Tako-Tsubo Transient Left Ventricular Apical Ballooning Is Associated With a Left Anterior Descending Coronary Artery With a Long Course Along the Apical Diaphragmatic Surface of the Left Ventricle

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**Introduction and objectives.** Tako-tsubo-like transient left ventricular apical ballooning has been described in Japan, but few cases have been reported in Western countries. We report one of the first series outside Japan, which provides new information on the coronary anatomy of this disorder.

**Patients and methods.** From January 1998 to February 2003 we observed 11 patients with a clinical suspicion of acute myocardial infarction, normal coronary arteries, and transient tako-tsubo-like systolic left ventricular apical ballooning. We compared the coronary anatomy in these 11 patients with that in 44 controls matched for age and sex: 22 with normal coronary arteries and 22 with acute myocardial infarction related with an obstructive thrombus in the left anterior descending coronary artery.

**Results.** As in Japanese patients, tako-tsubo syndrome in Caucasian patients frequently occurs in women in their seventh or eighth decades of life, and is usually preceded by emotional or physical stress. The left anterior descending in our patients with tako-tsubo syndrome was longer overall, and its recurrent diaphragmatic segment was longer, than in controls. To compare these groups we designed a measure termed recurrent segment index (left anterior descending recurrent segment length/total left anterior descending length × 100). In tako-tsubo syndrome this index was 22.3 (1.5)% vs 10.9 (6.7)% in normal controls (P<0.001), and 11.3 (7.7)% in acute myocardial infarction patients (P<0.001). Patients with acute myocardial infarction and a high recurrent segment index (≥16%) had ventriculographic findings of systolic apical ballooning identical to those in patients with tako-tsubo syndrome.

**Conclusions.** All our patients with tako-tsubo syndrome had a left anterior descending with a long recurrent segment. The identical ventriculographic findings in patients with tako-tsubo syndrome and those with acute myocardial infarction with a long recurrent segment may be due to a common etiology.

**Key words:** Myocardial stunning. Coronary disease. Myocarditis.
INTRODUCTION

In Japan, a new clinical disorder characterized by extensive akinesia with ballooning without significant coronary lesions has recently been described.\(^1\)\(^-\)\(^4\) Patients present chest pain, electrocardiographic (ECG) changes and slight enzyme level elevation similar to patients presenting acute myocardial infarction (AMI) or other forms of acute coronary syndrome (ACS). Sato et al.\(^1\) first described this disorder in 1990 and proposed the term tako-tsubo-like left ventricular dysfunction due to the shape taken by the left ventricle (LV). Angiograms showed extensive systolic LV ballooning taking the form of a container traditionally used in Japan to catch octopus and known as a tako-tsubo (Figura 1A).\(^1\)\(^,\)\(^2\) The condition has a benign prognosis and segment changes affecting contractility recover in a few weeks. Typically, the disorder affects older women with few cardiovascular risk factors and is frequently triggered by emotional or physical stress.\(^1\)\(^,\)\(^6\) Acute phase ECG changes involve ST segment elevation mainly along the anterolateral surface with pathologic Q waves that evolve with the appearance of negative T waves and Q wave regression. These changes suggest an ischemic event in anterolateral territory. The discovery of extensive LV apical akinesia has led several authors to discount the idea that the territory involved may correspond to a single coronary artery.\(^1\)\(^-\)\(^3\)

Except for some isolated cases\(^7\)\(^-\)\(^9\) and one recent European series,\(^10\) all the series reported come from Japan.\(^1\)\(^-\)\(^6\) Even though it is more than 10 years since research began, the etiology of the disorder is still unknown.

This study describes one of the first series of tako-tsubo-like ventricular dysfunction with ballooning from outside Japan. Based on the anatomy of the left anterior descending coronary artery (LAD) of our patients, we formulated a hypothesis as to the etiology of the entity.

