Tako-Tsubo cardiomyopathy: New insights into the possible underlying pathophysiology

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Abstract   Tako-Tsubo cardiomyopathy is characterised by an atypical distribution of left ventricular (LV) dysynergy with apical ballooning and compensatory basal hyperkinesis. Coronary angiography is normal. Several substrates have been put forward to explain the underlying pathophysiology such as raised catecholamine levels (due to physical or emotional stress), multivessel epicardial coronary spasm or diffuse microvascular spasm. However, the pathophysiology has not yet been fully clarified. We present a series of cases whose findings could explain the mechanism underlying this syndrome. Four consecutives patients, all female, were admitted with the clinical features typical of Tako-Tsubo syndrome. In all, severe widespread transient LV mid-apical a/dyskinesia was associated with a mid-cavity dynamic obstruction which resolved prior to the resolution of the LV wall motion abnormalities. In all cases the dynamic LV obstruction was related to localised mid-ventricular septal thickening. After improvement in wall motion, a low-dose strain/strain rate dobutamine stress-echocardiography (DSE) was performed to determine the underlying ischaemic substrate. This provoked an LV mid-cavity gradient at peak dose in all. Regional deformation changes during DSE showed the affected myocardium to have the typical response diagnostic of regional stunning.
Conclusion: We postulate that an important unrecognised factor in the development of Tako-Tsubo cardiomyopathy is the presence of abnormal myocardial functional architecture (such as localised mid-ventricular septal thickening), which in the presence of dehydration and/or raised catecholamine levels due to physical or emotional stress, leads the development of a severe transient LV mid-cavity obstruction. This effectively sub-divides the LV into two functionally different chambers with a marked increase in wall stress in the high pressure distal apical chamber. This, in combination with the abnormal high circulating catecholamine levels, induces widespread sub-endocardial ischaemia which is unrelated to a specific

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coronary artery territory. With rehydration/fall in catecholamine levels the inter-ventricular gradient resolves and distal function recovers. Low dose SR/S DSE confirms that the distal ischaemic substrate is myocardial stunning.

Introduction

''Tako-Tsubo'' cardiomyopathy is characterised by the finding of transient left ventricular (LV) dysynergy (typically apical ballooning with concomitant compensatory basal hyperkinesis). It has also been called the Ampulla Syndrome, Broken Heart Syndrome, Neurogenic Stunned Myocardium or Acute Stress Cardiomyopathy. Typically, the area of myocardium involved does not correspond to any specific coronary artery territory.

Clinically it is characterised by the acute onset of chest pain and is associated with ECG changes such as ST elevation, ST depression or deep T wave inversion which mimic an acute coronary syndrome. Myocardial CK and Troponin T or I levels are often slightly elevated. At coronary angiography there are no significant coronary artery lesions despite the presence on left ventricular angiography of typical apical ballooning with compensatory basal hyperkinesis (Fig. 1). It is a rare and under recognised syndrome, prevalent in women, typically in the elderly (although few cases are described in younger women), who present with a history of recent emotional or physical stress. With conservative treatment, the apical ballooning resolves spontaneously within an average of 18 days (range 9–53 days). Myocardial perfusion studies typically show a reduced apical uptake which normalizes in 25–90 days. Cardiac MRI studies performed within the first 5 days using delayed hyperenhancement imaging with gadolinium, demonstrated no evidence of either scar or of the typical mid-myocardial gadolinium uptake characteristic of myocarditis.[1–7]

