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Transient stress cardiomyopathies in the elderly: Clinical & Pathophysiologic considerations

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Abstract

Transient stress-induced cardiomyopathies have been increasingly recognized and while rare, they tend to affect elderly women more than other demographic groups. One type, often called tako-tsubo cardiomyopathy (TTC), is typically triggered by significant emotional or physical stress and is associated with chest pain, electrocardiogram (ECG) changes and abnormal cardiac enzymes. Significant left ventricular regional wall motion abnormalities usually include an akinetic "ballooning" apex with normal or hyperdynamic function of the base. A second type, often called neurogenic stunned myocardium, typically associated with subarachnoid hemorrhage, also usually presents with ECG changes and positive enzymes, but the typical wall motion abnormalities seen include normal basal and apical left ventricular contraction with akinesis of the mid-cavity in a circumferential fashion. The pathophysiology, clinical care and typical courses, are reviewed.

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Keywords: Stress-cardiomyopathy; Tako-tsubo cardiomyopathy; Subarachnoid hemorrhage; Neurogenic stunned myocardium

1 Case presentations

1.1 Case 1

A 78-year-old woman who was notified of her son's death in a sudden accident earlier in the day was presented to the Emergency Department with chest pain and dyspnea. Her presenting electrocardiogram (ECG) is shown in Figure 1. Her admission labs were notable for a mildly elevated white blood cell count, a normal hematocrit and platelet count. Her cardiac enzymes showed a total creatine kinase (CK) of 94 ng/mL, a CK-MB of 4 ng/mL (quotient 4%), and a troponin of 0.21 ng/mL. The patient was diagnosed with a probable acute myocardial infarction. She was given 325 mg aspirin, 600 mg of clopidogrel, and an intravenous heparin bolus and drip were administered. The patient was urgently taken to the cardiac catheterization laboratory. En route to the lab, the patient became hypotensive and, upon arrival, was started on a dopamine infusion. Coronary angiography showed only mild luminal irregularities, but the patient's blood pressure remained low, and an intra-aortic balloon pump (IABP) was placed with good effect. Echocardiography was performed, and representative still frames showing apical ballooning/akinesis are depicted in Figure 2. The patient's CK peaked at 153 ng/mL, the CK-MB at 11 ng/mL (quotient peaked at 7%) and the troponin-I at 2.20 ng/mL. After the catheterization, the patient's heparin drip was discontinued, as was her clopidogrel. The patient's hemodynamics improved and both the dopamine and the IABP were weaned off. A follow-up ECG after catheterization is shown in Figure 3.

1.2 Case 2

An 83-year-old previously healthy woman was presented after slipping and falling on some gravel and hitting her head. She complained of a severe headache and was brought

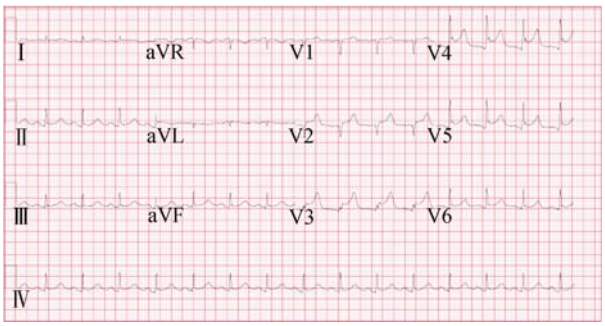

Figure 1. Admission electrocardiogram of Case 1.

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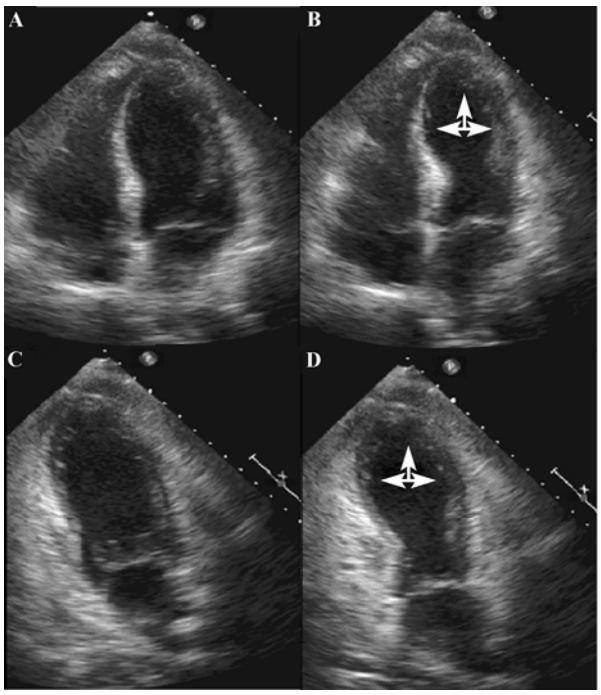

