Acute and Reversible Cardiomyopathy Provoked by Stress in Women From the United States

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Background—A clinical entity characterized by acute but rapidly reversible left ventricular (LV) systolic dysfunction and triggered by psychological stress is emerging, with reports largely confined to Japan.

Methods and Results—Over a 32-month period, 22 consecutive patients with this novel cardiomyopathy were prospectively identified within a community-based practice in the Minneapolis–St. Paul, Minn, area. All patients were women aged 32 to 89 years old (mean 65±13 years); 21 (96%) were ≥50 years of age. The syndrome is characterized by (1) acute substernal chest pain with ST-segment elevation and/or T-wave inversion; (2) absence of significant coronary arterial narrowing by angiography; (3) systolic dysfunction (ejection fraction 29±9%), with abnormal wall motion of the mid and distal LV, ie, “apical ballooning”; and (4) profound psychological stress (eg, death of relatives, domestic abuse, arguments, catastrophic medical diagnoses, devastating financial or gambling losses) immediately preceding and triggering the cardiac events. A significant proportion of patients (37%) had hemodynamic compromise and required vasopressor agents and intra-aortic balloon counterpulsation. Each patient survived with normalized ejection fraction (63±6%; P<0.001) and rapid restoration to previous functional cardiovascular status within 6±3 days.

Conclusions—A reversible cardiomyopathy triggered by psychologically stressful events occurs in older women and may mimic evolving acute myocardial infarction or coronary syndrome. This condition is characterized by a distinctive form of systolic dysfunction that predominantly affects the distal LV chamber and a favorable outcome with appropriate medical therapy. (Circulation. 2005;111:472-479.)

Key Words: cardiomyopathy ■ magnetic resonance imaging ■ angiography ■ heart failure ■ women

A
cute and rapidly reversible left ventricular (LV) dysfunction triggered by profound psychological stress is a recently recognized clinical scenario. Prior reports have largely been confined to Japanese patients, which raises the possibility of a geographically restricted cardiovascular syndrome.1–6 This clinical entity is of substantial general medical interest owing to its presentation, which mimics myocardial infarction and acute coronary syndrome, potentially unfavorable consequences, and a high likelihood of survival with appropriate medical therapy. Therefore, it is timely to report the present sizable and prospectively assembled patient cohort from the United States that demonstrates the clinical profile of this cardiomyopathy.

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Methods

Patient Population

Between August 2001 and April 2004, 22 patients presented to our emergency and hospital facilities in the Minneapolis-St. Paul, Minn, area with (1) acute onset of a cardiovascular event, usually associated with substernal chest pain, initially regarded as ST-segment elevation myocardial infarction/evolving coronary syndrome; (2) systolic dysfunction, predominantly characterized by akinesia/hypokinesia of the mid-to-distal portion of the LV chamber, with hypercontractile basal LV; and (3) absence, by angiography, of significant atherosclerotic luminal narrowing in each of the 3 epicardial coronary arteries (0 to <25%).

Clinical Assessment

Each patient was assessed with history and physical examination, 12-lead ECG, serum troponin, coronary arteriography, and LV angiogram (an average of 6±1 hours after admission to the hospital), with echocardiography and cardiac MRI (CMR) obtained after admission.

CMR was performed in each patient with a Siemens Sonata 1.5-T scanner. Standard TrueFISP (fast imaging with steady-state precession; TI=240 to 300 ms) cine images were acquired in 3 long-axis slices and 11 to 15 short-axis slices, 7 mm in thickness with a 3-mm interslice gap, which achieved full ventricular coverage. A delayed enhancement protocol was used 10 to 20 minutes after intravenous administration of gadolinium-DTPA (0.2 mmol/kg) with breath-hold inversion-recovery turboFLASH (fast low-angle shot) or segmental...
TrueFISP sequences. Regional wall-motion abnormalities (eg, hypokinesia, akinesia, or dyskinesia) were assessed in the 17-segment model of the LV chamber in 21 patients who had CMR studies obtained within the first 5 days after admission. In each of these patients, abnormalities were assigned to coronary arterial vascular territories, according to previously established criteria. Echocardiographic studies were performed in a standard fashion.

Results

Demographics and Clinical Presentation

All 22 study patients were female, 32 to 89 years old (mean 65±13 years); 21 (96%) were ≥50 years, and all were white (Table). Body weight was a mean (±SD) of 146±41 pounds. Prior cardiovascular history was unremarkable, with no coronary artery or valvular heart disease, chest pain, myocardial infarction, or heart failure.