The pathophysiologic mechanisms underlying the transient left ventricular apical ballooning are unclear. Several possible explanations have been proposed such as focal myocarditis, catecholamine toxicity, multivessel coronary spasm, impaired coronary microcirculation and myocardial stunning but all have been disputed. Kurisu et al.[1] retrospectively examined 30 Japanese patients (28 female). They measured plasma catecholamine concentration (6 patients), tested spasm provocation with ergonovine and acetylcholine (14 patients), took endomyocardial biopsies (3 patients) and measured viral titres (7 patients). A clear single underlying cause was not found in this group: coronary spasm (ergonovine or acetylcoline) could be induced in 10 patients (in 4 patients a single vessel coronary spasm, in 6 patients a multivessel coronary spasm). Virus titres were not elevated. Norepinephrine levels were elevated in 3 patients.
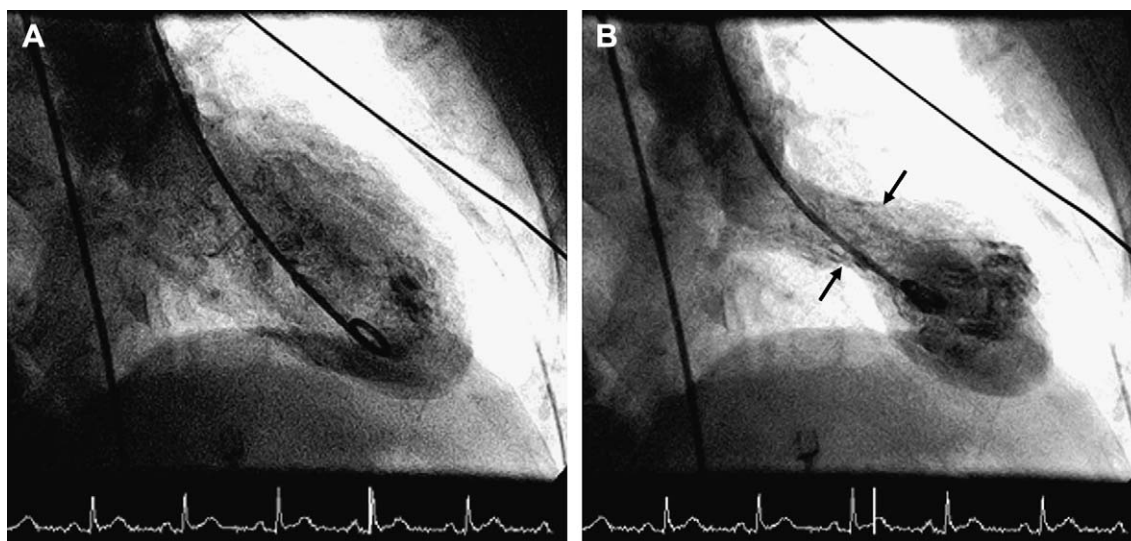

Figure 1 Case 2. End-diastolic and end-systolic left ventriculograms on admission. (A) End-diastole, (B) end-systole. End-systolic ventriculogram looks like a 'Japanise pot' (Tako-Tsubo) with a round bottom and a narrow neck (arrowed).

Recently, Wittstein et al.[8] demonstrated elevated plasma catecholamine levels at admission in a series of 19 patients from United States presenting with myocardial stunning due to sudden emotional stress. Scuteri et al.[9] examined 11 patients, all women, with apical ballooning syndrome. Six underwent ergonovine stress echocardiography which was negative in all 6 patients. This finding would seem to rule out the coronary spasm hypothesis in these patients. Furthermore, in 2 patients they found that a left ventricular mid-cavity obstruction could be induced during low-dose dobutamine study. The authors hypothesize that this could play a role in the pathogenesis of apical ballooning in some cases. However, the presence of LV mid-cavity gradient had not been sought for during the acute presentation. Thus, to date, a uniform mechanism explaining this syndrome remains unclear.

We report a consecutive series of four cases of Tako-Tsubo syndrome in which the clinical findings would suggest a possible mechanism which would lead to an explanation of the interacting pathophysiologies underlying the Tako-Tsubo syndrome.

Methods

Between April and September 2004, 4 consecutive female patients (mean age = 73 years) presented with the typical clinical features and investigative findings of Tako-Tsubo syndrome. Clinical data, including coronary angiography were available for review in every case. One had correlative cardiac magnetic resonance imaging data. Standard cardiac ultrasound data (including Doppler myocardial imaging data) were acquired with a Vivid Seven ultrasound scanner (GE, Vingmed, Norway) at admission and at 2 weeks follow-up when the wall motion abnormalities had visually resolved. In addition to the resting studies, a low-dose dobutamine stress-echocardiography with Doppler myocardial imaging (DMI) data acquisition for regional strain/strain rate quantitation was performed at the 2 weeks follow-up investigation. For the latter studies, dobutamine was infused at 2.5, 5, 10, 15, 20 mcg/kg/min for 3 min steps. Echocardiographic data were acquired at low-dose (5 mcg/kg/min), intermediate dose (10 mcg/kg/min), peak dose (20 mcg/kg/min), and recovery. For functional analysis, the left ventricle was divided into the 16 standard myocardial segments. Doppler myocardial velocity imaging data were acquired for subsequent post-processing to derive regional deformation curves from each myocardial wall segment (septal, antero-septal,

