*Original Article*

# Takotsubo cardiomyopathy in the intensive care unit

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*Aims:* An angiographic examination is necessary for the diagnosis of takotsubo cardiomyopathy (TTC). However, in the intensive care unit (ICU), intensivists often see patients in whom TTC cannot be diagnosed because they cannot undertake angiography due to the patient's poor general condition. We defined such cases as clinical TTC (cTTC) and investigated the incidence and background of cTTC in the ICU at Kansai Medical University Hospital (Osaka, Japan).

*Methods:* The study involved 5,084 patients who were admitted to the ICU of Kansai Medical University Hospital between January 2013 and December 2017. We retrospectively investigated the frequency and background of TTC and cTTC.

*Results:* Of the 5,084 patients, 5 (0.09%) patients admitted to the ICU were diagnosed as having TTC and 19 patients (0.37%) were diagnosed as having cTTC. The most common primary disease among the evaluated patients was sepsis ($n$ = 10) followed by subarachnoid hemorrhage (SAH) ($n$ = 5). Ten of the 335 patients with sepsis (3.0%) were admitted to the ICU with complications due to cTTC. Their blood pressure and heart rate on admission tended to be high, and their Sequential Organ Failure Assessment scores tended to be low. Five of the 172 patients with SAH (2.9%) were admitted to the ICU with complications due to cTTC. These patients were often classified as grade 5 on the Hunt and Hess scale.

*Conclusion:* Our study suggests that patients with sepsis or SAH are complicated with cTTC in the ICU. In addition, there might be no correlation between the severity of sepsis and the development of TTC.

**Key words:** Intensive care unit, left ventricular apical ballooning, sepsis, subarachnoid hemorrhage

## BACKGROUND

TAKOTSUBO CARDIOMYOPATHY (TTC) was first described by Dote *et al.*[1] Since then, many cases have been reported around the world. Takotsubo cardiomyopathy is diagnosed according to the definitions of the Mayo Clinic and Japanese Circulation Society (with the former definition used more frequently internationally)[2] based on four conditions: (i) transient hypokinesis, akinesis, or dyskinesis of the left ventricular midsegments with or without apical involvement and abnormalities of regional wall motion extending beyond a single epicardial vascular distribution; this is often, but not always, triggered by stress; (ii) the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (iii) new electrocardiographic abnormalities (ST-segment elevation and/or T-wave inversion) or modest cardiac troponin elevation; (iv) the absence of pheochromocytoma and myocarditis.

In the intensive care unit (ICU) setting, where severe conditions such as sepsis, stroke, or multiple trauma are treated, patients showing cardiac wall motion abnormalities have a suspected diagnosis of TTC. However, an accurate diagnosis of TTC cannot be made because cardiac angiography cannot be carried out due to the poor general condition of the patient; we have defined such cases as clinical TTC (cTTC). We investigated the incidence and background of cTTC in the ICU.

## METHODS

THIS STUDY INVOLVED 5,084 patients who were admitted to the ICU of Kansai Medical University Hospital (Osaka, Japan) between January 2013 and December 2017. We retrospectively investigated the frequency and background of TTC and cTTC.

Clinical TTC was defined based on the patient fulfilling conditions (i), (iii), and (iv) of the diagnostic criteria for TTC, detailed above, in which the patient presented

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wall motion abnormalities that extended beyond a single epicardial vascular distribution on echocardiography.

Our ICU is controlled by the Department of Emergency and Critical Care, which has a role in critical intensive care, and the coronary care unit – a different care unit – is controlled by the Department of Cardiology, which has a role in treating cardiovascular disease at our hospital. In other words, the patients who required a differential diagnosis for chest pain or acute myocardial infarction were treated in the coronary care unit and were excluded from our study.

All statistical analyses were undertaken using SPSS version 25.0 (IBM, Armonk, NY, USA). Differences between sepsis and sepsis complicated by cTTC and between subarachnoid hemorrhage (SAH) and SAH complicated by cTTC were compared using the Mann–Whitney *U*-test and Fisher's exact test. A *P*-value of <0.05 was considered to indicate statistical significance.

## RESULTS

OF THE 5,084 patients admitted to the ICU, 5 (0.09%) were diagnosed as having TTC and 19 (0.37%) were diagnosed as having cTTC. The median age of onset of cTTC was 74 ± 3.6 years and the 63% of the patients were women. With regard to cardiometabolic risk factors, 10 patients (53%) had hypertension and 1 (5%) was diabetic. The most common primary disease on admission was sepsis ($n$ = 10, 53%). Sources of infection included respiratory tract infections in seven patients, biliary tract infections in two patients, and cerebral meningitis in one patient. The second most common primary disease on admission was SAH in five patients (26%), and all were derived from internal causes. A mechanical ventilator was used for 14 patients (74%), and a catecholamine agonist was given to seven patients (37%).

