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RESEARCH ARTICLE

BROKEN HEART SYNDROME: UPDATE

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ABSTRACT

Broken heart syndrome (BHS), which was first reported in 1991, is an acute cardiomyopathy that mimics an acute coronary syndrome with left ventricular systolic dysfunction without obstructive coronary artery disease. Its prevalence is approximately 1.2-2% in patients with acute coronary syndrome undergoing coronary catheterization. Chest pain is the most common clinical presentation. Sudden cardiac death due to ventricular fibrillation could be the first clinical manifestation. The patients are mostly postmenopausal women. BHS is a diagnosis of exclusion and has no single definitive diagnostic test. Nevertheless, most of the patients have an excellent prognosis. This review provides a general overview of BHS and focuses on current practices in diagnosis, prognosis, and treatment, as well as update current information on the pathophysiology.

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INTRODUCTION

Broken heart syndrome (BHS), which was first reported in 1991 (Dote *et al*., 1991), is an acute cardiomyopathy that mimics an acute coronary syndrome (ACS) with left ventricular systolic dysfunction (LVSD) without obstructive coronary artery disease (Dote *et al*., 1991). BHS can be triggered by emotional or stressful situations or by sympathomimetic drug administration (Abraham *et al*., 2009). Although BHS is commonly observed in postmenopausal women (Azzaarelli *et al*., 2006), it has also been reported in men and young women. BHS, which is also known as Takotsubo cardiomyopathy, stress cardiomyopathy, and transient apical ballooning, is considered part of acute myocardial infarction without obstructive coronary artery disease (Niccoli *et al*., 2015). The term Takotsubo originated from the Japanese word for an octopus trap and was used to refer to BHS because of the characteristic wall motion abnormalities of the left ventricle, including hypokinesia of the left ventricular apex (apical ballooning) with hyperkinetic function of the basal segments of the left ventricle resembles the shape of a Japanese octopus trap (Gianni *et al*., 2006) (Figure 1). The aim of this article was to summarize the clinical presentation, diagnosis, prognosis, risk stratification, and management of BHS, as well as its pathogenesis.

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Epidemiology

BHS is a rare syndrome. However, BHS cases have been increasing in the last 20 years (Minhas *et al*., 2015) as a result of a large increase in early diagnostic coronary angiography frequency in patients with ACS (Shao *et al*., 2012). The prevalence of BHS is approximately 1.2–2% in patients with ACS undergoing coronary catheterization (Lyon *et al*., 2012). BHS is most commonly seen in postmenopausal women (Parodi, 2007; Komamura *et al*., 2014; Kuo *et al*., 2010). Kuo *et al*. (2010) concluded that a lack of estrogen replacement in postmenopausal women may predispose them to BHS. According to current data from the large International Takotsubo Registry, approximately 90% of patients with BHS are women with a mean age of around 66.4 years (Templin *et al*., 2015).

Clinical presentation

Most of the patients with BHS present with chest pain (approximately 76%) (Templin *et al*., 2015). Dyspnea is the second common clinical manifestation (approximately 47%) (Templin *et al*., 2015). Some BHS cases manifest with syncope (7.7%) (Templin *et al*., 2015), which is usually related to arrhythmias (Bybee *et al*., 2004; Yamasa *et al*., 2002; Fazio *et al*., 2008). Sudden cardiac death due to ventricular fibrillation could be the first clinical manifestation, and it was reported in approximately 3% of BHS cases (Raddino *et al*., 2008; Soni

and LeLorier, 2005). Cardiogenic shock was observed in approximately 15% of BHS cases (Tsuchihashi *et al*., 2001). Thromboembolic events due to left ventricular apical thrombi have been reported in 0.8–14% of patients (Bybee *et al*., 2004; Kurisu *et al*., 2011). Ventricular thrombosis incidence in BHS cases is 2.5–9% (Bybee *et al*., 2004; Kurisu *et al*., 2011). Moreover, Templin *et al*. (2015) identified triggering factors in 70–75% of BHS cases. Physical triggering factors (such as surgery, acute asthma, stroke, epilepsy, and head injury) were reported in approximately 36%, emotional triggering factors (such as sadness from the death of loved one, a relationship ending, financial problems, anxiety, and distress regarding public speaking) in 27.7%, and both factors in approximately 7.8% of BHS patients (Templin *et al*., 2015).

