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BRIEF REPORT

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Takotsubo Cardiomyopathy (Acute Left Ventricular Apical Ballooning Syndrome) Occurring in the Intensive Care Unit

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Abstract *Objective:* Diagnosis of Takotsubo cardiomyopathy (also known as stress cardiomyopathy or acute left ventricular apical ballooning syndrome) can be challenging in patients who are being treated for other diseases in the intensive care unit, because symptoms could erroneously be attributed to the underlying disease or patients may not experience symptoms due to analgesia and sedation. The aim of our study was to assess clinical features of Takotsubo cardiomyopathy occurring in the intensive care unit. *Design:* Prospective observational study. *Setting:* University hospital. *Patients:* Six consecutive patients diagnosed with Takotsubo cardiomyopathy who were being treated for other diseases in the intensive care unit. *Interventions:* None. *Measurements and main results:* Sudden hemodynamic deterioration (i.e., sudden hypotension, tachycardia or drop in monitored stroke volume) requiring vasopressor support was the presenting symptom in five of the six patients. Only one patient was able to report angina-like chest pain, all others were unable to experience symptoms due to analgesia and sedation. The electrocardiogram was abnormal in all patients upon diagnosis, demonstrating either ST-segment elevation ($n = 2$) and/or T-wave inversion ($n = 5$). Mild elevation of cardiac enzymes disproportionate to the extent of wall motion abnormalities on left ventriculography was present in all patients. All patients survived their acute event. *Conclusions:* Sudden hemodynamic deterioration requiring vasopressor support and/or ECG abnormalities consisting of ST-segment elevation, ST-segment depression or T-wave inversion may be the presenting symptom of Takotsubo cardiomyopathy in the intensive care unit and should be included in the diagnostic algorithm.

Keywords Takotsubo cardiomyopathy · Stress cardiomyopathy · Acute apical ballooning · Left ventricular apical ballooning · Intensive care unit

Introduction

Takotsubo cardiomyopathy (TTC; also known as stress cardiomyopathy or acute left ventricular apical ballooning syndrome) consists of a sudden onset of transient akinesia or dyskinesia of the apical and mid-portions of the left ventricle, without significant coronary artery stenosis, often accompanied by chest pain, dynamic reversible ST–T-segment abnormalities, and elevation of cardiac enzymes, disproportionate to the extension of regional wall motion abnormalities [1]. The syndrome affects mostly women and has predominantly been reported in the Japanese population. However, several series have recently been published outside Japan [1, 2, 3, 4]. In the majority of cases a triggering emotional stressor (e.g., a friend's death) or physical stressor (e.g., surgery) can be identified.

Clinical presentation in patients who develop TTC outside of the hospital mimics acute myocardial infarction,

and diagnosis is straightforward if the treating physician is familiar with the syndrome. However, in hospitalized patients who are being treated for other diseases (e.g., exacerbation of chronic obstructive lung disease) diagnosis can be challenging, because symptoms could erroneously be attributed to the underlying disease or symptoms could be lacking (e.g., in sedated or intubated patients).

The purpose of our study was to assess clinical characteristics of patients who developed TTC while being treated for other diseases in the intensive care unit (ICU).

Materials and methods

Among 20 consecutive patients who were diagnosed with TTC between January 2004 and May 2005 at our institution, six (three of them women) could be identified who at the time of diagnosis were being treated in the ICU for other diseases. Diagnosis of TTC was based on the following criteria: (1) reversible akinesia or dyskinesia of the apical and mid portions of the left ventricle beyond a single major coronary artery vascular distribution on left ventriculography; (2) no coronary artery stenosis $> 50\%$ of the luminal diameter on coronary angiography; (3) elevation of cardiac enzymes disproportionate to the extent of regional wall motion abnormalities; (4) an abnormal electrocardiogram consisting of ST-segment elevation or T-wave inversion; and (5) absence of any of the following conditions: pheochromocytoma, known causes of neurogenic stunned myocardium (i.e., subarachnoid hemorrhage, stroke, subdural hematoma, head injury), hyperthyroidism, pancreatitis, poisoning, trauma,

