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QUARTERLY FOCUS ISSUE: HEART FAILURE

Natural History and Expansive Clinical Profile of Stress (Tako-Tsubo) Cardiomyopathy

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Objectives This study was designed to define more completely the clinical spectrum and consequences of stress cardiomyopathy (SC) beyond the acute event.

Background Stress cardiomyopathy is a recently recognized condition characterized by transient cardiac dysfunction with ventricular ballooning.

Methods Clinical profile and outcome were prospectively assessed in 136 consecutive SC patients.

Results Patients were predominantly women (n = 130; 96%), but 6 were men (4%). Ages were 32 to 94 years (mean age 68 ± 13 years); 13 (10%) were ≤50 years of age. In 121 patients (89%), SC was precipitated by intensely stressful emotional (n = 64) or physical (n = 57) events, including 22 associated with sympathomimetic drugs or medical/surgical procedures; 15 other patients (11%) had no evident stress trigger. Twenty-five patients (18%) were taking beta-blockers at the time of SC events. Three diverse ventricular contraction patterns were defined by cardiovascular magnetic resonance (CMR) imaging, usually with rapid return to normal systolic function, although delayed >2 months in 5%. Right and/or left ventricular thrombi were identified in 5 patients (predominantly by CMR imaging), including 2 with embolic events. Three patients (2%) died in-hospital and 116 (85%) have survived, including 5% with nonfatal recurrent SC events. All-cause mortality during follow-up exceeded a matched general population (p = 0.016) with most deaths occurring in the first year.

Conclusions In this large SC cohort, the clinical spectrum was heterogeneous with about one-third either male, ≤50 years of age, without a stress trigger, or with in-hospital death, nonfatal recurrence, embolic stroke, or delayed normalization of ejection fraction. Beta-blocking drugs were not absolutely protective and SC was a marker for increased noncardiac mortality. These data support expanded management and surveillance strategies including CMR imaging and consideration for anticoagulation. (J Am Coll Cardiol 2010;55:333–41) © 2010 by the American College of Cardiology Foundation

Stress (tako-tsubo) cardiomyopathy (SC) is a rapidly reversible form of acute heart failure reported to be triggered by stressful events and associated with a distinctive left ventricular (LV) contraction pattern. Whereas the presentation of SC has been described by several investigators (1–7), there is a paucity of data from large and prospectively identified patient cohorts studied for extended periods of time following the initial event. Therefore, we assembled a substantial and consecutive group of patients with SC from a single institution to define more completely the broad clinical spectrum and long-term consequences of this recently recognized condition.

Methods

Patient population. Between August 2001 and November 2008, 136 consecutive patients presented with SC to the emergency and hospital facilities of the Minneapolis Heart Institute and Abbott Northwestern Hospital (Minneapolis, Minnesota). The first 22 patients identified formed the basis for our initial SC report (1). These patients are now included in the present study group of 136 patients, now with extended follow-up. Patients shared the following diagnostic profile: 1) an acute cardiac event typically presenting with substernal chest pain; 2) systolic dysfunction with marked LV contraction abnormality, extending

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Abbreviations and Acronyms

CMR = cardiovascular magnetic resonance
ECG = electrocardiogram
EF = ejection fraction
LV = left ventricle/ventricular
RV = right ventricle/ventricular
SC = stress cardiomyopathy

beyond the geographic territory of a single epicardial coronary artery, assessed with LV angiography, cardiovascular magnetic resonance (CMR) imaging, or 2-dimensional echocardiography; and 3) absence of obstructive atherosclerotic coronary artery stenosis (i.e., ≤50% luminal narrowing of the epicardial arteries by angiography).

The clinical status of surviving study patients was assessed as of November 1, 2008, by telephone interview, clinic visit, and/or medical records. Follow-up period from initial SC event to most recent assessment (or death) was 2.3 ± 2 years (range 0.1 to 7.1 years). To examine temporal trends in the presentation of SC, we compared the 46 patients presenting during our early experience (August 2001 through February 2005), before the publication of 2 initial U.S. studies of SC (1,2), with our later experience of 90 patients (March 2005 through November 2008).

CMR imaging. At the discretion of the attending cardiologist, CMR imaging was performed in 95 patients shortly after admission. CMR was performed with a Siemens Sonata 1.5-T scanner (Siemens, Erlanger, Germany). Standard fast imaging with steady-state precision: inversion time = 240 to 300 ms (also known as TrueFISP) 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, achieving full ventricular coverage. A delayed enhancement protocol was employed 10 to 20 min after intravenous administration of gadolinium–diethylenetriamine pentaacetic acid (0.2 mmol/kg) with breath-hold inversion-recovery fast low-angle shot (Turbo-FLASH) or segmental TrueFISP sequences (8). Regional wall motion was assessed using the 17-segment model of the LV chamber (9).

