7-1-2021

Concurring hypertrophic cardiomyopathy and takotsubo cardiomyopathy: Assessment and management

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Recommended Citation

Abozenah M, Kadado AJ, Aljamal A, Sawalha K, Salerno C, Battisha A, Hernandez-Montfort J, and Lotfi A. Concurring hypertrophic cardiomyopathy and takotsubo cardiomyopathy: Assessment and management. Heart Lung 2021; 50(4):546-557.

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Heart & Lung 50 (2021) 546–557

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

Concurring hypertrophic cardiomyopathy and takotsubo cardiomyopathy: Assessment and management

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ARTICLE INFO

Article History:
Received 19 June 2020
Revised 12 September 2020
Accepted 6 October 2020
Available online 2 November 2020

Keywords:
Takotsubo cardiomyopathy
Hypertrophic cardiomyopathy
Left ventricular outflow tract peak gradient
Left ventricular outflow tract obstruction
Shock

ABSTRACT

The prevalence of takotsubo cardiomyopathy (TCM) has been on the rise, but co-occurrence with hypertrophic cardiomyopathy (HOCM) remains rare. Although presenting patient demographics were similar to those in TCM, the potential for hemodynamic compromise was significantly compounded by the presence of underlying HOCM. Management was similar to standalone TCM, although use of inotropic agents and mechanical support appears to be more prevalent. Despite the increased potential for complications and the paucity of data regarding management, outcomes appear to be mostly favorable in both the hospitalization period and at follow-up. Interestingly, despite a new diagnosis of HOCM in about half the cases described, which signifies no significant left ventricular outflow tract (LVOT) gradient prior to TCM, half of those patients had a persistently elevated LVOT gradient after resolution of TCM. This poses a question of whether or not TCM can predispose to LVOT obstruction in HOCM patients even after its resolution.

Introduction

Hypertrophic obstructive cardiomyopathy (HOCM) and takotsubo cardiomyopathy (TCM) are two distinct myocardial disease entities that rarely coexist.[1] HOCM is the most common genetic cardiomyopathy and the most common cause of sudden cardiac death, yet there is an overwhelming lack of high-level evidence regarding the approach to its work-up and management.[2] Takotsubo cardiomyopathy is a newer entity however, first described in the late 20th century in Japan,[3] where its name was derived from the Japanese word for "octopus trap" which it resembles in appearance in its most classical form.[4] Contrary to HOCM, it is an acquired condition most commonly affecting postmenopausal women who suffer a severe psychological or physical stressor, although cases without an identified precipitating stressor have been reported.[5]

While the approach to either entity as separate conditions is common practice, treating both entities occurring together may be a challenge to healthcare providers. The lack of guidelines in managing these patients is likely related to the rarity of this occurrence. Herein we present a systematic review of the literature describing 18 cases of TCM overlapping with HOCM. We aim to identify patterns that may be suggestive of their coexistence on initial presentation, as well as clues to delineate severity of illness prior to decompensation. Additionally, we aim at providing potential management approaches in treating this rare entity.

Methods

A combination of the following search terms was used to identify articles in the PubMed/Scopus databases up until August 2019: takotsubo cardiomyopathy (including the hyphenated version tako-tsubo), stress cardiomyopathy, broken heart, and hypertrophic cardiomyopathy. The bibliographies of identified manuscripts were also utilized. A total of 47 records were identified with the described search terms in the English literature. Of them, 20 were excluded after identification as cohort studies, commentaries, letters or editorials. Twenty-seven remaining records were identified as case reports. Of these, 17 manuscripts that describe cases identifying takotsubo cardiomyopathy and hypertrophic obstructive cardiomyopathy were included. Case reports identifying sigmoid hypertrophy were excluded. Fig. 1 represents a PRISMA flowchart showing study screening and selection process.

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https://doi.org/10.1016/j.hrtlng.2020.10.006
0147-9563/

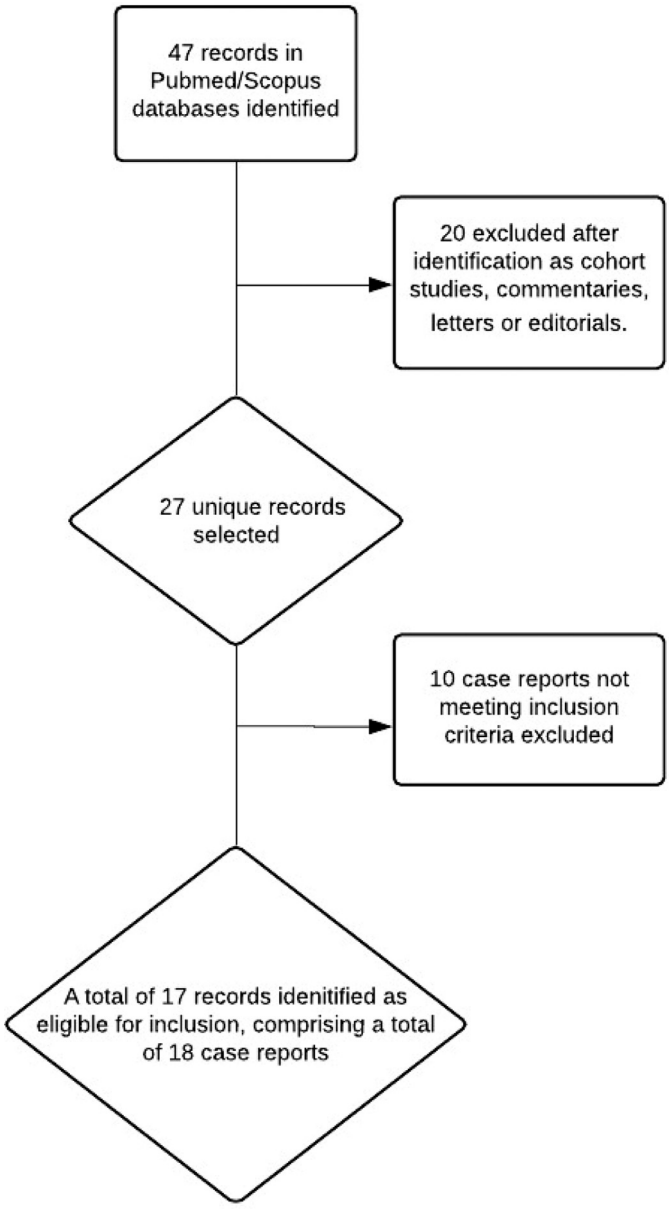

Fig. 1. PRISMA flowchart showing study screening and selection process.