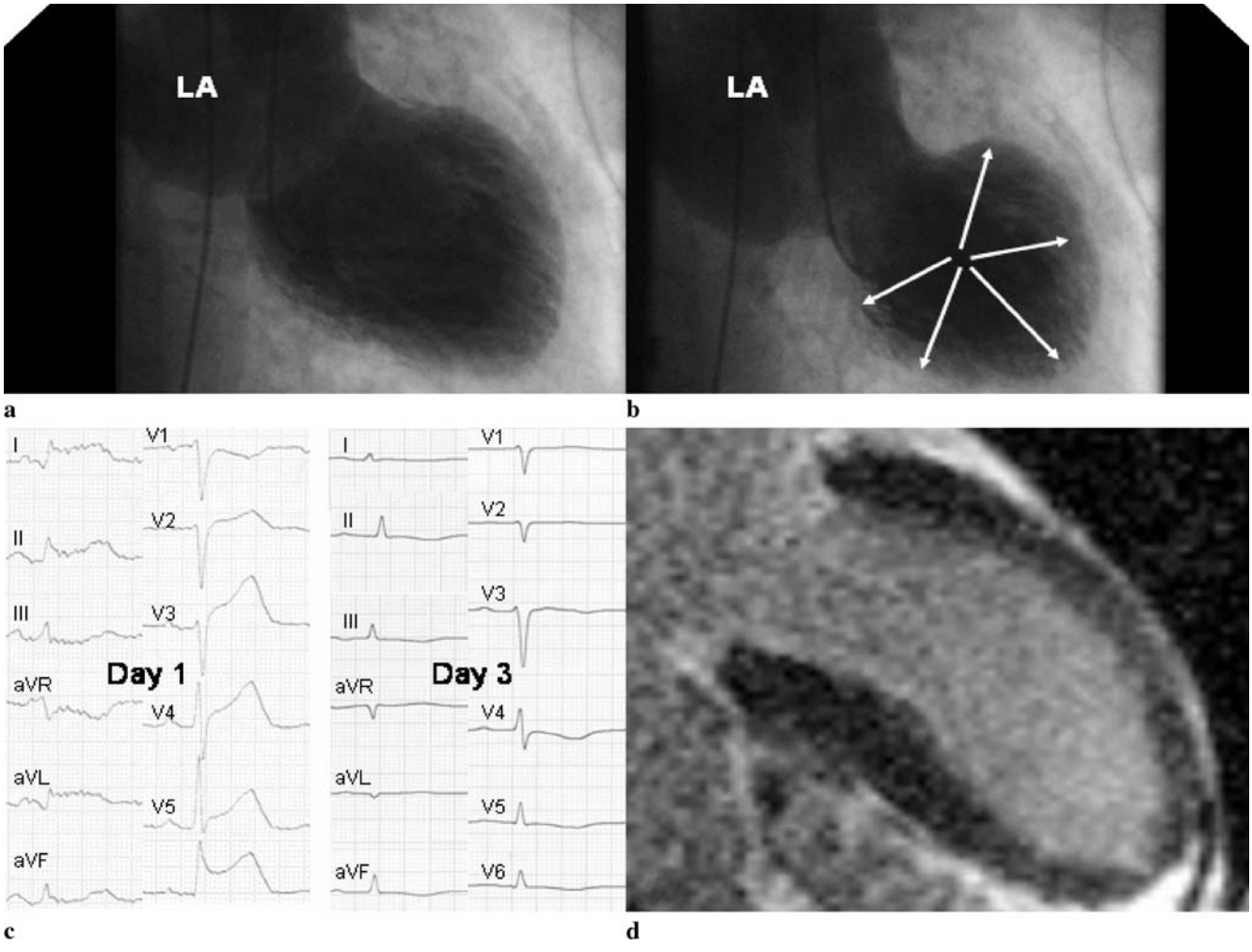

Fig. 1 **a**, **b** Left ventriculography during diastole (**a**) and systole (**b**) demonstrating apical and mid-ventricular akinesis. **c** Serial electrocardiograms of patient 1. On admission, ST-segment elevation was present in leads I, II, aVL, aVF, and V2–V6. On day 3, ST segments had returned to baseline and inverted T-waves were present in leads II, III, aVF, and V4–V6. **d** Contrast-enhanced cardiovascular magnetic resonance image demonstrating lack of delayed hyperenhancement