Diagnosis

BHS is a diagnosis of exclusion, and no single definitive diagnostic test for BHS exists. Currently, there are seven different proposed diagnostic criteria for BHS (Table 1), and the Mayo Clinic criteria are the most widely recognized.

The 2004 expert consensus listed the proposed Mayo Clinic diagnostic criteria for BHS (Bybee *et al*., 2004), and in 2008, the criteria were modified as follows (Prasad *et al*., 2008):

1. Transient hypokinesia, akinesia, or dyskinesia of the middle segments of the left ventricle with or without the involvement of the apex based on echocardiography or ventriculography; regional wall movement abnormalities belonging to a single coronary artery supply; and a stressful participating trigger that is often, but not always, available.
2. No evidence of an obstructive coronary disease or acute plaque ruptures by coronary angiography.
3. New electrocardiogram abnormalities (ST elevation with or without T-wave inversion) or a moderate increase in cardiac troponin levels.
4. Absence of pheochromocytoma and myocarditis.

Differential diagnosis of BHS involves the following conditions: ACS, peri/myocarditis, dilated cardiomyopathy, hypertrophic cardiomyopathy, aortic dissection, pulmonary embolism, pneumothorax, esophageal spasm, gastroesophageal reflux disease, Boerhaave syndrome (spontaneous esophageal rupture). Furthermore, a recent study published on March 2017 proved that tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) can differentiate BHS from ACS better than troponin T (Parkonen *et al*., 2017).

Pathophysiology

Various theories have been proposed to explain the pathogenesis of BHS; however, the exact mechanism remains unknown. Currently, the most accepted hypotheses are as follows:

The catecholamine hypothesis

Lyon *et al*. (Lyon *et al*., 2008) described the stimulus trafficking theory based on the results of three experimental studies (Heubach and Kaumann, 2004; Heubach *et al*., 2003; Daaka *et al*., 1997); at normal physiological epinephrine levels, epinephrine binding to ß$_2$-adrenoreceptors on ventricular cardiomyocytes stimulates the G_s protein-adenylyl cyclase-protein kinase A pathway, resulting in strengthened myocardial contractile function (positive inotropic effect). High epinephrine levels (supraphysiological levels) lead to a switch in ß$_2$-adrenoreceptors binding, i.e., from G_s protein to G_i protein, which in turn induces a negative inotropic effect on myocardial contractile function (Figure 2). In addition, Mori *et al*. (1993) proved that the density of ß-adrenoreceptors in dogs' left ventricular apex is higher than that in the left ventricular base. This finding could explain the left ventricular apex involvement in patients with BHS. Wittstein *et al*. (2005) published a study of 19 patients with LVSD after acute emotional stress; the plasma catecholamine levels were noticeably higher in patients with stress-induced cardiomyopathy than in those with Killip class III myocardial infarction. Abraham *et al*. (2009) reported a series of cases with stress cardiomyopathy that occurred immediately after the administration of catecholamines and ß-adrenergic agonists during diagnostic investigations or procedures. Furthermore, Nef *et al*. (2009) described an intensified activity of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway in BHS, which is anti-apoptotic and could contribute to a prompt recovery of cardiomyocytes and a favorable outcome.

The endothelial vasomotor dysfunction hypothesis

Numerous studies support this hypothesis. Martin *et al*. (2010) reported reduced endothelial function and heightened vascular reactivity resulting from acute mental stress in patients with a history of BHS. Galuito *et al*. (2010) investigated 15 patients with BHS and found that adenosine infusion leads to a complete recovery from altered myocardial perfusion and myocardial dysfunction; their study strongly suggested that reversible coronary microvascular dysfunction could play a role in the pathophysiology of BHS. A Japanese study of 8 females with BHS reported that endothelial cell apoptosis of coronary microvessels was observed in biopsied myocardial specimens (Uchida *et al*., 2010). Moreover, a recent study published on March 2017 in JAMA Cardiology confirmed the occurrence of microvascular coronary dysfunction in 15 consecutive patients with BHS by invasive physiological assessment of the coronary arteries using a pressure wire and intravenous adenosine administration (Rivero *et al*, 2017).

