Distinctive Hypertrophic Cardiomyopathy Anatomy and Obstructive Physiology in Patients Admitted With Takotsubo Syndrome

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Clinical spectrum of hypertrophic cardiomyopathy (HC) has been expanded to include patients with mild or no thickening of the left ventricle (LV), who nevertheless have outflow tract obstruction at rest or after exercise, due to systolic anterior motion (SAM) and ventricular septal contact, with mitral valve elongation and papillary muscles anomalies. Apical ballooning mimicking a takotsubo syndrome (TS) wall motion pattern can occur in HC with mild septal thickening when latent obstruction becomes unrelenting. To define the prevalence of anatomic abnormalities characteristic of HC in patients diagnosed with TS, we analyzed echocardiograms of 44 unselected TS patients, age 67±12 years, 95% women including studies performed before the event (n = 11, median 515 days) and after recovery of left ventricular function (n = 33, median 92 days, interquartile range = 29 to 327) and compared the findings to 60 age and sexed matched controls. Analysis of echocardiograms was blinded to event timing, and patient vs. control status. During the ballooning event, 13 patients (30%) had SAM including 9 with LV outflow obstruction, peak gradients 71±40 mmHg, as well as: ventricular septal thickening (16 ± 4 mm), elongated anterior leaflets (30 ± 3mm), and increased mitral coaptation to posterior wall distance (17 ± 5 mm), consistent with diagnosis of the HC phenotype. Compared to 31 TS patients without SAM, study patients with SAM had longer anterior leaflets (30 ± 3 vs 26 ± 4 mm, p = 0.006), thicker septum (16 ± 4 vs 12 ± 3 mm), increased coaptation to posterior wall distance (17 ± 5 vs 14 ± 4 mm, p < 0.04) and reduced distance from coaptation to septum (19 ± 5 vs 27 ± 5, p < 0.001). In the 13 patients with SAM, morphologic characteristics of HC persisted after normalization of LV function. In conclusion, a subset of patients experiencing TS events demonstrates a constellation of morphologic abnormalities characteristic of HC that persist after recovery of LV wall motion. These findings suggest that dynamic outflow obstruction may cause apical ballooning in susceptible patients. **(Am J Cardiol 2020;125:1700−1709)**

The clinical definition of hypertrophic cardiomyopathy (HC) has recently expanded to include patients who have mild or normal left ventricular (LV) thickness, yet have outflow tract obstruction at rest or after exercise responsible for typical heart failure symptoms.[1−3] These patients have mitral leaflet elongation, papillary muscle abnormalities, and systolic anterior motion of the mitral valve (SAM), all characteristic of obstructive HC, as well as abnormal electrocardiogram (ECG) patterns, familial HC pathogenic genetic variants, typical histopathology findings on septal myectomy muscle, and sudden death events. Thus, intrinsic HC-related anatomic abnormalities of the mitral valve apparatus may lead to outflow obstruction even when septal thickening is not marked.[1−3] Since outflow obstruction may cause ballooning in some HC patients with mild septal thickening,[4−13] we hypothesized that some patients diagnosed with takotsubo syndrome (TS) could have the same anatomic abnormalities predisposing to outflow obstruction, but are not recognized as having HC due to mild or absent septal thickening. Wall motion abnormalities in these patients could be caused by excessive afterload and supply-demand ischemia. Therefore, we have assessed whether an HC obstruction-prone phenotype occurs in TS patients during, before, and after the ballooning event.

Methods

For this case-control retrospective study, we conducted an electronic medical record query for all patients enrolled

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at NYU Langone Health between January 2010 and December 2016 who had been hospitalized with the diagnosis of acute TS, or stress cardiomyopathy. Diagnosis of TS required (1) evidence of regional LV wall motion abnormality beyond a specific epicardial coronary distribution, (2) new potentially ischemic ECG abnormalities or elevated cardiac troponin, and (3) acute coronary angiography demonstrating absence of obstructive coronary artery disease or acute plaque rupture. Patients were excluded if they had a prior episode of TS, did not have both an acute-episode angiogram and a technically adequate acute-episode echocardiogram on the day of admission, or had pheochromocytoma, myocarditis, or prior diagnosis of HC. We identified 59 patients with a discharge diagnosis of acute TS from 2010 to 2016 based on our electronic medical record search. After applying these eligibility criteria, the TS study group consisted of 44 patients.

Sixty age-matched women controls with normal LV wall motion on rest and exercise echocardiography were randomly selected from our echocardiography database. Potential controls were excluded if they had moderate or more valvular regurgitation, mild or more valvular stenosis, or HC on rest echocardiography. Exercise echocardiography was considered normal if there were no LV wall motion abnormalities after achieving 85% of predicted maximal heart rate without significant valvular regurgitation, outflow obstruction, or pulmonary hypertension. In control patients, clinical indications for normal rest and exercise echocardiography included atypical chest pain (43%), dyspnea (32%), palpitations (10%), preoperative evaluation (10%), and others (5%). NYU Review Board approved this research; consent was waived owing to retrospective study.

A physician echocardiographer selected an acute study, the first echocardiogram on the TS admission for subsequent blinded analysis; he also identified echocardiograms that were performed for clinical indications before and after the ballooning episode, assuring that there was then resolution of the LV wall motion abnormalities. Echocardiograms were then analyzed independently by 2 readers in random order blinded to patient identity and timing. Mean values were recorded. Differences of >10% between observers were resolved by consensus.

Left ventricular end-diastolic and end-systolic dimension, basal and mid anterior septal thickness, posterior wall thickness, and LV outflow tract diameter were measured on parasternal short and long-axis views in standard fashion. Diastolic and systolic ventricular volumes and LV ejection fractions were calculated using Simpson's method. We measured the septal-aortic angle between the anterior septum and the anterior wall of the aorta. LV outflow tract obstruction was defined by peak Doppler velocity >1.8 m/s when associated with SAM.

