



# Apical and Midventricular Transient Left Ventricular Dysfunction Syndrome (Tako-Tsubo Cardiomyopathy)\*

## Frequency, Mechanisms, and Prognosis

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**Background:** The frequency and potential differences between patients with apical (“typical”) and midventricular (“atypical”) ballooning have not been described.

**Methods:** Consecutive patients with the diagnosis of a troponin-positive acute coronary syndrome (ACS) were prospectively included into a registry (n = 3,265). Of those, 2,944 patients underwent left-heart catheterization and form the study population. Demographic, clinical, and angiographic data including assessment of microvascular dysfunction (Thrombolysis in Myocardial Infarction [TIMI] blush grade, corrected TIMI frame count), as well as clinical outcome were assessed in all patients.

**Results:** In patients with troponin-positive ACS, the frequency of transient cardiomyopathy was 1.2% (35 of 2,944 patients). Typical apical wall motion abnormality was observed in 21 of 35 patients (60%), as compared to an atypical (midventricular) pattern in 14 of 35 patients (40%). Both groups did not differ regarding demographic, clinical, laboratory, or angiographic parameters. Scintigraphy and PET studies were performed in 17 of 35 patients (49%) with transient cardiomyopathy, and showed a strong correlation between location of wall motion abnormality and myocardial metabolism defects, with a significantly higher apical decrease in glucose uptake in patients with a typical pattern.

**Conclusions:** Transient cardiomyopathy affects approximately 1% of patients with a troponin-positive ACS. A typical apical wall motion abnormality is seen in only 60% of patients. Transient cardiomyopathy, also termed *Tako-Tsubo cardiomyopathy*, therefore should no longer be regarded as an exclusively apical ballooning syndrome, but rather a transient left ventricular dysfunction syndrome with an apical or midventricular pattern of wall motion abnormality.

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**Key words:** acute myocardial infarction; myocardial stunning; Tako-Tsubo cardiomyopathy

**Abbreviations:** ACS = acute coronary syndrome; CK = creatine kinase; CTFC = corrected Thrombolysis in Myocardial Infarction frame count; FDG = fluorodeoxyglucose; LAD = left anterior descending artery; LCX = left circumflex coronary artery; MBG = myocardial blush grade; NSTEMI = non-ST-elevation myocardial infarction; PET = positron emission tomography; RCA = right coronary artery; SPET = single-photon emission tomography; STEMI = ST-elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction

**T**ransient and reversible left ventricular dysfunction, also termed *Tako-Tsubo cardiomyopathy*, has been recognized recently as a novel entity within the spectrum of acute coronary syndromes (ACSs).<sup>1–4</sup> Despite the recognition and description of the disease in Japan, the United States, and Europe,<sup>2,5,6</sup> clinically relevant characteristics of transient Tako-

Tsubo cardiomyopathy such as the frequency of the disease within the spectrum of ACSs and the

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prognosis of these patients are unclear. Furthermore, recent reports<sup>7,8</sup> have shown that some pa-

**Table 1—Characteristics of 2,944 Consecutive Patients With Troponin T-Positive ACS\***

Characteristics	NSTEMI	STEMI	Tako-Tsubo Cardiomyopathy
Patients	1,860 (63.2)	1,049 (35.6)	35 (1.2)
Age, yr	69 ± 8	61 ± 7	72 ± 9
Male gender	1,302 (70.0)	786 (74.9)	2 (5.7)†
Body mass index, kg/m <sup>2</sup>	27.6 ± 2.4	27.0 ± 3.3	24.7 ± 5.9
Diabetes mellitus	534 (28.7)	205 (19.5)	8 (22.9)
Arterial hypertension	1,352 (72.6)	724 (69.0)	26 (74.3)
Hypercholesterolemia	1,190 (64.0)	597 (56.9)	12 (34.3)†
Current smoking	801 (43.1)	547 (52.1)	7 (20.0)†
Family history of coronary artery disease	502 (27.0)	341 (32.5)	6 (17.1)†

\*Data are presented as No. (%) or mean ± SD. Arterial hypertension is defined as BP ≥ 140/90 mm Hg or receiving antihypertensive medication.

Hypercholesterolemia is defined as ≥ 160 mg/dL low-density lipoprotein cholesterol or intake of lipid level-lowering medication.