Other testing. Ejection fraction (EF) was assessed on initial admission by LV angiography (n = 100; 74%), 2-dimensional echocardiography (n = 34; 25%), CMR (n = 1; 0.5%), and CT angiogram (n = 1; 0.5%). At follow-up, EF was assessed by echocardiography (n = 76; 60%), CMR (n = 49; 39%), and LV angiography (n = 1; 1%). Left ventricular outflow tract gradients were measured with continuous-wave Doppler.

Statistics. SURVIVAL ANALYSIS. For those SC patients discharged from the hospital after the initial event, the fraction surviving at each follow-up time was estimated using the Kaplan-Meier method (10). The expected fraction surviving at each time after diagnosis was computed (10) by assigning to each patient the probability of surviving after presentation, appropriate to patient age at diagnosis and sex, and based on U.S. Census data from Minnesota (11). Actual and expected surviving fractions were compared using the 1-sample log-rank test, which also provides an estimate and confidence interval for the standardized mortality ratio and 95% confidence interval. All computations used the "survival" package (version 2.34-1) of the R software system, version 2.7.2R (Development Core Team 2008).

OTHER ANALYSES. Continuous measures are reported as mean ± SD and assessed with paired or unpaired Student *t* test, as appropriate. Categorical measures were compared with standard chi-square test. GB-STAT statistical software, version 9.0 (Dynamic Microsystems, Silver Spring, Maryland) was used in analyses, and statistical significance was defined as $p < 0.05$. This investigation met the federal regulatory requirements for exemption from institutional review board oversight and as such was granted a waiver from informed patient consent.

Results

Clinical features. PRESENTATION. At initial hospitalization, the 136 patients with SC events were 32 to 92 years of age (mean age 68 ± 13 years), 13 (10%) were ≤50 years of age, 130 (96%) were women, and 6 (4%) were men (Figs. 1 to 4). The most common presenting cardiovascular symptoms were substantial chest pain (n = 85; 63%), exertional dyspnea (n = 25), and syncope (n = 4). Two other patients presented to the hospital in asystole or ventricular fibrillation (1 of whom survived). The remaining 20 patients with SC were identified during the management or monitoring of noncardiac conditions.

In 121 patients (89%), careful history-taking identified significant stressful events immediately preceding (within about 12 h) the presentation of SC under diverse circumstances (Table 1). These events were regarded as emotionally mediated in 64 patients (47%), usually involving personal or family life crisis events, or alternatively due to a physical trigger in 57 (42%), most commonly acute noncardiac illness (n = 36) or a medical/surgical procedure or diagnostic test (n = 9). These circumstances are detailed in Table 1.

Among the patients with physical triggers, exposure to catecholamine and beta-agonist drugs in doses routinely administered in clinical practice were disproportionately associated with SC events (n = 13), including: inhaled albuterol or salmeterol for acute respiratory failure (n = 10, including 1 each with subcutaneous epinephrine or dopamine), intravenous dobutamine during stress echocardiography (n = 1) and phenylephrine for hypotension during spinal surgery (n = 1), and intranasal phenylephrine for unrelenting epistaxis (n = 1). In the remaining 15 (11%) study patients (age 73 ± 14 years; 14 women), a stress trigger could not be elicited, despite repeated questioning.

MEDICATIONS. Of the 136 SC patients, 58 were taking cardioactive drugs for control of blood pressure at the time of their event either alone or in combination, including beta-blockers (n = 25), angiotensin-converting enzyme inhibitors (n = 24), calcium channel blockers (n = 12), angiotension-II receptor blocker (n = 11), and clonidine (n = 3).

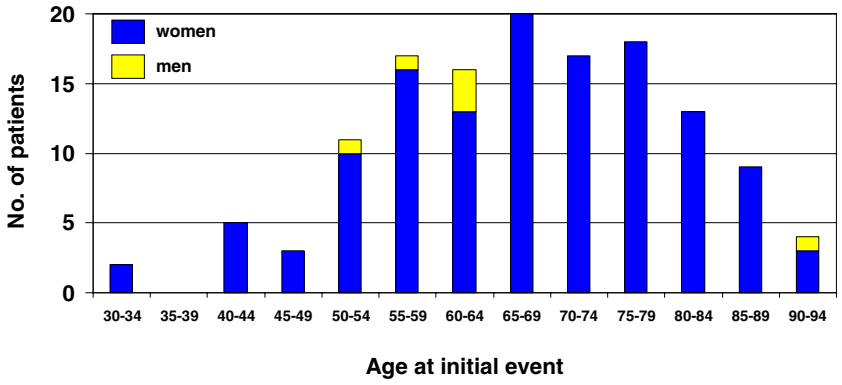

Figure 1 Ages at Stress Cardiomyopathy Presentation, by Sex

Ages at initial stress cardiomyopathy event, shown separately by sex.