PATIENTS AND METHODS

Between January 1998 and April 2003 we identified 11 patients who fulfilled the following criteria: a) suspected ACS based on the presence of chest pain, ECG changes and enzyme elevation; b) transient tako-tsubo-like systolic ballooning found in angiograms and 2D echocardiograms of the LV and, and c) absence of significant coronary artery obstruction (no stenosis >50%) in the three principal coronary arteries. All patients underwent angiographic studies of the LV and coronary angiography, 21±12 h (range, 5-36 h) after the onset of symptoms (Figure 1 A and B). In all patients, anatomical characteristics of the epicardial coronary arteries were studied. To determine whether a single coronary artery could supply the entire akinetic course of the LV, we retrospectively analyzed the LV dimensions of patients. We measured LAD length (in mm) of the left lateral projection from the LAD ostium to the visible end of its course, tracing the route of the artery with Quantcor\(^\text{®}\) 1.1 software (Pie Medical Imaging, Maastricht, Netherlands). We designated the apical point of the LAD as that which was furthest from the LAD ostium (Figure 2). We defined an LAD recurrent (diaphragmatic) segment as that part of the vessel between the apical point of the LAD and the visible end of the coronary artery (Figure 2). When the apical point of the LAD coincided with the visible end of the artery, we considered the patient lacked a recurrent segment. We calculated an LAD recurrent segment index using the following formula:

\[
\text{LAD recurrent segment length/total left anterior descending length} \times 100
\]

To determine whether patients had abnormally developed LAD recurrent segments we took the same measurements in 44 controls: 22 with chest pain without enzyme level elevation with normal coronary arteries, and 22 with AMI due to obstructive thrombus lesion in the LAD without evidence of lesions in other coronary arteries. The first control group was made up of patients with chest pain but without angiographic evidence of coronary heart disease, a characteristic they had in common with patients with tako-tsubo syndrome. The second control group was enrolled on the assumption that patients with tako-tsubo syndrome are initially diagnosed with suspected anterior wall AMI. In order to match controls to patients with tako-tsubo syndrome, we searched our database retrospectively and enrolled consecutive women patients of 60-80 years who met the control group criteria. Each control group included twice as many patients as those enrolled in the tako-tsubo group.

Enzyme levels were determined on admission and every 8 hours until peak values had been recorded. Creatine kinase (CK) >220 UI/L was considered pathologic. Troponin I (TnI) was determined in 4 patients and troponin T (TnT) in the other 7. Levels of TnI>0.6 ng/mL and TnT>0.1 ng/mL were considered pathologic. In 3 patients, viral antibody titers were evaluated in the first 24 h and 2 weeks after the onset of symptoms.
A 12-lead ECG was performed on admission and every 8 hours during the first 3 days. Later, patients underwent daily ECGs until discharge (Figure 3). All patients had a 2D echocardiogram on admission and weekly thereafter (Figure 4). One patient in the tako-tsubo group underwent a second angiographic study 17 days after admission (Figure 1C and D). In the other 10 patients, changes in global and segmental ventricular function were recorded by 2D echocardiogram (Figure 4).

**Statistical Analysis**

Continuous variables are expressed as mean ± standard deviation (SD). Ejection fraction in acute and subacute phases was compared with the Wilcoxon test for paired data. Tako-tsubo patients and controls were compared for total LAD length, LAD recurrent segment length and LAD recurrent segment index using the Mann-Whitney U test for non-paired data. Statistical significance was set at $P<.05$.

**RESULTS**

Clinical characteristics of patients with tako-tsubo syndrome (n=11) appear in Table 1. Patients were white and 9 of them (82%) were women. Average age was 72±12 years (range, 41-84 years). Ten patients
were admitted for suspected angina (91%) and 1 patient presented at the Emergency Room after fainting; 6 patients (55%) reported suffering physical or emotional stress prior to the onset of symptoms.

On admission, ECG findings for all patients showed ST segment elevation $\geq 1$ mm in more than 3 leads.
consecutive leads, especially V3 to V6, and lead I (Figure 3A). During hospitalization, markedly negative T waves developed in 9 patients (82%), particularly in leads V2 to V6, and lead I (Figure 3B). In these patients, negative T waves were still present on discharge at 15±10 days (range, 5-35). In the other 2 patients, ST segment recovered without developing negative T waves. Peak CK value was 272±227 UI/L (range, 126-889) but only 4 patients (36%) presented values above the normal range. All 11 patients had high TnI or TnT values (mean, TnT, 0.46±0.3 ng/mL [range, 0.2-1.2] and mean TnI, 4.0±2.6 ng/mL [range, 1.6-7.4]). Viral antibody titers against enterovirus, ECHO virus, Coxsackie virus, influenza A and influenza B were normal in those patients analyzed.