†p < 0.05 vs NSTEMI and STEMI.

tients do not present with “typical” apical but rather “atypical” midventricular dysfunction. The aim of this study was, therefore, to evaluate the frequency, mechanisms, and prognosis of patients with apical and midventricular reversible left ventricular dysfunction among patients presenting with a diagnosis of a troponin-positive ACS.

## MATERIALS AND METHODS

### Patient Population and Clinical Assessment

Between January 2003 and December 2005, all patients with a diagnosis of a troponin-positive ACS admitted to the emergency facilities at University Hospital Lübeck were prospectively included into a database (n = 3,265). Troponin T was measured quantitatively using an enzyme-linked immunosorbent assay (ES 300 system; Roche Diagnostics; Mannheim, Germany). The cut-off for a positive troponin T test result was set at 0.1 ng/mL.

In our institution, immediate (in patients with ST-elevation myocardial infarction [STEMI]) or rapid (< 12 h in non-ST-elevation ACS) coronary angiography is routinely performed in patients presenting with marker-positive chest pain. Common reasons for not undergoing invasive evaluation in this patient group are failure to obtain informed consent, very high bleeding risk or active uncontrolled bleeding, and a noncardiac-related very short life expectancy. Of the entire patient cohort, 2,944 patients underwent left-heart catheterization (Table 1). Of those, 35 patients (1.2%) fulfilled the following criteria of transient cardiomyopathy (adopted from Bybee et

al<sup>1</sup>): (1) transient akinesis or dyskinesis of the left ventricular apical and midventricular segment with regional wall-motion abnormalities extending beyond a single epicardial vascular distribution; (2) no angiographic evidence for plaque rupture or intracoronary thrombus formation; (3) new ECG abnormalities (ST-segment elevation or T-wave inversion); and (4) absence of recent head trauma, intracranial bleeding, pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy. Typical transient cardiomyopathy was defined by predominantly apical left ventricular wall motion abnormalities, whereas atypical transient cardiomyopathy was defined by predominantly midventricular wall motion abnormalities with a preserved contractile function of the apical segment.

A control group of 35 patients with successfully recanalized “first-time” anterior STEMI and left anterior descending artery (LAD) as the infarct-related artery have been included mainly for two reasons: (1) to compare the prognosis of Tako-Tsubo cardiomyopathy with a clearly defined patient population that also shows acute myocardial dysfunction of the anterior wall, and (2) to compare the degree of microcirculatory disruption observed in Tako-Tsubo cardiomyopathy with a patient population with well-accepted microvascular dysfunction. The control group was pair matched with the Tako-Tsubo group stratified for sex, left ventricular ejection fraction, and cardiovascular risk factors.

Each patient was assessed with history and physical examination, 12-lead ECG, complete laboratory evaluation, coronary angiography, and left ventricular angiography. Repetitive echocardiography was obtained during the hospital course. Myocardial perfusion scintigraphy and fluorodeoxyglucose (FDG)-positron emission tomography (PET) studies were performed in a randomly chosen subgroup of 17 of 35 patients (49%). A systematic clinical follow-up (mean follow-up period, 17 ± 12 months) was available for all patients. A subgroup of 25 of 35 patients (71%) with transient cardiomyopathy, and 32 of 35 patients (91%) with STEMI underwent repeat assessment of left ventricular function by echocardiography.

All clinical data were verified by independent hospital chart review and source documentation. Hypertension was defined as BP ≥ 140/90 mm Hg or the administration of antihypertensive medication. Hypercholesterolemia was defined as ≥ 160 mg/dL low-density lipoprotein cholesterol, or intake of lipid level-lowering medication. Diabetes was defined according to the American Diabetes Association 1997 classification.<sup>9</sup> The study protocol was approved by the local ethics committee.

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Coronary angiography was performed with a frame rate of 12.5/s, and coronary angiograms were analyzed off-line (Quant-Cor, CAAS II; Siemens; Erlangen, Germany). Quantification of epicardial blood flow and microvascular integrity was graded by two independent, experienced interventionalists blinded to all patient data. The flow in the LAD coronary artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) myocardial flow grade criteria: TIMI grade 0 = no flow within the native vessel; TIMI grade 1 = faint, slow filling of the native vessel, without opacification of the distal vessel; TIMI grade 2 = slow filling of the entire vessel length, and TIMI grade 3 = brisk, normal flow within the entire vessel.

