Coronary Artery Disease in Takotsubo Cardiomyopathy

Dariusch Haghi, MD; Theano Papavassiliu, MD; Karsten Hamm, MD; Jens J Kaden, MD; Martin Borggrefe, MD; Tim Suselbeck, MD

Background Significant coronary artery disease (CAD) is generally considered as an exclusion criterion for the diagnosis of takotsubo cardiomyopathy (TC). However, this may not be justified in all cases, because TC and CAD may coincide.

Methods and Results Among 821 consecutive patients who underwent urgent left heart catheterization for suspected acute coronary syndrome between December 2004 and August 2006 those with a final diagnosis of TC who also had a stenotic lesion (diameter stenosis on quantitative coronary angiography >50% and <75%) of the left anterior descending artery were evaluated. Four patients met the inclusion criteria. Previous coronary angiograms were available for 2 of these patients and showed no change in the angiographic appearance of the lesions. Intravascular ultrasound study was performed in the other 2 patients and demonstrated negative remodeling and no signs of plaque rupture, thrombus, positive remodeling or intimal dissection.

Conclusions The present study supports the notion that TC and CAD are not mutually exclusive disease entities. Excluding the diagnosis of TC on the sole basis of an incidental finding of CAD may not be justified in all cases. Rather, a case-by-case decision process seems more appropriate. (Circ J 2007; 71: 1092–1094)

Key Words: Apical ballooning syndrome; Coronary artery disease; Takotsubo cardiomyopathy

Takotsubo cardiomyopathy (TC) is characterized by the finding of transient left ventricular (LV) wall motion abnormalities (WMA), typically accompanied by chest pain, dynamic reversible ST–T segment abnormalities and mild elevation of cardiac enzymes disproportionate to the extent of regional WMA! The majority of patients present with a recent history of emotional or physical stress2–4 Prolongation of the QT interval is another common feature of the syndrome5,6 The pathophysiology of this enigmatic disease remains unknown; however, catecholamine excess7 and coronary microvascular dysfunction8,9 seem to play an important role.

Abe and Kondo10 and Bybee et al11 have proposed criteria for making the clinical diagnosis of TC. Although the criteria by Abe and Kondo require exclusion of ischemic myocardial stunning, the criteria by Bybee et al (Mayo Clinic criteria) are stricter and require absence of obstructive coronary artery disease (CAD). The vast majority of recently published studies (for a comprehensive review refer to Gianni et al12) have excluded patients with significant CAD. However, as awareness of this syndrome is increasing and the number of new diagnoses is growing, it seems justified to assume that the chances of incidentally discovering CAD in these patients are also on the rise. Thus, if TC is a unique syndrome, is it then justified to exclude patients with characteristics of the syndrome just because they have concomitant CAD? The following study presents our experience with this subgroup of patients.

Methods

From December 2004 to August 2006, 821 patients underwent urgent left heart catheterization for suspected acute coronary syndrome (ACS) at our institution. Among these, 4 patients were finally diagnosed with TC, but also had an incidental finding of a non-critical lesion (diameter stenosis on quantitative coronary angiography >50% and <75%) of the left anterior descending artery (LAD) and one of the following: (1) previous coronary angiogram within the past 6 months; or (2) an intravascular ultrasound study (IVUS) of the LAD within 24 h of presentation. The diagnosis of TC was based on the following criteria: (1) extensive reversible LV WMA of the LV apex and mid portion (classical TC) or LV base and mid portion (variant TC) on left ventriculography; (2) dynamic ST–T segment abnormalities; and (3) elevation of cardiac enzymes.

The performance of this study was consistent with the standards of the local ethical committees at our institution.

