Concise Definitive Review

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Stress-Induced Cardiomyopathy

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Objectives: Reversible stress-induced cardiac dysfunction is frequently seen as a complication of a multitude of acute stress states, in particular neurologic injuries. This dysfunction may be difficult to distinguish between that caused by myocardial ischemia and may impact both the treatment strategies and prognosis of the underlying condition. Critical care practitioners should have an understanding of the epidemiology, pathophysiology, clinical characteristics, precipitating conditions, differential diagnosis, and proposed treatments for stress-induced cardiomyopathy.

Data Sources: MEDLINE database search conducted from inception to August 2014, including the search terms "tako-tsubo," "stress-induced cardiomyopathy," "neurogenic cardiomyopathy," "neurogenic stress cardiomyopathy," and "transient left ventricular apical ballooning syndrome". In addition, references from pertinent articles were used for a secondary search.

Study Selection and Data Extraction: After review of peer-reviewed original scientific articles, guidelines, and reviews resulting from the literature search described above, we made final selections for included references and data based on relevance and author consensus.

Data Synthesis: Stress-induced cardiomyopathy occurs most commonly in postmenopausal women. It can be precipitated by emotional stress, neurologic injury, and numerous other stress states. Patients may present with symptoms indistinguishable from acute coronary syndrome or with electrocardiogram changes and wall motion abnormalities on echocardiogram following neurologic injury. Nearly all patients will have an elevated cardiac troponin. The underlying etiology is likely related to release of catecholamines, both locally in the myocardium and in the circulation. Differential diagnosis includes myocardial infarction, myocarditis, neurogenic pulmonary edema, and nonischemic cardiomyopathy. Although the natural course of stress-induced cardiomyopathy is resolution, treatment strategies include sympathetic blockade and supportive care.

Conclusions: Stress-induced cardiomyopathy may mimic myocardial infarction and is an important condition to recognize in patients with underlying stress states, particularly neurologic injuries. (*Crit Care Med* 2015; 43:686–693)

Key Words: catecholamines; heart failure; neurogenic stress cardiomyopathy; stress-induced cardiomyopathy; tako-tsubo cardiomyopathy; transient left ventricular apical ballooning syndrome

Cardiac dysfunction is often seen following neurologic injuries, in particular subarachnoid hemorrhage (SAH) and traumatic brain injury (TBI), and is associated with increased mortality and poor outcome (1–3). Transient electrocardiogram (ECG) changes, in particular ST elevations and T wave inversions, in patients with intracerebral hemorrhages (ICH) without subsequent evidence of myocardial ischemia on autopsy have been well described (4–6). Often, these ECG changes are accompanied by left ventricular (LV) dysfunction (7). In many patients, this cardiomyopathy is also reversible, further suggesting that the cardiac changes seen in neurologic injury are not mediated by ischemia (8). This phenomenon is not unique to patients with SAH; a similar condition has been well described in patients without coronary artery disease who are exposed to significant emotional stress, and other cases have been described in instances of elevated catecholamine release (9) as well as in various acute medical conditions. This syndrome has gone by many names in the literature, including "broken heart syndrome" (10), tako-tsubo cardiomyopathy (11), transient LV apical ballooning syndrome (12), neurogenic stunned myocardium, and neurogenic stress cardiomyopathy (13). Each of these syndromes shares a common pathophysiology and clinical findings, which we will refer to collectively in this review as stress-induced cardiomyopathy. Here, we will review the history, epidemiology, pathophysiology, clinical characteristics, precipitating conditions, differential diagnosis, and proposed management of stress-induced cardiomyopathy. Throughout, we highlight the distinctive elements that help to differentiate this self-resolving cardiomyopathy from other conditions, most specifically ischemia-induced disorders.

HISTORY

Tako-tsubo cardiomyopathy, or apical ballooning syndrome, was initially described in the Japanese population in the early

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Figure 1. Japanese tako-tsubo pot. Photograph by Sarah H. Lee.