Myocardial blush grade (MBG) on the final angiogram was based on the visual assessment of contrast opacification of the myocardial territory subtended by the infarct vessel, as described previously.<sup>10</sup> MBG was assessed for the LAD, the left circumflex coronary artery (LCX), and the right coronary artery (RCA) and classified as grade 0–3. MBG grades 0 and 1 were combined in the results and were considered “abnormal.” From multiple orthogonal projections, the single view was chosen that best isolated the myocardial infarct zone in question.

The corrected TIMI frame count (CTFC) was determined on the final angiogram to objectively assess coronary blood flow as a continuous variable.<sup>11</sup> A CTFC value  $\geq 24$  was considered abnormal. Patients were considered to have microvascular dysfunction in any coronary territory when MBG or CTFC were abnormal.

Intraobserver and interobserver variability in the assessment of MBG and CTFC were determined from a random sample of 25 films scored by A.K. and P.W.R. Assessment of intraobserver variability demonstrated a  $\kappa$  value of 0.91 for the MBG and a mean deviation of  $0.5 \pm 0.5$  frames for the CTFC. Assessment of interobserver variability demonstrated a  $\kappa$  of 0.88 for the MBG and a mean deviation of  $1.0 \pm 0.6$  frames for CTFC.

#### *Myocardial Perfusion Scintigraphy and FDG-PET Studies*

A total of 17 of 35 patients (49%) with transient cardiomyopathy underwent myocardial perfusion scintigraphy and FDG-PET studies 2 to 6 days after hospital admission (mean, 4 days). Myocardial perfusion scintigraphy was performed using the following specifications: 440 megabecquerels of <sup>99m</sup>Tc-methoxyisobutyl isonitrile; triple-head gamma camera (3000XP; Marconi/Philips; Cleveland, OH); single PET (SPET) 120 min after injection; 120°; 6° per step; 50 seconds per step; 128 × 128; iterative reconstruction (ISA software Luig; Bovenden, Germany); and filtered back projection (low pass). The following FDG-PET protocol was used: oral glucose load with 200 mL of oligosaccharid 90 min before administration of 4 IU insulin and 250 megabecquerels of FDG; coincidence gamma camera (Axis, Marconi/Philips); emission tomogram 30 min after injection; 180°; 6° per step; 50 seconds per step (decay corrected); list mode; photopeak 511 kiloelectron volts; energy window 30%; and iterative reconstruction. Follow-up myocardial perfusion scintigraphy and FDG-PET studies were performed in six patients 6 to 12 days after the initial evaluation (mean, 9 days).

All scans were analyzed semiquantitatively as described by Ito et al<sup>12</sup> by an experienced nuclear cardiologist blinded to all clinical variables of the patients. In brief, the left ventricle was divided into nine regions on PET/SPET images, and the degree of abnormalities in each region was scored according to five grades, from normal (0) to severely abnormal (4). For data presentation, data from the midventricular and basal segments were grouped and compared between patients with typical and atypical dysfunction patterns.

Continuous data are presented as mean  $\pm$  SD. Univariate comparison of continuous variables was performed using the Mann-Whitney *U* test. Qualitative data are presented as frequencies, and comparison between quantitative data were performed with  $\chi^2$  statistics. A two-sided *p* value  $< 0.05$  was considered statistically significant. Statistical analysis was performed using a commercially available statistical package (SPSS for windows, Version 12.0; SPSS; Chicago, IL).

## RESULTS

### *Patient Characteristics and Outcome*

Among 2,944 patients undergoing invasive evaluation due to ACS and a positive troponin test result, the diagnosis of non-STEMI (NSTEMI) was established in 63.2% of patients, STEMI in 35.6% patients, and transient cardiomyopathy in 1.2%. Patients with a transient cardiomyopathy were significantly older and most often female (94%), as compared to patients with STEMI or NSTEMI (Table 1). In patients with transient cardiomyopathy, significant ST-segment elevation on hospital admission was documented in 24 of 35 patients (69%). In 30 of 36 patients (86%), a trigger (emotional stress or disease-related stress) could be identified. Emotional stress triggers (15 of 30 patients) included nearly fatal drowning, funeral visit, and violent robbery, whereas disease-related stress triggers (15 of 30 patients) included massive pneumonia and asthmatic states.

One-month and 12-month follow-ups were complete in all patients; mean follow-up time was  $17 \pm 12$  months. Complete recovery of left ventricular function at hospital discharge was observed in 30 of 35 patients (86%); mean ejection fraction increased from  $50 \pm 13$  to  $68 \pm 12\%$  ( $p < 0.01$ ). Three patients (9%) died during the initial hospitalization (days 5 to 7 after admission), all due to septic shock (pneumogenic,  $n = 2$ ; urosepsis,  $n = 1$ ). Two patients (6%) had a second episode of transient cardiomyopathy (3 months and 20 month after the initial event, respectively). At long-term follow-up, all 25 patients undergoing repeat echocardiography showed complete recovery of left ventricular function.

