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The broken heart syndrome

Throughout history, mankind has had an intuitive understanding of the connection between emotional stress and the heart. Descriptions of "heartache" and "dying from a broken heart" have appeared in the literary works of diverse cultures for centuries. Similarly, the medical literature is replete with descriptions of sudden death and myocardial infarction (MI) in the setting of fear, anxiety, and bereavement.[1,2] In the modern era, reports of sudden death and MI have been well documented in populations subjected to emotionally traumatic events such as natural disasters[3] and acts of war,[4] but the direct effect of acute emotional stress on cardiac contractile function has remained obscure.

Recently, a novel syndrome of transient left ventricular (LV) systolic dysfunction precipitated by acute emotional or physical stress has appeared in the medical literature.[5–7] For years this syndrome has been underrecognized and misdiagnosed, and only now are physicians beginning to appreciate the constellation of clinical features that characterize it.

This brief review will highlight those distinguishing features, provide some historical background of this relatively new syndrome, and review what is known about its possible pathophysiologic mechanisms.

A SYNDROME WITH SEVERAL NAMES

In 1980, Cebelin and Hirsch reported a series of murder victims who had been emotionally and physically traumatized prior to their deaths. At autopsy, no internal injuries were identified, but most of the victims had extensive myocardial contraction band necrosis.[8] This histologic finding, frequently observed in high catecholamine states, suggested to the authors that these victims may have died from the deleterious effects of catecholamines on their hearts, and they referred to the condition as "human stress cardiomyopathy." This term reappeared in the medical literature in 1997 when Pavin et al reported two cases of reversible LV dysfunction precipitated by acute emotional stress.[9] Stress cardiomyopathy was an obscure and almost unheard of condition in Western medical literature at the time of Pavin's publication. In the Japanese literature, however, reversible LV dysfunction precipitated by acute emotional or physical stress had already been well described. In 1990, Satoh et al were the first to refer to this syndrome as takotsubo cardiomyopathy,[10] named after the octopus trapping pot with a wide base and narrow neck that they believed resembled the unusual shape of the left ventricle in patients with this syndrome.

Throughout the 1990s, takotsubo cardiomyopathy appeared in Japanese journals in the form of case reports and small case series. Ironically, when Japanese authors finally introduced this syndrome to a Western audience in 2001,[5] they referred to it as transient LV apical ballooning, a name they perhaps felt would be more descriptive to and more easily remembered by Western physicians.

In February 2005, the clinical and neurohumoral features of myocardial stunning due to emotional stress were presented in the *New England Journal of Medicine*.[6] This study referred to the syndrome as stress cardiomyopathy, but because several of the patients had presented following the death of a loved one, the name "broken heart syndrome" was also introduced. The article received a great deal of media coverage (perhaps in part due to it being released just before Valentine's Day) and brought international attention to a syndrome that just a few years earlier had been almost unheard of. In the year and a half since that publication, the number of journal articles regarding this syndrome has increased considerably, and at the present time the names *stress cardiomyopathy*, *takotsubo cardiomyopathy*, *LV apical ballooning syndrome*, and *broken heart syndrome* are used interchangeably to refer to this condition.

PREVALENCE

It is difficult at present to know the true prevalence of this syndrome. A few retrospective series have estimated the prevalence to be about 2% of patients pre-

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senting with suspected acute coronary syndromes.[11–13] These series likely underestimate the true prevalence because they report only the patients who undergo coronary angiography and do not include patients in medical, surgical, and neurologic intensive care units, where the syndrome is common but often unrecognized. This notion is suggested by one prospective study that reported that of the 92 consecutive patients admitted to the medical intensive care unit for a noncardiac illness, 26 (28%) had echocardiographic evidence of LV apical ballooning.[14]

It will likely require several years and more widespread recognition of this syndrome by physicians in diverse subspecialties before its true prevalence is known.