Distance from mitral coaptation to anterior septum and posterior wall were measured in parasternal long-axis during early systole (Figure 1). Lengths of the anterior and posterior leaflets were measured at end-diastole in the apical 3-chamber view.[2] The protrusion height of mitral leaflets into the LV cavity and residual leaflet length were measured from the early systolic 3-chamber view.[2] Chordae were excluded. Mitral regurgitation was qualitatively assessed from grades 0 to 4. Angle between systolic ejection flow (by color Doppler) and LV posterior wall was measured on parasternal views. Distance from papillary muscles to the septum and posterior wall and transverse diameter of papillary muscles were measured.[2] Anomalous anteriorly displaced papillary muscles or thickened chordae that inserted into the anterior mitral leaflet resulting in anterior tenting of the mitral valve were noted.[14–18]

Continuous variables are reported as mean ± standard deviation or medians and interquartile range. Categorical variables were summarized as frequencies and proportions. Differences between continuous variables were determined by 2-sample Student's t-tests between TS patients and controls. Categorical variables were analyzed by chi-square. Correlations between continuous variables were estimated using Pearson's correlation coefficients. Multivariable

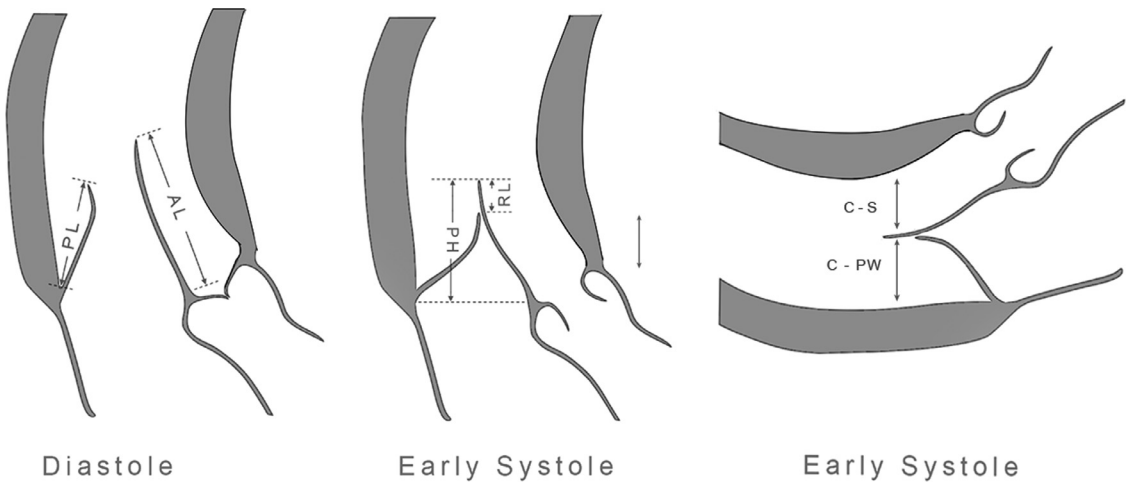

Figure 1. Mitral valve measurements. Schematic drawing of echocardiographic 3-chamber views in diastole *(left panel)*, and at the moment of systolic mitral coaptation *(middle panel)*; and parasternal view at the moment of systolic mitral coaptation *(right panel)*, showing where measurements were made.[2] AL = anterior leaflet; C-PW = coaptation to posterior wall; C-S = mitral coaptation point to septum; PH = protrusion height; PL = posterior leaflet; RL = residual leaflet.

logistic regressions were performed with TS/control as dependent outcomes at the time of admission and at the time of recovery, respectively. The candidate covariates included the significant variables from the univariate analyses comparing TS patients and controls. The final models were selected by backward variable selection. Odds ratios and their 95% confidence interval (CI) were estimated. Significance was decided at p-value < 0.05. All analyses were performed in R version 3.5.1.

Results

The clinical characteristics of the 44 TS patients (age 67 ± 12 years, 95% women) are summarized in Table 1 and (online Table 1). TS wall motion types were apical (n = 38), midventricular (n = 4), and focal (n = 2). Twenty-four patients (55%) had an identifiable precipitating event, emotional in 12, and associated with a significant medical illness in 12.

Of the 44 TS patients, 13 (30%) had clinical evidence consistent with HC (age 66 ± 14; 12 women) during the ballooning event including: dynamic SAM in all 13, including 9 with mitral-septal contact responsible for LV outflow tract obstruction in whom resting peak outflow gradients were 71 ± 40 mmHg, and basal ventricular septal thickening 16 ± 4 mm. In addition, these 13 patients had other anatomical features that promote subaortic gradients in HC: elongated anterior mitral leaflets, 30 ± 3 mm (range 23 to 33 mm), increased distance from posterior wall to the mitral valve coaptation point at end-diastole, 17 ± 5 mm (range 7 to 26 mm) and anomalous anterolateral papillary muscles or shortened and thickened chordae in 46%.

Table 1
Clinical characteristics of 44 patients with takotsubo syndrome

Variable	
Age at diagnosis (years)	66.9±12
Women	42 (95%)
White	32 (73%)
BMI (kg/m^2)	24.8±6.8
Precipitating event	24 (55%)*
Smoker	21 (48%)
Hypertension	24 (55%)
Diabetes mellitus	4 (9%)
Coronary artery disease	1 (2%)§
Chronic kidney disease	1 (2%)
Pulmonary disease	12 (27%)
Hypertrophic cardiomyopathy	0
Chest pain	26 (59%)
Peak troponin I (ng/mL)	2.5±2.1
Median BNP (pg/ml)	4540¶
Hemoglobin (g/dL)	13.2±1.9
White blood cell count (10^9/ml)	11.5±8
Creatinine (mg/dL)	0.83±0.4
ST-segment elevation	23 (52%)
ST-segment depression	2 (5%)
T-wave inversion	34 (77%)
QTc (ms)	460±52
QTc prolongation	20 (46%)
Chest pain	26 (59%)

Values are mean ± standard deviation. QTc = QT interval corrected for heart rate.