anterior, lateral, posterior, and inferior) as previously described in our work.[10] Peak systolic strain (ε_{sys}) and maximal strain (ε_{max}) were calculated. The ε_{sys} was defined to be the magnitude of deformation measured from end diastole to end systole. The ε_{max} was defined to be the magnitude of deformation from end diastole to maximal shortening. From these two measurements, a post-systolic strain index (PSI) was calculated using the following equation: $PSI = (\varepsilon_{max} - \varepsilon_{sys})/\varepsilon_{sys}$. Late (6 months–1 year) follow-up resting ultrasound studies were available in all patients which confirmed complete normalisation of regional deformation indices.

Results

Clinical and echocardiographic findings are shown in Table 1.

Case 1

A 74-year-old woman was referred following chest tightness and a collapse immediately after playing tennis. Immediately prior to this she had felt hot, sweaty and vomited once, but had no other symptoms. She had no relevant past medical history. Her admission resting ECG showed right axis deviation, right bundle branch block and widespread deep T wave inversion. Troponin I levels were raised at 4.26 μg/l. An initial cardiac ultrasound study showed the typical features of widespread apical ballooning of the left ventricle. A conservative management strategy was pursued as she remained clinically well. Repeat echocardiography, performed at day 10, showed a normal LV cavity size (EDV Simpson biplane equation 75 ml), with mild apical hypokinesia and evidence of abnormal persisting post-systolic thickening on anatomical M-mode in the previously ballooning myocardium around the LV mid-wall and apex. There was a localised mid-basal septal thickening (end-diastolic wall thickness = 1.2 cm compared to 0.9 cm in the mid-apical septum) (Fig. 2) but this was not causing any significant LV mid-cavity/outflow gradient at rest. There was a mild reduction in global systolic LV function. Correlative coronary angiography confirmed unobstructed coronary arteries.

On day 20 a low-dose dobutamine stress-echocardiogram was performed. At peak dose a dynamic LV mid-cavity gradient of 80 mmHg was induced (Fig. 3). Strain curve analysis of the acquired data showed the typical features of stunned myocardium with normalisation of the

Table 1 Clinical and echocardiographic findings

	Sex	Age	Potential trigger	ECG	Enzymes	ED mid-septal thickness (cm)	ED thickness septal apical segments (cm)	Peak intracavity dynamic gradient (day 1) (mmHg)	Recovery dynamic gradient (day 20) (mmHg)	DSE provoked dynamic gradient (day 20) (mmHg)	DSE stunning response
Case 1	F	74	Dehydration/heat/exercise	Widespread deep T wave inversion	Trop T = 4.26[a], CK = 200[b]	1.2	0.9	80	10	80	yes
Case 2	F	72	Dehydration/exercise	ST elevation in V3–V6	Trop T = 1.82[a], CK = 160[b]	1.4	1.2	63	12	64	yes
Case 3	F	71	Hip replacement/stress	ST elevation in V3–V6	Trop T = 4.2[a], CK = 156[b]	1.3	1.0	64	8	60	yes
Case 4	F	75	Type B dissection/stress	LBBB	Trop T = 1.2[a], CK = 300[b]	1.3	1.0	70	10	60	yes

DSE: Low-dose dobutamine stress-echocardiography; ED: end-diastolic.
[a] μg/l.
[b] U/l.

abnormal deformation in the apical myocardial segments.[11] At 1 year follow-up, LV systolic deformation was entirely normal with no evidence of abnormal residual post-systolic deformation in the apical segments.