PATIENT DEMOGRAPHICS AND PRESENTING SYMPTOMS

Although the initial reports of this syndrome were all from Japan, broken heart syndrome has now been reported in patients with diverse ethnic backgrounds from all over the world. As these reports have increased, it has become clear that this condition affects primarily postmenopausal women. In a recent systematic review of the literature, 88.8% of the reported cases were in women, with a mean age in the series reviewed ranging from 58 to 77 years.[15] This gender predisposition is similar to that at our center, where 80% of the cases have been women and the mean age is 60 years (unpublished data).

Patients can present with symptoms identical to those of an acute MI, with chest pain and shortness of breath being the most common.[15] In our experience, although the majority of patients are stable at the time of presentation, about one third have more serious clinical presentations including pulmonary edema, hypotension, cardiogenic shock, and ventricular arrhythmias (unpublished data).

DIAGNOSTIC CLUES

Although no single clinical feature is diagnostic of broken heart syndrome, a series of clinical clues can help solidify the diagnosis.

An acute event

Broken heart syndrome is typically precipitated by a sudden emotional or physical stressor. Patients with this condition do not present with chronic symptoms. Rather, they tend to be individuals without significant cardiac history who suddenly present with chest pain and/or shortness of breath after experiencing acute emotional or physical stress. In our experience, the most common emotional stressors include extreme grief, often due to the loss of a loved one, or extreme fear (eg, being held up at gunpoint, motor vehicle accident, public speaking). The most common physical stressors include neurologic insults, respiratory distress, and surgical procedures. The precipitating event may not always be obvious, but a thorough history will elucidate it in most cases.

Electrocardiographic features

Patients with broken heart syndrome can present with a variety of electrocardiographic (ECG) findings. At the time of admission, the ECG can look normal, can have nonspecific ST- and T-wave changes, or can demonstrate Q waves and ST-segment elevation. In the original descriptions from Japan, ST-segment elevation was considered an important feature of this syndrome. In the largest retrospective series of apical ballooning from Japan, 90% of the patients had ST-segment elevation,[5] but this finding appears to be less common in series reported from the United States.[6,7]

If ST-segment elevation is present, it is most commonly seen in precordial leads, and there is less inferior reciprocal ST-segment depression than is typically seen with an anterior ST-segment elevation MI.[16] Within 24 to 48 hours of the acute presentation, the ECG frequently develops some characteristic features that include a markedly prolonged QT interval and deep T-wave inversion in both precordial and limb leads.[6] The QT interval prolongation usually improves within a couple of days, but the T-wave abnormalities can take days, weeks, or even months to normalize.

Cardiac enzymes

Most patients with broken heart syndrome have elevated cardiac enzymes at the time of admission, but these elevations are usually quite mild. Though patients typically present with severe LV dysfunction, cardiac enzymes are much lower than those typically observed with an acute MI. In a study from our institution, despite a mean ejection fraction of 20% at the time of admission, the troponin I was only 0.18 ng/mL (interquartile range, 0.08 to 0.69 ng/mL; normal, < 0.06 ng/mL).[6]

Unique pattern of LV dysfunction

Perhaps the most distinguishing feature of this syndrome is the unusual LV contractile pattern at the time of admission. There is frequently akinesis or dense hypokinesis of the apical and midventricular segments, with sparing of the basal segments