### *Apical vs Midventricular Transient Cardiomyopathy: Angiography, Myocardial Perfusion Scintigraphy, and FDG-PET Studies*

At presentation, the global left ventricular ejection fraction by angiography was  $50 \pm 13\%$ . Whereas epicardial flow in the LAD artery was normal or nearly normal in all patients with transient cardiomyopathy, the microcirculation in the LAD artery as

assessed by the TIMI MBG and the CTFC was impaired in 25 of 35 patients (71%). Furthermore, impairment of the coronary microcirculation was also present in the RCA and/ or the LCX in the majority of patients (24 of 35 patients, 69%), irrespective of the type of wall motion abnormality (apical vs midventricular). Significant coronary artery disease, angiographic evidence for plaque rupture, or intracoronary thrombus formation could not be observed in either patient.

A typical apical wall motion abnormality as assessed by angiography was observed in 21 of 35 patients (60%). Patients with transient cardiomyopathy and a typical apical pattern did not differ significantly from patients with a midventricular (atypical) wall motion abnormality pattern (Table 2, Fig 1).

Myocardial perfusion scintigraphy showed a more pronounced decrease in myocardial perfusion in patients with apical dysfunction as compared to patients with a midventricular pattern (Fig 2, 3). FDG-PET studies revealed a significant and overproportional decrease in glucose metabolism in corresponding segments (Fig 2, 3).

*Matched Comparison With STEMI*

The time interval between symptom onset and hospital presentation (symptom-to-hospital time) was significantly longer in patients with transient cardiomyopathy as compared to patients with STEMI (Table 3). Despite comparable troponin values at presentation, maximum creatine kinase (CK)/CK-MB values were significantly higher in patients with STEMI. There was no difference regarding the magnitude of an impairment in myocardial microcirculation. Thirty-day mortality rates were nearly identical in patients with transient cardiomy-

opathy or matched patients with STEMI (8.6% vs 11.4%, all in hospital). One-year mortality rates were 8.6% in patients with transient cardiomyopathy and 20% in STEMI patients ( $p < 0.05$ ).

DISCUSSION

Transient left ventricular dysfunction, or Tako-Tsubo cardiomyopathy, is a clinical syndrome that is increasingly recognized. Although described in 1991,<sup>13</sup> questions regarding frequency, pathophysiology, and outcome of this syndrome remain. The major findings of this study are the following: (1) transient cardiomyopathy accounts for 1.2% cases of troponin-positive ACSs, (2) the disease presents with an inverse perfusion/metabolism mismatch, and (3) a typical apical wall motion abnormality is observed in 60%, as compared to an atypical (midventricular) pattern in 40% patients. Based on these data, Tako-Tsubo cardiomyopathy should not longer be regarded as an apical ballooning syndrome but rather a transient left ventricular dysfunction syndrome.

*Frequency, Diagnosis, and Prognosis in Transient Cardiomyopathy*

The true incidence of this syndrome within a population is unknown. We prospectively evaluated patients presenting with ACS and a positive troponin test result. Among these patients, the frequency of transient cardiomyopathy was 1.2%. A report<sup>14</sup> only including patients with STEMI reported a frequency of 2.2%. In a recent metaanalysis,<sup>3</sup> 82% of patients with transient cardiomyopathy presented with ST-segment elevation on admission as compared to 69% in our series. Among patients with suspected ACS in Japan, three studies<sup>12,15,16</sup> reported a frequency of

**Table 2— Characteristics of Patients With Apical (Typical) and Midventricular (Atypical) Transient Cardiomyopathy\***

Characteristics	Apical (n = 22)	Midventricular (n = 13)	p Value
Male gender	1 (4.5)	1 (7.7)	1.0
Age, yr	72.3 ± 7.8	70.4 ± 10.2	0.53
ST-segment elevation	14 (63.6)	10 (76.9)	0.41
30-day mortality	3 (13.6)	0 (0.0)	0.28
Troponin T at hospital admission, µg/L	0.7 ± 1.2	0.4 ± 0.4	0.35
CK maximum, U/L	253 ± 206	541 ± 1,098	0.24
TIMI flow grade, LAD	2.7 ± 0.5	2.9 ± 0.3	0.11
TIMI frame count, LAD	28.8 ± 8.3	25.2 ± 10.3	0.27
TIMI blush grade, LAD	2.0 ± 1.2	2.4 ± 1.0	0.37
Impaired microcirculation, LAD	15 (68.2)	10 (76.9)	0.61
Impaired microcirculation, LCX	14 (63.6)	10 (76.9)	0.41
Impaired microcirculation, RCA	14 (63.6)	10 (76.9)	0.41
Left ventricular ejection fraction, %	51 ± 14	50 ± 12	0.88

\*Data are presented as No. (%) or mean ± SD.



