

Response Letter

Dear Editors and Reviewer,

Thank you very much for your letter and advice. We have revised the manuscript (Manuscript NO.: 59431, Case Report), and would like to re-submit it for your consideration. Point-by-point responses to the reviewer and editors' comments are listed below this letter. We have also submitted all required accompanying documents.

We thank editors and reviewer for their constructive criticisms that have helped us to improve the manuscript. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in World Journal of Clinical Cases.

Thank you for your consideration and please feel free to contact us if we can improve our manuscript in any way.

With best wishes,

Yours sincerely,

Corresponding author: Hao-Yu Wu
MD, PhD, Chief Doctor, Research Fellow
wxs5132006@163.com

Responds to the reviewer's comments

We would like to express our sincere thanks to you for the constructive and positive comments. Please feel free to contact us if we can improve our manuscript in any way.

Replies to 3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to the issues raised in the peer review report. Authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and make point-by-point responses to the issues raised in the peer-review report(s), which are listed below:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Recurrent Takotsubo cardiomyopathy triggered by emotionally stressful events: A case report Wu et al. This well written case report has merit in raising awareness of clinicians to consider this rare entity. - What is the optimal pharmacological treatment of TCM since the patient was treated after the first episode with diltiazem and perindopril and after the 3rd perindopril and metoprolol? - What were the stressful events? - Why is ventriculography superior to TTE in diagnosing ballooning? Or is it? - Comment on 3 normal coronary angiograms in 3 years... - The 3 TTEs revealed EFs of 52, 47 and 55% hardly great differences please comment, not remarkably improved in this reviewer's opinion. - The term nonobstructive coronary artery disease is inappropriate, please modify throughout the text, should be no evidence of CAD - Explain troponin as predictors of in-hospital prognosis page 8 - Why are BNP higher in TCM? - Comment on the low rate of ventriculography in your center. Is this standard of care? Isn't echo good enough in TCM, please explain.

(1) What is the optimal pharmacological treatment of TCM since the patient was treated after the first episode with diltiazem and perindopril and after the 3rd perindopril and metoprolol?

Answer: The management of patients with TCM is largely supportive and conservative. There are no published randomized control trials, but β -blockers and angiotensin-converting enzyme inhibitors have proven effective according to some case reports. Evidence-based guidelines specifically for treatment of TCM do not exist.

Due to the unawareness of TCM, the patient treated after the first episode with diltiazem and perindopril with a suspected diagnosis of coronary artery spasm. The patient was treated with perindopril and metoprolol with a diagnosis of TCM until

the third hospitalization with a left ventriculogram.

We summarized this point in the text (DISCUSSION, paragraph 3). We hope that we have answered and clarified the comment to your full satisfaction and look forward to your further reply. Please feel free to contact us if we can improve our manuscript in any way.

(2) What were the stressful events?

Answer: The first stress event was a quarrel with her husband. The second stress event was a quarrel with her husband again. The third stress event was business failure.

We added the stressful events in the text (CASE PRESENTATION, History of present illness). We hope that we have answered and clarified the comment to your full satisfaction and look forward to your further reply. Please feel free to contact us if we can improve our manuscript in any way.

(3) Why is ventriculography superior to TTE in diagnosing ballooning? Or is it?

Answer: Transthoracic echocardiography is a non-invasive imaging technique to verify a suspected diagnosis of TCM. Key echocardiographic features during the acute phase consist of a large area of dysfunctional myocardium extending beyond the territory of a single coronary artery and usually characterized by symmetrical regional abnormalities involving the mid-ventricular segments of the anterior, inferior, and lateral walls (a circumferential pattern). However, the wall motion abnormalities of TCM may recover in hours and may be missed if imaging is delayed. Many hospitals, especially our hospital, cannot do emergency echocardiography. At the same time, some echocardiographers lack the knowledge of TCM. Therefore, selective echocardiography may not be able to find the typical ultrasonic manifestations of TCM. But patients need urgent coronary angiography to exclude STEMI or NSTEMI because they present with cardiac chest pain that could be interpreted as an ACS, and urgent ventriculography can be performed at the same time to verify a suspected diagnosis of TCM. Emergency coronary angiography and ventriculography can be performed in chest pain centers. Therefore, ventriculography is frequently used in the diagnosis of TCM.

We summarized this point in the text (DISCUSSION, paragraph 6). We hope that we have answered and clarified the comment to your full satisfaction and look forward to your further reply. Please feel free to contact us if we can improve our manuscript in any way.

(4) Comment on 3 normal coronary angiograms in 3 years...

Answer: Obstructive coronary artery disease is often considered to be the most common cause of chest pain. The patient need urgent coronary angiography to exclude NSTEMI because she presented with cardiac chest pain and elevated troponin I. Coronary angiography is also necessary during the chronic stage to confirm the presence or absence of a significant stenotic lesion or a lesion involved in the abnormal pattern of ventricular contraction. In diagnosing TCM, it is essential to exclude significant coronary stenosis and coronary artery dissection. So the patient performed 3 coronary angiograms in 3 years. TCM was missed diagnosis until the third hospitalization with a left ventriculogram.

