Stress-Induced Cardiomyopathy

Ricardo E. Ronderos, MD, PhD, Gustavo Avegliano, MD, and Gonzalo Dallasta, MD

Corresponding author
Ricardo E. Ronderos, MD, PhD
Instituto Cardiovascular de Buenos Aires; Instituto de Cardiologia La Plata; Universidad Nacional de La Plata Argentina; Calle 6 N 212, La Plata 1900, Argentina.
E-mail: trotare@hotmail.com

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Stress-induced cardiomyopathy is a relatively uncommon syndrome with difficult definition. Cases with transient and reversible left ventricular dysfunction, precipitated by emotional stress and without coronary artery disease, are called takotsubo syndrome, left ventricular apical ballooning, and broken heart syndrome. Many names used to refer to this syndrome are related to the shape of the left ventricle and/or the precipitating factors, but there is not yet a consensus about the proper name. Situations related to physical stress, such as intracranial bleeding, have similar patterns, including the absence of previous cardiac involvement. The increased blood levels of endogenous catecholamine, and increase of myocardial catecholamine in areas with high density of sympathetic innervations, seem to be the mechanisms for myocardial cell necrosis with eosinophilic transverse bands. The localized spasm of the epicardial coronaries, or diffuse microcirculatory dysfunction, is also one of the proposed mechanisms. There are still some areas of controversy that have no definite answer.

Introduction

Definition: the first problem

Stress cardiomyopathy is an uncommon syndrome in which controversial mechanisms are involved. Traditionally, stress cardiomyopathy refers to patients with left ventricular (LV) reversible wall motion abnormalities, without significant coronary artery lesions and/or coronary vasospasm. The prevalence according to this definition seems to be low [1••], and a few of this situation's names include takotsubo syndrome, inverted takotsubo, LV apical ballooning, and broken heart syndrome (Table 1) [1••,2–5].

The presence of cardiac disorders occurring during acute subarachnoid hemorrhage, and in other settings of physical stress such as major surgeries, has been previously described [6••,7].

In these patients without cardiac diseases, findings are similar to those described in cases precipitated by emotional stress. These noncardiac diseases, complicated at times by sudden and reversible LV failure, usually are not different from the classic LV apical ballooning or broken heart syndromes [4,5]. Looking in this direction, prevalence is actually higher (Table 1) [8].

But moreover, there are a lot of situations in cardiac patients with recognized coronary artery disease and/or other cardiomyopathies such as hypertrophic cardiomyopathy, in whom transient abnormal LV function is present with reversible behavior, that also resemble the findings of broken heart syndrome.

It is not easy to define *stress cardiomyopathy* without controversy, unless we take pure definitions as a starting point, going later to the possibility of appearance of this same syndrome in multiple clinical scenarios.

In 1980, Cebelin and Hirsch [9] reported a series of murder victims who had been emotionally and physically traumatized prior to death [10]. All of them showed extensive myocardial contraction band necrosis at autopsy [8]. These histological findings, related to high catecholamine levels, suggest the deleterious effects of catecholamine in the heart and introduced the concept of human stress cardiomyopathy.

During the 1990s, the Japanese literature described a series of unique patients with reversible LV dysfunction precipitated by acute emotional or physical stress. Satah et al. [11] were the first to describe this syndrome as takotsubo syndrome. The dysfunctional left ventricle takes a shape similar to a Japanese takotsubo, a vessel used to capture octopuses by Japanese fisherman (Fig. 1).

Starting in the 2000s, the Western literature received the first communications from Japan, explaining takotsubo syndrome as a LV apical ballooning involving transient apical wall motion abnormalities with normal coronary arteries, making the comprehension easier for Western physicians [12].

All these cases are related to localized dysfunction of LV motion at the apex, a situation that could be explained by acute spasm of the left anterior descending artery, despite that this mechanism was not able to be reproduced during coronary catheterization (Fig. 1).

In our experience, acute LV dysfunction, with reversible wall motion abnormalities, could be present without any

Table 1. Different names used in stress cardiomyopathy

Broken heart syndrome (any reversible LV wall motion abnormalities with LV dysfunction)
Takotsubo syndrome (apical and midventricular LV dysfunction)
Inverted takotsubo (isolated midventricular wall motion abnormalities)
Apical ballooning syndrome (same as takotsubo syndrome)
LV dysfunction associated with intracranial hemorrhage, head trauma, etc.

LV—left ventricular.

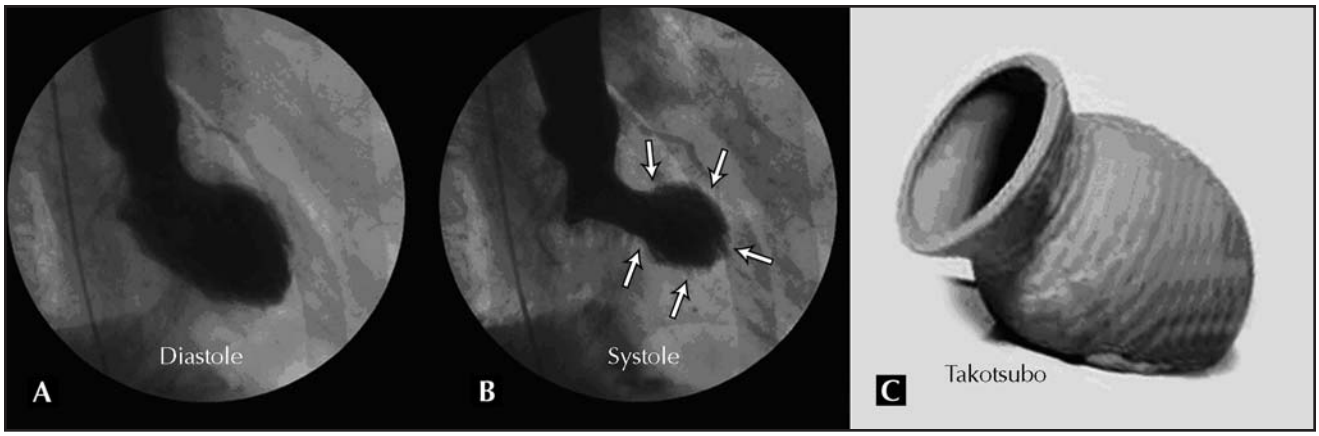


Figure 1. End-diastolic volume (**A**), end-systolic volume (**B**), and shape of the left ventricle in a takotsubo patient (**C**). Normal position of takotsubo in comparison with right anterior oblique position in left ventriculography. A *takotsubo* is a classic bowl used to capture octopuses in Japanese culture.

relation to a single coronary territory [13•]. This experience is not uncommon and was largely covered by other authors (Fig. 2 and Fig. 3) [3,14,15•]. Noninvasive cardiac imaging such as three-dimensional (3D) echocardiography and MRI helped to recognize and follow up these patients (Fig. 3 and Fig. 4). When middle and rarer basal wall motion reversible abnormalities are present, mechanisms such as coronary spasm cannot easily be explained.