* Twelve patients had precipitating emotional event and 12 patients had emotional precipitant.

§ One patient had severe narrowing of a nondominant right coronary artery that did not explain the extent of wall motion observed.

¶ Measured in 15 patients.

Four of the 13 patients (31%) experienced complicated clinical courses including, 3 with pulmonary edema, and 2 with hypotension requiring phenylephrine, and 3 who required intravenous beta blockade to normalize outflow obstruction.

Compared to TS patients without SAM, those with SAM showed thicker septum (16 ± 4 vs 12 ± 3 mm, p = 0.001), longer anterior leaflets (30 ± 3 vs 26 ± 4 mm, p = 0.006), greater mitral protrusion height above the annulus (20 ± 4 vs 13 ± 7 mm. p = 0.001), and increased distance from posterior wall to coaptation (17 ± 5 vs 14 ± 4 mm, p < 0.04). Table 2 shows comparisons between TS patients with and without morphologic features of HC showing that multiple features are clustered in these patients. Patients with anomalous papillary muscles/chordae correlated (and were clustered) with greater anterior septal thickness, anterior mitral coaptation position, and greater mitral protrusion height. Moreover, in the 44 TS patients the magnitude of outflow tract velocity correlated with HC characteristics of anterior septal thickness, protrusion height, anterior mitral coaptation position, and grade of mitral regurgitation; anterior septal thickness correlated with mitral protrusion height (for all correlations r > ± 0.5 and p < 0.001). Examples of patients with a TS ballooning event and distinctive HC anatomy and obstructive physiology appear in Figures 2 to 4.

Echocardiograms were performed on 33 TS patients after recovery of LV function (median of 92 days) including 11 of the 13 patients who had SAM during their events. Patients who had SAM during their TS events continued to have features of obstructive HC after recovery of LV function compared with TS patients without SAM: anterior septal thickening 15 ± 4 versus 11 ± 3 mm (p < 0.002), posterior septal thickening 14 ± 3 versus 10 ± 3 mm (p < 0.002), anterior leaflet elongation 28 ± 5 versus 24 mm (p < 0.04), and increased posterior wall to coaptation 16 ± 5 versus 12 ± 3 mm (p < 0.05).

Overall, we blindly analyzed a total of 148 echocardiograms: 60 control studies, 44 patients during their acute TS episodes, 33 after normalization of LV function, and 11 before the TS event. (Comparison of clinical characteristics of TS and control patients shown in supplemental Table 2.) Eleven patients had echocardiograms for clinical indications before their TS event when their LV function was normal (median of 515 days). The pre-TS study was performed in 3 for chest pain, 2 for preoperative evaluation, 2 for arrhythmia, 1 for systolic murmur, 1 for hypertension, 1 for transient ischemic attack, and 1 because of a systemic illness. At the time of the TS event, we found significant differences in septal and mitral valve variables between the TS patients and controls, particularly among the 13 TS patients with SAM, as highlighted in the scatterplots in Figures 5 and 6 and Table 3 and online Table 3. In these scatterplots, it was the highlighted 13 patients with SAM, the obstructive HC subgroup of the 44 TS patients, that had septal thickening and mitral leaflet abnormalities that

Table 2
Comparisons between patients with and without SAM, with and without outflow tract obstruction, and with and without anomalous papillary muscle/chordae in 44 TTS patients on admission

Variable	SAM			LVOT obstruction			Anomalous papillary muscle		
	No (n = 31)	Yes (n = 13)	p	No (n = 35)	Yes (n = 9)	p	No (n = 27)	Yes (n = 15)	p
Anterior VS (mm)	11.7 ± 3	15.7 ± 4	0.001	12.3 ± 4	15.2 ± 3	0.029	11.8 ± 3	15.0 ± 3	0.005
Posterior VS (mm)	11.4 ± 3	14.1 ± 4	0.011	11.8 ± 3	14.1 ± 3	0.057	11.5 ± 3	13.2 ± 4	0.107
Coaptation point to septum (mm) PLAX	26.7 ± 5	18.7 ± 5	<0.001	25.9 ± 6	18.3 ± 5	0.001	26.1 ± 6	21.7 ± 6	0.026
Coaptation point to posterior wall (mm) PLAX	13.9 ± 4	16.9 ± 5	0.034	14.1 ± 4	18.0 ± 6	0.016	14.1 ± 4	16.2 ± 4	0.145
Anterior leaflet length (mm)	26.1 ± 4	29.9 ± 3	0.006	26.2 ± 4	30.6 ± 3	0.004	26.4 ± 5	29.0 ± 3	0.064
Posterior leaflet length (mm)	12.6 ± 4	15.4 ± 5	0.054	12.4 ± 4	17.4 ± 5	0.002	12.5 ± 4	15.2 ± 4	0.046
Residual leaflet length (mm)	1.5 ± 2.7	6.0 ± 2	<0.001	2.0 ± 2.8	5.5 ±3.3	0.003	1.8 ±3.0	4.4 ± 3	0.013
Protrusion height (mm)	13.0 ± 7	19.8 ± 4	0.001	13.6 ± 6	19.1 ± 4	0.017	13.4 ± 7	17.8 ± 6	0.039

LVOT = left ventricular outflow tract; PLAX = parasternal long axis view; SAM = systolic anterior motion; VS = ventricular septum.

differed from the controls. In addition, because of the persistence of the obstructive HC phenotype, studies performed before and after recovery from the ballooning episodes showed similar differences in septal thickness and anterior mitral valve length between TS patients and controls. In TS patients, there were no differences in septal thickness or anterior leaflet length when comparing acute studies to those performed before or after the event.

The grade of mitral regurgitation was higher in the TS patients than in controls during the acute event, but not after recovery or pre-event. The significant differences between TS patients and controls in septal thickness, mitral leaflet length, and anterior position of the mitral valve in the LV, persisted after measurements were corrected for body surface area. Results were unchanged after excluding the 2 male TS patients.