On admission, all 11 patients presented akinesia with ballooning in 2D echocardiograms (Figure 4). Left ventriculograms performed at 21±12 hours (range, 5-36) after the onset of symptoms showed tako-tsubo-like apical akinesia, a form of left ventricular systolic dysfunction characterized by extensive apical akinesia with normal or hypercontractile baseline segments (Figure 1). In all patients, serial echocardiograms showed left ventricular systolic function recovery at 13±8 days (range, 3-31) (Figure 4). One patient underwent a coronary angiogram that confirmed normal LV contractility (Figure 1). Left ventricular ejection fraction on admission was 37±9% (range, 20%-50%) whereas on discharge it was 64±9% (range, 58%-75%; P=.003). All patients with tako-tsubo-like disorder underwent early coronary angiograms that showed an absence of epicardial coronary lesions >50% in the 3 principal coronary arteries.

### Dimensions of the left anterior descending coronary artery

Total LAD length in patients with tako-tsubo-like disorder was 133.0±13.4 mm (range, 110.8-147.4) versus 113.6±15.4 mm (range 78.3-144.9) in controls with normal coronary arteries (P=.004) and 105.9±20.0 mm (range, 67.9-137.4) in controls with AMI and a single LAD lesion (P=.001). In all 11 patients with tako-tsubo syndrome, the LAD around the LV apex extended along the diaphragmatic surface of the LV (Figure 2). We also found an LAD recurrent segment in 18 of the 22 controls with normal arteries (82%) and in 18 of the 22 controls with AMI with a single LAD lesion (82%). However, LAD recurrent segment length in patients with tako-tsubo syndrome was 29.6±3.6 mm (range, 24.8-34.9) versus 13±8.5 mm (range, 0-26.8) in controls with normal coronary arteries (P<.001) and 12.9±9.4 mm (range, 0-31.4) in controls with AMI (P<.001). Moreover, LAD recurrent index was 22.3%±1.5% (range, 18.7%-23.8%) in patients with tako-tsubo syndrome, 10.9%±6.7% (range, 0%-21.4%) in controls with normal coronary arteries (P<.001) and 11.3%±7.7% (range, 0%-26.2%) in controls with AMI (P<.001; Figure 5 and Table 2). If we exclude patients without recurrent segment, LAD recurrent segment index in patients with tako-tsubo syndrome was greater than in the control groups (22.3%±1.5% vs 13.3%±4.6% and 13.8%±6.0%, respectively; P<.001 for both comparisons).

### Left ventriculogram in patients with tako-tsubo syndrome and in controls with AMI and single LAD lesion

By definition, patients with tako-tsubo syndrome had extensive LV apical akinesia with tako-tsubo-like systolic ballooning (Figure 1). In contrast, only 4 of the 22 patients (18%) with AMI and a single LAD lesion presented ballooning (Figure 6). These 4 patients had LAD recurrent indices of 16%, 19%, 19%, and 26%, respectively (22.0%±4.4%). The remaining 18 controls in this group had LAD recurrent indices <16% (8.0%±6.0%).

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**Table 1. Characteristics of Patients With Tako-Tsubo Syndrome**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>High Blood Pressure</th>
<th>Diabetes</th>
<th>Hypercholesterolemia</th>
<th>Tobacco</th>
<th>Prior Stress</th>
<th>Reason for Attending Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>F</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Physical</td>
<td>Syncope</td>
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<td>2</td>
<td>76</td>
<td>F</td>
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<td>–</td>
<td>+</td>
<td>–</td>
<td>Emotional</td>
<td>Chest pain</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>F</td>
<td>+</td>
<td>–</td>
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<td>F</td>
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</tr>
<tr>
<td>5</td>
<td>41</td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Chest pain</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>F</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Emotional</td>
<td>Chest pain</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>F</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Emotional</td>
<td>Chest pain</td>
</tr>
<tr>
<td>8</td>
<td>75</td>
<td>F</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>Physical</td>
<td>Chest pain</td>
</tr>
<tr>
<td>9</td>
<td>77</td>
<td>F</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>Physical</td>
<td>Chest pain</td>
</tr>
<tr>
<td>10</td>
<td>71</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Chest pain</td>
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<tr>
<td>11</td>
<td>84</td>
<td>M</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Chest pain</td>
</tr>
</tbody>
</table>