Figure 2. Case 1, echo still frames. (A): Apical 4 chamber view, diastole; (B): Apical 4 chamber view, systole; (C): Apical 2 chamber view, diastole; (D): Apical 2 chamber view, systole. Arrows indicate akinetic areas.

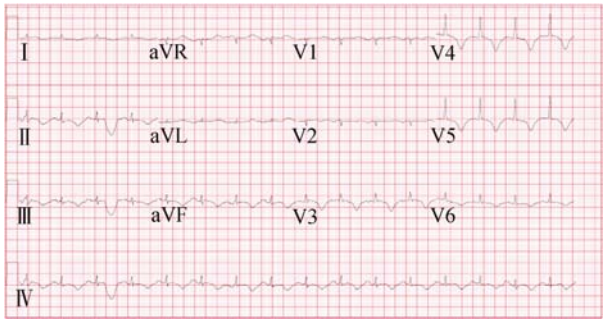

Figure 3. Follow-up electrocardiogram of Case 1.

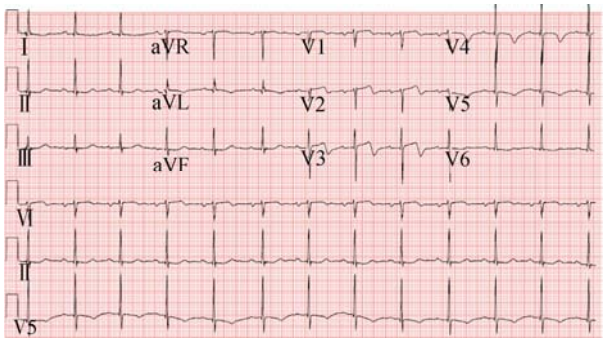

Figure 4. Admission electrocardiogram of Case 2.

to the Emergency Department. A head computed tomogram (CT) showed a large subarachnoid hemorrhage. Although she was somnolent, she was able to answer some questions and denied any current or past chest pain. Her routine admission ECG is shown in Figure 4. Cardiac enzymes were drawn and an echocardiogram was ordered. The enzymes showed a CK 75 ng/mL, with a CK-MB at 3 ng/mL (quotient peaked at 4%) and the troponin-I was 0.41 ng/mL. The echocardiogram was notable for normal left ventricular (LV) size and function at the base and apex, with akinesis of the mid-cavity, circumferentially (see Figure 5).

2 Introduction

Transient stress induced cardiomyopathies (TSIC) can occur in a variety of different contexts. This review will discuss two particular phenotypes, more common in older women. One called Tako-tsubo cardiomyopathy (TTC) is associated with stress (often emotional) and another typically related with subarachnoid hemorrhage, is often called neurogenic stunned myocardium (NSM).

For this paper, a targeted literature review was performed to highlight the main features of the described syndrome(s) emphasizing the most important aspects of the presentation, the underlying pathophysiology, and clinical management.

"Tako-tsubo cardiomyopathy" is also referred to as, "Left Ventricular Apical Ballooning Syndrome", and more colloquially "Broken Heart Syndrome." This syndrome was first described in Japan in 1991,[1] but has been increasingly recognized elsewhere. The entity is characterized by transient apical LV dysfunction without significant coronary artery disease. The disorder is more common in older populations and in women, with series finding the mean age between 62~75 years old, and with 82%~100% of the cases being women.[2,3] The common features at presentation include substernal chest pain, or dyspnea, usually preceded by an acute emotional or physiologic stress. Examples of triggers include the death of a loved one, attending a funeral, being the victim of a robbery, suffering a large gambling loss, undergoing a medical procedure, and suffering a medical illness (including infection, such as pneumonia and other diagnoses requiring ICU admission).[3–6] However, an identifiable stress may not be uncovered in approximately 30% of cases.[3] There are often ECG abnormalities (in a large prospective study, 87% of patients had ECG abnormalities[3]), which most often include anterior ST elevation on presentation and evolutionary T-wave changes (deep T-wave inversions with QT interval prolongation).[7]