Case 2

A 72-year-old woman was admitted with chest discomfort after playing golf on a hot day. Her resting ECG showed ST elevation in leads I and II, V3–V6. Troponin T was 1.82 μg/l and CK 160 U/l. Coronary angiography demonstrated normal coronary arteries. The left ventriculogram showed the typical apical ballooning of Tako-Tsubo Syndrome with marked mid-apical dyskinesia and hyperkinesis of the basal segments (Fig. 1). Echocardiography performed on the same day showed normal left ventricular size with a marked area of mid-basal myocardial septal thickening (end-diastolic wall thickness = 1.4 cm compared to 1.2 cm in the mid-apical septum) (Fig. 2) and mid and apical akinesia involving all LV walls with severely reduced systolic function. A standard Doppler blood pool study showed the presence of a dynamic left ventricular mid-cavity obstruction at the site of the area of the abnormal mid-septal thickening with a maximum intra-cavity dynamic gradient of 63 mmHg (Fig. 3). Anatomical M-mode[12] analysis of the apical segments showed a marked reduction in systolic thickening and post-systolic thickening. Strain imaging showed reduced systolic strain with marked post-systolic deformation in all apical segments (Fig. 4). This pattern was diagnostic of post-ischaemic myocardium.[11] Echocardiography 14 days later showed the apical akinesia to have completely recovered on visual inspection. However, on deformation imaging there was an increase in systolic strain towards normal values but there was a persistence of abnormal post-systolic shortening in apical segments. There was no residual mid-cavity obstruction. On day 20 a low-dose dobutamine stress-echocardiography was performed using the same protocol described above. At peak dose a dynamic intra-cavity gradient of 64 mmHg was induced. This gradient resolved during the recovery period. The DSE response of the apical myocardial segments was further normalisation indicating that this was resolving stunning[11] (Fig. 5). At 6 months follow-up strain/strain rate imaging data showed normal systolic deformation with no evidence of significant post-systolic shortening.
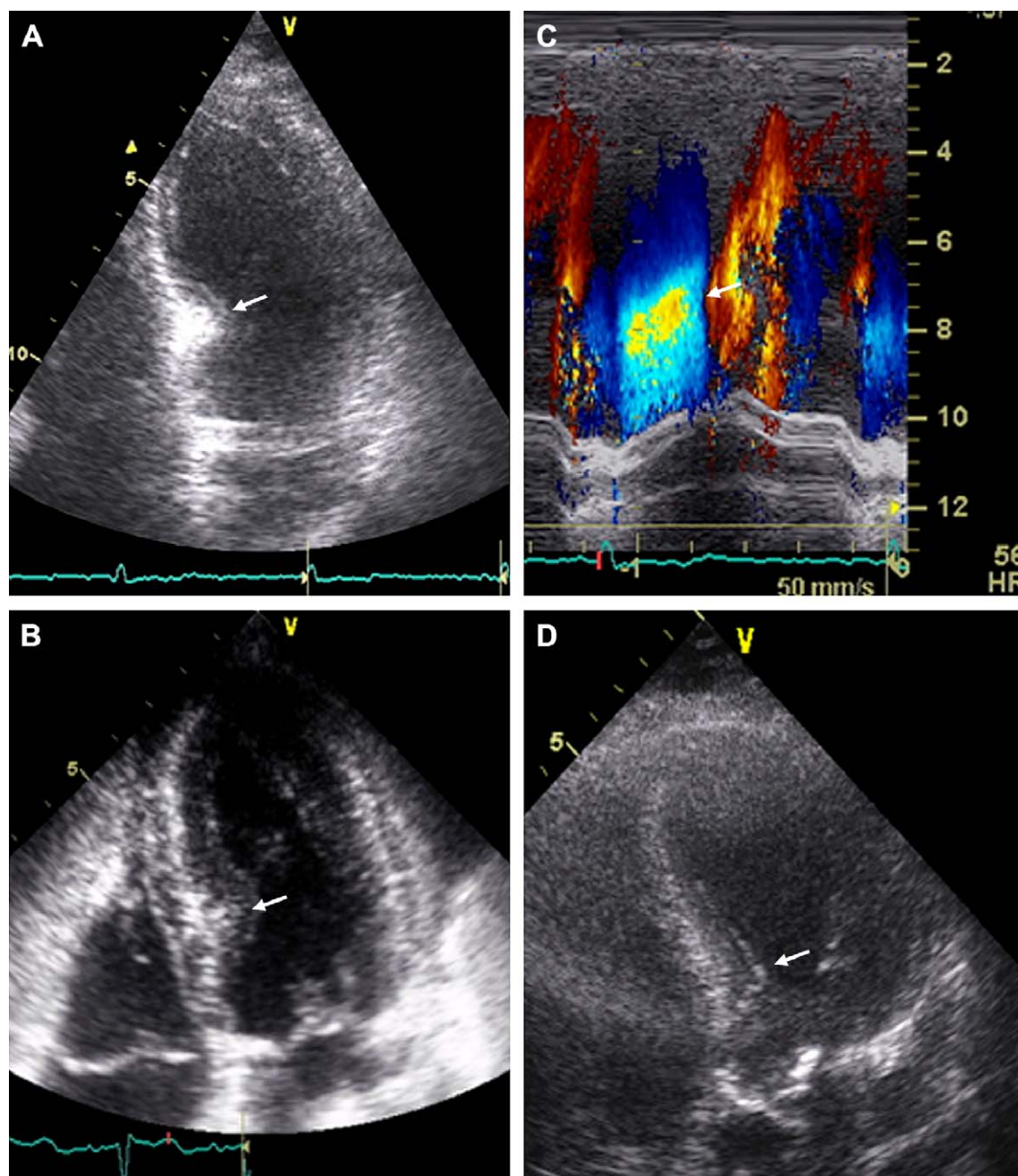
Figure 2 (A,B,D) Left ventricular 4-chamber view in Cases 1, 2 and 3, respectively. The area of mid-basal septal thickness is arrowed. (C) Color M-mode across the left ventricle showing the presence of a region of flow acceleration in correspondence of the mid-basal septal thickness.

