Improving the diagnosis : Takotsubo cardiomyopathy vs. acute myocardial infarction

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Dedication

A huge thanks goes to my mom and dad for whom I am forever grateful. I cannot express how lucky I am to have such strong role models to look up to. I would never have made it this far without your love and encouragement. I love you guys!

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Introduction

Takotsubo cardiomyopathy, also known as “broken heart syndrome”, or stress-induced cardiomyopathy, is an emerging condition characterized by weakening of the left ventricle of the heart often as a result of severe emotional or physical stress such as a sudden illness, the loss of a loved one, a serious accident, or a natural disaster such as an earthquake (Prasad, Lerman, Rihal 2008). First described in Japan in 1990, the appearance of the bulging left ventricle (Figures 1 and 2) during contraction in broken heart syndrome resembles a takotsubo, a pot historically used by Japanese fishermen to trap octopus (Derrick, 2009). Despite several pathogenetic mechanisms having been proposed such as multi-vessel epicardial spasm, catecholamine-induced myocardial stunning, spontaneous coronary thrombolysis, and acute microvascular spasm, the exact cause of takotsubo cardiomyopathy is still under debate. The most widely accepted mechanism explains a sudden surge of catecholamines which stun the heart and trigger changes in myocardium or coronary blood vessels, or both, thus preventing the left ventricle from contracting effectively (Javed et al., 2015). Many case reports have demonstrated acute, severe, reversible, left ventricular dysfunction that coronary ischemia, aortic valvular lesions, or myocarditis cannot explain. Presenting with many similar symptoms, takotsubo cardiomyopathy is extremely difficult to distinguish from acute myocardial infarction. Several diagnostic tests are available to readily distinguish between the two, and there are various sets of defining criteria that have been modified through the years for both broken heart syndrome and myocardial infarction. The differentiation between takotsubo cardiomyopathy and myocardial infarction is critical to the type of treatment patients will receive and the future complications these patients may experience. Currently, there are no specific guidelines regulating the treatment of takotsubo cardiomyopathy. Prognosis of patients with takotsubo cardiomyopathy is excellent, with most

patients fully recovering within one to four weeks (Akashi, 2008). Regardless of cause, transient left ventricular apical ballooning syndrome is under-recognized and should be considered a unique type of acute coronary syndrome (Bybee et al., 2004). This review will highlight the differences between takotsubo cardiomyopathy and acute myocardial infarction, as well as explain key diagnosis criteria. Healthcare providers, including physician assistants, need to become familiar with this syndrome in order to first recognize it and secondly, treat it properly.

Takotsubo cardiomyopathy is rising in incidence and makes up a relevant part of patients with acute coronary syndrome. The prevalence is described to be 1.2-2.0% and takotsubo cardiomyopathy was diagnosed in 0.02% of all hospitalizations in 2008 (Galiuto et al., 2010). Interestingly, the syndrome affects mostly postmenopausal women. More than 90% of reported cases are in women ages 62-75 years old (Bybee et al., 2004). Research suggests that at least 6% of women evaluated for a heart attack actually have this disorder, which has only recently been reported in the United States and may go largely unrecognized (Prasad, 2010). A possible explanation for the preponderance of women is the lower estrogen concentration in the postmenopausal time frame. In experimental studies, estrogen supplements diminished the over-activation of the heart by stress hormones like epinephrine (Sinning, 2010). Age-related changes in sympathetic nervous system regulation and endothelial function also suggest that postmenopausal women are at a greater risk for cardiac events than premenopausal women (Adameova, 2009). On the contrary, men appear to be somehow protected against the stress-induced adverse cardiac effect of catecholamines than women (Litvinov, 2009). Evolutionary and biological aspects, such as sex hormones, may play an important role in the pathophysiology of takotsubo cardiomyopathy.

There is also a crucial psychological aspect of broken heart syndrome not seen in myocardial infarction that plays a critical role in the pathophysiology of the phenomenon. Patients with takotsubo cardiomyopathy have unusual characteristics, including a disproportionate occurrence in postmenopausal women and a strong association with mental and physical stress (Nguyen, 2009). Several studies suggest that no mental disorders have been linked to broken heart syndrome, while others list depression and anxiety as associated factors. After chart review, Nguyen et al., found that at least 50% of patients admitted for takotsubo cardiomyopathy did indeed have depression. Psychiatric disorders, including depression and anxiety, play an important role in coronary artery disease, and have been shown to actually worsen health outcomes in patients who experienced a myocardial infarction. Depression increases the incidence of coronary disease in patients with no apparent cardiac disease at the time of the initial survey for depression (Behrens et al., 2008). Anxiety and panic attacks have acute episodic presentations and have the potential to initiate cardiac syndromes (Nguyen, 2009). Some studies suggest that anxiety is the actual causal factor in the association between depression and cardiac disease. A study by Lacey et al., found there to be no association between previous psychiatric illnesses and development of takotsubo cardiomyopathy. Summers, Lennon, and Prasad state that if chronic psychiatric conditions and cardiovascular risk factors were confirmed to play a role in the pathophysiology, it would be important to clearly identify and treat them with a view to preventing recurrence.

Literature Review

Myocardial Infarction

Every year about 735,000 Americans have a myocardial infarction, or “heart attack”, of these, 525,000 are a first heart attack and 210,000 happen in people who have already had a heart attack (Mozaffarian, 2015). More than 3 million people each year are estimated to have an acute ST-elevation myocardial infarction (STEMI), with more than 4 million having a non-ST-elevation myocardial infarction (NSTEMI) (White & Chew, 2008). A myocardial infarction, or “heart attack”, occurs when blood flow stops to a certain part of the heart causing damage to the heart muscle. The term myocardial infarction reflects cell death of cardiac myocytes caused by ischemia, which is the result of a perfusion imbalance between supply and demand. A myocardial infarction may be the first manifestation of coronary artery disease, or it may occur repeatedly, in patients with established disease (Thygesen et al, 2007). Progression of atherosclerosis is triggered and enhanced by several factors, such as hypertension, smoking, obesity and hyperlipidemia, which can cause mediating diseases or directly affect the arterial wall (Boersma, 2003). Clinically, there are 5 types of myocardial infarction classified (Figure 3). Myocardial infarction may be defined from a number of different clinical, electrocardiographic, biochemical, imaging, and pathological characteristics.