The inflammatory hypothesis

Several studies support the contribution of inflammatory factor in the pathophysiology of BHS. Nef *et al*. (2007) identified inflammatory cells and cytoskeletal proteins in myocardial biopsies of eight patients who presented with BHS. Other studies observed a late gadolinium enhancement in patients with BHS using cardiac magnetic resonance imaging (Eitel *et al*., 2010; Avegliano *et al*., 2010).

The matrix metalloproteinase hypothesis

As is known, matrix metaloprotinase 8 (MMP 8) is an extracellular enzyme that cleaves the collagen in the connective tissues. Recently, Parkonen *et al*. (2017) described low matrix metalloproteinase 8 levels in patients with BHS lead to a worsening of transient myocardial fibrosis, which may in turn play a role in the reduced left ventricular (LV) function in BHS.

Treatment

In patients with hemodynamic stability in the acute phase, treatment with ß-blockers, angiotensin-converting enzyme

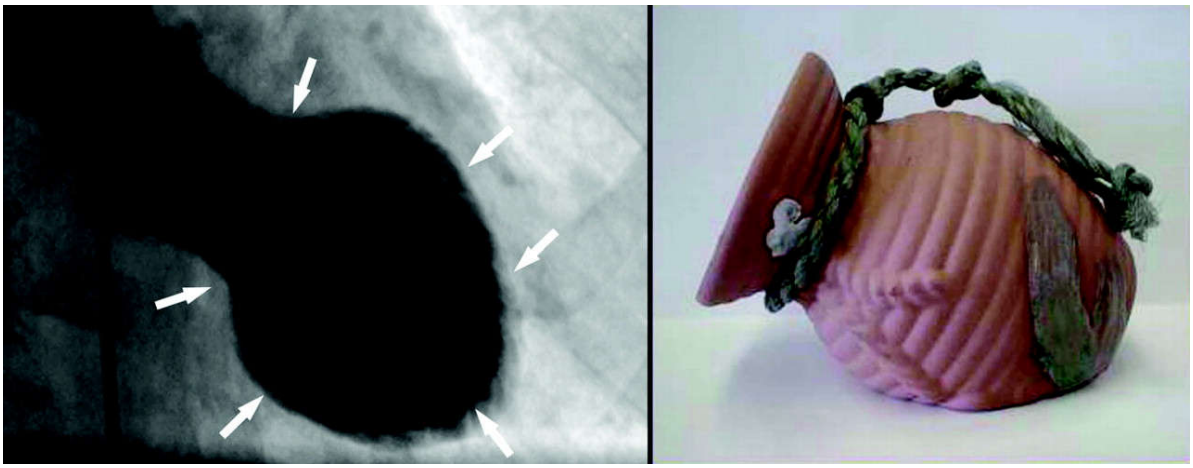

Fig. 1. A: Left ventriculography shows anteroapical and inferoapical dyskinesis (apical ballooning). B: The Japanese octopus trap (takotsubo), from Witzke et al. with permission (Witzke et al., 2003)