SEX. Clinical presentation and demographics of SC did not differ between male and female patients. At the time of their initial SC event, the 6 male patients were 65 ± 15 years of age, predominantly experiencing physical triggers (n = 4). The 130 women were 68 ± 13 years of age (p = 0.63 vs. men) at the time of their event, predominantly with emotional triggers (n = 63).

ECG and biomarkers. On admission, ST-segment elevation mimicking acute anterior myocardial infarction was the most common electrocardiogram (ECG) finding, occurring in 67 patients (49%). The ECG findings in the remaining 69 patients without ST-segment elevation were diverse and included: diffuse T-wave inversion (n = 22; 16%), healed anterior infarction (n = 26; 19%); nonspecific (n = 17; 13%);

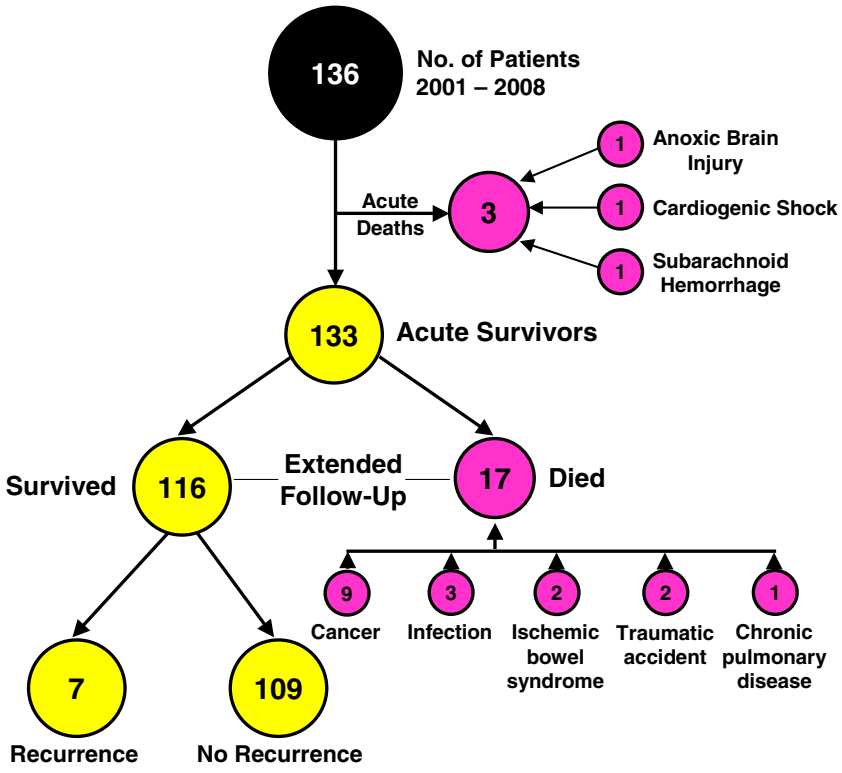

Figure 2 Clinical Course and History of Patients With Stress Cardiomyopathy

Flow diagram showing clinical course and natural history of 136 patients with stress cardiomyopathy.

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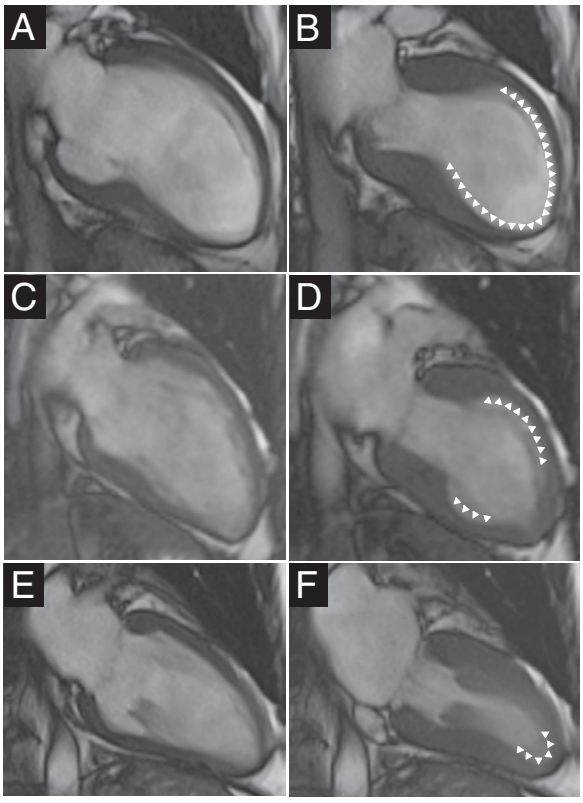

Figure 3 **Diversity of LV Contraction Patterns in SC, as Demonstrated by CMR in Vertical Long-Axis View**

(A, C, and E) Diastole; **(B, D, and F)** systole. Three types are depicted: **(A, B)** most common pattern of mid and apical left ventricular (LV) akinesia **(arrowheads)**; **(C, D)** mid-LV akinesia **(arrowheads)** with sparing of apical region; and **(E, F)** apical LV contraction abnormality only **(arrowheads)**. CMR = cardiovascular magnetic resonance; SC = stress cardiomyopathy.

left bundle branch block (n = 2; 1%); or normal (n = 2, 1%). On admission, troponin T was elevated in 125 patients (92%), 0.6 ± 1.8 ng/ml (range 0.01 to 5.2 ng/ml), and peak in-hospital troponin release was 0.6 ± 0.7 ng/ml (range 0.01 to 5.2 ng/ml). No relation was evident between ECG pattern, troponin level, clinical features and outcome, or LV contraction pattern.

