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GUEST EDITORIAL

Dynamic LV obstruction in apical ballooning syndrome: The chicken or the egg

Please see page 53 for the article by Merli et al. (doi: 10.1016/j.euje.2005.08.003) to which this editorial pertains.

The apical ballooning syndrome: a distinct entity

Between 1990 and 2001 several cases of a new heart syndrome have been reported in Japan, all in Japanese journals. This syndrome consisted of acute onset, transient left ventricular apical wall motion abnormalities with chest symptoms, electrocardiographic changes and minimal myocardial enzymatic release mimicking acute myocardial infarction in patients without significant stenosis on coronary angiogram.

It was named ''Tako-tsubo'' – shaped cardiomyopathy due to its unique ''short neck round – flask'' – like left ventricular apical ballooning resembling the *Tako-Tsubo* (Japanese for octopus pot or trap) of Japan. These reports received little or no attention in Western literature, until in 2001 a series of 88 patients were published,[1] retrospectively enrolled from cardiovascular institutes of Angina Pectoris–Myocardial Infarction investigations in Japan. In addition to describing symptoms and electrocardiographic and hemodynamic findings, this publication suggested that emotional or physical stress might play a key role in this acute cardiomyopathy since in a majority of cases a preceding aggravation of underlying disorders or acute emotional and physical problems could be identified. Because until then virtually all reports had been confined to Japanese patients, many Western cardiologists believed that it concerned a geographically restricted cardiovascular syndrome, if not a misinterpretation of rare cases of aborted anterior myocardial infarction or variant angina. But in 2003, a first European series of 13 white patients were described,[2] underscoring that this syndrome also exists outside Japan. Again the complete recovery of left ventricular function within three weeks was reported, despite the sometimes dramatic initial presentation.

It was now obvious that clinicians in the Western world should also be aware of the existence of this syndrome because this syndrome mimicking acute myocardial infarction may inadvertently expose patients to futile administration of fibrinolytic agents and, maybe more importantly, because we urgently need more information on the pathophysiology and optimal treatment of this condition.

Over the last two years, apart from numerous case reports from all over the world, two series from the United States with 22[3] and 19 patients,[4] respectively, have been published, in which the authors focused on emotional stress as the trigger provoking the syndrome.

Hence, it has become obvious that this syndrome is a distinct clinical entity with the following characteristics:

(1) Reversible (over two–three weeks) balloon-like left ventricular wall motion abnormality at the apex with hypercontraction of the basal segments, in most cases extending far beyond the perfusion territory of a single coronary artery.
(2) ST–T abnormalities on electrocardiogram, often mimicking acute myocardial infarction and most often accompanied by QT-prolongation.
(3) Chest pain and/or dyspnoea in most patients.
(4) Absence of significant coronary arterial narrowing by angiography.

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(5) Induced by physical and emotional stress in most cases.
(6) Most patients are elderly females.
(7) The prognosis for survivors is favourable.
(8) In the absence of longer known causes of reversible left ventricular wall motion abnormalities, including subarachnoid haemorrhage, pheochromocytoma crisis, acute myocarditis and tachycardia induced cardiomyopathy.

Pathophysiology

Since the first description of this syndrome, many hypotheses have been formulated, ranging from coronary artery spasm over direct catecholamine toxicity and myocarditis to left ventricular outflow tract obstruction. Obviously, the recognition of ''apical ballooning'' as a distinct entity does not necessarily imply that all cases have the same underlying pathophysiology. Indeed, the major variation in clinical presentation suggests that different mechanisms may be at play in different patients with a similar clinical picture. The severe myocardial hypocontractility with very limited release of cardiac enzymes and complete recovery over a relatively short period of time is reminiscent of myocardial stunning. Also, the observed ECG abnormalities included symmetrical diffuse T-wave inversion and QT-prolongation, a pattern that has been associated with left ventricular stunning in unstable ischaemic syndromes. By definition, stunned myocardium results from prolonged postischaemic left ventricle dysfunction after brief myocardial ischaemia. However, in none of the patients described hitherto were there definite evidence for an obstructive or flow limiting lesion on coronary angiography performed immediately after the onset of symptoms. Transient vasospasm of an epicardial coronary artery may explain this discrepancy. Arguing against this hypothesis is the observation that the area of akinesia does not correspond nicely to the perfusion territory of a single coronary artery — that is, in most patients it extends well beyond the perfusion territory of the left anterior descending artery, as well in the anterior and in the inferior portion of the left ventricle. Multiple vasospastic angina has also been postulated to be a cause of stunned myocardium in this condition. In the series of Tsuchihashi et al.[1] vasospasm could be provoked in no more than 10 of 48 patients (21%) and similar percentages are reported in other reports. Given this limited incidence of confirmed vasospasm, multiple vasospasm seems unlikely to be a main cause of this syndrome in most patients. In addition, it is not clear why multiple vasospasm would invariably afflict the same large apical portion of the left ventricle.