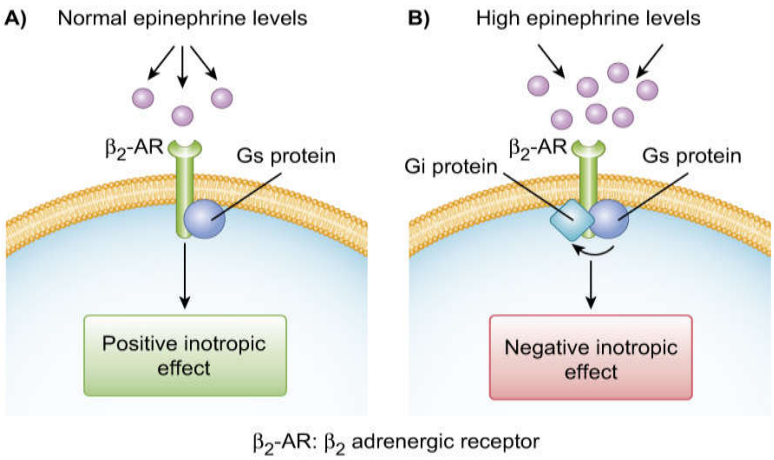

Fig.2. Proposed stimulus trafficking theory

Table 1. The proposed criteria for the diagnosis of BHS (Scantlebury and Prasad, 2014)

Diagnostic criteria	Left ventricular wall movement abnormalities belonging to a single coronary artery supply	Classic apical ballooning type	Transient	Complete recovery within few weeks	New ECG abnormalities (ST elevation, T-wave inversion, or LBBB	Moderate increase in cardiac biomarkers	Exclusion of coronary culprit lesion	Exclusion of myocarditis	Exclusion of pheochromo cytoma
Mayo Clinic 2004	×	×	×	×	×		×	×	×
Modified Mayo Clinic 2008	×	×	×		×	×	×	×	×
Japanese 2007		×		×		×	×	×	×
Johns Hopkins 2012	×			×	×	×	×		
Gothenberg 2013	×		×			×	×	×	×
Tako-tsubo Italian Network 2014	×		×	×	×	×	×	×	
Madias 2014	×		×				×	×	×

(ACE) inhibitors, and diuretics is recommended. Temporary anticoagulation may be recommended until improvement of LV function. In cases of hemodynamic instability, the use of cardiopulmonary support techniques and even renal replacement therapy is required (Patel *et al*., 2007; Bybee *et al*., 2006). The administration of levosimendan as a non-catecholamine inotrope may be helpful for patients with BHS-related cardiogenic shock (Lyon *et al*., 2008; Padayachee, 2007). However, no guidelines or consensus with regard to the long-term treatment for patients with BHS after recovery of LV function exists.

Prognosis and risk stratification

Complete recovery is observed in approximately 95% of BHS cases (Elesber *et al*., 2007). The in-hospital mortality rate is around 1–2% (Dib *et al*., 2008; Sharkey *et al*., 2010). Recently, Sobue *et al*. (2010) reported a higher in-hospital mortality rate

in patients with physically triggered BHS than in patients with non-physically triggered BHS (20.9 vs. 2.6%). A new study, which was first published on March 2017 in the American Journal of Cardiology (Nayeri *et al*., 2017), showed that early rehospitalization (i.e., within 30 days of discharge) of BHS patients is associated with diminished survival. On statistical analysis of data from the International Takotsubo Registry, an increased occurrence of acute complications in younger patients with BHS with physical triggers was shown, (Templin *et al*., 2015). Moreover, Sattler *et al*. (2017) reported an increased incidence of cancer among patients with BHS, and the outcomes in these patients with malignant diseases are worse. Postmenopausal women are at high risk for BHS (Parodi, 2007; Komamura *et al*., 2014; Kuo *et al*., 2010; Templin *et al*., 2015). However, some studies (Templin *et al*., 2015) considered patients with the following conditions to have a higher risk of developing BHS: migraine, connective tissue disorders, pulmonary hypertension, hyperthyroidism, hyperlipidemia, subarachnoid hemorrhage, smoke, stress, and anxiety.

Conclusion

BHS is an acute heart failure that mimics an acute myocardial infarction; it can be fatal, and the number of BHS cases is increasing continuously. The diagnosis of BHS remains challenging. Moreover, the etiology of BHS is still unknown; in this study, we discussed the most accepted hypotheses to explain the pathophysiology. The treatment of BHS in the acute phase is similar to that of acute heart failure. However, no guidelines or consensus with regard to the long-term treatment of BHS patients after LV function recovery exists. Future studies on BHS are warranted to improve diagnostic accuracy and develop treatment strategies for patients with BHS.

Conflict of interest

The authors declare no conflict of interest.

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