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DISCUSSION

We have presented one of the first series of tako-tsubo-like ventricular dysfunction described in white patients. Our study compares the epicardial coronary anatomy of patients with tako-tsubo syndrome with that of patients with normal coronary arteries and patients with AMI and a single LAD lesion. Patients with tako-tsubo syndrome all had long LAD extending beyond the apex along the diaphragmatic segment of the left ventricle (recurrent segment). This recurrent segment was longer in patients with tako-tsubo syndrome than in control groups. Moreover, ballooning, present in all patients with tako-tsubo syndrome, was identified in controls with AMI and a single LAD lesion only when the LAD recurrent index was high (in this series, ≥16%).

Since Sato et al described tako-tsubo syndrome in 1990,1 many retrospective studies carried out in Japan have been published.4,6 Clinical, biochemical, electrocardiographic and ventriculographic aspects of the disorder are well documented and our data coincide with those reported for Japanese patients. Consequently, our series shows the disorder is not unique to the Japanese and confirms results of the Belgian study reported by Desmet et al.10

Tako-tsubo syndrome is generally agreed to be a form of myocardial stunning but the etiology is as yet unknown. One hypothesis suggests we are dealing with an acute myocarditis. However, Kurisu et al3 report negative results in endomyocardial biopsies (3 patients) and viral antibody titers (7 patients) that indicate this is unlikely. Abe et al6 did not find a rise in viral antibody titers in 6 patients with tako-tsubo syndrome and in endomyocardial biopsies they found interstitial fibrosis in specimens taken from all 6 patients with slight inflammatory cell infiltration in 3 of them. These changes were not considered compatible with a diagnosis of myocarditis. We did not find a rise in viral antibody titers in any of the 3 patients analyzed.

Previous research has pointed to the direct toxic effect of catecholamine as a possible cause of symptoms. The fact that the disorder is frequently preceded by stress (in our series, 55% of patients presented physical or emotional stress) implies that the adrenergic system may sometimes be involved in the pathology of the disorder. However, in the only series in which noradrenalin plasma values have been recorded,5 titers were normal or slightly raised in the 6 patients analyzed. This issue needs to be resolved in future studies.

Another hypothesis is that of coronary artery spasm. Results of provocative testing with acetylcholine were only positive in 21% of patients.4 Transient dynamic obstruction of LV outflow tract has also been suggested as a possible cause. However, Abe et al6 reported that none of the patients in their series presented a significant intraventricular gradient (>30 mm Hg) and Tsuchihashi et al4 found only 18% of patients in their series presented transient intraventricular gradient.

Authors who have studied tako-tsubo syndrome in series of patients agree that the behavior of the ventricular dysfunction and the rapid recovery coincide with developments observed in patients with myocardial stunning. The most frequent cause of myocardial stunning is atherosclerosis.11 The absence of significant coronary artery stenosis in patients with tako-tsubo syndrome does not exclude transient coronary artery obstruction as a possible cause. The discovery that all

TABLE 2. Dimensions of Left Anterior Descending Coronary Artery in Patients With Tako-Tsubo Syndrome and in Controls*