In the majority of cases described to date, triggering conditions that precede onset were described to consist of exposure to internal (emotional) and external stresses (trauma, surgical procedure, exacerbation of a pre-existing condition). This suggests that the enhanced sympathetic activity plays a major part in the origin of this syndrome. This is supported by the recent observation of markedly higher plasma catecholamine levels at presentation among patients with stress-induced cardiomyopathy than among those with Killip class III myocardial infarction.[4] If not by catecholamine-mediated epicardial coronary arterial spasm or microcirculatory dysfunction, myocardial stunning in this setting might be the result of direct myocyte injury by elevated catecholamine levels.[4] There is evidence that apical myocardium has enhanced responsiveness to sympathetic stimulation, potentially making the apex more vulnerable to sudden surges in circulating catecholamine levels.

Alternatively, a base-to-apex perfusion gradient, similar to that described in patients with coronary risk factors, could result in regional differences in myocardial blood flow in the setting of catecholamine-mediated epicardial or microvascular vasoconstriction.

Yet another track of hypotheses calls mechanical factors into play. Villareal et al. observed left ventricular outflow tract (LVOT) obstruction in three patients with a similar syndrome.[5] They hypothesised that patients with a sigmoid interventricular septum, small LVOT, and reduced left ventricular volumes (primarily 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. With LVOT obstruction, apical and anterior wall stress and left ventricular filling pressures increase while systemic blood pressure decreases. Increased oxygen demand and reduced coronary perfusion pressure may combine to produce myocardial ischaemia, stunning, regional wall motion abnormalities and associated T-wave changes. This hypothesis may explain the female preponderance in the patients presenting with this syndrome.

In this issue of the journal, Merli et al.[6] wander a similar path. They describe four patients, all female, who were admitted with the clinical features typical of Tako-Tsubo syndrome. In all

but one of four, severe widespread transient left ventricular mid-apical a- or dyskinesia was associated with a mid-cavity dynamic obstruction which resolved prior to the resolution of the left ventricular wall motion abnormalities and this dynamic obstruction was found to be related to a localised mid-ventricular septal thickening. After improvement in wall motion, they performed a low-dose Strain/Strain Rate dobutamine stress echocardiography that provoked a left ventricle mid-cavity gradient at peak dose in all four patients, while the affected myocardium showed the typical response diagnostic of regional stunning. Based on these findings, they postulate that the presence of an abnormal myocardial functional architecture, such as localised mid-ventricular septal thickening, could be an important unrecognised factor in the development of Tako-Tsubo cardiomyopathy: in the presence of dehydration and/or raised catecholamine levels due to physical or emotional stress, this mid-ventricular septal thickening could lead to the development of a severe transient left ventricular mid-cavity obstruction, effectively subdividing the left ventricle into two functionally different chambers with a marked increase in wall stress in the high pressure apical chamber. This, in combination with the abnormal high circulating catecholamine levels, could induce widespread subendocardial ischaemia, unrelated to a specific coronary artery territory. With rehydration or fall in catecholamine levels the intraventricular gradient would resolve and distal function would recover.

This hypothesis sounds very plausible. Indeed, it almost sounds too good to be true. The authors postulate that the observed mid-ventricular septal thickening is ''an important factor'' in the development of apical ballooning. Just how important is the observation of a dynamic left ventricular mid-cavity obstruction at the site of an abnormal mid-septal thickening during dobutamine stress echocardiography in four out of four patients and on admission in three out of four patients? Does this imply a true causal relationship? Or is the observed septal thickening rather a predisposing or contributing factor, or an absolutely necessary prerequisite, i.e. can patients with a perfectly normal septum never fall subject to the apical ballooning syndrome? Or is this just a chance finding? Obviously, a report on four patients can never provide definite answers to these questions, but it can be hypothesis-generating and constitute an impetus for future research.