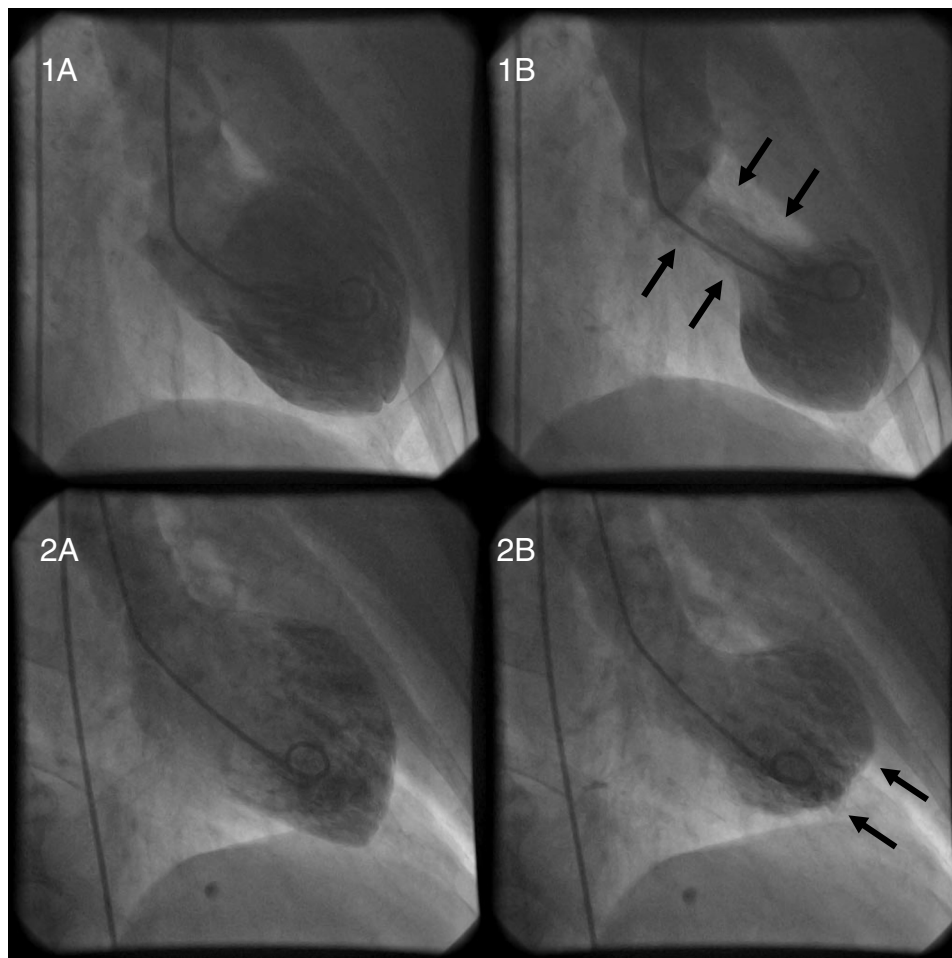


FIGURE 1. Left ventricular angiograms showing a typical apical dysfunction in diastole (*top left, 1A*) and systole (*top right, 1B*). The arrows mark the anterior and inferior basal hypercontractility. An example of an atypical midventricular dysfunction is shown in diastole (*bottom left, 2A*) and systole (*bottom right, 2B*). The arrows mark the systolic movement of the apex directed toward the basis of the heart.