The vast majority of patients (n=20) had initial clinical findings consistent with acute coronary syndrome, including ST-segment elevation myocardial infarction, recent abrupt onset of severe substernal chest pain (n=20), and/or marked hypotension (blood pressure ≤90/60 mm Hg; n=11). One patient presented with acute dyspnea (patient 17) and another in cardiac arrest (ventricular fibrillation; patient 2). No patient had clinical evidence of volume overload with pulmonary congestion or peripheral edema. Time from initial symptom onset to hospital admission was 10±16 hours (range 0.5 to 72 hours), and time to the start of cardiac catheterization was 16.5±16 hours. Relevant history included smoking (n=13), hypercholesterolemia (n=9; statins n=8), hypertension (n=3), obstructive lung disease (n=3), or diabetes (n=2). No patient was taking cardioactive medications before admission or had a history of Raynaud’s syndrome or use of vasoconstrictor substances such as cocaine or triptans.

Premonitory Events

Each patient experienced particularly stressful incidents immediately preceding onset of symptoms (ie, within minutes or hours on the same day; Table). In 19 patients, these were acute psychological triggers, such as confrontations and arguments with friends or relatives (including domestic abuse), or emotionally charged counseling sessions; the unexpected death of a close relative; receipt of a catastrophic diagnosis; devastating financial and gambling losses; fear of invasive medical procedures; or disorientation while driving an automobile. Three other events were triggered by physical or disease-related circumstances, eg, exacerbation of chronic pulmonary disease, grand mal seizure, and home accident (hip fracture).

Clinical Testing

Electrocardiogram

Initial ECGs showed 3 patterns consistent with myocardial ischemia (Figure 1): (1) convex ST-segment elevation (2 to 3 mm), usually in V1 to V3 (n=13), associated with T-wave inversion in the same leads in 10 patients on admission and with evolution in 3 others; (2) T-wave inversion (without ST elevation), usually in I, AVL, and precordial leads, and becoming more prominent and diffuse with time (n=5); and (3) absence of ST-segment and T-wave abnormalities (n=4) but presence of subsequent T-wave inversion in precordial leads in 3 patients.

Other abnormalities were QS (or Q) waves, usually in V1 to V3 (n=10), low (<0.5 mV) limb-lead voltages (n=12), and corrected QT interval (QTc) >450 ms (n=16). ST-segment elevation resolved by hospital discharge in all 13 patients, but QS (Q) waves did not change.

Troponin

Initial serum troponin was normal in 6 patients (troponin T ≤0.04 ng/mL; troponin I <0.3 ng/mL), mildly increased in 4 (troponin T 0.05 to 0.09 ng/mL), and definitively abnormal in 12 (troponin T 0.1 to 5.2 ng/mL; troponin I 0.8 to 14.8 ng/mL). Of the 6 patients with normal admission troponin levels, peak levels were abnormal by 48 hours in 3 but remained unchanged in the other 3 patients (Table).

Angiography and Hemodynamics

Each patient demonstrated LV systolic dysfunction with substantially reduced ejection fraction (29±9%; range 15% to 40%). All exhibited a large wall-motion abnormality that involved akinesia or hypokinesia of the distal one half to two thirds of the LV chamber, which created a distinctive “apical ballooning” appearance, associated with basal hypercontractility at end systole (Figure 2). Patient 2 demonstrated multifocal vasospasm of the left circumflex and anterior descending coronary arteries, reversed by administration of intracoronary nitroglycerin (Figure 3). LV end-diastolic pressures were 18±6 mm Hg and were >15 mm Hg in 15 patients (68%).

Cardiac Magnetic Resonance Imaging

CMR was performed within 5 days after admission in 21 patients (3±1 days) and at 13 days in 1 patient (Figure 4). Delayed gadolinium hyperenhancement was not present in 21 of 22 patients, consistent with viable myocardium and the absence of myocardial scar and infarction. Patient 2, who presented in cardiac arrest, showed hyperenhancement confined to the LV apex, which represented a small infarct.

LV wall-motion abnormalities as assessed by CMR were virtually confined to the midventricular and distal segments of the LV (Figure 5). In 20 of the 21 patients (95%) with early post-event CMR, abnormal regional wall motion involved areas of the LV beyond the vascular distribution of a single coronary artery, ie, 2 vascular territories in 1 patient and 3 territories in the other 19 patients (Table).