In the 13 TS patients with SAM, we assessed how many obstruction-related abnormalities differed between TS and controls on univariate analysis by > 2 standard deviations. These four factors were ventricular septal thickness, protrusion height, anterior position of mitral coaptation, and anomalous papillary muscle/chordae. Three patients with SAM had all 4 factors, 4 had 3 factors, 4 had 2 factors and 2 had just one. Eighty-five percent of TS patients with SAM had 2 or more factors; in contrast, only 26% of those without SAM had 2 or more factors.

Compared with the 60 control patients, multivariable analysis of measurements on admission that were independently associated with TS were anterior leaflet length (OR 1.45 per 10 mm increase, 95% confidence interval [CI] 1.18 to 1.8; p < 0.001), protrusion height (odds ratio [OR] 1.26 per 10 mm increase, 95% CI 1.04 to 1.53; p = 0.018), and coaptation point to posterior wall (OR 1.27 per 10 mm increase, 95% CI 1.009 to 1.59; p = 0.042). At the time of recovery from TS variables that were independently associated with TS were anterior septal thickness (OR 1.32 per 10 mm increase, 95% CI 1.07 to 1.63; p = 0.01), anterior leaflet length (OR 1.18 per 10 mm increase, 95% CI 1.02 to 1.36; p = 0.03, and coaptation point to posterior wall (OR 1.22 per 10 mm increase, 95% CI 1.02 to 1.47; p = 0.03).

During the ballooning episode, 8 TS patients (18%) had segmental akinesia or severe hypokinesia of the RV. None of these patients was in the obstructed group with SAM or outflow obstruction. There was no difference in the age of TS patients with and without SAM. There was no difference in the frequency of hypertension between TS and control patients (online Table 2).

Discussion

In a subset of 30% of TS patients, we found abnormalities of the ventricular septum and mitral valve clustered together with SAM and peak LV outflow gradients (average 71 mmHg) as evidence of obstructive HC.[1–3,14–16,19] On blinded measurement, they had SAM, septal thickness averaging 16 mm, elongated anterior and posterior mitral leaflets, mitral coaptation planes anteriorly displaced in the LV, and frequent anomalous anterolateral papillary muscles or shortened chordae (Figures 2 to 4 and supplemental figure). These abnormalities were distinctly different from the larger group of 70% of TS patients who did not have SAM or LVOT obstruction. When LV function recovered the abnormalities of septum and mitral valves persisted in the patients initially with SAM, as would be expected in HC. We propose that in a subset of apical ballooning patients HC may be initially overlooked when it is overshadowed by the dramatic presentation of an acute coronary syndrome with wall motion abnormalities, especially when the septal thickening is mild and when the obstruction is latent. HC is the "great masquerader of cardiology"; the true diagnosis can elude detection for years.[20] Here it has taken on another guise, mimicking the larger group of non-HC TS patients with LV ballooning. Histopathologic examination of the myectomy specimen of 1 TS patient who had surgery 3 months after the event showed typical findings of HC (Figure 4). Indeed, patients with TS and outflow obstruction are phenotypically quite similar to 21 reported patients with known, diagnosed HC and mild septal thickening in whom clinical course was punctuated by apical ballooning (online Table 4).[4–13]