major bleeding and cardiac arrest. Laboratory tests, serial electrocardiograms and echocardiography were performed according to the standard protocol for management of acute coronary syndromes at our institution. Reversibility of regional wall motion abnormalities could be demonstrated by transthoracic echocardiography in all cases. Echocardiography was performed in a standard fashion. Two patients also underwent gadolinium-enhanced cardiovascular magnetic resonance imaging. Cardiovascular magnetic resonance images were acquired on a 1.5-T Siemens Sonata unit as previously described [5]. Results are expressed as mean ± standard deviation. Wilcoxon's matched pairs test was used to compare significant differences between ejection fraction on admission and on follow-up examination.

Results

Patients' characteristics are presented in Table 1. Mean age was 68 ± 8 years (range 51–72 years, median 68 years). Significant preceding physical stress consisted of continuous positive airway pressure ventilation via face mask for exacerbation of chronic obstructive lung disease ($n = 2$), hip surgery ($n = 1$), and endotracheal intubation and mechanical ventilation for various reasons [iatrogenic fluid overload following hip surgery ($n = 1$), pleural decortication and chest tube insertion for lung abscess due to carcinoma of the lung ($n = 1$), pneumonia ($n = 1$)]. In four patients TTC occurred within 24 h after onset of physical stress. One patient presented in cardiogenic shock and had angina-like chest pain. One patient (no. 5) was discovered incidentally because of occurrence of new onset giant negative T waves on a routine electrocardiogram. Sudden hemodynamic deterioration was the presenting symptom in the remaining four patients. All of them were on ventilatory assistance and unable to express chest pain or dyspnea due to analgesia and sedation. Hemodynamic deterioration consisted of unexplained hypotension and/or tachycardia in three of these patients and of sudden decrease in stroke volume while being monitored using the Pulse Contour Cardiac Output system (PiCCO®) in one. Systolic blood pressure dropped from 130 mmHg to 60 mmHg in patient 1, from 140 mmHg to 90 mmHg in patient 2, from 130 mmHg to 65 mmHg in patient 3, and from 120 mmHg to 85 mmHg in patient 4. In patient 6 stroke volume index dropped from 47 ml/m^2 to 28 ml/m^2. None of the patients required vasopressor support prior to development of TTC, but five patients needed vasopressor therapy to maintain adequate blood pressure thereafter (Table 1). Of the two patients with an underlying infection (patients 1 and 6) none fulfilled diagnostic criteria [6] of severe sepsis or septic shock [6] at the time TTC developed. However, one of them (patient 6) was recovering from septic shock and vasopressor therapy had been terminated 1 day prior to development of TTC.

Left heart catheterization was performed within 24 h of onset in all patients and demonstrated akinesia or dyskinesia of left ventricular apical and mid-portions on left ventriculography (Fig. 1a, b). No intraventricular pressure gradient was detected during catheter pullback. Coronary angiography was normal in 4 patients. Two patients had mild coronary artery disease with diameter stenosis $< 50\%$. No coronary vasospasm was observed. All patients had an abnormal electrocardiogram (Table 1) consisting of ST-segment elevation ($n = 2$) and/or T-wave inversion ($n = 5$) upon diagnosis (Fig. 1c). Resolution of ST-segment elevation with subsequent development of T-wave inversion occurred on day 2 ($n = 1$) and day 3 ($n = 1$). Transient prolongation of the QT interval appeared in 4 patients. The peak value for creatinine kinase was 320 ± 218–U/l (range 25–560–U/l, median 333–U/l), and the peak value for troponin I was 3.6 ± 6.3 µg/l (range 0.6–16.3 µg/l, median 1.25 µg/l). Initial ejection fraction as assessed by left ventriculography was substantially reduced in all patients (37 ± 7%; range 25–46%, median 37%). Follow-up echocardiography performed 19 ± 17 days later (range 4–52 days) demonstrated reversibility of regional wall motion abnormalities and significant improvement of left ventricular function (65 ± 8%; range 51–72%, median 68%; $p < 0.027$) in all patients.

