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Takotsubo Cardiomyopathy and Left Ventricular Outflow Tract Obstruction

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Takotsubo cardiomyopathy often presents to the cardiac catheterization laboratory masquerading as acute ST-elevation myocardial infarction (STEMI). Some of these patients present in shock secondary to dynamic left ventricular outflow tract (LVOT) obstruction. The typical patient is an elderly, hypertensive female with sigmoid deformity of the intraventricular septum. The management of hemodynamic instability in these patients is different from patients with STEMI. While hemodynamic instability in the setting of STEMI is usually treated with inotropic agents and intraaortic balloon counterpulsation, these therapies can increase LVOT pressure gradients in patients with takotsubo cardiomyopathy and lead to deepening of shock and worse outcomes. Thus accurate diagnosis and correct management are essential to prevent mortality in these patients, who will usually go on to have good long-term outcomes. This case report and literature review addresses the clinical characteristics, outcome, and management of these patients. (J Interven Cardiol 2009;22:444–452)

Case Presentation

An 82-year-old female without known history of coronary artery disease was admitted to hospital with a small bowel obstruction. She underwent laparotomy for lysis of adhesions and appeared to be recovering well. On the 7th postoperative day, she was noted to have a relative tachycardia (100 beats/minute) and hypotension (100 mmHg systolic) that were higher and lower respectively than over the previous several days. The patient was asymptomatic but an electrocardiogram (ECG) (Fig. 1) demonstrated marked ST-segment elevation in the anterior leads. She was transferred for emergency cardiac catheterization that showed minor irregularities of the left anterior descending artery but no evidence of obstructive coronary disease. Epicardial coronary blood flow was angiographically normal (TIMI grade 3). Her systemic blood pressure during the procedure was only 75 mmHg systolic. The intraarterial pressure tracing showed a "spike and dome" pattern (Fig. 2). A pigtail catheter introduced retrograde into the left ventricle showed an intraventricular systolic pressure of approximately 135–145 mmHg. Pullback of the catheter across the left ventricular outflow tract (LVOT) and aortic valve demonstrated a gradient approaching 70 mmHg (Fig. 2). Contrast ventriculogram showed apical ballooning (Fig. 3) with hyperdynamic function of the basal constrictors. There was also dramatic and angiographically evident systolic obstruction of the LVOT. Left ventricular (LV) end diastolic pressure was 25–30 mmHg. Intravenous administration of 5 mg metoprolol resulted in a rise in systolic blood pressure to approximately 100 mgHg and reduced the outflow tract gradient to around 50 mmHg. An echocardiogram performed in the cath lab showed a sigmoid septum with basal septal hypertrophy and obvious systolic anterior motion (SAM) of the mitral valve with outflow tract obstruction (Fig. 4). The echo-derived outflow tract gradient (obtained after metoprolol administration) was approximately 40 mmHg. The patient's subsequent

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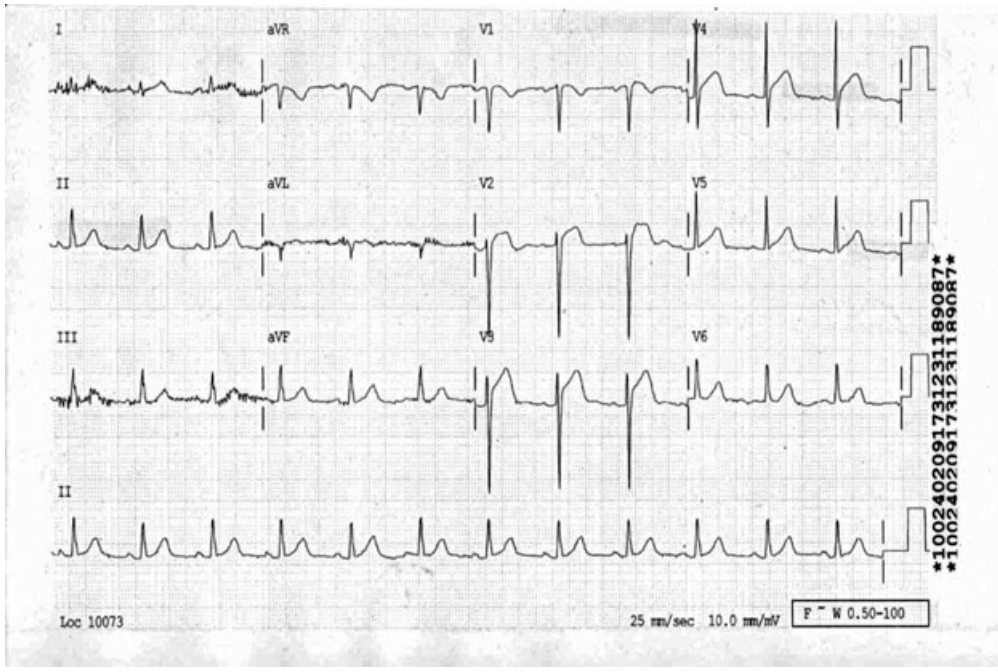