What was the incidence of left ventricular obstruction in other published series? While many case reports make no mention of it, 12 out of 72 patients (18%) in Tsuchihashi's series[1] and only two out of 13 patients in our report[2] had a significant intraventricular gradient on an early echocardiogram. Sharkey et al.[3] mention five patients with hypotension and receiving dobutamine (out of a total of 22) who developed dynamic left ventricular obstruction due to mitral valve systolic anterior motion, which rapidly resolved after termination of the drug. Finally, Wittstein et al. make no mention of an intraventricular gradient in any of their 19 patients, although all patients underwent transthoracic echocardiography within 24 h after the onset of symptoms.[4] On the contrary, they describe moderate-to-severe dysfunction in the mid-ventricle on the initial echocardiogram.

Hence it is impossible to calculate the true incidence of any form of acute intraventricular obstruction in the early phase of the apical ballooning syndrome, but it certainly seems very unlikely to be higher than 20%.

If intraventricular obstruction was an important factor in this syndrome — as Merli et al. suggest — how can the until now reported low incidence be explained? Did those different authors miss a present gradient on the initial echocardiogram, because they were focused too much on other details? This seems an unlikely explanation. Or did they perform the first ultrasound examination at too late a time point in the course of the disease, i.e. at a time when the intraventricular gradient had resolved in most cases? In this respect, it is regrettable that Merli et al.[6] did not report the exact timing of their initial echocardiogram in relation to the onset of symptoms.

Since the apical ballooning syndrome most often clinically presents as an acute coronary syndrome, most patients are indeed rushed to the catheterization laboratory and echocardiography is often postponed until later. It is thus conceivable that an initially present intraventricular gradient has eventually resolved by the time of the echocardiogram. On the other hand, a significant intraventricular gradient in the apical ballooning syndrome should not be overlooked during cardiac catheterization, and a majority of the patients reported to date did undergo an echocardiogram early on and were not found to have a gradient.

All these suggest that the mechanism proposed by Merli et al. may at most play a contributory part and is not a prerequisite in most patients. Indeed, we must bear in mind that we are dealing with a syndrome that does not necessarily has an identical pathophysiology in all patients, similar to the syndrome of shock, that is the final common result of diverse pathophysiological processes (cardiogenic, septic, obstructive, …).

Could the observed intraventricular gradient be a consequence rather than a cause of apical ballooning? And can the inducibility of a mid-ventricular gradient during dobutamine stress echocardiography be no more than a chance finding? Studying 237 patients without dobutamine stress echocardiography provoked ischaemia, Dawn et al. observed a dynamic left ventricular obstruction in 83 (35%) patients during high dose dobutamine administration: 54 (22.8%) showed provoked left ventricle mid-cavitary obstruction and 29 (12.2%) outflow tract obstruction.[7] In view of these findings, it is not surprising to find a dynamic left ventricular obstruction in a significant minority of patients with the apical ballooning syndrome, since they have markedly elevated catecholamine levels[4] while the basal portions of their left ventricles already have to compensate for the extensive apical dysfunction. In the same respect, it is not very surprising that an intraventricular gradient could be provoked in all four patients in the present study, albeit at a lower dobutamine dosing. In addition, according to the mechanism proposed by Merli et al., the intraventricular gradient would resolve with falling catecholamine levels or rehydration. In clinical practice, these patients seem to start improving after one or two days while — in contrast — the study by Wittstein et al.[6] found catecholamine levels to be still markedly elevated after three—five days. The latter data suggest that the catecholamine surge is not just the short-lived direct result of a transient emotional or physical stress, but rather that this stress triggers a kind of catecholamine ''avalanche'', that has not stopped by the time the patient is clinically improving.

In summary, the present study by Merli et al. has created more questions than it has answered, but, in doing so, it has provided the cardiological community with new parameters to focus our attention on when confronted with these patients.

Therapy and prevention of recurrence

Indeed, since it is now estimated that about one percent of initially perceived myocardial infarctions turn out to be cases of apical ballooning and since recurrences of this condition have been reported, we urgently need to learn more about the pathophysiology of this condition, not only to treat our patients in the best possible way, but also to be able to predict the chance of recurrences or even prevent recurrences.

Eventually, the optimal approach may not be the same for all patients presenting with this syndrome, since various pathophysiological mechanisms may underlie the final clinical picture. In addition, the treatment of choice may depend on the stage of the condition. Indeed, while some of these patients have been successfully treated with β-adrenoceptor blockade, α-adrenoceptor agonism and volume expansion, many others have received positive inotropic agents and intra-aortic balloon counterpulsation.

Since the optimal treatment of some patients presenting with this syndrome may thus be detrimental to other patients, it is of vital importance that the cardiological community gather this needed information. It seems logical that repeated echocardiography will play a major role herein, and the authors of the present paper have undoubtedly provided us with a new focus of our attention.

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