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Laboratory Aspects of Broken Heart Syndrome

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ABSTRACT

Broken Heart Syndrome (BHS) is the weakness of the heart muscle due to emotional stress or physical stress, called cardiomyopathy. The main etiology is a sudden release of stress hormones (catecholamines), such as norepinephrine, epinephrine, and dopamine. About 90% of BHS patients are females with an average age of 67-70 years, and most of them are post-menopausal females. The most widely supported pathological theories are catecholamine-induced cardiotoxicity and microvascular dysfunction. The clinical condition resembles acute myocardial infarction, consisting of chest pain, electrocardiographic changes, elevated cardiac biomarkers, and heart wall motion abnormalities. There is transient systolic dysfunction in the apical and/or middle segment of the left ventricle resembling acute myocardial infarction but an absence of coronary artery obstructive disease. There are BHS criteria according to Mayo Clinic. Laboratory tests can be performed by examining Natriuretic Peptides, cardio myonecrosis markers (Troponin I and T, creatinine kinase, and myoglobin), and catecholamines. There is no single established biomarker for initial diagnosis of BHS that distinguishes it from STEMI. It was found that the most accurate ratio as a marker capable of differentiating BHS from STEMI in early stages was NT-proBNP/TnI ratio. The InterTAK diagnostic score was used to predict the probability of BHS, differentiating it from ACS in an acute stage, prior to coronary angiography. The main differential diagnosis of BHS is ACS, besides acute myocarditis infectious. Patients with BHS should be treated as ACS until proven otherwise. The prognosis for BHS patients is generally very good.

Keywords: Broken heart syndrome, catecholamine-induced cardiotoxicity

INTRODUCTION

Broken Heart Syndrome (BHS) is the rapid and severe weakness of the cardiac muscles due to intense emotional or physical stress, called cardiomyopathy, that often causes acute heart failure, deadly ventricular arrhythmia, and ventricular rupture. Broken Heart Syndrome is also known as stress cardiomyopathy, stress-induced cardiomyopathy, takotsubo cardiomyopathy, reversible left ventricular dysfunction, Apical Ballooning Cardiomyopathy or Apical Ballooning Syndrome (ABS), or neurogenic myocardial stunning. In 1998, a left ventriculogram in the Circulation journal caught the attention of many doctors due to the term "Broken heart" given by the author.[1-3]

Broken heart syndrome has received global acceptance as a unique cardiovascular disease that resembles acute myocardial infarction, there is transient wall motion abnormality of the left ventricular apex accompanied by emotional or physical stress that usually fully recovers. Systolic dysfunction is temporary at the apical segment, and/or the middle segment of the left ventricle that resembles acute myocardial infarction but without the presence of obstructive coronary artery disease. An image similar to a traditional Japanese octopus fishing rod (Takotsubo) on the echocardiogram or left ventriculogram of a patient with BHS (Figure 1).[2,4]

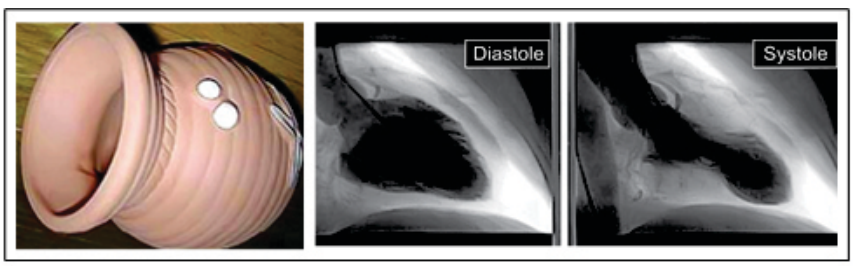


Figure 1. Takutsubo. The left ventriculogram of a patient with BHS shows apical dyskinesis (ballooning)[5]

EPIDEMIOLOGY AND ETIOPATHOGENESIS

Based on the literature, about 90% of BHS patients are females in the 67–70 years old age range. Most BHS cases are experienced by a post-menopausal female. Females over 55 years old have 5x the risk of suffering from BHS compared to females under 55 years old, and 10x the risk compared to males. BHS has been found in children, with the youngest patient being a premature neonate that was born in the 28th week of pregnancy.[4,6]

Broken heart syndrome starts with a triggering factor such as stress in 70% of patients, being either severe physical or emotional stress. Ten percent of the emotional stress can be caused by excessive happiness causing happy heart syndrome type BHS.