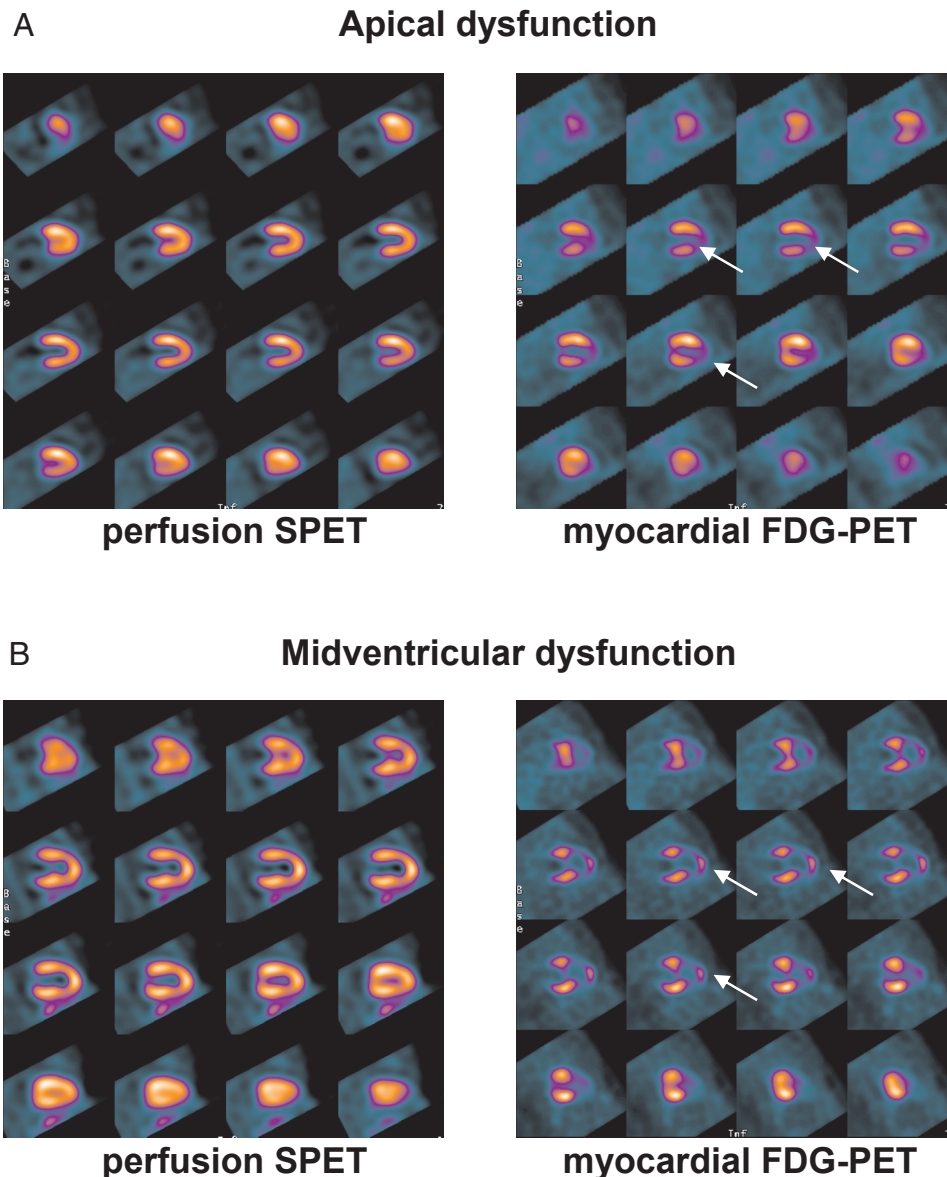
transient cardiomyopathy between 1.7% and 2.2%. Based on these data, transient cardiomyopathy seems to account for 1 to 2% of ACS cases. Therefore, it is likely that > 10,000 patients with transient cardiomyopathy will be admitted to US hospitals annually.<sup>17</sup>

At present, that outcome of transient cardiomyopathy has been reported to be favorable, with only three deaths during hospitalization in 286 patients (in-hospital mortality rate, 1.0%).<sup>3</sup> It has to be taken into account, however, that the frequency of Tako-Tsubo cardiomyopathy in patients with sudden cardiac death is unknown. None of those patients hospitalized died due to a primarily cardiac cause. However, a ventricular rupture in case of a patient with transient cardiomyopathy has been described.<sup>18</sup> Here, we report a 30-day mortality rate of 8.6%, which is not significantly different from a pair-matched group with acute anterior STEMI undergoing successful percutaneous coronary

intervention from our database. Interestingly, all deaths of our transient cardiomyopathy patients were not primarily related to cardiac dysfunction but rather a result of the underlying condition that may have triggered Tako-Tsubo cardiomyopathy (severe pneumonia, urosepsis) and consecutive septic shock. Once the acute phase of the underlying disease has been survived, nearly all patients are expected to have a full clinical and myocardial (functional) recovery.<sup>3</sup> Seven cases (7 of 102 patients, 7%) of a recurrent episode of transient cardiomyopathy have been described in the literature, which correlates very well with the 6% recurrence rate as observed in our series.