We summarized this point in the text (DISCUSSION, paragraph 6). We hope that we have answered and clarified the comment to your full satisfaction and look forward to your further reply. Please feel free to contact us if we can improve our manuscript in any way.

(5) The 3 TTEs revealed EFs of 52, 47 and 55% hardly great differences please comment, not remarkably improved in this reviewer's opinion.

Answer: The 3 TTEs with EFs of 52%, 47% and 55% were performed by an experienced transthoracic echocardiogram doctor in our department, and the EF differed by about 10% each time. Therefore, we think there are some differences in EF values among the three times. We hope that we have answered and clarified the comment to your full satisfaction and look forward to your further reply. Please feel free to contact us if we can improve our manuscript in any way.

(6) The term nonobstructive coronary artery disease is inappropriate, please modify throughout the text, should be no evidence of CAD.

Answer: Thanks for your constructive comments. We have modified the term "nonobstructive coronary artery disease" to "no evidence of coronary artery disease (CAD)" throughout the text. Please feel free to contact us if we can improve our manuscript in any way.

(7) Explain troponin as predictors of in-hospital prognosis page 8.

Answer: Troponin is elevated in the setting of membrane leak caused by acute myocardial necrosis. Frequently significant troponin rise, proportional to the hypokinetic area.

We summarized this point in the text (DISCUSSION, paragraph 5). We hope that we have answered and clarified the comment to your full satisfaction and look forward to your further reply. Please feel free to contact us if we can improve our manuscript in any way.

(8) Why are BNP higher in TCM?

Answer: BNP has pathophysiologic importance as a cardiac hormone in congestive heart failure and an elevated plasma concentration of BNP is an established marker of left ventricular dysfunction. The production and release of BNP is related to ventricular distention with or without myocyte necrosis. Because TCM is a disease primarily causing distention of the ventricles and characterized by reversible myocardial dysfunction, a greater increase in plasma BNP compared with Troponin T or CKMB has been demonstrated, compared with acute coronary syndrome. Thus Plasma BNP levels are usually greater in TCM.

We summarized this point in the text (DISCUSSION, paragraph 5). We hope that we have answered and clarified the comment to your full satisfaction and look forward to your further reply. Please feel free to contact us if we can improve our manuscript in any way.

(9) Comment on the low rate of ventriculography in your center. Is this standard of care? Isn't echo good enough in TCM, please explain.

Answer: Obstructive coronary artery disease is frequently considered to be the cause of chest pain. Due to the unawareness of clinicians, many cases of TCM may be underdiagnosed, although our department is the National Chest Pain Center. Therefore, the low rate of ventriculography in our center may be related to physicians' insufficient awareness of TCM. We added this point in the text with red color.

Transthoracic echocardiography is a non-invasive imaging technique to verify a suspected diagnosis of TCM. Key echocardiographic features during the acute phase consist of a large area of dysfunctional myocardium extending beyond the territory of a single coronary artery and usually characterized by symmetrical regional abnormalities involving the mid-ventricular segments of the anterior, inferior, and lateral walls (a circumferential pattern). However, the wall motion abnormalities of TCM may recover in hours and may be missed if imaging is delayed. Many hospitals, especially our hospital, cannot do emergency echocardiography. At the same time, some echocardiographers lack the knowledge of TCM. Therefore, selective echocardiography may not be able to find the typical ultrasonic manifestations of TCM. But patients need urgent coronary angiography to exclude STEMI or NSTEMI because they present with cardiac chest pain that could be interpreted as an ACS, and urgent ventriculography can be performed at the same time to verify a suspected diagnosis of TCM. Emergency coronary angiography and ventriculography can be performed in chest pain centers. Therefore, ventriculography is frequently used in the diagnosis of TCM.

We summarized this point in the text (DISCUSSION, paragraph 6). We hope that we

have answered and clarified the comment to your full satisfaction and look forward to your further reply. Please feel free to contact us if we can improve our manuscript in any way.

Responds to editors

We would like to express our sincere thanks to the reviewer for the constructive and positive comments. Please feel free to contact us if we can improve our manuscript in any way.

Replies to 1 MANUSCRIPT REVISION DEADLINE

We request that you submit your revision in no more than 14 days.

Answer: We submit our revision in no more than 14 days after receiving mail.

Replies to 2 PLEASE SELECT REVISE THIS MANUSCRIPT OR NOT

Please login to the F6Publishing system at <https://www.f6publishing.com> by entering your registered E-mail and password. After clicking on the "Author Login" button, please click on the "Manuscripts Needing Revision" under the "Revisions" heading to find your manuscript that needs revision. Clicking on the "Handle" button allows you to choose to revise this manuscript or not. If you choose not to revise your manuscript, please click on the "Decline" button, and the manuscript will be WITHDRAWN.