The latest studies show that physical and mental pressure due to social economic conditions during the COVID-19 pandemic caused a lot of people to suffer from BHS. The increase in BHS is due to psychological, social, and economic pressure caused by the pandemic, such as isolation, lack of interaction, keeping distance, and economic factors that are aggravating human life.[6-9]

The exact etiology of this syndrome is unknown, but the most plausible cause is the sudden release of stress hormones, such as norepinephrine, epinephrine, and dopamine, causing cardiac stunning. Stunning the heart triggers changes in the cardiac myocytes and coronary perfusion (catecholamine-induced cardiotoxicity and microvascular dysfunction).[7]

DIAGNOSIS

Patients with BHS have clinical conditions that resemble acute myocardial infarction, consisting of chest pain, electrocardiographic changes, an increase in cardiac biomarkers, and abnormalities of heart wall motion. Clinical symptoms of BHS are almost indistinguishable from the acute coronary syndrome. Chest pain is sometimes accompanied by dyspnea, palpitation, diaphoresis, nausea, or syncope. Broken heart syndrome criteria according to Mayo Clinic (modified in 2008), are temporary hypokinesis, akinesis, and dyskinesis in the left ventricular mid-segments, with or without the involvement of the heart apex; wall motion abnormalities that spread through the blood vessels distributed to the epicardium; the presence of a trigger (often but not always) usually in the form of stress; There is no presence of coronary arterial obstructive disease or proof of angiograph that shows acute plaque rupture; ECG abnormality in the form of a recent ST elevation and/or T wave inversion. A moderate increase of serum cardiac troponin; Is not accompanied by phaeochromocytoma or myocarditis, significant head injury, intracranial bleeding, or other causes of myocardial dysfunction.[10,11]

Various examinations can be used according to indications and if the facilities are available, such as laboratory examinations, electrocardiography, echocardiography, heart catheterization, nuclear imaging, Magnetic Resonance Imaging (MRI), and histological examinations. Laboratory examinations that can be done to diagnose BHS are Natriuretic Peptides (NP), cardio myonecrosis marker (Troponin I and T, creatinine kinase, and myoglobin), and catecholamine. Atrial Natriuretic Peptide (ANP), B-type Natriuretic Peptide (BNP), and C-type Natriuretic Peptide (CNP), N-terminal proBNP (NT-proBNP) are groups of natriuretic peptide. As a response to cardiac overload, ANP is synthesized by the atria, BNP is synthesized by the ventricle, and CNP is synthesized by the nervous and vascular endothelial tissues; Troponin T dan I are biomarkers of myocardial injury. CKMB is considered a marker for myocardial injury and is a sensitive and specific clinical marker for myocardial infarction. The measurement of CKMB is done through electrophoresis or immunoassay. CKMB is usually abnormal for 3–4 hours after myocardial infarction, peaks at 10–24 hours, and is normal in 72 hours; Catecholamine is a group of biogenic amines from tyramine/phenylalanine that contains a catechol core, is arranged from pyrocatechol molecules and the aliphatic part of amine, produced by activation of the sympathetic nervous system. It has an important physiological effect as a neurotransmitter in the central and peripheral nervous system and is also a hormone, such as epinephrine, adrenaline, norepinephrine, and L-dopa.[3,10]

The International Takotsubo Diagnostic Criteria (InterTAK) diagnostic score developed by the International Takotsubo Registry, can be considered in symptomatic patients without an ST-elevation. provides a model for doctors to assess the probable diagnosis of BHS, differentiating it from ACS in the acute stadium that can be easily used in the Emergency Room and does not require imaging modalities. Depending on the prevalence of the disease this means that patients with a score ≤ 70 points have a low/intermediate probability of having BHS and patients with a score > 70 points have a high probability of having BHS (Table 1).[4,12]

Table 1. InterTak diagnostic score[12]

Criteria	Points
Female	25
Emotional trigger	24
Physical trigger	13
Absence of ST-segment depression	12
Psychiatric disorders	11
Neurologic disorders	9
QTc prolongation	6

DIFFERENTIAL DIAGNOSIS

Acute coronary syndrome is the main differential diagnosis of BHS because both diseases have a significant overlapping clinical presentation. Acute myocarditis infection also a differential diagnosis of BHS. The differences of the three can be seen in Table 2.[13,14]