#### *Myocardial Blood Flow*

Studies<sup>14,19</sup> have suggested microvascular dysfunction to be a potential pathophysiologic mechanism in transient cardiomyopathy. Kurisu et al<sup>19</sup> found a



**FIGURE 2.** Corresponding perfusion SPET and FDG-PET studies in patients with typical apical dysfunction (*top panels, A*) and atypical midventricular dysfunction (*bottom panels, B*). Myocardial glucose metabolism is affected to a greater extent than perfusion comparable to postischemic stunned myocardium in both conditions. FDG-PET studies reveal a severe impairment of glucose uptake in apical and midventricular segments in patients with a typical pattern (arrows), whereas in patients with an atypical pattern the glucose uptake in the apex of the left ventricle is not affected (arrows).

significantly higher TIMI frame count in Tako-Tsubo patients as compared to a control group. These data were confirmed by a report<sup>14</sup> showing abnormal TIMI frame counts in one or more major epicardial vessels in patients with transient cardiomyopathy. These findings are very well in line with our observation that microvascular integrity in transient cardiomyopathy is impaired in all coronary arteries in many patients. Furthermore, microvascular dysfunction in the LAD is comparable to that of patients with acute anterior STEMI after recanaliza-

tion of the infarct-related artery (Table 3). In contrast, Abe et al<sup>20</sup> did not find abnormalities in coronary microcirculation using Doppler guidewire technology and contrast echocardiography.

Nuclear studies have been performed in a subgroup of patients. However, our myocardial perfusion and FDG-PET studies revealed that myocardial glucose metabolism seems to be affected to a greater extent than perfusion. The disease presents with an “inverse mismatch” typical for the appearance of postischemic “stunned” myocardium.<sup>21</sup> Our current