We measure the serum troponin I value as a marker of myocardium injury; in these cases the average troponin I value was approximately 100 times higher than the standard value.

Angiographic examinations could not be undertaken in 14 patients (74%) because of their poor general condition. In the remaining five patients (26%), coronary angiography or computed tomography heart scans were carried out, and the patients were diagnosed as having TTC. No patients developed complications associated with the use of a contrast agent.

Seven patients (37%) were treated with systemic heparin without hemorrhagic complications. Three patients (16%) died in the hospital. The causes of death were associated with the primary disease on admission and were not associated with cardiovascular failure due to TTC. In addition, neither the performance nor non-performance of angiographic examinations was associated with patient prognosis ($P$ = 0.53; Table 1).

We compared the patients with sepsis with those with sepsis and cTTC. During the previous 5 years at our institution, 335 patients were hospitalized with sepsis in the ICU, and 10 of these patients (3%) were complicated by cTTC. The blood pressure and heart rate of these patients with sepsis and cTTC on arrival were higher than those in the patients with sepsis alone. However, there were no significant differences in the use of catecholamines between the two groups ($P$ = 1.0). In addition, their Sequential Organ Failure Assessment (SOFA) scores were lower than those of the patients with sepsis alone, and there were significant differences in the coagulation, cardiovascular, and renal components of the SOFA score between the two groups (Table 2). Electrocardiograms (ECG) undertaken in the patients with sepsis showed negative T waves in six patients and ST segment elevation in three patients. The remaining patient had negative T waves after ST segment elevation. The time from ST change to normalization of the ECG took a median of 6 days, whereas the time to normalization from the

**Table 1.** Characteristics of 19 patients with clinical takotsubo cardiomyopathy admitted to the intensive care unit

| | $n$ = 19 (%) |
|---|---|
| Complications of cardiometabolic risk factors | |
| Hypertension | 10 (53) |
| Diabetes | 5 (26) |
| Underlying critical illness | |
| Sepsis | 10 (53) |
| SAH | 5 (26) |
| Others | 4 (21) |
| Examination | |
| None | 14 (74) |
| CAG | 3 (16) |
| CT heart scan | 2 (10) |
| Treatment | |
| Observation | 12 (63) |
| Systemic heparin | 7 (37) |
| Outcome | |
| Mortality | 3 (16) |
| Survival | 16 (84) |
| Outcome in patients with angiographic examination | |
| Mortality | 1 (7.0) |
| Survival | 13 (83) |

CAG, coronary angiography; CT, computed tomography; SAH, subarachnoid hemorrhage.

appearance of negative T waves took a median of 15 days. In addition, improvement of cardiac function took almost the same amount of time as normalization of the ECG.

We compared the patients with SAH to those with SAH and cTTC. In the previous 5 years, 172 patients were hospitalized at our institution with SAH in the ICU, and 5 (2.9%) were complicated by cTTC. The patients with SAH complicated by cTTC tended to be classified as Hunt and Hess grade 5 (Table 3).

**Table 3.** Comparison between cases of subarachnoid hemorrhage (SAH) and SAH complicated by clinical takotsubo cardiomyopathy (cTTC)

| Variable | SAH $n = 172$ | SAH + cTTC $n = 5$ | *P*-value |
|---|---|---|---|
| Age (years) | 66 (18, 93) | 64 (43, 76) | 0.60 |
| Female sex | 107 (62%) | 5 (100%) | 0.16 |
| Blood pressure on admission (mmHg) | 139 (46, 263) | 125 (83, 150) | 0.14 |
| Hunt and Hess scale | 3 (1, 5) | 5 (2, 5) | 0.13 |

## DISCUSSION

ALTHOUGH PREVIOUS STUDIES showed TTC to be associated with sympathetic nervous activation, microvessel vasoconstriction, and oxidant stress, the mechanisms have not been clearly identified.[3] These studies also showed that TTC was associated with the triggers of physical and mental stress. Eitel *et al.*[4] reported physical stress as the trigger of TTC in 40% of cases, mental stress in 30%, and unknown in 30%.

Throughout the study period, we found a number patients who could not be accurately diagnosed as having TTC because an angiographic examination could not be carried out due to their poor general condition.

Krishnamoorthy *et al.*[5] reported that the prevalence of TTC was 0.02% among all admitted patients. When a patient who has no history of cardiovascular disease is affected by a more serious disease that requires intensive care in unusual circumstances, such as in the ICU, the risk of TTC would further increase. Few studies have reported on the frequency and background of TTC in the ICU. We suggest it is important to recognize the frequency and background of cTTC when treating patients with severe conditions. In fact, the incidence of TTC in our ICU was 4.5 times higher than that in the study of Krishnamoorthy *et al.*, and that of cTTC was 18.5 times higher.