1990s, as a transient cardiomyopathy frequently following stressful events, with the absence of coronary artery disease (12, 14). The name "tako-tsubo" is derived from the term for the Japanese octopus catcher pot, which resembles the appearance of the left ventricle during systole on echocardiogram (15) (**Fig. 1**). The syndrome typically results in dysfunction of the LV apex although variations on this pattern have also been described (12, 16). Ako et al (17) were among the first to note similarities in the pattern of LV dysfunction in patients with neurologic conditions such as brain death and SAH with those patients diagnosed with tako-tsubo cardiomyopathy. In both traditional tako-tsubo cardiomyopathy without neurologic injury and in patients with LV dysfunction following neurologic injury, the syndrome is nearly always reversible, and coronary angiography is normal. Earlier definitions of tako-tsubo cardiomyopathy excluded patients with conditions such as head trauma, intracranial hemorrhage, and pheochromocytoma (12). Since 2003, many authors have suggested that tako-tsubo cardiomyopathy and the neurogenic stress cardiomyopathy seen in SAH and brain death are the same disease, with the shared mechanism of excessive catecholamine release (7, 9). We maintain that these entities are likely the same disease: stress-induced cardiomyopathy.

EPIDEMIOLOGY

The epidemiology of stress-induced cardiomyopathy in the absence of neurologic injury is well described. The majority of patients (80–90%) are women, predominantly postmenopausal women (11, 12). Many cases (14–70%) are preceded by a stressor, either emotional or physical. Although the majority of patients without neurologic injury present with chest pain or dyspnea, cardiogenic shock and ventricular fibrillation at presentation have been described in less than 5% of patients (11). The frequency of patients presenting with acute coronary syndrome who are found to have stress-induced cardiomyopathy is 1–2% (16), although the condition may be higher among postmenopausal women presenting with acute coronary syndrome (18).

Stress-induced cardiomyopathy is relatively common in patients with severe neurologic injury. ECG abnormalities occur in 25–75% of patients with SAH (6, 13), in particular prolongation of the corrected QT (QTc), T-wave inversions, and ST segment changes. LV dysfunction occurs in 10–20% of patients with SAH (3, 19). Known risk factors for the development of stress-induced cardiomyopathy include female gender, poor-grade SAH, elevated troponin levels, and prior stimulant drug use (7, 19, 20).

PATHOPHYSIOLOGY

The presumed etiology of stress-induced cardiomyopathy is excessive sympathetic stimulation of the myocardium, likely mediated by the brain. Even in patients without neurologic injury who present with stress-induced cardiomyopathy, there is evidence of abnormal cerebral blood flow to the hippocampus, brain stem, and basal ganglia, suggesting activation of these areas as part of the cascade of events that begins the catecholamine release (21). In the acute phase of SAH, there are profound increases in catecholamines both in the plasma and the cerebrospinal fluid (22), which have been associated with the subsequent development of cardiac dysfunction in several studies (23, 24). Some contradictory studies have found no association between the levels of circulating catecholamines and myocardial dysfunction (19, 20). However, in addition to excessive circulating catecholamines, substantial local release of norepinephrine occurs from myocardial nerve endings following neurologic injury (25). Further supporting an adrenergic mechanism, iatrogenic catecholamine excess alone can induce transient LV dysfunction without evidence of ischemic heart disease (10). Sympathectomy, but not adrenalectomy, prevents cardiac dysfunction in animal studies of SAH, further supporting the role of local catecholamines in the pathogenesis of this disease (26). Aside from SAH, reversible LV dysfunction has been described in other situations where catecholamines are clearly elevated, such as in the setting of a pheochromocytoma (27). Catecholamines may lead to cardiac dysfunction via microvascular dysfunction or direct toxicity. Although several investigators have demonstrated normal perfusion in neurogenic stress cardiomyopathy (28, 29), other reports suggest decreased perfusion (30, 31) as well as impaired glucose uptake (16), suggesting impaired microvascular blood flow. Cardiac metabolism may be altered in the absence of abnormal perfusion as well (32). Finally, the coronary microvasculature may demonstrate impaired reactivity, leading to microvascular dysfunction (33). Direct catecholamine toxicity to cardiac myocytes is an alternative mechanism for cardiac dysfunction.

