Takotsubo Cardiomyopathy: A Brief Review

Hilman Zulkifli Amin*, Lukman Zulkifli Amin, Ariel Pradipta
Indonesian Medical Education and Research Institute, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Corresponding author:
Hilman Zulkifli Amin, MD, PhD
Indonesian Medical Education and Research Institute, Faculty of Medicine,
Universitas Indonesia
Jl. Salemba Raya No. 6, Jakarta, Indonesia, 10430.
Phone: +6281294053354.
Email: hilman_amin@yahoo.co.id

Received: October 2nd, 2018 – Accepted: August 21th, 2019

Abstract

Takotsubo cardiomyopathy is a reversible cardiomyopathy with a unique morphological feature of the left ventricle characterized by an apical ballooning appearance known for approximately known 25 years. Catecholamine drive plays an essential role in the pathogenesis and pathophysiology of Takotsubo cardiomyopathy; hence, it is also called stress cardiomyopathy. Physical stress could also have an impact and leads to a greater variety of characteristics in Takotsubo cardiomyopathy.

Supportive and symptomatic medication remains the mainstay therapy with priority to improving the function of the left ventricle for several days and full recovery in 3-4 weeks. Due to its similarity with myocardial infarction, Takotsubo cardiomyopathy requires careful diagnosis and management for the best possible outcome.

Keywords: Takotsubo, cardiomyopathy, reversible

Introduction

Takotsubo cardiomyopathy (TC) is defined by a temporary and reversible systolic abnormality of the left ventricle's apical area resembling myocardial infarction (MI) in the nonexistence of coronary artery disease (CAD) [1]. This clinical entity was initially described approximately 25 years ago [2]. The word "Takotsubo" is a container used by the Japanese to catch octopus, which has a circular bottom and narrow neck, which resembles the heart's condition in TC to a certain degree [3]. There are various types of left ventricular (LV) function abnormalities within this disease [4]. The prevalence is 1.0-2.5%, with most cases to occur in post-menopausal women [3,5]. Many conditions have been linked to TC, like over-stimulation of the sympathetic system, microvascular and myocardial tissue metabolism abnormality, and coronary artery vasospasm [3]. Despite frequently being underdiagnosed, complete understanding is needed to optimize the management of the disease. This review will briefly explain the main features of TC, including definition and management protocol.

Materials and Methods

Various papers from Pubmed in relation to Takotsubo cardiomyopathy were thoroughly selected and appraised. The results from those papers are discussed and summarized to complete the current review paper.

Definition and Diagnosis

The well-accepted TC diagnosis criteria is from Mayo Clinic and consists of four components: 1) temporary hypokinesis, dyskinesis or akinesis in LV segments with or without apical involvement; aberration in regional wall motion exceeding past a single vascular distribution; the existence of stress elicitation; 2) the lack of significant coronary artery disease; 3) recent changes detected in the electrocardiogram (ECG) (ST-segment elevation and/or T-wave inversion) or significant elevation of serum cardiac troponins; and 4) non-existence of pheochromocytoma or myocarditis [6]. The summary of the diagnosis criteria for TC is shown in table 1. Usage of diagnostic modalities combinations such as ECG, cardiac biomarkers, echocardiography, coronary angiography, and cardiac magnetic resonance (CMR) imaging will add value to a more precise way in diagnosing TC. Mostly, ECG shows recent abnormalities resembling ACS like ST-segment elevation, especially in the anterior leads (56%) and T-wave inversion (39%). Other forms of ECG abnormalities that may also appear are QT-prolongation, ventricular tachycardia (VT), ventricular fibrillation (VF), and torsade de pointes [7]. Furthermore, a study by Kosuge et al. found that the combination of ST-segment depression in aVR and the absence

Table 1: Summary of TC diagnosis criteria [6].

