

Peer Review File

Article Information: <https://dx.doi.org/10.21037/apm-21-855>

Reviewer A

Comment 1-In this paper, wall motion abnormality at the apex is described as a characteristic of Takotsubo cardiomyopathy, but it is reported that left ventricular wall motion abnormality in Takotsubo syndrome is recognized not only at the apex but also in other regions.

Reply 1

Thank you for your comments. We have read your comments carefully and agree with your comments. It has been shown that left ventricular dysfunction in Takotsubo syndrome includes not only the classic apical ballooning, but also different morphologies such as mid-ventricular ballooning and, rarely, local ballooning of other segments (*Ghadri et al. European Heart Journal. 39 (2018) 2047–2062*), this is mentioned in our **discussion** section (see Page 9, line 188-191). However, no abnormal changes other than apical were found in this patient.

Page 9, line 188-191

Although apical ballooning has been classically described as the manifestation of TTS by angiography and TTE, it has been shown that left ventricular dysfunction in TTS includes not only classic apical ballooning but also different morphologies, such as mid-ventricular ballooning and, rarely, local ballooning of other segments.

Comment 2-It is necessary to suspect acute coronary syndrome in the electrocardiogram shown in Fig. 1a, and it is desirable to be transported to the appropriate hospital regardless of knowledge of Takotsubo syndrome.

Reply 2

We would like to thank you for your constructive comments and suggestions. We agree with your comments. When we encounter a situation like this, it is desirable to be transported to the appropriate hospital regardless of knowledge of Takotsubo syndrome.

Fig. 1a showed the ECG on 4 months after onset when the patient came to our hospital (the fourth hospital). If we look only at Fig. 1a, the patient does need to be considered for the possibility of myocardial ischemia. Fig. 1a showed that a Q-wave present in lead III (didn't mean a myocardial infarction absolutely) but their corresponding T-waves were upright, which could indicate an old myocardial infarction. Bidirectional or inverted T-waves could be seen in the anterior wall, and mild ST-segment depression in V4-6, suggesting the possibility of myocardial ischemia. Combined with the patient's ECG 4 months ago, the Q-wave in lead III already existed, and there was no obvious occlusion in the coronary angiography on the 12th day of onset, therefore, we considered a Q-wave in lead III was not caused by coronary heart disease. Based on the patient's clinical manifestations, ECG and imaging examination, it was more supportive of the presence of Takotsubo syndrome in the early stage of onset, whereas the ECG at our hospital was more like the recovery phase ECG, and when we provided symptomatic supportive treatment such as cough suppression, the patient's cough symptoms rapidly improved. Therefore, we did not consider the presence of acute coronary syndrome in the patient.

According to your suggestion, in the description of the **case presentation** regarding the ECG, we added some data "a Q-wave visible in lead III" in the text. (see Page 4, line 71; Page 5, line 93-94, line 106-107)

Changes in the text:

Page 4, line 71

The electrocardiogram (ECG) showed sinus tachycardia, shallow T-waves inversion in leads V2-V5, and a Q-wave visible in lead III (Fig. 1a).

Page 5, line 93-94

The ECG shows sinus rhythm, occasional ventricular premature beats, and Q-waves visible in lead III (Fig. 1b).

Page 5, line 106-107

The ECG showed diffuse and deep T-waves inversion in leads I and II, AVL, V2-V9, and Q-waves visible in lead III (Fig. 1c).

Comment 3-*The reviewers also think that there is little evidence that Takotsubo syndrome developed 4 months ago. Changes in ECG and left ventricular wall motion abnormalities in Takotsubo syndrome and how long these abnormalities persist should be discussed.*

Reply 3

Thanks for your valuable advice. This case was a retrospective diagnosis. According to the patient's past medical history, cardiac ultrasound and left ventriculogram images, etc. we considered that she should be diagnosed with Takotsubo syndrome when she visited the second hospital four months ago.