Case 3

A 71-year-old woman presented with chest pain and dyspnoea 3 days after uncomplicated hip surgery. ECG showed ST elevation in V3–V6. Peak Troponin I was 4.2 µg/l and CK was 156 U/l. Coronary angiography demonstrated normal coronary arteries. The left ventricular angiogram showed the typical apical ballooning of Tako-Tsubo syndrome. Echocardiography showed normal left ventricular size with a localised mid-basal septal area of myocardial thickening (end-diastolic wall thickness = 1.3 cm compared to 1.0 cm in the mid-apical septum) (Fig. 2) and apical akinesia with a left ventricular mid-cavity dynamic gradient of maximal 64 mmHg (Fig. 3). Regional strain/ strain rate imaging showed the presence of reduced systolic deformation (ε_{sys} = 5%) with
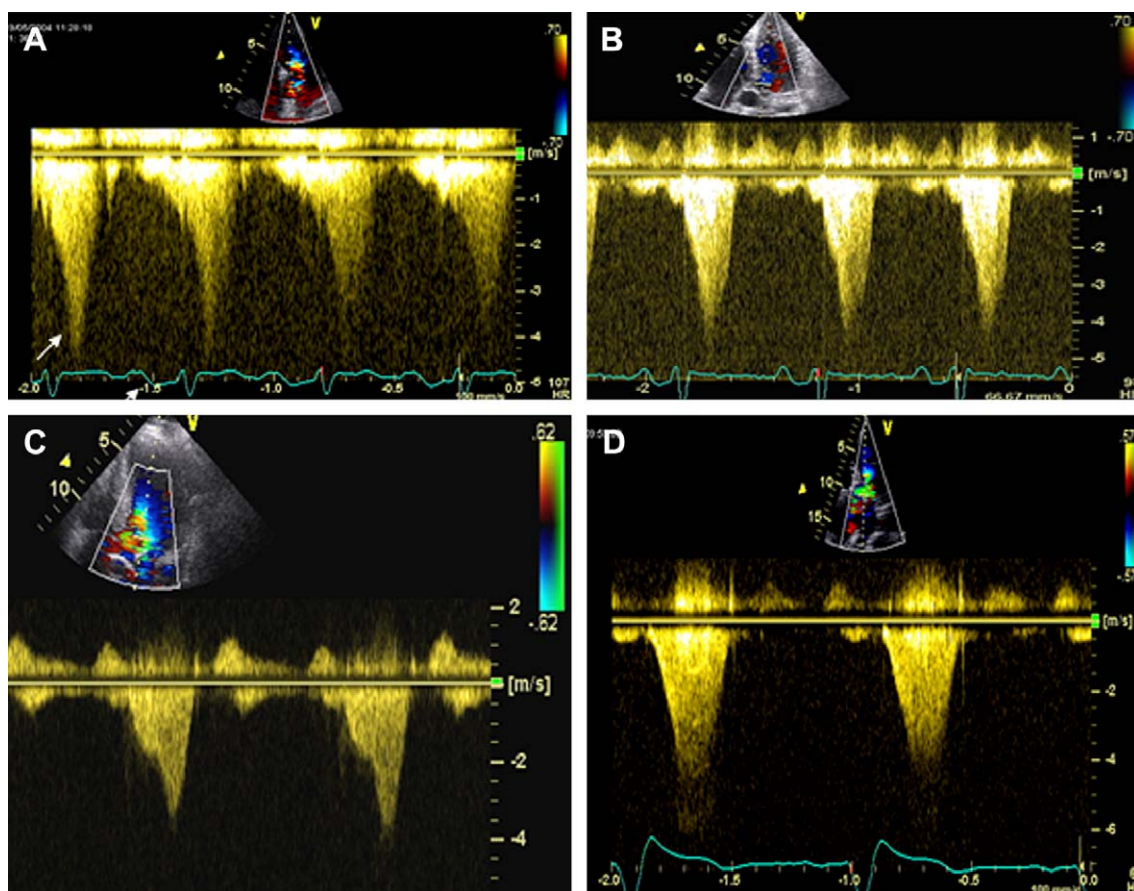
Figure 3 Continuous wave velocity flow profile of the left ventricular peak mid-cavity dynamic gradient recorded on admission in Cases 1, 2, 3 and 4 (A,B,C and D, respectively).