Results

Seventeen records, comprising a total of eighteen cases, were identified to describe coexisting takotsubo and hypertrophic cardiomyopathies, the majority occurring during or after 2011 (Table 1). The majority of the patients described were females (77.8%), with the median age of the cases described being 66.2 years. Half of the patients outlined had a known history of hypertrophic cardiomyopathy (50%). One third of the patients described had known hypertension prior to presentation (33%), whereas known ischemic cardiac disease was rare (11%). Report of home medications was not uniform across all cases described, however, of those reported on, beta-blocker therapy was the most common (39%), followed by cibenzoline (11%) and calcium channel blockers (6%) (Table 1).

Chest pain was the commonest presenting complaint (72%), followed by shortness of breath (39%). Of the 11 cases with documented hemodynamic status, the majority were normotensive (55%), but almost half presented in or developed shock (45%) during their hospital course, despite only 36% being noted to be tachycardic. Though 7 cases did not have documented hemodynamic parameters, it is assumed that these patients did not have shock which brings the prevalence of shock in the cases described down to 28%. A new murmur was identified in half of the cases presented (50%), with 22% of patients found to be in volume overload on exam. Electrocardiogram changes were common in all patients, with ST-segment elevation and T-wave inversions occurring most frequently (50% each). Troponin elevation was noted on laboratory work-up in 100% of reported levels (83% of all patients). All cases presented displayed apical akinesis demonstrated on either echocardiography or left ventriculography. In the absence of angiographically significant coronary artery disease this would be the classic diagnostic finding of the most common subtype of takotsubo cardiomyopathy, the apical variant. This was used as the diagnostic criteria for takotsubo cardiomyopathy in the cases presented. Echocardiography revealed a reduced left ventricular ejection fraction in 82% of cases with a reported ejection fraction, whereas systolic anterior motion of the mitral valve (SAM) occurred 67% of the time and mitral regurgitation was identified in 44% of cases. All cases, but one, with documented mitral regurgitation also had SAM (88%). The majority of patients had documented elevation of the left ventricular outflow tract (LVOT) pressure gradient on echocardiography or left ventriculography (78%). Atrial fibrillation with rapid ventricular response developed in three patients (17%) during their hospital course, two of which had associated cardiogenic shock. Causality between atrial fibrillation and shock was able to be demonstrated in both cases, as the patients were hemodynamically stable prior to onset of atrial fibrillation with rapid ventricular response, and there was a lack of evidence for other sources of shock.[6,7]

Medical management was most commonly implemented, noted in 78% of cases. Thirty-nine percent of patients were managed in an intensive care unit setting with the remainder of cases managed on general medical or step-down floors, although that is not entirely clear. The most common medical management was in the form of beta-blocker therapy (72%), and 92% of patients who received beta-blockers did so via the oral, versus intravenous, route. Other common medications utilized included angiotensin converting enzyme (ACE) inhibitors (28%) and diuretics (22%). All patients presenting with hypotension/shock required brief vasopressor support (28% of all cases). Calcium channel blocker and antiarrhythmic use was not common (6% and 17%, respectively). Short-term mechanical support was rarely indicated (11% for intra-aortic balloon pump and 6% for extracorporeal membrane oxygenation). Interventional and surgical management was also rarely utilized on initial presentation, with transcatheter alcohol septal ablation and surgical septal myectomy utilized in one patient each (6% each).

Outcomes were mostly favorable, and the majority of patients improved with management as outlined above (94%) with only one death occurring (6%) due to non-cardiac causes. No mechanical cardiac complications occurred in any of the patients described. At follow-up, less than half the patients (44%) had a persistent LVOT pressure gradient either at rest or with provocation (by exercise or dobutamine), however, only a fraction of those patients were symptomatic (25%). Both symptomatic patients with a persistent LVOT pressure gradient subsequently underwent transcatheter alcohol septal ablation, with resultant improvement in pressure gradient and symptoms afterwards (Table 2). Of those with a persistent LVOT pressure gradient at follow-up, 63% had a preserved LVEF whereas the remainder of patients had no reported LVEF at follow-up.

Discussion

Our study reveals several trends and outcomes across all cited cases. Patients presenting with concomitant HOCM and TCM do not significantly differ in demographics or comorbidities compared to TCM alone, which is expected given that the acute presentation mostly pertains to TCM rather than HOCM. Medical management

Table 1
Summary of cases reporting on patients diagnosed with TCM and HOCM.