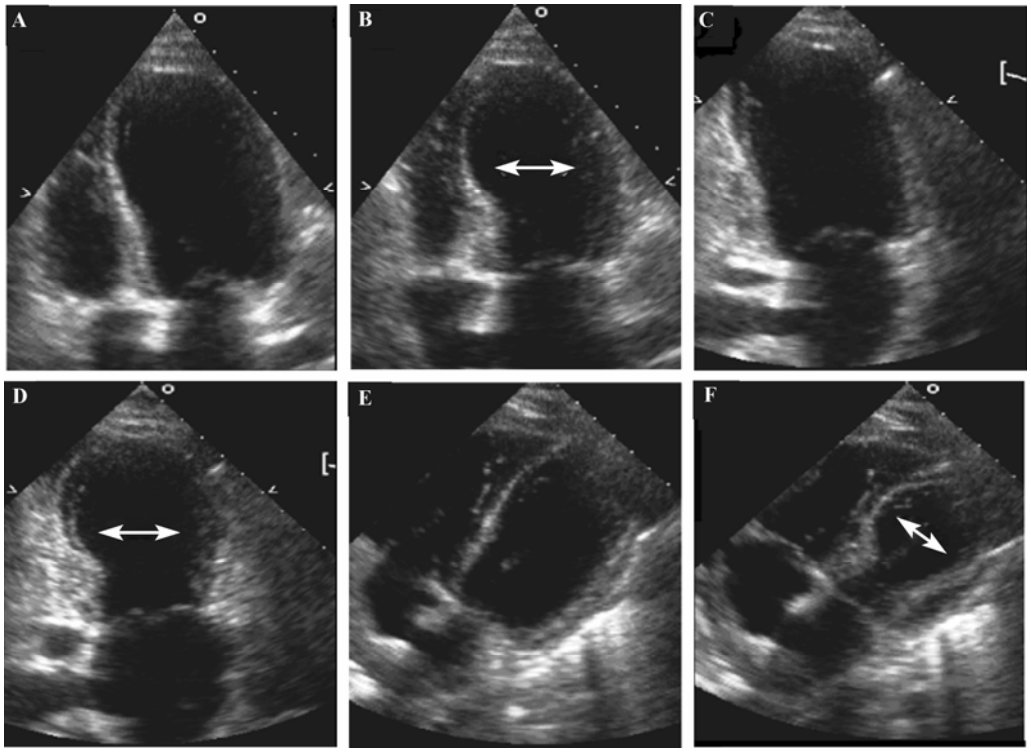

Figure 5. Case 2, echo still frames. (A): Apical 4 chamber view, diastole; (B): Apical 4 chamber view, systole; (C): Apical 2 chamber view, diastole; (D): Apical 2 chamber view, systole; (E): Subcostal 4 chamber view, diastole; (F): Subcostal 4 chamber view, systole. Arrows indicate akinetic areas.

Cardiac biomarkers are usually elevated, but at low levels (rates as high as 90%[3]), with the first set drawn often showing the highest values.[8,9]

There are wall motion abnormalities present on imaging (including echocardiography, left ventriculography, magnetic resonance imaging) in greater than one or in a non-coronary distribution. Typical cases of TTC show normal to hyperdyanmic basal contraction with mid/distal and apical akinesis (or "ballooning").[8] In fact, the name "Tako-tsubo" was coined because of the similarity of the LV morphology to traditional Japanese octopus traps (see Figure 6). Other patterns, as well as biventricular dysfunction, have been described and will be discussed below.

Figure 6. Traditional japanese octopus trap.

Because the presentation involves chest pain and ECG changes with abnormal cardiac enzymes, it has been estimated that the entity accounts for about 2% of suspected acute coronary syndromes (ACS).[1,10]

There have been diagnostic criteria proposed by a group at the Mayo Clinic (all four required for diagnosis)[10,11] that include: (1) Transient hypokinesis, akinesis or dyskinesis of the LV mid segments with or without apical involvement. The regional wall motion abnormalities typically extend beyond a single epicardial coronary distribution. A stressful trigger is often, but not always present. (2) The absence of obstructive coronary disease or angiographic evidence of acute plaque rupture. (3) New ECG abnormalities (either ST-segment elevation and/or T-wave inversion) or a modest elevation of cardiac troponin. (4) The absence of pheochromocytoma or myocarditis.