Presentation

The most common presenting symptom of an acute myocardial infarction is chest pain, usually lasting at least 20 minutes. Other symptoms include shortness of breath, diaphoresis, epigastric discomfort, nausea, vomiting, and upper extremity or jaw pain. These symptoms are not specific to myocardial infarction and can be misdiagnosed or attributed to gastrointestinal,

neurological, pulmonary, or musculoskeletal disorders (Thygesen et al, 2007). More atypical signs and symptoms include nausea, vomiting, and back pain. Women in particular can have very atypical presentations, often experiencing warning symptoms as early as a month in advance. The most frequent prodromal symptoms include fatigue, sleep disturbances, and shortness of breath (McSweeny, 2003). In a 2003 study done by McSweeney et al, acute chest pain was absent in 43% of women experiencing an acute myocardial infarction.

Pathophysiology

Myocardial infarction is defined by pathology as myocardial cell death due to prolonged ischemia. Cell death is categorized pathologically as coagulation and/or contraction band necrosis, which usually evolves through oncosis, but can result to a lesser degree from apoptosis (Thygessen, 2007). After the onset of myocardial ischemia, cell death is not immediate but takes a finite period to develop, sometimes as little as 20 minutes. Complete necrosis of all myocardial cells at risk requires at least 2-4 hours or longer depending on the presence of collateral circulation to the ischemic zone, persistent or intermittent coronary arterial occlusion, the sensitivity of the myocytes to ischemia, pre-conditioning, and/or the individual demand for myocardial oxygen and nutrients (Thygessen, 2007). Partial or complete epicardial coronary artery occlusion from plaques vulnerable to rupture or erosion is the most common cause of myocardial infarction, accounting for approximately 70% of fatal events (White & Chew, 2010). Epidemiological studies have underscored the contribution of lifestyle factors in the development of atherosclerosis and myocardial infarction. In the INTERHEART study of over 15,000 patients, 90% of myocardial infarctions were attributable to modifiable risk factors such as

smoking, dyslipidemia, hypertension, abdominal obesity, and diabetes in men (94% in women) (Yusuf et al, 2004).

Diagnosis

Diagnosis of a myocardial infarction is made through various tests including biomarker evaluation, EKG, and several imaging tests such as echocardiography, x-ray, and MRI. Myocardial cell death can be recognized by the appearance in the blood of different proteins released into circulation from the damaged myocytes: myoglobin, cardiac troponin T and I, CKMB, and LDH. Myocardial infarction is diagnosed when blood levels of sensitive and specific biomarkers such as cardiac troponin or CKMB are increased in the clinical setting (Jaffe, 2006). The preferred biomarker for myocardial necrosis is cardiac troponin (T or I), which has nearly absolute myocardial tissue specificity as well as high clinical sensitivity. The EKG is an integral part of the diagnosis work-up of patients with suspected myocardial infarction. It allows initial categorization of the patient with a suspected myocardial infarction into one of three groups: STEMI, NSTEMI, and undifferentiated chest pain (nondiagnostic EKC). EKG abnormalities of myocardial ischemia or infarction may be found in the PR segment, the QRS complex, and the ST segment or T-waves. Acute or evolving changes in the ST-T waveforms or the presence of Q-waves potentially allow clinicians to date the event, to suggest the infarct-related artery, and to estimate the amount of myocardium at risk (Thygessen, 2007). The earliest change in a STEMI is the development of hyperacute or peaked T-waves, followed by S-T elevation. NSTEMI is characterized by S-T depressions and/or T-wave inversions without S-T elevation. Echocardiographic examination of patients with acute myocardial infarction is a means for detecting a local contraction disturbance in the affected myocardial zone, in agreement

with electrocardiographic localization of the infarction (Weissman, 2014). Echocardiography make it possible to localize and define the extent of injury. The earliest detectable changes in myocardial ischemia or an acute MI are regional LV and potentially also right ventricular wall motion abnormalities.

Treatment

Once the diagnosis of acute myocardial infarction has been made, the early management of the patient involves the simultaneous achievement of several goals: relief of ischemic pain, assessment of hemodynamic state and correction of any abnormalities, initiation of reperfusion therapy with primary percutaneous coronary intervention or fibrinolysis, antithrombotic therapy to prevent re-thrombosis or acute stent thrombosis, and beta blocker therapy to prevent recurrent ischemia and life-threatening ventricular arrhythmias (Cannon, et al., 2002). This is then followed by the in-hospital initiation of different drugs that may improve the long-term prognosis. These drugs include antiplatelet therapy, angiotensin-converting enzyme inhibitors, statin therapy, and anticoagulation (Goodman et al., 200). Lifestyle modifications such as increasing activity levels and changing dietary habits are also crucial to the long-term prognosis of a myocardial infarction.

Prognosis

Myocardial infarction is a major cause of death and disability worldwide. Mortality after a myocardial infarction is highest during the first months of the infarction, after which it levels off (Thygesen, 2007). It is well established that a series of factors related to the size of the infarction and reduction of myocardial contractility are related to deteriorated prognosis as well

as presence of angina pectoris, and ventricular dysrhythmias. Long-term prognosis is also dependent on pre-infarct risk factors such as diabetes, hypertension, cholesterol levels, as well as smoking habits before and after the infarction (White & Chew, 2008).

Complications

Myocardial infarction is one of the leading health problems in the world with many implications. Complications of acute myocardial infarction range from ischemic, mechanical, arrhythmic, embolic, and inflammatory disturbances. Nevertheless, circulatory failure from severe left ventricular dysfunction or one of the mechanical complications of myocardial infarction account for most fatalities (Grasso, 2014). The many complications of myocardial infarction include angina, re-infarction, heart failure, cardiogenic shock, mitral valve dysfunction, aneurysms, life-threatening arrhythmias, sinus or atrioventricular node dysfunction, and pericarditis. With the advent of primary percutaneous coronary intervention and stent placement, risk of reinfarction has dropped substantially, to approximately 3% during the first 90 days after MI (JAMA, 2007). Patients with post-infarction angina have a worse prognosis with regard to sudden death, reinfarction, and acute cardiac events, compared with those without such symptoms (Grasso, 2014).

Psychological Aspect

Extensive research has shown depression to be a significant risk factor of coronary heart disease (Kent, 2009). The prevalence of depression in coronary heart disease is approximately three times higher than the general population (Richard, 2011). In a recent study which included more than 4,000 patients suffering from depression and myocardial infarction, the factor

depression triplicated the risk of dying after the heart attack, if inadequately treated (Koch, 2013) Similarly, anxiety spectrum disorders (panic disorder, PTSD, generalized anxiety), both with or without depressive symptoms, increase significantly the risk of heart attacks (Koch, 2013). Of the proposed mechanisms linking depression and cardiac disease, the strongest evidence pertains to platelet over-activation in depression and to the multiple deleterious effects of depression on behavior and adherence to the medical regimen (Kent, 2009). Antidepressant drugs, irrespectively which class is chosen, improve the outcome and mortality of myocardial infarction (Koch, 2013).

