Transient Left Ventricular Apical Ballooning (Tako-tsubo): The Syndrome that Mimics Acute Myocardial Infarction

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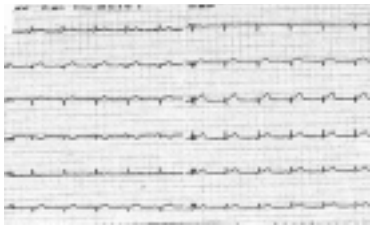
A novel heart syndrome with a unique morphologic left ventricular apical ballooning feature was reported in Japan 14 years ago, in patients presenting with a clinical and electrocardiographic picture of acute myocardial infarction [1]. This syndrome is manifested by: a) transient left ventricular apical wall motion abnormalities; b) no evidence of significant coronary stenosis on coronary angiography; and c) no evidence of cardiac or extracardiac pathology such as an old MI, cardiomyopathy, myocarditis, pheochromocytoma, subarachnoid hemorrhage, etc., which could explain the electrocardiographic and/or echocardiographic picture [Figure 1]. Because the morphologic feature of early left ventriculography or echocardiography revealed a balloon-shaped left ventricle with basal hyperkinesis and apical akinesia, and because the end-systolic ventriculogram demonstrated a short-neck round flask resembling "Tako-tsubo" (a Japanese octopus trap), the syndrome was named "Tako-tsubo."

Clinical features

The clinical features of transient apical ballooning have been described by both Japanese [2–6] and, recently, western investigators [7] who retrospectively analyzed patients fulfilling the above criteria. Acute MI based on symptoms and/or ECG changes was suspected in most of these patients. The mean age of the patients was 62–74 years, with a preponderance of females (82–100%) [2–4,7,8]. Aggravation of an underlying disease was present in 43–74% and emotional stress in 27% [2,3]. Chest symptoms occurred in only 53–67% [2,3,7].

ECG findings in the hyper-acute phase revealed ST elevation in 82–90% of the Japanese [2,3,5] and in 38% of the western [7] series. ST segment elevation was usually present in V_2-V_5 precordial leads, and in many patients was simultaneously widespread at the inferior, posterior and precordial leads – a finding that cannot be explained by impairment in the territory of only one coronary vessel. Ten percent developed Q waves (frequently found in V_3-V_4) that persisted to the sub-acute phase. T wave inversion was observed in precordial or limb leads in the acute and sub-acute phase in 97% of the patients even without ST elevation.



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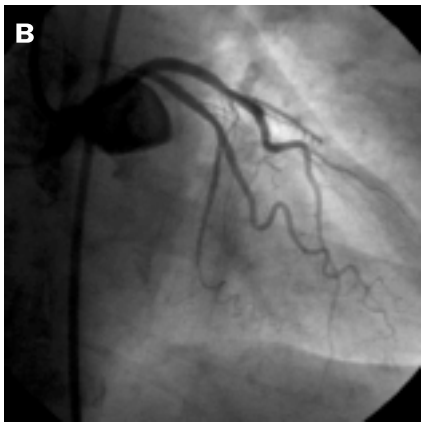

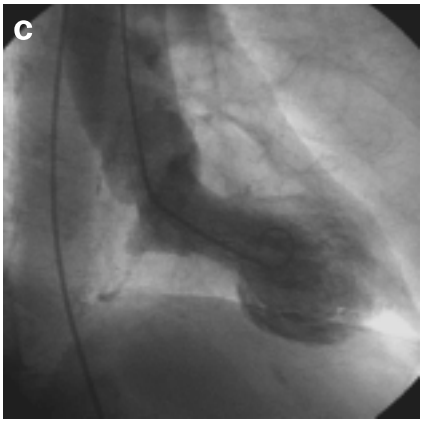

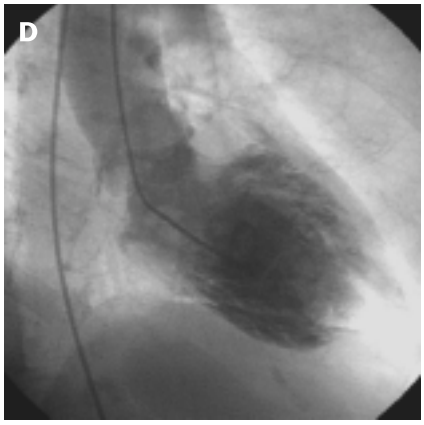

Figure 1. An 82 year old woman who presented with chest pain. **[A]** ECG showing ST elevation in inferior antero-lateral and posterior leads. **[B]** On coronary angiography no coronary artery stenosis is seen. End-systolic **[C]** and end-diastolic **[D]** left ventriculograms showing extensive akinesia of the apical and mid-portions of the left ventricle.

