

February 16, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Edited Manuscript NO: 8436.doc).

**Title:** Takotsubo cardiomyopathy: pathophysiology, diagnosis, and treatment

**Author:** Kazuo Komamura, Miho Fukui, Toshihiro Iwasaku, Shinichi Hirotsu, and Tohru Masuyama

**Name of Journal:** *World Journal of Cardiology*

**ESPS Manuscript NO:** 8436

The manuscript has been improved according to the suggestions of reviewers:

**1** Format has been updated.

Reviewers' comments were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

**2** Revision has been made according to the suggestions of the **reviewer 00227547**

*Comment: "The manuscript by Komamura et al is a well written review of the Takotsubo cardiomyopathy. Another review "Initial clinical presentation of Takotsubo cardiomyopathy with-a focus on electrocardiographic changes: A literature review of cases" by Sanchez-Jimenez, which is published is also worthwhile and should be cited."*

Response: We agree with the comment and cited that review by Sanchez-Jimenez as reference #19 in the revised manuscript.

**3** Revision has been made according to the suggestions of the **reviewer 00646232**

**(1)** *Comment 1: "In Epidemiology Section: There are some reported cases of TCM that occurred in children and young adults. "*

Response: We agree with that. We rewrote the previous sentence to "Although the average age at diagnosis is 68 years, some cases occurred in children and young adults<sup>[10,11]</sup>." in the revised manuscript. Revised sentences in the text are highlighted in red.

- (2) *Comment 2: “In Diagnosis Section: 1- Diagnosis should include history and clinical examination. The most common presenting symptoms are chest pain and dyspnea, although palpitations, nausea, vomiting, syncope, and rarely, cardiogenic shock have been reported. One of the more unique features of TCM is its association with a preceding emotionally or physically stressful trigger event, occurring in approximately two thirds of patients. Unlike acute coronary syndrome where peak occurrence is the morning hours, TCM events are most prevalent in the afternoon when stressful triggers are more likely to take place. Physical examination findings are nonspecific and often normal, but the patient may have the clinical appearance of having acute coronary syndrome or acute congestive heart failure.”*

Response: Thank you for your important comment. We completely agree with that. We added the following sentences into the *Diagnosis* section of original manuscript: “As indicated in both diagnostic criteria, physical examination findings are nonspecific and often normal, but the patient may have the clinical appearance of having acute coronary syndrome or acute congestive heart failure<sup>[14-16]</sup>. The most common presenting symptoms in diagnostic criteria are chest pain and dyspnea, although palpitations, nausea, vomiting, syncope, and rarely, cardiogenic shock<sup>[14-16]</sup>.”

And we also added the following sentences into the section of *An acute and stressful trigger*: “One of the more unique features of TCM is its association with a preceding emotionally or physically stressful trigger event, occurring in approximately two thirds of patients<sup>[17]</sup>. Unlike acute coronary syndrome where peak occurrence is the morning hours, TCM events are most prevalent in the afternoon when stressful triggers are more likely to take place.”

- (3) *Comment 3: “MRI angiography and coronary computed tomography (CT) angiography should be mentioned as one of the possible diagnostic tools. Cardiac magnetic resonance imaging may be a diagnostic modality uniquely suited for establishing the diagnosis of TCM by accurately visualizing regional wall motion abnormalities, quantifying ventricular function, and identifying reversible injury to the myocardium by the presence of edema/inflammation and the absence of necrosis/fibrosis. This technology may give new insight into the pathophysiology of TCM and be of potential use at acute presentation, broadening recognition and improving clinical outcomes. In addition to evaluating wall-motion abnormalities and LVEF, cardiac MRI has been found to differentiate TCM, characterized by the absence of delayed gadolinium hyperenhancement, from myocardial infarction and myocarditis, in which the opposite occurs. Although not indicated in the initial evaluation of patients with TCM, reports are emerging of*

*the use of coronary computed tomography (CT) angiography in the subsequent evaluation of patients with the disorder."*

Response: Thank you for your important comment. We completely agree with that. We added the following sentences into the section of *Ventricular "ballooning"*: "Cardiac magnetic resonance imaging (MRI) may be a diagnostic modality suited for establishing the diagnosis of TCM by accurately visualizing regional wall motion abnormalities, quantifying ventricular function, and identifying reversible injury to the myocardium by the presence of inflammation and the absence of fibrosis. This technology may give new insight into the pathophysiology of TCM and be of potential use at acute presentation, broadening recognition and improving clinical outcomes. In addition to evaluating wall-motion abnormalities and LVEF, cardiac MRI has been found to differentiate TCM, characterized by the absence of delayed gadolinium hyperenhancement, from myocardial infarction and myocarditis, in which the opposite occurs<sup>[17]</sup>. Although not indicated in the initial evaluation of patients with TCM, medical reports are emerging of the use of coronary computed tomography (CT) angiography in the subsequent evaluation of patients with TCM."