Before discussing the pathophysiologic process and clinical, biochemical, and imaging findings, we should agree on the definition of *stress-induced cardiomyopathy*, including all those syndromes with transient and reversible LV dysfunction with wall motion abnormalities, without previous cardiac or coronary disease, involving or not involving a single coronary territory, and precipitated by emotional or physical stress (Table 2). Later in the discussion, we can include the role of catecholamine infusion for diagnostic or therapeutic procedures [16••,17].

Predisposition and precipitating factors

The role of emotional factors (eg, death of a loved one, criminal situations, accidents and other tragedies, and fear and panic situations) is well-described. Physical stresses, such as torture, pain, acute neurologic syndromes, main surgical procedures, and head or other major trauma, are also precipitating factors [4,9,10,18–20].

Other situations causing high levels of catecholamines, such as endogenous production in pheochromocytoma, have also been reported. The use of exogenous infusion of catecholamines as therapy (septic shock, cardiogenic shock) or for diagnostic purposes (dobutamine stress echocardiography) was also proposed as a precipitating mechanism (Table 2) [16••,17,21,22].

Prevalence and demographics

Different presentations of stress cardiomyopathy have different triggering factors. In cases induced by emotional stress, women are much more affected than men, reaching 80% to 88% in different registers [1••,23••]. The Japanese literature indicates that the syndrome occurs more frequently in postmenopausal women [8,11,12]. Prevalence of these syndromes is only 1.5% to 2.2% of patients admitted to emergency rooms with the diagnosis of acute coronary syndromes [1••,24,25].

On the other hand, in intensive care units and among patients with intracranial bleeding, mostly secondary to subarachnoid hemorrhage, prevalence has reached 28% to 30%, without previous cardiac involvement [1••,6••].

Although the syndrome was not shown to be age related, most series showed a median age of 60 years. In our experience and in the European population, this age is prevalent, but it is not rare for younger women to be affected (Fig. 2 and Fig. 3) [23••]. Emotional stress–mediated cardiomyopathy clearly seems to occur more frequently in women.

Clinical, Electrocardiography, and Biochemical Findings

Clinical presentation includes a wide menu of symptoms. Chest pain with or without hypotension, shortness

