

## **Takotsubo (stress) cardiomyopathy: insights gleaned from the Christchurch Earthquake experience**

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On 12 June 2014, a search on medical literature website PubMed using the word “takotsubo” yielded 2058 articles. “Takotsubo” is a pot with a round bottom and narrow neck used for trapping octopuses in Japan.

Originally described in the 1980s by the Japanese, the typical patient with takotsubo cardiomyopathy has during systole ballooning of the left ventricular apex resembling a “takotsubo”<sup>1</sup>—a disease also commonly known as apical ballooning syndrome. Today, two other less common variants are described: the mid-ventricular ballooning pattern (20–30% of patients) and the inverted ballooning pattern involving the basal part of the left ventricle (1–2%).<sup>2</sup>

In a series of 136 consecutive patients with takotsubo cardiomyopathy from Minneapolis, USA (6 men and 130 women), 15 (11%) had no identifiable trigger, 64 (48%) had the syndrome precipitated by intensely stressful emotional events (hence its other name stress cardiomyopathy or “broken heart” syndrome) and 57 had syndrome precipitated by stressful medical events ranging from acute respiratory failure, neurological emergencies, medical procedures (often surgery with anaesthesia), infections and the use or withdrawal of medications or drugs.<sup>3</sup>

Excitation of the sympathetic nervous system or excess of catecholamines (including iatrogenic situations such as dobutamine cardiac stress tests) are thought to be the common pathway that precipitates an attack.<sup>1–4</sup>

The area of left ventricular involvement (occasionally right ventricle also involved) does not correspond at all to any single coronary artery perfusion territory arguing against a primary coronary problem in its pathophysiology. Despite having a left ventricular ejection fraction substantially lower than that in ST elevation acute myocardial infarction,<sup>2</sup> takotsubo syndrome is often considered more benign with reversible ventricular dysfunction.

This idea of having a more benign course was challenged by a recent meta-analysis including 2120 patients with takotsubo cardiomyopathy (87% women, mean age 68, and 40% with preceding acute medical illnesses—“secondary takotsubo”) which found an in-hospital mortality of 4.5%.<sup>5</sup>

Male gender and “secondary takotsubo” predicted mortality, about 40% of which were from direct cardiac complications including heart failure/shock, ventricular arrhythmia, ventricular rupture and thromboembolism (mainly from left ventricular mural thrombus over the akinetic area).

The left ventricular dysfunction in the classical form of takotsubo (i.e. ballooning of the left ventricular apex) is often worsened by left ventricular outflow tract obstruction from hyper-contractility of the left ventricular basal segments causing systolic anterior motion of the mitral valve and mitral regurgitation.<sup>1,2</sup>

The annual recurrence rate for takotsubo cardiomyopathy, as reviewed by another recent meta-analysis, was 1–2% with another 10–15% of patients having persistent or recurrent symptoms.<sup>6</sup> Obviously, any clinical criteria for diagnosing takotsubo cardiomyopathy are a compromise of sensitivity and specificity, and it is well possible that the syndrome exists in milder forms which may even escape clinical attention.

In this issue of the *Journal*, Chan et al reported the Christchurch experience of 21 patients (all women, mean age of 68 years) who had takotsubo cardiomyopathy after the 2011 February earthquake.<sup>7</sup>

Table 1 highlights some reported patient characteristics from their study with general comments.

**Table 1. Patients’ characteristics in Chan et al’s *NZMJ* article<sup>7</sup>**

Findings	Comments
ECG changes (often ST elevation or deep T inversion) without epicardial coronary disease	Takotsubo is not an uncommon “STEMI misdiagnosis” causing cath lab activation for an intended primary angioplasty <sup>8</sup>
Prolonged QT interval, more prolongation at discharge	Typical progressive QT lengthening, often with deep T inversion, during the in-hospital course of the disease. While it can precipitate torsades de pointe, a polymorphic ventricular tachycardia, and cause sudden death, this is generally rare <sup>1,2</sup>
Typical apical ballooning in 19 of 21 patients and 2 had the mid wall variant sparing the apex	Consistent with literature <sup>2</sup>
Left ventricular ejection fraction of 39% (IQR 30–45%) with short hospitalisation, rapid recovery of ejection fraction on follow-up (67%) and zero 1-year mortality	This ejection fraction is ~10% higher than that from 259 takotsubo patients from the Minneapolis Heart Institute <sup>2</sup> and may explain the better outcome of the Christchurch cohort
Only moderately elevated cardiac biomarkers such as troponins level suggesting only modest myocardial damage	Takotsubo is characteristically not associated with late enhancement (evidence of fibrosis or infarction) despite being edematous on cardiac MRI studies. <sup>1,2,9</sup>
Two patients had history of takotsubo before 2011; whereas after discharge three patients required re-hospitalisation for cardiac causes.	Consistent with literature for recurrent takotsubo and recurrent cardiac symptoms. <sup>6</sup>
The patient with apical variant in the 2010 September earthquake presented with the mid-wall variant in 2011	Consistent with the literature that recurrence of takotsubo in the same patient can be with a different variant. <sup>1,2</sup>

Chan et al provided new information, assessing psychological wellbeing. Their psychometric questionnaires showed that none had a high level of health anxiety, general anxiety or depression. Four patients had symptoms suggestive of borderline post-traumatic stress disorder.<sup>7</sup> These findings have obvious practical value in health care. However, there could be deeper implications from studying the psychology of takotsubo patients.