CMR imaging. LV contraction abnormalities characterized by CMR imaging (n = 95) showed substantial variability with respect to the patterns of akinesis/dyskinesis and ventricular ballooning including: 1) combined mid-ventricular and distal (apical) LV (n = 72); 2) mid-LV only (n = 16); 3) distal (apical) LV only (n = 7) (Fig. 3). Right ventricular (RV) akinesia was also present in 23 patients, associated only with the mid-LV (n = 5) and combined mid- and distal LV contraction patterns (n = 18) (Fig. 4). Patients with RV contraction abnormalities had lower LV ejection fraction (26 ± 8%) than did patients with normal RV contractility (32 ± 11%; p = 0.003). No relation was evident between LV or RV contraction patterns and clinical presentation, mortality, age, sex, ECG pattern, peak troponin, and type of stress trigger.

Of the 79 patients with abnormal contraction involving the distal portion of the LV chamber, 33 nevertheless showed localized sparing of the most apical segment (i.e., #17 in the American Heart Association model) (9). Only 1 study patient (a 51-year-old woman) showed delayed enhancement consistent with scarring of the distal LV, not typical for myocarditis (12), and associated with the highest peak troponin value (i.e., 5.2 ng/ml).

Acute management and complications. OUTCOME. Three patients (2%) died in the acute phase during hospitalization, including 1 from cardiogenic shock (age 92 years) despite aggressive supportive therapy with inotropic drugs (Fig. 2). The second patient (age 58 years) died of anoxic brain injury after cardiac arrest and mechanical ventilation, and the third (age 89 years) of traumatic intracerebral hemorrhage.

Intraventricular apical thrombi were identified in 5 patients (4 in LV and 1 in both LV and RV), and by CMR in 3 of these including the RV thrombus (Fig. 4). Of the 5 patients, 2 experienced embolic events: cerebral in 1 and both cerebral and pulmonary in 1. Three of these 5 patients were treated with warfarin with no subsequent events. In addition, 13 patients developed dynamic obstruction to LV outflow (gradients, 54 ± 48 mm Hg) due to systolic anterior motion of the mitral valve and mitral-septal contact, and in 7 patients, following the intravenous administration of inotropic agents for hypotension (Fig. 4). In each, outflow obstruction resolved and 12 patients survived.

EJECTION FRACTION. On admission, EF was 32 ± 11% (range 15% to 55%). Of the 136 patients, 131 (96%) had at least 1 follow-up EF determination and 126 of these had eventual return to normal ejection fraction (≥50%). Of the 126 patients, at first follow-up (in-hospital after 3.3 ± 3.4 days or post-discharge after 51 ± 52 days), 94 had EF within normal limits (mean 54 ± 11%), but in 32 it remained <50%. Of these latter 32 patients, 26 had normal EF subsequently at 76 ± 137 days after discharge (i.e., 59 ± 7%).

Six other patients (5%) (age 76 ± 7 years with initial EF only 26 ± 7%), showed delayed EF normalization (57 ± 6%) over at least 2.5 months and up to 12 months following their event.

In 5 of the 131 patients, follow-up EF determination performed in-hospital (range 1 to 13 days) demonstrated improvement from 26 ± 11% to 40 ± 4%, p < 0.05, but none achieved normal range, however, and later EF determinations were not performed.

Follow-up. SURVIVAL. Of the 136 patients, 116 (85%) have survived over the follow-up period since their SC event for 2.9 ± 2 years (range 0.1 to 7.4 years, mean age 69 ± 13 years) (Figs. 2 and 5); 110 were women and 6 were men. Of these 116 survivors, 44 (38%) have achieved age ≥75 years.

Seventeen other patients (15%) died after hospital discharge at age 51 to 92 years (mean age 73 ± 12 years), all from noncardiac causes, most commonly cancer (Fig. 2). The interval from initial SC event to death was 4 months to 4.7 years (mean 1.3 ± 1.5 years).