First, stress-induced catecholamine release for sympathetic activation plays a central role in the pathophysiology of Takotsubo syndrome (*Lyon et al. Eur J Heart Fail. 18 (2016) 8-27*). For this patient, cervical spondylopathy probably led to cerebral ischemia attack and secondary vagal excitation, presenting as sweating, nausea, and repeated vomiting, which caused the excessive loss of body fluid and hypotension, and then led to high sympathetic tone. She was sent to the first hospital on the first day, then was treated with vasopressors, dopamine, and dobutamine, which further activated sympathetic adrenergic receptors, and finally the manifestations of Takotsubo syndrome presenting as further hypotension and orthopnoea. Thus, she was transferred to a municipal hospital (the second hospital) on the third day of onset. The ECG showed diffuse and deep T-waves inversion in leads I, II, AVL, V2-V9. The research showed that the ECG in Takotsubo syndrome demonstrates temporal evolution typically with a

resolution of initial ST-segment elevation, followed by progressive T-waves inversion and QT interval prolongation over several days, with subsequent gradual resolution of T-waves inversion and QT interval prolongation over days to weeks and thereafter T-waves inversion remained the most prevalent ECG abnormality up until 3 months. Seventeen percent of patients had residual T-waves inversion up until 1 year. (*Ghadri et al. European Heart Journal. 39 (2018) 2047–2062; Bennett et al. International Journal of Cardiology 169 (2013) 276–280*). Therefore, we speculated that the patient may have had ST-segment elevation in the early stages of onset, whereas the ECG at our hospital was more like the patient's ECG in the recovery phase.

Furthermore, the patient accepted cardiac catheter examinations and cardiac ultrasound on the 12th day of onset (the second hospital). Left ventriculography showed that she did have left ventricular outflow tract stenosis and cardiac ultrasound revealed local interventricular septum hypertrophy at the basement (17.8 mm), left ventricular outflow tract narrow (9.6 mm) with increased blood flow velocity (335 cm/s), decreased ejection fraction of left ventricle (40%). Left ventricular wall movement was poor coordinated, which supported our diagnosis. We speculated that the patient's outflow tract obstruction was more serious in the early stage of onset. When the patient came to our hospital (the fourth hospital), we suspected the possibility of Takotsubo syndrome and asked the cardiac ultrasound specialist to repeat and observed the patient's ventricular septum changes and found that the patient no longer had outflow tract stenosis, but the ventricular septum was still unevenly thickened (11-14 mm). However, compared with the first cardiac ultrasound result (17.5mm) on the 12th day of onset, the thickness was significantly reduced. Recent studies have shown subtle long-term clinical and echocardiographic consequences even after 6 to 12 months in Takotsubo syndrome (*Lee et al. J Cardiovasc Imaging. 28 (2020) 50-60; Kobayashi et al. Echocardiography. 34 (2017) 523-529*), which supports our conclusion.

At last, the patient's cardiac ultrasound showed uncoordinated ventricular wall motion on the 12th and 19th day of the onset (checked in the second hospital and the third hospital respectively). When the patient came to our hospital 4 months after onset (the fourth hospital), left ventricular wall motion was coordinated. A study showed that

wall motion abnormalities usually resolve within 4 to 8 weeks of the acute event (*Tak et al. WMJ. 117 (2018) 171-174*). The ventricular wall motion had recovered when the patient came to our hospital four months after onset, which further proved that she had reversible ventricular myocardial abnormalities, this is an important feature of Takotsubo syndrome.

Reviewer B

Major

Comment 1- *Left ventriculography revealed ‘no’ abnormality. However, TCM should show abnormal wall motion. Is this case really TCM?*

Reply 1

Thanks for your comments. The patient accepted left ventricular radiography on the 12th day of onset (the second hospital). The cardiac catheterization doctor at the second hospital ignored the stenosis of the left ventricular outflow tract and believed that there was no abnormality. In the case presentation, we used the term 'no' abnormality, which has two meanings: first, we just stated the patient's diagnosis and treatment processes at that time and the conclusion on the left ventricular angiography report form in the second hospital. Second, we used inverted commas for the word 'no' to indicate that we questioned the results of the external hospital. We re-examined the patient's left ventriculogram images, although the patient's left ventricular bulge was not as typical as in other cases, she did have left ventricular outflow tract stenosis. This is a characteristic manifestation of Takotsubo syndrome. In addition, the ECG revealed diffuse T-waves inversions in most of the leads while cardiac enzymes were negative with slightly elevated TNT levels. It indicated an evident disparity between widely dysfunctional myocardium and limited myocardial necrosis, which was a classical clinical performance of Takotsubo syndrome. Moreover, this was accompanied by the lack of significant coronary artery stenosis that could explain the extensively involved myocardium, which was another clinical characteristic of

Takotsubo syndrome. It has been mentioned in **Discussion** section (see Page 8, line 168-174).