Structural cardiac changes have been described in patients with significant neurologic injury as well as in other states of excessive catecholamine release, including pheochromocytoma and tetanus (27, 28, 34, 35). These changes are consistently described as focal myocytolysis or myofibrillary degeneration, also termed "contraction band necrosis." The pathologic studies consistently report a lack of findings suggestive of infarction, such as coagulative necrosis or the presence of neutrophils

(36), and similar pathological results have been described in animals following administration of catecholamines (34). The direct damage to myocytes by catecholamines may be mediated by cyclic adenosine monophosphate–driven calcium overload (1, 35, 37). The preferential distribution of adrenergic receptors in the apex of the heart may explain the fact that apical dysfunction of the left ventricle is the predominant pattern in stress-induced cardiomyopathy although other patterns may be seen as well (9, 38). Patients with polymorphisms resulting in greater catecholamine sensitivity are also at an increased risk for developing cardiac abnormalities following neurologic injury (39). There may also be a selection bias in the noted variations between neurologicly mediated stress-induced cardiomyopathy and traditionally described tako-tsubo cardiomyopathy without neurologic injury, as apical ballooning is more often associated with ST elevations on ECG; these patients may be more likely to undergo diagnostic testing including cardiac catheterization and echocardiogram (9).

Hormones may play a role in the pathogenesis of stress-induced cardiomyopathy. Estrogen may attenuate the cardiac response to catecholamines, offering an explanation for the higher frequency of stress-induced cardiomyopathy in postmenopausal women (40). In addition, stress-induced cardiomyopathy has been described in the postpartum period as an entity distinct from a peripartum myopathy. One proposed mechanism for this is the abrupt drop in estrogen levels following delivery, combined with a high physical and emotional stress state (41). However, this attenuation by estrogen fails to explain the overall predilection for females to be affected by stress-induced cardiomyopathy. There may be gender-related differences in the autonomic nervous system that may partially explain the higher rates of this condition in women (42). Thyroid hormones may also affect the pathophysiology of SIC, although further research is needed to elucidate the exact mechanism. Thyrotoxicosis can precipitate stress-induced cardiomyopathy, and proposed mechanisms suggest that hyperthyroidism can mimic a state of hyperadrenergic activity (43). However, other studies have found a correlation between lower T3 levels and myocardial contractility in patients with SIC (44). It is unclear if this association is simply a manifestation of the physiological stress state or whether there exists a causal relationship. Recent reports of increased serotonin levels in patients with stress-induced cardiomyopathy are of uncertain significance (45).

CLINICAL CHARACTERISTICS

Clinically, patients with isolated stress-induced cardiomyopathy may come to medical attention primarily because of their cardiac symptoms, presenting with chest pain, dyspnea, or syncope (12). In patients with severe neurologic injury or other medical conditions, the first signs of cardiac dysfunction may be cardiogenic shock or, in less severe cases, mild elevation in cardiac enzymes accompanied by ECG changes (13). A wide variety of abnormalities may be noted on ECG, including sinus tachycardia, sinus bradycardia, ST-segment elevations or depressions, T-wave inversions, and prolonged QTc intervals (**Fig. 2**). These changes have been consistently