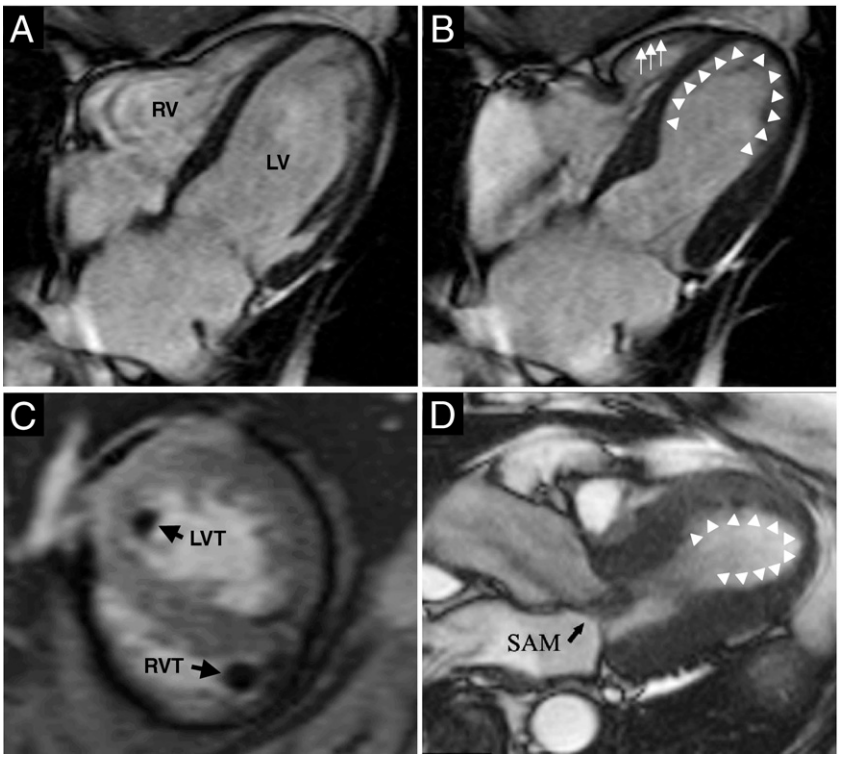

Figure 4 **Additional Abnormalities in SC Demonstrated by CMR**

(A, B) In this horizontal long-axis image, right ventricular (RV) free wall akinesia **(white arrows)** is evident in systolic **(B)** compared with diastolic **(A)** and is associated with typical mid- and apical LV akinesis **(white arrowheads)**. **(C)** In the short-axis view, left ventricular thrombus (LVT), and a right ventricular thrombus (RVT), which was responsible for pulmonary embolization, are evident. From the same patient shown in **A and B**. **(D)** Dynamic obstruction to LV outflow produced by systolic anterior motion (SAM) and mitral-septal contact, following administration of an inotropic agent for hypotension. A mid- and apical LV contraction abnormality is also present **(arrowheads)**. Abbreviations as in Figure 3.

When analyzed for all-cause mortality, survival of the study patients with SC after their initial event was significantly reduced compared with that expected in an age- and sex-matched general population from Minnesota ($p = 0.016$; standardized mortality ratio: 1.7; 95% confidence interval [CI]: 1.1 to 2.7) (Fig. 5). The excess in mortality for SC patients occurred predominantly in the first year after diagnosis (including 9 patients who died of cancer, 4 with SC events linked to their malignancy).

The standardized mortality ratio during the first year after diagnosis was 6.8 (95% CI: 4.0 to 11.5), whereas during subsequent years, the standardized mortality ratio was 0.6 (95% CI: 0.3 to 1.4; $p < 0.0001$, comparing <1 year vs. ≥1 year).

RECURRENCES. Seven patients (5%, all women) experienced additional nonfatal SC episodes at age 51 to 85 years (mean age 66 years) (Table 2, Fig. 2); 6 of these had 1 SC event recurrence 3 weeks to 3.8 years after the first (including 1 with ventricular fibrillation) and the other patient experienced 3 SC recurrences (0.8 to 4.4 years after the first episode). In 5 of the 7 patients with SC recurrences, the initial and subsequent events involved similar stress triggers (either emotional [n = 4] or physical [n = 1]), and in 4 of the 5 the circumstances of the events were similar or virtually identical.

Three of these 7 patients were taking beta-blocking agents at the time of their first recurrent SC event, and the patient with 3 recurrences was taking beta-blockers on the occasion of each event. No clinical or demographic feature distinguished the patients with recurrent SC from the other study patients.

TEMPORAL TRENDS. During the 7.4 years of this study, the number of SC diagnoses increased from 46 patients (34%) during the first 3.6 years to 90 patients (66%) during the later 3.8 years. This was associated with a shift in the predominant stress trigger from emotional (32 of 46 [70%]), to physical (44 of 90 [49%]; $p = 0.0004$).