<table>
<thead>
<tr>
<th></th>
<th>Tako-Tsubo (n=11), Mean±SD (range)</th>
<th>Controls N (n=22), Mean±SD (Range)</th>
<th>Controls AMI (n=22), Mean±SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total length of LAD, mm</td>
<td>133±13.4 (110.8-147.4)</td>
<td>113.6±15.4 (78.3-144.8)</td>
<td>105.9±20.0 (67.8-137.4)</td>
</tr>
<tr>
<td>Length of recurrent segment, mm</td>
<td>29.6±3.6 (24.8-34.9)</td>
<td>13.0±8.5 (0-26.8)</td>
<td>12.9±9.4 (0.0-31.4)</td>
</tr>
<tr>
<td>LAD recurrent index, %</td>
<td>22.3±1.5 (18.7-23.8)</td>
<td>10.9±6.7 (0-21.4)</td>
<td>11.3±7.7 (0-262)</td>
</tr>
<tr>
<td>LAD recurrent index, †%</td>
<td>22.3±1.5 (18.7-23.8)</td>
<td>13.3±6.6 (6.1-21.4)</td>
<td>13.8±6.0 (3.5-26.2)</td>
</tr>
</tbody>
</table>

*LAD indicates left anterior descending coronary artery; controls N, controls with normal coronary arteries; AMI, acute myocardial infarction.
†Excluding those patients without recurrent segment (controls with normal coronary arteries, n=18; controls with AMI, n=18).
patients in our series presented a marked LAD recurrent segment with a long course along the diaphragmatic surface of the LV leads us to suggest that a coronary event in the LAD may produce extensive apical akinesia along the LV diaphragmatic surface. This was found in patients with AMI with a significant LAD lesion with long course diaphragmatic segment as we have seen in controls with LAD recurrent index ~16%. The existence of AMI in patients with normal coronary arteries is well known.12,13 Even though the etiology of AMI with normal coronary arteries is unknown, it has been suggested as a possible cause of transient coronary thrombosis (eventually related to spasm).14 The proportion of patients with AMI and normal coronary arteries is 1±6%.15 As occurs in patients with tako-tsubo syndrome, patients with AMI and normal coronary arteries frequently present few cardiovascular risk factors; however, they are usually young.

LAD Anatomy in Patients With Tako-Tsubo Syndrome Compared With Controls

In all our patients with tako-tsubo syndrome, the LAD followed a long course after the apex of the LV and consequently supplied a large part of the diaphragmatic surface of the LV. In series of patients with normal hearts, 72% and 90% of patients, respectively, had an LAD recurrent segment.6,17

In our study, 82% of controls with normal coronary arteries and 82% of controls with AMI had an LAD recurrent segment. In patients with tako-tsubo syndrome, both the LAD and LAD recurrent segment were longer than in controls.

Implications for the Etiology of the Entity

Our findings on the existence of a longer LAD recurrent segment do not mean that this anatomical variation predisposes individuals to suffer this disorder. In fact, when an obstructive thrombus occurs in long LAD recurrent segment (in our series ≥16%), the left ventriculogram also shows a type of akinesia that is identical to that of patients with tako-tsubo syndrome (Figure 6). In these patients, apical akinesia is permanent, whereas in patients with tako-tsubo syndrome it is transient. If an LAD obstruction is resolved within a few hours of the onset of symptoms (due to spasm or spontaneous thrombolysis) before an angiographic study is conducted, the patient may be diagnosed with tako-tsubo syndrome. Tako-tsubo-like transient ventricular dysfunction syndrome may be caused by a prolonged obstruction of the thrombus that is spontaneously resolved in patients with a long LAD and long course along the diaphragmatic surface of the LV.

Limitations of the Study

This study involved relatively few patients with tako-tsubo syndrome and our findings about LAD recurrent segment length need to be confirmed in larger series. Larger series of patients are also needed if we are to establish a cutoff point for LAD recurrent segment index at which an obstructive thrombus of this type can produce a ventriculogram with tako-tsubo-like morphology.

CONCLUSIONS

This series describes Spanish patients with tako-tsubo syndrome, or transient ventricular dysfunction
with ballooning, and confirms that the entity is not exclusively found in Japanese patients. In all of our patients, the LAD supplies a large part of the diaphragmatic territory of the LV. When patients with AMI and a single obstructive thrombus in the LAD had an LAD recurrent index ≥16%, the left ventriculogram showed a morphology indistinguishable from that of tako-tsubo syndrome. The LAD recurrent index in our 11 patients with tako-tsubo syndrome was ≥16%. Although the etiology of tako-tsubo-like ventricular dysfunction is still unknown, our findings are compatible with a common etiology of tako-tsubo syndrome and acute myocardial infarction.

REFERENCES