significant post-systolic deformation ($\varepsilon_{max} = -13\%$; PSI = 1.6) in the abnormally contracting mid and apical LV walls. This pattern was diagnostic of post-ischaemic myocardium.[11] Echocardiography at day 20 post admission showed complete normalisation of the apical wall motion abnormalities and an absence of abnormal post-systolic deformation in the mid-apical walls. There was no residual LV intra-cavity gradient at rest. Cardiac MRI with gadolinium late-enhancement showed no evidence of myocardial scar. A low-dose dobutamine stress-echocardiography was performed in the manner described above. At peak dose an intra-cavity dynamic peak gradient of 60 mmHg was induced. The gradient resolved during recovery. The DSE response of apical myocardial segments was typical for stunned myocardium. At 6 months follow-up systolic deformation was normal in all left ventricular segments.

Case 4

A 75-year-old woman was admitted with acute chest pain radiating to her back. This was found to be due to an acute type B localised thoracic aortic dissection. The ECG showed left bundle branch block. Troponin T was 1.2 μg/l and CK was 300 U/l. She had normal coronary angiography and no evidence of any ascending aortic or aortic valve abnormality. Echocardiography performed at admission showed normal left ventricular cavity size with characteristic severe mid-apical LV ballooning and hypercontractility of basal segments. The left ventricular mid-basal septum had a localised area of increased thickness (end-diastole 1.3 cm compared to 1.0 cm in the mid-apical septum). There was a mid-cavity dynamic obstruction of 70 mmHg. After she was rehydrated the mid-cavity dynamic gradient disappeared. After 2 weeks of conservative treatment, LV function had fully recovered. A low-dose dobutamine stress-echocardiogram was performed in the manner described above. At peak dose an intra-cavity dynamic peak gradient of 60 mmHg was induced. The gradient resolved during recovery. The DSE response of apical myocardial segments was typical for stunned myocardium. At 6 months follow-up systolic deformation was normal in all left ventricular segments.
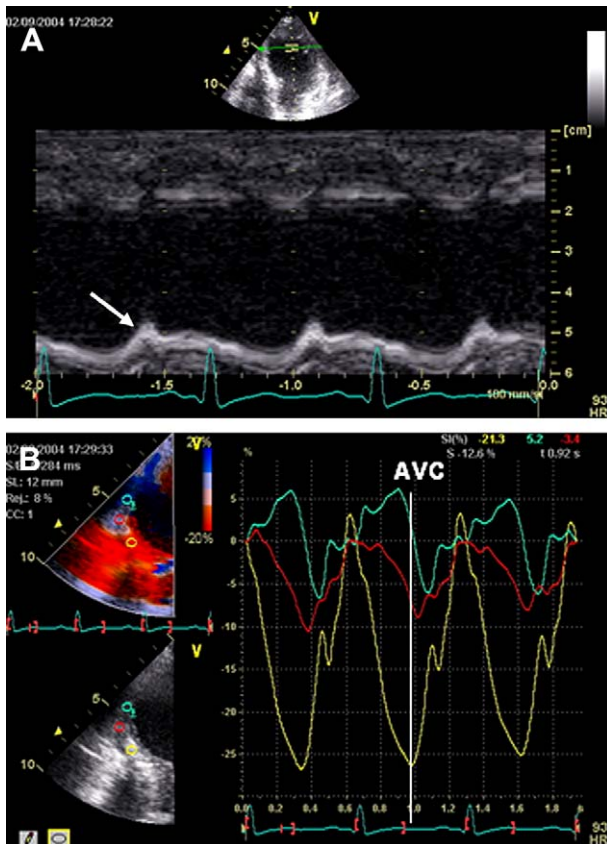
Figure 4 (A) Case 2. Anatomical M-mode of the apical septum on admission showing the absence of systolic thickening with marked post-systolic thickening (arrow). (B) Strain curve of the corresponding septal segment showing reduced apical systolic deformation ($\varepsilon_{sys} = -4\%$) with significant post-systolic deformation ($\varepsilon_{max} = -10\%$; PSI = 150%, pattern consistent with post-ischaemic myocardium) and normal systolic deformation in the mid-septum.