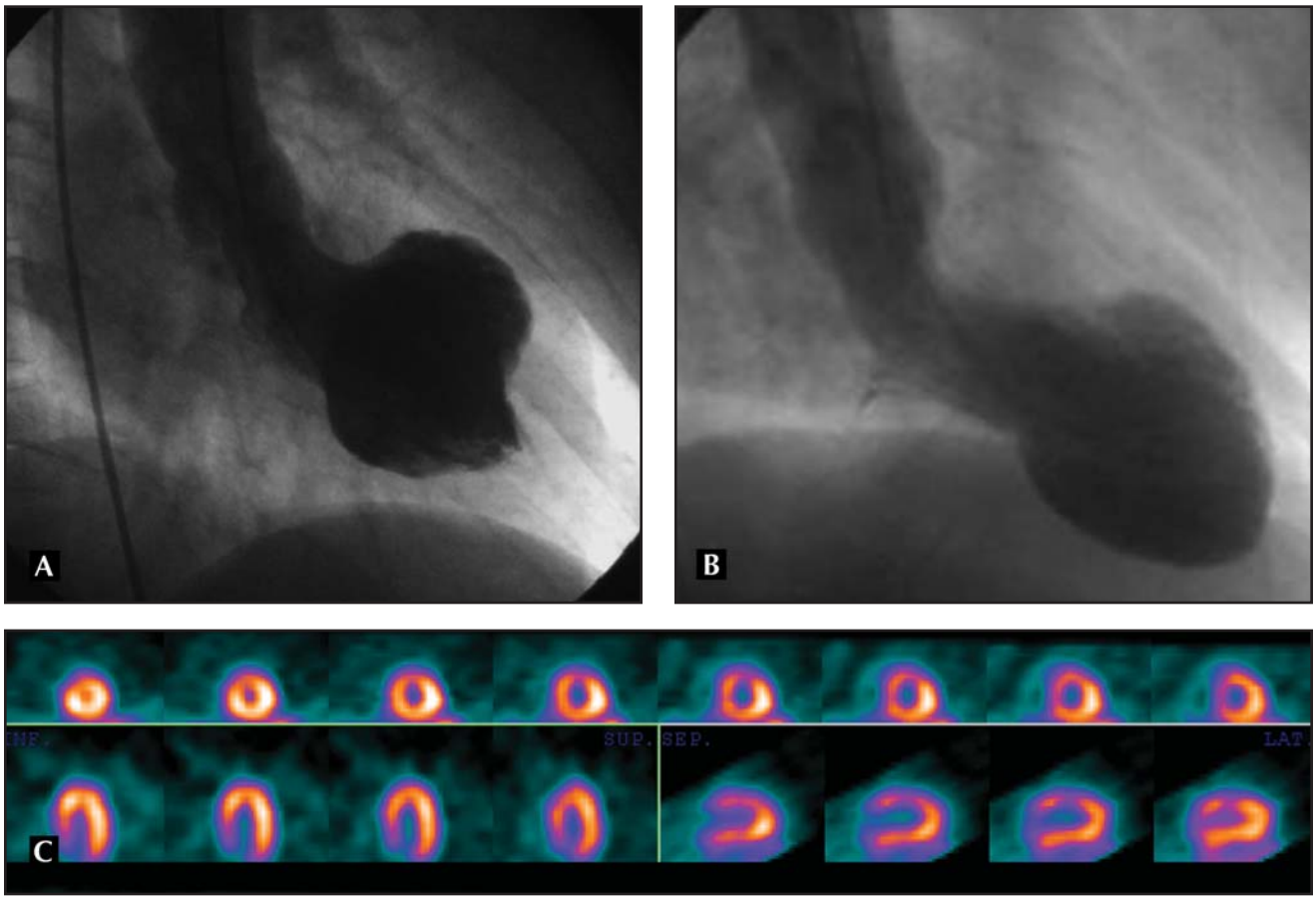


Figure 2. A, A 31-year-old woman with chest pain at admission. **B**, A 45-year-old woman with chest pain at admission. Both patients in *Panels A* and *B* experienced major emotional stress. Note the different pattern of left ventricular (LV) wall motion abnormalities in these end-systolic LV ventriculographies. **C**, Rest sestamibi single photon emission CT from the second case, showing normal perfusion 24 hours after admission.

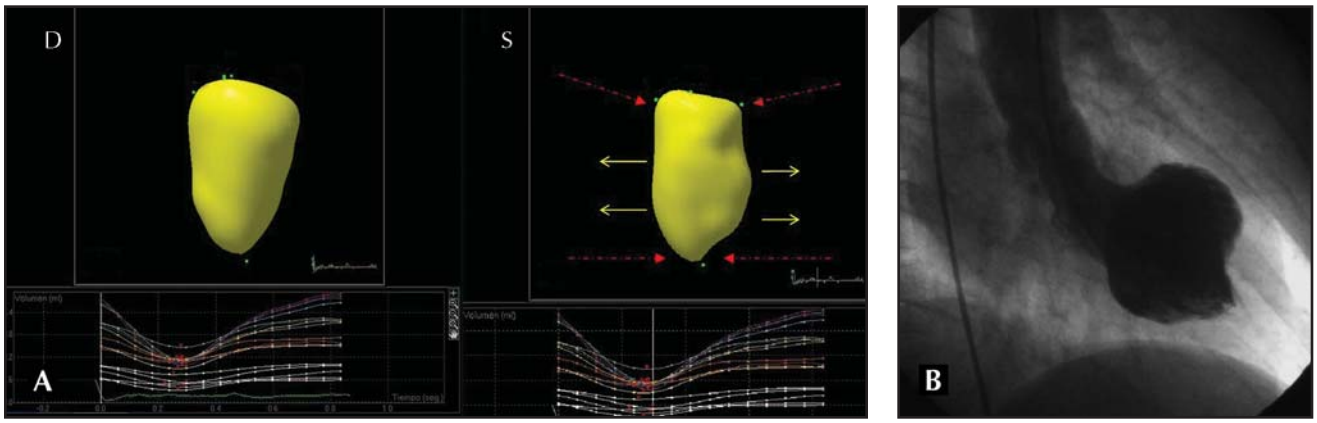


Figure 3. A, Three-dimensional echocardiography, showing left ventricular cavity at end-diastole (*D*), and end-systole (*S*). *Yellow arrows* show noncontracting middle segments, and *red arrows* show normal contracting apical and basal segments. **B**, Right anterior oblique ventriculography at end-systole. Note the normal contraction of apex and basal left ventricle.

of breath, acute pulmonary edema, and/or cardiogenic shock are some of the reported clinical presentations [1••,4,23••,24–26].

Electrocardiography changes are reported since massive ST elevation in precordial leads, until mild nonspecific ST and T-wave changes, these last options seem to be more representative of acute stress cardiomyopathy (Fig. 4) [25–27,28•].

After 24 to 48 hours, electrocardiography mainly shows deep T-wave inversion, specifically in precordial leads without new Q waves, and frequently QT interval prolongation [1••,27]. QT interval usually improves quite quickly, but T-wave inversion can remain for days or even weeks [1••,4,27,28•].

Biological markers of myocardial damage such as creatinine phosphokinase and troponin I or T are usually high,

Table 2. Precipitants of stress cardiomyopathy

Acute emotional stress
Acute physical stress
Intracranial bleeding
Head trauma
Ischemic stroke
Acute medical illness, including sepsis
Surgical procedures
Overproduction of endogenous catecholamines (pheochromocytoma)
Administration of exogenous catecholaminergic agents
Inhaled β-agonists
Cocaine
Amphetamines
Diagnostic (dobutamine stress echocardiography)
Therapeutic epinephrine (eg, cardiogenic shock)

but lower than in patients with acute myocardial infarction and equivalent extension. In some series, troponin I reached 0.18 ng/mL (normal 0.06 ng/mL) [1••,5,29].

Wall Motion Abnormalities: Role of Imaging

The most salient feature of this syndrome is the unusual LV contractile pattern noted at the time of admission. Echocardiography plays a major role in achieving this diagnosis. Both two-dimensional and 3D imaging allow the recognition of the contractile pattern, mainly when the apex is involved. When medial segments are involved, 3D imaging appears particularly useful for achieving the diagnosis (Fig. 3 and Fig. 4).

Myocardial contrast echocardiography seems to be a useful tool to clarify the mechanisms involved in the myocardial injury. The few data currently available, both in humans and in dog models, failed to demonstrate abnormalities in the microcirculation [30].

With the use of radioisotopes such as ^{201}Tl or ^{123}I-BMIPP, more abnormalities in myocardial fatty acid metabolism than in myocardial perfusion have been described [4,31], despite some studies suggesting abnormal perfusion and glucose metabolism using positron emission tomography ^{13}N ammonia and fluorodeoxyglucose (Fig. 2) [31,32,33•].