3 Specific patterns of wall motion abnormalities

In a large prospective, multi-center trial of patients fitting the above criteria for TTC, Cardiac Magnetic Resonance Imaging (CMR) was performed on 93% of 256 subjects, and results showed apical ballooning in 82%, mid-ventricular dysfunction in 17% and basal dysfunction in 1%. In

34% there was biventricular dysfunction (which was more frequent associated with a preceding identifiable stresses, as well as longer hospital stays).[3] The LV ejection fractions of those patients were also lower, and they were more likely to have pleural effusions, suggesting the right ventricular (RV) dysfunction may have led to some degree of right heart failure. As was the case with LV dysfunction, RV recovery was near universal.

Other smaller series have revealed lower rates of RV involvement (26% of 34 patients),[12] and in a small series of 35 patients from a consecutive registry of ACS in Germany, 60% had typical wall motion abnormalities (*i.e.*, apical ballooning), and 40% had what has been called an atypical pattern (mid-cavity dysfunction).[13]

In individual cases, the particular pattern of expression of these stress cardiomyopathies may relate to the distribution of sympathetic nerves in the heart, the pattern of local release of catecholamines, or differences in neurologic input to the myocardium, any of which may be influenced by age and menopausal/estrogen state. This type of multifactorial explanation has been proposed by others, and is further discussed below.[3]

4 Other causes of LV systolic dysfunction

Other causes of LV dysfunction include obstructive epicardial coronary artery disease, idiopathic dilated cardiomyopathy, viral cardiomyopathy, myocarditis, hypertrophic cardiomyopathy.

5 Acute complications

Patients with TTC can suffer a number of acute complications, such as pulmonary edema, cardiogenic shock, transient left ventricular outflow tract (LVOT) obstruction, acute mitral regurgitation from chordal tethering, or systolic anterior motion of the anterior leaflet of the mitral valve, and LVOT obstruction.[2,4,6,10,14] Bradyarrhythmias, and tachyarrhythmias have been reported, including (uncommonly) ventricular tachycardia or fibrillation. Free wall rupture, and apical thrombus formation, potentially leading to thromboembolic complications, have been described.[3,10]

6 Prognosis (in-hospital and subsequent)

Overall, the prognosis is good. In cases of TTC, in-hospital mortality is low and ranges from 0% to 8%.[2–4,6,10] and generally, close to 1% (the 8% listed is from a series of only 13 patients where one died[14]). In the largest prospective series to date, in-hospital mortality was 1.6%.[3] In the large prospective, multi-center study noted above, 1.6% (4 of 256) of patients died during their initial hospitalization and an additional 1.6% died during the one to six months of follow-up. In-hospital deaths were from ventricular fibrillation (two patients), cardiogenic shock, and hypoxic brain injury. During follow-up, the deaths were attributed to pulmonary embolism, renal cell carcinoma, chronic obstructive pulmonary disease, and cardiac arrest. Patients who survive the acute episode typically recover normal LV function within one to four weeks.[4,6,14–16]. The recurrence rate is also low. In the series of 88 patients mentioned above, there were two recurrences in an average 13 months of follow-up.[4] In a series of 100 patients followed for an average of 4.4 years, 31 patients had recurrent chest pain and 10 had a recurrence of TTC.[17] Overall, the prognosis is favorable.

7 Pathophysiology

There are a number of theories regarding the pathophysiology of TTC, which include epicardial coronary vasospasm, microvascular dysfunction, catecholamine induced myocardial dysfunction, neurologically mediated myocardial dysfunction, myocarditis, and coronary artery disease that was not apparent on angiography.[10]

8 Evidence

Coronary vasospasm has been postulated as the etiology because epicardial coronary artery disease seen on catheterization is not present, too minor in severity or in the incorrect distribution to explain the extensive pattern of wall motion abnormalities seen in TTC. This hypothesis is supported by some cases of observed spontaneous or inducible spasm, but it is not universally present, and transient spasm would not explain persistent ST segment elevation in the absence of coronary stenoses.[4,15] In a 2006 systematic review of studies of TTC, only 1.4% of cases demonstrated spontaneous multivessel spasm, and only 28% developed multivessel spasm with provocation (with ergonavine or acetylcholine).[8] Thus, while spasm may play some role, it does not seem to be a primary etiology of the syndrome.