Figure 1. Twelve-lead electrocardiogram (ECG) at presentation. Note marked ST-elevation in anterior precordial leads.

course was uneventful. Oral metoprolol was initiated. A repeat echocardiogram 3 days later showed apical hypokinesis but essentially no outflow tract gradient.

Discussion

Takotsubo cardiomyopathy, also called ampullary cardiomyopathy and apical ballooning syndrome, is

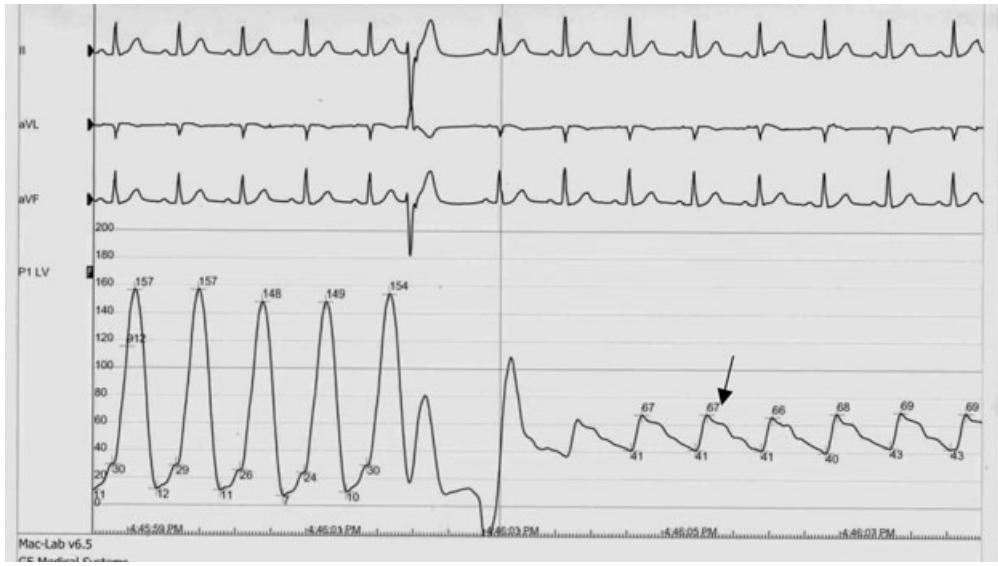

Figure 2. Hemodynamic tracing-pullback of pigtail catheter from the left ventricle to aorta. Note gradient of around 70 mmHg on pullback from left ventricle to aorta. Arrow shows bifid aortic waveform ("spike and dome") characteristic of dynamic LVOT obstruction.