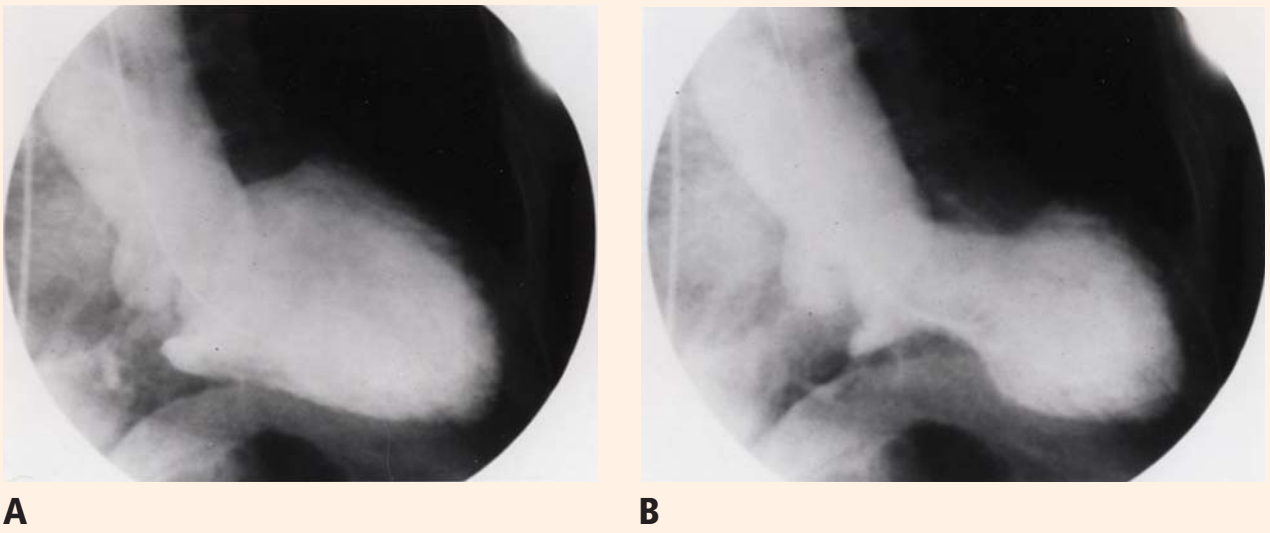

FIGURE 1. Contrast-enhanced ventriculography during diastole (A) and systole (B) in a patient with broken heart syndrome. Note the akinesis of the apex and midventricle with normal contractility of the base. Reprinted, with permission, from reference 6. Copyright © 2005 Massachusetts Medical Society. All rights reserved.

(Figure 1). As mentioned earlier, this contractile pattern has been referred to as both takotsubo cardiomyopathy and LV apical ballooning.

Absence of significant coronary disease

Because patients with broken heart syndrome frequently present with chest pain, dynamic ECG changes, troponin elevation, and focal wall motion abnormalities, coronary angiography is recommended unless there is an obvious contraindication. The vast majority of patients have either normal coronary arteries or mild luminal irregularities, and significant luminal stenoses have been rarely reported.[5–7]

Recovery of LV systolic function

Rapid and complete recovery of LV systolic function is one of the hallmarks of this syndrome. Despite the presence of extensive wall motion abnormalities at the time of admission, complete recovery of systolic function has been reported in all series to date.[15]

In our experience, significant improvement in systolic function frequently occurs during the first week following the initial presentation, and we recommend that patients hospitalized for several days have a repeat echocardiogram prior to discharge. The anterior wall frequently takes the longest to fully recover, but the majority of patients have completely normal LV systolic function by the end of the third week. As a general rule, if systolic function has not normalized after 4 to 6 weeks in a patient suspected of having the broken heart syndrome, the diagnosis should be reconsidered.

TREATMENT

The treatment of broken heart syndrome involves primarily supportive care. For hemodynamically stable patients, diuretics are used to treat congestion, and angiotensin-converting enzyme (ACE) inhibitors and beta-blockers are frequently used during the period of LV recovery.

There is no consensus on how long to continue these medications, but it is our practice to stop them once LV function has completely recovered. There are simply no data at this time to support that chronic use of ACE inhibitors and beta-blockers in these patients improves survival or helps to prevent recurrence. Unless there is a contraindication, anticoagulation should also be considered during the first few days until apical contractility begins to improve.