MI = myocardial infarction

T wave inversion deepened maximally and the QTc interval was prolonged twice (at 3 days and at 2–3 weeks). The ECG changes were usually sustained, even after the resolution of Tako-tsubo-like left ventricular dysfunction [8]. Coronary angiography performed within 48 hours confirmed normal epicardial arteries (<50% stenosis) [2–7].

Cardiac enzymes and markers

Creatine kinase was elevated moderately in the range of 209–1,625 IU/L in 56% [2] of the patients. The MB fraction of creatine kinase rose moderately in all patients in the small series of 13 patients [7]. Maximum troponin I concentrations ranged from 2.0 to 97.6 μg/L [7]. Troponin I [7] and troponin T [5] were positive in all patients who were assessed.

Hemodynamics and left ventricular function

Patients exhibiting apical ballooning had decreased ejection fraction, mean 40% (range 10–62%), which significantly improved in the sub-acute phase [2,3]. In the acute phase, intraventricular pressure gradient was elevated in 18% of patients (13 of 72 patients in the largest Japanese series published) [2] and it disappeared in the sub-acute phase. Interestingly, administration of intravenous propranonlol decreased the gradient, with improvement in wall motion and amelioration of ECG abnormalities [9].

Complications and outcome

The Tako-tsubo syndrome mimics acute MI in its clinical presentation and ECG changes in the hyper-acute phase. Elevated creatine kinase and troponin levels represent myocardial injury. Fifteen percent of the patients developed cardiogenic shock [2]. The mortality rate was low, with 1% in-hospital deaths. Recurrences and death during 2 years of follow-up was 2% and 1% respectively [2]. LV function improved in most of the patients [2,3].

Etiology

Despite the fact that more than 10 years have elapsed since the first case was published, there is still debate concerning the main pathophysiology of this syndrome. It was noted that most patients suffered from physical and/or emotional stress that precipitated the acute event, which might suggest that sympathetic activity plays a major role in the pathophysiology of this syndrome. Since coronary angiography revealed no significant coronary stenosis, several etiologies were proposed:

- **Coronary vasospasm**

Coronary vasospasm tests [3], using ergonovine or acetylcholine, induced epicardial single coronary spasm and multi-vessel coronary spasm in only a few patients. When diffuse vasospasm was observed, there was no ST segment elevation. Lack of coronary vasospasm was demonstrated in 4 of 7 patients with Tako-tsubo cardiomyopathy [5]. Therefore, the pathophysiology of the syndrome cannot be explained by coronary spasm.

- **Coronary microcirculation**

Several techniques, such as contrast-enhanced echocardiography, intracoronary Doppler guide-wire, coronary flow reserve and TIMI frame count, used to test the coronary microcirculation, yielded contradictory results [2–4,10]. Myocardial contrast-enhanced echocardiography revealed a contrast-enhanced myocardium at the apex in the acute phase, demonstrating intact microcirculation. Intracoronary Doppler guide-wire used to evaluate diastolic to systolic velocity was >1.7 (normally the diastolic flow is faster than the systolic, and a ratio <1.7 is considered to be caused by significant stenosis). Coronary flow reserve (tested by injecting nitroglycerin and adenosine and comparing basal to maximal flow velocity) was also in the normal range and did not support damage to the microcirculation. Other investigators [10] demonstrated contradictory results by using coronary flow reserve. Kurisu et al. [4] used the TIMI frame count method to show that coronary blood flow is severely impaired in all coronary microcirculation in the acute phase. Coronary blood flow improved but the impairment was sustained (compared with normal controls) after resolution of apical ballooning LV dysfunction. Consequently, there is still debate as to whether microcirculation is primarily involved. In addition, the possibility of delayed recovery of impaired microcirculation due to transient wall motion abnormality cannot be excluded.