Case	Age and Gender	Past Medical History	Presenting symptoms	Physical Exam	Blood work	EKG	Coronary angiogram	Left Ventriculography	Echocardiogram findings	Course	Outcome
Akita et al.[30]	66 F	HOCM on bisoprolol and cibenzoline	Presyncope	–	–	New negative T wave in leads V1–3	–	–	SAM of the mitral valve, and increasing severity of mitral regurgitation, with left ventricular outflow tract (LVOT) gradient at 109 mmHg	Echocardiography and cardiac MRI 1 month later showed wall motion abnormality had resolved and the LVOT gradient decreased, but was still significant. NYHA III dyspnea and fatigue persisted due to an insufficient dose of bisoprolol and cibenzoline (doses could not be increased due to side effects)	Percutaneous transluminal septal myocardial ablation was performed. Repeat echocardiogram showed a post-procedural LVOT gradient of 3 mmHg. Systolic anterior motion was absent, mitral regurgitation decreased, and basal obstruction disappeared.
Arakawa et al.[16]	62 F	None	Chest pain, syncope in the setting of emotional stress	Hypotension and grade 4/6 systolic murmur at the apex	Troponin I level 1.53 ng/mL	ST-segment elevation in I, aVL and V3-V6	Normal coronaries	Akinesis of apical, anteroapical, and inferoapical walls. MR and hyperdynamic function of the basal segments of the LV. On pullback, a 50-mmHg gradient was noted	SAM; Severe MR	On day 13, dobutamine stress echo showed a dynamic LVOT gradient of 250 mmHg with a late peaking developed during stress, which was accompanied by severe MR due to SAM. Endomyocardial biopsy of the right ventricular septum showed hypertrophied and bizarre myocytes with myocyte disarray	Discharged on Bisoprolol 2.5 mg daily. NYHA Class I
Benavides et al.[31]	67 F	Asymmetric septal hypertrophic cardiomyopathy	Atypical chest pain in the setting of emotional stress	Grade 3/6 systolic ejection murmur at the left second intercostal space. S4 heart sound.	Troponin I level 1.7 ng/mL	Normal sinus rhythm with ST segment elevations in the precordial leads	Normal coronaries	Apical ballooning	Reduced left ventricular ejection fraction of 35% with anteroseptal and apical akinesis, with systolic anterior motion of the mitral valve causing a left ventricular outflow tract gradient of 35 mm Hg	Uncomplicated hospital course, discharged 3 days later	Follow-up echocardiogram 2 weeks later demonstrated an ejection fraction of 65% and systolic anterior motion of the mitral valve with no change in the previously reported left ventricular outflow tract gradient
Brabham et al.[32]	48 M	Hyperlipidemia	Persistent, sharp, left-sided chest pain, shortness of breath, and diaphoresis	Grade 2/6 systolic murmur at right upper sternal border	CKMB 6.25 ng/ml (normal ≤4.9 ng/ml) and Troponin I 1.14 ng/ml (normal ≤0.06 ng/ml)	Q waves in V1 –V2 and 1–2 mm of ST elevation in V2 –V4	Mild luminal irregularities in all coronaries	Severe hypokinesis of the apical, anterior apical, and inferior apical walls with hyperdynamic function of the base	Asymmetric septal hypertrophy. Akinesis of the distal anterior, distal septal, distal inferior, distal lateral, and apical walls.	Admitted to the cardiac ICU, uncomplicated hospital course, discharged 3 days later	Discharged on beta-blocker, angiotensin-converting enzyme inhibitor, statin, aspirin. One year later presented

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Table 1 (*Continued*)

Case	Age and Gender	Past Medical History	Presenting symptoms	Physical Exam	Blood work	EKG	Coronary angiogram	Left Ventriculography	Echocardiogram findings	Course	Outcome
									EF 43%. SAM and mid-systolic notching of the aortic valve. LVOT Doppler revealed a peak gradient of 96 mmHg, increasing to 105 mmHg with the Valsalva maneuver		with progressive exertional dyspnea, chest pain, and presyncope. Underwent alcohol ablation of the proximal septum through the first septal perforator
Daralmmori et al.[1]	70 F	Hypertension	Sudden onset shortness of breath	Normal	Troponin I increased from 2.04 ng/mL to 5.89 ng/mL (normal range 0–0.15 ng/mL)	ST-elevation in the precordial leads from V2 to V4	Mild atherosclerotic coronary artery disease, but no significant stenosis	Typical apical ballooning with a globally reduced ejection fraction estimated at 35%	LV septal wall thickness of 24 mm, and systolic anterior motion (SAM) of the anterior mitral valve leaflet. Peak systolic pressure gradient below the level of aortic valve of 20 mmHg at rest, increasing to 70 mmHg after Valsalva maneuver	Discharged on medical treatment including beta blocker, statins, and low dose aspirin	3 months later, the patient was asymptomatic whereas transthoracic echocardiography continued to show the same gradient of 50 mmHg across the LVOT
Elhosseiny et al.[28]	67 M	HOCM, hypertension, dyslipidemia, and coronary heart disease with stents in the left anterior descending artery and left circumflex. Noncompliant with home medications.	Chest pain	Harsh systolic murmur over left sternal border	Troponin 1.5 ng/mL (normal: < 0.05)	T wave inversions from V3 to V5 on admission	Non-obstructive coronary artery disease, patent stents, and an intracavitary gradient of 50 mmHg on pullback	_	Normal ejection fraction with severe hypokinesis of the apical wall. Dynamic obstruction during Valsalva in the outflow tract, peak velocity of 613 cm/s and an estimated peak gradient of 150 mmHg	Started on Metoprolol succinate daily	One month later, repeat echocardiogram showed a normal ejection fraction with a resolution of the apical hypokinesis and an exercise-induced LVOT of 80 mm Hg
Gordon et al.[33]	66 M	HOCM, hypertension	Syncope, polyuria, polydipsia, nausea	Irregularly irregular heart rate	Troponin 13.8 ng/mL	Atrial fibrillation with rapid ventricular response as well as ST elevations in leads II, III, aVF, and V3–V6	Normal coronaries	Anterolateral, apical, and inferoapical dyskinesis and basal anterior and basal inferior wall hyperkinesis; ejection fraction (EF) was 20%	Apical hypokinesis; EF was 35–40%	HgbA1c of 11.8 later revealed a new diagnosis of diabetes mellitus. DKA was controlled by day 4 of hospital stay. Atrial fibrillation was rate controlled with carvedilol and diltiazem	Repeat echocardiogram on day 5 showed documented resolution of apical ballooning. EF improved to 45%
65 F	Smoking,	hypertension	Chest tightness, shortness of breath	_	Cardiac markers cited as "positive"	T-wave inversions in leads II, III, aVF, V3-V6	Mild coronary artery disease	Asymmetric septal wall thickening, LVOT gradient 40 mmHg, SAM of mitral leaflet, severe MR	Hyperkinesis of the ventricle at the base, akinesis at the apex, severe MR and an overall picture of apical ballooning. On pullback, a gradient of	Underwent septal myomectomy	A repeat echocardiogram 5 days after the surgery documented the disappearance of the LVOT gradient and MR and a significant improvement in LV apical wall motion