Discussion

To date the pathophysiology of Tako-Tsubo syndrome has not been clearly established. One hypothesis has suggested that epicardial coronary spasm could be the sole aetiology and due to a stress trigger. Currently this hypothesis is the favoured explanation. Others have suggested that microvascular spasm alone might explain the clinical findings. Yet either of these hypotheses can account for the marked discrepancy between the distribution of the transient wall motion abnormalities and the distribution of epicardial coronary artery flow. Thus, there must be other factors involved. One mechanism that could explain the above findings is the combination of an induced severe transient mid-ventricular cavity dynamic gradient combined with a catecholamine induced reduction in sub-endocardial flow. Such

a dynamic mid-cavity obstruction would separate the left ventricle into two chambers, a proximal chamber at normal pressure with normal wall stress and an apical chamber at high pressure with high wall stress. This alone would reduce sub-endocardial coronary flow in the apical chamber. Such a dynamic intra-cavity obstruction would be accentuated by hypovolaemia. The added increase in circulating catecholamines would only potentiate the decrease in sub-endocardial coronary flow. Such a combined mechanism would account for the discrepancy between epicardial coronary vessel supply territory and the diffuse apical nature of the myocardial contraction abnormalities which would thus be restricted only to the high pressure apical chamber. Why then is the resultant myocardial substrate that of stunned myocardium and why is there no progression to sub-endocardial infarction? Again the proposed underlying mechanisms would account for this. As sub-endocardial ischaemia becomes intense in the distal chamber, sub-endocardial contractile function will fail and the myocardium around the walls of the high pressure chamber will fail to generate pressure and the precipitating intra-cavity pressure gradient will fall in turn relieving the sub-endocardial ischaemia. As the epicardial vessels are unobstructed flow will return to the inner wall. In theory, the process could then repeat itself until catecholamine levels fell without the distal myocardium progressing to infarction. Such a sequence of events would require a primary abnormality in the ventricular myocardium which would allow the induction of a severe mid-cavity gradient. This could either be caused by an abnormal region of localised septal hypertrophy or an abnormal arrangement of left ventricular fibre distribution. Such an abnormality has already been observed by Scuteri et al.[9] in some of their patients, but they did not scan all patients on admission and thus may have missed the presence of an intra-cavity dynamic gradient.