It has been reported that TTC is frequently detected in elderly female patients,[6] and we recognized the same tendency in our study. Patients with TTC were reported to have subjective symptoms similar to those of acute myocardial infarction in a previous study, including – but not limited to – chest pain, dyspnea, and palpitation.[7] In contrast, the

**Table 2.** Comparison between cases of sepsis only and sepsis complicated by clinical takotsubo cardiomyopathy (cTTC)

| Variable | Sepsis $n = 325$ | Sepsis + cTTC $n = 10$ | *P*-value |
|---|---|---|---|
| Age (years) | 73 (14, 98) | 79 (32, 92) | 0.170 |
| Female sex | 138 (43%) | 7 (70%) | 0.110 |
| Blood pressure on admission (mmHg) | 117 (39, 214) | 137.5 (117, 183) | 0.009 |
| Use of catecholamine | 55 (17%) | 1 (10%) | 1.000 |
| Heart rate on admission (b.p.m.) | 100 (32, 176) | 111.5 (99, 121) | 0.200 |
| Temperature (°C) | 37 (27.5, 42) | 36.3 (35.5, 38.9) | 0.640 |
| Respiratory rate (breaths/min) | 23 (9, 48) | 26.5 (17, 32) | 0.110 |
| WBC > 12,000/μL, WBC < 4,000/μL | 216 (66%) | 7 (70%) | 1.000 |
| SIRS | 3 (0, 4) | 3 (2, 4) | 0.438 |
| WBC (/μL) | 12,100 (300, 61,300) | 14,100 (1,800, 19,400) | 0.740 |
| CRP (mg/L) | 17.3 (0.017, 60.2) | 0.575 (0.022, 38) | 0.002 |
| SOFA score | 7 (0, 17) | 5 (3, 8) | 0.099 |
| PLT (/μL) | 14.5 (0.2, 9.8) | 22.7 (12.2, 42.7) | 0.008 |
| T-BIL (mg/dL) | 0.9 (0.2, 9.8) | 0.8 (0.5, 3.6) | 0.885 |
| MAP (mmHg) | 84 (24.3, 163.6) | 97 (68, 135) | 0.040 |

CRP, C-reactive protein; MAP, mean arterial pressure; PLT, platelets; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; T-BIL, total bilirubin; WBC, white blood cells.

patients with cTTC in our study did not complain of these symptoms as the effects of the primary disease. All of the patients with cTTC in our study showed ECG changes or an increase in cardiac enzyme levels.

There are two typical patterns of TTC: one is contractile dysfunction at the base of the heart, and the other is excessive contraction of the cardiac apex.[8] All of the cTTC patients in our study showed the former pattern. The ECG often shows T-wave inversion in the anterior precordial leads,[9] and 12 patients (80%) showed T-wave inversion in our study. Kosuge *et al.*[10] reported that the combination of the presence of ST-segment elevation in lead aVR and the absence of ST-segment elevation in lead V1 identified TTC with 91% sensitivity, 96% specificity, and 95% accuracy. In our 19 patients with cTTC, only three had ST-segment elevation in lead aVR, and 17 patients had an absence of ST-segment elevation (Fig. 1).

Our results differed from those of Kosuge *et al.*[10] and there were various types of ECGs in our case. We consider that the reason for the discrepancies might be related to the timing of the evaluation of the ECG, which in our patients might be different from the actual time of cTTC onset. Kosuge *et al.*[10] studied the ECG findings in patients who were admitted within 6 h of symptom onset. In our study, cTTC was detected in ECG changes in the ICU during treatment for other diseases, such as sepsis or SAH. In addition, there could be a differences in patients' characteristics.

Takotsubo cardiomyopathy is treated not only by removing stress factors but also by treatment with antithrombotic drugs, in cases involving thrombosis, and diuretic drugs, in cases involving excess fluid. Abanador-Kamper *et al.* reported that treatment with antithrombotics and cardiac failure therapy within the first 2 months was achieved without the risk of bleeding and that the short-term survival rate was high. They also reported that aspirin, oral anticoagulation, and low molecular weight heparin (among other therapies) were used for antithrombotic therapy.[11] The selection of these medications was not clearly determined. We treated cTTC patients with antithrombotic drugs due to the thrombogenic risk in patients with spontaneous echo contrast on echocardiography. We used systemic heparin as the antithrombotic drug because the patients could not withstand tube feeding.