For hemodynamically unstable patients, reported treatment has included inotropic therapy, vasopressor support, and intra-aortic balloon counterpulsation. At our institution, because we believe that catecholamine excess may be responsible for the myocardial stunning seen with this syndrome, we prefer intra-aortic balloon counterpulsation for hemodynamically unstable patients, and we try to avoid the administration of exogenous catecholamines whenever possible. In addition, inotropes have been associ-

TABLE 1
Plasma catecholamine and neuropeptide levels at the time of admission in patients with broken heart syndrome and Killip class III myocardial infarction

	Broken heart syndrome (n = 13)	Killip class III MI (n = 7)	Normal value
Catecholamine precursor (pg/mL)			
Dihydroxyphenylalanine	2,859 (2,721–2,997)*	1,282 (1,124–1,656)	1,755†
Catecholamines (pg/mL)			
Epinephrine	1,264 (916–1,374)*	376 (275–476)	37†
Norepinephrine	2,284 (1,709–2,910)*	1,100 (914–1,320)	169†
Dopamine	111 (106–146)*	61 (46–77)	15†
Neuronal metabolites (pg/mL)			
Dihydroxyphenylglycol	2,706 (2,382–3,131)*	1,625 (1,412–1,702)	800†
Dihydoxyphenylacetic acid	2,758 (2,573–3,077)	1,513 (1,211–1,648)	1,497†
Extraneuronal metabolites (pg/mL)			
Metanephrine	178 (140–187)	106 (89–124)	59†
Normetanephrine	216 (130–319)	160 (145–170)	55†

MI = myocardial infarction
* $P < .01$ vs Killip class III MI.
† Data are from Goldstein et al.[26]
Adapted from reference 6.

ated with left ventricular outflow tract obstruction in some patients with this syndrome.[7] Whichever form of hemodynamic support is chosen, most patients only require it for a short time and typically demonstrate rapid clinical improvement.

PROGNOSIS AND RECURRENCE

In general, the prognosis of patients with this condition is quite favorable. The in-hospital mortality rate of cases reported in the literature is only 1.1%.[15] When discussing prognosis, it is important to distinguish the patients who present following emotional stress from those who present following a variety of physical stressors. In the 7 years that we have been following patients with this condition, none of the patients with emotional stress have died. We have observed a higher mortality among those who present following physical stress, but typically LV function fully recovers in these patients as well, and the ultimate cause of death is noncardiac.

Although patients can have recurrent symptoms of chest pain, recurrence of the full-blown syndrome appears to be relatively uncommon. Based on a review of the series published to date, the recurrence rate is only 3.5%,[15] which is similar to the rate at our institution.

POSSIBLE PATHOPHYSIOLOGIC MECHANISMS

Catecholamines appear to be central

Increased sympathetic tone may play an important role in the pathogenesis of myocardial stunning following emotional and physical stress. Patients with stress-induced cardiomyopathy have markedly elevated levels of plasma catecholamines and stress neuropeptides at the time of admission compared with patients with Killip class III MI **(Table 1)**.[6] The marked elevation in plasma norepinephrine and epinephrine in these patients reflects activation of both the sympathoneural and adrenomedullary hormonal systems, respectively. In addition, enhanced sympathetic activity in patients with takotsubo cardiomyopathy has been suggested by the increased washout rate of the norepinephrine analogue ^{123}I-metaiodobenzyl-guanidine (MIBG) using myocardial scintigraphy.[12]

Mechanism is elusive, but theories abound

Even if one accepts that catecholamines are central to the pathogenesis of broken heart syndrome, the precise mechanism in which enhanced sympathetic stimulation leads to myocardial stunning is unknown. Ischemia due to multivessel epicardial spasm has been suggested, but there are several compelling reasons to question this hypothesis.

• Spontaneous epicardial spasm during angiography has been rarely reported in the literature, and even the administration of provocative agents such as ergonovine and acetylcholine has failed to induce epicardial spasm in the majority of patients reported.[15]

• It is difficult to explain the LV apical ballooning pattern based on an epicardial vascular distribution, and even multivessel spasm would not account for selective sparing of the basilar segments.