In one patient cardiovascular magnetic resonance imaging was performed early in the course of disease (day 3) and demonstrated no significant improvement of left ventricular function (ejection fraction 41%) compared to baseline (ejection fraction 40%). In the second patient who underwent cardiovascular magnetic resonance imaging, on day 24, left ventricular function had significantly improved (ejection fraction 34% vs 70% at baseline). Delayed hyperenhancement, which is indicative of necrosis and decreased viability, was absent in both patients (Fig. 1d). All patients survived their acute event. However, one patient (patient 1) died of acute respiratory distress syndrome and multiorgan failure which was attributed to the underlying lung abscess due to lung cancer.

Discussion

TTC is increasingly being recognized in European and American populations. In the four most recently published series of the disease in the Western population [1, 2, 3, 4] the majority of cases were triggered by sudden emotional stress and only few cases were provoked by physical stress. Ruiz Baillen et al. [7] recognized reversible left ventricular dysfunction as a possible complication in critically ill patients without known heart disease by performing serial electrocardiograms and echocardiograms. In a recently published study, Park et al. [8] also exclusively focused on patients in the ICU. They report on 92 consecutive patients admitted to the ICU for various noncardiac illnesses, of whom 26 developed TTC as assessed by serial echocar-

Table 1 Patient characteristics

Characteristic	Patient number					
	1	2	3	4	5	6
Age (years)	68	61	68	75	77	58
Sex	F	F	F	M	M	M
Stress event	Mechanical ventilation, pleural decortication, chest tube insertion	CPAP, exacerbated COLD	Mechanical ventilation, iatrogenic fluid overload 10 days after hip surgery	Hip surgery	CPAP, exacerbated COLD	Mechanical ventilation for pneumonia
Presenting symptom	Hypotension	Hypotension	Hypotension	Cardiogenic shock	Incidental due to ECG changes	Decrease in monitored stroke volume
ECG abnormalities						
ST elevation	I, II, aVL, V2–V6	–	V2–V6	I, II, III, aVF, V2–V6	–	–
T-wave inversion	I, II, aVF, V2–V6	I, II, III, aVF, V3–V6	–	V3–V6	I, aVL, V2–V6	I, II, aVL, V2–V6
QT prolongation	+	–	–	+	+	–
Peak CK (U/l) [normal range: 0–145]	126	25	288	545	560	377
Peak troponin I (μg/l) [normal range: 0–0.4]	1.9	0.6	0.5	16.3	2.2	0.16
Initial ejection fraction (%) by ventriculography	25	34	34	40	46	42
Follow-up ejection fraction (%) by echocardiography	51	70	66	72	69	62
Time until follow-up (days)	4	13	15	16	16	52
Vasopressor	Norepinephrine, dobutamine	Norepinephrine	Epinephrine	Dobutamine	None	Norepinephrine

CK creatinine kinase, *CPAP* continuous positive airway pressure, *COLD* chronic obstructive lung disease.

diographic examinations. However, none of the patients in those studies underwent coronary angiography, and obstructive coronary disease could not be excluded with certainty in any of the patients. Thus, the report presented here is the first on ICU patients using the widely accepted, stricter criteria for the definition of TTC.