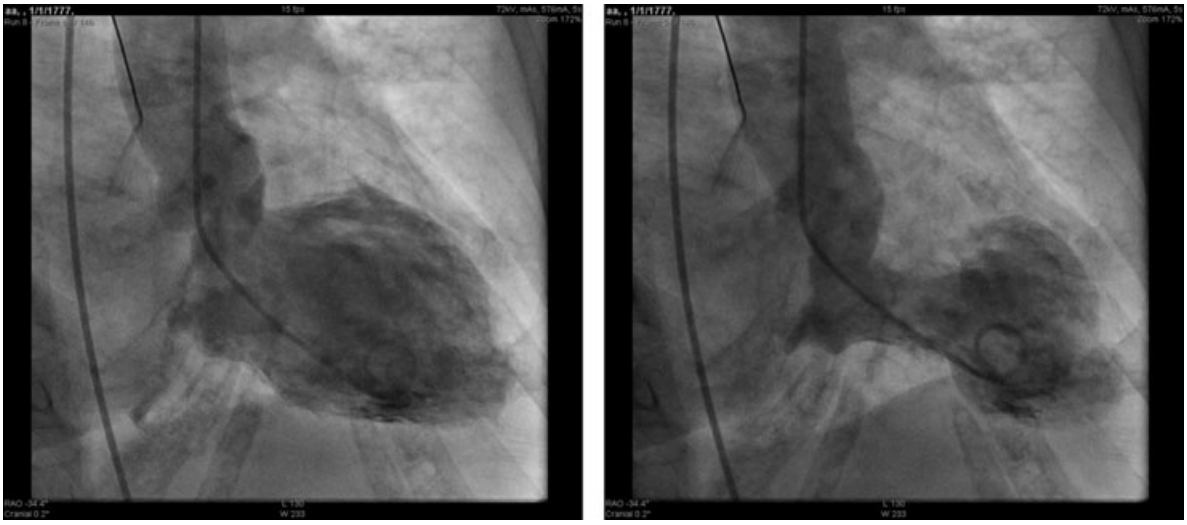

Figure 3. Contrast left ventriculogram. Left panel in diastole; right panel in systole. Note prominent apical ballooning and hyperdynamic contraction of basal segments.

observed in 0.7–2.5% of patients with suspected acute coronary syndrome (ACS).[1,2] The following clinical characteristics were summarized in a recent systematic review of 28 published case series:[3] A majority of cases were described in women (91%) with a mean age ranging from 62 to 76 years. It most commonly presents with chest pain (84%) and dyspnea (20%) following an emotionally or physically stressful event in about two-thirds of patients. ECG on admission shows ST-segment elevation in 71% and is accompanied by usually mild elevations of cardiac-specific troponin in 85%. Despite dramatic clinical presentation and substantial risk of heart failure, cardiogenic shock, and arrhythmias, the long-term prognosis is usually good. Most patients have resolution of LV dysfunction. The in-hospital mortality rate is said to be approximately 2%, and over 95% of patients experience full recovery. The underlying etiology is thought to be based on an exaggerated sympathetic stimulation.

