Asymptomatic takotsubo syndrome occurring during Holter monitoring

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SUMMARY
Asymptomatic takotsubo syndrome was observed during periodic Holter monitoring in a man in his 60s undergoing maintenance dialysis. No emotional or physical stress was noticed. The electrocardiographic changes at onset were determined, and repeated ST elevation and progressive formation of giant negative T waves were recorded.

BACKGROUND
Although the postonset takotsubo syndrome electrocardiographic course is known as acute myocardial infarction-like ST elevations, reports describing the electrocardiographic changes during onset of this disease are scarce.

CASE PRESENTATION
A man in his 60s had been diagnosed with coronary spastic angina by coronary angiogram with spasm provocation when he was in his 50s and was being treated with medications (nifedipine Controlled release (CR) 40 mg/day, nicorandil 15 mg/day). He had experienced no chest symptoms since starting the medications. No significant ST changes had been noted on previous periodic electrocardiographic examinations (figure 1A). The patient was fitted with a Holter monitor as regular testing for sinus bradycardia (Rubenstein type I) in November 2020. The patient experienced no chest symptoms during the recording. Next day, after removing monitoring device, he was subsequently seen on an outpatient basis. Electrocardiography for regular check-up showed giant negative T waves in multiple leads (figure 1B), and echocardiography showed decreased wall motion on the apex (figure 2A,B, video 1). A blood sample showed mildly elevated troponin T (0.109 ng/dL). Based on the diagnostic assessment, acute coronary event was suspected, and the patient was immediately hospitalised. Emergent coronary angiography showed no significant coronary artery stenosis (figure 3A,B). Left ventriculography of right anterior oblique) view showed a narrow neck and apical ballooning during systole (figure 3C,D, video 2). Left ventriculography of left anterior oblique view showed that apical wall motion was severely decreased while basal portion of left ventricular septum and posterolateral wall normally contracted (video 3). Takotsubo syndrome was considered a possible diagnosis, and other diseases were excluded according to the guideline.1 As the patient did not experience any physical or emotional stress and had no chest symptoms during the clinical course from before onset to hospital discharge, it was concluded that he had asymptomatic takotsubo syndrome.

Holter monitoring performed before admission showed a consistent sinus rhythm; no significant arrhythmias were recorded. Holter monitoring showed repeated ST elevations for 20–60 min, followed by a return to the baseline and the gradual formation of negative terminal T waves. Every time ST changes repeated, T wave inversion becomes deeper and deeper and the giant negative T wave was gradually formed in a period of half a day (figure 4).

Figure 1 ECG findings. (A) The ECG 4 months before. (B) The ECG recorded just after the Holter monitoring. (C) The ECG 4 weeks after the onset. (D) The ECG 8 weeks after the onset.

Figure 2 Echocardiogram (four-chamber view). Images of echocardiogram recorded right after onset in systole (A) and diastole (B) revealed that apical wall motion decreased severely. Images of echocardiogram in chronic phases(4 weeks after onset) showed complete recovery of wall motion abnormality (C:systole, D:diastole).
INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS
Coronary angiography performed immediately after hospitalisation showed no significant coronary artery stenosis (figure 3A,B), and acute coronary syndrome was therefore ruled out. The patient’s clinical course showed no significant elevations in cardiac enzymes (peak creatine kinase, 157 U/L) or inflammatory markers (peak C reactive protein, 0.17 mg/dL), thus excluding acute myocarditis. Cerebrovascular disease and pheochromocytoma were excluded based on cerebral CT, truncal CT and quantitation of plasma catecholamines. The possible presence of a catecholamine-producing tumour was investigated by 123I-MIBG (metaiodobenzylguanidine) scintigraphy and was ruled out.

TREATMENT
The patient had no subjective symptoms even after the hospitalisation. There was no haemodynamic deterioration and maintenance dialysis was performed without any difficulties. Consequently, no additional agents were administered, and a conservative approach of watchful observation was implemented. Echocardiography revealed gradually ameliorated wall motion of left ventricle and there was no major complications. The patient was discharged on the fourth day of hospitalisation.

