

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Takotsubo Syndrome and Nitric Oxide Bioavailability

*Michael Demosthenous, Konstantinos Triantafyllou
and Nikolaos Koumallos*

Abstract

Takotsubo cardiomyopathy, also known as broken heart syndrome or stress cardiomyopathy, is a form of transient left ventricular dysfunction. Severe apical and mid left ventricular hypokinesis with hypercontractility of the basal segments is observed. Numerous underlying causes and pathophysiological mechanisms have been proposed including sudden sympathetic activation and increase in the circulating levels of catecholamines resulting in multivessel coronary spasm. Another possible mechanism related to catecholamine-mediated myocardial stunning is direct myocyte injury. Increasing data show that endothelial dysfunction and depleted nitric oxide bioavailability are common in patients with Takotsubo cardiomyopathy. In this chapter we examine in depth the relation between endothelial dysfunction and Takotsubo syndrome.

Keywords: Takotsubo cardiomyopathy, broken heart syndrome, nitric oxide, endothelial dysfunction, ADMA

1. Introduction

Takotsubo cardiomyopathy (TC), also known as broken heart syndrome or stress cardiomyopathy, is a form of transient left ventricular (LV) dysfunction. Severe apical and mid left ventricular hypokinesis with hypercontractility of the basal segments is observed [1–4]. The name derives from the fact that the shape of the LV of patients with Takotsubo syndrome resembles the octopus fishing pot used in Japan where the first studied case of TC was done by Sato et al. in the early 1990s (**Figure 1(a)** and **(b)**).

The InterTAK diagnostic score is a score that predicts the probability of Takotsubo cardiomyopathy and differentiates from acute coronary syndrome. Female sex and emotional stress yield the highest score. Other predisposing factors include physical stress, psychiatric disorders, and neurological disorders.

Takotsubo cardiomyopathy usually presents with shortness of breath, hypotension, angina or syncope. Laboratory work may reveal elevated troponin levels. Electrocardiogram may show signs of ischemia, such as T wave inversion or even ST elevation [1]. Coronary angiogram typically reveals normal coronary arteries.