Microvascular dysfunction has been suggested as an etiology as well. Some invasive studies have noted abnormal TIMI frame counts and flow measurements to be abnormal in some studies/cases.[18] It has also been noted that intracoronary nicorandil (dilates the coronary microcirculation) can decrease ST elevation.[19] Microvascular dysfunction has also been proposed by nuclear imaging

techniques, including positron emission tomography (PET), which also suggest a role for abnormal cardiac sympathetic nervous function. Studies using N-13 ammonia PET showed a decrease in coronary flow reserve in the LV myocardial apex in the acute phase of TTC,[20] and other studies, using ^{123}I-metaiodobenzylguanidine, suggest abnormalities of cardiac sympathetic nervous function in patients with the disorder.[21]

Other theories, which are not mutually exclusive, also involve catecholamines. Abnormally high levels of serum catecholamines,[8] 2~3 times higher than in patients with myocardial infarction, have been seen in patients with TTC,[16] although other studies have reported normal levels.[22] Exposure to catecholamine or beta-agonists used for clinical purposes (e.g., dobutamine stress testing) have caused similar findings, providing more evidence of a role of catecholamines in the syndrome, and similar to cases described in patients with pheochromocytoma,[9] and sepsis-related apical ballooning, who also have been shown to have elevated catecholamine levels as well.[23]

Another hypothesis is catecholamine induced myocardial dysfunction, as opposed to vascular. Biopsy data are not plentiful but some have shown signs of catecholamine toxicity, such as interstitial fibrosis, mononuclear/macrophage infiltrates, contraction band necrosis, intracellular glycogen accumulation, extracellular collagen accumulation, and increased extracellular matrix proteins, which resolve.[5,16,24] Apoptotic and autophagic cell death were excluded in an electron microscopic and immunohistochemical analysis.[24] Beta-receptor stimulation can alter calcium regulation resulting in intracellular calcium overload and contractile dysfunction.[25,26]

Neurologically mediated myocardial stunning has been proposed as an etiology, with the purported pathway being endothelial dysfunction with, or without, adrenergic abnormalities. Immobilized rats (presumably the immobilization is a stress) have been observed with inducible apical and mid-ventricular wall motion abnormalities, as well as ST segment elevation on ECG.[27] These were not reproduced after pre-treatment with amosulalol (an α- and β-adreno-receptor antagonist).[28] There is some evidence that estrogen also attenuates the effect in ovariectomized female rats.[27]

Myocarditis has been hypothesized as an etiology, and although the condition could be focal, biopsy studies have not been generally supportive. Lastly, another proposal has been to implicate coronary artery disease not apparent on angiography. This has been proposed based on an intra-vascular ultrasound study that revealed evidence of ruptured plaques not apparent on angiography,[29] but another study failed to confirm this.[30] A similar hypothesis involves the theory that transient occlusion of a long, "wrap-around" left anterior descending coronary artery could result in transient apical myocardial stunning, but in one study the presence of such a vessel was low, thus, ruling this out as an anatomic substrate in most patients.[22]

9 Evaluation and management

In the literature, there are no guidelines from major professional societies regarding the care of patients with TTC, but in the literature, there is a general consensus on reasonable interventions.[10,11,31] The initial management of patients with stress-induced cardiomyopathy is largely supportive, and involves attempting to alleviate the triggering physical, or emotional stress, and hydration. The use of medications and the duration of therapy are not established, but most experts favor the use of standard medications for systolic heart failure (at least short-term). An important point is that patients who present with typical ST segment elevation myocardial infarction (STEMI) should be treated as such, with consideration of urgent cardiac catheterization or fibrinolysis, per standard guidelines, since the vast majority of these patients will have typical STEMI. It has been estimated only 1.5%~2.2% of presentations typical for STEMI have had stress-induced cardiomyopathy (about 17,000 per year in the United States).[13] Diagnostic criteria have been proposed and are listed above.