Results

All patients were women and all patients underwent left heart catheterization within 24 h of presentation (Table 1). The LV apex was involved in 3 patients (classical TC) and was spared in 1 (variant TC). Reversibility of the initial WMA could be demonstrated by echocardiography. The LAD wrapped around the LV apex in all cases. Two patients had previous angiograms for chronic stable angina 6 weeks (patient 1) and 3 months (patient 2) prior to presentation and 2 patients (patients 3 and 4) underwent IVUS of the LAD using a commercially available system (Volcano Therapeutics). Compared with the previous angiogram, no change in the appearance of the LAD lesion was demonstrable in patients 1 and 2 (Fig 1). IVUS imaging in patients 3 and 4 (Fig 2) showed a non-calcified soft plaque with negative remodeling in patient 3 and a calcified plaque with...
Table 1 Patients’ Characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
<td>Age (years)</td>
<td>73</td>
<td>64</td>
<td>74</td>
<td>77</td>
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<tr>
<td>Peak CK (U/L)</td>
<td>152</td>
<td>154</td>
<td>2,407</td>
<td>81</td>
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<tr>
<td>[normal range: 0–145]</td>
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<tr>
<td>Peak troponin I (ng/L)</td>
<td>0.93</td>
<td>&lt;0.03</td>
<td>12.64</td>
<td>1.34</td>
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<tr>
<td>[normal range: 0–0.4]</td>
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<tr>
<td>Preceding stressor</td>
<td>Argument</td>
<td>Surgery</td>
<td>Lying helplessly on the floor after syncope</td>
<td>–</td>
</tr>
<tr>
<td>Presenting symptom</td>
<td>Angina</td>
<td>Angina</td>
<td>Mild dyspnea</td>
<td>Angina</td>
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<td>ECG abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ST elevation</td>
<td>V2–4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ST depression</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>T-wave inversion</td>
<td>FU: I, II, aVL, V2–6</td>
<td>I, aVL, V2–6</td>
<td>FU: I, aVL, V2–6</td>
<td>II, III, aVF, V2–6</td>
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<tr>
<td>Type</td>
<td>Classical</td>
<td>Variant</td>
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<td>QCA diameter stenosis of LAD (%)</td>
<td>69</td>
<td>57</td>
<td>55</td>
<td>53</td>
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</table>

CK, creatine kinase; FU, follow-up; QCA, quantitative coronary angiography; LAD, left anterior descending artery.

Fig 1. Left ventriculogram of patient 2 in diastole (A) and systole (B). Note the ballooning of the midventricular segments. Coronary angiography in the same patient demonstrating stenosis of the left anterior descending artery 6 weeks prior to presentation (C), upon presentation (D) and 4 weeks later (E).

Fig 2. Left ventriculogram of patient 3 (A) and patient 4 (D) in systole. Note the ballooning of the apical and midventricular segments. Coronary angiography demonstrating stenosis of the left anterior descending artery (arrow) in patient 3 (B) and patient 4 (E). Corresponding intravascular ultrasound images of the lesions (C and F).
an arc of calcium of 100° and negative remodeling in patient 4. No signs of plaque rupture, thrombus, positive remodeling or intimal dissection were present. Two patients (patients 2 and 3) also underwent gadolinium-enhanced cardiovascular magnetic resonance (CMR) imaging, which did not show areas with late gadolinium enhancement (LGE).

**Discussion**

The present study results support the notion that TC and CAD are not mutually exclusive disease entities, which should not come as a surprise, because patients with TC are mostly elderly and have a high priori likelihood of having risk factors for CAD. In their recent review of relevant studies on TC Gianni et al. report a mean age of 58–77 years and an incidence of diabetes in 11%, of current or past smoking in 23%, of dyslipidemia in 25% and of hypertension in 43% of patients with TC.

Two patients in our small series had an identical angiographic appearance of their LAD lesion when compared with a previous angiogram. Although this observation does not entirely rule out a potential causative role of the lesion, it makes it rather unlikely. More convincingly, the LV WMA observed in patient 2 are much more likely to be caused by TC than obstructive CAD, as this is a typical example of the variant form of TC. Two other patients in our series underwent IVUS upon presentation with no evidence of plaque rupture. Again, we cannot entirely exclude that we might have missed ruptured plaques, if the cavity was small and filled with thrombus, but this also seems rather unlikely. One patient in our study (patient 3) had an unusually high level of creatinine kinase. As this patient had lain helplessly on the floor for many hours prior to presentation, we assumed that some of the rise in her creatinine kinase was from muscle injury. This assumption was supported by the observation that LGE, which is indicative of myocardial fibrosis, was absent on CMR imaging.

The reluctance of clinicians to attribute the findings in a patient with an ACS-like presentation and obstructive CAD on angiography to a poorly understood syndrome with an obscure pathogenesis rather than to the familiar concept of plaque rupture seems quite understandable. Some researchers go even farther and regard plaque rupture as the general pathogenic mechanism underlying TC. In their IVUS study of 5 patients with clinical features of TC Ibanez et al. found a single, ruptured, atherosclerotic plaque in the mid LAD and no additional atherosclerosis at other sites within the LAD. However, a rapidly growing body of evidence clearly argues against the hypothesis of plaque rupture as the underlying cause of TC. For example, variants of TC without involvement of the LV apex are, as well as right ventricular involvement, now increasingly being recognized. Both phenomena cannot adequately be explained by the concept of plaque rupture. Besides, the mere finding of a ruptured plaque does not establish its pathogenic role, as ruptured plaques also occur in patients with stable angina and even in asymptomatic patients. In conclusion, excluding the diagnosis of TC on the sole basis of an incidental finding of CAD may not be justified in all cases. Rather, a case-by-case decision process seems more appropriate.

**References**