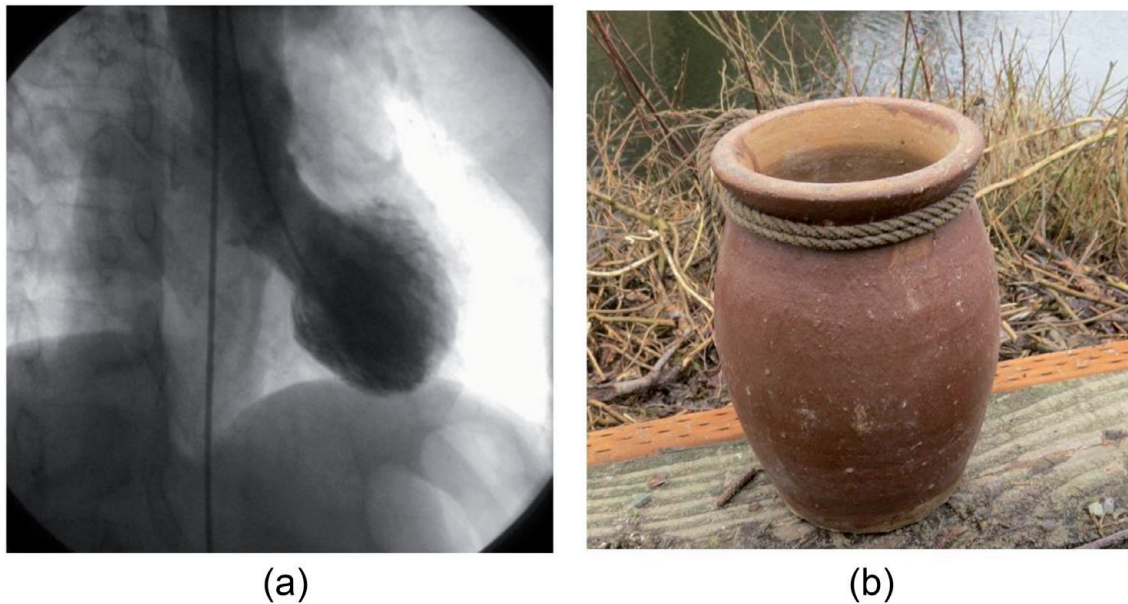


Figure 1.
(a) Angiogram of a patient with Takotsubo cardiomyopathy showing the apical ballooning of the left ventricle. (b) The Takotsubo fishing pot after syndrome was named. You can appreciate the resemblance with angiographic image on the left.

2. Pathophysiology

The pathophysiology of TC is quite complex and a number of different mechanisms have been proposed, including sudden sympathetic activation and increase in the circulating levels of catecholamines resulting in multivessel coronary spasm [5–15]. Coronary vasospasm and sympathetic mediated microvascular dysfunction have been observed in patients with TC.

According to Gupta et al. [16], the pathophysiology of sympathetic mediated coronary vasospasm and microvascular dysfunction can be divided in two phases.

According to the authors, the first phase starts with cognitive centers of the brain. As a response to stress, the hypothalamic-pituitary-adrenal axis is activated and releases catecholamines. In the case of TC, catecholamine and brain natriuretic peptide (BNP) levels are elevated significantly more than in patients with decompensated heart failure after an acute coronary syndrome. Catecholamine levels then start to decline, but remain significantly higher than in patients with acute coronary syndromes even a week after the event. On the other hand, plasma BNP levels decline rapidly, compared to patients with acute coronary events, and this is in parallel with the rapid improvement of the LV systolic function in TC. During the second phase, myocardial stunning occurs as a result of increased catecholamine levels.

3. Proposed mechanisms of Takotsubo syndrome

Plasma catecholamine levels are shown to be closely correlated with TC. In a study by Wittstein et al. [8], plasma catecholamine levels in 13 patients with stress-related myocardial dysfunction were compared with those in 7 patients who presented with acute pulmonary edema after myocardial infarction (Killip class III). The study showed that plasma catecholamine levels (epinephrine, norepinephrine, and dopamine) at presentation were markedly higher among patients with stress-induced cardiomyopathy than among those with Killip class III myocardial infarction. According to the results of this study, patients with stress cardiomyopathy had

supraphysiologic levels of plasma catecholamines. Initial plasma levels were several times those of patients with myocardial infarction and remained markedly elevated even a week after the onset of symptoms [8].

The mechanism underlying the association between sympathetic activity and myocardial stunning is unknown.

Increased catecholamine levels result in either direct cardiomyocyte damage through increased calcium levels or in vascular spasm and microvascular dysfunction, which leads to ischemia [5–7]. Abnormal coronary flow in the absence of obstructive disease has recently been reported in patients with stress-related myocardial dysfunction [17]. Increased sympathetic activity and vascular spasm also cause an increase in left ventricular afterload adding even more to the pathophysiology of TC [8].

Oxygen-derived free radical circulating levels can be increased by catecholamines and they can cause myocardial injury, which can be attenuated by antioxidants [18]; they can also interfere with sodium and calcium channels, increasing trans-sarcolemmal calcium influx resulting in myocyte dysfunction [19].

Oxidative stress often exaggerates myocardial stunning by affecting calcium homeostasis and causing excitation-contraction uncoupling resulting in myocardial dysfunction [6–8]. The histopathology of the myocardium in this condition differs from that found in ischemic insults and includes a neutrophil-predominant inflammation, contraction band necrosis, and fibrosis [9]. These changes probably reflect calcium cardiotoxicity rather than ischemic necrosis. The pattern of ventricular wall abnormality in TC also points toward a neurally mediated mechanism of cardiac injury [11–13].

One other possibility is ischemia resulting from epicardial coronary arterial spasm. Increased sympathetic tone from mental stress can cause vasoconstriction in patients without coronary disease [20].