Takotsubo Cardiomyopathy

Takutsubo cardiomyopathy or stress-induced cardiomyopathy is an acute reversible cardiac syndrome characterized by transient left ventricular dysfunction associated with apical and mid-ventricular contractile abnormalities and sparing of basal segments (Purgason, 2006). The syndrome is triggered by emotional or physical stress and mimics acute coronary syndrome, although the coronary arteries are essentially normal. Takotsubo cardiomyopathy is predominantly seen in postmenopausal women with no known cardiac risk factors. Differentiating this syndrome from an acute myocardial infarction is often difficult since many of the presenting signs and symptoms are very similar. In a population admitted to the hospital due to risk of myocardial infarction, takotsubo-like presentation may occur in some 7-8% (Koch, 2013). This condition probably accounts for ~1% to 2% of all cases of suspected acute myocardial infarction (Prasad, 2007).

Presentation

Without a thorough history and physical examination, the diagnosis of takotsubo cardiomyopathy can be easily confused with acute coronary syndrome (Purgason, 2006). Acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non—ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Patients presenting with broken heart syndrome have a variety of symptoms. The most common symptom of patients presenting with takotsubo syndrome is chest pain, combined in nearly all cases with acute onset of dyspnea (Sinning, 2003). Other signs and symptoms include diaphoresis, nausea, and vomiting. Syncope and cardiac arrhythmias are less common presenting signs. Takutsubo symptoms are indistinguishable from those of a heart attack with EKG changes and changes in cardiac enzymes also being consistent with those of a heart attack. The most prominent feature initially seen is ST-segment elevation especially in the precordial leads, V3-V6 (Kurisu, 2002). As the process continues, deep diffuse T-wave inversion, marked prolongation of the QT-interval, and new Q-waves develop (Purgason, 2006). The ST-segment and T-wave changes present with broken heart syndrome ST-T are also seen in myocardial infarction, however, these changes are often not restricted to a specific territory of a coronary artery and can be present in any of the territories representing a specific coronary artery. (Sinning, 2010). EKG is not a reliable tool to be used in the early diagnosis of takotsubo cardiomyopathy, the syndrome can only be distinguished by coronary angiography and left ventriculography which shows regional transient myocardial dysfunction, localized at the left ventricular apex and usually extended beyond a single vessel territory, and absence of significant coronary lesion (Galiuto et al 2010). Cardiac enzymes (troponin, creatine kinase, creatine kinase MB) can be elevated in both stress

cardiomyopathy and acute myocardial infarction (Purgason, 2004). However, patients with an AMI will have dramatically increased enzymes. In stress cardiomyopathy, the enzymes will elevate minimally and peak concentration will be near the initial values (Bybee, Prasad 2004).

In general, most patients presenting with takutsubo cardiomyopathy are postmenopausal females with a mean age of 62-76 years (Javed, 2007). Abhishek et al, found that women 55 years and older, had 4.8 times higher odds of having takotsubo cardiomyopathy than younger women. Researchers suspect that older women are more vulnerable because of reduced levels of estrogen after menopause. In studies with rats, ones given estrogen while under stress had less ventricle dysfunction and higher levels of certain heart-protective substances (Prasad, 2006). Sex hormones also play an important role in the sympathetic neurohormonal axis and coronary vasoreactivity (Purgason, 2004). Increased sympathetic activity (stress) or estrogen deficiency may lead to inappropriate vasoconstriction of microvessels (Nyugen, 2000). Another theory states that men have a higher density of adrenergic receptors in the membrane of cardiomyocytes compared with women, which may result in improved protection against a severe catecholamine surge. Evolutionary evidence suggests that men were exposed to more physical stress then women and, thus, might have developed several mechanisms to cope with the negative effects of stressors (Stollberger, 2011).

Pathophysiology

Several theories exist regarding the pathophysiology and what happens to the heart during takotsubo cardiomyopathy. The accepted hypothesis for onset of takotsubo syndrome is an overload with stress hormones (catecholamines). Stressful events trigger the release of huge amounts of epinephrine, norepinephrine and dopamine, resulting in takotsubo syndrome

(Sinning, 2003). Patients with takotsubo cardiomyopathy have higher catecholamine levels than do patients with myocardial infarction (Wittstein, 2005). Several studies suggest that high concentrations of catecholamines result in myocardial toxicity, causing direct injury to the cardiac cells (Purgason, 2006). Catecholamines at low concentrations are considered to be beneficial in regulating heart function by exerting a positive inotropic effect; however, at high concentrations, they produce deleterious actions seriously damaging the myocardium after chronic exposure (Adameova, 2008). This direct toxin to myocardial cells is supported by histologic findings from animal studies and autopsy findings from takotsubo patients who document myofibrillar degeneration, contraction band necrosis, and leukocyte infiltration (all signs of damaged heart cells) (Uyeama, 2004). Catecholamine activity is not uniformly distributed in the heart muscle. The effect of catecholaminerigic stimulation may be emphasized in the apical region which favors myocardial hypoxia in the apex (Koch, 2013). This lack of oxygen then may cause hypoxia and ventricular wall dyskinesia. The left ventricular apex is predominantly affected since this is an area of distal coronary vascularization. Several anatomic and physiologic factors might contribute to left ventricle apical wall motion abnormalities: 1) the left ventricle apex does not have a three-layered myocardial structure; 2) the easy loss of elasticity of the LV apex after excessive expansion; 3) the fact that the LV apex the border zone (locus minoris) of the perfusion area of major coronary arteries; and 4) the delay of functional recovery from global dysfunction (Tsuchihashi, 2001). In essence, too much stimulation of the sympathetic nervous system results in a drastic release of catecholamines, leading to a stunned myocardium (Purgason, 2006). More direct evidence for the role of catecholamines in disease pathogenesis was obtained from animal studies which have shown that iatrogenic administration

of catecholamines or stress immobilization can lead to reversible left ventricular apical ballooning (Uyeama, 2004).

The common underlying psychological factor is stress with activation of the HPA-axis and hypercortisolemia (Koch, 2003). The hypothalamic pituitary, adrenal axis (HPA-axis) is the central stress response system. Various stressful stimuli are known to activate the sympathetic nervous system to release catecholamines and the HPA axis to release glucocorticoids into circulation. Although initial actions of both catecholamines and gloucocorticoids are beneficial for the function of the cardiovascular system, their delayed effects on the heart are deleterious. (Adameova, 2001). Emotional stress can precipitate severe, reversible left ventricular dysfunction in patients without coronary artery disease. Exaggerated sympathetic stimulation is probably central to the cause of this syndrome (Wittstein, 2005).

