Author's response to reviews

Title: Recurrent Tako-Tsubo cardiomyopathy (TTC) in a pre-menopausal woman. Late sequelae of a traumatic event?

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Author's response to reviews: see over
“Recurrent Tako-Tsubo cardiomyopathy (TTC) in a pre-menopausal woman. Late sequelae of a traumatic event?” by Jochen Hefner, Herbert Csef, Stefan Frantz, Nina Glatter and Bodo Warrings

Dear Mr. Tacbobo,

Thank you for letting us see the helpful reviewers’ comments which we have substantially responded to. We now submit a revised paper for your consideration and hope that this will be satisfactory.

Corrections are in red. Below is our point by point response to the reviewers.

Sincerely,

Jochen Hefner
We highly appreciate the very helpful reviewer’s comments with regard to our manuscript. Please find a detailed list of our responses below. The manuscript has been corrected accordingly. Please find corrections in red ink.

Reviewer #1

This is an interesting case report of fourfold tako tsubo cardiomyopathy (TTC) in a pre-menopausal woman.

*Thank you.*

However, in my opinion, there are some issues that require clarification or adjustment

Minor issues:

1) References: To my knowledge, the first paper about TTC is SATO H, TATEISHI H, UCHIDA T, DOTE K, ISHIHARA M. Stunned myocardium with specific (tsubo-type) left ventriculographic configuration due to multi vessel spasm. In: Kodama K, Haze K, Hori M, eds. Clinical Aspects of Myocardial Injury: From Ischemia to Heart Failure. Kagakuhyouronsya Co; Tokyo, 1990: pp. 56-64

*This is indeed right. We corrected the reference. Please see page 4, lines 81-83 and reference 1:*

“This Tako-Tsubo cardiomyopathy is a syndrome first described by Sato et al. in 1991 [1] consisting of transient wall motion abnormalities most often involving the apical ventricle.”

2) Define at first use with acronym or abbreviation in parentheses: page 4 line 82: added “electrocardiogram” before (ECG).

*Agreed. The manuscript has been corrected accordingly. Please see page 4, lines 83-85:*

“Abnormalities of the electrocardiogram (ECG) and myocardial enzyme release may mimic acute coronary syndrome (ACS) in the angiographic absence of coronary artery disease [2].”
Major issues:

1) Background: Appropriately, the authors stress that TTC “is not entirely benign”. However, it would also be important to add that this cardiomyopathy should be reconsidered as a clinical condition at high risk for lethal arrhythmias, in a subpopulation with QTc > 500 msec in acute phase. TTC is one of the causes of acquired long QT syndrome. Antipsychotic and antidepressant drugs and psychiatric illnesses (anorexia nervosa) are known to increase the risk of QT prolongation: the combination with TTC makes the acute and subacute prognosis of this disease much more severe than usual.

_We fully agree with this important comment. The manuscript has been tuned up accordingly and the respective references were added. Please see page 4, lines 88-93 and references 7,8:_

“For example, prolongation of the QT-interval is a well known finding in patients with acute TTC [7]. In a subgroup of patients, the severe prolongation of the QT-interval (QTc>500ms) may be a marker for the risk of sudden death [7]. Furthermore, in patients with pre-existing long QT syndrome or concomitant psychiatric diseases and respective medication, TTC may lead to lethal arrhythmias [8].”

2) Case Presentation: page 6 line 144, 145 “Tentative diagnosis was non-STEMI myocardial infarction as ECG was normal and Troponin T levels rose to 0.22ng/ml”: it is possible that the first ECG is normal but it is very unlikely that subsequent ECG are normal. However, I think that is important one figure of abnormal ECG.

_This is a very helpful comment. A figure of an abnormal ECG has been added. Please see page 7, lines 164-166, and figure 2:_

“ECG showed T-wave inversions in leads V2-V3 (Figure 2), and Troponin T levels were at 0.14ng/ml.”

3) Case Presentation: page 7 line 173, 174 “During the fourth event and because of a depressive syndrome, medication with Mirtazapine was initiated”. It is interesting to know whether the patient had taken other antidepressants and/or neuroleptics. The use of serotonin and norepinephrine reuptake inhibitor was associated with TTC. An excess of catecholamines may play a major pathogenetic role. These drugs may have precipitated TTC by increasing plasma catecholamine concentration in a predisposed patient.
Thank you for this helpful comment. The history of the patient has been amended and the problem of SNRIs has been addressed. Respective references were added. Please see page 7-8, lines 179-184 and references 45-47:

“During the fourth event and due to a depressive syndrome, psychosomatic support was once again recommended. This time the patient agreed and for the first time, an antidepressant was administered. Because of latest reports of TTC associated with the use of serotonin and noradrenaline reuptake inhibitors, we selected Mirtazapine in order to avoid increased plasma catecholamine concentrations [45-47].”

Reviewer #2

It is indeed a quite interesting case report.

Thank you for this kind comment.

Referring back to my case report and literature review titled,“Tako Tsubo Cardiomyopathy following Colonoscopy: Insights on pathogenesis” published in International Journal of Cardiology 2011 Mar 17;147(3):e46-9. (DOI:10.1016/j.ijcard.2009.01.034) has actually put forth the hypothetical association of concurrent sympathetic over activity and vagal withdrawal with the development of TTC.

This is a very helpful comment. The possible pathomechanism has been included and the paper has been cited. Please see page 5, lines 106-108 and reference 22:

“In latest reports, a hypothetical association of concurrent sympathetic over activity and vagal withdrawal has been proposed [22].”
According to the editorial request, the following changes have also been made:

- The manuscript has been revised by the authors in order to improve the style of written English.

- The title page has been modified according to the instructions.

- The author names and addresses in the manuscript and the submission system have been harmonized.

- The affiliations of the authors are indicated by numbers.

- There were no acknowledgments added.

- One figure was added according to reviewer #1. Figure legends are included in the main manuscript.

  The figure files were revised.

- The patient consent form is removed.

- The manuscript now conforms to the journal style.