Brinjikji *et al.* reported that 31% of cases of TTC were complicated by heart failure. In their study, 6.7% of TTC patients were complicated by heart failure to the extent that it affected their respiratory status.[12] Five of the 19 (26%) patients in the present study were complicated by heart failure but could be treated with diuretic

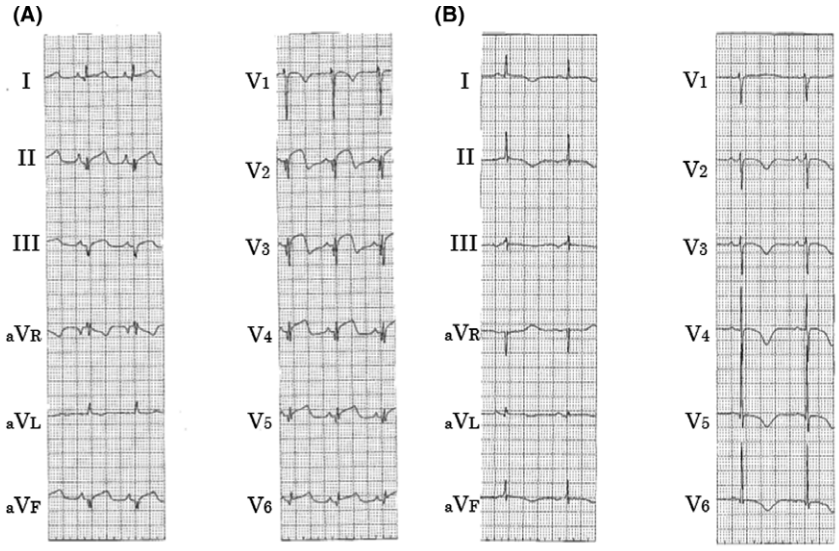


**Figure 1.** A, Representative electrocardiogram (ECG) of a patient with subarachnoid hemorrhage, admitted to the intensive care unit, at diagnosis of clinical takotsubo cardiomyopathy (cTTC). There are ST-segment elevations in II, aVF, and V2–V5, as well as inversed T waves in aVR and V1–V3. This shows the combination of the presence of ST-segment elevation in lead aVR and the absence of ST-segment elevation in lead V1. B, Representative ECG of a patient with sepsis at diagnosis of cTTC. There are inversed T waves in I–III, aVF, and V2–V6. This does not show the presence of ST-segment elevation in lead aVR, but does show the absence of ST-segment elevation in lead V1.

drugs. In addition, the presence of heart failure was not associated with the prognosis. Brinjikji *et al.* reported that patients with TTC sometimes developed severe complications such as cardiogenic shock or ventricular fibrillation that required an intra-aortic balloon pump, but these complications were not detected in the patients in our study.

Clinical TTC patients were most frequently complicated by sepsis in our study, which was similar to findings reported by Park *et al.*[13] However, no reports have explained the relationship between TTC and the severity of sepsis. Our results revealed that the septic patients with cTTC had lower SOFA scores than the patients without cTTC. This indicates that further study is needed to understand the relationship between the degree of physical stress experienced and the development of TTC.[14] We consider that our patients with cTTC could be the part of catecholamine-induced cardiomyopathy because it is said that both of these disease developed by catecholamine. Takotsubo cardiomyopathy has diagnostic criteria, however, catecholamine-induced cardiomyopathy does not. In our study we diagnosed our patients with TTC.

In a previous study, the ECG in patients with TTC showed ST-segment elevation on admission and progressively deepened T wave inversion after approximately 3 days,[9] which was different from the ECG patterns in our patients. We consider the reason for this to be that the timing of the evaluation of the ECG in our patients might be different from the actual time of cTTC onset.

The second most frequent complication in the TTC patients in our study was SAH. We more frequently observed a higher severity of SAH in the patients complicated with cTTC than in those without cTTC. This could support the hypothesis that TTC is induced by activation of the sympathetic nervous system due to cerebral hemorrhage.[14]

The present study has three limitations. First, our definition of cTTC could include cases of myocardial ischemia, which shows a similar clinical course to TTC, as cardiac function improves with the development of collateral circulation. Second, it was possible that there were cases of cTTC that could not be diagnosed. Finally, the size of our study population was small.

## CONCLUSION

WE INVESTIGATED THE frequency and background of TTC and cTTC in patients in the ICU at Kansai Medical University Hospital. There are patients in the ICU in whom TTC cannot be diagnosed according to the criteria. Our results suggested that cTTC most commonly develops in ICU patients with sepsis or SAH. In addition, there might be no correlation between the severity of sepsis and the development of TTC.

## DISCLOSURE

Approval of the research protocol: The present study was approved by the institutional ethics committee of Kansai Medical University.
Informed consent: The Ethics Committee waived the requirement for informed consent due to the retrospective nature of the study.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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