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Table 1 (*Continued*)

Case	Age and Gender	Past Medical History	Presenting symptoms	Physical Exam	Blood work	EKG	Coronary angiogram	Left Ventriculography	Echocardiogram findings	Course	Outcome
									40 mmHg was noted		
Modi et al.[34]	54 F	Motor neuron disease	Chest pain, new systolic murmur and hypotension	_	Troponin T elevated at 0.37 mcg/L	Anterolateral T wave inversion	A muscle bridge in the mid-left anterior descending artery, apical ballooning and mitral incompetence. Left ventricle to aorta pullback gradient was 25 mm Hg	_	Apical left ventricular ballooning, hypercontractile basal regions and severe functional mitral regurgitation. Septal hypertrophy was noted at 1.9 cm with SAM of the MV	Due to profound hypotension, adrenaline and dobutamine were commenced and IABP inserted. MV replacement was deemed unsuitable due to her history of advanced motor neuron disease	Following withdrawal of the IABP and inotropes, hemodynamic parameters and mitral regurgitation improved significantly but she died 3 days later due to pneumonia and motor neuron disease related respiratory muscle weakness
Nalluri et al.[35]	81 F	HOCM s/p ICD placement (due to syncopal episodes), paroxysmal atrial fibrillation, pulmonary embolism, lung cancer, GI bleed	Shortness of breath at rest associated with mild substernal chest pressure and one episode of non-bloody vomiting	Bilateral rales, a harsh systolic crescendo-decrescendo murmur along the left lower sternal border, and a grade 2 lower extremity pitting edema	Troponin I 1.26 ng/mL (normal <0.05 ng/mL), CK-MB 13.3 ng/mL (normal <6.3 ng/mL), BNP 3472 pg/mL (normal <99 pg/mL)	Sinus tachycardia with intermittent ventricular pacing with new ST-T wave abnormalities in anterolateral leads	No significant CAD	_	EF of 20%–25% (significant hypokinesis of apical, apical lateral, and apical septal walls with a hyperdynamic basal inferoseptal and anterolateral walls), SAM of mitral valve causing a dynamic LVOTO (peak gradient >90 mm Hg), and severe mitral regurgitation with a posteriorly directed jet	Hospital course complicated by cardiogenic shock with worsened congestive heart failure and atrial fibrillation with rapid ventricular response. she was started on phenylephrine and amiodarone infusion	Over a period of three days, her condition improved. Weaned off the phenylephrine drip and switched to oral amiodarone. Repeat echo day 5 showed an EF 74% with mild hypokinesis of the apical and apical septal walls, and peak LVOT gradient was reduced to 22 mm Hg.
Ochiumi et al.[36]	84 F	HOCM	Chest pain	_	_	Negative T waves in leads I, aVL, and V1-V6 leads	No significant coronary stenosis	Apical ballooning with excessive contractions at the base of the heart. Left ventricular outflow pressure gradient 100 mmHg in the mid and basal portions of the left ventricle	_	_	Ten days later, follow-up echocardiography showed normalization of the wall motion abnormality and an improvement in the left ventricular outflow pressure gradient
Patrianakos et al.[37]	49 M	HOCM, alcohol abuse	Chest pain	Grade II/VI systolic murmur at the left parasternal border	Troponin I elevation 2.5 ng/ml	New ST-T segment elevation in leads V3–6	Normal coronaries	Apical ballooning with basal hyperkinesis and low ejection fraction	Asymmetric basal septal wall hypertrophy of 18 mm, LV mid-apical dyskinesia with compensatory basal hyperkinesis, SAM of the mitral valve with outflow tract, LVOT obstruction, EF 30%	Started on metoprolol 100 mg twice per day	A repeat echocardiogram after 2 days, revealed normalization of wall motion and LVEF, resolution of SAM and LVOT obstruction and reappearance of the midventricular obstruction at the level of papillary muscles with velocities up to 2.5 m/s

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Table 1 (*Continued*)