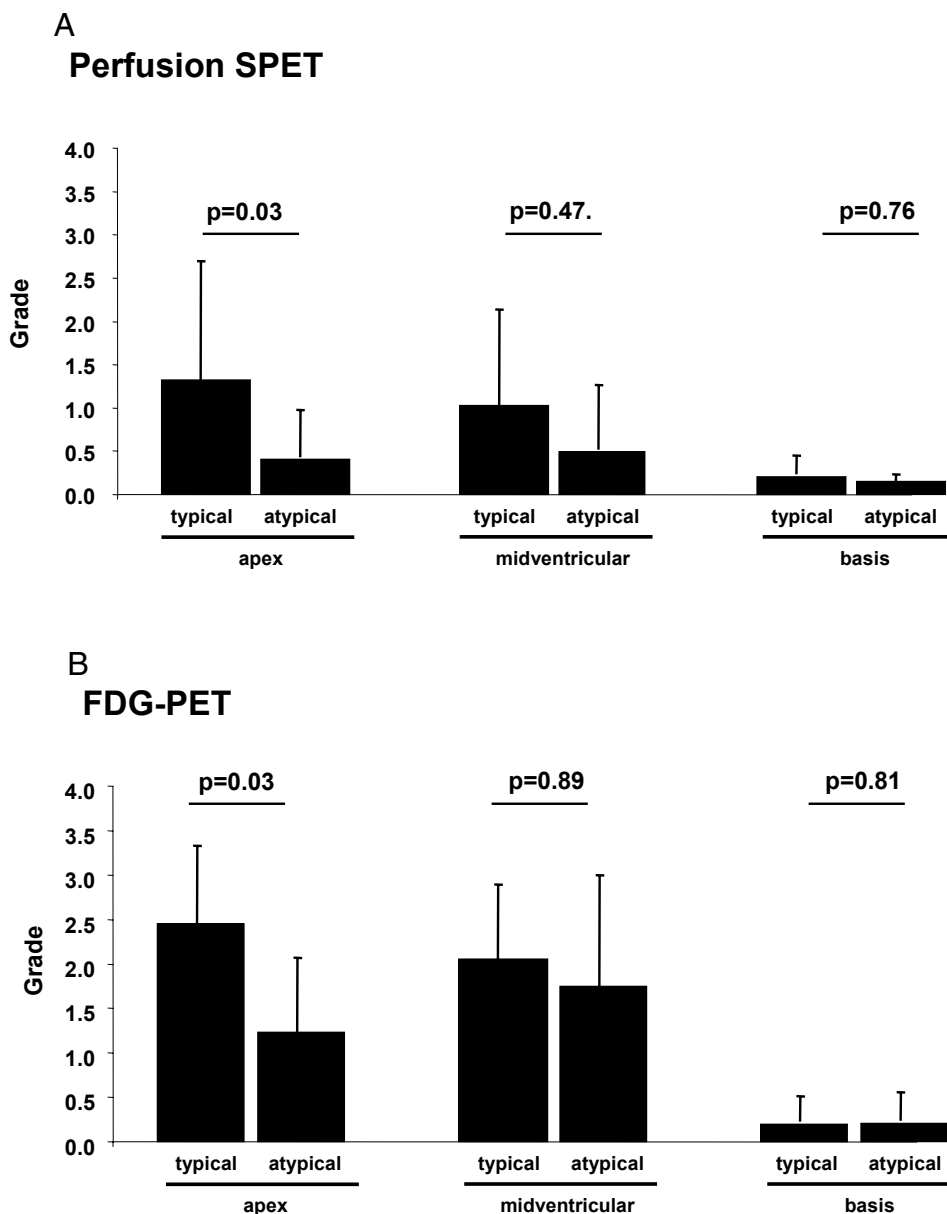


FIGURE 3. Semiquantitative evaluation of perfusion SPET (*top, A*) and FDG-PET (*bottom, B*) studies in patients with typical apical dysfunction and atypical midventricular dysfunction.

**Table 3—Characteristics of Patients With Transient Cardiomyopathy ( $n = 35$ ) and Pair-Matched Patients With Acute Anterior STEMI ( $n = 35$ )\***

Characteristics	Tako-Tsubo Cardiomyopathy	STEMI	p Value
Male gender	2 (5.7)	2 (5.7)	1.0
Age, yr	71.6 $\pm$ 8.7	67.3 $\pm$ 13.0	0.10
ST-segment elevation	24 (68.6)	35 (100)	< 0.001
T-inversion	21 (60.0)	5 (14.3)	< 0.001
Symptoms to hospital admission, h	11.5 $\pm$ 11.1	4.2 $\pm$ 2.3	< 0.001
30-day mortality	3 (8.6)	4 (11.4)	1.0
TIMI flow grade, LAD	2.8 $\pm$ 0.4	2.7 $\pm$ 0.5	0.80
TIMI frame count, LAD	27.5 $\pm$ 9.1	28.4 $\pm$ 10.8	0.09
TIMI blush grade, LAD	2.2 $\pm$ 1.1	1.9 $\pm$ 1.1	0.37
Left ventricular ejection fraction, %	50.4 $\pm$ 12.9	49.2 $\pm$ 14.5	0.72

\*Data are presented as No. (%) or mean  $\pm$  SD.

findings of mildly reduced myocardial perfusion in the absence of epicardial obstruction, however, support the hypothesis of impaired coronary microcirculation as a causative mechanism of the syndrome.

### *Typical vs Atypical Transient Cardiomyopathy*

A few reports<sup>7,8</sup> have suggested that wall motion abnormality in transient cardiomyopathy might not exclusively be located in apical segments but also in the midventricular segments of the left ventricle. In this study, for the first time, a systematic comparison of patients with and without typical transient cardiomyopathy was performed. No differences in demographic, clinical, angiographic, laboratory parameters, or outcome were found. However, left ventricular wall motion abnormalities, myocardial perfusion scintigraphy, and FDG-PET studies showed a strong correlation between location of wall motion abnormality and myocardial perfusion/metabolism defects (Figs 1–3). It can be therefore concluded that the inverse perfusion-metabolism mismatch does not only characterize pathophysiologic features of the syndrome. It also reflects the regional distribution of myocardial dysfunction, perfusion, and glucose uptake in patients with a typical or atypical pattern. Although highly speculative, differences in myocardial receptor density (*ie*,  $\beta$ -adrenergic receptors) and/or distribution as well as respective differences in downstream effects may not only be responsible for the development of transient cardiomyopathy but also for the differential location of wall motion abnormalities. Based on these data, Tako-Tsubo cardiomyopathy should not longer be regarded as an apical ballooning syndrome, but rather a transient left ventricular dysfunction syndrome with an apical or midventricular pattern.

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