The 'broken heart' syndrome

What can be learned from the tears and distress?

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*Il pleure dans mon coeur
Comme il pleut sur la ville;
Quelle est cette langueur
Qui pénètre mon coeur?*

Paul Verlaine (1844 – 1896)

Tako-tsubo-like left ventricular dysfunction

It is not very often that a novel cardiac syndrome provokes such a great interest from cardiologists worldwide. In 1991, cardiologists from Hiroshima, Japan were the first to report a cardiac syndrome with female preponderance exhibiting transient left ventricular apical ballooning, electrocardiographic changes, and minimal myocardial enzymatic release mimicking acute myocardial infarction without significant epicardial coronary artery disease.¹ The cardiologists from the Hiroshima City Hospital originally proposed the term tako-tsubo-like left ventricular dysfunction, because the typical shape on end-systolic left ventriculogram resembles a tako-tsubo (octopus trap) with a round (akinetic) apex and narrow (hyperkinetic) base. Based on the first series of 30 patients from this group, published ten years later, they believed that simultaneous multivessel coronary spasm was one of the main causes.² Of note, in their series of 30 patients acute coronary angiography revealed no coronary artery disease in 25 patients, and only moderate single coronary artery disease in five patients. Three patients showed spontaneous multivessel coronary spasm. In ten patients, coronary spasm could be provoked by either

ergonovine or acetylcholine.² Vasospastic ischaemia is supposed to be more common in Japan than in the rest of the world.³

The broken heart syndrome

Fifteen years later, two almost simultaneously published papers in the New England Journal⁴ and Circulation⁵ demonstrated that this syndrome was not confined to Japanese patients. These reports reconfirmed that profound (psychological) stress was the main clinical scenario of this acute but rapidly reversible left ventricular systolic dysfunction and that it mainly occurred in the hearts of older, postmenopausal women. Their tears and pain are the same, but the stress factor covers the full spectrum of the emotional domain. After these two seminal publications, stress-induced cardiomyopathy was recognised all over the world. The public press also got hold of the news that the folkloric myth of the broken heart was finally scientifically proven: 'A woman's heart can be broken, but given proper attention a broken heart can be mended!'

Why it has taken science so long to discover what folklore has recognised for centuries is probably due to the fact that immediate coronary angiography in ST-segment elevation acute coronary syndromes only became standard practice a few years ago. While in the thrombolytic era the clinical picture would have been characterised as 'successful thrombolysis', nowadays, when one is faced with normal coronary arteries, a reversible stress cardiomyopathy should be suspected and ruled out by a left ventriculogram or noninvasive imaging techniques.

In this Journal, interesting cases from Enschede and Maastricht, the Netherlands are presented.^{6,7} The first article demonstrates the characteristic features by MRI, the second article by echocardiographic imaging. In the Netherlands, R. Michels and colleagues from Eindhoven were the first to report myocardial bridging associated with takotsubo syndrome (TTS) and the first to report of TTS associated with dynamic left ventricular outflow tract obstruction with systolic anterior motion and mitral regurgitation.⁸

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From ischaemia-mediated stunning to 'scary sigmoid septum'

The three most characteristic features of this syndrome are the reversible nature of the extensive but local wall motion abnormalities, the apparent provocation by (emotional) stress and the female predominance. The first-mentioned characteristic resembles myocardial stunning, a condition caused by transient ischaemia. The link with stress suggests an exaggerated sympathetic stimulation, a concept that was substantiated by the study by Wittstein demonstrating that plasma catecholamine levels at presentation were markedly higher among patients with stress-induced cardiomyopathy than among those with Killip class III myocardial infarction.⁴ More evidence for an exaggerated sympathetic stimulation or sensitivity and for the preference of this entity to distress the hearts of women has come from studies in ovariectomised female rats in which the syndrome of local apical ballooning provoked by restraining stress could be prevented by β -blockade and attenuated by oestrogen supplementation.^{9,10} Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors: a possible animal model of takotsubo cardiomyopathy. Oestrogen attenuates the emotional stress-induced cardiac responses in the animal model of takotsubo (apulla) cardiomyopathy. However, the exact mechanism of this sympathetically mediated dysfunction resembling myocardial stunning is not known. Ischaemia resulting from epicardial coronary spasm or microvascular spasm has been postulated as a causative mechanism. Another putative mechanism would be a direct catecholamine-mediated myocyte injury. This results in a transient metabolic knock-out with an impaired glucose and fatty acid metabolism uncommon to stunning caused by ischaemia¹¹ and is accompanied by an apparent neuronal knock-out or functional denervation as well.¹²

What remains is the question why the myocardial affliction is localised in this entity. An explanation for apical affliction would be that the distal (apical) myocardium is considered most vulnerable to adrenergic aggression,¹³ also suggested by a similar distribution of left ventricular wall motion abnormalities in pheochromocytoma-related cardiomyopathy.³ However, recently several other forms have been described.¹⁴⁻¹⁶ Therefore, several types can now be described (table 1). Finally, the reason for the much more common occurrence in post-menopausal women is also unclear.

Table 1. Transient ventricular cardiomyopathies.²⁰

Type I	Apical ballooning takotsubo cardiomyopathy
Type II	Mid-ventricular ballooning
Type III	Apical sparing cardiomyopathy
Type IV	Basal ballooning
Type V	Other segmental involvement

Sex hormones may have an influence on vasoreactivity and the neurohumoral axis. Elderly women are also known to develop abnormal basal thickening (sigmoid septum). A dynamic left ventricular outflow tract obstruction provoked during dobutamine stress¹⁷ has also been observed in patients with healed takotsubo syndrome (personal communication P.G. Melman). A severe transient left ventricular mid-cavity obstruction, caused by an abnormal myocardial architecture in the presence of dehydration and raised catecholamine levels following physical or emotional stress, has been put forward as a new theory. This subdivides the left ventricle into two functionally different chambers with a marked increase in wall stress in the high pressure distal chamber. With rehydration / fall in catecholamine levels the gradient resolves and distal function recovers.¹⁸ Hopefully, the SEAS Study (Serial Echocardiography After Subarachnoid haemorrhage) evaluating cardiac abnormalities using subarachnoid haemorrhage as a model for sympathetic stress will shed more light on the pathophysiological mechanism of the 'broken heart' syndrome.¹⁹

To end the affaire

For daily clinical practice

In case of an acute coronary syndrome with normal coronary arteries, perform a left ventriculogram, or assess left ventricular function by noninvasive techniques. Admit the patient for monitoring because death due to ventricular rupture or fibrillation can occur in the acute phase. Rule out a subarachnoidal haemorrhage or other high catecholamine states such as a pheochromocytoma. Check for dehydration and after further conservative management, check for a sigmoid septum and advise ample hydration in stressful situations to avoid another 'broken heart'. The role of (low-dose) β -blockade in the treatment of TTS is a point of discussion and warrants further investigation. ■

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