Management

Acute patients were treated according to established guidelines for ST-elevation myocardial infarction or acute coronary syndrome with combinations of negative inotropic agents (β-blockers, orally or intravenously), aspirin, nitrates (sublingual or intravenous), and heparin. Vasopressor agents (eg, dobutamine and dopamine) were administered to 8 patients with marked hypotension to sustain cardiac output and systemic blood pressure; 4 of these patients also required mechanical and hemodynamic support with intra-aortic balloon counterpulsation (for 1 to 2 days). One received thrombolytics (patient 7), and 2 received IIb/IIIa antagonists (patients 8 and 12) because of the clinical misperception of an error.
### Clinical Features in 22 Patients With Acute and Reversible Stress Cardiomyopathy With LV Systolic Dysfunction

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<th>Patient No.</th>
<th>Age/Gender</th>
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<th>HR</th>
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<th>Troponin, ng/mL*</th>
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<th>Heparin</th>
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</table>

WMAs indicates wall-motion abnormalities; BP, blood pressure (in mm Hg); HR, heart rate at presentation (in bpm); B-B, β-blockers; ASA, aspirin; NTG, nitroglycerin; ABPC, intra-aortic balloon pump counterpulsation; ST-E, ST-segment elevation; LVEDP, LV end-diastolic pressure; LVOT-O, LV outflow tract obstruction; LAD, left anterior descending artery; LCirc, left circumflex; RCA, right coronary artery; HTN, (systemic) hypertension; SD, sudden death; T2D, type 2 diabetes mellitus; †, increased; chol, hypercholesterolemia (total cholesterol ≥200 mg/dL); COPD, chronic obstructive pulmonary disease; Ca, carcinoma; AF, atrial fibrillation; Dx, diagnosis; and MVP, mitral valve prolapse.

0 indicates absent; +, present; and —, data not relevant because CMR was not performed until the 13th post-event day.

*Reference values: troponin T (<0.01–0.04 ng/mL=normal; 0.05–0.09 ng/mL=intermediate increase; ≥0.1 ng/mL=abnormal); troponin I (<0.3 ng/mL=normal).

†Lowest blood pressure recorded during initial presentation.

‡Received intravenous fluids.

§Sublingual nitroglycerin administered by emergency medical personnel before emergency room admission.

*Presented in ventricular fibrillation (VF), preceded by sudden onset of chest pain due to multivessel focal 2-vessel coronary vasospasm; treated with DC cardioversion, epinephrine, atropine, and an implantable defibrillator for secondary sudden death prevention.

¶Patient with nonobstructive form of familial hypertrophic cardiomyopathy (septal thickness=16 mm).

§Presentation predominantly with acute dyspnea (underlying pulmonary disease).

**Assignment of LV segmental wall-motion abnormalities to expected vascular territories served by each of the 3 major epicardial arteries, as described previously.10

Evolving ST-segment infarction. Patients were discharged and maintained on medications, including ACE inhibitors or angiotensin receptor blockers (n=14), β-blockers (n=11), and calcium antagonists (n=3). Of the 22 patients, 19 (86%) were taking ACE inhibitors/angiotensin receptor blockers, β-blockers, or both after hospital discharge. Compared with the other 14 study patients, the 8 patients with hemodynamic compromise showed higher peak troponin values (9.1±10.1 versus 1.5±3.9 ng/mL; P<0.03) and lower initial ejection fraction (24±10 versus 31±7%; P=0.05). Patients with and without hemodynamic compromise did not differ significantly with respect to age (64±8 versus 67±16 years), follow-up ejection fraction (62±7 versus 63±5%), or frequency of ST-segment elevation (71% versus 57% of patients).

**LV Outflow Obstruction**

During administration of dobutamine, 5 patients (patients 12, 13, 15, 21, and 22) with hypotension developed dynamic
obstruction to LV outflow due to mitral valve systolic anterior motion, which rapidly resolved after termination of the drug. Outflow tract gradients, measured with continuous-wave Doppler, were small in 4 patients (25 to 30 mm Hg) and marked in 1 patient (100 mm Hg) with a mild phenotype of hypertrophic cardiomyopathy.11

**Follow-Up**

### Short-Term Follow-Up

Each of the 22 patients survived their acute event. In 21 patients, hospital discharge was prompt (6±3 days), at which time functional status had recovered and was restored to asymptomatic pre-event levels. Patient 2 with cardiac arrest had a 35-day hospitalization complicated by reversible anoxic encephalopathy. Other in-hospital complications were transient conduction abnormalities, including complete heart block (n=1), left anterior hemiblock, or posterior hemiblock (n=2); paroxysmal atrial fibrillation (n=2); and a small apical thrombus that resolved with heparin (patient 19).