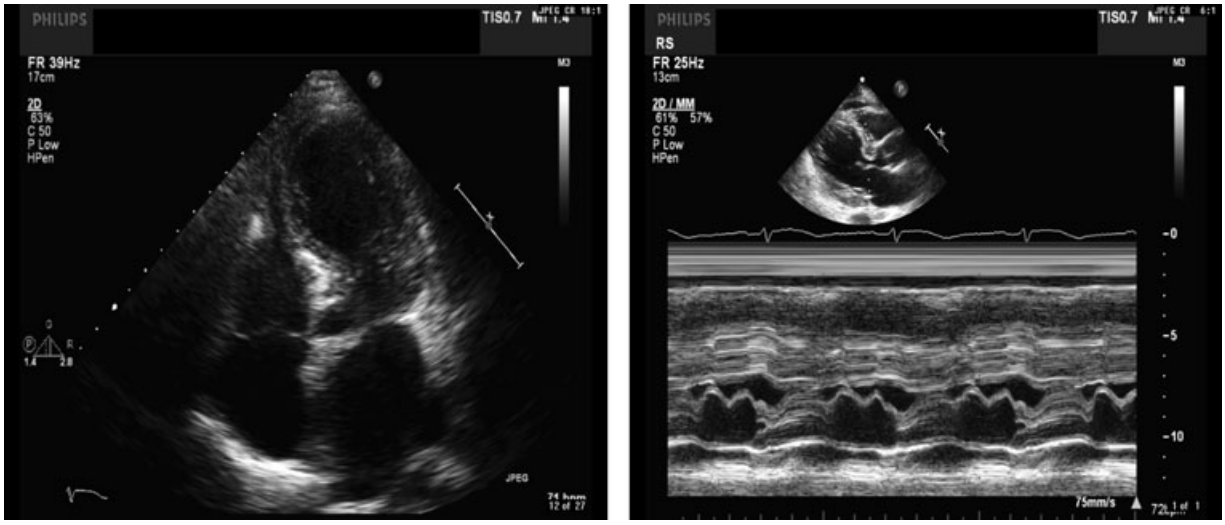

Figure 4. Two-dimensional echo (left panel) and M-mode echo (right panel) at presentation. Note apical ballooning on two-dimensional echo with almost complete apposition of basal segments. M-mode shows severe systolic anterior motion (SAM) of the anterior mitral leaflet (arrow).

LVOT Obstruction in Takotsubo Cardiomyopathy

Prevalence. A transient, dynamic intraventricular pressure gradient due to obstruction in the LV cavity can develop as a result of dyskinetic apical and midventricular segments with hyperdynamic function of the basal segments. A two-center retrospective survey found evidence of significant dynamic LVOT obstruction in 8/32 (25%) consecutive patients diagnosed with takotsubo cardiomyopathy over a 6-year period.[4] Two systematic reviews of takotsubo patients found this complication in 20/180 (11%)[5] and 21/133 (15.8%).[2]

Etiology. Villareal et al.[6] observed LVOT obstruction in three patients with a stress-induced cardiomyopathy. They hypothesized that patients with a sigmoid interventricular septum, small LVOT, and reduced LV volumes (primarily elderly women) and an abnormal orientation of a slack mitral apparatus have a geometrical predisposition to dynamic LVOT obstruction, which may manifest in the setting of intense adrenergic stimulation or hypovolaemia. Indeed, Merli et al.[7] studied four patients with the clinical features typical of takotsubo cardiomyopathy. In all four cases they documented: (1) a physical stress trigger, (2) the presence of abnormal mid-LV septal hypertrophy (mean 1.3 cm in end-diastole), (3) the presence of an important dynamic intracavity LV obstruction at the onset of symptoms, (4) a low-dose strain/strain rate dobutamine stress echo confirming that the distal ischemic substrate was myocardial stunning, and (5) a finding that an important intracavity LV dynamic obstruction could still be induced during a low-dose dobutamine challenge at follow-up when the functional features of the syndrome had resolved, thus indicating that these ventricles had the predisposition to develop midcavity obstruction if appropriately challenged. In fact, Villareal et al.[6] and Merli et al.[7] proposed that LVOT obstruction could be a major factor in the development of takotsubo cardiomyopathy. The hypothesis is that intense catecholaminergic stimulation leads to hypercontractile basal segment that increases the intraventricular pressure gradient leading to LVOT obstruction. This in turn would increases wall stress and cause hypoperfusion of the apex causing a state of oxygen mismatch and subendocardial ischemia resulting in apical ballooning. Moreover, it is also worth noting that the LV apex consists of only two (instead of three) layers of myofibers and, therefore, when severe hypoperfusion occurs, can more readily lose its elasticity after an abnormal expansion. This hypothesis may explain the female preponderance in the patients presenting with this syndrome. However, given that a majority of patients presenting with this syndrome are not reported to have significant LVOT obstruction, this mechanism is probably not a prerequisite in most patients but may rather play a contributory part in some.[1]

Clinical Characteristics. In the only series of takotsubo patients that studied specifically LVOT obstruction,[4] patients presenting with takotsubo cardiomyopathy and LVOT obstruction were older ($n = 8$, mean age 81 ± 4 years) than patients without LVOT obstruction ($n = 24$, mean age 68 ± 13). No patient had a familial history of hypertrophic cardiomyopathy. At admission, mean New York Heart Association functional class was significantly higher in the case of LVOT obstruction (1.8 ± 0.9 vs. 1.1 ± 0.1). Among patients with LVOT obstruction, mean dynamic intraventricular pressure gradient detected by echocardiography was 34 ± 16 mmHg (range 21–60 mm Hg). All patients with a gradient had SAM of the mitral valve associated with septal bulge and mitral regurgitation (mean degree of mitral regurgitation was 2.1 ± 0.7 vs. 0.9 ± 0.7 in patients without LVOT). At day 7, echocardiography did not reveal any residual dynamic intraventricular pressure gradient. Similarly, mean degree of mitral regurgitation significantly decreased at day 7, compared to baseline (1 ± 0.8).