9.1 Cardiac MRI in the diagnosis and evaluation of TTC

Although not yet widely available and practical for urgent care evaluation, CMR can be helpful in narrowing the differential diagnosis. TTC has been evaluated by CMR, most recently in a large prospective multi-center trial. Past reports suggested that, in general, there was an absence of delayed gadolinium enhancement,[6] but a more recent prospective study of CMRs performed < 72 h after admission, showed mild transmural late gadolinium enhancement in the wall segments with abnormal function in all eight patients which resolved on subsequent imaging (*i.e.*, was transient).[32] The proposed explanation of this difference is that the prior studies may have had a longer delay from presentation. In fact, one case report of a dobutamine stress test related case of TTC where CMR was done early in the course, showed late gadolinium enhancement that resolved on repeated imaging.[33] Timing may be one issue, but another may be the degree of delayed enhancement. In the recent large study noted above, using a higher cutoff value for necrosis/fibrosis detection, none of the patients studied had evidence of delayed enhancement, but did show myocardial edema, which they proposed be part of the diagnostic criteria.[3] Epicardial coronary stenosis related myocardial infarction on CMR is associated with permanent transmural, or subendo-

cardial delayed hyperenhancement,[34] and myocarditis which typically shows patchy subepicardial or intramyocardial gadolinium uptake/ delayed hyper-enhancement.[35,36] Lastly, CMR can also detect ventricular thrombi, which may form due to the wall motion abnormalities, and may escape visualization by echocardiography (although the use of echo contrast can enhance the sensitivity to detect thrombi on echocardiography).[37, 38] In one study of 256 patients, four LV thrombi were identified.[3]

9.2 Medical therapy

If there is adequate blood pressure, medical therapy usually includes a beta-blocker, unless the patient is bradycardic or hypotensive, an angiotensin converting enzyme inhibitor, or angiotensin II receptor blocker. Because catecholamines appear to play a significant role in the syndrome, and recurrences while uncommon, have been reported, many continue beta-blockers indefinitely. Diuretics should be administered for volume overload (e.g., pulmonary edema). Aspirin is usually given if there are risk factors for, or identified atherosclerotic disease, and a nitrate, or calcium channel blocker, if vasospasm is documented. Systemic anticoagulation should be considered if an LV thrombus is identified, or there is severe LV dysfunction.

9.3 Hypotension/Shock

Shock may result from severe LV systolic dysfunction (low ejection fraction) or from LVOT obstruction resulting from hyperdynamic basal LV function which has been described in up to 18% of cases.[10] Urgent echocardiography to evaluate for LVOT obstruction is indicated in hypotensive patients. With hypotension, fluids are often administered if there is no pulmonary edema, and inotropes, or dopamine, can be considered if there is no LVOT obstruction and hypotension is refractory to volume resuscitation. If moderate-to-severe LVOT obstruction is present, beta-blockers may reduce/resolve obstruction, and if they are not tolerated, or there is an inadequate response, an alpha agonist such as neosinephrine may be added with caution and close monitoring. An IABP can be considered, particularly for patients who donot respond to volume, and medications with, or without, the presence of LVOT obstruction are likely preferable to beta-agonists, for example, given the central role catecholamine excess appears to play in the pathophysiology. One caution is that the afterload reduction induced by an IABP could theoretically worsen LVOT obstruction (if present) and patients should be followed closely, perhaps with repeat echocardiography while the IABP is functioning.[6]

10 Subarachnoid hemorrhage (SAH) related LV dysfunction

A condition called “neurogenic stunned/stressed myocardium NSM” or “neurogenic stress cardiomyopathy” has been described in patients with subarachnoid hemorrhage (as well as other intracranial pathology such as seizures, and stroke).[39]

10.1 Presentation

NSM is most often seen in post-menopausal women with more serious hemorrhages.[39] Often patients are asymptomatic, but sometimes shock and/or heart failure can ensue. The diagnosis is usually suspected after abnormalities are noted on cardiac testing such as ECG or echocardiography performed either for symptoms or for another indication.

Approximately 8% of patients with SAH have regional wall motion abnormalities.[40] These were noted to occur mostly in female patients who had abnormal cardiac enzymes and a less favorable neurologic status.[41–43] The pattern of LV dysfunction is usually described as mid-cavity akinesis, with a subset (from 30% to as high as 40%[42, 44]) showing an apical ballooning, Tako-tsubo-like, pattern. Other patterns have also been described, but generally involve more than a single coronary artery territory.