MRI shows the absence of myocardial infarction when imaging in late enhancement mode with gadolinium [34]. Nevertheless, in our experience, MRI performed during the acute phase of this syndrome shows a mild late myocardial enhancement with gadolinium, which completely disappears after 3 months. These findings suggest the presence of transient interstitial edema over-imposed to the area of transient wall motion abnormality. Similar to other studies, we have seen the absence of permanent late enhancement (Fig. 4 and Fig. 5) [35,36••,37].

Of all the clinical imaging tools, echocardiography seems to be the most useful, depicting serially the distribution and evolution of the wall motion abnormalities.

Coronary Angiography

In a clinical presentation of acute coronary syndrome, with high troponin levels and acute echocardiography changes, the use of coronary angiography is recommended. The absence of significant epicardial coronary lesions is the common finding; these findings have been confirmed by the absence of coronary artery disease when imaging the coronary arteries with high-resolution intravascular ultrasound (Fig. 6) [1••,4,23••,37].

Some publications have shown mild or rarely significant coronary obstruction [4]. The issue is how to interpret the presence and role of these coronary findings, in the context of this clinical scenario of acute wall motion abnormalities present without a clear coronary territory distribution.

LV Recovery, Clinical Follow-up, and Prognosis

The hallmark of this syndrome is the achievement of complete recovery of LV function. This recovery process can be very short (2 or 3 days; Fig. 3) or can take longer, which occurs particularly in anterior wall motion abnormalities. The absence of full recovery after 4 to 6 weeks should indicate reconsideration of this diagnosis [1••,2,4,5,11,12,23••].

Irrespective of the fact that most published data suggest full recovery of LV function, in our experience some small areas of mild abnormal wall motion persist, particularly in the anterior wall of patients with hypertrophic cardiomyopathy (Unpublished data).

The recurrence rate is quite low (not higher than 3.5%, with a range of 2%–10%) [23••]. Mortality varies in patients with emotional stress when compared with patients in whom the event was precipitated by physical stress. In the first group, the mortality rate does not exceed 1.1%, whereas in groups with other physical stresses such as intracranial bleeding, in whom LV abnormalities usually disappear, the mortality rate is higher but frequently not secondary to cardiac events [1••,4].

Pathophysiology

Inflammation, catecholamines, and parasympathetic activity: brain–heart connection

Myocardial necrosis with transverse contraction bands is always present along the involved and damaged myocardium [9,10]. Contraction band necrosis is characterized by hyper-contracted sarcomeres, dense eosinophilic transverse bands, and an interstitial mononuclear inflammatory infiltrate [6••,38,39].

These inflammatory changes are mediated by calcium overload due to different mechanisms, but are frequently

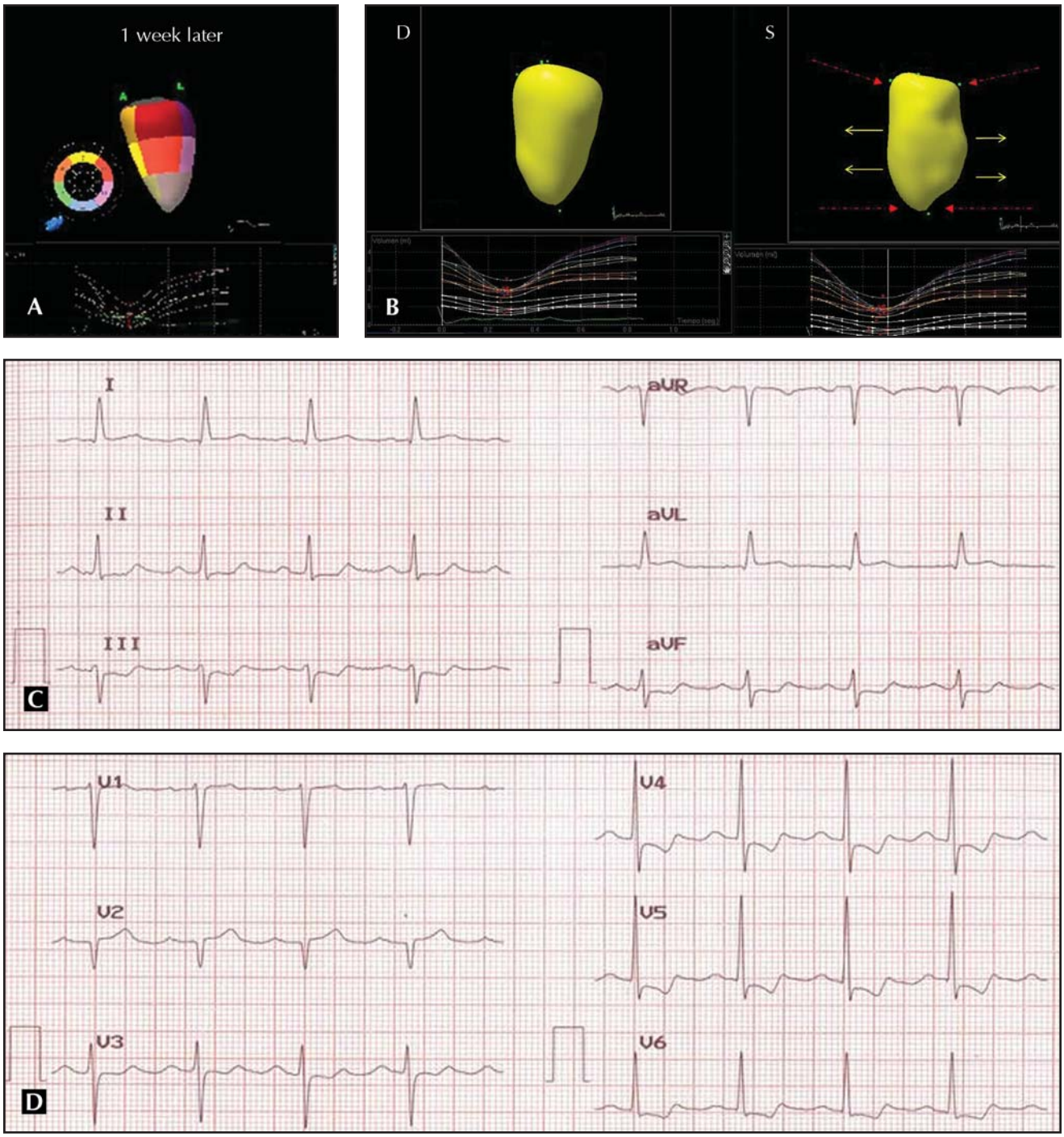
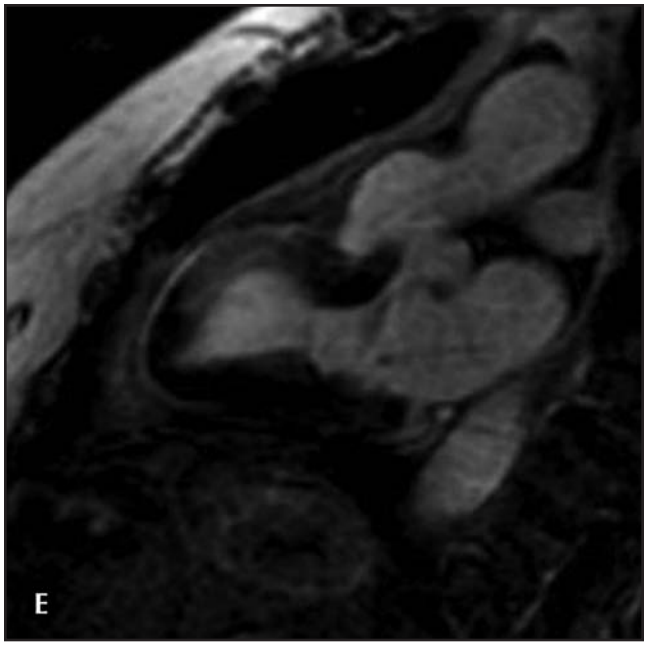