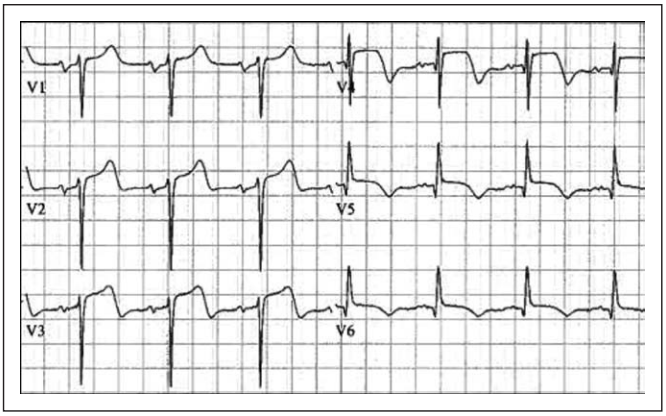

Figure 2. Electrocardiogram of patient admitted with subarachnoid hemorrhage showing ST elevations, prolongation of corrected QT, and T-wave inversions. Coronary angiography demonstrated no evidence of coronary artery disease.

described in patients with SAH or with LV dysfunction following emotional stress as well as in cases of iatrogenic catecholamine-induced cardiomyopathy (10, 13, 31). In addition to abnormalities on ECG, patients often have an increase in cardiac enzymes. Creatine kinase MB fraction is not as sensitive as cardiac troponin, which has been reported to have a sensitivity approaching 100% in the diagnosis of patients with a stress-induced cardiomyopathy (31, 46, 47). The peak elevation in troponin level is typically at the time of presentation although there are rare reports of patients with delayed peaks in troponin level (31, 47). The peak troponin levels are typically less than one would see in a true myocardial infarction (48). In addition, elevation of B-type natriuretic peptide is predictive of regional wall motion abnormalities in SAH (49) and has also been reported in iatrogenic catecholamine-induced cardiomyopathy (10).

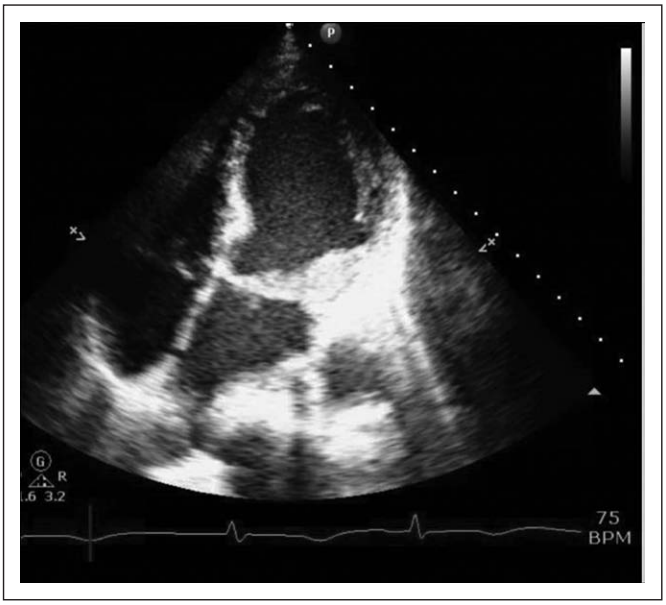

Figure 3. Echocardiogram (four-chamber apical view) of patient with subarachnoid hemorrhage and stress-induced cardiomyopathy showing apical ballooning.

The classic pattern of wall motion abnormalities seen on echocardiogram in stress-induced cardiomyopathy is one of apical ballooning or hypokinesia of the apex of the heart with hypercontractility of the basal segments (50) (**Fig. 3**). Many previously described diagnostic criteria have included this pattern in their definitions, which may cause some bias in the true frequency of this pattern. The dysfunction always involves the left ventricle and may be described as hypokinesis, akinesis, or dyskinesis of the mid segments with or without apical involvement, extending beyond a single epicardial vascular distribution (15, 16). There have also been reports of an inverted pattern of cardiomyopathy with hypokinesis of the basal and midventricular segments of the myocardium with sparing of the apex, which may be more common in patients with an underlying neurologic etiology (27, 51). It is unclear if this variation is the result of different pathophysiology or represents a selection bias in the patients without underlying critical illness, who are more likely to undergo extensive cardiac workup in the setting of ST elevations on ECG, which is more commonly associated with apical ballooning (9). Right ventricular involvement has also been described in anywhere from 26% to 32% of patients with LV apical ballooning. These patients are more likely to have a lower LV ejection fraction, pleural effusions, and a longer hospital stay (52, 53).