Reversible ventricular dysfunction might result from epicardial coronary artery spasm and consequently, regionally stunned myocardium (Sato, 1990). However, in a systematic review, a multivessel spasm was found in only 1.4% of patients administered with epinephrine, making this hypothesis unlikely to explain the pathogenesis of takotsubo syndrome (Akashi, 2008). Multivessel epicardial spasm and regionally stunned myocardium would not explain the discrepancy between severe apical ventricular dysfunction and only slightly increased levels of cardiac enzymes (Akashi, 2008). Neither spontaneous or inducible coronary arterial spasm have been found in most cases of takotsubo cardiomyopathy (Deshmukh et al, 2012). Accordingly, myocardial stunning resulting from epicardial coronary artery spasm does not seem to cause takotsubo cardiomyopathy.

Several studies have shown that during takotsubo syndrome, patients develop an impaired microvascular function as resembled by reduced coronary flow reserve in echocardiography

measurement (Sinning, 2010). Because abnormal left ventricular wall motion occurs in a relatively large area of the apical myocardium in patients with takotsubo cardiomyopathy, and because the abnormalities are dynamic rather than fixed, disturbances in the coronary microcirculation may occur (Akashi, 2008). Elesber et al demonstrated the presence of microvascular dysfunction in a significant proportion of patients and noted a correlation between microvascular dysfunction and the severity of myonecrosis and EKG abnormalities. The possibility remains that the microcirculatory abnormalities result from increased mechanical wall stress as a consequence of apical ballooning (Elesber, 2007). In summary, the available pathophysiological information from several studies, indicates that the apical ballooning characterizing takotsubo cardiomyopathy reflects toxic high local concentrations of catecholamines, not coronary artery or microvascular disease (Akashi, 2008).

In recent reports, patients suffering from takotsubo syndrome often had a malign disease manifesting itself in the following time frame (Sinning, 2010). Patients with cancers such as lung, liver, esophageal, and uterine have all been reported as developing takotsubo cardiomyopathy in the later stages if the disease. Screening patients for malign diseases and motivating for preventative tests should, therefore, be mandatory, although a proof of takotsubo syndrome as paraneoplastic disease is still lacking (Burgdorf, 2010).

Diagnosis

Several diagnostic tests can be performed in order to better diagnose takotsubo cardiomyopathy including a measurement of catecholamine and cardiac enzyme levels, cardiac MRI, cardiac catherization, echocardiography, and myocardial biopsy, as well as EKG.

Cardiac Enzymes

During initial presentation to the hospital, most of the patients have mildly elevated biomarkers of myocardial necrosis such as troponin, creatine kinase and creatine kinase-MB (Sinning, 2010). Despite severe symptoms or transient wall motion abnormailities seen on echocardiography, some patients may present with normal concentrations of the cardiac enzymes (Abe, 2004). Hemodynamic biomarkers, especially B-type natriuretic peptide (BNP) and its more stable variant Nt-pro BNP, are important to monitor the severity and the clinical course of patients with tako-tsubo syndrome and the concentration at admission is an important indicator for complications during the hospital stay (Akashi, 2003). The secretion pattern of BNP in takotsubo patients is quite similar to that in myocardial infacrtion patients (Nef, 2007). Patients with a high BNP or Nt-pro BNP concentration are more likely to have an adverse outcome reflecting the fact of diminished ejection fraction and hemodynamic impairment. Declining BNP concentration on the other hand might be a valuable marker showing the improvement over time. (Simon, 2005).

Cardiac MRI

Though not included in the current AHA diagnostic criteria, magnetic resonance imaging (MRI) is increasingly being used in patients with suspected takotsubo cardiomyopathy. Several patients with takotsubo cardiomyopathy have been evaluated by cardiac MRI to assess subendocardial necrosis with delayed contrast enhancement techniques (Akashi, 2008). Cine MR imaging precisely delineates dyskinesia or hypokinesia of involved myocardial segments and offers precise assessment of functional recovery during follow-up (Sinning, 2010). Delayed enhancement imaging primarily using T2-weighted sequences visualizes areas of irreversible

myocardial injury in several instances such as myocardial infarction or myocarditis, which are often lacking in patients with takotsubo cardiomyopathy (Gerbaud, 2008). Both MRI and histopathological findings can differentiate patients with takotsubo cardiomyopathy from those with acute myocardial infarction resulting from coronary artery occlusion (Akashi, 2008). MRI is increasingly used as a diagnostic tool in patients with suspected takotsubo cardiomyopathy.

Cardiac Catherization/Coronary Angiography

Although left ventricular dysfunction is transient and there is no evidence of obstructive epicardial coronary disease, an increasing number of angioplasty procedures have been performed for presumed acute coronary syndromes (Akashi, 2008). Coronary angiogram shows left main stem, left anterior descending, left circumflex, and right coronary artery patent with no evidence of spasm or atherosclerosis (Prasad, 2007). Left ventriculography demonstrated characteristic apical ballooning and hypokinesia with good basal contractility. No evidence on angiogram was found of blockages in the coronary arteries, which is the most common cause of myocardial infarction. Patients diagnosed with takotsubo cardiomyopathy without the use of coronary angiography, have a higher in-hospital mortality compared to those diagnoses with the use of coronary angiography. This is possible due to false inclusion of ACS patients in the former group.

Most patients with Takotsubo cardiomyopathy have no coronary artery disease, however, concomitant coronary artery disease is not excluding takotsubo syndrome because the wall motion defects are often no located in the territory of a single coronary artery (Haghi, 2007).

Echocardiography

As an important diagnostic procedure, transthoracic echocardiography has to be performed to monitor the transient change in systolic function. Especially important is a close monitoring of the diminished wall motion (Sinning, 2010). During the acute phase, echocardiography reveals balloon-like left ventricular wall motion abnormalities at the apex with hypercontraction of the basal segment of the ventricle without pericardial effusion (Abe, 2003).