MANAGEMENT, THERAPY, AND PROGNOSIS

Patients with BHS should be treated as ACS until proven otherwise. Securing the airway, breathing, circulation, intravenous access, and giving supplemental oxygen, as well as cardiac monitoring should be prioritized. Tests in the emergency room should include electrocardiography, chest radiography, cardiac biomarkers, Brain Natriuretic Peptide (BNP) and other appropriate laboratory tests.[3]

The prognosis of patients with BHS are generally very good, with nearly 95% of patients making full recovery within 4-8 weeks. There are those who experience several fatal complications such as left ventricular wall rupture. Complications occur in 20% of BHS cases, especially in the early stages, namely left heart failure with and without pulmonary edema, cardiogenic shock, left ventricular outflow obstruction, mitral regurgitation, ventricular arrhythmias, left ventricular mural thrombus formation, left ventricular wall rupture, and death. Mortality ranges from 1%-3.2%. There are only a few recurrent cases of BHS. The mechanisms underlying the susceptibility of relapse are still not understood. It has been reported that the recurrence of BHS is 10%.[3,8]

DISCUSSION

It is interesting that 80% of BHS occurs in postmenopausal women. Estrogen exerts a protective effect on the cardiovascular system, including protective vasodilatory effects, protection against atherosclerosis and endothelial dysfunction, and protection of the myocardium, by downregulating beta-adrenergic receptors. Post-menopausal females who do not receive estrogen replacement therapy lose this protection and may be more susceptible to stress-related catecholamine spikes.[1,7]

BNP precursors (pro-BNP) are stored in secretory granules in ventricular myocytes, after being synthesized in the ventricles during cardiac muscle stretching, pro-BNP will be broken down by protease into 2 parts, namely the active form (BNP) and NT-proBNP (the more stable part). BNP and NT-pro BNP can be used as tools for early diagnosis (predictors) of ventricular dysfunction. In a healthy state, the concentrations of BNP and NT-proBNP are equal, but in patients with cardiomyopathy, the levels of NT-proBNP are 2-10 times higher than BNP. Elevated BNP and NT-proBNP occur in heart diseases such as heart failure, ACS, valvular heart disease, pericardial disease, atrial fibrillation, myocarditis, and cardioversion. In BHS, there is reversible left ventricular dysfunction without myocardial ischemia or necrosis, leading to an increase in NP. BNP is secreted into the circulation in response to increased distension and stretching of the heart wall. Changes in wall stretching and volume overload (overload) as well as ventricular remodeling stimulates BNP release as a marker of ventricular dysfunction. BNP has been correlated with the degree of basal hyperkinesis. NT-proBNP levels rise in the first 24 hours after the onset of symptoms with slow and

Table 2. Differential diagnosis of BHS[13,14]

	BHS	ACS	Acute Myocarditis Infection
Age	>50 y.o.	Any age	Young age
Gender	90% female	Male and female	Male and female
Trigger of emotional or physical stress	Yes	No	No
Pericardial effusion	(+)	(±)	(±)
Troponin	(+)	(+++)	(+)
NT-proBNP	(+++)	(+)	(+)
Coronary angiography	Normal	Obstruction (+)	Normal
Increased LED and CRP	(-)	(-)	(+)

incomplete resolution 3 months later. NT-proBNP levels have been shown to correlate with plasma catecholamine levels and the severity of left ventricular dysfunction. BNP and NT-proBNP can be increased 3-5 times (more than troponin) and are considered more useful diagnostic biomarkers for the diagnosis of BHS. The concentration of NT-proBNP is greater in TTC than in STEMI. Several studies observed circulating catecholamine levels in the acute phase and found that nearly 75% of BHS patients had markedly higher elevations than patients with STEMI.[3,10]

Currently, there is no single biomarker established for the initial diagnosis of BHS that differentiates it from STEMI. The following results are obtained for a patient with BHS: An increase of minimal serum CKMB; An increase of troponin I and/or T serum and plasma natriuretic peptide; Plasma catecholamine levels increase 2-3 times; may not increase either; An increase of serum NT-proBNP. A decrease of NT-proBNP shows a good prognosis as it can predict the worsening and recovery of cardiac muscles.[10]