Furthermore, the patient's cardiac ultrasound showed uncoordinated ventricular wall motion on the 12th and 19th day of the onset (checked in the second hospital and the third hospital respectively). When the patient came to our hospital 4 months after onset (the fourth hospital), left ventricular wall motion was coordinated. A study showed that wall motion abnormalities usually resolve within 4 to 8 weeks of the acute event (*Tak et al. WMJ. 117 (2018) 171-174*). The ventricular wall motion had recovered when the patient came to our hospital 4 months after onset, which further proved that she had reversible ventricular myocardial abnormalities, this was an important clinical feature of Takotsubo syndrome.

Therefore, based on the above points, we retrospectively diagnosed the patient with Takotsubo syndrome. We added some data “the conclusion on the left ventriculography report form revealed ‘no’ abnormality (Fig. 3c, d)” in the text. (see Page 6, line 126-127)

Changes in the text:

Page 6, line 126-127

The conclusion on the left ventriculography report form revealed ‘no’ abnormality (Fig. 3c, d).

Comment 2-Several echocardiography have been performed. How did asynergy change on echocardiography?

Reply 2

Thank you for your comments. The first hospital the patient attended was the local county hospital, which lacked the relevant medical equipment, thus she did not accept a transthoracic echocardiography examination. The patient's transthoracic

echocardiography showed uncoordinated ventricular wall motion on the 12th and 19th day of the onset (checked in the second hospital and in the third hospital respectively). When the patient came to our hospital 4 months after onset (the fourth hospital), transthoracic echocardiography indicated that left ventricular wall motion was coordinated. The results of the patient's three cardiac ultrasounds are shown in the table below:

	LA (mm)	LV (mm)	IVsd (mm)	LPVW d (mm)	EF (%)	LVOT (mm)	PFV (cm/s)	Ventricular wall motion
12st	41.0	47.0	10.2- 17.8	9.0	40.0	9.6	355.0	uncoordinate d
19st	35.7	48.2	11.7	11.7	60.0	no signs	none	uncoordinate d
4 months	41.0	48.0	11.0-14.0	11.0	59.0	no signs	none	coordinated

Note: LA: left atrium; LV: left ventricle; IVsd: interventricular septal thickness at diastole; LPVWd: left ventricle posterior wall at diastole; EF: ejection fraction; LVOT: left ventricular outflow tract; PFV: peak flow velocity of left ventricular outflow tract. LVWM: left ventricular wall movement.

A study showed that wall motion abnormalities usually resolve within 4 to 8 weeks of the acute event (*Tak et al. WMJ. 117 (2018) 171-174*). The ventricular wall motion had recovered when the patient came to our hospital four months after onset, which further proved that she had reversible ventricular myocardial abnormalities, this was an important feature of Takotsubo syndrome.

According to your suggestion, in the description of the case presentation regarding patient's three cardiac ultrasounds, we added some data for the changes in ventricular wall motion on cardiac ultrasound (see Page 4, line 77-80; Page 6, line 118-124; Page 6-7, line 132-136).

Changes in the text:

Page 4, line 77-80

Transthoracic echocardiography (TTE) revealed left atrial enlargement (41 mm), normal left ventricle (48 mm), uneven thickening of the interventricular septum (11-14 mm), slight mitral valve regurgitation, ejection fraction of 59%, and fair coordination of left ventricular wall motion (Fig. 2).

Page 6, line 118-124

TTE revealed left atrial enlargement (41 mm), normal left ventricle (47 mm), local interventricular septum hypertrophy at the basement (17.8 mm), normal thickness of left ventricle posterior wall (9 mm), left ventricular outflow tract narrow (9.6 mm) with increased blood flow velocity (335 cm/s), slight mitral valve regurgitation, decreased ejection fraction of left ventricle (40%), and poorly coordinated left ventricular wall movement.