Case	Age and Gender	Past Medical History	Presenting symptoms	Physical Exam	Blood work	EKG	Coronary angiogram	Left Ventriculography	Echocardiogram findings	Course	Outcome
Roy et al.[38]	43 F	Alcohol abuse, hypertension, previous tobacco abuse	Confusion, agitation, and shortness of breath	Tachycardia, nontender hepatomegaly, and mild pitting edema in the lower extremities	Troponin T level of 0.27 ng/mL (normal, <0.03 ng/mL)	Sinus tachycardia with T-wave inversions and nonspecific ST-T–wave abnormalities in the anterolateral leads	Normal coronaries	–	EF 47% with hyperdynamic basal function. Dilated, akinetic apex that suggested an apical variant of stress-induced cardiomyopathy	On day 6, repeat echo showed minimal improvement in LVEF and no change in the apical ballooning and akinesis	Discharged from the hospital on β-blocker and angiotensin-converting enzyme (ACE) inhibitor therapy. 2 weeks later, repeat echo showed that apical wall-motion abnormalities had resolved, and the LVEF had returned to normal at 69%. Newly apparent hypertrophy of the LV myocardium at the apex, with additional involvement of the right ventricular apex, was consistent with apical-variant HCM
Roy et al.[38]	70 F	Stress-induced cardiomyopathy with subsequent resolution, mild CAD, ongoing tobacco use, hypertension, hyperlipidemia	Epigastric and chest pain that radiated to her back and jaw	Mild epigastric tenderness without guarding or rebound	Troponin T level of 0.3 ng/mL and a CKMB level of 10 ng/mL (normal, <3.8 ng/mL)	Sinus tachycardia, T-wave inversion in the anterolateral leads, and poor precordial R-wave progression	Mild, nonobstructive CAD	Apical ballooning syndrome	LVEF of 0.39 with akinesis and dilation of the mid and apical LV segments, suggesting an apical variant of takotsubo cardiomyopathy	Discharged from the hospital 5 days later on therapy with aspirin, a β-blocker, an ACE inhibitor, and a statin	One month later, repeat echo revealed an LVEF of 65% without regional wall-motion abnormalities. LV apex was thickened, with an "ace of spades" cavity configuration that suggested apical HCM
81 F	HOCM	Sudden onset shortness of breath	Stage II/VI harsh and late peaking systolic ejection murmur at the fourth left intercostal space	Troponin I 8.86 ng/mL	ST segment elevation and the disappearance of the R wave in the precordial leads	No significant CAD	–	Dyskinesis of the apical segment along with significant basal hyperkinesis with an LV ejection fraction of 50%. SAM of the mitral leaflet and mitral regurgitation. Pressure gradient at LVOT was estimated to be 107 mmHg.	Course complicated by atrial fibrillation, cardiogenic shock necessitating noradrenaline administration followed by cardioversion	She was later stabilized and started on 5 mg Bisoprolol daily. Repeat echo on day 22 showed normal LV wall motion with no apical ballooning or basal hyperkinesis. LVOT peak velocity significantly decreased as a result of the disappearance of basal hyperkinesis and SAM of the mitral leaflet, with significant improvement in MR.	
Singh et al.[25]	79 F	HOCM	Sudden onset chest pain	Apical 3/6 systolic murmur and	Troponin T 2.5 ng/mL	Anterolateral wall ischemia		Severe mitral regurgitation,	Basal hypertrophied septum,	Stabilized with oxygen,	2-month follow-up visit, the

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Table 1 (*Continued*)

Case	Age and Gender	Past Medical History	Presenting symptoms	Physical Exam	Blood work	EKG	Coronary angiogram	Left Ventriculography	Echocardiogram findings	Course	Outcome
				pulmonary edema			No obstruction of the coronary arteries	anteroapical ballooning, and basal hyperkinesis with an EF 25%	resting LVOT obstruction ~ 20 mmHg, severe mitral valve regurgitation, and apical akinesis	diuretics, and β-blockers, and she was discharged from the hospital on the 4th day	apical ballooning had completely resolved (LVEF, 0.65), and the dynamic LVOT obstruction was relatively less severe
Sossalla et al.[40]	78 F	HOCM s/p trans-coronary ablation of septal hypertrophy	Acute dyspnea and anginal chest pain	–	Elevated Troponin (level not specified)	–	No obstruction of the coronary arteries	Apical ballooning with septal hyperkinesis	Sever mitral regurgitation, systolic anterior motion of the mitral valve, and LVOT obstruction with a peak gradient of 120 mmHg	Severe refractory cardiogenic shock with renal and hepatic failure prompting urgent VA-ECMO with an inability to be weaned off, requiring bail-out trans-coronary alcohol ablation of septal hypertrophy; VA-ECMO weaned off 1 day after septal ablation and she was discharged on guideline-recommended medications for systolic heart failure	Follow-up at 8 weeks revealed no limiting heart failure symptoms and a good quality of life; Echo showed an EF of 55% with mild-moderate mitral regurgitation and no significant LVOT gradient
Vassiliou et al.[24]	63 F	None	Acute chest pain	Ejection systolic murmur at the left parasternal border	_	Anterior precordial lead ST-segment elevation	Normal coronaries	Basal hyperkinesis with apical akinesis consistent with takotsubo cardiomyopathy and moderate mitral regurgitation	LVOT obstruction due to systolic anterior motion of the mitral valve and moderate mitral regurgitation	Pulmonary edema and incipient cardiogenic shock, which responded to treatment with a combination of intravenous diuretics and intravenous esmolol	3 months later, ECG changes resolved and an MRI scan showed LV function had normalized. Continued evidence of significant left ventricular hypertrophy and dynamic obstruction following low-dose dobutamine, consistent with hypertrophic cardiomyopathy

Table 2
Grouped characteristics and outcomes identified across cases.