In a study of 66 consecutive hospitalized patients with Takotsubo Cardiomyopathy (TTC) or BHS and 66 patients with STEMI, cardiac biomarkers were determined within 12 hours of admission and compared with demographic, clinical, and echocardiographic findings. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the higher diagnostic accuracy of the NT-proBNP/TnI ratio in differentiating patients in the TS and STEMI groups, compared to the ratio of NT-proBNP/CKMB mass and NT-proBNP levels alone. There is evidence that the following ratios are able to differentiate BHS from STEMI at an early stage, namely: NT-proBNP/TnI ratio and NT-proBNP/CKMB mass ratio. The most accurate marker was the NT-proBNP/TnI ratio (Table 3 and Figure 2).[3,10]

When pairwise comparisons were used, the ratios of NT-proBNP/TnI and NT-proBNP/CKMB mass differentiated TS from STEMI more accurately than when using NT-proBNP alone (Table 4).[10]

Table 3. Differentiating BHS from STEMI using AUC values for ROS analysis[10]

	AUC	95% CI	p-value
NT-proBNP	0.6635	0.5669-0.7600	0.0574
NT-proBNP/TnI	0.8755	0.8121-0.9389	0.0009
NT-proBNP/CKMB mass	0.8466	0.7746-0.9186	0.0002

AUC = Area Under the Curve ROC = Receiver Operating Characteristics

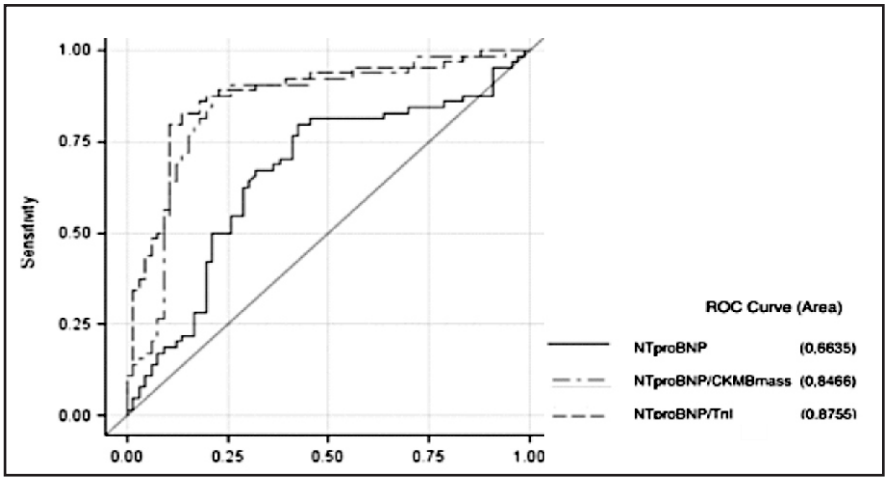
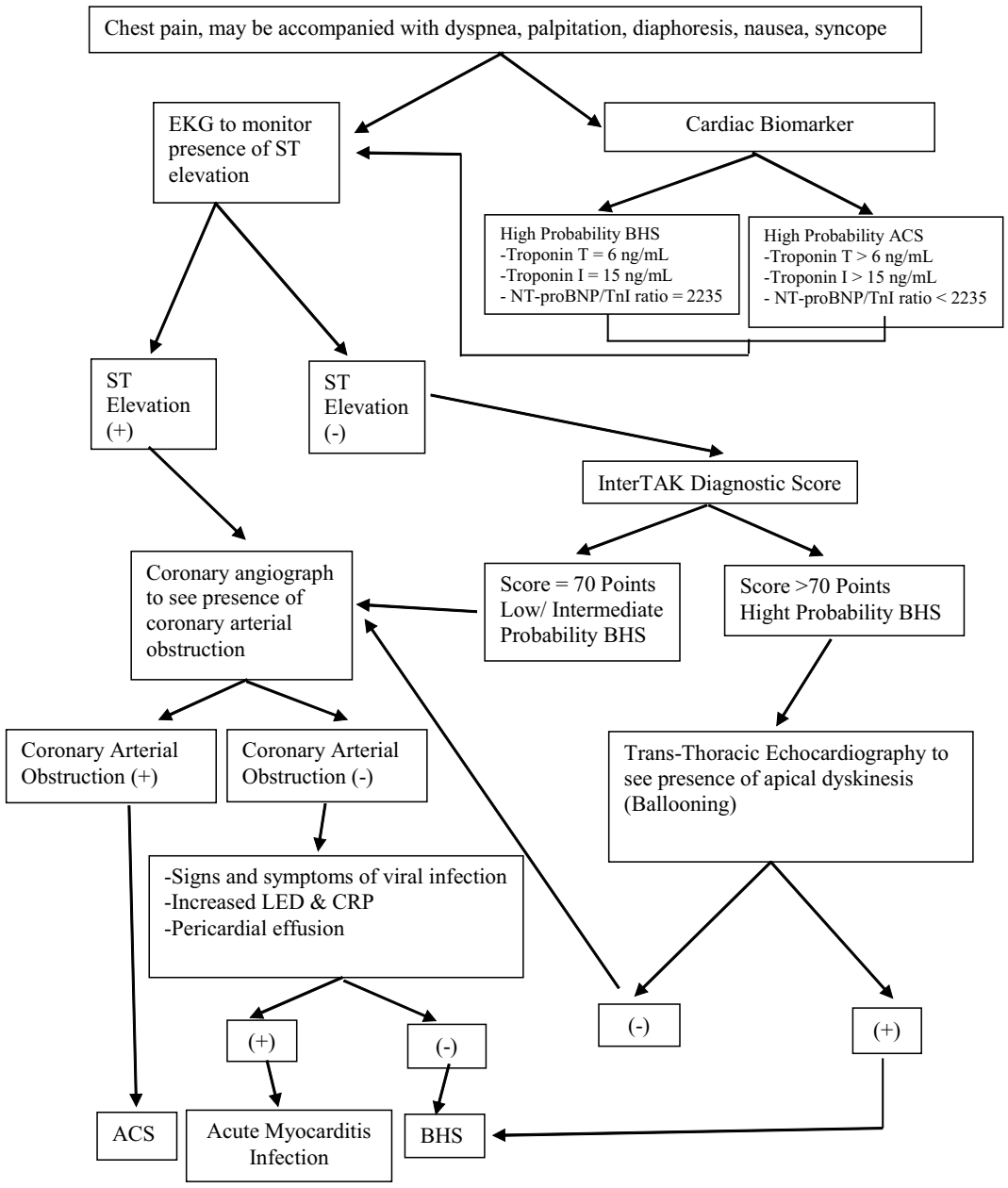