Figure 4. A, Three-dimensional echocardiography shows end-systolic shape of left ventricle 1 week after admission. **B**, End-diastolic frame (*D*), and end-systolic frame (*S*) at admission. **C** and **D**, Echocardiogram in this 32-year-old woman with chest pain after the death of a loved one. **E**, MRI 24 hours after admission; note the mild gadolinium late enhancement and abnormal shape secondary to middle segment impairment. **F**, MRI 30 days later. There is no gadolinium late enhancement, and left ventricular shape is normal at end-systole.

described in high-circulatory catecholamine states as pheochromocytoma and subarachnoid hemorrhage. This damage could be secondary to catecholamine-mediated myocyte viability, through cyclic adenosine monophosphate calcium overload [1••,4,6••,22,30].

This problem has been seen in repeated ischemic injuries followed with reperfusion, as well as in catecholamine excess. Experiments with high doses of catecholamine infusion in rats reproduced the eosinophilic infiltration and the necrosis, with transverse contraction bands in myocytes [40].

Inflammation is strongly related to brain connections. Sympathetic and parasympathetic activities are regulated by the brain at the hypothalamus. Cholinergic anti-inflammatory reflexes are combined with a systemic anti-inflammatory reflex. Although increased



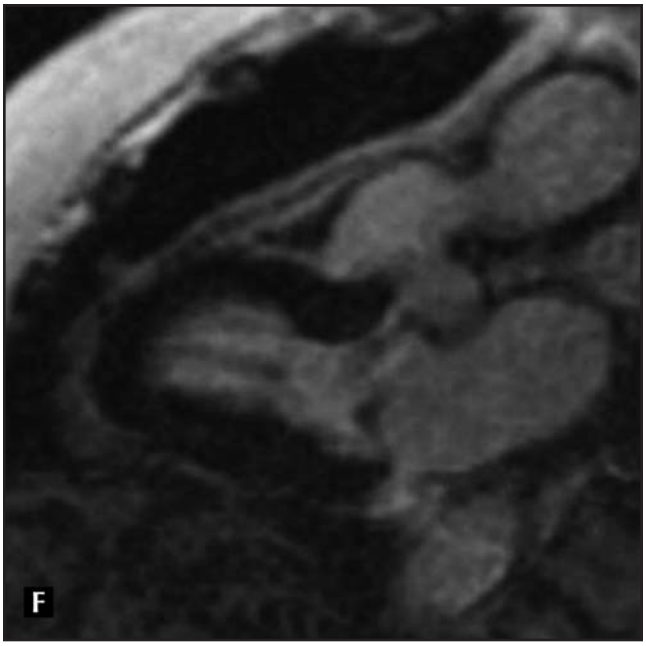


Figure 4. Continued.

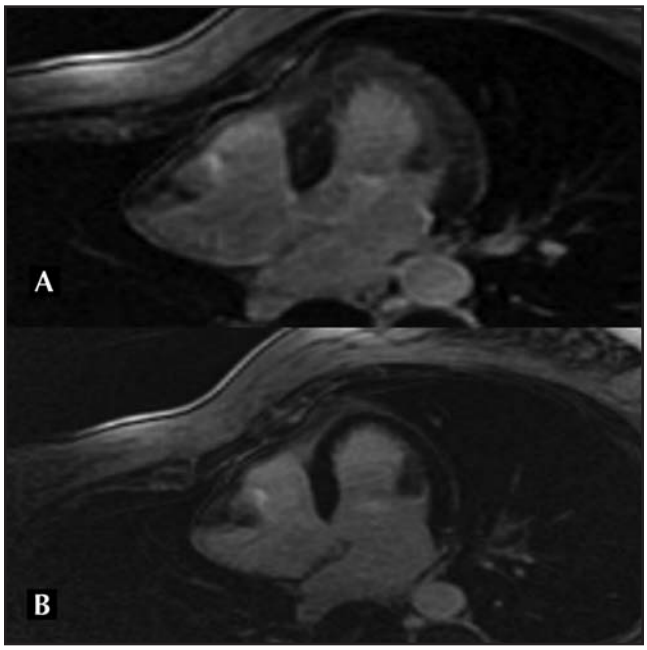


Figure 5. A, MRI showing mild gadolinium late enhancement in the area of acute wall motion abnormality in takotsubo-like syndrome 24 hours after admission. **B**, Same patient 30 days later without any gadolinium late enhancement.

sympathetic activity drives many events in coronary artery disease and heart failure, and β-adrenergic blockade is associated with improved outcomes, the presence of diminished parasympathetic tone also is related to adverse outcomes in cardiovascular disease, suggesting the key role of the autonomic system in maintenance of cardiac homeostasis [41••,42••].