Page 6-7, line 132-136

TTE on the 19th day showed an almost normal size of cardiac chambers (left atrium 35.7 mm, left ventricle 48.2 mm, right atrium 27.6 mm, right ventricle 26.9 mm), mildly thick interventricular septum (11.7 mm), left ventricle posterior wall (11.7 mm), a normal ejection fraction of left ventricle (60%), and left ventricular wall motion that remained uncoordinated.

Minor

Comment 3-What was the BNP level at the third hospital? Has it improved?

Reply 3

Thank you for your comments. We would also be interested to know what the patient's BNP level was at the third hospital. Unfortunately, the patient only had a recheck of the transthoracic echocardiography, and the BNP level was not checked at

the third hospital.

Reviewer C

Comment 1-in accordance with current guidelines please use the term ‘takotsubo syndrome’ (TTS) rather than takotsubo cardiomyopathy. In brief, it underlines the acquired character of this entity, not inherited.

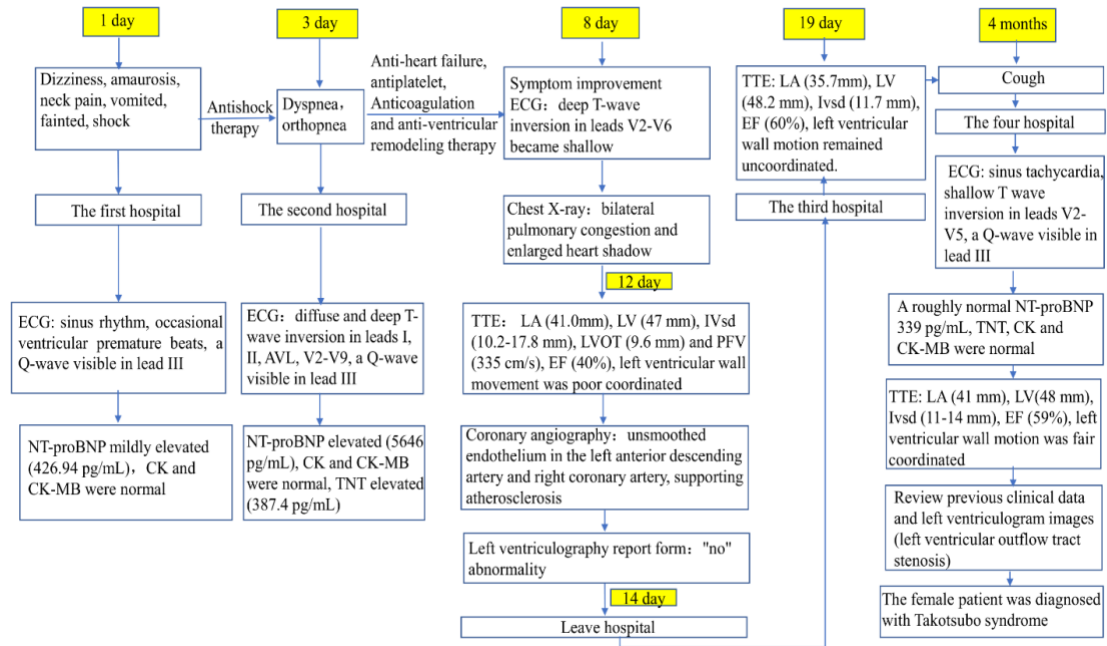
Reply 1

Thanks for your valuable advice. We substituted the term that ‘takotsubo cardiomyopathy’ by the term that ‘takotsubo syndrome (TTS)’. Please see the revised manuscript.

Comment 2-your timeline is a little disturbed – it is hard to tell how long before admission and the heart shock occurrence the patient had started coughing

Reply 2

Thank you for your thoughtful advice. Based on your suggestion, we have added a flow chart to the online supplementary material according to the onset time of patient. It is helpful for the reader to understand the condition progression.



Supplement figure: The timeline of the patient’s medical historical. TTE: transthoracic echocardiography. LA: left atrium; LV: left ventricle; IVsd: interventricular septal thickness at diastole; EF: ejection fraction; LVOT: left ventricular outflow tract; PFV: peak flow velocity of left ventricular outflow tract.

We added “A summary of the timeline was shown in supplement fig.2” (see Page 7, line 136-137).