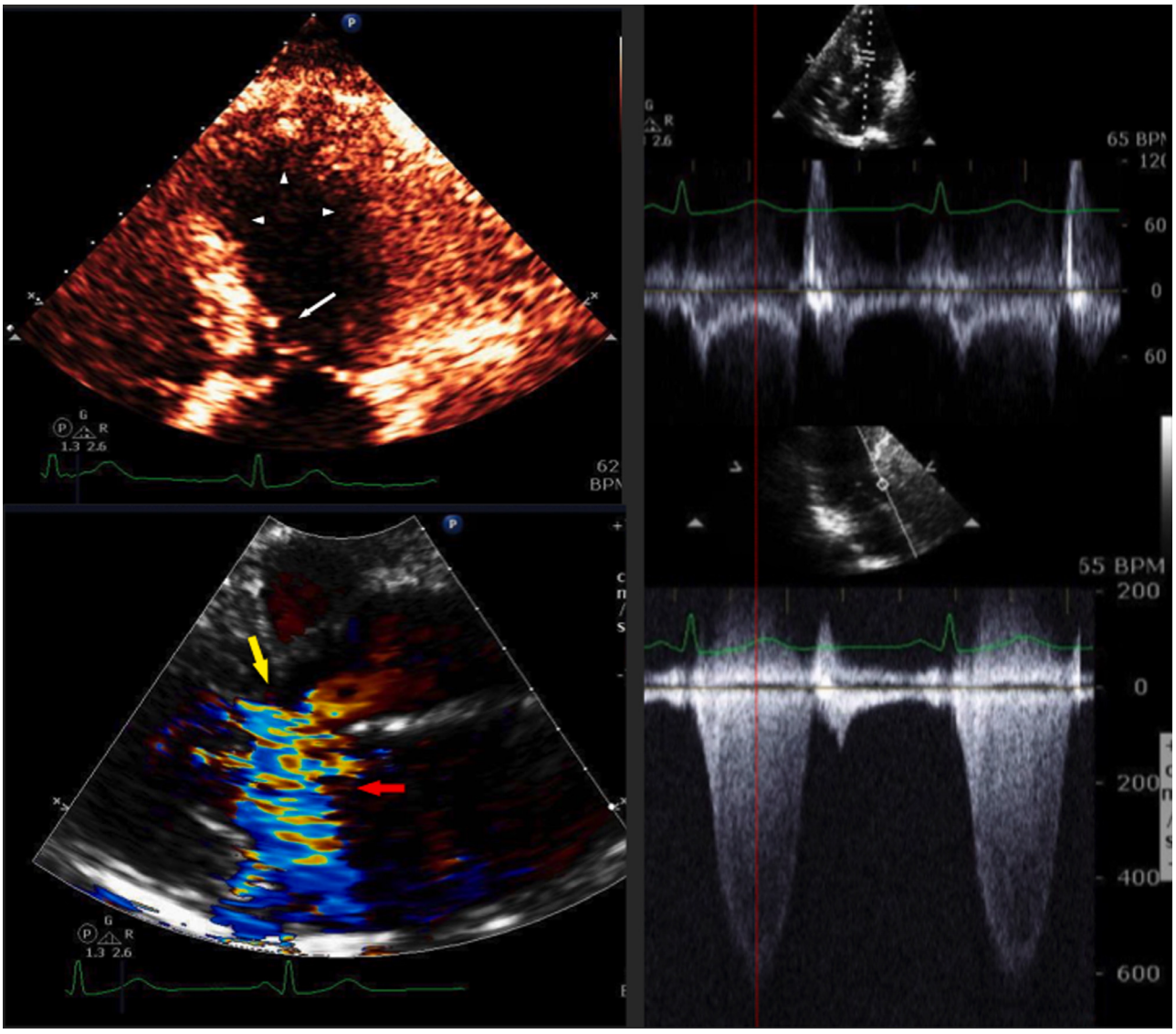

Figure 2. Mild-thickness HC, outflow obstruction, and acute ballooning. A 63-year-old woman without prior cardiac history admitted for near syncope, collapse, with hypotension, acute myocardial infarction, and troponin $I = 0.64$ ng/ml. Coronary arteries were angiographically normal; there was apical ballooning with preserved basilar motion on LV cineangiography and 3 to 4+ mitral regurgitation. Aortic pressure was 89/51; catheter outflow gradient was 100 mmHg. *(Left upper panel)* Echocardiogram performed concomitantly *(systolic frame)* showed apical and mid-LV ballooning and hypokinesia *(arrowheads)* and mitral-septal contact *(white arrow). (Left lower panel)* Color Doppler *(systolic frame, right panel)* showed severe MR *(red arrow)* and turbulence in the LV outflow tract *(yellow arrow)*. A video of this patient's severely hypokinetic, ballooned apex is shown in the online supplement. *(Right panel)* PW Doppler tracing acquired at the entrance of the outflow tract from the echocardiogram acquired on admission showed a mid-systolic drop in PW Doppler velocities, the "lobster claw abnormality." The nadir of the drop of the PW Doppler occurs at the same time in the cardiac cycle as the peak of the CW gradient in the outflow tract (139 mmHg, at bottom) shown by the *red dotted line*.[26,27] In the upper panel, the PW velocity in mid-systole is quite low 20 cm/s. This nadir is lower than usually seen when LV function is normal, and is due to the LV systolic dysfunction. This patient had premature closure of the aortic leaflets. After intravenous metoprolol, the outflow gradient fell from 100 to 40 mmHg and the blood pressure rose to 105/80 mmHg.

It is now recognized that some HC patients with mild or no septal thickening have symptomatic left ventricular outflow obstruction due to elongated mitral leaflets and papillary muscle abnormalities, which are their primary substrate for LV outflow obstruction.[1–3,19] These structural mitral apparatus abnormalities position the valve into the ejection flow stream where the leaflets are prone to be swept toward the septum.[17,18,21,22] Here we add to the description of these HC patients with mild thickening that an event in their clinical course may mimic TS.

Catecholamine excess with abnormal LV adrenergic receptor expression leading to catecholamine-induced myocardial stunning has been proposed as the predominant disease mechanism in TS[23] as has coronary microvascular dysfunction.[24] However, our observations that a subset of TS patients have abnormalities of their mitral valves, not seen in controls, challenges the theory that TS is only caused by direct catecholamine toxicity to the myocardium. In HC, genetically determined inefficient energy utilization[25] renders the LV sensitive to