(4) *Comment 4: "Differential diagnosis of TCM should be added include the following: Esophageal spasm, Gastroesophageal reflux disease, Myocardial infarction, Myocardial ischemia, Unstable angina, Acute Coronary Syndromes Angina Pectoris, Aortic Dissection, Myocarditis, Acute pericarditis, Pneumothorax, Cardiogenic pulmonary edema, Pulmonary embolism, "Boerhaave Syndrome, "Cardiac Tamponade, "Cardiogenic Shock, Cocaine Cardiomyopathy, Dilated Cardiomyopathy, Hypertrophic Cardiomyopathy, "Coronary Artery Vasospasm.*

Response: Thank you for your important comment. We completely agree with that. We added the following sentences at the last part of **Diagnosis** section: "Differential diagnosis of TCM includes the following: Esophageal spasm, Gastroesophageal reflux disease, Myocardial infarction, Myocardial ischemia, Unstable angina, Acute Coronary Syndromes Angina Pectoris, Aortic Dissection, Myocarditis, Acute pericarditis, Pneumothorax, Cardiogenic pulmonary edema, Pulmonary embolism, Boerhaave Syndrome, Cardiac Tamponade, Cardiogenic Shock, Cocaine Cardiomyopathy, Dilated Cardiomyopathy, Hypertrophic Cardiomyopathy, Coronary Artery Vasospasm."

(5) *Comment 5: "The exact etiology of takotsubo cardiomyopathy (TCM) is still unknown, but several theories have been proposed and are being investigated. These include multivessel*

*coronary artery spasm, impaired cardiac microvascular function, impaired myocardial fatty acid metabolism, acute coronary syndrome with reperfusion injury, and endogenous catecholamine-induced myocardial stunning and microinfarction.*”

Response: We completely agree with that. We added the following sentences to the beginning part of **Pathophysiology** section: “The exact etiology of TCM is still unknown, but various theories have been proposed and are being investigated. These include multivessel coronary artery spasm, impaired cardiac microvascular function, impaired myocardial fatty acid metabolism, acute coronary syndrome with reperfusion injury, and endogenous catecholamine-induced myocardial stunning and microinfarction.”

(6) *Comment 6: “Risk factors should be added as sub title including: significant emotional or physical stressor.”*

Response: We agree with that. We newly added **Risk factor** section following the **Pathophysiology** section and added the following sentences:

“Significant emotional or physical stressor

A high prevalence of mood disorders and antidepressant use were reported in patients with TCM<sup>[49]</sup>. This may have pathogenic importance since patients with depressive disorders have decreased vagal tone and an increased adrenomedullary hormonal response to stressful events<sup>[50]</sup>, and some patients with depression have very high-noradrenaline spillover<sup>[51]</sup>.

Genetic propensity

Specific polymorphisms of alpha- and beta adrenergic receptors have been associated with neurogenic stunned myocardium following subarachnoid hemorrhage, a condition that almost certainly shares an overlapping pathophysiology with TCM<sup>[52]</sup>. While adrenergic receptor polymorphisms have not been identified yet in patients with TCM, patients with this disorder appear to have an increased frequency of the L41Q polymorphism of the G protein coupled receptor kinase 5 (GRK5) compared to a control population<sup>[53]</sup>. The L41Q polymorphism of GRK5 attenuates the beta-adrenergic receptor’s response to catecholamine stimulation. In the setting of catecholamine stimulation, ventricular ballooning might result from either a negative inotropic effect due to beta-receptor uncoupling or from ischemia resulting from an imbalance between alpha1-adrenergic coronary vasoconstriction and beta-adrenergic vasodilation. These reports suggest the exciting possibility that individual susceptibility to TCM may in part be genetically influenced.”

We also added the following 5 references according to the above-mentioned changes in the manuscript:

“Mudd JO, Kapur NK, Champion HC, Schulman SP, Wittstein IS. Patients with stress-induced (Takotsubo) cardiomyopathy have an increased prevalence of mood disorders and antidepressant use compared to patients with acute myocardial infarction. *J Cardiac Fail* 2007;13(Supplement 2):S176 PMID: 19358948 [doi:10.1016/j.jacc.2009.02.020](https://doi.org/10.1016/j.jacc.2009.02.020)

Cevik C, Nugent K The role of cardiac autonomic control in the pathogenesis of tako-tsubo cardiomyopathy. *Am Heart J* 2008;156:e31 PMID: 18760115 [doi:10.1016/j.ahj.2008.06.016](https://doi.org/10.1016/j.ahj.2008.06.016)

Barton DA, Dawood T, Lambert EA, Esler MD, Haikerwal D, Brenchley C, Socratous F, Kaye DM, Schlaich MP, Hickie I, Lambert GW. Sympathetic activity in major depressive disorder: Identifying those at increased risk? *J Hypertens* 2007;25:2117–2124 PMID: 17885556

Zaroff JG, Pawlikowska L, Miss JC, Yarlagadda S, Ha C, Achrol A, Kwok PY, McCulloch CE, Lawton MT, Ko N, Smith W, Young WL. Adrenoceptor polymorphisms and the risk of cardiac injury and dysfunction after subarachnoid hemorrhage. *Stroke* 2006;37:1680–1685 PMID: 16728691

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 PMID: 20023040 [doi:10.1093/eurjhf/hfp173](https://doi.org/10.1093/eurjhf/hfp173)”

4 References and typesetting were corrected, and highlighted in red.

Thank you again for publishing our manuscript in the *World Journal of Cardiology*.

Sincerely yours,

A handwritten signature in black ink that reads "Kazuo Komamura". The signature is written in a cursive style with a large, sweeping flourish at the end.

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