A third possible mechanism of catecholamine-mediated myocardial stunning is direct myocyte injury. Elevated catecholamine levels decrease the viability of myocytes through cyclic AMP-mediated calcium overload [21].

4. Nitric oxide: endothelial dysfunction and Takotsubo cardiomyopathy

In 1980, Furchgott and Zawadzki [22] identified the “endothelium-derived relaxing factor” (later recognized as the free gas nitric oxide (NO)) as responsible for the relaxation of vascular smooth muscle cells in response to acetylcholine.

NO is synthesized by the enzyme NO synthase (NOS). This enzyme was first identified and described in the late 1980s. The enzyme NOS catalyzes the biosynthesis of NO through a reaction involving the conversion of L-arginine to L-citrulline [23]. NOS is a dimer consisting of two identical monomers, which can be divided into two major domains: the C-terminal reductase and the N-terminal oxygenase domain [24]. It contains binding sites for flavin adenine nucleotide (FAD), nicotinamide adenine dinucleotide phosphate (NADPH) and flavin mononucleotide (FMN) in close relation with cytochrome P-450 reductase. The latter binds haem, tetrahydrobiopterin (BH₄), and L-arginine, which acts as a substrate.

There are three different NOS isoforms, which differ between them in structure and function [25]. Endothelial NOS (eNOS) and neuronal NOS (nNOS) are Ca²⁺-dependent enzymes (despite the fact that eNOS can be activated in an Ca²⁺-independent manner) [26]. Inducible NOS (iNOS) is only expressed at high levels after induction by cytokines (thus the name inducible) or other inflammatory agents. Its activity is independent of intracellular Ca²⁺ levels. The three NOS isoforms are similar in the way that they have regions of high homology

(the oxygenase and the reductase domains) while at the same time each isoform exhibits unique features, which signify their specific functions.

The main source of endothelial NO production is eNOS. Specific properties of eNOS enable the enzyme to perform its specialized functions. These are Ca^{2+} sensitivity and the post-translational modifications, which facilitate sub-cellular localization. These properties enable eNOS to respond not only to hemodynamic forces but to neurohormonal agents as well. There are several factors such as estrogens, hypoxia, and exercise that are known to modify its expression, likely having an impact on cardiovascular function.

4.1 Physiological role of NO: role of NO in vasomotion (vasorelaxation)

As mentioned above, Furchgott and Zawadzki [22] first demonstrated that endothelium reversed the intrinsic constrictive effects of acetylcholine on the vascular smooth muscle through the release of NO. Numerous experimental and clinical studies confirmed that all the arterial endothelium, and to a lesser extent vein endothelium, releases NO. When the endothelium is normal, vasoconstriction is counteracted by the potent vasorelaxing effect of NO. The importance of NO in vasodilation varies between vascular beds and among animal species. Chemical modifications of the guanidino group of L-arginine result in compounds that inhibit NO synthase. NG-nitro-L-arginine (L-NA), NG-monomethyl-L-arginine (L-NMMA), and NG-nitro-L-arginine methyl ester (L-NAME) inhibit the release of NO from endothelial cells, indicating that there is continuous release of NO, which maintains the vasodilator tone.

4.2 The role of L-arginine analogues in eNOS function

ADMA is an amino acid that circulates in plasma, is excreted in urine, and is found in tissues and cells [27–29]. ADMA synthesis involves methylation of arginine residues by protein arginine methyltransferases (PRMTs) [30]. During methylation, either one or two methyl groups are added to the guanidine nitrogens of arginine, which are incorporated into proteins. There are two types of PRMT. Type 1 catalyzes the formation of ADMA and type 2 catalyzes the formation of symmetric dimethylarginine (SDMA) through the methylation of both guanidino nitrogens. Both PRMTs can monomethylate as well. Monomethylation leads to the formation of another asymmetrical form called NG-monomethyl-L-arginine (L-NMMA) [31].