N = 18 cases; mean age: 66.2 years; males 22.2%, females 77.8%	*N* (%)
Comorbidities	
Hypertrophic Obstructive Cardiomyopathy	10 (56)
Hypertension	6 (33)
Hyperlipidemia	3 (17)
Coronary artery disease	2 (11)
Home medication [4 cases with no report of home medication)	
Beta-blocker	7 (39); 2 non-compliant
Calcium channel blocker	1 (6)
Cibenzoline	2 (11)
Presenting symptoms	
Chest pain	13 (72)
Shortness of breath/dyspnea	7 (39)
Hemodynamic status (7 cases without documented vital signs)	
Tachycardia	4 (22)
Hypotension/Shock	5 (28)
Exam findings (5 cases without documented physical exam)	
Murmur	9 (50)
Volume overload	4 (22)
Troponin elevation	15 (83) [3 remaining cases with no report of troponin levels]
EKG changes (1 case without reported EKG findings)	
ST elevations	9 (50)
T-wave inversion	9 (50)
Non-specific EKG changes	1 (6)
Coronary angiogram	17 (94)
LV ventriculogram	14 (78) [3 cases with no report on LV ventriculogram]
Systolic anterior motion of mitral valve on echocardiogram	12 (67) [1 case with no echocardiogram findings reported)
Mitral regurgitation on echocardiogram	8 (44)
Reduced ejection fraction on echocardiogram or LV ventriculogram	9 (50) [7 cases with no comment on EF; including the case without an echocardiogram report]
Elevated rest or provoked LV outflow tract gradient on echocardiogram or LV ventriculogram	14 (78)
Medical management [2 cases without reported management]	
Beta-blocker	13 (72) [12 oral and 2 intravenous]
Calcium channel blocker	1 (6)
Angiotensin converting enzyme inhibitor	5 (28)
Diuretic	4 (22)
Antiarrhythmics (Amiodarone, Cibenzoline)	3 (17)
vasopressors	5 (28)
In-patient mechanical support	
Intra-aortic balloon pump (IABP)	2 (11)
Extra-Corporeal Membrane Oxygenation (ECMO-VA)	1 (6)
Transcatheter alcohol IV septal ablation	1 (6)
Surgical IV septal myectomy	1 (6)
Death	1 (6)

with beta-blocker therapy was most common, with other interventional/surgical procedures a rarity. While guidelines in managing these cases are nonexistent and management may be challenging, outcomes appear favorable with only a single identified death in our review.

Hypertrophic cardiomyopathy is a hereditary disease of heart muscle cells, and is by far the most common genetic cardiomyopathy, or heart muscle disease. First described in the medical literature as far back as 1868 by Vulpian, its current nomenclature only emerged in the mid 1900s after English pathologist Robert Donald Teare reported autopsy findings of 8 patients with asymmetric cardiac hypertrophy in 1957.[6] HOCM is known to result in LVOT obstruction in the setting of reduced cardiac preload and/or tachycardia, predisposing to cardiogenic shock and sudden death. This classically is presented as a case of sudden death in an athlete during strenuous physical exertion. Though generally thought of as a cardiomyopathy of the young, HOCM may be asymptomatic for decades, with the initial diagnosis occurring during middle age or beyond.[7–9] Diagnosis is usually achieved using Doppler echocardiography, although rarely more advanced diagnostic studies such as cardiac MRI are needed. Management comprises avoidance of preload reduction, implantation of automated cardiac defibrillators in certain settings, septal ablation therapy or myectomy, and ultimately cardiac transplantation.[7,10]

Takotsubo cardiomyopathy, on the other hand, is an acquired condition affecting heart musculature as a result of stress.[11] Since its first description in Japan, TCM has been increasingly recognized, in large part due to more readily available cardiac catheterization as well as a better definition of the syndrome in the literature. Its pathogenesis remains unclear despite multiple proposed theories including, but not limited to, catecholamine surge, LVOT obstruction with compensatory basal hyperkinesia, impaired coronary microcirculation, and multivessel coronary spasm.[11] Diagnosis requires ruling out obstructive coronary artery disease followed by utilizing cardioprotective medications for management pending resolution of myocardial dysfunction over time as the disease follows its natural course, generally to complete resolution within 8 weeks.

Presenting features

In the reported cases, the presenting symptoms of TCM in patients with underlying HOCM was not different from that in patients without HOCM. The concurrent presence of both entities can lead to angina, low cardiac output, shortness of breath, syncope, and exertional dyspnea. In our study, 72% and 39% presented with chest pain and shortness of breath respectively, with pre-syncope/syncope also described in 11%. LVOT obstruction is commonly reported in 10–33% of patients presenting with TCM, with rates as high as 50% previously

reported.[12-19] In HOCM, LVOT obstruction is more prevalent, with 33% of patients reported to have LVOT obstruction at rest and another 33% with physiological provocation, such as with exercise.[20] Interestingly, our findings showed an elevated LVOT gradient in 78% of patients, a more pronounced rate compared to either as a stand-alone entity. This is also important to consider when viewing rates of persistent LVOT obstruction at follow-up. Additionally, our review showed an incidence of cardiogenic shock in 28% of patients as compared to less than 10% in patients with TCM alone.[21] From this we can infer that hypotension and shock are likely to occur more frequently with both entities than in those with TCM alone. We hypothesize that this is potentially related to the increased rates of LVOT obstruction, though this statement cannot be made conclusively in the absence of an analysis to confirm it. Although TCM may sometimes mask underlying HOCM, given discovery of HOCM in some cases described here occurred only after resolution of TCM, a patient presenting with TCM and cardiogenic shock should raise suspicion for an underlying HOCM.

Management

The management of both entities together can be challenging. Patients presenting with TCM are commonly managed similarly to patients in acute decompensated heart failure. Diagnosis comprises ruling out acute coronary syndrome via diagnostic cardiac catheterization [29850871], with management focusing on cardiac protective therapy using negative inotropy with beta-blockers, vasodilators, diuretics and vasopressor agents when shock ensues.[3] However, the presence of concomitant HOCM and TCM may render such therapeutic strategies contraindicated. Careful phenotype profiling and continuous monitoring are warranted in such rare cases. Treatment primarily revolves around resolution of the LVOT obstruction, which is commonly achieved with supportive care and the use of beta-blockers and fluid resuscitation. Unlike hypotension related to LV dysfunction, care must be taken not to use inotropic agents in the treatment of hypotension/shock related to LVOT obstruction given the likely dynamic nature of the obstruction and decreased ventricular filling with beta-receptor agonism will decrease left ventricular diameter and worsen the degree of obstruction.[15,22] If severe LVOT obstruction and hypotension preclude the use of beta blocker therapy, alpha-receptor agonists may be used with caution. Pure alpha -receptor agonists like phenylephrine may reduce the LVOT gradient by increasing afterload and improving hemodynamics. Beta-blockers can later be slowly added to reduce inotropy and basal hyperkinesis as patients enter the recovery phase. The optimal use of vasopressor agents is speculative and based solely on our understanding of the pathophysiology of HOCM and TCM as stand-alone entities, hence a recommendation regarding optimal vasopressor therapy cannot be made conclusively, but alpha-receptor agonists might be the preferential agents for the reasons outlined above.