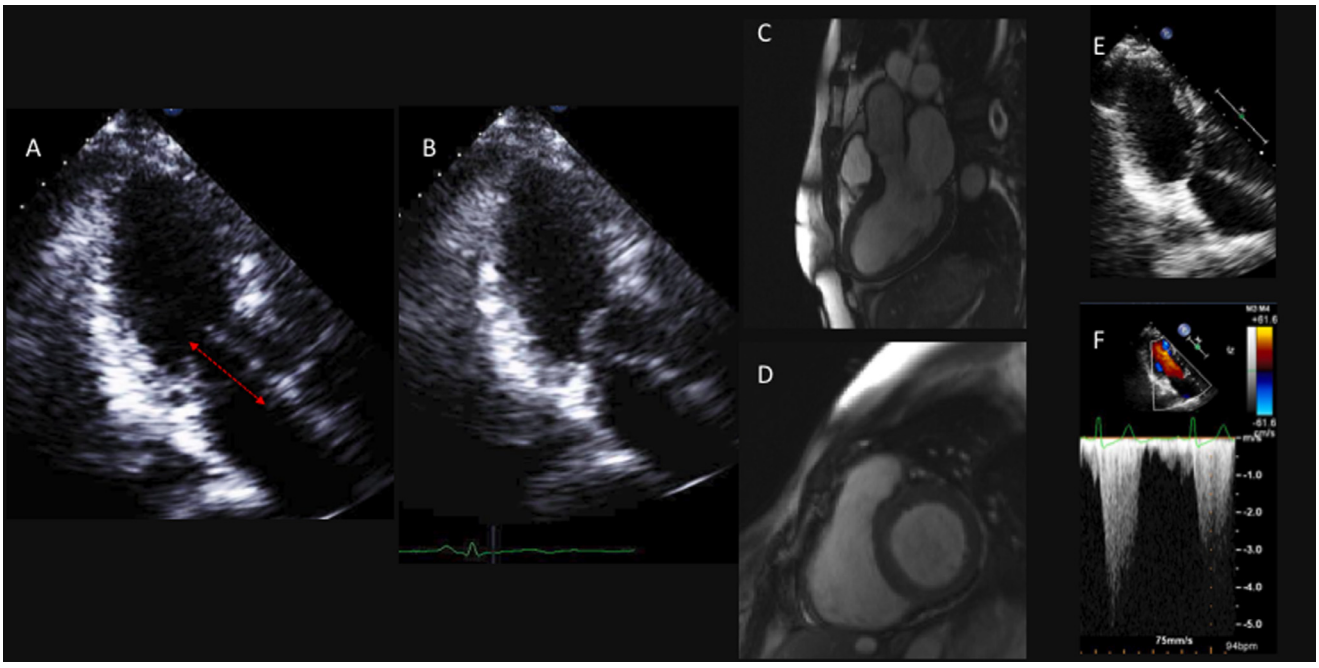

Figure 3. Same patient as Figure 2. Echocardiogram the day after admission: (A) diastolic frame showing an elongated anterior mitral valve leaflet 32 mm (anterior leaflets > 28.6 mm are >2 SD above our normal average.) (B) Systolic frame showing SAM and protrusion into the LV cavity. (C and D) MRI 2 days later, after wall motion had normalized, showing that the anterior septum and anterior wall were only mildly thickened, 13 mm. (E and F) Stress echocardiogram 22 months after the ballooning episode, done because she continued to have exercise related chest discomfort and dyspnea especially after eating; resting LV wall motion had normalized and there was no resting outflow gradient. She could not complete stage 1 of the Bruce protocol. Blood pressure response was flat. After exercise, there was mitral-septal contact and peak outflow gradient was 81 mmHg. This patient had very mild-septal-thickening HC with ballooning due to outflow obstruction presenting clinically as TS. After recovery of LV systolic function, she had severe gradients provocable after exercise.

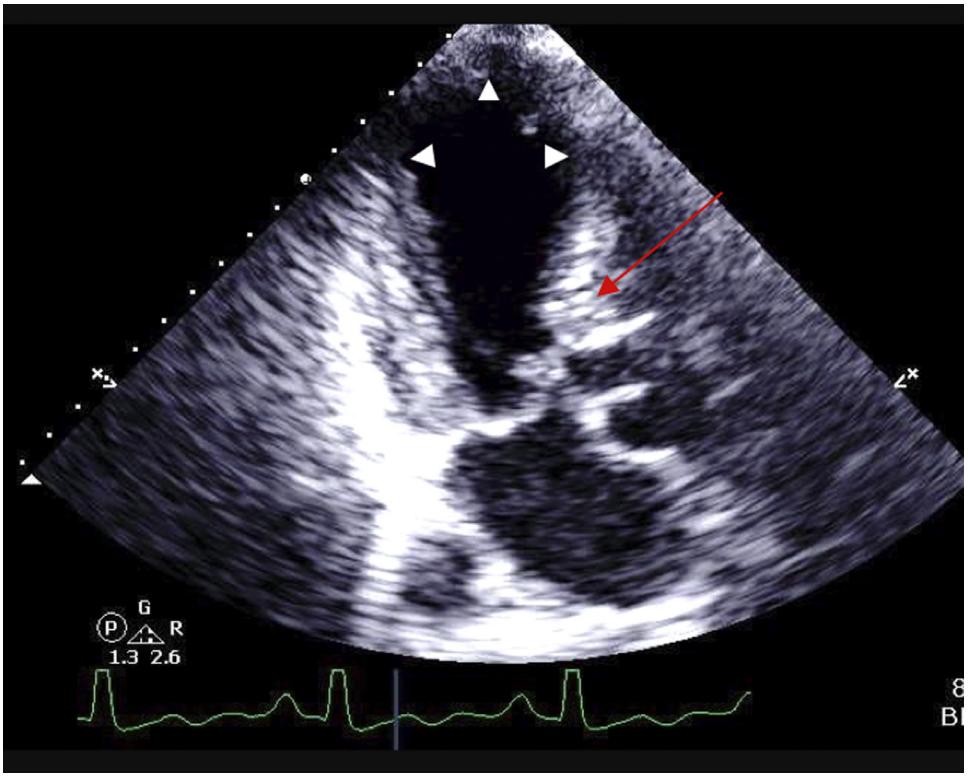

Figure 4. Echocardiogram of a patient with modest-septal-thickening HC and takotsubo-like apical ballooning. Admission echocardiogram, apical 3-chamber view in systole showing very modest septal thickness *(red arrow)*, SAM with mitral septal contact, and LV apical ballooning (white arrowheads). Outflow gradient was 76 mmHg. Three months later after recovery of LV systolic function patient had surgical septal myectomy and mitral valve repair. Microscopic histopathology of the myectomy showed intramural coronary arteries narrowed by intimal and medial hyperplasia and surrounded by perivascular fibrosis, with interstitial fibrosis as well. There was mild myocyte hypertrophy with enlarged myocyte nuclei.