Myocardial Biopsy

Most patients with takotsubo cardiomyopathy who underwent myocardial biopsy have shown the same results: interstitial infiltrates consisting primarily of mononuclear lymphocytes, leukocytes, and macrophages; myocardial fibrosis; and contraction bands with or without overt myocyte necrosis (Akashi, 2008). This type of change is often related to high catecholamine plasma concentrations responsible for interference with sodium and calcium transporters possibly resulting in myocyte dysfunction (Wittstein, 2003). These findings probably reflect consequences of high intra cellular concentrations of Ca^{2+}, and it has been proposed that Ca2+ overload in myocardial cells produces the ventricular dysfunction in catecholamine cardiotoxicity (Lyon, 2008). In cases where identification of the causal relationship of the decreased wall motion is not detectable, biopsies should be taken to search for phenotypes of myocarditis or to verify the typical morphology of contraction band necrosis as a result of the hypothesized overload with stress hormones (Nef, 2008).

Electrocardiogram (EKG)

The EKG findings in takotsubo cardiomyopathy (Figure 4) include ST-elevation in precordial leads, subsequent T-wave inversion, as well as Q-wave formation. These changes normalize in a timeframe of hours (Sinning, 2010). The reported EKG changes in patients with takotsubo cardiomyopathy such as ST-elevation and T-wave inversion are often seen in myocardial infarction, making these findings insufficient to differentiate between acute anterior myocardial infarction and takotsubo cardiomyopathy (Bybee, 2007). The EKG would not be a useful tool early on to distinguish a definite diagnosis between BHS and AMI. The ST segment is elevated in both groups, however, the T-wave inversion is deeper and the QT-interval is more prolonged in stress-induced cardiomyopathy (Kurisu, 2004). The clinical changes and EKG alterations resemble the same characteristics as in acute coronary syndrome, however, the coronary arteries often show no impaired blood flow or only marginal changes (Sinning et al, 2010).

Currently, takotsubo cardiomyopathy is classified as an acquired cardiomyopathy according to the American Heart Association Guidelines. In 2008, Bybee and colleagues proposed an algorithm consisting of four separate criteria in order to better diagnose the syndrome. The Mayo Clinic Criteria includes: 1) transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger; 2) the absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture; 3) new EKG changes (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and 4) absence of pheochromocytoma and myocarditis (Prasad, 2008). Patients with several other conditions such as subarachnoid

hemorrhage, head trauma or bleed, and cocaine abuse may also show regional contractile abnormalities, and must also be ruled out. High plasma concentrations of catecholamines in patients with pheochromocytoma are well known to introduce reversible cardiomyopathy (Lyon, 2008). It has been mentioned that substantial number of patients with typical takotsubo cardiomyopathy characteristics may be excluded because they do not fulfill the existing criteria.

Treatment

Establishing a uniform therapy for takotsubo cardiomyopathy is a difficult task, as patients have to be diagnosed with the syndrome first. Once the patient is diagnosed with stress cardiomyopathy, management follows guidelines established for ACS and standard supportive care for heart failure (Purgason, 2006). There are no specific treatments for left ventricular failure characterizing takotsubo cardiomyopathy because cardiac function is usually normalized within a few weeks. Clinicians usually recommend standard heart failure medications such as beta blockers, ACE inhibitors, and diuretics. Beta blockers should reduce sympathetic tone and are also used for maintenance treatment, but use of beta blockers in the acute phase of Broken Heart syndrome are still under debate. ACE-I are indicated according to left ventricular dysfunction and may be supplemented by aldosterone antagonists later on (Koch, 2013). Although there is little evidence on long-term therapy, beta blockers may be continued indefinitely to help prevent recurrence by reducing the effects of adrenaline and other stress hormones. (Prasad, 2007). There is currently no research stating how long these patients need to remain on medications after resolution. There seems to be a difference of opinions regarding platelet aggregation inhibitors and, if necessary, anticoagulation. Pilgrim et al. suggest therapeutic anticoagulation should always be considered, as thrombus formation can develop due

to contraction abnormalities. During the time the contraction abnormality lasts, therapeutic use of heparin and aspirin may be of benefit (Pilgrim, 2008). However, because apical ballooning increases the risk of cardiac rupture, Akashi et al believe it is still controversial whether treatment with aspirin or heparin is indicated (Akashi, 2008).

Inotropic agents such as digoxin and dobutamine should not be administered due to the integral mechanism of epinephrine in patients with takotsubo cardiomyopathy (Sinning, 2010). Implantation of an intra-aortic balloon pump to avoid administration of inotropic agents could be a proper initial treatment. The genetic basis and the resulting changes to protein biosynthesis is a promising target for further research and could result in the description of therapeutic targets (Sinning, 2010).

Because estrogen treatment is beneficial in preventing the animal model of takotsubo cardiomyopathy, such treatment might be considered in elderly women who have suffered an episode of takotsubo cardiomyopathy. Clinical trials and future research still need to be performed in this area.

Broken heart syndrome needs an interdisciplinary approach, combining treatment of heart failure and psychiatric disorder. First patients should be treated as having a myocardial infarction until the opposite, namely takotsubo, is proven in order to avoid tissue damage. (Koch, 2013). There is no doubt that psychotherapeutic approaches based on stress and coping models must be involved in treatment and care of those patients who lack sufficient resilience to cope with life events. Psychotherapeutic interventions are important, as functional coping strategies have demonstrated to improve cardiovascular rehabilitation and the immune system in patients with stress-induced disorders (Koch, 2013). When a psychosomatic disease occurs such as heart disease caused by stress, a maladaptive coping strategy is usually involved. The patient did not

have the resources or knowledge of various coping strategies, and was not able to modify their way of thinking in time in order to deal with the problem. Learning suitable skills to solve the underlying conflict would be crucial in preventing broken heart syndrome (Koch, 2013).

Prognosis

Despite the initial severity of takotsubo cardiomyopathy, the overall prognosis is generally impressive, with a complete regression of the contraction abnormality often resolved with 6-8 weeks. Patients with stress cardiomyopathy follow a similar recovery to patients who suffer an AMI and are usually discharged within a week (Purgason, 2006). However, in the first 30 days and during hospital admission, mortality is reported at 9-10%, similar to patients suffering from myocardial infarction (Sinning, 2010). In long-term follow up, the recurrence rate of takotsubo syndrome is 11.4% (Elesber, 2007).

Complications

Possible complications of takotsubo cardiomyopathy include left heart failure, cardiogenic shock, ventricular arrhythmias, left ventricular thrombosis formation, left ventricular wall rupture, conduction abnormalities including heart blocks, and atrial fibrillation (Purgason, 2006). Heart failure, with or without pulmonary edema, is the most common clinical complication (Akashi, 2008). Despite the life-threatening complications during the acute phase, a complete regression of the contraction abnormality is often reported. (Sinning, 2010). Most of the abnormalities in systolic function and ventricle wall movement clear up in one to four weeks, and most patients recover fully within two months (Prasad, 2007). Death is rare, but heart failure occurs in about 20% of patients. Complications during the course of takotsubo syndrome are not

scare and takotsubo syndrome is not a benign disease; pulmonary edema, life-threatening arrhythmias, and cardiogenic shock are not uncommon and have to be treated (Sinning, 2010).