Discussion

The present large series of prospectively identified patients with SC from a single institution describe an expansive clinical profile during acute presentation and also provides additional insights into the natural history of this cardiomyopathy. The typical SC patient has been characterized as an older woman

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Table 1 Examples of Emotional and Physical Stressors Triggering Heart Failure in SC Patients

Emotional (n = 64)
Anger/frustration (n = 10)
Heated argument with family members, friend, or landlord over rent
Frustration regarding work environment or personal property
Argument with husband (afflicted by dementia)
Frustration related to organizing a community event
Related to financial or employment problems (n = 7)
Gambling loss including passing bad checks
Personal business failure with loss of life savings
Recognition of large business debt
Stress during meeting with management at work
Stressful beginning to a new job
Grief/loss (n = 18)
Notification of recent sudden death in a close relative or friend
Tenth anniversary of son's death
Cardiac arrest in husband (patient performed cardiopulmonary resuscitation)
Husband with post-operative cardiac arrest and anoxic encephalopathy
Multiple deaths of family members in close proximity
Advised of son's death in military
Sense of loss after retiring from life-long occupation
Impending death of husband from cancer
Expressing grief at memorial service for public figure (U.S. senator)
Death of 2 pet dogs
Reflecting on death of son-in-law during church meeting
Interpersonal conflict (n = 14)
Lengthy divorce culminating in sale of her home of 28 years
Separation from husband
Severe depression with suicidal ideation
Failure to keep up with daughter during bicycle race
Discussing family estrangement during psychological counseling
Discussing brother's methamphetamine addiction and alcoholism
Relocation of permanent residence
Physical domestic abuse by spouse
Estrangement from daughter
Overwhelming emotion during 50th wedding anniversary
Informed that best friend was moving a great distance
Upsetting phone call from friend
Sexual abuse by relative
Panic/fear/anxiety (n = 15)
Accidental fall outdoors in winter with hip fracture (feared freezing to death)
Flat tire while driving a remote road in Minnesota (without cell phone)
Legal deposition regarding motor vehicle accident
Lost while driving in unsafe neighborhood at night
Overwhelmed by new computer software at work
Lost with flat tire while driving mother to physician
Poultry barn burned down (fearing loss of chickens)
Anxiety regarding a public speaking event
Sudden illness of husband
Basement flood during intense thunderstorm
Anxiety about elevated blood pressure/paroxysmal atrial fibrillation
Anxiety about elective cardioversion for atrial fibrillation
Panic while trying to load belongings into car during bitter cold
Fall at home while alone with fear of not being found
Fall at home with hip fracture; unable to call help
Panic attack during lung biopsy for suspected malignancy
Physical (n = 57)
Acute respiratory failure (n =15)
Exacerbation of chronic obstructive pulmonary disease*
Pulmonary embolism
Laryngeal obstruction from neoplasm
Respiratory distress from influenza
Acute epiglottitis requiring intubation
Central nervous system conditions (n = 10)
Subarachnoid hemorrhage
Brain contusion from accidental fall
Ruptured cerebral aneurysm
Vasculitis
Migraine headache
Seizure
Brain abscess
Malignancy† (n = 6)
Advanced or metastatic cancer
Chemotherapy for metastatic colon or esophageal cancer
Metastatic carcinoid tumor
Infection (n = 3)
Urosepsis
Spinal fusion wound infection
Peritonitis from ischemic bowel
Post-surgical/fracture (n = 8)
Hysterectomy and bilateral oophorectomy
Knee arthroplasty
Discectomy and T12-S1 fusion for scoliosis‡
Cholecystectomy
Decompression of spinal stenosis
Pericardicentesis
Hip fracture
Other (n = 15)
Nosebleed treated with phenylephrine
Accidental home insulin overdose
Intentional Phenergan overdose
Dobutamine stress test
Gastrointestinal bleeding/gastroenteritis with dehydration
Acute rejection of renal transplant
Diabetic/nondiabetic gastroparesis
Anorexia with profound weight loss
Allergic drug reaction
Prolonged viral illness/dehydration
Hypertensive crisis
Withdrawal from alcohol

*11 total cases. †Linkage of stress cardiomyopathy (SC) and cancer was established if onset of event was directly due to symptoms from the malignancy, chemotherapy, or initially learning of the diagnosis. ‡SC was recognized clinically during general anesthesia.

experiencing an intensely stressful event that acts as a trigger for acute, but reversible, heart failure with systolic dysfunction (13–16). However, based on our data, the clinical profile of SC is considerably broader, with an important minority of patients relatively young (≤50 years of age; range to 32 years) or men. Also, unexpectedly 11% of patients related no emotional or physically stressful event immediately before hospitalization, despite demonstrating typical angiographic and ECG features of this condition (17–19). This latter observation has implications for both the nomenclature and pathophysiology of this condition. Indeed, the descriptive term used here and commonly in the literature, stress cardiomyopathy (13,17,20,21), does not reliably describe all affected patients with this syndrome, each of whom do in fact demonstrate transient ventricular ballooning.