By and large, the clinical characteristics described in El Mahmoud's[4] series is reflected in the collection of cases collected from the published literature (Table 1). The age range of patients presenting with LVOT obstruction is 61–89 years. Almost all cases reported in the literature were female. Only one patient had a history of hypertrophic cardiomyopathy (Table 1). While not all cases reported on the presence of SAM and mitral regurgitation, a significant number of cases presented with SAM and at least moderate mitral regurgitation. LVOT gradients ranged from 20 mmHg to 100 mmHg and LV ejection fraction ranged from 25% to 41%. In conclusion, based on the available data on patients presenting with this complication, the typical patient is an older hypertensive female with sigmoid deformity of the intraventricular septum, may present with hypotension or shock, and typically has at least some degree of SAM and mitral regurgitation.

Table 1. List of Published Cases of Takotsubo Cardiomyopathy with Left Ventricular Outflow Tract Obstruction Extracted from Case Reports or Case Series

Source	Country	LVOT Obstruction/ Whole Cohort	Women/ Whole Cohort	Mean Age	Cardiogenic Shock/ IABP/ Inotrope Support	LVEF on Initial Presentation (%)	Transient Dynamic Intraventricular Gradient Range (mmHg)	MR/SAM	Outcome
Tsuchihashi[14]	Japan	12/88	76/88	67 (whole cohort)	NA	41% (whole cohort)	30	NA	No residual gradient on follow-up (13–53 days).
El Mahmoud[4]	France	8/22	8	81	2/8 cardiogenic shock	41%	21–60	MR/SAM	LV function significantly improved on follow-up echo (7, 31, and 365 days) without LVOT gradient after 7 days.
Parodi[15]	Italy	5/68	5	74 (whole cohort)	NA	33% (whole cohort)	43–100	All patients with mod–severe MR/SAM	Patients with MR had significantly more depressed left ventricular ejection fraction on admission and slower normalization. Only three patients showed no early improvement in mitral regurgitation severity; two of these died while in the hospital. At discharge, no patient had evidence of residual LVOT obstruction caused by systolic anterior motion.
Sharkey[16]	US	5/22	5	75	2/5 IABP + 5/5 IV dobutamine	29%	25–100	SAM	Gradients resolved after cessation of dobutamine. LV systolic dysfunction and wall-motion abnormalities reversed rapidly, returning to normal range during the recovery 24–29 days after admission. Good clinical outcome out to 12 ± 11 months.
Merli[7]	UK	4	4	73	NA	NA	63–80 (midventricular septal thickening noted in all cases)	NA	Gradient <10 mmHg on day 20 but all gradients were induced with infusion of IV dobutamine on day 20.
Pillière[17]	France	3/12	3	65 (whole cohort)	NA	44%	NA	NA	All patients recovered from wall motion abnormalities, and left ventricular ejection fractions rapidly at 1 month and 1 year.

Continued.

Table 1. Continued.

