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Review

Tako-tsubo cardiomyopathy

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Abstract

Tako-tsubo cardiomyopathy(TC) is a recently described acute cardiac syndrome, which the latest cardiomyopathy classification of the European Society of Cardiology describes as an unclassified cardiomyopathy. TC mimics acute myocardial infarction(AMI) and is characterised by ischaemic chest symptoms, an elevated electrocardiogram ST-segment, and moderately increased levels of cardiac disease markers. However, patients with TC have no coronary angiogram-detectable or non-obstructive coronary arterial disease(CAD), and left ventriculography documents transient left apical and middle ventricular wall dysfunction. In this review, we describe TC and evaluate epidemiological, clinical and instrumental features, pathophysiological mechanisms, therapy and prognosis of this syndrome, with a view to raising awareness of the disease.

Keywords: Tako-tsubo cardiomyopathy; epidemiology; pathophysiological mechanisms; electrocardiography; cardiac biomarkers; coronary angiography; left ventriculography; therapy; prognosis

INTRODUCTION

Tako-tsubo cardiomyopathy(TC) was initially recognised in the Japanese population and first described in 1991 by Dote *et al*[1], but has recently been reported in the USA and Europe. The term 'tako-tsubo' was proposed by Dote and colleagues, and literally means 'fishing pot for trapping octopus'. Tako-tsubo cardiomyopathy mimics acute myocardial infarction (AMI) and is characterised by ischaemic chest symptoms, ischaemic electrocardiographic changes, slightly or moderately increased levels of cardiac disease markers, and transient left apical and middle ventricular wall dysfunction. But patients with TC have no coronary angiogram-detectable or non-obstructive coronary arterial disease. Left ventriculography shows the shape of the apex to resemble a balloon, and this syndrome is also called 'acute apical ballooning syndrome'. The syndrome can be triggered by profound physical or psychological stress and is also known as 'stress cardiomyopathy' or 'broken-heart syndrome'.

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EPIDEMIOLOGY

The true prevalence of this syndrome remains uncertain, as all the assessments of the prevalence of this syndrome came from consecutive patients presenting with suspected acute coronary syndrome(ACS). Klinceva *et al* evaluated the prevalence of stress-induced myocardial stunning during a 4-year period (2002-2005), and it was estimated to be 0.07%[2]. Pillie′re *et al* also assessed the same data[3]. In a study from the USA, Bybee *et al* reported that the apical ballooning syndrome accounted for 2.2% of the ST-segment elevation ACS patients presenting at their institution[4]. A recent study evaluated the prevalence of this syndrome in Japan, and reported that among patients presenting with suspected ACS, this syndrome accounted from 1.7% to 2.2% of all cases[5].

Many studies have demonstrate that this syndrome occurs predominantly in postmenopausal women. Rami *et al* found the prevalence of Tako-Tsubo syndrome was 3.1% in women versus 0.03% in men[6]. The explanation for a female predominance of the syndrome is also unclear. However, the reason may be related to postmenopausal alterations of endothelial function in

response to reduced oestrogen levels, and cardiac vagal tone and baroreflex sensitivity decrease significantly in postmenopausal women[7].

CAUSES AND INCENTIVE

While the exact causes of this syndrome is unknown, it may also be caused by an imbalance between myocardial blood supply and demand.

The onset of TC is often preceded by emotional or physical stress. An emotional stressor, such as the unexpected death of a relative or friend, a catastrophic medical diagnosis, devastating business or gambling losses, was identified, as was a physical stressor, such as exhausting work, asthma attack, gastric endoscopy, and exacerbated systemic disorders. However, in 30%-40% cases no preceding emotional or physical stressful event was identified[8].

PATHOPHYSIOLOGICAL MECHANISMS

The cause of TC is unknown, so the exact pathophysiological mechanisms of this syndrome are unclear. However, speculatively, it may represent a catecholamine-mediated myocardial stunning that results from a combination of myocardial ischaemia related to diffuse microvascular dysfunction and, in some cases, multivessel epicardial spasm and metabolic injury.