A multitude of specific triggers preceded SC events, most commonly emotion-mediated. However, we found the frequency of physically related stressors was high (i.e., 43%), particularly with the administration of certain pharmacologic agents. For example, the use of beta-agonist bronchodilator drugs contributed to heart failure onset in some patients with acute respiratory failure from chronic obstructive pulmonary disease or asthma. In other patients, administration of exogenous catecholamines (i.e., phenylephrine, norepinephrine, or dobutamine [during routine stress test-

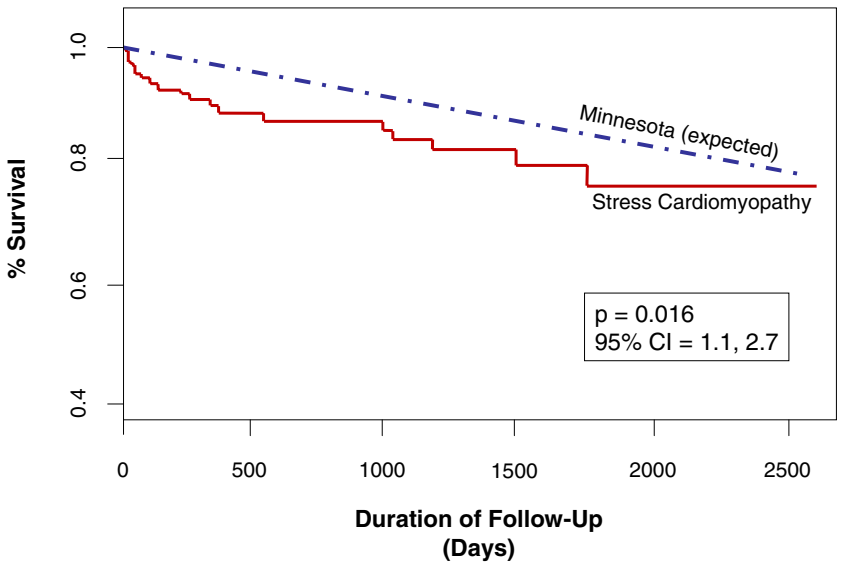

Figure 5 **Kaplan-Meier Survival Curves for Stress Cardiomyopathy Patients Versus That Expected in the General Population**

Kaplan-Meier survival curves for 136 patients with stress cardiomyopathy **(solid red line)** compared with that expected in an age- and sex-matched general population from Minnesota **(broken blue line)**. CI = confidence interval.

ing]) appeared to trigger SC (21). Finally, SC occurred in 1 patient who was unconscious during general anesthesia, which suggests an autonomic nervous system mechanism.

Taken together, these observations underscore the importance of heightened index of suspicion for SC in common clinical circumstances such as routine medical or surgical procedures, administration of drugs, and standard diagnostic testing (22,23). However, the dramatic presentation of SC in response to such common provocations is exceedingly rare overall.

Five percent of our surviving study patients experienced recurrent and remarkably similar SC episodes (usually emotional), demonstrating a unique propensity for stress-triggered heart failure and systolic dysfunction. The explanation for this peculiar susceptibility to SC remains elusive. Nevertheless, these observations underscore the importance of educating patients regarding the small but real risk of SC recurrence and the value of lifestyle modification to avoid exposure to identifiable emotional or physical stressors.

SC has been regarded as a largely reversible form of acute heart failure associated with LV remodeling and systolic dysfunction. However, our experience underscores that SC is not entirely benign, as about 5% of patients experienced either cardiac arrest (and survived) or died during hospitalization despite appropriate aggressive treatment (24). That some patients do not survive their acute SC event only underscores the importance of prompt recognition and targeted management with respect to systemic hypotension, ventricular tachyarrhythmias, dynamic LV outflow obstruction, and ventricular thrombi.

The inference from the assembled literature is that LV contraction abnormalities and systolic dysfunction in SC uniformly normalize rapidly at or before hospital discharge (13–16). However, we found evidence in an important minority of patients for a considerable delay in this process. Whereas 95% of patients ultimately showed follow-up EF values >50%, normalization was delayed for 2.5 to 12 months in 5% of patients.

The clinical course following SC events after hospital discharge is incompletely defined. Notably, our follow-up analysis showed that the survival of SC patients was reduced compared to that expected for an age- and sex-matched general population; in each case, mortality was due to noncardiac diseases (predominantly cancer), most frequently in the first year following the initial SC event. These data suggest that SC itself may represent a marker for generally impaired health and well-being, albeit in contrast to an earlier report (19). On the other hand, fully one-third of our patients who survived their initial event have achieved normal life expectancy (i.e., age ≥75 years).

During the most recent years, the number of identified cases increased dramatically with two-thirds enrolled in the last 50% of the study period, which was associated with a shift in the predominant stressor from emotional to physical.

