class at admission, none required surgery for profound hemodynamic compromise. Consequently, none in that report could show the immediate recovery of systolic function we observed after surgical relief of the LVOT obstruction. We present, from prior

publications, a plausible mechanism whereby LVOT obstruction in HCM could lead to apical ballooning. It is possible that the patients reported here are similar to those reported in a subset of patients with takotsubo syndrome. But to explore this possibility, a consecutive series of takotsubo patients would have to be evaluated for the anatomic and dynamic features of HCM patients reported here, including abnormalities of the mitral apparatus. This would also represent a departure from the widely excepted proposed neurohumoral mechanism for takotsubo syndrome.[52] This was outside the scope of the present research. Another limitation is the following: since this is a retrospective database study requiring consent, it is possible that not all HCM patients treated at our institutions were enrolled. This may impact the estimated frequency of apical ballooning in HCM, and its apparently favorable prognosis with treatment targeting obstruction.

5 | CONCLUSIONS

The clinical course of patients with hypertrophic cardiomyopathy and latent LVOT obstruction can rarely be complicated by LV apical ballooning when obstruction becomes severe and unrelenting with high gradients, 92 ± 37 mm Hg. This complication of HCM, occurring in 0.9% of HCM patients from two large referral centers, is associated with a morphologic phenotype of modest localized basal anterior septal thickening and frequently, mitral valve structural abnormalities that predispose to SAM and LVOT obstruction. Severe hemodynamic instability is a common clinical complication during the acute ballooning episode and occurred in half of our patients. Beta-blockade is the mainstay of pharmacologic treatment, but three patients required urgent surgery to relieve obstruction for refractory cardiogenic shock in two, and refractory heart failure in one.

As reviewed in this manuscript, dynamic systolic dysfunction to a lesser degree is common in obstructive HCM patients, even when the ejection fraction is normal or high. We propose as a hypothesis that the patients described herein suffer from the same phenomenon, albeit much more severely. We propose that their paradoxical apical ballooning is caused by sudden worsening of latent LVOT obstruction, afterload-mismatch, and supply demand ischemia. Since obstruction is latent both before and after the ballooning event, when LV systolic function is normal, provocation with Valsalva's maneuver, standing, and exercise echocardiography is essential for a full appreciation of the dynamic obstructive nature of the pathology.

DISCLOSURE

There are no financial disclosures or conflicts related to this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Movie S1. A 70 year old patient with HCM and latent LVOT obstruction presented 10 years after his initial diagnosis with near

syncope, heart failure and hypotension evolving to refractory cardiogenic shock. The first 2 movies are soon after admission with the ballooning event. The 3rd movie was done postoperatively. Parasternal long-axis echocardiogram showing a mild septal bulge, SAM, and mitral-septal contact. There is ballooning of the apical and mid-LV segments with akinesia there. Systolic LVOT gradient was 90 mm Hg. Orange arrow shows the SAM. White arrowheads indicate the akinetic septum and posterior wall.

Movie S2. Apical 3-chamber view in the same patient. There is a very long anterior mitral valve leaflet 39 mm long, 19.5 mm/m^2(elongated >16 mm/m^2). There is ballooning of the apical and mid-LV segments. The anterior septal and posterior wall are akinetic while the apex was severely hypokinetic. The video demonstrates the very long anterior mitral valve leaflet (orange arrow), the akinetic septum and posterior wall (small white arrowheads), and the septal bulge (red arrow).

Movie S3. Postoperative long-axis echocardiogram performed 4 days after surgery to relieve LVOT obstruction with a mitral valve replacement and limited myectomy. Yellow arrow points to the bioprosthetic mitral valve. Paradoxical septal motion is present due to the LBBB from the myectomy. Nine years after surgery to relieve his severe LVOT obstruction and shock he is well, and NYHA I. He has paroxysmal atrial fibrillation. Mitral valve replacement was explicitly selected in the two cardiogenic shock patients because of the only modest septal thickening and to assure that only one pump run would be necessary.

Movie S4. A 73-year-old female was diagnosed with HCM and latent LVOT gradients with symptoms of dizziness and episodic dyspnea. Three and a half years later she developed severe orthostatic hypotension and heart failure symptoms with mild exercise. When acute dyspnea at rest occurred, she was found to have apical ballooning on TTE. Video loops from her TEE in the operating room are shown, performed before cannulation, before surgical septal myectomy. Yellow arrowheads in lower loops point to the apical ballooning. Red arrow points to mitral-septal contact. Note the poor mid-LV systolic function on the short axis loop.

Movie S5. Same patient as Movie S4. TEE video loops performed immediately after myectomy and completion of cardiopulmonary bypass showing resolution of the severe LV systolic dysfunction.

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