Although an increase in sympathetic activity could result in an increase in cardiac risk, the mechanisms of parasympathetic protection through inflammatory inhibition are not clear.

The vagus nerve innervates the cardiovascular system, as well as other visceral organs such as the liver, spleen, and gut. Several experiments in animal models have described the role of the vagus nerve in modulating anti-inflammatory response [42••]. Moreover, several studies have shown an inverse relationship between parasympathetic tone and vascular mortality [42••].

In humans, abnormal heart rate variability, a measure of parasympathetic activity, has been shown to be associated with elevated levels of cytokines such as interleukin-6 and C-reactive protein (CRP) [42••]. CRP levels are strongly and inversely related to abnormal heart rate variability in patients with unstable angina [43].

The systemic anti-inflammatory reflex is slow and diffuse, whereas the cholinergic anti-inflammatory reflex is quick, precise, and integrated, typically releasing inflammatory cytokines at the site of inflammation [42••].

If parasympathetic tone is important, sympathetic connections are more evident in the production of cardiac effects and cardiac damage. After the work of Pavlov and Selye, it is recognized that electrolyte-steroid cardiopathy with necrosis cannot be avoided by adrenalectomy, suggesting that the process is not mediated by circulating catecholamines but through direct neural connection to the heart rather than by a humoral, bloodborne route [44].

Nevertheless, there is evidence of high levels of circulating catecholamine in patients with stress cardiomyopathy. Wittstein et al. [5] showed that high levels of dihydroxyphenylalanine, dihydroxyphenylglycol, and dihydroxyphenylacetic acid among 95 patients with stress cardiomyopathy were approximately two times the values of patients with acute myocardial infarction and two or three times higher than in

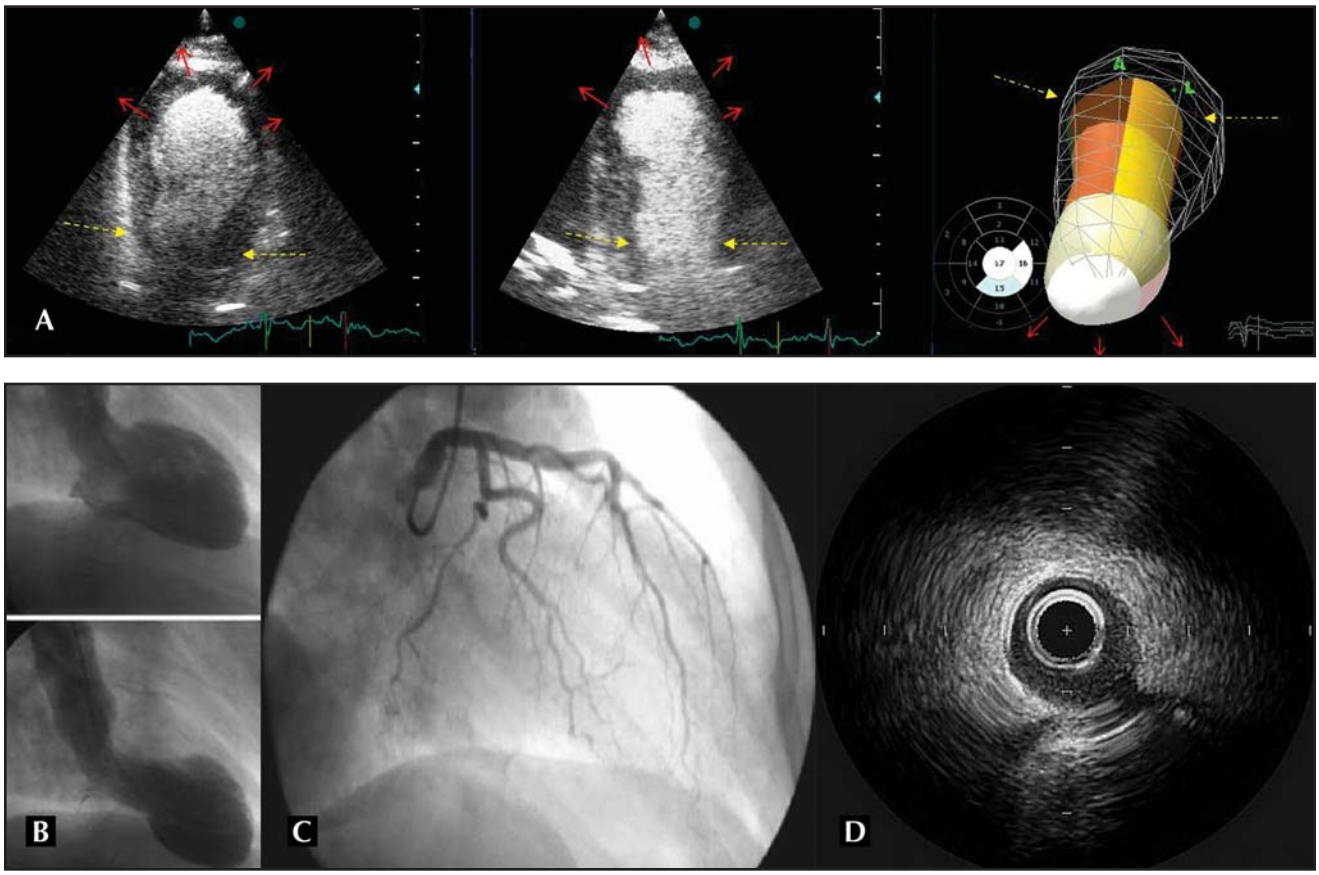


Figure 6. A, End-systolic frames of three-dimensional echocardiography and myocardial contrast echocardiography, showing apical ballooning and mild abnormal perfusion at the apex. *Red arrows* point out areas of abnormal wall motion. **B**, Angiography with left ventricular ventriculography showing apical ballooning. **C**, Normal left anterior descending artery (LAD) in the same patient at admission. **D**, Normal intravascular ultrasound from the proximal LAD.

normal subjects, consistent with the presence of enhanced catecholamine synthesis, neuronal reuptake, and neuronal metabolism, respectively. Plasma levels of metanephrine and normetanephrine, which are extraneuronal catecholamine metabolites, were also proportionally increased among patients with stress cardiomyopathy. Plasma levels of neuropeptide Y, which is stored with catecholamines in postganglionic sympathetic nerves and adrenal chromaffin cells and released during stress, are markedly higher in patients with stress cardiomyopathy, as are plasma levels of brain natriuretic peptide and serotonin [5].