Because of the potential role that catecholamines and excessive sympathetic stimulation play in the pathophysiology of this condition, as suggested here and by other investigators (2,21), hypothetically, beta-blocking drugs would be expected to provide a measure of pharmacologic protection against SC. However, our data indicate that

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Table 2 Patients With Recurrence of SC

Patient #	Event	Age (yrs)/ Sex	Interval from Initial Event	Drugs at SC Event	Stressor	% EF (Admission)	ECG	Stress Trigger
1	Initial*	51/F	—	Premarin	E	15	STE	Reflecting on brother's death and ordeal of incest
	Recurrence 1	51	3 weeks	Diltiazem nitroglycerin (IV)	E	65	STE	Same
2	Initial	53/F	—	Estrace	E	30	T-inversion	Death of 4 family members within a short period of time, including both parents
	Recurrence 1	55	1.2 yrs	Estrace	E	40	Normal	Family conflict over execution of wills
3	Initial	53/F	—	Verapamil Estratest	E	15	STE	Lost while driving at night
	Recurrence 1	54	0.8 yrs	Atenolol Lisinopril Estraderm	E	25	Healed MI	Discussing family during psychotherapist session
	Recurrence 2	54	1.5 yrs	Carvedilol Amlodipine Lisinopril Estraderm	E	25	Healed MI	During discussion of anxiety related to SC events
	Recurrence 3	57	4.4 yrs	Carvedilol Amlodipine	E	20	Healed MI	Discussing divorce of daughter
4	Initial	65/F	—	Enalapril Digoxin	E	30	Nonspecific	Heated argument over father's death
	Recurrence*	68	2.9 yrs	Metoprolol Enalapril Digoxin	None	25	Nonspecific	Stressor absent
5	Initial	66/F	—	None	E	30	Nonspecific	Gambling loss/passing bad checks
	Recurrence 1	70	3.8 yrs	None	E	35	Nonspecific	Conflict at home over relationships
6	Initial	78/F	—	None	P	30	STE	Accidental fall with brain contusion
	Recurrence 1	79	1.1 yrs	Metoprolol	P	35	STE	Accidental fall with subdural hematoma
7	Initial	83/F	—	Clonidine and flecainide	P†	40	Nonspecific	Sustained VT induced by flecainide
	Recurrence	85	2.3 yrs	Digoxin Clonidine Isordil	E	20	STE	Flat tire while driving alone

*Presentation in ventricular fibrillation. †Flecainide administered for symptomatic premature ventricular beats, appeared to trigger wide-complex monomorphic VT and marked systemic hypertension.
E = emotional; ECG = electrocardiogram; EF = ejection fraction; IV = intravenous; MI = myocardial infarction; P = physical; SC = stress cardiomyopathy; STE = ST-segment elevation; VT = ventricular tachycardia.

these drugs administered in traditional dosage did not absolutely prevent either the first or recurrent SC episodes; in other words, 20% of these events occurred while beta-blockers were administrated. Within our observational study design it was not possible to determine whether cardioactive drugs provided relative risk reduction for SC.

Our observations have certain other management implications. For example, the dyskinetic/akinetic ventricular segments can provide the structural basis for intracavitary thrombus formation. A small proportion of our patients had intraventricular thrombi (while in sinus rhythm), with or without disabling thromboembolic events suggesting a potential protective role decided on a case-by-case basis for prophylactic warfarin anticoagulation. In addition, CMR identified ventricular thrombi not visualized by echocardiography, underscoring the important diagnostic contribution of this imaging modality in SC.

Furthermore, using CMR, we observed a diversity of contraction patterns during the acute phase of SC, underscoring the peculiar vulnerability of both right and left ventricles in this condition (25–27) (Figs. 3 and 4). Expectedly, akinesia/dyskinesia most commonly involved both the mid- and apical portions of LV in about 75% of patients (4,5,13). However, the remaining 25% of patients showed segmental contraction abnormalities confined to either mid- (28) or apical LV. Our latter small subgroup with akinesia confined to the distal LV is distinctive from the generally recognized patterns in this condition (13–16), although each of these patients had a clinical profile otherwise consistent with SC. Finally, a sizable minority of our patients also showed more diffuse cardiac involvement with akinesia of the RV wall (26,27). We did not encounter SC patients with abnormal contraction limited to the basal LV, as reported by other investigators (20,29).

Conclusions

This consecutive series of SC patients represents the largest cohort reported to date in detail, demonstrating a clinical heterogeneity perhaps not widely appreciated. In this regard, small but important subsets of patients (together comprising 35% of the overall study population) were identified with either male sex, relatively youthful onset ≤50 years, in-hospital death, nonfatal recurrent SC events, absence of a stress trigger, and delay in normalization of ejection fraction. Beta-blocking drugs in standard dosages

(and other cardioactive drugs) failed to provide absolute protection against either initial or recurrent SC events, and therefore have an unproven benefit in this condition. Occurrence of intraventricular thrombi (and embolic stroke) should raise consideration for prophylactic anticoagulation in some patients.

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