LV systolic dysfunction and wall-motion abnormalities reversed rapidly, returning to normal range (ejection fraction 63±6%), assessed by CMR (n=13; Figure 3) or 2D echocardiography (n=9) during the recovery 24±29 days after admission and as early as 5 days or less in 7 patients.

### Long-Term Follow-Up

Each of the 22 patients were alive 12±10 months (range 1 to 32 months) after their initial cardiac event; 20 experienced virtually complete recovery with normal activity, whereas patients 2 and 3 continue to have chest pain. Patients 2 and 4 survived a second similar clinical event triggered by psychological stress 3 and 10 months after the first occurrence, respectively; at the time of the second event, patient 2 was taking aspirin and a statin drug, and patient 4 was taking a β-blocker, calcium channel blocker, aspirin, statin, ACE inhibitor, and sublingual nitroglycerin.

### Discussion

We describe a prospective clinical experience over a 2.5-year period in which 22 women had sudden and unexpected onset of a reversible cardiomyopathy triggered by profound psychological or physical stress. Initial presentation typically mimicked acute myocardial infarction or evolving acute myocardial ischemia. Among the 19 patients who were alive at 2.5 years, hospital discharge was prompt (6±3 days), at which time functional status had recovered and was restored to asymptomatic pre-event levels. Patient 2 with cardiac arrest had a 35-day hospitalization complicated by reversible anoxic encephalopathy. Other in-hospital complications were transient conduction abnormalities, including complete heart block (n=1), left anterior hemiblock, or posterior hemiblock (n=2); paroxysmal atrial fibrillation (n=2); and a small apical thrombus that resolved with heparin (patient 19).

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coronary syndrome (but without coronary artery disease) in which major impairment in myocardial contractility was characterized by a distinctive ballooning appearance of the mid and distal (apical) LV, sparing only the hypercontractile basal LV.3,6

Patients with similar clinical profiles have only recently been reported, primarily but not exclusively in Japan1–6,12; the designation “tako-tsubo” cardiomyopathy has been attached, which describes the resemblance of the LV angiogram to an octopus trap. The striking predilection for Japanese patients in the literature1–6 and the largely anecdotal case reports from other parts of the world13–19 initially suggested a unique geographic and/or racial distribution, with origins in Asian culture. Indeed, this cardiomyopathy has yet to achieve recognition within the greater physician community in most parts of the world; the present patient series constitutes the most substantial report of this syndrome from North America and the largest series from any region outside Japan.

Each of our 22 patients survived their cardiac event (and an additional episode in 2 patients) and achieved normal activity levels by hospital discharge. This uniformly favorable clinical outcome is notable as a few deaths have been reported with tako-tsubo cardiomyopathy3,20 and given the presentation of patients in the present study who required aggressive treatment including hemodynamic stabilization with vasopressor agents and intra-aortic balloon counterpulsation (in almost 40%). Indeed, the marked initial impairment in LV contractility (ejection fraction 29/11006 9%) in these patients normalized (to ejection fraction of 63/11006 6%) with supportive treatment.

Each of the profound clinical events in the present report were preceded immediately by intense episodes of psychological or physical stress, which represented a lifetime crisis in 70%: unexpected death of a close relative or friend, confrontational arguments, domestic abuse, catastrophic medical diagnosis, or devastating business or gambling losses. Common themes for these circumstances were interpersonal conflicts, hopeless situations, or losses in life, which often involved elderly patients living alone. The similarity of these events and the distinct temporal relationship between the stress and LV dysfunction substantiates a causal linkage that cannot be regarded simply as coincidental and is reminiscent of previous hypotheses that associated psychological stress with sudden cardiac death.21