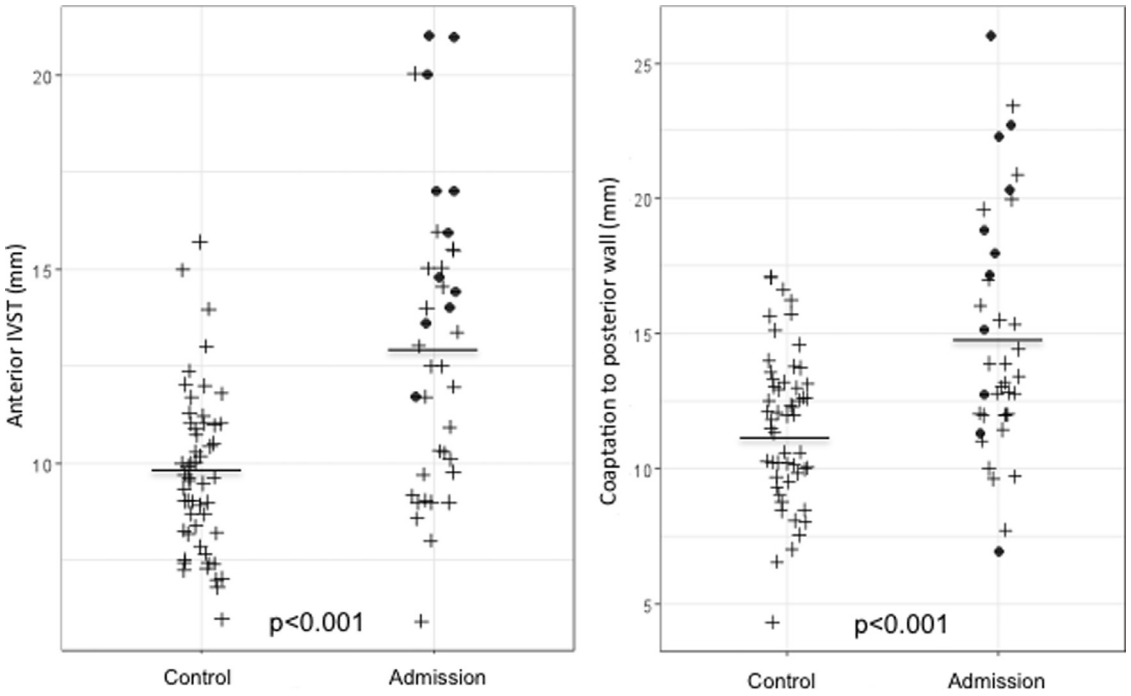

Figure 5. Scatter plots of anterior septal thickness, and distance from the coaptation point of mitral valve to the posterior wall in 60 control patients and 44 TS patients on admission for ballooning. Patients with SAM are shown with *solid black circles*. IVST = interventricular septal thickness.

afterload-mismatch. Supply-demand ischemia results from high LV pressures, coronary hypoperfusion and narrowed intramural coronaries. Contractile impairment of varying severity occurs in HC with high gradients, even when ejection fraction is normal or high. These phenomena have been termed "paradoxical reversible systolic dysfunction,"[26–28] collectively evidence of instantaneous systolic heart failure in face of afterload. Systolic impairment is paradoxical because HC is understood as a hyperdynamic condition. With gradients ≥60 mmHg there is a ubiquitous reversible mid-systolic drop in LV PW Doppler ejection velocities and flow, termed the "lobster claw abnormality"[26,27] due to premature termination of segmental contraction.[26] Ballooning in HC is a more severe manifestation of dynamic dysfunction due to sudden outflow obstruction.

Besides phenotypic similarity, characteristics of the prior reports of 21 patients with obstructive HC and apical ballooning with gradients ≥ 50 mmHg illuminate the TS issues discussed here (online Table 4).[4–13] Among a large unselected clinical HC cohort ballooning events were estimated to occur in ∼1% of patients; ballooning HC patients had relatively thin septum averaging 15 mm compared with 20 mm in those without ballooning.[5] Ballooning has not occurred in non-obstructive HC. Latent mitral-septal contact is demonstrated by exercise echocardiography when the LV recovers, thus substantiating that SAM is inherent to their HC and not attributable to the ballooning, per se. Ballooning in HC occurs predominantly in women (71%). Overall, women with HC more frequently have obstruction, heart failure symptoms, and adverse outcomes compared with men. Three HC patients experienced severe refractory hemodynamic compromise requiring urgent surgical relief of outflow obstruction, 2 for cardiogenic shock and 1 for heart failure. Reversal of LV dysfunction and clinical improvement occurred within hours of surgically abolishing LV obstruction, compelling evidence that ballooning was due to the obstruction.[4,5]

Dynamic LV outflow tract obstruction due to SAM has been observed in 11% to 33% of TS cases.[29–31] It has previously been posited that outflow obstruction results from a narrowed hyperkinetic outflow tract, with development of Venturi forces there due a functional alteration of LV geometry. However, the preponderance of evidence regarding SAM in HC is that it is caused by flow drag, the pushing force of flow and not by a Venturi effect.[21,22,32] Outflow velocities are low in obstructive HC when SAM begins, precluding Venturi forces as a mechanism.[18,32] The debate concerning outflow obstruction as a cause for ballooning[33] is reminiscent of the controversy in the 1970s and 1980s that it might not cause severe HC-related symptoms, since proven incorrect. Based on data from the present study, on previous observations of LV ballooning in obstructive HC, and on credible pathophysiologic mechanisms we propose that in a subset of patients clinically diagnosed with TS, mitral-septal contact is not a result of the wall motion abnormalities but instead is the cause of severe systolic dysfunction.

On blinded measurements of all TS patients, we found abnormalities of the mitral leaflets, papillary muscles, and basal septum were more frequent in TS patients than in controls, but this was because of the subset of TS patients with obstructive HC and ballooning, not because all TS patients have HC anatomy and physiology (Figures 5 and 6). Individual patients may have different causes for developing TS. We present evidence of distinctive HC