1.	Temporary hypokinesis, dyskinesis, or akinesis in LV segments with or without apical involvement; aberration in regional wall motion exceeding past a single vascular distribution; the existence of stress elicitation.
2.	No presence of significant coronary artery disease.
3.	Recent changes in electrocardiography (ECG) (ST segment elevation and/or T-wave inversion) or significant elevation of cardiac troponin serum levels.
4.	Non-existence of pheochromyctoma or myocarditis

of ST-segment elevation in V1 could reveal TC with 91% sensitivity, 96% specificity, and 95% predictive accuracy [8]. In addition, as shown by other studies, in order to distinguish between anterior MI and TC, ECG should reveal no reciprocal changes and Q waves with the ST-elevation ratio in leads V4-6 to V1-3 > 1, and also the absence of ST-depression or following inferior ST elevation [9].

In-line with ECG findings, TC also shows an elevated level of cardiac biomarkers showing myocardial disturbance [10]. In 90% of patients, the troponin levels are elevated, often mistakenly diagnosed as ACS [11]. Nevertheless, contradictive to ACS, the highest level of troponin mostly would be <1ng/ml. B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) have also been found to be frequently increased up to 3-4-fold higher compared to patients with ACS [12]. From one study, significantly elevated levels of these biomarkers were not related to pulmonary congestion or pulmonary capillary wedge pressure, but associated with reduced ejection fraction (EF) and elevated plasma catecholamine levels, hence revealing TC pathogenesis and its severity [12].

The pathognomonic finding of TC during echocardiography is apical ballooning involving LV. This unique morphology was reported to appear in 75% of patients [2]. In 25% of patients, the morphology was reported to follow a mid-ventricular ballooning pattern due to mid-LV akinesis, with no disturbance of apical and basal contraction [13-14]. Furthermore, an impaired LVEF with typical systolic anterior motion (SAM) could also be found within this case. To provide more significant evidence of TC, CMR is an important imaging investigation. CMR could show particular imaging characteristics like right ventricular (RV) involvement and differentiate it from other cardiomyopathies [15]. However, due to difficulties in distinguishing between TC and ACS, coronary angiography could demonstrate a critical role in diagnosing TC. Coronary angiography could more accurately prove normal coronary artery or non-significant atherosclerosis. In addition, a myocardial biopsy could also be performed if there are no contraindications, mostly to show interstitial infiltrates with mononuclear lymphocytes, leukocytes, macrophages, myocardial fibrosis, and contraction bands. Inflammatory reaction and contraction bands show different features in TC and MI and it may reveal coagulation necrosis in the case of coronary artery obstruction [16].

Cause, pathophysiology and mechanisms

The precise cause, pathogenesis, and pathophysiology of TC are still uncertain. Many hypotheses have been linked with the occurrence of TC. Recently, the most accepted theories are catecholamine-induced cardiotoxicity and microvascular dysfunction, in addition to the complex and integration of neuroendocrine physiology, eventually involving the cognitive centers of the brain and hypothalamic-pituitary-adrenal axis [17,18].

A study by Wittstein et al. revealed that the plasma levels of epinephrine were critically elevated in TC patients, with emotional stress as its major precipitating factor. In addition, the study also indicated that the serum catecholamine concentration was two to three folds higher in TC than MI patients [19]. Moreover, other studies also substantiate the catecholamine theory further through exogenously administered catecholamine and pheochromocytoma, resulting in similar features of TC [20-21]. Excessive levels of catecholamines released by the sympathetic nervous system caused by a stressful condition could result in intracellular calcium overload and cardiac dysfunction through b(1)- adrenoreceptor signal transduction pathway (Figure 1) [4]. Calcium overload in myocardial cells consequently