The asymmetrical forms (ADMA and L-NMMA) are natural inhibitors of all NOS isoforms, whereas the symmetrical form (SDMA) is not. ADMA and L-NMMA inhibit all three isoforms of NOS [32, 33]. L-NMMA may also uncouple NOS leading to the generation of free radicals and more specific of superoxide [34]. Superoxide formation by this process further results in myocardial injury seen in TC.

Increased sympathetic activity and alterations in NO synthesis attributable to accumulation of ADMA is now recognized as an important mechanism involved in cardiovascular complications [35].

ADMA plasma levels are found to be related to insulin resistance, blood pressure, carotid intima thickness, and age even in healthy individuals, free from cardiovascular disease [36, 37] suggesting that increased ADMA levels are a marker for arteriosclerotic changes.

4.3 Endothelial dysfunction and TC

Increasing data show that endothelial dysfunction is common in patients with TC, which could explain the two of the proposed mechanisms reported at the

beginning of this chapter: propensity for epicardial and/or microvascular coronary artery spasm. Indeed, endothelial dysfunction may be a crucial link between myocardial dysfunction seen in TC and stress [38]. Consequently, the reversible LV dysfunction seen in TC may be the result of myocardial stunning due to this ephemeral myocardial ischemia caused by endothelial dysfunction. This mechanism, attenuated by endothelial dysfunction, may also be the cause of high prevalence of TC in postmenopausal women due to estrogen level depletion, which is related to vasomotor abnormalities [39–41].

Under physiological circumstances, estrogens are beneficial for coronary microcirculation. Estrogens have a pivotal role in improving coronary blood flow through endothelium-dependent or independent mechanisms [41]. Reduced estrogen levels in menopause positively affect endothelial dysfunction and sympathetic drive [40]. Through this effect, postmenopausal estrogen deficiency possibly facilitates the occurrence of TC, especially when emotional stress is in the equation.

Endothelial dysfunction is closely associated to the traditional risk factors for cardiovascular disease. On the other hand, traditional risk factors for cardiovascular disease (smoking, dyslipidemia and hypertension) are present in patients with TC in a non-negligible prevalence [42–44]. In addition, there is growing evidence that patients with TC also have various comorbidities, including neurological, pulmonary, kidney, and liver disease [42], conditions mostly associated with endothelial dysfunction and might therefore constitute a previously unrecognized predisposing factor for TC [45].

5. Conclusion

TC is now a well-recognized syndrome with a very complex pathophysiology. Increased sympathetic activity and plasma catecholamine levels have a pivotal role in the expression of TC. Recent data suggest that endothelial dysfunction and NO depletion are crucial predisposing factors for this syndrome and could be a crucial link between emotional stress and myocardial dysfunction.

Author details


Michael Demosthenous¹, Konstantinos Triantafyllou² and Nikolaos Koumallos^{2*}

¹ Department of Cardiac Surgery, St. Michael's Hospital, University of Toronto, Toronto, Canada