A complication reported with an especially adverse outcome is RIGHT ventricular involvement during takotsubo syndrome. Despite sporadic reports on right ventricular involvement, research to date has mainly focused on left ventricular pathology. In a study of 25 patients done by Elesber et al, right ventricular dysfunction was present in eight patients and was associated with lower ejection fractions, longer hospitalizations, and more complications such as severe congestive heart failure, use of intra-aortic balloon pumps, and need for cardiopulmonary resuscitation (Haghi, 2006). Observation of these patients shown the majority also having pleural effusions. Attributing to the lack of evidence regarding right ventricular involvement in takotsubo cardiomyopathy, is the difficulties in echocardiographic assessment of right ventricular morphology, and the often impressive left ventricular dysfunction associated with the syndrome.

Psychological Aspect

Broken heart syndrome is characterized by onset of symptoms mimicking coronary artery disease and is commonly linked with experience of significant stress (Wittstein, 2005). Patients with this syndrome report a stressful life event occurring within hours of presentation. Almost as a rule, intense emotional stress precedes the acute disorder, which leads to acute adjustment disorder with anxious-depressive syndromes or every now and then panic-like attacks with hyperventilation (Koch,2013). Psychiatric disease, particularly depression and stress disorders, worsen the outcome of cardiovascular disease substantially (Koch, 2013). Broken heart syndrome is a recently recognized condition that is also proposed to be associated with

psychiatric illness. However, findings suggest that the clinical assessment of psychiatric risk factors is unlikely to assist identification of patients at increased risk of stress cardiomyopathy (Lacey, 2014). Factors included: lifetime history of depression, lifetime history of any anxiety disorder, lifetime history of any mental disorder, past experience of trauma, and history of mental disorder in first degree relatives. A study by Lacey et al, found that of ten psychiatric risk factors examined, only neuroticism significantly differed between participants with broken heart syndrome and healthy volunteers and that there was no association between previous psychiatric illness and development of broken heart syndrome. (Lacey, 2013). Clinical assessment of psychiatric risk factors may not identify patients at increased risk of broken heart syndrome (Lacey, et a 2014).

Discussion

Many similarities and differences exist between acute myocardial infarction and takotsubo cardiomyopathy. Both conditions present with many of the same symptoms including chest pain, shortness of breath, nausea, vomiting, and diaphoresis. Epigastric discomfort and pain radiating to the jaw are unique to myocardial infarction, while a severe emotional trigger is almost always seen with takotsubo cardiomyopathy. Association with a stressful event might suggest the diagnosis of takotsubo cardiomyopathy, but it is not sufficient to differentiate from ACS. Similar studies and tests are used to diagnose both acute myocardial infarction and takotsubo cardiomyopathy, with each condition having its own findings. Cardiac enzymes such as troponin, myoglobin, and CK-MB all rise with myocardial infarction, while these levels are only slightly elevated with takotsubo cardiomyopathy. EKG changes related to both myocardial infarction and takotsubo cardiomyopathy include ST-elevation or depression, T-wave changes, and the presence of Q-waves. While these changes will normalize much more quickly (hours vs. days) with takotsubo cardiomyopathy, the diagnose between acute MI and takotsubo cardiomyopathy cannot be made with EKG. Echocardiography helps to localize and define the extent of myocardial infarction, as well as visualize any wall motion abnormalities. The classic pattern seen with takotsubo cardiomyopathy of hypokinesis, akinesis or dyskinesis of the apical and mid-ventricular segments, extending beyond a single epicardial coronary distribution, is perhaps one of the most helpful diagnostic features distinguishing between takotsubo cardiomyopathy and acute MI (Thygessen, 2007). Cardiac MRI visualizes areas of irreversible myocardial injury in several instances such as myocardial infarction or myocarditis, which are often lacking in patients with takotsubo cardiomyopathy. One of the most defining diagnostic tools used to differentiate the two conditions is the cardiac catherization or angiogram. In most

cases of takotsubo cardiomyopathy, no evidence on angiogram is found of blockages in the coronary arteries, which is the most common cause of myocardial infarction.

Treatment for both conditions is also comparable including the use of beta-blockers, ACE-inhibitors, ARB's, and diuretics. Morphine, nitroglycerin, and supplemental oxygen with the addition of statins, anti-platelets, and anticoagulants fare used in the treatment of myocardial infarction. The role of aspirin, anti-platelets, and anticoagulants are controversial in treating takotsubo cardiomyopathy. Reperfusion is the key in successful outcomes of myocardial infarction. Complications of both myocardial infarction and takotsubo cardiomyopathy include heart failure, cardiogenic shock, mitral valve dysfunction, aneurysms, life-threatening arrhythmias, atrial fibrillation, and pericarditis. Complications are more often seen with acute myocardial infarction ad are often more severe. than takotubo cardiomyopathy. Mortality is increased dramatically with acute myocardial infarction, often having a much worse prognosis than takotsubo cardiomyopathy.

Major differences exist regarding the pathophysiology of each condition. Wittstein and colleagues in 2005 studied 19 patients mostly women (95%) with a median age of 63 years, with stress cardiomyopathy to demonstrate features that differentiate this from acute myocardial infarction and to determine its cause. Although initially indistinguishable from an acute coronary syndrome, some characteristics of broken heart syndrome, such as the involvement of a myocardial area that extends beyond a single coronary vessel territory and that completely and rapidly recovers in a few days or weeks, together with the slight elevation in serum cardiac enzyme levels, make broken heart syndrome a unique model of transient and completely reversible myocardial dysfunction, in the absence of significant epicardial coronary artery disease (Galuti, 2010). The clinical changes and EKG alterations resemble the same

characteristics like in acute coronary syndrome; however, the coronary arteries often show no impaired blood flow or only marginal changes (Sinning, 2010). The inflammatory changes and contraction bands distinguish takotsubo cardiomyopathy from coagulation necrosis, as seen in myocardial infarction resulting from coronary artery occlusion (Akashi, 2008).