PRECIPITATING CONDITIONS

Stress-induced cardiomyopathy, although commonly described in the SAH population, occurs in many other situations associated with catecholamine excess. It has been described in association with epileptic seizures (54), and pathological studies from patients who have died during status epilepticus show contraction band necrosis, similar to that described above (55). Among patients with neurologic injuries, stress-induced cardiomyopathy has also been described in patients with the Guillain-Barré syndrome, acute myelitis, brain tumors, reversible posterior leukoencephalopathy syndrome, subdural hematomas, TBI, encephalitis, hydrocephalus, neuroleptic malignant syndrome, ischemic strokes, opiate withdrawal, and tetanus (9, 35, 56–58). In addition, there have been reports of the same syndrome in patients with pheochromocytoma (27), sepsis (35, 56), systemic lupus erythematosus (59), anorexia nervosa (60), thyrotoxicosis (43), following liver transplantation (61), and diabetic ketoacidosis (62). In patients without another identifiable cause, a recent acute emotional stress frequently precedes the syndrome (51).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for stress-induced cardiomyopathy includes acute myocardial infarction, myocarditis, neurogenic pulmonary edema, and preexisting nonischemic cardiomyopathies. In patients presenting with clinical signs of acute coronary syndrome, coronary angiography is typically warranted. The time course of ECG changes and resolution of echocardiogram changes may be indistinguishable from that of a reperfused acute myocardial infarction or a minimal enzymatic release acute myocardial infarction (63). Myocarditis may present in a similar manner, and in high-risk patients who undergo angiography, coronary arteries will be normal. If clinical suspicion is high for myocarditis, endomyocardial biopsy may be considered for diagnosis, typically if the symptoms remain for several weeks. Cardiac MRI (CMRI), if available, may also help differentiate between a stress-induced cardiomyopathy and myocarditis (64). Patients with severe neurologic injury are also at risk for development of neurogenic pulmonary edema, which is likely similarly mediated by sympathetic stimulation, and may coexist with stress-induced cardiomyopathy or cause pulmonary edema in the absence of cardiac dysfunction (65). Elevated troponin levels following SAH is a risk factor for both stress-induced cardiomyopathy and acute lung injury, which may be caused by neurogenic pulmonary edema (66). Hemodynamic augmentation by vasoactive agents in the setting of SAH may also lead to diastolic dysfunction in patients with underlying hypertension, and subsequent development of pulmonary edema may be confused with stress-induced cardiomyopathy (67). Finally, patients with symptoms of heart failure in the setting of normal coronary angiography may have an underlying nonischemic cardiomyopathy.

MANAGEMENT AND PROGNOSIS

The natural course of the stress-induced cardiomyopathy syndrome is near-complete resolution over several days to weeks (68). A large study of patients presenting with acute coronary syndrome and a pattern of apical ballooning on echocardiogram with normal coronary angiography found no increase in 4-year mortality compared with matched controls and a 1–2% annual recurrence rate (69). A large meta-analysis found an in-hospital mortality rate of 1.1% and a recurrence rate of 3.5% in patients with transient LV apical ballooning syndrome, although this study excluded patients with SAH (11). Male patients have a higher mortality rate but also were found to have significantly higher rates of underlying critical illness (70). Overall, the primary predictor of mortality in stress-induced cardiomyopathy is related to the underlying condition (71). Complications such as LV thrombus, cerebral infarct, and life-threatening arrhythmias have been described infrequently, with prolongation of the QTc noted as a risk factor for the development of life-threatening arrhythmias (59, 60, 72–74). Elevated WBC count and brain natriuretic peptide are associated with worse clinical outcome in patients without neurologic disease with stress-induced cardiomyopathy (75). In patients with neurologic injury, the presence of cardiomyopathy is associated with pulmonary edema, prolonged intubation, and cerebral vasospasm (7) as well as poor neurologic outcome and increased mortality (2, 3, 76). The role of elevated troponin alone in predicting outcome in patients with neurologic injury remains uncertain (77, 78). Stress-induced cardiomyopathy is frequently seen in patients developing brain death and may not be a contraindication to heart donation (79, 80). Repeat evaluation is reasonable in the short term as cardiac function in this setting may improve over hours to days (81).