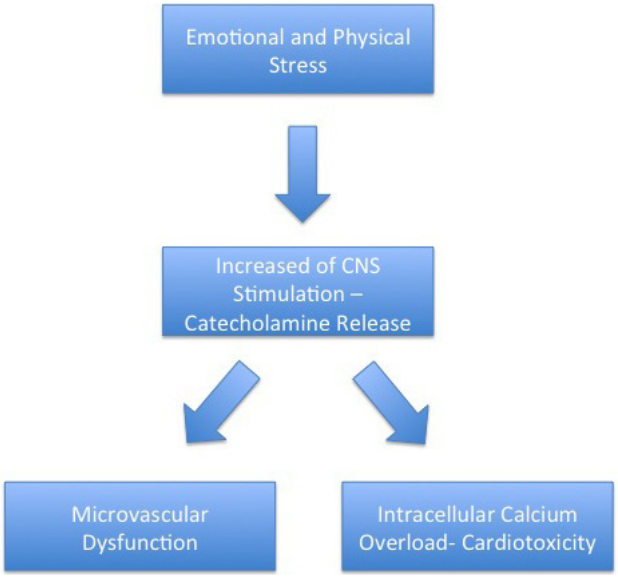

Figure 1: Mechanism of Takotsubo Cardiomyopathy.

leads to ventricular dysfunction and catecholamine cardiotoxicity [22]. Conditions with high catecholamine levels also affected the b(2)- adrenoreceptor resulting in myocyte injury because of calcium leakage due to hyperphosphoryl-

ation of the ryanodine receptor [23]. Nevertheless, cardiotoxicity caused significant changes in myocardial features with contraction band necrosis, inflammatory cell infiltration, and fibrosis [24].

It is important to note that a recent body of evidence also revealed that there is a higher prevalence of TC due to physical triggers than that of an emotional trigger. In addition, it was generally agreed that the absence of an isolated trigger should not exclude the diagnosis of this disorder. Due to a large number of possible causes that remain unknown until now, TC may manifest a wide variety of features.

Patients with TC also constantly demonstrated microvascular dysfunction features [26]. These features include the impairment of endothelium-dependent vasodilatation, excessive vasoconstriction, and abnormality of myocardial perfusion (Figure 1) [27]. A study by Uchida et al. revealed that thorough endothelial cell apoptosis was shown by myocardial biopsy [28].

Risk factors of TC include estrogen deficiency, emotional or physical stress, and genetic factors. Most of the patients with TC are postmenopausal women. A study conducted by Ueyama et al. reported that rats who were subjected to stressful conditions and then underwent ovariectomy demonstrated lower LV function than rats with estradiol supplementation [29]. In addition, estrogen may intensify the transcription of cardioprotective factors such as heat shock protein and atrial natriuretic peptide, hence defend from cardiotoxic elements such as catecholamines, calcium overload, and oxidative stress [29-30].

Emotional stress is also playing a major role as a precipitating factor in the occurrence of TC. Stress promotes the response of the sympathetic system, which can be linked to the occurrence of TC [31]. Genetic factors also demonstrated a possible role for TC occurrence. One study revealed that patients with TC have L41Q polymorphism of the G protein-coupled receptor (GRK5) more often than the control group [32]. L41Q polymorphism of GRK5 reacts to catecholamine stimulation and diminishes the reaction of b-adrenergic receptors. In addition, Mediterranean and Asian women have a higher susceptibility to this dysfunction [33-34].

In more detail, several emotional or psychological stressors have been known to initiate the onset of TC, and the structures that mediate these responses are found in central and autonomic nervous systems [35]. The stressors cause brain activation, elevate cortisol, and catecholamine bioavailability. Both circulating epinephrine and norepinephrine released from adrenal medullary chromaffin cells, and norepinephrine released locally from sympathetic nerve endings are significantly increased in the acute phase of TC. This process, which has a functional counterpart of transient apical left ventricular ballooning, initiates myocardial damage through several mechanisms, which are direct catecholamine toxicity, adrenoceptor-mediated damage, epicardial and microvascular coronary vasoconstriction and/or spasm, and elevated cardiac workload. In addition, other risk factors, such as estrogen deprivation, may have a facilitating role, possibly through endothelial dysfunction, as mentioned previously [35].