Between the seventh and ninth days, all catecholamines and metabolites are half of the peak values but remain higher in comparison with patients with acute myocardial infarction Killip and Kimball class III. In contrast, brain natriuretic peptide decreases rapidly in patients with stress cardiomyopathy, correlating with the improvement in LV systolic function, whereas it does not in patients with acute myocardial infarction with similar LV dysfunction [5].

The presence of increased catecholamine levels and their metabolites, associated with the presence of unclearly defined changes in parasympathetic anti-inflammatory reflexes and activity, may help to explain the electrocardiography serial changes; alterations in electrocardiography are the best window to see autonomic nervous system changes [5].

Moreover, there is evidence pointing out the relationship between high levels of catecholamine and the presence of eosinophilic infiltration in the myocytes, both induced by cellular calcium overload, as one of the mechanisms for transverse contraction bands in the affected myocardium (Fig. 7) [40].

This pathophysiologic mechanism may explain the abnormal distribution of myocardial damage in the left ventricle, without a direct correlation to the perfusion territories of the coronary arteries.

Also, the frequent involvement of the apical and/or middle wall segments, instead of the basal segments, could be correlated with the particular distribution of innervations of the entire heart [5,45,46].

Keeping in mind the role of catecholamine and the different ways to induce the reversible myocardial damage called stress cardiomyopathy, it is mandatory to describe the use of catecholamine both for diagnostic and therapeutic purposes (Fig. 8).

There are some publications describing the presence of syndromes similar to stress cardiomyopathy during dobutamine stress echocardiography. Silberbauer et al. [47] described a 75-year-old woman with higher levels of anxiety having a classic takotsubo-like apical ballooning during regular dobutamine–atropine

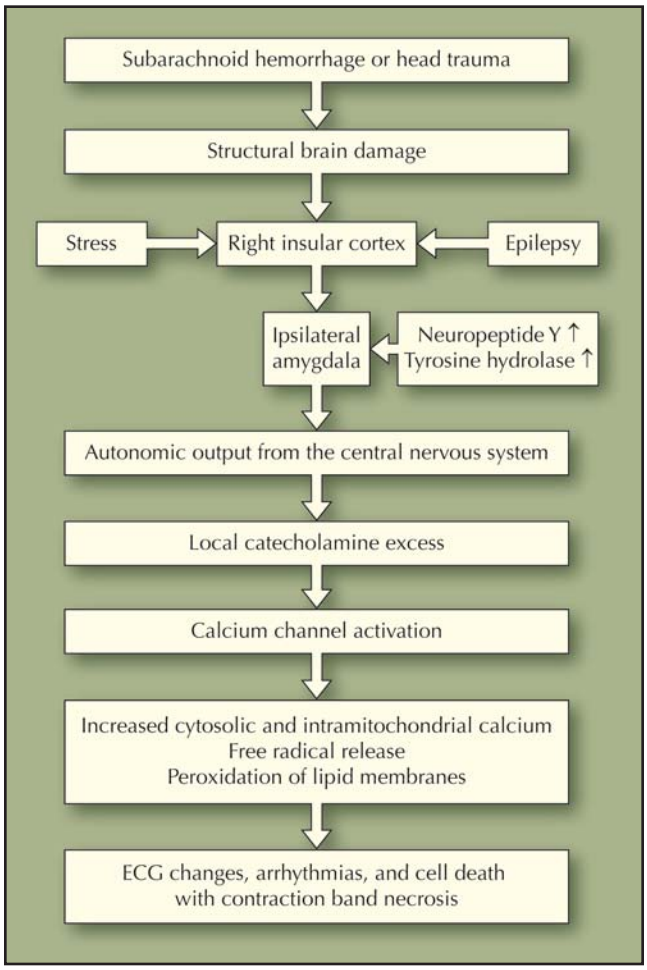


Figure 7. Algorithm with the probable mechanism of catecholamine release and the effects on myocardium myocytes. ECG—echocardiography. (*Adapted from* Bybee and Prasad [49].)

stress echocardiography. In this case, apical ballooning was reversible, and troponin I and echocardiography changes were present associated with classic chest pain in a patient with normal coronaries, without the demonstration of coronary spasm [47].

Abraham et al. [16••] studied three patients with dobutamine infusion in which apical, medial, or basal ballooning was present, always at peak-dose dobutamine (30–40 μg/kg/min) with all clinical echocardiogram and biochemical characteristics of stress cardiomyopathy.

This group also studied six patients without previous cardiac disease, in whom epinephrine was used in high doses during plastic surgery or treatment for complications of suicide attempt or vasovagal syndrome, which had the findings of a characteristic stress cardiomyopathy [16••].

Coronary spasm, microcirculatory spasm, and disregulation

Are all of these catecholamine-related effects the cause of spasm in epicardial coronary vessels? Is there any evidence that this mechanism explains the reversible myocardial stunning characteristic of stress cardiomyopathy? There is not. Most publications discuss the lack of evidence for spontaneous or induced coronary vasospasm, and microvascular spasm.

How to relate this syndrome to the previous knowledge of Prinzmetal angina, or induced epicardial coronary spasm present in mild atherosclerotic patients, is difficult.

Presently, there is no evidence of localized epicardial vessel spasm or evidence of microcirculation dysregulation as the main mechanism for stress cardiomyopathy. In the few cases with abnormal thallium 201 uptake or decrease in 18 fluorodeoxyglucose uptake and abnormal ^{13}N ammonia coronary flow measurements, these changes could be the consequence instead of the cause of myocardial damage or stunning [32,33•].