David *et al* showed that patients with TC often have coexisting CAD, implying that the presence of CAD should not be an exclusion criterion for the diagnosis of TC. Whether these two conditions simply coexist because of a high prevalence of CAD in the general population or whether coronary atherosclerosis in some way is related to the development of TC is unknown[9]. Several investigators have documented microvascular dysfunction in patients with TC and studies evaluating myocardial perfusion using single photon emission computed tomography(SPECT) showed moderate or severe myocardial ischaemia. It is possible that TC and obstructive CAD could be different clinical manifestations of a similar pathological process[10]. Volkhard *et al* reported impaired coronary microcirculation when they assessed the function of the coronary microcirculation[8]. Although the coronary angiographic pattern usually shows absence of obstructive coronary lesions, results of these studies showed moderate or severe decreased myocardial perfusion, which could be interpreted as direct evidence for impairment of the coronary microcirculation as a causative mechanism of this syndrome. But Abe *et al* evaluated the coronary microcirculation using contrast echocardiography and found that abnormalities in the coronary microcirculation do not contribute significantly to the syndrome[11]. Many studies have evaluated the presence of either spontaneous or provocable multivessel epicardial spasm during angiography. Spontaneous multivessel epicardial spasm was experienced by only a few patients during coronarography. Some investigators using provocative tests to evaluate inducible coronary spasm with different drugs have reported different results.

Catecholamines probably play an important role in the syndrome. Some researchers have suggested that the syndrome could be a result of catecholamine-associated stunning of the myocardium, which is provoked by emotional or physiologic stress. In some studies, plasma levels of catecholamines and their metabolites were measured and it has been found that the levels of catecholamines were two to three times higher in patients with TC[12]. Animal studies showed that in experimental models, by pretreatment with adrenoceptor blockade, the induced reversible left ventricular apical ballooning that occurred after experiencing emotional stress was normalized[13]. Furthermore, there is some evidence suggesting that the apical myocardium may be more susceptible to sympathetic stimulation and may be more vulnerable to sudden catecholamine surges[14].

Some research suggested a possible role for a transient dynamic left ventricular outflow tract obstruction(LVOTO) in the pathogenesis of this syndrome[6,15]. In these patients, the clinical and haemodynamic situation improved after the gradient disappeared. Thus, at least in some patients, a possible mechanism for TC could be a dynamic LVOT obstruction preceding the ischaemic event. Once present, the dynamic obstruction elevates left ventricular filling pressures, increasing myocardial oxygen demand at the mid-to-apical cavity. Some patients, primarily older women, may have a sigmoid interventricular septum, small LVOT and reduced left ventricular volume, which may manifest a dynamic LVOT obstruction when catecholamines surge.

CLINICAL AND INSTRUMENTAL FEATURES

Symptoms

In a study by Gianni *et al*, the most common presenting clinical symptoms were chest pain and dyspnoea, reported in 67.8% cases. Chest pain was the cardinal presenting symptom, and dyspnoea occurred in 17.8%. However, more serious clinical presentations such as cardiogenic shock and ventricular fibrillation have also been reported, 4.2% and 1.5% respectively[16]. There have also been isolated cases of syncope reported as the presenting symptom[17].

Electrocardiographic features and cardiac biomarkers

The major electrocardiographic change observed in

the acute phase is elevation of the ST segment. The elevation may be present just for several hours, then normalization of the ST-segment occurs, followed by negative T-waves in V1-V6, and aVL, which persist for weeks to months. The QT interval could be prolonged and may shorten over weeks. ST elevation was detected in 81.6%, usually involving the precordial leads(83.9%). T-wave abnormalities were seen in 64.3% patients and Q waves were present in 31.8% patients. Rarely, ST-depression and the development of Q waves have been observed[18,19].

Studies have also measured serum levels of troponin I and creatine kinase-MB(CK-MB) fraction levels. Troponin I was positive in 86.2% and CK-MB levels were elevated in 73.9% However, in this particular syndrome cardiac biomarker levels were usually only slightly elevated compared to the extent of tissue involved, and the rapid decrease to normal enzymatic plasma levels suggests a reversible myocardial dysfunction, compared with typical AMI[20].