Clinical characteristics

Most common clinical characteristics of patients with TC are chest pain and dyspnea [3]. One study revealed that chest pain was present in 185 of 273 patients (67.8%, 95% CI: 62.0-73.0%; range: 20-94.7%) and dyspnea in 40 of 225 patients (17.8%, 95% CI: 13.3-23.3%; range: 4.5-55.5%). More critical clinical presentations like cardiogenic shock (4.2% (95% CI: 2.4-7.4%)) and ventricular fibrillation (VF) (1.5% (95% CI: 0.65-3.9%)) can also be identified [3]. The clinical characteristics are similar with CAD, so diagnostic approach to this clinical entity needs to be done meticulously.

Treatment and prognosis

Due to its resemblance to MI, first management should focus on the treatment of CAD. Hence, one of the diagnostic criteria of TC is theexclusion of CAD. Therefore, initial therapy includes oxygen inhalation, intravenous heparin, aspirin, and b-blockers [36]. After excluding CAD and further confirmation of TC, aspirin can be stopped. In TC, b-blocker usage is reasonable due to possible high catecholamine state. However, its usage should be avoided when coronary vasospasm is suspected on first presentation [36]. In addition, angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) could also be used as part of regional wall motion abnormality (RWMA) management. Furthermore, anticoagulation therapy should be continued even after TC diagnosis confirmation. This therapy is useful to prevent LV apical thrombosis and possible embolic events [36].

However, when patients with TC come to the hospital in the acute phase, supportive and symptomatic treatment should be given. Hemodynamically unstable patients may need cardiopulmonary support, continuous venovenous hemofiltration, and intra-aortic balloon pump [37-39]. Other supporting therapies like diuretics and nitroglycerin may show benefit, since 20% of patients with TC have congestive heart failure (CHF) as a complication [19, 40].

The in-hospital mortality rates varied from 0-8% with recurrence rate range from 0-15% [13, 40-44]. Patients with TC have great prognosis, the recovery rate being 96% [41]. The LV function may begin to recover in several days and fully recuperates in 3-4 weeks [4]. Last but not least, even though therapy guidelines for TC have yet to be arranged, the majority of patients were treated with antithrombotic and heart failure medication for up to twelve months in one of the most recent studies on the subject. Left ventricular function and myocardial edema recovered rapidly within the first two months, with the outcome analysis showing a low bleeding rate and a high short-term survival. Hence, antithrombotic and heart failure therapy might bring significantly benefits in TC management [45].

Conclusion

TC is a transient and reversible cardiomyopathy with good prognosis. The hallmark feature of TC is apical ballooning

in LV similar in its outlook with the so called 'Takotsubo', which is a pot for octopus fishing used in Japan. Due to its similar features to MI, a careful diagnosis and management should be performed. Catecholamine levels play a vital role in pathogenesis and pathophysiology of TC, hence it is also called stress cardiomyopathy. TC risk factors include estrogen deficiency, emotional and physical stress, and genetic factors. The mainstay therapy is supportive treatment and is reported to be effective as TC patients' LV function generally begins to restore in several days and fully recuperates in 3-4 weeks.

Conflict of Interest

The authors confirm that there are no conflicts of interest.