Angina-like chest pain is the presenting symptom in the majority of cases with TTC. However, patients in the ICU may not experience chest pain due to sedation or may suffer from diseases that can cause chest discomfort themselves (e.g., exacerbated asthma [4] or rib fractures [1]). In our small series only one patient experienced chest pain, while the remaining five were unable to do so due to analgesia and sedation. Acute hemodynamic deterioration occurred in five of six cases and was the diagnostic clue leading to further investigations (cardiac markers, electrocardiogram, echocardiogram) in the majority of cases. Interestingly, while in the series by Desmet et al. [1] the ECG was normal upon admission in 5 of 13 patients, it was abnormal in all our six patients upon diagnosis, demonstrating either ST-segment elevation or T-wave inversion. Although the pattern of ST-segment abnormalities not attributable to a single coronary artery vascular territory (Fig. 1c) can raise the suspicion of TTC, emergency coronary angiography is warranted in the majority of cases to exclude obstructive coronary artery disease. This is particularly important, because on the one hand fibrinolytic therapy in TTC is of no benefit but can potentially be harmful, and on the other hand emergency revascularization in a patient who is in shock due to obstructive coronary artery disease can be life-saving [9]. It should also be kept in mind that in patients with ST-segment elevation myocardial infarction and a culprit lesion distal to both the first septal and diagonal branches, electrocardiographic abnormalities may be indistinguishable from those observed in TTC [10].

Reversible myocardial dysfunction in critically ill noncardiac patients is a well-known entity that has extensively been reviewed elsewhere [11]. Many different pathological states have been associated with reversible myocardial dysfunction, among them central nervous system disorders (e.g., subarachnoid hemorrhage), acute respiratory failure, trauma, anaphylaxis, pancreatitis, cardiac arrest, sepsis, hyperthyroidism and pheochromocytoma. The clinical course of reversible myocardial dysfunction observed in some of these diseases (e.g., subarachnoid hemorrhage or pheochromocytoma) is similar to that of classical TTC. Thus, it can be assumed that some of these entities are manifestations of the same underlying pathology with excessive sympathetic activation and resultant transient left ventricular stunning playing a key pathophysiological role [12]. The importance of emotional stress as a trigger for TTC has been clearly demonstrated in recently published series [1, 2, 3, 4] and in an animal model of TTC using immobilization stress in rats [13]. However, stressors are not always identifiable in TTC, and while admission to an ICU is a stressful event for almost every patient, only a minority of patients suffer from TTC. Thus, it remains far from clear what other pathogenic factors are necessary for TTC to develop in the ICU.

Sepsis-induced left ventricular dysfunction might also be thought to represent a possible explanation for the phenomenon observed in those two patients in our series who had an underlying infectious disease. Sepsis-induced myocardial dysfunction has been reviewed extensively elsewhere [14, 15, 16] and is now generally accepted to play an important role in human septic shock [14]. However, a closer look at the many studies performed in this field reveals that the vast majority of them have focused on parameters of global left ventricular function such as stroke volume and ejection fraction; data on segmental left ventricular dysfunction are scarce. Even in echocardiographic studies of left ventricular function in septic shock, information on left ventricular regional wall motion abnormalities is either lacking [17, 18] or available only for a very small number of patients ($n = 6$) [19]. Thus, an overlap between sepsis-induced cardiomyopathy and TTC cannot be excluded. Interestingly, in their study on left ventricular performance in septic shock 20 years ago, Ellrodt et al. [20], using serial radionuclide ventriculography, reported reversible segmental wall motion abnormalities as well as ECG abnormalities in some of their patients. Furthermore, in their recently published study Park et al. [8] identified sepsis to be the only independent variable associated with the development of TTC. Clearly more research is necessary on this important issue.

The prognosis of TTC has uniformly been reported as good [1, 2, 3, 4, 21]. It seems that this holds true even in the subset of patients who have comorbidities that require treatment in the ICU. The only patient in our series who did not survive the index hospitalization despite improvement of left ventricular function was thought to have died because of multiorgan failure due to lung abscess.

The major limitation of our study is the fact that we did not systematically screen patients admitted to the ICU for the presence of TTC. Thus, we cannot draw any firm conclusions on the prevalence of TTC among ICU patients. We also may have missed patients with TTC who had different presenting signs that were not adequately appreciated.

In conclusion, sudden hemodynamic deterioration requiring vasopressor support might be the presenting symptom of TTC in the ICU and should be included in the diagnostic algorithm. ECG abnormalities consisting of ST-segment elevation, ST-segment depression or T-wave inversion can also be a manifestation of TTC and their appearance should prompt further appropriate work-up.

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