The lack in demonstration of abnormal perfusion by myocardial contrast echocardiography is also a main reason to reject this mechanism as a cause of myocardial stress damage.

Treatment and Management

The treatment of stress cardiomyopathy involves primary supportive care. For hemodynamically stable patients, diuretics are used for congestion, and angiotensin-converting enzyme (ACE) inhibitors and β-blockers are frequently used during the period of LV recovery. The question is how long to maintain these drugs after recovery. Despite the lack of evidence, our experience suggests discontinuation of medications as soon as LV function is recovered.

There are no data supporting the use of β-blockers or ACE inhibitors to prevent new syndromes and/or improve survival. For hemodynamically unstable patients, inotropic support and vasodilators are commonly used. In our opinion, the role of catecholamine in the physiology of this process makes these drugs relatively contraindicated. Balloon counter pulsation and vasodilators seem to be a better choice, despite that there are no valid data to support this evidence [4]. Moreover, some data suggest the inappropriate effect of inotropics in apical ballooning, creating a medium ventricle gradient and obstruction that could impair LV function [48]. Whichever hemodynamic support is chosen, it should be maintained for a short period due to the fast recovery of LV stunned myocardium.

Conclusions

Stress cardiomyopathy is a syndrome with a wide spectrum of clinical presentations, with different names. Currently there is not enough evidence to explain the pathophysiologic mechanisms of this disease, as well as the role of sympathetic activity; cardiac innervations and catecholamine seem to be well defined.

Based on these issues, it should be pointed out that all clinical presentations secondary to precipitating factors such as emotional or physical stress, in the absence of coronary artery disease, should be aggregated as a common syndrome, and all the proposed names should be considered as *stress-induced cardiomyopathy*. The absence

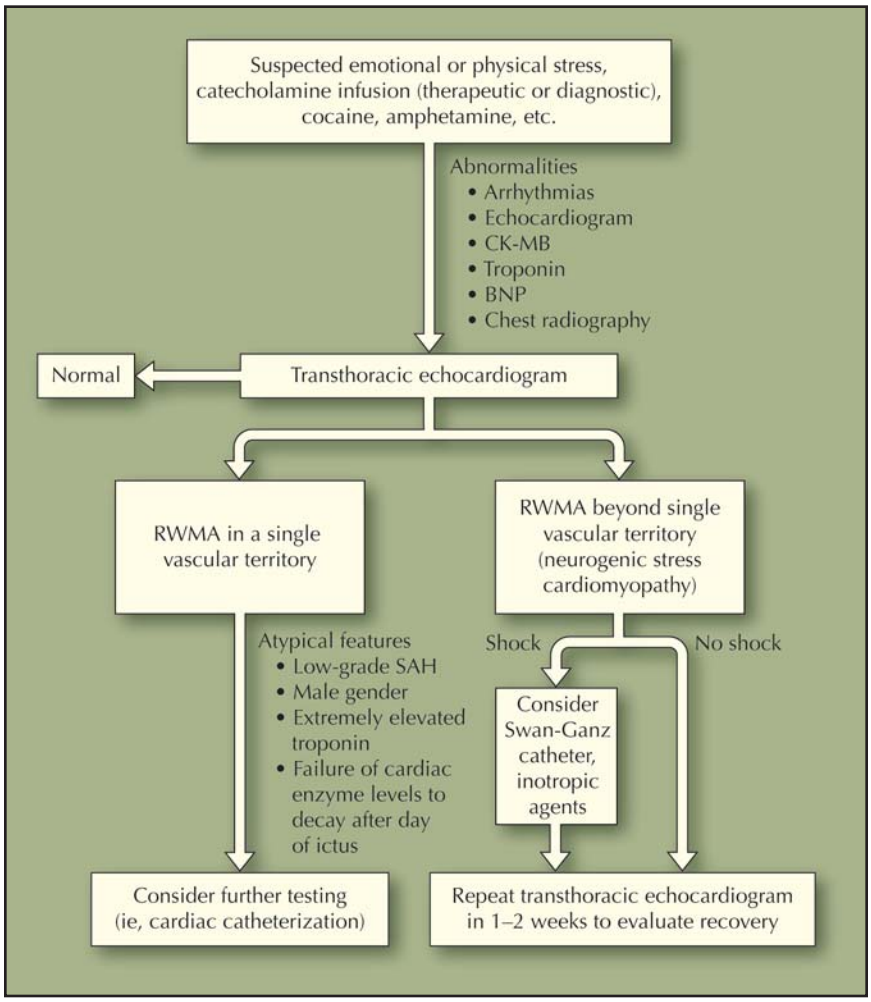


Figure 8. Algorithm with the proposed diagnostic and therapeutic approach in acute coronary syndromes with suspicion of stress-induced cardiomyopathy. BNP—brain natriuretic peptide; CK-MB—creatine kinase MB; RWMA—regional wall motion abnormality; SAH—subarachnoid hemorrhage. (*Adapted from* Lee et al. [6••].)

of coronary artery disease is a clue for the diagnosis, and portrays good prognosis and the expectance of full LV dysfunction recovery.

However, we should search for more evidence to include patients with previous cardiac involvement in this same syndrome, because this better understanding of the role of catecholamine will certainly improve the treatment and outcome of patients with stress-related complications.

There is a lot of evidence regarding the deleterious effect of catecholamine in the natural history of heart failure and the large impact of β-blockade in the mortality of these patients. Why not include the sudden effects of sympathetic activity and/or high levels of endogenous or exogenous catecholamine in chronic cardiac patients producing additional cardiac damage such as stress cardiomyopathy, despite the presence of previous coronary or other cardiac disease?

Stress cardiomyopathy recognition implies better understanding and management of classic syndromes, and additional knowledge to treat emotional or physical stress as a complication of chronic cardiac diseases.

As expressed above, the presence of these complex autonomic nervous system mechanisms in patients with previous coronary and/or cardiac involvement, and the effects of emotional or physical stress, are fairly difficult to understand. In the scope of evidence-based medicine, forming hypotheses reflecting new understanding of old mechanisms could be a difficult path to travel.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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