

Peer Review File

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Reviewer A

Comment 1: 132-135: "The frequency of keywords and centrality data suggests that TTS has various names, belongs to the heart failure syndrome category, and is closely related to myocardial infarction, which often needs to be differentiated in clinical practice, including electrocardiogram (ECG) findings of "st segment elevation".

Regarding our expertise in this specific topic, this is just wrong. However, if I missed something, you should at least cite the source of this information.

Reply 1: Although it is mentioned that TTC is a reversible heart failure and is a condition characterized by signs and symptoms of acute myocardial infarction in the article titled "Takotsubo cardiomyopathy: a new form of acute, reversible heart failure"¹, the idea is really incorrect based on the current understanding of TTS. The data can only indicate that TTS has a clinical presentation similar to heart failure or infarction, so I have modified this sentence to "The frequencies of keywords and centrality data suggest that TTC has various names, and that it can present as left-sided heart failure or as a myocardial infarction-like manifestation on the electrocardiogram, such as "st-segment elevation", which often needs to be distinguished in clinical practice."

Changes in the text: we have modified our text as advised (see Page 7, line 138-141)

Comment 2: 222-224: "Less attention has been paid to the present condition before the demarcation line, as TTS is generally considered a relatively benign condition with rapid recovery of left ventricular function." According to the current state of science, this is not correct. Increasing evidence suggests that Takotsubo has a similar mortality rate to ACS.

Reply 2: We used the consensus published by ESC in 2015 as the cut-off for the TTS study. It is the inappropriate perception of TTS before the cut-off that is described here, and the recognition that the mortality rate of TTS is comparable to that of ACS after the cut-off, which we also describe in the text.

Changes in the text: we have modified our text as advised (see Page 3, line 45-47; Page 11, line 238-240.)

Comment 3: 249-250: risk factors are mixed in the context of development and prognosis. You should further elaborate on what exactly you wanted to describe.

Reply 3: Here we briefly cite a few examples of risk factors for TTC in order to simply show that research on risk factors is not yet complete and that other risk factors need to be further investigated.

We have made some revisions and additions in the manuscript.

Changes in the text: we have modified our text as advised (see Page 12, line 252-256)

Comment 4: 273-277: The transition from catecholamines to cortisol and then to baroreceptors is perhaps a bit too quick, lacking citations for the reader to delve into the related literature.

Reply 4: We have made some revisions in the manuscript.

Changes in the text: we have modified our text as advised (see Page 14, line 286-302)

Comment 5: 286-288: Patients with AF compared to normal patients without AF might show the same effect? Discuss or describe further..

Reply 5: We agree with your point of view. In the current state of research, no study has explored the effects of TTC on the prognosis of atrial fibrillation (AF), so it is not known whether the poor prognosis of TTC with AF is caused by the AF itself. Therefore, we cannot claim that patients with AF show the same effect as normal people without AF. We can only observe this phenomenon. This problem deserves further study from researchers. In addition, we added some evidence that AF is associated with TTC prognosis.

Changes in the text: we have modified our text (see Page 15, line 313-319)

Reviewer B

Comment: I would say that yours is an “out of line” essay, at the borders between clinical cardiology, semeiotics, anthropology, mathematics and biostatistical sciences, and... I hope to help with my generally sympathetic comments to your cause. Taking alternative paths sometimes is useful at other times is not...

After dedicating significant time to read your essay, I must say that I am not sure of your aims: are after improving our understanding of the TTS pathophysiology? Do you want to underline the confusion in the current literature on TTS? Do you attempt to suggest that a new language and technique is the best way to understand TTS?

Apparently, the authors decided to use a new method to search and interpret medical literature, based on CiteSpace software, a new and generally unknown discipline (“a visualization technology” apparently). You should probably increase the explanation of the presently hardly-understandable new technique: that should include a more complete quote of the sources on bibliometric analysis software by Chaomei Chen et al. The bulk of the “chosen literature” (see the references: 34 out of 2349 “reviewed”) is defined by its popularity. Be aware that the discipline studying TTS is not at all conclusive and clear on the same nature of this entity: after some 30ys since the name TTC (or transient apical ballooning cardiomyopathy in the fashion of a Takotsubo) was introduced, we do not know its causes, its strict testing (by way of a test able to reproduce the entity, like only achievable by the acetylcholine test).

You must recognize that your language is new in many aspects and the innovation results frequently not to be understandable to the expected readership (English-speaking cardiologists, I assume).

I would tentatively suspect that you started with the notion that TTS is a known entity (caused by catecholamines surge or stress) and that this is the firm opinion of the “holders of truth on TTS”, but I propose to you that TTS continues to fundamentally be a fascinating but confusing entity, that needs progress in basic research, more than an elaboration on the words that literature is using. This reviewer proposes to you the notion that words are not necessarily the reality or the “truth” but only means to understand it. Your essay seems to imply that medicine discourse could be taken as a probability game: elaborating words can generate a novel understanding, but I am not

sure about it.

Incidentally, your comments about estrogens and endothelial dysfunction (or microvascular dysfunction) should probably mention the sources and the literature about acetylcholine testing and coronary spasm (this is the missing hypothesis on TTS pathophysiology you don't mention but somebody believes).

Also, about the basic name of TTS: if you look at Table 1 in your text, you must realize that 9 out of 10 papers (the most quoted!) talk about TTC (cardiomyopathy is indeed the basic common denominator we discuss not the variable, unessential associated conditions).

I firmly believe you could have something important to say on TTC, but your Methods and elaboration of "Results" must be improved.

Reply 1: In the methods section, we used the visualization tool of Chao-Mei Chen's team to perform an econometric analysis of the literature on TTS, and the main addition we made, as you suggested, was the explanation of new technique.

Changes in the text: we have modified our text as advised (see Page 5, line 90-92; Page 5, line 106-109; Page 8, line 165-166; Page 10, line 208-209)

Reply 2: We aim to contribute to the advancement of research by providing an overview of the current knowledge of the disease, and exploring the hot spots and frontiers of research. Furthermore, we use citespace to make our conclusions more objective.

Reply 3: We have revised and supplemented the results, such as the content of acetylcholine testing and coronary artery spasm, as well as the deficiencies of the research.

Changes in the text: we have modified our text as advised (see Page 13, line 265-281; Page 16, line 348-352.)

Reply 4: Also, based on the article results and your suggestions, we changed the "TTS" to "TTC".

Reply 5: We had a native speaker revise the language of the manuscript. We are confident that our research will lead to more collisions and sparks of knowledge.

¹ Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. *Circulation*. 2008 Dec 16;118(25):2754-62. doi: 10.1161/CIRCULATIONAHA.108.767012. PMID: 19106400; PMCID: PMC4893309.