- **Metabolic versus perfusion defects**

Myocardial single-photon emission computed tomography (using technetium-99m tetrofosmin or thallium-201) was used to assess perfusion and metabolism [2–4]. Rest tomographic myocardial imaging was performed during the acute phase, in the sub-acute phase and after a few months. Most of the patients, but not all, showed decreased uptake at the apex of the left ventricle. The abnormality returned to normal between 25 and 90 days after the onset of symptoms. This finding was explained by impaired myocardial perfusion. As the mechanism of Tc uptake by myocytes is via a metabolism-dependent process localized to the mitochondria, any abnormalities in the mitochondria can cause scintigraphic abnormalities. Thus, few investigators have suggested that the scintigraphic abnormality may be explained by metabolic and/or structural defects rather than by perfusion abnormalities [2,3]. On the other hand, by using SPECT studies with iodine-123 beta methyl-p-iodophenyl penta decanoic acid, which assesses the perfusion and fatty acid metabolism, several studies [4] have shown that the reduced uptake of ^{123}I-BMIPP in the apex in the acute phase is sustained even after the resolution of Tako-tsubo LV dysfunction. These studies suggested that Tako-tsubo-like LV dysfunction may essentially be stunned myocardium due to impaired multi-vessel coronary microcirculation. Further studies involving more patients and basic experiments are therefore required to resolve the question whether the defect is primary metabolic or reduced microcirculation perfusion.

LV = left ventricular

SPECT = single-photon emission computed tomography

^{123}I-BMIPP = iodine-123 beta methyl-p-iodophenyl penta decanoic acid

- **Sympathetic innervations and catecholamine levels**

Moriya et al. [11] and others [2,12] evaluated Tako-tsubo cardiomyopathy with SPECT – myocardial scintigraphy with I-123 meta-iodibenzyl guanidine. MIBG-like guanetidine has active uptake to neuron endings. There was decreased uptake of MIBG in the apex. These data suggest discrepancy of sympathetic innervations in the apical versus basal region as a possible explanation of this unique syndrome.

Catecholamine levels [5,13] were measured and found to be normal or slightly elevated in patients with apical ballooning, a factor that does not rule out catecholamine oversensitivity as a possible explanation of the syndrome. Recently, experiments in rats [14] demonstrated that activation of cardiac adrenoceptors might partially explain the pathophysiology. Left ventriculography of rats experiencing emotional stress induced reversible LV apical ballooning, which was normalized by pretreatment with adrenoceptor blockade.

- **Pathology**

Endomyocardial biopsies [3,5,13,15] or necropsy [7] were performed in several patients during the acute phase of apical ballooning. Interstitial fibrosis and small amounts of cellular infiltrates or normal myocardial tissue were observed. These findings exclude myocarditis as the etiology of apical ballooning.

Diagnosis

The clinical syndrome of transient left ventricular ballooning mimics acute MI. A balloon-like appearance of the apex with basal hyper-contraction on echocardiography might suggest an accurate diagnosis before angiography and contrast ventriculography are performed [2–4]. The balloon-like LV dysfunction is transient and cardiomyopathy should be ruled out. On coronary angiography there is no evidence of significant coronary stenosis.

Therapy

The treatment is supportive, with special attention to patients with cardiogenic shock, heart failure and arrhythmia. There is complete resolution of LV dysfunction in most patients, occurring days to weeks from onset of symptoms.

Detection of the dynamic LV outflow tract obstruction optimizes pharmacologic treatment, which should be directed toward decreasing this obstruction by cautious administration of beta-blockers.

Conclusions

A new clinical syndrome, the "Tako-tsubo"-like left ventricular apical dysfunction, with chest symptoms and ECG changes that mimic acute MI has been reported in the last decade. Only a few reports by Japanese researchers have been published in the western literature. The prevalence of the syndrome in Japan is between 1.5 and 2.2% (in suspected acute MI patients who underwent coronary angiography) [5,6], but seems to be under-diagnosed in the western world. Most of the patients are middle-aged to elderly women with physical or emotional stress as the precipitating event. The combination of a normal coronary angiogram and transient LV apical dyskinesia (that normalizes within days) predisposes the diagnosis. During the hyperacute phase it is difficult to clinically differentiate between the syndrome and ST elevation MI. Since the symptoms and initial ECG mimic acute MI, it is likely that some of the patients might receive unnecessary thrombolytic therapy. The clinical course and prognosis are different from that of acute MI due to coronary occlusion, with lower mortality (1%) and complete LV recovery.

MIBG = meta-iodibenzyl guanidine

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