Figure 2. Comparisons of NT-proBNP, NT-proBNP/CKMB mass and NT-proBNP/TnI ROC curve[10]

Table 4. Differentiating BHS from STEMI using pairwise comparisons[10]

	Estimate	95% CI	p-value
NT-proBNP/TnI; NT-proBNP alone	0.2120	0.1323-0.2917	<0.001
NT-proBNP/CKMB mass; NT-proBNP alone	0.1831	0.1084-0.2578	<0.001

ALGORITHM*



***Algorithm Modification**

CONCLUSION

Broken heart syndrome is a rapid and severe weakness of the heart muscle due to intense emotional stress or physical stress, called cardiomyopathy. Most cases of BHS occur in postmenopausal women, due to the loss of the protective effect of estrogen and becoming more susceptible to stress-related catecholamine spikes.

The most widely supported theory of BHS pathogenicity is catecholamine-induced cardiotoxicity and microvascular dysfunction. The clinical presentation of BHS patients resembles AMI, consisting of chest pain, electrocardiographic changes, elevated cardiac biomarkers, and wall motion abnormalities. Coronary syndrome is the main differential diagnosis of BHS. Laboratory tests that can be performed on BHS are Natriuretic Peptides (NP) examination, cardio myonecrosis markers (Troponin I and T, CKMB), and catecholamines. No single biomarker for the initial diagnosis of BHS differentiates it from STEMI. The

most accurate marker capable of differentiating BHS from STEMI at an early stage is the NT-proBNP/TnI ratio. The InterTAK diagnostic score is used to differentiate BHS and ACS in the acute stage, where patients with a score > 70 points have a high probability of suffering from BHS. BHS patients have normal coronary angiography and intact coronary vessel walls on intravascular ultrasound, which differentiates them from ACS.

Broken heart syndrome patients should be treated as ACS until proven otherwise. Addressing the airway, breathing, circulation, intravenous access, administering supplemental oxygen, and cardiac monitoring should be prioritized. The prognosis for BHS patients is generally very good.

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