Cardiac catheterisation and Echocardiography

The coronary angiographic pattern usually shows the absence of coronary disease or only mild coronary atherosclerosis(< 50%); coronary spasm may be visible or may be provoked by drugs in up to 80% of patients[21]. Left ventriculography documents akinesis in the apical, diaphragmatic and / or anterolateral segments, and hyperkinesis in the basal segments. During the acute phase, all patients had an abnormal left ventricular ejection fraction(mean: 0.39-0.49) that improves rapidly over a period of days to weeks(mean:0.60-0.76) on follow-up[22].

Typically transthoracic echocardiogram shows the apical ballooning of the left ventricle(distal segments akinesis or diskinesis) in the presence of a preserved basal myocardial segment function, which may even be hyperkinetic. The akinesia is more extensive than the area supplied by any one coronary vessel[23]. Ibanez *et al* found that the left anterior descending(LAD) coronary artery had a long course around the LV apex, supplying an extensive portion of the diaphragmatic LV aspect[24]. Occasionally, a left intraventricular gradient with high velocity in the basal segment may be detected. A study showed that about 25% patients among Tako-Tsubo syndrome cases exhibited LVOT obstruction, and the prevalence of septal bulge was 100% in those patients with LVOT obstruction[6]. Mid-ventricle and apical wall-motion abnormalities completely resolved in all the surviving patients.

THERAPY

There are no studies specifically evaluating different therapies. The treatment of this syndrome is entirely empirical and should be individualized according to the patients' characteristics. Patients with TC should be monitored like patients with ACS. Most data regarding treatment have been derived from patients initially treated for ACS, and diagnosed later as TC. Patients receive aspirin, β -blockers, angiotensin-converting-enzyme(ACE) inhibitors, intravenous diuretics, and cardiac catheterisation is performed if needed.

Whether anticoagulation should be administered in cases with large apical akinesia is controversial, but short-term anticoagulation may be considered to prevent left ventricular mural thrombus formation especially in patients with markedly depressed left ventricular function.

Patients with TC should be monitored for symptoms of cardiogenic shock, heart failure and arrhythmias. Heart failure may require aggressive pharmacological treatment with inotropic drugs and mechanical circulatory support such as intra-aortic balloon pumps and left ventricular assist devices. Those with hypotension should be evaluated by echocardiography or cardiac catheterisation to exclude intracavitary gradient. If a dynamic outflow pressure gradient is identified, nitroglycerine, inotropic drugs and ACE inhibitors should be immediately discontinued, and intravenous beta-blockers should be administered. Although no randomised studies are available, it seems reasonable to give beta-blockers to patients in the acute and chronic phases, possibly to prevent recurrences[25].

PROGNOSIS

Prognosis seems to be favourable and the in-hospital death rate ranged from 0% to 8% in the various studies. Bybee *et al* reported the in-hospital death rate was 1%[22]. At the time of this study, evaluation of the true recurrence rate was limited as follow-up was not reported in all patients, and in patients assessed during follow-up, the time of the follow-up varied widely. In this report, about 0%-8% of cases experienced a recurrence when similar stressful events occurred[22].

CONCLUSION

TC is an uncommon abnormality with signs and symptoms that mimic those of AMI. TC should be considered by physicians as a possible diagnosis when patients, especially postmenopausal women whose onset of symptoms coincides with psychological or physical stressor, have chest pain with ischaemic alteration on electrocardiogram mimicking AMI. The pathophysi-ology remains unknown, but catecholamine-mediated myocardial stunning is the most favoured explanation. Apical ballooning is reversible and patients have dramatic improvements in left ventricular wall-motion and ejection fraction after the onset of signs

and symptoms, and the prognosis is generally favourable. TC initially is undistinguishable from a myocardial infarction and the general physician should consider this syndrome like ACS and have knowledge about its existence.

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