Antiarrhythmics routinely used to manage HOCM patients in the outpatient setting, such as cibenzoline,[23] do not appear to serve an important role in the acute in-patient management of the patients described. However, management of arrhythmias (particularly atrial fibrillation with rapid ventricular response) is beneficial, be it using a rate-control or a rhythm-control strategy.[20] Patients with volume overload should undergo diuresis slowly and cautiously to avoid precipitation of LVOT obstruction which could result in obstructive cardiogenic shock. Intravenous fluid resuscitation may be warranted in patients not in volume overload on initial presentation and may serve to prevent or slow down progressive worsening of LVOT obstruction, particularly in those with borderline low blood pressures. Given the increased risk of complications that can be seen in this patient population, most notably cardiogenic shock, it is prudent to have the cardiology service involved as soon as coexisting HOCM and TCM is identified. Management on a cardiac step-down floor or in an intensive care setting may also prove beneficial. In the cases reviewed, only 20% of patients in cardiogenic shock requiring vasopressor support received an alpha-selective agent, while 60% received agents that synergize both alpha- and beta-adrenergic receptors and 20% received non-adrenergic vasopressors with action primarily on the peripheral vasculature (vasopressin). Most patients described did not present in volume overload. In patients receiving diuresis, most tolerated it well, however, diuresis might have predisposed the patient described by Daralammori et al. to develop an elevated pressure gradient across the LVOT.[1]

The features of TCM are expected to be reversed with time and appropriate medical therapy. As such, continued surveillance with echocardiography may be necessary to monitor disease progression. If symptoms are not adequately controlled, follow-up with structural cardiology specialists may be warranted to determine if any procedure for HOCM may be necessary to further lower the LVOT gradient and relieve symptoms. Outcomes appear favorable when managing this rare occurrence. Only 1 non-cardiac death was described in the cases we report. Most patients had favorable outcomes at follow-up as well, as evidenced by the lack of persistent LVOT PG on follow-up in more than half of all cases, per results from rest or stress echocardiography in most instances. Time to resolution of LVOT PG is uncertain given the great variability in follow-up intervals in the cases described, although most follow-up was commonly performed within 4 weeks of discharge. Additionally, of those with persistent LVOT PG at follow-up (44%) only 25% were symptomatic and required definitive invasive management of HOCM. Interestingly, of the patients with a new diagnosis of HOCM at the time of hospitalization, 38% had an elevated LVOT PG at follow-up. Given the fact that those with a new diagnosis of HOCM were asymptomatic previously likely due to a normal LVOT PG, it would be expected that their PG normalizes after resolution of the acute TCM. Persistence of elevated PG after TCM resolution in HOCM patients who were previously asymptomatic poses the question of whether a history of TCM increases the risk of developing a newly elevated LVOT PG in HOCM patients, even after resolution of TCM (Fig. 2 represents a proposed management algorithm for patients diagnosed with TCM and HOCM).

Coincidence or causality?

Whether patients with known HOCM have a predisposition to TCM is currently unclear. Several potential mechanisms may relate the two entities. A catecholamine surge may result in increased wall stress and exacerbate resting LVOT gradient, resulting in increased intraventricular pressure, apical wall stress and subendocardial ischemia, leading to the phenomenon of TCM.[24] Additionally, baseline decreased coronary reserve and systolic coronary squeezing in HOCM may predispose to wall-motion abnormalities in the setting of increased wall stress related to a sympathetic surge.[25-27] Trigger identification in the cases we present revealed that 61% of cases described had a known preceding physical or psychosocial trigger, which is similar to the frequency of identified preceding trigger in TCM alone (about 70%). In cases without a reported trigger however, it is possible that TCM occurred in the setting of worsening LVOT obstruction secondary to HOCM, particularly as evidenced by the case described by Elhosseiny et al. who reports TCM occurring in a patient with HOCM after exercise in the setting of medication non-compliance.[28]

A statement regarding whether or not developing TCM worsens underlying HOCM-associated LVOT obstruction/gradient cannot be conclusively made either using the data provided. Although it is possible that developing TCM might have predisposed HOCM patients to developing a new or worsening elevated LVOT PG, this conclusion is speculative at this point given lack of pre-hospitalization LVOT PG for most patients precluding a more certain statement regarding this. The theory is that the previously undiagnosed HOCM patients likely