Source	Country	LVOT Obstruction/ Whole Cohort	Women/ Whole Cohort	Mean Age	Cardiogenic Shock/ IABP/ Inotrope Support	LVEF on Initial Presentation (%)	Transient Dynamic Intraventricular Gradient Range (mmHg)	MR/SAM	Outcome
Rosenmann[18]	Israel	3/5	2/3	61	NA	NA	70–100	Severe MR/SAM1 HOCM	At discharge four patients had normal LV function and one was mildly impaired with no LVOT gradient.
Villareal[6]	US	3	3	69	1/3 IABP + dobutamine	NA	40–64	3/3 SAM + 1/3 severe MR	Beta blocker treatment resulted in resolution of the gradient and clinical improvement. 30-day follow-up echo showed normalization of ventricular function and gradient.
Bybee[19]	US	2/16	2	84	NA	39% (whole cohort)	NA	NA	Entire series alive median 5.5 months follow-up.
Elian[20]	Israel	2/13	12/13	68 (whole cohort)	IABP	32% (sigmoid septum was found in all but one of the patients)	30	NA	One patient died of cardiogenic shock during hospitalization. Mean follow-up of 16 months showed normal LVEF in all patients but one, in whom LVEF increased from 30% to 45%.
Desmet[13]	Belgium	2/13	2	66	2/2 IABP	NA	79–90	NA	Outcome in one patient was good. The other underwent mitral valve replacement 7 months after presentation due to symptomatic MR with LVOT obstruction caused by SAM in the absence of significant septal hypertrophy.
Kyuma[8]	Japan	2/3	3	69	Hypotension	36%	45–140	No MR or SAM	Intravenous propranolol decreased the intraventricular gradient significantly. Normal LV function within 2 months.
Brunetti[21]	Italy	2/2	2	78	1/2 IABP + inotropes	25%	60–63	Mod-severe MR/SAM	Good clinical outcome with normalization of LVEF, SAM, and MR within 1 month.
Kurisu[22]	Japan	1	1	78	Transient biventricular dysfunction	44%	60 (LV) 28 mmHg on right ventricular pullback	Mod MR/SAM	Follow-up cardiac catheterization after 16 days showed normal wall motion with no pressure gradients. Dobutamine stress caused a pressure gradient of 60 mmHg between the left ventricular apex and the aorta.

Continued.

Table 1. Continued.

Source	Country	LVOT Obstruction/ Whole Cohort	Women/ Whole Cohort	Mean Age	Cardiogenic Shock/ IABP/ Inotrope Support	LVEF on Initial Presentation (%)	Transient Dynamic Intraventricular Gradient Range (mmHg)	MR/SAM	Outcome
Chandrasegaram[12]	Australia	1	1	65	Shock unresponsive to IABP	NA	60–70	Severe MR/SAM	Underwent mitral valve replacement with St. Jude mechanical prosthesis. Postoperatively there was no LVOT obstruction. LVEF was within normal limits by the 10th postoperative day.
Ohba[23]	Japan	1	1	89	Hypotensive	NA	60	Severe MR/SAM	Beta blockers readily abolished LVOT obstruction. Left ventriculography performed on the 20th day showed normal wall motion without intraventricular pressure gradient and MR.
Ionescu[24]	UK	1	1	65	Cardiogenic shock	NA	>60	Mod MR/SAM	Repeat echo 2 days later showed marked improvement of subaortic obstruction and the disappearance of MR. Three months later LVEF was normal without SAM or MR.
Matsuoka[25]	Japan	1	1	86	Cardiogenic shock unresponsive to catechola-mines.	NA	60	NA	On day 3, sudden death occurred during defecation with ventricular fibrillation. The administration of catecholamine for shock probably exacerbated the pressure gradient in the left ventricle resulting in intractable ventricular fibrillation.
Kurisu[26]	Japan	1	1	85	No	NA	64 mmHg only in the beat after the PVC	Mod MR/SAM	After 1 week, follow-up echo showed normal wall motion.
Lalonde[27]	Canada	1	1	48	IABP + IV dobutamine	35–40%	40	Severe MR/SAM	Dobutamine was replaced with noradrenaline and patient improved hemodynamically. Repeat echo on day 8 revealed normal LV function with no LVOT obstruction.
Caselli[28]	Italy	1	1	60	NA	30%	65	SAM	LVEF normalized within 2 weeks.
Metzel[29]	US	1	1	71	IV dobutamine	35%	45	SAM	Intraventricular gradient improved once dobutamine was stopped. LVEF normalized within 6 weeks.

LVOT = left ventricular outflow tract; IABP = intraaortic balloon pump; MR/SAM = mitral regurgitation/systolic anterior motion; IV = intravenous.