Currently, there are no universally accepted diagnostic guidelines used in the treatment of takotsubo cardiomyopathy. The Mayo Clinic diagnostic criteria were originally proposed in 2004 and subsequently modified in 2008, and are the most widely used in clinical practice and research. In the absence of a single diagnostic test, the Mayo Clinic diagnostic criteria seek to succinctly incorporate the key features that help to differentiate takotsubo cardiomyopathy from its main differentials, namely ACS, myocarditis, and pheochromocyoma (Scantlebury, 2014). Figure 5 provides a summary of the proposed criteria and features that are and are not shared with the Mayo Clinic Criteria. The underlying principle shared by all diagnostic criteria is the absence of a coronary lesion that could account for wall motion abnormality (Scantelbury, 2014). Currently, takotsubo cardiomyopathy is a diagnosis of exclusion, and there is much need for a diagnostic pathway that can be used when patients present with signs and symptoms of takotsubo cardiomyopathy. Figure 6 illustrates a proposed diagnostic pathway that may help in differentiating the two conditions.

Conclusion

The diagnosis of takotsubo cardiomyopathy or acute myocardial infarction can almost be impossible to make at times. Presenting with many of the similar symptoms, using many of the same diagnostic tests and tools, and having only minimal differences, the two conditions offer a challenge for healthcare providers, including physician assistants. By possibly being the first contact patients may have, physician assistants, especially those working in the emergency setting, have a unique role in the treatment of these patients. Future research is needed to better understand takotsubo cardiomyopathy, but progress is being made. Recently, more forms or takotsubo cardiomyopathy have been identified including, a left ventricular apical ballooning variant (classic takotsubo), an inverted or reverse takotsubo variant, or a mid-ventricular takotsubo variant (Litvinov, 2009). The University Medical Center Mainz (Germany) is currently conducting a study recruiting patients with a history of takotsubo syndrome to investigate causes, phenotype, and especially the genetic background underlying the disease (Sinning, 2010). Takotsubo cardiomyopathy is rising in incidence and makes up a relevant part of patients with acute coronary syndrome, increasing its awareness will help clinicians to better understand, diagnose, and manage this condition.

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Figures

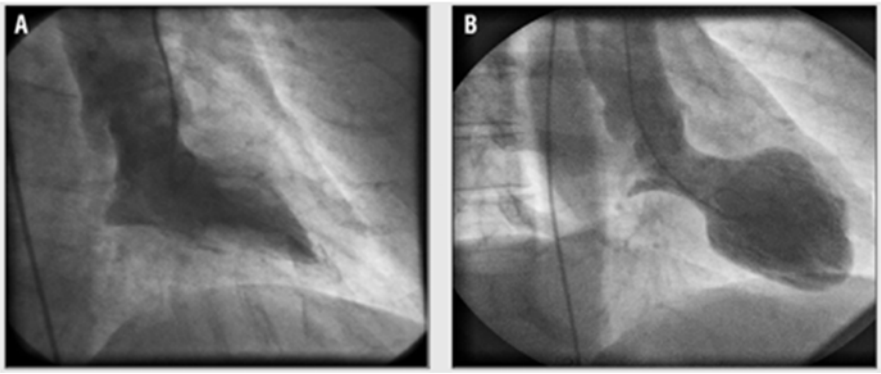

Figure 1: (A) Angiogram of normal left ventricle in systole shows contraction of all myocardial segments. (B) Angiogram of left ventricle with takotsubo defect shows contraction of the base with akinesis of the apex. (Derrick, 2009)

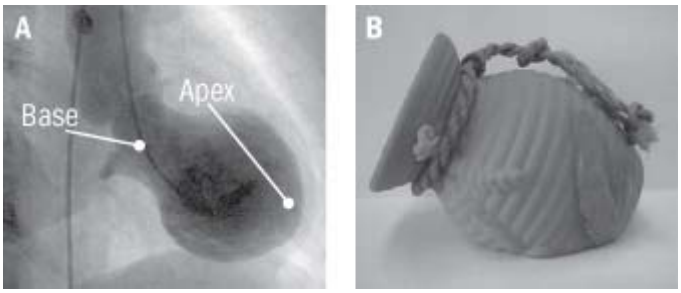

Figure 2: (A) X-ray of left ventricle showing apical ballooning (B) a Japanese pot used to trap octopus (Prasad, 2007)

CLINICAL CLASSIFICATION OF DIFFERENT TYPES OF MYOCARDIAL INFARCTION
Type 1: Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2: Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension or hypotension
Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumable new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers
Type 4a: Myocardial infarction associated with PCI
Type 4b: Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5: Myocardial infarction associated with CABG

Figure 3: Clinical Classification of Myocardial Infarction (Thygesen, 2007)

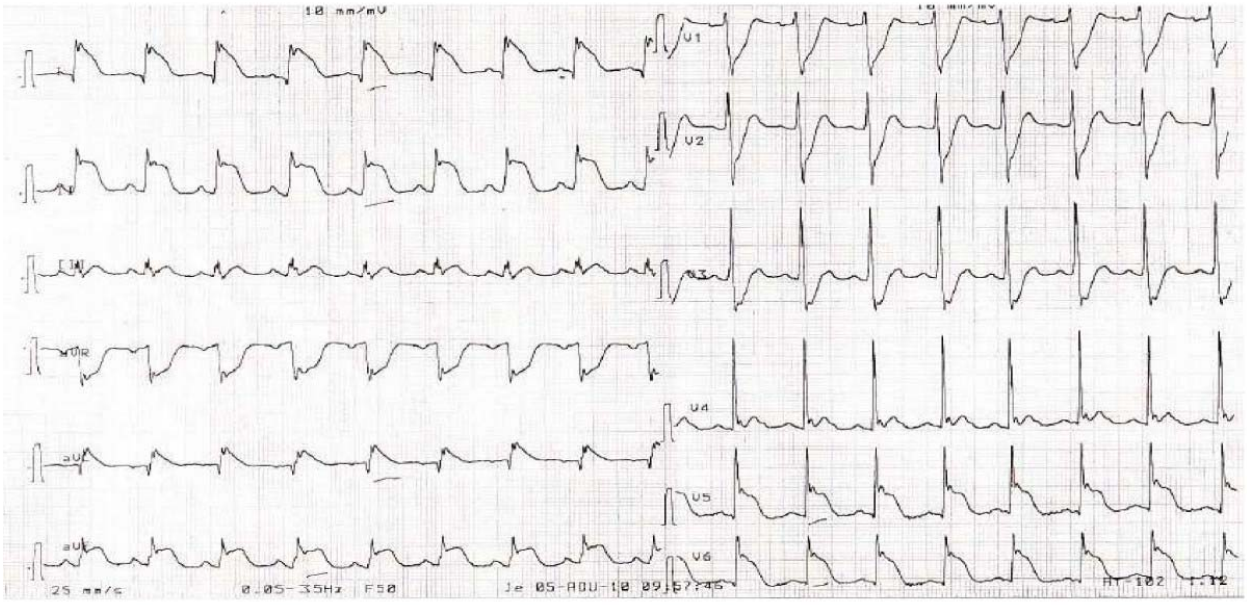

Figure 4: Takotsubo cardiomyopathy seen on EKG in a 62-year-old woman following the death of a family member (Richard, 2011)