• Most patients have only mild cardiac enzyme elevation, and many have no evidence of ST-segment elevation on admission ECG, findings that seem unlikely in the setting of diffuse epicardial spasm.

An alternative explanation is microcirculatory dysfunction. Using a Doppler flow wire at the time of coronary angiography, Kume et al demonstrated a significant reduction in coronary flow reserve and flow velocity in patients with takotsubo cardiomyopathy.[17] Bybee et al used the Thrombolysis in Myocardial Infarction (TIMI) frame count, a well-validated index of coronary blood flow, to assess coronary flow in patients with LV apical ballooning.[11] Patients with apical ballooning had significantly higher TIMI frame counts compared with controls, and the majority had evidence of abnormal flow in all three epicardial vessels.[11] Although these findings suggest the potential role of microvascular dysfunction in patients with this syndrome, it is unknown whether it is the primary cause of the myocardial stunning or simply a secondary phenomenon.

A third possible mechanism of sympathetically mediated myocardial stunning is the direct effect of catecholamines on cardiac myocytes. Catecholamines can decrease myocyte viability through cyclic adenosine monophosphate-mediated calcium overload,[18] which histologically can result in a unique form of myocyte injury called contraction band necrosis. Contraction band necrosis is characterized by hypercontracted sarcomeres, dense eosinophilic transverse bands, and an interstitial mononuclear inflammatory infiltrate. It has been described in clinical states of catecholamine excess such as pheochromocytoma[19] and subarachnoid hemorrhage,[20] and it has been observed in patients with stress cardiomyopathy as well.[6]

In a rat model of emotional stress, LV apical ballooning can be induced by immobilization stress and attenuated with the administration of alpha- and beta-receptor antagonists.[21] These observations suggest that stress-induced myocardial stunning is due to adrenergic receptor stimulation, though stunning due to ischemia cannot be definitively excluded. Further work with experimental animal models will be necessary to elucidate the precise mechanism.

REMAINING QUESTIONS

The increasing clinical awareness of the broken heart syndrome has raised several interesting questions that to date remain unanswered.

• Why does this syndrome affect primarily postmenopausal women? Sex hormones exert important influences on the sympathetic neurohormonal axis[22] as well as on coronary vasoreactivity,[23] but sex-related differences in catecholamine metabolism and responsiveness remain poorly understood.

• What accounts for the unusual LV contractile pattern seen with this syndrome? Proposed mechanisms include increased responsiveness of the apex to sympathetic stimulation,[24] and the development of apical subendocardial ischemia due to transient LV midcavity obstruction,[25] but a widely accepted explanation for the apical ballooning pattern remains elusive.

• Is the broken heart syndrome simply an exaggeration of the normal stress response, or do individuals with this condition have some pathologic defect, such as abnormal catecholamine production or metabolism, that renders them particularly susceptible to acute stress?

• What are the cellular and molecular mechanisms of stress-induced myocardial stunning?

The answers to these questions will undoubtedly be complex, but in time will provide tremendous insight into both the pathogenesis of broken heart syndrome and the intricacies of the heart-brain relationship.

REFERENCES

1. **Engel GL.** Sudden and rapid death during psychological stress. Folklore or folk wisdom? Ann Intern Med 1971; 74:771–782.
2. **Lecomte D, Fornes P, Nicolas G.** Stressful events as a trigger of sudden death: a study of 43 medico-legal autopsy cases. Forensic Sci Int 1996; 79:1–10.
3. **Leor J, Poole WK, Kloner RA.** Sudden cardiac death triggered by an earthquake. N Engl J Med 1996; 334:413–419.
4. **Meisel SR, Kutz I, Dayan KI, et al.** Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. Lancet 1991; 338:660–661.
5. **Tsuchihashi K, Ueshima K, Uchida T, et al.** Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. J Am Coll Cardiol 2001; 38:11–18.
6. **Wittstein IS, Thiemann DR, Lima JA, et al.** Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 2005; 352:539–548.
7. **Sharkey SW, Lesser JR, Zenovich AG, et al.** Acute and reversible