Management and Outcome

Patients with takotsubo cardiomyopathy who develop hypotension must be evaluated for a dynamic intraventricular pressure gradient in the LV cavity and LVOT, as the treatment of this complication is different from that in other patients with cardiogenic shock. Echocardiography or left heart catheterization can be used for this evaluation. Dynamic intraventricular obstruction in patients with this syndrome is managed by fluid resuscitation and administration of beta blockers to increase LV end-diastolic volume and diastolic ventricular filling time respectively.[8] Beta blockers can and should be used in patients with cardiogenic shock due to LVOT obstruction.[9] α_1-agonists (phenylephrine) can be used to support blood pressure by increasing afterload with subsequent reduction of the intraventricular gradient (as has been described with acute myocardial infarction).[10] Dynamic LVOT obstruction can lead to significant hemodynamic compromise. Failure to recognize LVOT obstruction as being responsible for this can lead to erroneous therapies, such as initiation of vasoactive amines and insertion of intraaortic balloon counterpulsation device, both of which can lead to worsening of intraventricular gradient and hypotension.[11]

Outcome of patients presenting with LVOT seems favorable and does not seem to be worse than other patients with takotsubo cardiomyopathy. Of the 65 patients we identified in the English literature, only two died. Almost all patients had complete recovery of LV function and abolition of the LVOT gradient on follow-up echocardiogram or left heart catheterization (Table 1). In one reported case, despite maximal medical therapy including intraaortic balloon pump placement, SAM with severe mitral regurgitation persisted eventually requiring mitral valve replacement.[12] One other patient underwent mitral valve replacement 7 months after the episode due to mitral regurgitation and SAM in the absence of significant septal hypertrophy.[13] Both patients did well after surgery.

Summary

Takotsubo cardiomyopathy is an increasingly recognized clinical syndrome often presenting emergently to the catheterization laboratory. While the overall outcome of these patients is good, there are a number of well-described complications. Dynamic LVOT obstruction with persistent hypotension and even shock should be considered in the differential diagnosis of patients presenting with shock. The typical patient is an elderly, hypertensive female with sigmoid deformity of the intraventricular septum. An accurate diagnosis is essential to prevent institution of potentially detrimental therapies. Diagnostic testing includes left heart catheterization and/or echocardiography. Treatment consists of fluid resuscitation and beta blockers despite the presence of hypotension or shock. The prognosis of these patients is good and does not seem to differ from takotsubo patients without LVOT obstruction.

References

1. Desmet W. Dynamic LV obstruction in apical ballooning syndrome: The chicken or the egg. Eur J Echocardiogr 2006;7:1–4.
2. Gianni M, Dentali F, Grandi AM, et al. Apical ballooning syndrome or takotsubo cardiomyopathy: A systematic review. Eur Heart J 2006;27:1523–1529.
3. Pilgrim TM, Wyss TR. Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: A systematic review. Int J Cardiol 2008;124:283–292.
4. El Mahmoud R, Mansencal N, Pilliére R, et al. Prevalence and characteristics of left ventricular outflow tract obstruction in Tako-Tsubo syndrome. Am Heart J 2008;156:543–548.
5. Bybee KA, Kara T, Prasad A, et al. Systematic review: Transient left ventricular apical ballooning: A syndrome that mimics ST-segment elevation myocardial infarction. Ann Intern Med 2004;141:858–865.
6. Villareal RP, Achari A, Wilansky S, et al. Anteroapical stunning and left ventricular outflow tract obstruction. Mayo Clin Proc 2001;76:79–83.
7. Merli E, Sutcliffe S, Gori M, et al. Tako-Tsubo cardiomyopathy: New insights into the possible underlying pathophysiology. Eur J Echocardiogr 2006;7:53–61.
8. Kyuma M, Tsuchihashi K, Shinshi Y, et al. Effect of intravenous propranolol on left ventricular apical ballooning without coronary artery stenosis (ampulla cardiomyopathy): Three cases. Circ J 2002;66:1181–1184.
9. Chockalingam A, Tejwani L, Aggarwal K, et al. Dynamic left ventricular outflow tract obstruction in acute myocardial infarction with shock: Cause, effect, and coincidence. Circulation 2007;116:e110-e113.
10. Haley JH, Sinak LJ, Tajik AJ, et al. Dynamic left ventricular outflow tract obstruction in acute coronary syndromes: An important cause of new systolic murmur and cardiogenic shock. Mayo Clin Proc 1999;74:901–906.
11. Brown ML, Abel MD, Click RL, et al. Systolic anterior motion after mitral valve repair: Is surgical intervention necessary? J Thorac Cardiovasc Surg 2007;133:136–143.
12. Chandrasegaram MD, Celermajer DS, Wilson MK. Apical ballooning syndrome complicated by acute severe mitral regurgitation with left ventricular outflow obstruction–case report. J Cardiothorac Surg 2007;2:14.
13. Desmet WJ, Adriaenssen BF, Dens JA. Apical ballooning of the left ventricle: First series in white patients. Heart 2003;89:1027–1031.