Coronary angiography demonstrating a lack of obstructive coronary disease or acute plaque rupture is part of the

proposed Mayo Clinic diagnostic criteria for stress-induced cardiomyopathy (12), and as such, any patient presenting with ECG and clinical data suggestive of either an ST-elevation myocardial infarction or a high-risk non–ST-segment elevation myocardial infarction should be evaluated with coronary angiography to assess the need for percutaneous coronary intervention (PCI). In patients with absolute or relative contraindications to coronary angiogram and/or anticoagulation, the clinician should attempt to use additional data to further risk stratify the patient. Pending workup, it is reasonable to initiate aspirin in these patients, barring a contraindication such as ICH. CMRI at the time of presentation may assist in distinguishing SIC from true myocardial ischemia as well as aid in distinguishing it from myocarditis, as mentioned earlier (64, 82). Echocardiography with a typical apical ballooning pattern can also be helpful in further distinguishing between obstructive coronary disease and SIC. Finally, novel tools are being developed that may help predict SIC using the product of the troponin and ejection fraction, although these tools need further validation (83). In patients demonstrating patterns more consistent with obstructive coronary disease, the risk-benefit ratio may shift in the setting of a relative contraindication and may push the clinician to accept the risk of anticoagulation and/or PCI. See **Figure 4** for guidelines in the evaluation and management of patients with suspected SIC.

Although the natural course of the cardiomyopathy is resolution, there is some evidence to support administration of pharmacological α- and β-blockade as therapy, and this is a reasonable treatment option to consider. Previous reports demonstrated improvements in the ECGs in patients with SAH after administration of propanolol (84). The same authors went on to perform a randomized placebo controlled study in which they found necrotic myocardial lesions on autopsy in all of the patients administered placebo and in none of the patients receiving propanolol and phentolamine (85). Animal models further support the prevention of myocardial lesions with α- and β-blockade in neurologic injury and stress (86, 87). However, other studies have found no significant effect in severity of cardiomyopathy in patients receiving β-blockade prior to injury (88). β-blockade should be avoided in the setting of acute heart failure with hemodynamic instability as this may worsen hypotension. Patients with SAH are unique in that they are at risk for vasospasm and often have a need for augmentation of blood pressure, limiting the ability to administer these agents even in the setting of normotension. Although β-blockade has not been reported to have adverse effects due to unopposed α-adrenergic effects from elevated levels of catecholamines in the setting of stress-induced cardiomyopathy, it is reasonable to consider a β-blocker with some α-blocking properties, such as labetalol.

In the setting of refractory hypotension, antihypertensive medications such as β-blockers should be held. In these patients, focus should remain on prevention of further damage, and although additional studies are needed in this field, it is reasonable to limit further catecholamine toxicity by avoiding sympathetic vasopressors and favoring inotropic agents without catecholamine activity, such as milrinone in the setting of cardiogenic shock (13, 89). Evidence for avoiding sympathetic