Answer: We choose to revise our manuscript. We hope that the revised version of the manuscript is now acceptable for publication in the journal.

Replies to 4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Answer: This manuscript has been edited for proper English language, grammar, punctuation, spelling, and overall style by a highly qualified native English speaking editor at American Journal Experts (AJE). Language editing certificate has been uploaded as an attachment (59431-Non-Native Speakers of English Editing Certificate).

Replies to 5 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: 1 Scientific quality: The manuscript describes a case report of the recurrent takotsubo cardiomyopathy triggered by emotionally stressful events. The topic is within the scope of the WJCC. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: This well written case report has merit in raising awareness of clinicians to consider this rare entity; and (3) Format: There are 4 tables and 1 figure. A total of 26 references are cited, including 15 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A. A language editing certificate issued by AJE was provided. 3 Academic norms and rules: The authors provided the written informed consent and CARE Checklist-2016; Please provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement; No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by Natural Science Basic Research Program of Shaanxi Province and Science and Technology Development Incubation Fund Project of Shaanxi Provincial People's Hospital. The topic has not previously been published in the WJCC. The corresponding author has one published articles in the BPG. 5 Issues raised: (1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

Answer: The signed Conflict-of-Interest Disclosure Form has been uploaded as an attachment (59431-Conflict-of-Interest Disclosure Form).

The Copyright License Agreement has been uploaded as an attachment (59431-Copyright License Agreement).

Approved grant application form(s) or funding agency copy of any approval document(s) has been uploaded as an attachment (59431-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)).

Original figure documents have been uploaded as an attachment (59431-Figures.ppt).

(2) Editorial office director: I have checked the comments written by the science editor.

Answer: Thank you very much.

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Answer: Thank you very much.

Replies to **6 STEPS FOR SUBMITTING REVISED MANUSCRIPT**

Step 1: Author Information

Please click and download the Format for authorship, institution, and corresponding author guidelines, and further check if the authors names and institutions meet the requirements of the journal.

Answer: We have checked that the authors names and institutions met the requirements of the journal.

Step 2: Manuscript Information

Please check if the manuscript information is correct.

Answer: We have checked that the manuscript information was correct.

Step 3: Abstract, Main Text, and Acknowledgements

(a) Guidelines for revising the content: Please download the guidelines for Original articles; Review articles; and Case report articles for your specific manuscript type (Case Report) at: <https://www.wjgnet.com/bpg/GerInfo/291>. Please further revise your manuscript according to the guidelines for revising the content.

Answer: We have further revised our manuscript according to the guidelines for revising the content.

(b) Format for Manuscript Revision: Please update the format of your manuscript according to the guidelines and requirements for manuscript revision and the format

for manuscript revision. Please visit <https://www.wjgnet.com/bpg/GerInfo/291> for the article type-specific guidelines and formatting examples.

Answer: We have updated the format of our manuscript according to the guidelines and requirements for manuscript revision and the format for manuscript revision.

(c) Requirements for article highlights: If your manuscript is an original study (basic study or clinical study), meta-analysis, or systemic review, the “Article Highlights” section should be provided. Detailed writing requirements for “Article Highlights” can be found in the Guidelines and Requirements for Manuscript Revision.

Answer: The “Core tip” has been provided in the text.

Step 4: References

Please revise the references according to the Format for references guidelines, and be sure to edit the reference using the reference auto-analyser.

Answer: We have revised the references according to the Format for references guidelines, and be sure to edit the reference using the reference auto-analyser.

Step 5: Footnotes and Figure Legends

(a) Requirements for figures: Please provide decomposable Figures (whose parts are all movable and editable), organize them into a single PowerPoint file, and submit as “59431-Figures.ppt” on the system. The figures should be uploaded to the file destination of “Image File”.

Answer: We have provided decomposable Figures (whose parts are all movable and editable), organize them into a single PowerPoint file, and submit as “59431-Figures.ppt” on the system. The figures have been uploaded to the file destination of “Image File”.

(b) Requirements for tables: Please provide decomposable Tables (whose parts are all movable and editable), organize them into a single Word file, and submit as “59431-Tables.docx” on the system. The tables should be uploaded to the file destination of “Table File”.

Answer: We have provided decomposable Tables (whose parts are all movable and editable), organize them into a single Word file, and submit as “59431-Tables.docx” on the system. The tables have been uploaded to the file destination of “Table File”.

Step 6: Automatically Generate Full Text Files

Please download the "Full Text File" or click "Preview" to ensure all the contents of the manuscript automatically generated by the system are correct and meet the requirements of the journal.

Answer: We have downloaded the "Full Text File" to ensure all the contents of the manuscript automatically generated by the system are correct and meet the requirements of the journal.

Step 7: Upload the Revision Files

For all required accompanying documents (listed below), you can begin the uploading process via the F6Publishing system. Then, please download all the uploaded documents to ensure all of them are correct.

Answer: We have submitted all required accompanying documents.