² Department of Cardiac Surgery, Hippocraton General Hospital, Athens, Greece

*Address all correspondence to: koumallosn@yahoo.gr

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy. *Circulation*. 2008;**118**:2754-2762
- [2] Kurowski V, Kaiser A, von Hof K, Killermann DP, Mayer B, Hartmann F, et al. Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy) frequency, mechanisms, and prognosis. *Chest*. 2007;**132**:809-816
- [3] Schneider B, Athanasiadis A, Schwab J, Pistner W, Gottwald U, Schoeller R, et al. Complications in the clinical course of tako-tsubo cardiomyopathy. *International Journal of Cardiology*. 2014;**176**:199-205
- [4] Hurst RT, Prasad A, Askew JW, Sengupta PP, Tajik AJ. Takotsubo cardiomyopathy: A unique cardiomyopathy with variable ventricular morphology. *JACC: Cardiovascular Imaging*. 2010;**3**:641-649
- [5] Stein AB, Tang XL, Guo Y, Xuan YT, Dawn B, Bolli R. Delayed adaptation of the heart to stress: Late preconditioning. *Stroke*. 2004;**35**:2676-2679
- [6] Ueyama T, Kasamatsu K, Hano T, Yamamoto K, Tsuruo Y, Nishio I. Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors: A possible animal model of "tako-tsubo" cardiomyopathy. *Circulation Journal*. 2002;**66**:712-713
- [7] Kume T, Kawamoto T, Okura H, Toyota E, Neishi Y, Watanabe N, et al. Local release of catecholamines from the hearts of patients with tako-tsubo-like left ventricular dysfunction. *Circulation Journal*. 2008;**72**:106-108
- [8] Wittstein IS, Thieman DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *The New England Journal of Medicine*. 2005;**352**:539-548
- [9] Frustaci A, Loperfido F, Gentiloni N, Caldarulo M, Margante E, Russo MA. Catecholamine-induced cardiomyopathy in multiple endocrine neoplasia: A histologic, ultrastructural, and biochemical study. *Chest*. 1991;**99**:382-385
- [10] Ueyama T, Kawabe T, Hano T, Tsuruo Y, Ueda K, Ichinose M, et al. Upregulation of heme oxygenase-1 in an animal model of takotsubo cardiomyopathy. *Circulation Journal*. 2009;**73**:1141-1146
- [11] Pierpont GL, DeMaster EG, Cohn JN. Regional differences in adrenergic function within the left ventricle. *The American Journal of Physiology*. 1984;**246**:824-829
- [12] Simoes MV, Marin-Neto JA, Maciel BC. Variable regional left ventricular dysfunction in takotsubo cardiomyopathy syndrome. *Echocardiography*. 2007;**24**:893
- [13] Kawano H, Okada R, Yano K. Histological study on the distribution of autonomic nerves in the human heart. *Heart and Vessels*. 2003;**18**:32-39
- [14] Cortese B, Robotti S, Puggioni E, Bianchi F, Lupi G, Brignole M. Transient left ventricular apical ballooning syndrome: All that glitters is not apical. *Journal of Cardiovascular Medicine*. 2007;**8**:934-936
- [15] Brandspiegel HZ, Marinchak RA, Rials SJ, Kowey PR. A broken heart. *Circulation*. 1998;**98**:1349
- [16] Gupta S, Goyal P, Idrees S, Aggarwal S, Bajaj D, Mattana J. Association of endocrine conditions

with takotsubo cardiomyopathy: A comprehensive review. *Journal of the American Heart Association*. 2018 Oct 2;7(19):e009003. DOI: 10.1161/JAHA.118.009003

[17] Bybee KA, Prasad A, Barsness GW, et al. Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. *The American Journal of Cardiology*. 2004;**94**:343-346

[18] Singal PK, Kapur N, Dhillon KS, Beamish RE, Dhalla NS. Role of free radicals in catecholamine-induced cardiomyopathy. *Canadian Journal of Physiology and Pharmacology*. 1982;**60**:1390-1397

[19] Bolli R, Marban E. Molecular and cellular mechanisms of myocardial stunning. *Physiological Reviews*. 1999;**79**:609-634

[20] Lacy CR, Contrada RJ, Robbins ML, et al. Coronary vasoconstriction induced by mental stress (simulated public speaking). *The American Journal of Cardiology*. 1995;**75**:503-505

[21] Mann DL, Kent RL, Parsons B, Cooper G. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation*. 1992;**85**:790-804

[22] Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature*. 1980;**288**(5789):373-376

[23] Mayer B, Hemmens B. Biosynthesis and action of nitric oxide in mammalian cells. *Trends in Biochemical Sciences*. 1997;**22**(12):477-481

[24] Hemmens B, Mayer B. Enzymology of nitric oxide synthases. *Methods in Molecular Biology*. 1998;**100**:1-32

[25] Stuehr DJ. Structure-function aspects in the nitric oxide synthases. *Annual Review of Pharmacology and Toxicology*. 1997;**37**:339-359