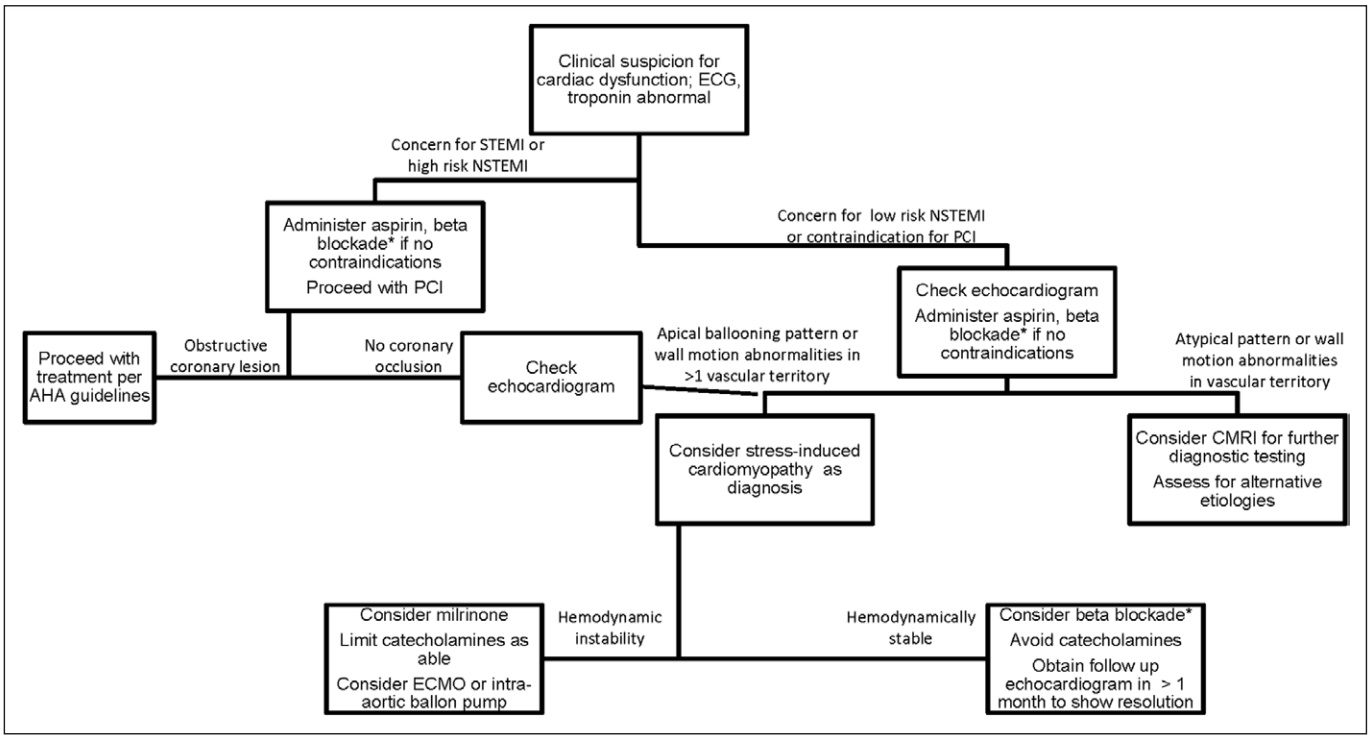

Figure 4. Evaluation and management of stress-induced cardiomyopathy. *Avoid β-blockade if hypotension is present. AHA = American Heart Association, CMRI = cardiac MRI, ECG = electrocardiogram, ECMO = extracorporeal membrane oxygenation, NSTEMI = non–ST-elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction.

agents comes from reports of SIC induced by iatrogenic doses of epinephrine (10) as well as cases reported in the setting of pheochromocytoma (27). In patients with substantial need for hemodynamic support, aortic balloon pump counterpulsation is also a reasonable strategy and may improve neurologic outcome in patients with SAH (90–92). In the setting of refractory heart failure, extracorporeal life support has been described as a bridge to recovery as well (93), although this approach should be reserved for the most severely ill patients, and may not be appropriate in patients with intracranial hemorrhages who cannot be anticoagulated.

CONCLUSIONS

Stress-induced cardiomyopathy is a self-resolving syndrome that may present as a mimic to ischemic heart disease or as a complication during critical illness, particularly those diseases involving the neurohumoral axis. It is more common in postmenopausal women; however, in atypical populations, it may herald a greater mortality related to the underlying illness. The pathophysiology is mediated through catecholamine activity, and early recognition of the disease with supportive care is critical. Limiting further exposure to adrenergic stimulation and considering α- and β-blockade are appropriate treatment strategies.

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