14. Tsuchuhashi K, Ueshima K, Uchida T, et al. Angina pectoris-myocardial infarction investigations in Japan. Transient left ventricular apical ballooning without coronary artery stenosis: A novel heart syndrome mimicking acute myocardial infarction. Angina pectoris — myocardial infarction investigations in Japan. J Am Coll Cardiol 2001;38:11–18.
15. Parodi G, Del Pace S, Salvadori C, et al. Tuscany registry of Tako-Tsubo cardiomyopathy. Left ventricular apical ballooning syndrome as a novel cause of acute mitral regurgitation. J Am Coll Cardiol 2007;50:647–649.
16. Sharkey SW, Lesser JR, Zenovich AG, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. Circulation 2005;111:472–479.
17. Pillière R, Mansencal N, Digne F, et al. Prevalence of takotsubo syndrome in a large urban agglomeration. Am J Cardiol 2006;98:662–665.
18. Rosenmann D, Balkin J, Butnaru A, et al. Transient left ventricular apical ballooning. Report of 5 Israeli patients. Cardiology 2006;105:124–127.
19. Bybee KA, Prasad A, Barsness GW, et al. Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. Am J Cardiol 2004;94:343–346.
20. Elian D, Osherov A, Matetyky S, et al. Left ventricular apical ballooning: Not an uncommon variant of acute myocardial infarction in women. Clin Cardiol 2006;29:9–12.
21. Brunetti ND, Ieva R, Rossi G, et al. Ventricular outflow tract obstruction, systolic anterior motion and acute mitral regurgitation in Tako-Tsubo syndrome. Int J Cardiol 2008;127:e152–e157.
22. Kurisu S, Inoue I, Kawagoe T, et al. Takotsubo-like transient biventricular dysfunction with pressure gradients. Intern Med 2005;44:727–732.
23. Ohba Y, Takemoto M, Nakano M, et al. Takotsubo cardiomyopathy with left ventricular outflow tract obstruction. Int J Cardiol 2006;107:120–122.
24. Ionescu A. Subaortic dynamic obstruction: A contributing factor to haemodynamic instability in tako-tsubo syndrome? Eur J Echo 2008;9:384–385.
25. Matsuoka H, Kawakami H, Koyama Y, et al. "Takotsubo" cardiomyopathy with a significant pressure gradient in the left ventricle. Heart Vessels 2000;15:203.
26. Kurisu S, Inoue I, Kawagoe T, et al. Brockenbrough–Braunwald–Morrow phenomenon in Tako-Tsubo cardiomyopathy. Int J Cardiol 2007;115:123–125.
27. Lalonde G, Beaulieu Y. Tako-Tsubo cardiomyopathy. Can J Cardiol 2005;21:1213–1216.
28. Caselli S, Passaseo I, Giannantoni P, et al. 2- and 3-dimensional echocardiographic analysis of an unusual transient apical ballooning. J Am Soc Echocardiogr 2008;21:511.e1–511.e4.
29. Metzl MD, Altman EJ, Spevack DM, et al. A case of Takotsubo cardiomyopathy mimicking an acute coronary syndrome. Nat Clin Pract Cardiovasc Med 2006;3:53–56.