There are usually ECG abnormalities, including a prolonged QTc, as well as T wave (typically deep, symmetrical inversions) and ST abnormalities.[40,45] Cardiac troponins, when abnormal (about 20%~30% of cases) are usually only mildly elevated, with the first measured sample showing the highest value. Complications can include shock, heart failure, LV thrombus formation and both tachy- and brady-arrhythmias.[40, 45] B-type natriuretic peptide may be elevated and is associated with visualized wall motion abnormalities, impaired LV ejection fraction, diastolic dysfunction, pulmonary edema and in-hospital mortality.[46] Generally, if the patient survives, their LV dysfunction improves, although this can take days to weeks.[42, 47]

“Neurogenic pulmonary edema” is another condition that has been described. Initially, it was thought that patients with SAH developed pulmonary edema independent of cardiac dysfunction. However, more recent work suggests that there is some overlap between the syndromes.[47,48]

10.2 Pathophysiology

Pathophysiologic therories for NSM are similar to those described in TTC, and include multivessel vasospasm, microvascular dysfunction, catecholamine poisoning/stunning (maybe local only) causing contraction band necrosis. Neurologically mediated “stunning” via hypothalamic neural

stimulation may trigger sympathetic activation.

In a dog model of SAH, wall motion abnormalities were induced without evidence of coronary vasospasm, and microvascular perfusion was normal by contrast echocardiography.[49] Elevated levels of serum catecholamines have been measured in humans, as well as in animal models, and elevated levels have been correlated with cardiac enzyme elevation.[50-52] Pathologically, SAH is known to cause myocardial contraction band necrosis, and is distinct from coagulative necrosis that results from myocardial infarction. Other causes of contraction band necrosis include, head trauma, TTC, pheochromocytoma, near drowning, fatal status epilepticus and asthmaticus, which are states of excess sympathetic discharge.[39,53,54] However, in baboons, contraction band necrosis can occur even after bilateral adrenalectomy, but can be blocked by sympathectomy, suggesting that local release is sufficient, and elevated levels of circulating catecholamines are not required.[55] In addition, sudden increased intracranial pressure in dogs is associated with increase in circulating epinephrine and myocardial damage, thought due to hypothalamic dysfunction.[56]

10.3 Management

In general, in patients with SAH, NSM is thought to be a marker of the severity of SAH and predicts cerebral vasospasm,[39] and the treatment is usually supportive. In part due to contraindications to anticoagulation in patients with SAH, most are not taken to the catheterization lab. Hypotension or heart failure with decreased oxygen saturations can be particularly problematic in patients who have cerebral vasospasm. In fact, low cardiac output and pulmonary pathology can predict symptomatic cerebral vasospasm in patients with SAH.[41,47,57] Inotropes may be necessary to maintain cerebral perfusion and lessen cerebral vasospasm, but agents such as norepinephrine and phenylephrine should probably be avoided, since sympathetic excess probably caused the myocardial dysfunction.[39] Some have studied the use of alpha- and beta-blockers in the prevention of SAH associated cardiomyopathy with some success. Agents studied have included phentolamine, propranolol and atenolol.[58–60]

NSM has been reported with other neurologic disorders including ischemic strokes, seizures, brain tumors, subdural hematoma, closed head injury, Guillan-Barre Syndrome, reversible posterior leukoencephalopathy syndrome, acute myelitis and encephalitis.[61]

11 Shared pathophysiology

A shared pathophysiology between SAH related cardiomyopathy and TTC was first postulated by Ako *et al*.[62] in 2006, and has been strongly advocated recently in a 2011 paper.[61] Both are found more commonly in postmenopausal females, who share similar postulated pathophysciologic mechanisms with catecholamines thought to play a significant role, and a lack of strong support for other hypotheses, such as coronary vasospasm, and pathologic findings of contraction band necrosis.