cardiomyopathy provoked by stress in women from the United States. Circulation 2005; 111:472–479.
8. **Cebelin MS, Hirsch CS.** Human stress cardiomyopathy. Myocardial lesions in victims of homicidal assaults without internal injuries. Hum Pathol 1980; 11:123–132.
9. **Pavin D, Le Breton H, Daubert C.** Human stress cardiomyopathy mimicking acute myocardial syndrome. Heart 1997; 78:509–511.
10. **Satah H, Tateishi H, Uchida T, et al.** Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, eds. Clinical Aspect of Myocardial Injury, From Ischemia to Heart Failure [in Japanese]. Tokyo, Japan: Kagakuhyouronsya Co; 1990: 56–64.
11. **Bybee KA, Prasad A, Barsness GW, et al.** Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. Am J Cardiol 2004; 94:343–346.
12. **Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Musha H, Sasaka K.** ^{123}I-MIBG myocardial scintigraphy in patients with "takotsubo" cardiomyopathy. J Nucl Med 2004; 45:1121–1127.
13. **Elian D, Osherov A, Matetzky S, et al.** Left ventricular apical ballooning: not an uncommon variant of acute myocardial infarction in women. Clin Cardiol 2006; 29:9–12.
14. **Park JH, Kang SJ, Song JK, et al.** Left ventricular apical ballooning due to severe physical stress in patients admitted to the medical ICU. Chest 2005; 128:296–302.
15. **Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E.** Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J 2006; 27:1523–1529.
16. **Inoue M, Shimizu M, Ino H, et al.** Differentiation between patients with takotsubo cardiomyopathy and those with anterior acute myocardial infarction. Circ J 2005; 69:89–94.
17. **Kume T, Akasaka T, Kawamoto T, et al.** Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. Circ J 2005; 69:934–939.
18. **Mann DL, Kent RL, Parsons B, Cooper G.** Adrenergic effects on the biology of the adult mammalian cardiocyte. Circulation 1992; 85:790–804.
19. **Wilkenfeld C, Cohen M, Lansman SL, et al.** Heart transplantation for end-stage cardiomyopathy caused by an occult pheochromocytoma. J Heart Lung Transplant 1992; 11:363–366.
20. **Neil-Dwyer G, Walter P, Cruickshank JM, Doshi B, O'Gorman P.** Effect of propranolol and phentolamine on myocardial necrosis after subarachnoid haemorrhage. Br Med J 1978; 2:990–992.
21. **Ueyama T.** Emotional stress-induced Tako-tsubo cardiomyopathy: animal model and molecular mechanism. Ann NY Acad Sci 2004; 1018:437–444.
22. **Hinojosa-Laborde C, Chapa I, Lange D, Haywood JR.** Gender differences in sympathetic nervous system regulation. Clin Exp Pharmacol Physiol 1999; 26:122–126.
23. **Sader MA, Celermajer DS.** Endothelial function, vascular reactivity and gender differences in the cardiovascular system. Cardiovasc Res 2002; 53:597–604.
24. **Mori H, Ishikawa S, Kojima S, et al.** Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. Cardiovasc Res 1993; 27:192–198.
25. **Merli E, Sutcliffe S, Gori M, Sutherland GG.** Tako-Tsubo cardiomyopathy: new insights into the possible underlying pathophysiology. Eur J Echocardiogr 2006; 7:53–61.
26. **Goldstein DS, Eisenhofer G, Kopin IJ.** Sources and significance of plasma levels of catechols and their metabolites in humans. J Pharmacol Exp Ther 2003; 305:800–811.

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