Changes in the text:

Page 7, line 136-137

A summary of the timeline was shown in supplement fig.2.

Comment 3-in ‘Introduction’ paragraph you could add more details about TTS that you have found in literature for example how many patients (percentage) with suspected acute coronary event were subsequently diagnosed with TTS

Reply 3

We read your comments carefully and agree with you on this point. We added some

data in introduction about “how many patients (percentage) with suspected acute coronary event were subsequently diagnosed with TTS” (see Page 3, line 52-55).

Changes in the text:

Page 3, line 52-55

According to the statistical results, TTS is estimated to account for approximately 1% to 3% of all patients with suspected acute coronary syndrome, and this percentage can increase up to 5% to 6% if only female patients are considered [4, 5].

Comment 4-in ‘Case presentation’ using term “ill-looking” is not proper in the scientific paper, it can be widely interpreted and it would be more specific

Reply 4

I read your comments carefully and agree with you. The manuscript was thoroughly revised for grammatical and sentence structure errors by the Language Editing Services provided by Elsevier (webshop.elsevier.com). The revised manuscript was submitted for your kind consideration. We hope you will find this revised version acceptable for publication in Annals of Palliative Medicine.

We substituted the sentence that ‘the doctors saw an acutely ill-looking woman’ by the sentence that ‘she presented with pained facial appearance’, please see the section of case presentation (see Page 5, line102).

Changes in the text:

Page 5, line102

On admission, she presented with pained facial appearance, blood pressure 120/70 mmHg, heart rate 95 beats/min, and orthopnea.

Comment 5- please add reference values for the presented lab results

Reply 5

Thank you for your advice. We have added reference values for the presented lab results in the revised manuscript, please see the section of case presentation.

Comment 6-*when you write about drugs administrated to the patient, please write more specific which types of antiplatelets or anticoagulants were used.*

Reply 6

Thanks for your valuable advice. We have written the types of antiplatelets or anticoagulants were used. (see Page 6, line 111-114)

Changes in the text:

Page 6, line 111-114

She was diagnosed with acute coronary syndrome and treated with recombinant human BNP, dual anti-platelet therapy with aspirin and clopidogrel, low-molecular-weight heparin sodium (one time) anticoagulation, cholesterol modulation, and anti-ventricular remodelling.

Comment 7-*in ‘Discussion’ there is not enough information about risks and problems linked with misdiagnosing TTS– type 1 acute myocardial infarction.*

Reply 7

Thank you very much for your suggestion. We added some data about risks and problems linked with misdiagnosing TTS– type 1 acute myocardial infarction in the part of Discussion. (see Page 8-9, line 175-183)

Page 8-9, line 175-183

Patients with TTS tend to visit the hospital later and miss the opportunity for emergency coronary angiography, and are often misdiagnosed with myocardial infarction, leading to early revascularization with dual antiplatelet therapy and anticoagulant therapy given, increasing the economic burden of patients and the incidence of bleeding events. TTS has many similarities with acute myocardial infarction, however the prognosis of TTS is relatively better. There are many differences between the treatment and prognosis, so attention should be given to the identification between the two diseases in the diagnosis process to avoid misdiagnosis and delayed treatment.

Comment 8- again the phrase avoid turning a blind eye to the typical cases that occur in front of them” seems to be not professional

Reply 8

Thank you for your comment. We substituted the sentence that ‘avoid turning a blind eye to the typical cases that occur in front of them’ by the sentence that ‘avoid misdiagnosing the typical cases that occur in their patients’ (see Page 2, line 38-40; Page 10, line 212-214).

Page 2, line 38-40

We hope that through analysis of this case, primary doctors will have a deeper understanding of TTS and avoid misdiagnosing the typical cases that occur in their patients.

Page 10, line 212-214

We hope that through analysis of this case, primary doctors will have a deeper

understanding of TTS and avoid misdiagnosing the typical cases that occur in their patients.

Comment 9-please improve the quality of ECG, chest X-ray and photos attached to your manuscript

Reply 9

Thank you for your comment. We have improved the quality of ECG, chest X-ray and photos attached to our manuscript. However, the clarity of the chest X-ray was much lower than the usual chest film quality because the chest radiograph was a bedside chest radiograph in the second hospital.