References

1. Patankar GR, Choi JW, Schussler JM. Reverse takotsubo cardiomyopathy: two case reports and review of the literature. Journal of Medical Case Reports. 2013; 7:84.
2. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. J Cardiol. 1991; 21:203-214.
3. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J. 2006; 27:1523-2529.
4. Roshanzamir S, Showkathali R. Takotsubo cardiomyopathy a short review. Curr Cardiol Rev. 2013; 9:191-196.
5. Sharkey SW, Lesser JR, Maron MS, Maron BJ. Why not just call it tako-tsubo cardiomyopathy: a discussion of nomenclature. J Am Coll Cardiol. 2011; 57:1496-1497.
6. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J. 2008; 155:408-417.
7. Previtali M, Repetto A, Panigada S, Camprotondo R, Tavazzi L. Left ventricular apical ballooning syndrome: prevalence, clinical characteristics and pathogenetic mechanism in a European population. Int J Cardiol. 2009; 134:91-96.
8. Kosuge M, Ebina T, Hibi K, Morita S, Okuda J, Iwahashi N, et al. Simple and accurate electrocardiographic criteria to differentiate takotsubo cardiomyopathy from anterior acute myocardial infarction. J Am Coll Cardiol. 2010; 55:2514-2516.
9. Ogura R, Hiasa Y, Takahashi T, Yamaguchi K, Fujiwara K, Ohara Y, et al. Specific findings of the standard 12-lead ECG in patients with 'Takotsubo' cardiomyopathy: Comparison with the findings of acute anterior myocardial infarction. Circ J. 2003; 67:687-690.
10. Scantlebury DC, Prasad A. Diagnosis of takotsubo cardiomyopathy. Circ J. 2014; 78:2129-2139.
11. Sharkey SW, Maron BJ. Epidemiology and clinical profile of takotsubo cardiomyopathy. Circ J. 2014; 78:2119-2128.
12. Nguyen TH, Neil CJ, Sverdlov AL, Mahadavan G, Chirkov YY, Kucia AM, et al. N-terminal pro-brain natriuretic protein levels in takotsubo cardiomyopathy. Am J Cardiol. 2011; 108:1316-1321.
13. Sharkey SW, Windenburg DC, Lesser JR, Maron MS, Hauser RG, Lesser JN, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. J Am Coll Cardiol. 2010; 55:333-341.
14. Hurst RT, Asker JW, Reuss CS, Lee RW, Sweeney JP, Fortuin FD, et al. Transient midventricular ballooning syndrome: a new variant. J Am Coll Cardiol. 2006; 48:579-583.
15. Kohan AA, Yeyati EL, Stefano LD, Dragonetti L, Pietrani M, de Arenaza DP, et al. Usefulness of MRI in takotsubo cardiomyopathy: a review of the literature. Cardiovasc Diagn Ther. 2014; 4(2):138-146.
16. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. Circulation. 2008; 118:2754-2762.
17. Komamura K, Fukui M, Iwasaku T, Hirorani S, Masuyama T. Takotsubo cardiomyopathy: pathophysiology, diagnosis, and treatment. World J Cardiol. 2014; 6(7):602-609.
18. Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. Nat Rev Cardiol. 2015;12(7):387-97.
19. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC. Neurohormonal features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005; 352:539-548.
20. Abraham J, Mudd JO, Kapur NK, Klein K, Champion HC, Wittstein IS. Stress cardiomyopathy after intravenous administration of catecholamines and beta-receptor agonists. J Am Coll Cardiol. 2009; 53:1320-1325.
21. Marcovitz PA, Czako P, Rosenblatt S, Billecke SS. Pheochromocytoma presenting with Takotsubo syndrome. J Interv Cardiol. 2010; 23:437-442.
22. Frustaci A, Loperfido F, Gentiloni N, Caldarulo M, Morgante E, Russo MA. Catecholamine-induced cardiomyopathy in multiple endocrine neoplasia: a histologic, ultrastructural, and biochemical study. Chest. 1991; 99:382-385.
23. Ellison GM, Torella D, Karakikes I, et al. Acute beta-adrenergic overload produces myocyte damage through calcium leakage from the ryanodine receptor 2 but spares cardiac stem cells. J Biol Chem. 2007; 282:11397-409.
24. Templin C, Ghadri JR, Dieekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. N Engl J Med. 2005;373(10):929-938.
25. Nef HM, Mollmann H, Kostin S, Troidl C, Voss S, Weber M, et al. Takotsubo cardiomyopathy: intraindividual structure analysis in the acute phase and after functional recovery. Eur Heart J. 2007; 28:2456-2464.
26. Galiuto L, De Caterina AR, Porfidia A, Paraggio L, Barchetta S, Locorotondo G, et al. Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in apical ballooning ot tako-tsubo syndrome. Eur Heart J. 2010; 31:1319-1327.
27. Martin EA, Prasad A, Rihal CS, Lerman LO, Lerman A. Endothelial function and vascular response to mental stress are impaired in patients with apical ballooning syndrome. J Am Coll Cardiol. 2010; 56:1840-1846.
28. Uchida Y, Egami H, Uchida Y, Sakurai T, Kanai M, Shirai S, Nakagawa O, Oshima T. Possible participation of endothelial cell apoptosis of coronary microvessels in the genesis of takotsubo cardiomyopathy. Clin Cardiol. 2010; 33:371-377.
29. Ueyama T, Hano T, Kasamatsu K, Yamamoto K, Tsuruo Y, Nishio I. Estrogen attenuates the emotional stress=induced cardiac responses in the animal model of tako-tsubo (ampulla) cardiomyopathy. J Cardiovasc Pharmacol. 2003; 42 Suppl 1:S117-S119.
30. Migliore F, Bilato C, Isabella G, Iliceto S, Tarantini G. Haemodynamic effects of acute intravenous metoprolol in apical ballooning syndrome with dynamic left ventricular outflow tract obstruction. Eur J Heart Fail. 2010; 12:305-308.
31. Cevik C, Nugent K. The role of cardiac autonomic control in the pathogenesis of tako-tsubo cardiomyopathy. Am Heart J. 2008; 156:e31.
32. Spinelli L, Trimarco V, Di Marino S, Marino M, Iaccarino G, Trimarco B. L41Q polymorphism of the G protein coupled receptor kinase 5 is associated with left ventricular apical ballooning syndrome. Eur J Heart Fail. 2010; 12:13-16.
33. Cherian J, Angelis D, Filiberti A, et al. Can takotsubo cardiomyopathy be familial? Int J Cardiol. 2007; 121:74-75.