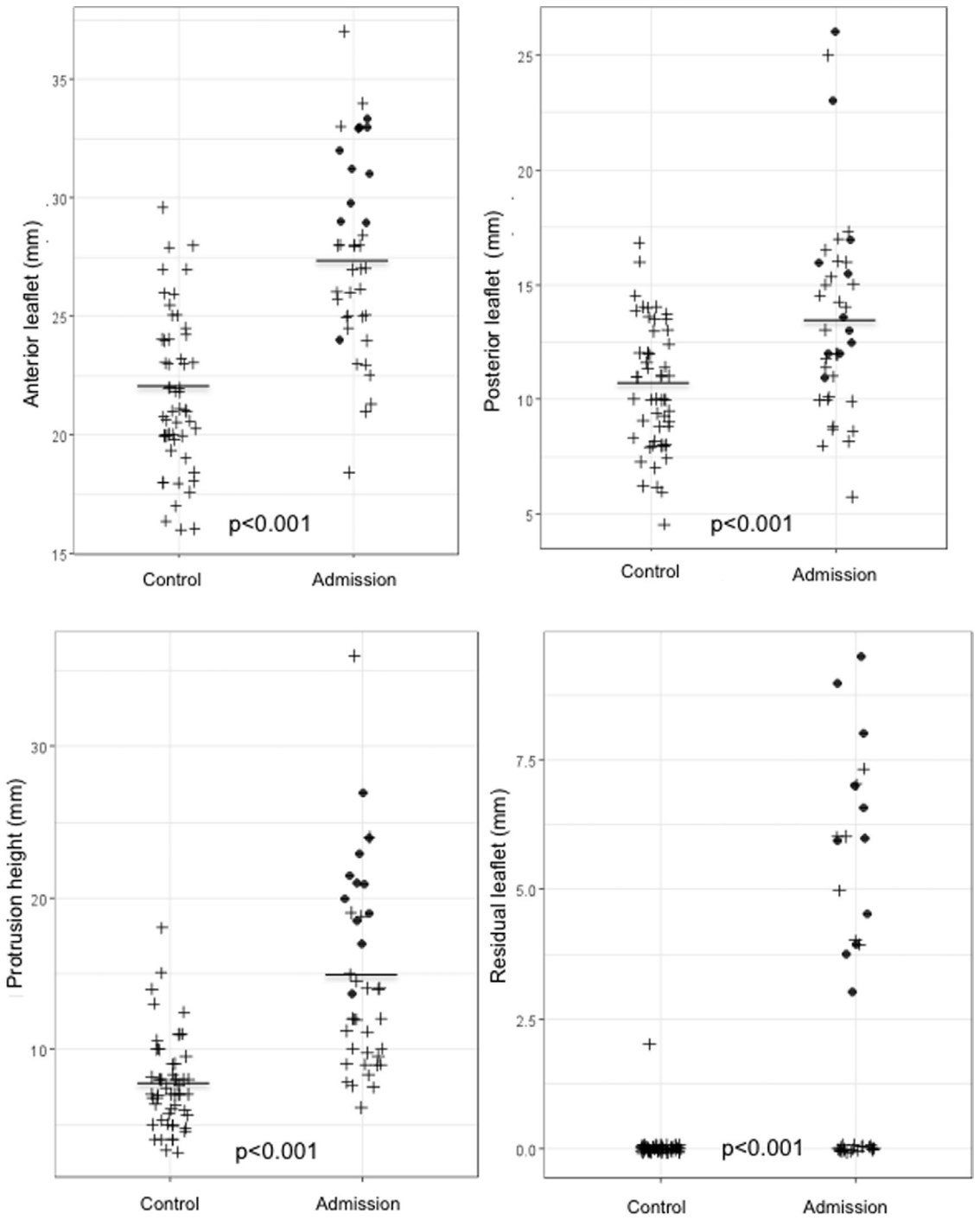

Figure 6. Scatter plots of anterior mitral leaflet length, posterior leaflet length, protrusion height, residual leaflet length in 60 control patients, and 44 TS patients on admission for ballooning. Patients with SAM are shown with *solid black circles*.

phenotype and obstructive physiology in a subset of TS patients. The larger group has normal septal thickness and mitral valves, and does not have SAM; in our study, this group included all patients with RV dysfunction. Here ballooning may be due to direct catecholamine toxicity, termed neurohumeral TS. In both groups TS may be triggered by a surge in catecholeamines but by different mechanisms, in the HC patients by obstruction, and in the neurohumeral group by direct toxicity. In TS patients with outflow obstruction, intravenous beta blocker decreased gradients and increased blood pressure.[34] Long-term treatment of TS has not been tested in a randomized trial; patients with and without obstruction may benefit from different measures. In an observational study of all TS, beta blockers were not associated with improved outcomes.[35] Selection of obstructive TS patients for beta blockade or more potent agents to reduce obstruction should be tested.

Table 3
Comparisons between controls and TTS patients on admission, after recovery, and before their ballooning episodes

Variable	Controls (n = 60)	Ballooning (n = 44)	p*	Recovery (n = 33)	p§	Preballooning (n = 11)	p#
Anterior IVS (mm)	9.7 ± 2	12.9 ± 4	<0.001	12.4± 4	<0.001	13.4 ± 4	<0.001
Posterior IVS (mm)	9.4 ± 2	12.2 ± 3	<0.001	11.6 ± 3	<0.001	12.3 ± 3	<0.001
Anterior leaflet length (mm)	22.0 ± 3	27.3 ± 4	<0.001	24.9 ± 5	<0.002	27.3 ± 6	<0.001
Posterior leaflet length (mm)	10.7 ± 3	13.4 ± 4	<0.001	12.2 ± 4	0.038	14.7 ± 4	<0.001
Residual leaflet length (mm)	0.0 ± 0.3	2.8 ± 3.3	<0.001	2.0 ± 3.7	<0.001	1.2 ± 2.7	0.001
Protrusion height (mm)	7.7 ± 3	15.0 ± 7	<0.001	10.7 ± 6	<0.003	11.6 ± 6	0.003
Coaptation point to septum (mm) PLAX	27.5 ± 4	24.3 ± 6	0.002	24.6 ± 6	<0.005	24.3 ± 6	0.017
Coaptation point to posterior wall (mm) PLAX	11.5 ± 3	14.8 ± 4	<0.001	14.3 ± 4	<0.001	13.3 ± 4	0.077
Mitral Regurgitation	0.75 ± 0.8	1.4 ± 1.2	0.001	1.1 ± 0.9	0.089	1.1 ± 0.94	0.218

* Comparing TTS patients on admission to control patients.
§ Comparing TTS patients after recovery of LV systolic function to control patients.
# Comparing preballooning TTS patients to control patients.

In conclusion, a subset of patients admitted with a clinical diagnosis of TS had a cluster of abnormalities characteristic of HC, including SAM, septal hypertrophy, and typical mitral abnormalities. Morphologic findings of HC persisted after LV wall motion normalized indicating they were inherent to the patient and not due to the TS presentation. Observations in this group, and prior documentation of systolic dysfunction in obstructive HC, support the view that acute LV outflow tract obstruction may cause ballooning. These observations expand our appreciation of the clinical spectrum of the dynamically obstructed LV into the acute care setting with therapeutic implications.

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Disclosures

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Supplementary materials

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