As the authors pointed out, their series is unique because the stress cardiomyopathy in all 21 patients was provoked by the relatively similar emotional stressor arising from the earthquake. The better ejection fraction and clinical outcomes in their cohort<sup>7</sup> may suggest a milder form of Takotsubo syndrome, unlike the more severe forms secondary to physical illnesses or affecting males.<sup>5</sup>

Their patients represented those who had “broken hearts” from the (Christchurch) earthquake. It may be logical to speculate that each individual has a risk to develop takotsubo syndrome given the appropriate emotional stressor, with higher risks in those who are more psychological predisposed.

Some very predisposed subjects (perhaps including some with extreme anxiety) may develop the syndrome with minimal stress. This hypothesis is well consistent with the Mineapolis series<sup>3</sup> and other reports<sup>1,2</sup> that a minority of takotsubo patients did not even have any identifiable preceding stress events.

There are some interesting recent findings from studies in rats,<sup>10</sup> where either immobilisation (a form of severe “emotional” stress for rats) or exogenous catecholamine can induce the equivalent of takotsubo cardiomyopathy. In a series of rat experiments, blood pressure was monitored through a catheter in the right carotid artery and cardiac morphology and function studied by echocardiography.<sup>10</sup>

Catecholamines were introduced intraperitoneally, testing isoprenaline ( $\beta_1/\beta_2$ -adrenoceptor agonist), epinephrine ( $\beta_1/\beta_2/\alpha$ -adrenoceptor agonist), norepinephrine ( $\beta_1/\alpha$ -adrenoceptor agonist), dopamine ( $\alpha/\beta_1/\beta_2$ -adrenoceptor agonist) and phenylephrine ( $\alpha$ -adrenoceptor agonist).

While all catecholamines induced takotsubo-like cardiac dysfunction, isoprenaline induced low blood pressure and predominantly apical dysfunction whereas the other catecholamines induced high blood pressure and basal dysfunction. In another set of experiments additionally infusing hydralazine or nitroprusside to rats that received epinephrine or norepinephrine (thus maintaining lower systolic blood pressure), the rats developed apical instead of basal dysfunction.

Conversely, infusion of phenylephrine (thus maintaining higher systolic blood pressure) after isoprenaline administration prevented apical ballooning. The authors concluded that different catecholamines induced different patterns of takotsubo-like cardiac dysfunction which also depended on afterload.<sup>10</sup>

These interesting animal findings somewhat echo with the clinical observation that the same patient can develop the different variants (apical versus mid-segment versus basal) of takotsubo cardiomyopathy over different period of time, as shown in the Christchurch report.<sup>7</sup>

One may speculate that an outpour of catecholamine (such as in patients with pheochromocytoma) may induce a takotsubo cardiomyopathy. The Christchurch study<sup>7</sup> used diagnostic criteria similar to the modified Mayo criteria in diagnosing takotsubo cardiomyopathy. It is noteworthy that the full modified Mayo criteria also require the exclusion of pheochromocytoma.<sup>1</sup>

Y-Hassan recently suggested the role of an acute cardiac sympathetic over-activation followed by disruption as the pathophysiology in takotsubo cardiomyopathy.<sup>4</sup> Cardiac sympathetic denervation had been noted for years in studies using <sup>123</sup>I-MIBG scans demonstrating cold spots in the myocardium with regional wall dysfunction.<sup>1,2</sup> Y-Hassan suggested that the cardiac sympathetic denervation may be due to excessive release of norepinephrine from myocardial sympathetic nerve terminals damaging both myocytes and nerve terminals.

The damage to the myocytes will be consistent with the evidence acutely of myocardial oedema in the involved myocardium demonstrated on cardiac MRI scan<sup>9</sup> and slow coronary flow to the involved myocardial region on angiography.<sup>1,2</sup>

The interesting theories aside, what can we take home from the Christchurch report? First and foremost, the report supports their practice in that it is (relatively) safe for early discharge for takotsubo cardiomyopathy triggered by earthquake, providing that patients are stable.

This is no minor issue given that any hospital system will be stretched much beyond its limits in the situation of a major earthquake. Secondly, patients have good outcomes without significant cardiac or psychological sequelae at least for the first year. This is so despite that patients were being exposed to significant aftershocks in Christchurch following February 2011.

One may speculate that beta-blockers would be particularly protective in these patients but a recent meta-analysis suggests that ACE-inhibitors/angiotensin receptor blockers rather than beta-blockers reduce risks for recurrence.<sup>6</sup> Among the 21 Christchurch patients, 9 were taking the former and 10 the latter at 1-year follow-up.<sup>7</sup> Lastly, Chan et al<sup>7</sup> are astute in highlighting that their patient cohort was unique with an identical single stressor.

The interested reader is welcome to search on the PubMed website the myriad of different clinical conditions that can precipitate takotsubo cardiomyopathy.

**Competing interests:** Nil.

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