In this report, we did not undertake systematic investigation of potential pathophysiological mechanisms; however,
the clinical presentation intuitively suggests catecholamine-mediated cardiotoxicity, in which the distal LV chamber is selectively vulnerable to a form of myocardial stunning \cite{22,23}, unrelated to atherosclerotic coronary disease-mediated myocardial ischemia. One of the patients in the present series presented with diffuse multifocal and multivessel coronary vasospasm \cite{24}, a causal mechanism suggested in some Japanese patients, that either spontaneously occurs or is provoked in the catheterization laboratory \cite{3,5}. Other pathophysiological mechanisms proposed for this cardiomyopathy include microvascular spasm \cite{3}, impaired fatty acid metabolism \cite{25}, and transient obstruction to LV outflow \cite{3}. We also observed

Figure 3. Coronary angiogram during chest pain in patient 2 with stress cardiomyopathy. Multifocal areas of vasospasm (arrows) are present in left circumflex (CX) and left anterior descending (LAD) coronary arteries. After nitroglycerin, vasospasm resolved completely.

Figure 4. Diastolic and systolic cine CMR images (horizontal long-axis) from patient 4. A, Acute phase with akinetic distal LV chamber and absence of systolic wall thickening (arrows). B, After clinical recovery, LV systolic function has normalized. Delayed postcontrast hyper-enhancement was absent, consistent with viable myocardium.
dynamic intraventricular pressure gradients, which were likely secondary to the administration of dobutamine in 5 hypotensive patients. Finally, patients in the present study are similar clinically to those with forms of nonischemic myocardial stunning reported in noncardiac diseases (eg, status asthmaticus, pheochromocytoma) and subarachnoid hemorrhage, conditions that also link a neurally mediated trigger to acute LV dysfunction.

Given the absence of significant, fixed atherosclerotic coronary artery disease on angiography in each of the patients in the present study and the substantial area of LV myocardial dysfunction evident on both angiography and CMR, it is highly unlikely that erosion or rupture of an otherwise nonobstructive plaque (followed by spontaneous thrombolysis) played a role in the cardiac events reported here. In particular, CMR studies identified diffusely distributed wall-motion abnormalities that encompassed LV myocardium in more than 1 coronary arterial vascular territory in 95% of patients and in the vascular distribution of all 3 epicardial coronary arteries in 90%.

Also, CMR studies performed during hospital admission were uniformly consistent with preserved myocardial viability (ie, absence of delayed hyperenhancement with gadolinium) without evidence of acute myocardial infarction, infiltrative or inflammatory processes (eg, myocarditis), necrosis and loss of cellular membrane integrity, or scar formation. Myocardial biopsies to exclude myocarditis were not routinely indicated or advisable under these clinical circumstances; however, patients in the present study would appear to differ substantially from the typical profile of myocarditis with regard to CMR wall-motion abnormalities and absence of typical mid-myocardial gadolinium uptake, as well as the observed ECG patterns. The mechanism (and significance) of troponin release in patients in the present study is uncertain. Therefore, based on our clinical, angiographic, and CMR data, another yet undefined pathophysiological process exclusive of coronary atherosclerosis or myocarditis is likely involved in this cardiomyopathic syndrome.

We found a striking predilection of this novel cardiomyopathy for women of advanced age, consistent with the 6-fold female-to-male predominance reported from Japan. All but 1 of our patients (95%) were >50 years of age (range up to 89 years), and most were postmenopausal. The explanation for this striking gender and age predilection is unresolved.

It is difficult to estimate the frequency with which this clinical entity occurs in the general population, although tako-tsubo syndrome has been identified in 1% of admissions for acute myocardial infarction in Japan. Our report of almost 1 case per month within an active cardiovascular practice is generally consistent with the report of Tsuchihashi et al from a multicenter Japanese population (ie, 125 cases in 9 years, or 14 per year). These observations suggest that this newly recognized cardiomyopathy has been underdiagnosed, and with greater visibility within the physician community, it will prove to be much more common than initially appreciated.

Recognition and understanding of the unique, reversible form of LV dysfunction reported here, triggered by psychological or physical stress, are of general medical interest and relevant to a wide range of practicing clinicians, particularly cardiologists. Presentation of this cardiovascular syndrome is an unexpected event, with initial management strategies being the responsibility of emergency medical facilities. This condition should now be considered within the differential diagnosis of acute coronary syndromes such as ST-elevation myocardial infarction and unstable angina, which may be difficult to distinguish. Prompt and aggressive pharmacological and hemodynamic support achieved rapid reversal of LV function and survival without long-term adverse sequelae.

References

enhancement to irreversible injury, infarct age, and contractile function.


Acute and Reversible Cardiomyopathy Provoked by Stress in Women From the United States
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