What other evidence exists which could support such a hypothesis? Elderly women are known to develop abnormal basal/mid-septal thickening (sigmoid septum)[13] the aetiology of which is unclear. This structural abnormality is known, in a sub-set of these patients, to be associated with the ability to develop a dynamic mid–cavity obstruction during either a dobutamine challenge or when such patients become dehydrated.[14] The female preponderance in localised septal hypertrophy in the elderly could in part account for the sex bias in the Tako-Tsubo patient population. Furthermore, patients with concentric left ventricular hypertrophy or sigmoid septum are known to
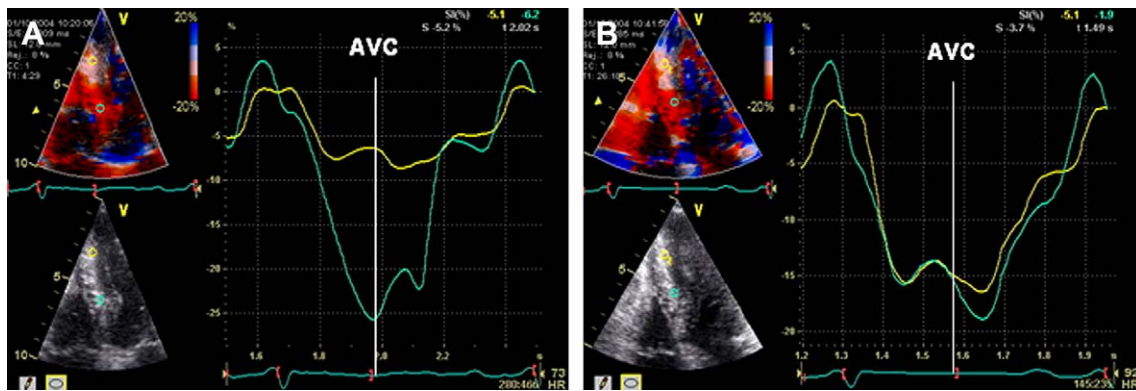
Figure 5 Case 2. Strain curve of basal and apical septum during low-dose dobutamine stress-echocardiography. (A) At baseline mid-basal systolic deformation is normal ($\varepsilon_{sys} = -20\%$) whereas apical systolic deformation is reduced ($\varepsilon_{sys} = -6\%$) with significant post-systolic deformation ($\varepsilon_{max} = -9\%$; PSI = 50%; pattern consistent with post-ischaemic myocardium). (B) At peak dose apical systolic deformation normalised: $\varepsilon_{sys} = -15\%$; $\varepsilon_{max} = -16\%$; PSI = 6%. This response is typical for stunning myocardium. AVC = Aortic valve closure.

develop high intra-cavity dynamic gradients when being weaned from cardiopulmonary bypass. These are most frequently caused by unrecognised hypovolaemia. These gradients can usually be reduced or eliminated by a combination of appropriate volume replacement and beta-blockade. Yet these patients do not often progress to develop a Tako-Tsubo response. Perhaps the difference here is the lack of the other prerequisite: the very high level of circulating catecholamines needed to induce the intense sub-endocardial vasoconstriction. Dawn et al.[15] found induced LV mid-cavity obstruction during DSE in 54 patients with no evidence of induced ischaemia. At follow-up this finding was not an independent predictor of occurrence of chest pain or syncope. This suggests that induced mid-cavity obstruction during beta-stimulation itself cannot identify patients who, in the absence of other concomitant factors, will subsequently develop a Tako-Tsubo syndrome.

Thus, having postulated that the abnormalities might be due to a unique combination of factors, we prospectively studied four patients with the clinical features typical of Tako-Tsubo syndrome. In all four cases we documented (1) a physical stress trigger, (2) the presence of abnormal mid-LV septal hypertrophy (mean 1.3 cm in end-diastole), (3) the presence of an important dynamic intra-cavity LV obstruction at the onset of symptoms, (4) low dose S/SR DSE confirmed that the distal ischaemic substrate was myocardial stunning and (5) that an important intra-cavity LV dynamic obstruction could still be induced during a low-dose dobutamine challenge at follow-up when the functional features of the Syndrome had resolved thus indication that these ventricles had the

predisposition to develop mid-cavity obstruction if appropriately challenged.

Therefore, we postulate that the pathogenesis of Tako-Tsubo cardiomyopathy is multifactorial and requires the ventricle (1) to have the predisposition to develop dynamic mid-cavity obstruction if provoked (2) to have a combination of either catecholamine stress or hypovolaemia to induce the gradient and (3) to have non-obstructed epicardial vessels to protect against sub-endocardial or full thickness infarction in the apical high pressure chamber.

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