Diagnostic criteria	Initial Mayo Clinic (2004)[21]	Revised Mayo Clinic (2008)[20]	Japanese (2007)[75]
Morphology			
Left ventricular wall motion abnormalities…	m	m	x
…extending beyond a single epicardial vascular distribution	m	m	x
Involvement of apical and mid-ventricular segments (classic apical ballooning pattern)	m	o	m
Mid-ventricular segments (with or without apical involvement)	x	o	x
Inclusion of right ventricular wall motion abnormalities	x	x	o
Dynamic outflow tract obstruction	x	x	o
Time course			
'Transient'	m	m	x
(Near) Complete recovery within days to weeks	x	x	m
Evidence of ischemia/myonecrosis	x	m	x
New and dynamic ST-segment deviation, T-wave inversion or left BBB	m	o	x
Typical evolution of ECG changes (see text) including QT prolongation	x	x	o
'Mild' or 'modest' increase in cardiac biomarkers	x	o	o
Exclusions			
Potential coronary culprit (eg, stenosis, evidence of plaque rupture, dissection, thrombosis or spasm)	m	m	m
Myocarditis	m	m	m
Pheochromocytoma	m	m	m
Cerebrovascular disease	m	x	m
Hypertrophic cardiomyopathy	m	x	x
Other pathological conditions that may explain regional dysfunction	x	x	m
Other features			
Symptoms similar to that of ACS	x	x	o
Elderly patient	x	x	o
Postmenopausal woman	x	x	o
Antecedent stressful event	x	o	o
Comorbidity with variety of illnesses	x	x	x
Normal or near normal filling pressures	x	x	x
Abnormal myocardial scintigraphy	x	x	o

m, mandatory; o, optional; x, no mention or not explicitly stated. Other abbreviations as in Tables 1,2.
*The John's Hopkins criteria did not specify left ventricle for the first criterion.

(Table 3 continued the next page.)

Figure 5: Proposed Diagnostic Criteria of Takotsubo cardiomyopathy (Scantlebury, 2016)

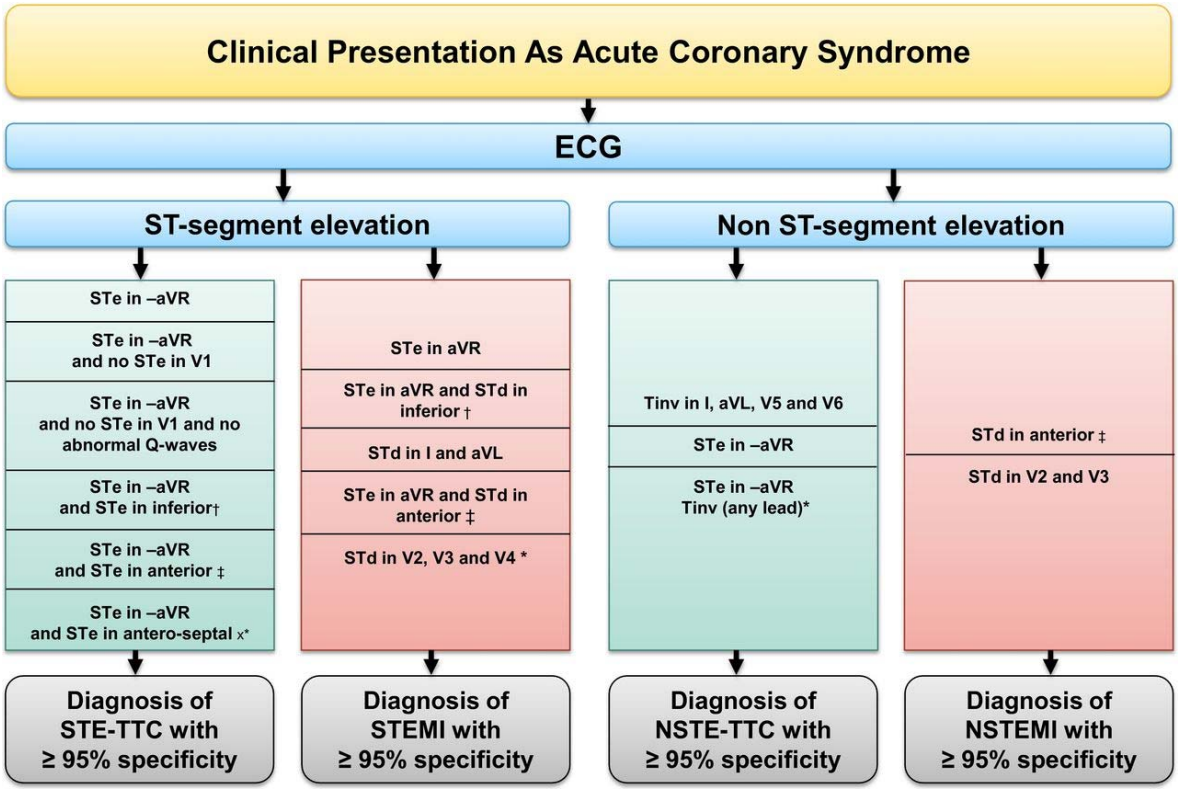

Figure 6: Proposed Diagnostic Pathway: Takotsubo vs. AMI (Franghei et al., 2016)

Abstract

Objective: To highlight key clinical and diagnostic features health professionals, including physician assistants, can use to better differentiate takotsubo cardiomyopathy from acute myocardial infarction. Increasing the awareness of takotsubo cardiomyopathy as a defined American Heart Association acquired cardiomyopathy that should be considered in any patient presenting with acute coronary syndrome symptoms.

Methods: Articles were searched using MEDLINE, PubMed, Google Scholar, EBSCO, and JSTOR databases.

Results: A total of 51 articles were found including original research, systematic reviews, clinical case studies, literature reviews, as well as clinical trials. Articles were limited to the years 2000-2016 and written in English.

Conclusion: Key diagnostic features differentiating takotsubo cardiomyopathy from acute myocardial infarction include specific EKG changes, extent of cardiac biomarker elevations, significant echocardiography findings, and the presence or absence of coronary artery damage. An emotional trigger is almost always found with takotsubo cardiomyopathy. Complications and prognosis are generally better with takotsubo cardiomyopathy.