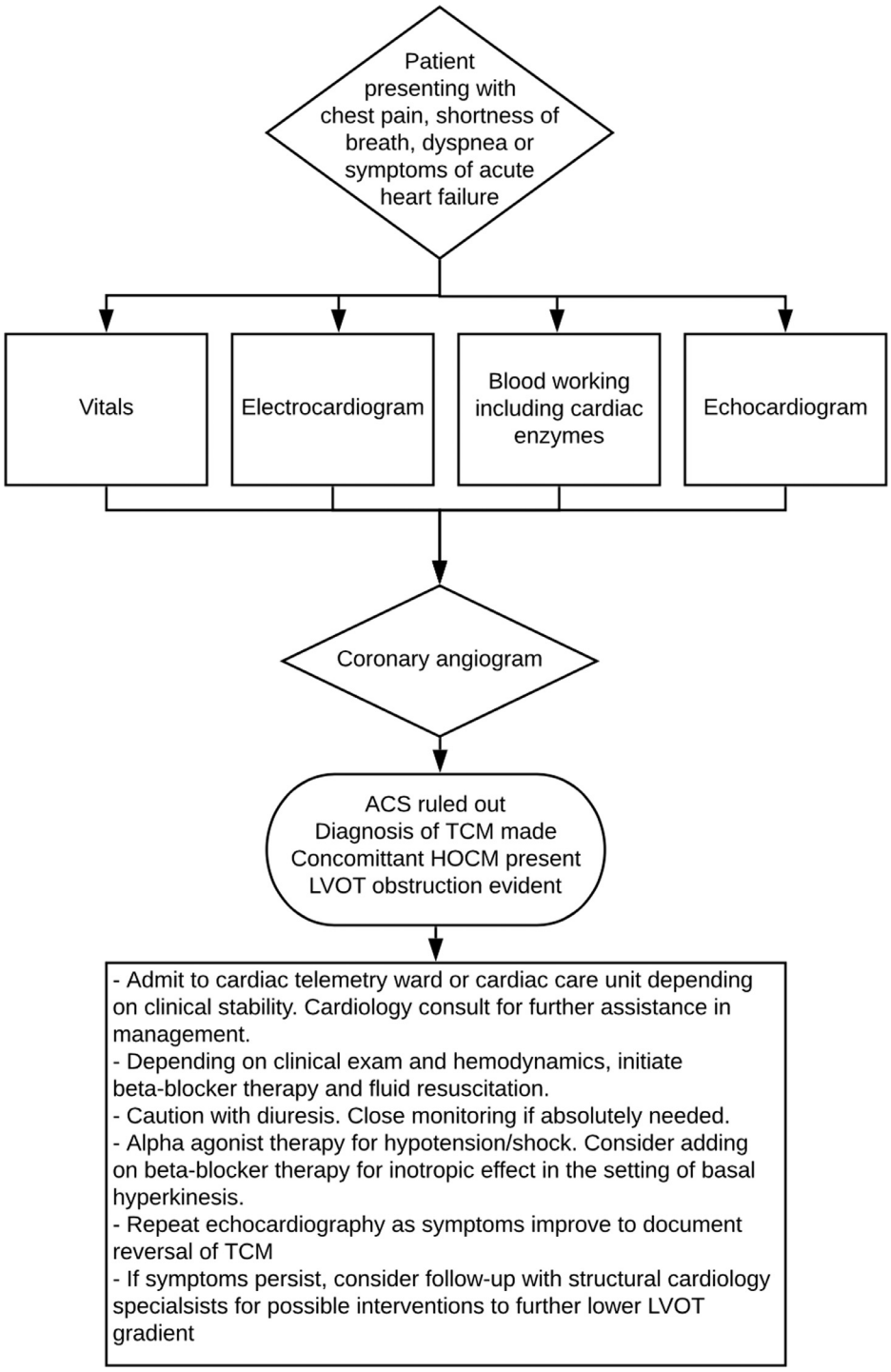

Fig. 2. Management algorithm for patients diagnosed with TCM and HOCM.

had a normal LVOT PG prior to hospitalization with HOCM given likely lack of symptoms, meaning that the 44% of them who had persistently elevated LVOT PG at follow-up likely had that as a new finding following TCM onset and resolution.

Limitations

The utilization of case reports imparts a potential selection bias of rather unusual and unique presentations of concomitant HOCM and TCM. The true prevalence of this entity is unknown and difficult to deduce solely from reported cases. More stable patients are less likely to be reported on and outcomes are possibly more favorable with fewer complications. Additionally, there is a high likelihood of missing the diagnosis of underlying HOCM in more stable patients, which might only be diagnosed at a later date after resolution of TCM and the acute presentation. Alternatively, it is equally possible that severe cases of coexisting HOCM and TCM might have been missed if those cases progressed to demise rapidly, prior to adequate diagnostic work-up. Furthermore, the variability in data reporting coupled with the small sample size made it not feasible to run an analysis on the data for identification of patterns or associations with important outcomes such as shock development and persistence of LVOT

obstruction at follow-up. Additional limitations included lack in uniformity of follow-up intervals, as well as inconsistencies in the testing performed at follow-up. Time to recovery is also difficult to gauge given the variability in follow-up intervals.

Conclusion

With advanced cardiovascular testing becoming more readily available, the prevalence of both HOCM and TCM is likely to continue to rise. Currently there exists no guidelines or data to guide the management of these cardiomyopathies when they coexist, posing a challenge to physicians. Since the first case describing both entities occurring together was reported in 2006,[29] numerous other cases have been reported. From the available reported cases, certain trends and management options can be deduced. Although the patients described in our study share similar characteristics with those presenting in TCM without underlying HOCM, they have a higher potential for decompensation. Presenting features are primarily chest pain and shortness of breath, secondary to the symptoms of TCM. Patients with underlying HOCM presenting with TCM had a higher prevalence of LVOT obstruction compared to either entity alone. Additionally, these patients were at a higher risk of developing cardiogenic shock as compared to those in TCM without underlying HOCM. Care should be taken in managing such patients with a potential for rapid decompensation of their hemodynamic parameters in the setting of slight changes in preload and/or afterload. Volume status should be monitored closely, and diuresis in the setting of volume overload should be undertaken cautiously, preferably under step-down or critical care level surveillance. Beta-blockade remains the cornerstone of medical management in this patient population, with cardiogenic shock preferentially managed using alpha-adrenoceptor agonism in an attempt at increasing afterload and reducing LVOT gradient, and as a result, LVOT obstruction. Similarly, intravenous fluid resuscitation may be warranted in patients not in volume overload, serving to reduce LVOT obstruction. Further prospective studies are needed to establish safe management guidelines in dealing with this rare and challenging presentation.

Declaration of Competing Interest

None.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Informed consent was not required as the study contains deidentified patient data, individual participants were not contacted and no intervention was performed

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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