OUTCOME AND FOLLOW-UP
Electrocardiography performed 4 weeks after the patient was discharged showed that biphasic T waves remained (figure 1C), and echocardiography showed that left ventricular contraction became normal (figure 2C,D, video 4). On electrocardiography 8 weeks after discharge, the negative T waves disappeared, and the findings were similar to those obtained before onset (figure 1D). The patients is still living their daily lives without symptoms.

DISCUSSION
Takotsubo syndrome is a condition in which transient cardiac dysfunction is seen in a region not subtended by a coronary artery. It is often characterised by an area of reduced wall motion centred on the apex in the shape of a ‘takotsubo,’ a Japanese word for an octopus trap. Although the cause is often considered to be emotional or physical stress, it is not obligatory for the diagnosis. There are several underlying mechanisms of takotsubo syndrome that have been considered. These include sympathetic activation, catecholamine release, endothelial dysfunction resulting from decreased oestrogen, coronary spasm and microangiopathy. These mechanisms can account for takotsubo syndrome as a sudden onset event. However, the present case had no emotional or physical stress that could produce catecholamine-excess condition. Although the patient had been diagnosed as coronary spastic angina, he had no anginal attack with medication during Holter monitoring. However, it cannot be ruled out that the microvascular spasm, which is considered...
to be one of the pathogenic mechanisms of takotsubo syndrome, may have repeatedly occurred asymptomatically.

In the acute phase of takotsubo syndrome, the electrocardiographic course is known to be marked appearance of acute myocardial infarction-like ST elevations in multiple leads, followed by the appearance of giant T waves with a characteristic negative component. Although the postonset electrocardiographic course is known, there have been very few reports describing the electrocardiographic changes during onset of this disease. Interestingly, the Holter monitoring in the present case showed repeated, ST elevations and remission for hours and giant negative T wave was gradually progressed. This suggests the existence of a type of takotsubo syndrome with a course of onset considerably longer than previously thought. Although all of the previously examined mechanisms can explain a sudden onset, they cannot explain a course of repeated ST elevations over a long period, as in the present case.

Yoshida et al reported the Holter recording during the onset of takotsubo syndrome for the first time, that was the sudden ST elevation coinciding with chest pain triggered by emotional stress. On the other hand, Kuboyama et al described a thyrotoxic patient who was diagnosed asymptomatic takotsubo syndrome by incidentally performed Holter monitoring, and the ECG findings were repetitive ST depression and elevation until fixed ST elevation. The former case can likely be explained by hitherto described mechanisms. The latter case and the present case showed that in some cases takotsubo syndrome occur latently without any symptoms with repeated ST elevations occurring for hours, in the manner that an octopus slowly crawls along the ocean bottom, resulting in specific wall motion abnormality.

These cases raise the possibility that the pathologic process of this disease could be gradually progressed and take hours for completion of diseased state in some cases.

If there is no opportunity for testing, these patients’ ECG abnormalities and the cardiac dysfunction could be ameliorated without leaving a trace. Pathophysiological cause of takotsubo syndrome with a long, asymptomatic course remains to be elucidated, and the incidence of this condition cannot be determined because of difficulties of diagnosis. Advances in its diagnosis and the understanding of its mechanism may become possible if the technology of comprehensive recording of electrocardiographic waveforms on cloud system with wearable devices like smart watches in combination with surveillance by artificial intelligence becomes common.

Although the prognosis of takotsubo syndrome is thought to be good in general, sudden death caused by takotsubo syndrome was reported, and so, there could be the cause-unknown sudden death attributed to asymptomatic takotsubo syndrome to some extent. Elucidation using a variety of modalities is expected in the future.

# Learning points

- To understand that takotsubo syndrome may occur in the absence of causes such as emotional/physical stress.
- To understand that takotsubo syndrome may be asymptomatic.
- To understand that there is a type of takotsubo syndrome that results in repeated ST elevation and remission for hours followed by giant negative T waves.

**Patient’s perspective**

While he was in hospital, he remarked to us ‘I had no symptoms at all, so I was very surprised to be diagnosed with takotsubo syndrome.’ This remark truly represents the horror of the disease. The frequency of asymptomatic takotsubo syndrome is unknown, but further elucidation is desired.
Kuboyama O, Tokunaga T, Kobayashi K, et al. A case of asymptomatic patient with hyperthyroidism documented the onset of takotsubo cardiomyopathy by Holter monitoring. *Int J Cardiol* 2011;151:e82–4.