[26] Ayajiki K et al. Intracellular pH and tyrosine phosphorylation but not calcium determine shear stress-induced nitric oxide production in native endothelial cells. *Circulation Research*. 1996;**78**(5):750-758

[27] van Mourik JA, Romani d WT, Voorberg J. Biogenesis and exocytosis of Weibel-Palade bodies. *Histochemistry and Cell Biology*. 2002;**117**(2):113-122

[28] McDermott JR. Studies on the catabolism of Ng-methylarginine, Ng, Ng-dimethylarginine and Ng, Ng-dimethylarginine in the rabbit. *The Biochemical Journal*. 1976;**154**(1):179-184

[29] Cooke JP. Does ADMA cause endothelial dysfunction? *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2000;**20**(9):2032-2037

[30] Clarke S. Protein methylation. *Current Opinion in Cell Biology*. 1993;**5**(6):977-983

[31] Vallance P et al. Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. *Lancet*. 1992;**339**(8793):572-575

[32] MacAllister RJ, Whitley GS, Vallance P. Effects of guanidino and uremic compounds on nitric oxide pathways. *Kidney International*. 1994;**45**(3):737-742

[33] Olken NM, Marletta MA. NG-methyl-L-arginine functions as an alternate substrate and mechanism-based inhibitor of nitric oxide synthase. *Biochemistry*. 1993;**32**(37):9677-9685

[34] Pou S et al. Mechanism of superoxide generation by neuronal nitric-oxide synthase. *The*

Journal of Biological Chemistry. 1999;**274**(14):9573-9580

[35] Tripepi G et al. Inflammation and asymmetric dimethylarginine for predicting death and cardiovascular events in ESRD patients. *Clinical Journal of the American Society of Nephrology*. 2011;**6**:1714

[36] Perticone F et al. Endothelial dysfunction, ADMA and insulin resistance in essential hypertension. *International Journal of Cardiology*. 2010;**142**:236

[37] Sydow K et al. Distribution of asymmetric dimethylarginine among 980 healthy, older adults of different ethnicities. *Clinical Chemistry*. 2010;**56**:111

[38] Naegele M, Flammer AJ, Enseleit F, et al. Endothelial function and sympathetic nervous system activity in patients with takotsubo syndrome. *International Journal of Cardiology*. 2016;**224**:226-230. DOI: 10.1016/j.ijcard. 2016.09.008

[39] Camici PG, Crea F. Microvascular angina: A women's affair? *Circulation. Cardiovascular Imaging*. 2015. DOI: 10.1161/CIRCIMAGING. 115.003252

[40] Vitale C, Mendelsohn ME, Rosano GM. Gender differences in the cardiovascular effect of sex hormones. *Nature Reviews. Cardiology*. 2009;**6**:532-542. DOI: 10.1038/nrcardio.2009.105

[41] Kaski JC. Cardiac syndrome X in women: The role of oestrogen deficiency. *Heart*. 2006;**92**(Suppl 3): iii5-iii9

[42] Pelliccia F, Parodi G, Greco C, et al. Comorbidities frequency in takotsubo syndrome: An international collaborative systematic review including 1109 patients. *The American Journal of Medicine*. 2015;**128**(6):654.e11-e19

[43] Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *The New England Journal of Medicine*. 2015;**373**:929-938

[44] Tornvall P, Collste O, Ehrenborg E, Järnbert-Petterson H. A casecontrol study of risk markers and mortality in takotsubo stress cardiomyopathy. *Journal of the American College of Cardiology*. 2016;**67**:1931-1936. DOI: 10.1016/j.jacc.2016.02.029

[45] Pelliccia F, Greco C, Vitale C, Rosano G, Gaudio C, Kaski JC. Takotsubo syndrome (stress cardiomyopathy): An intriguing clinical condition in search of its identity. *The American Journal of Medicine*. 2014;**127**:699-704. DOI: 10.1016/j.amjmed.2014.04.004