11.1 Demographics and phenotype: Postmenopausal women

There is a strong female predominance with the syndrome more common in post-menopausal women. In the largest prospective study to date, involving patients in Europe and North America, 256 patients with TTC were followed. In that population, 81% of patients were postmenopausal women.[3] Notably, however, a case of TTC was reported in a newborn, where the stress was near asphyxiation by umbilical cord during birth.[63]

It is natural to suspect that hormonal factors are playing a role. In fact, it has been reported that estradiol administration in ovariectomized rats can attenuate stress-induced LV function abnormalities.[27,64] Estradiol may impact the pathophysiology by modulating the sympathetic nervous system axis centrally including in the hypothalamus, and in the coronary microcirculation.[65]

Cerebral aneurysm related SAH is also more common in women. Although in general, the group of people at risk for SAH is younger than the population usually affected by stroke, the risk increases with age, and is 60% higher in the very elderly (over 85) than those between 45 and 55. Risk of SAH is about 25% higher in women over 55 compared to men the same age, probably reflecting the hormonal changes, such as a decrease in estrogen levels[66] that result from menopause, such as a decrease in estrogen levels.[66] In case histories of NSM published up to 2011, one review reported that 71% of the cases were described in women, and others have found female sex to be a risk factor for NSM after SAH.[60]

One series of 102 patients at a single center with TTC sought to evaluate differences between males and females with the disorder. While there were only 13 male patients, in 10 of them (77%), the disorder occurred during or immediately following medical treatment, or evaluation for another medical condition. This type of in-hospital onset was much higher than in women where it was seen in only 17%, and suggests physical stress may have more to do with the occurrence of TTC in males than in females.[67]

It has been proposed that the different patterns of wall motion abnormalities may, in part, be due to differences in

sympathetic nerve distribution in the myocardium, which itself may be age related. Small series have suggested there might be a relationship between age and the pattern of dysfunction. A series by Hurst of four patients with typical presentations for emotional or physical stress induced cardiomyopathy had midventricular dysfunction and a mean age of 53 (range: 37~69).[68] Reuss described three patients with "inverted" pattern (basal akinesis with normal mid and hyperdynamic apical LV function) whose average age was 31 (range: 30~32).[69] Another case of a patient who had a recurrence of stress-cardiomypathy, with her first episode at age 52, was characterized by midventricular hypo/akinesis and the recurrence (11 years later) showed apical ballooning.[70] This is in contrast to the reported demographics of patients with typical apical ballooning who are typically older 62~75 years, or so. On the other hand, a case of a patient has been reported that showed the reverse pattern, with apical ballooning at age 65 and midventricular variant at age 68.[71]

It has been hypothesized that this may be due to differences in the anatomic location of cardiac adrenergic receptors, the degree of excess sympathetic activity involved, or differing susceptibilities to sympathetic stimulation.[68] It would be a reasonable question to ask whether some of these changes may be age related, and possibly modulated by hormonal status.

The work done on ovariectomized rats showing that TTC changes, such as wall motion, ST elevation and tachycardia, can be attenuated by estradiol treatment is intriguing. The paths by which estrogen may impact the syndrome are multiple. Estrogen effects vagal tone and counteracts sympathetic nervous system activity, in animals[72] and humans,[73,74] possibly via the hypothalamus, and other central nervous system centers,[64] the adrenal gland,[75] as well as providing vasodilatory influences via the induction of endothelial nitric oxide synthase.[76]

12 Shared pathophysiology: Summary

In summary, the leading hypothesis at this point for both TTC and NSM, is that the pathophysiology is most likely related to neurologic myocardial stunning mediated by catecholamines, perhaps modulated by hormone status that affects the coronary microcirculation. Some cases may be due to multi-vessel (or large wrap-around left anterior descending coronary artery) epicardial spasm with metabolic injury to the myocardium. Furthermore, the precise pattern of wall motion abnormalities induced may be due to differences in beta-receptor density, or sensitivity, that may also be hormonally modulated.

13 Future directions

Further research should be aimed at clarifying the neuro-hormonal-cardiac pathways (including sympathetic nervous system abnormalities) that underlie the pathophysiology, as well as evaluating the optimal diagnostic and treatment strategies. Given the rarity of the disease, clinical studies will require a multi-center and/or registry approach.

14 Patients' course

The patient described in Case 1 was extubated, and her symptoms resolved. She was discharged on Aspirin 325 mg daily, Carvedilol 12.5 mg twice daily, Lisinopril 20 mg twice daily. A follow-up echocardiogram one month later showed resolution of the patient's wall motion abnormallities.

The patient described in Case 2 recovered well from her head trauma and a repeat echocardiogram showed normal LV function without regional wall motion abnormalities. No further cardiac evaluation was performed.

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