34. Pison L, De Vusser P, Mullens W. Apical ballooning in relatives. Heart; 2004; 90:e67.
35. Peliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo Syndrome. Circulation. 2017;135:2426-2441.
36. Kurisu S, Kihara Y. Clinical management of takotsubo cardiomyopathy. Circ J. 2014; 78:1559-1566.
37. Ptel HM, Kantharia BK, Morris DL, Yazdanfar S. Takotsubo syndrome in African-American women with atypical presentations: a single-center experience. Clin Cardiol. 2007; 30:14-18.
38. Cangella F, Medolla A, De Fazio G, Juliano C, Curcio N, Salemme L, Mottola G, Agusta M. Stress induced cardiomyopathy presenting as acute coronary syndrome: tako-tsubo in Mercogliano, Southern Italy. Cardiovasc Ultrasound. 2007; 5:36.
39. Bybee KA, Murphy J, Prasad A, Wright RS, Lerman A, Rihal CS, Chareonthaitawee P. Acute impairment of regional myocardial glucose uptake in the apical ballooning (takotsubo) syndrome. J Nucl Cardiol. 2006; 13:244-250.
40. Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, et al. Angina pectoris-myocardial infarction investigators in Japan. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. J Am Coll Cardiol. 2001; 38:11-18.
41. Kurisu S, Sato H, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, et al. Tako-tsubo- like left ventricular dysfunction with ST- segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. Am Heart J. 2002; 143:448-455.
42. Desmet WJ, Adriaenssens BF, Dens JA. Apical ballooning of the left ventricle: first series in white patients. Heart. 2003; 89:1027-2031.
43. Bronjikji W, El-Sayed AM, Salka S. In-hospital mortality among patients woth takotsubo cardiomyopathy: a study of the National Inpatient Sample 2008 to 2009. Am Heart J. 2012; 164:215-221.
44. Elesber AA, Prasad A, Lennon RJ, Wright RS, Lerman A, Rihal CS. Four-year recurrence rate and prognosis of the apical ballooning syndrome. J Am Coll Cardiol. 2007; 50:448-452.
45. Abanador-Kamper N, Kamper L, Wolfertz J, Pomjanski W, Wolf-Putz A, Seyfarth M. BMC Cardiovascular Disorders. 2017;17:225-234.