[Case report]

Takotsubo Cardiomyopathy Associated with Jet-Lag Syndrome in a Taiwanese Elderly Woman — a Case Report and Literatures Review

Chi-Sheng Chiou¹, Nen-Chung Chang¹, Chun-Ming Shih¹, Wei-Fung Bi¹, Chun-Yao Huang¹, Zhi-Yang Lai¹, Mei-Shu Lin²

Abstract

Takotsubo cardiomyopathy (CM) is still very rare in Taiwan. A 74-year-old Taiwanese woman came back from abroad for one week and suffered from a persisting and severe jet lag with sleep disturbance. She had a cold and experienced exacerbated bronchial asthma 3 days before the attack. She presented with sudden onset of chest pain after drinking 3 cups of coffee and taking a sauna for more than one hour. Upon admission, electrocardiogram (ECG) showed ST-segment elevation in leads II, III aVF, and V₃₋₆ while cardiac enzymes reported minimal elevation. Echocardiogram showed apical ballooning and basal hyperkinesias of the left ventricle (LV) in systole. Coronary angiogram on the second day read normal when ST-segment continued to elevate with ongoing chest pain. Negative T wave developed 3 days later. The ECG abnormality and LV dysfunction completely disappeared 6 months later. We diagnosed the case as Takotsubo CM. The activated myocardial adrenergic nervous system stimulated by acute and marked stress in this patient with more adrenergic innervations distributed in apex of LV might be the trigger for this novel cardiac syndrome.

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Key words: Takotsubo cardiomyopathy, ampulla cardiomyopathy, apical ballooning

¹Division of Cardiology, Department of Internal Medicine, Taipei Medical University and Hospital, and ²Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan

Correspondence: Nen-Chung Chang, MD, PhD, FACC
Address: 252 Wu-Hsing St., Taipei, Taiwan. Division of Cardiology, Department of Internal Medicine, Taipei Medical University and Hospital.
E-mail: nccchang@tmu.edu.tw
Introduction

A number of reports in Japan[1-6] during the past decade and in these 3 years in Europe[7] and the United States[8] described a unique syndrome characterizing clinical manifestation mimicking acute myocardial infarction (AMI). The features include ST-segment elevation on electrocardiogram (ECG), extensive but reversible apical ballooning with hyper-contractile basal segments during systole on echocardiogram (echo) and left ventricular (LV) angiogram, and minimal elevation of cardiac enzymes. Doctors usually diagnose these patients an AMI and undergo emergent coronary angiogram (CAG), but find no significant coronary artery stenosis in acute phase with ST-segment elevation and ongoing chest discomfort. LV morphology and ECG normalized within several weeks. This peculiar shaped LV was originally named by Sato et al[1] in 1990 as “Takotsubo (Ampulla)” cardiomyopathy (CM)[1,2]. Many cases have a preceding excessive emotional and/or physical stresses, however, the exact etiology has not yet been elucidated[3-5]. We presented a case of Takotsubo CM in a Taiwanese woman associated with a jet syndrome.

Case Report

A 74-year-old Taiwanese woman who was living in the United States came back to Taiwan one week before admission. She has been suffering from a severe and persisting jet lag and catching a cold with the exacerbation of bronchial asthma for 3 days. She presented with sudden onset of chest tightness radiating to bilateral shoulders after drinking 3 cups of coffee and taking a sauna for more than one hour. She asked for help due to persisting discomfort for 5 hours. On presentation, her conscious level was E₄M₆V₅ measured by Glasgow coma scale, blood pressure was 114/70 mmHg, temperature was 36.2 °C, and pulse was regular with 88 beats/minute and essentially equal in all four extremities. There was no cardiac murmur or extra sound on heart auscultation and no rales on lung auscultation. There was neither jugular venous engorgement nor leg edema. The neurologic examination showed no evidence of deviation or loss. Chest x-ray showed no active lesion. ECG showed concave ST-segment elevation in leads II, III, a VF and V₃₋₆ (Figure 1A) not detected on previous ECG with no reciprocal change. Cardiac enzymes revealed creatine kinase (CK) level of 125 IU/L (reference range: 15-100 IU/L), CK-MB level of 4.0 IU/L (reference range: 0-17 IU/L), and cardiac troponin-T level of 0.345 ng/ml (reference range: < 0.1 ng/ml). The patient...
received morphine injection, nitroglycerine and anticoagulant infusion and her chest pain did not relieve. ECG showed persistent ST-segment elevation with no dynamic change 8 hours later and CK, CK-MB and troponin-T were 112 IU/L, 3.0 IU/L, and 0.265 ng/ml 12 hours later, respectively. We did not perform emergent CAG due to clinical pictures were not typical of AMI. On hospital day 2, echo showed akinesis in wide LV apical region and hyperkinesia over basal portion (Figure 2A). The LV angiogram revealed apical ballooning and hyperkinetic basal portion during systole (Figure 3A). The CAG on hospital day 2 showed normal when the ST-segment still elevated with ongoing chest tightness (Figure 3B). On hospital day 3, ECG showed negative T wave in leads II, III, aVF and V3-6 (Figure 1B). On hospital day 4, ECG showed same negative T in II, III, aVF, and V3-6 with no new change. Mild chest pain persisted for one week. There was no fever or leukocytosis through the whole hospital course.

Reevaluation of ECG (Figure 1C) and echo (Figure 2B) 6 months later showed complete resolution.

**Discussion**

Takotsubo CM is a novel heart syndrome characterizing by transient and severe LV apical ballooning and basal hyperkinesias in acute stage[6-8]. Because the shape of LV resembled a round bottom and narrow neck bottle used in Japan for trapping octopus, the disease is called Takotsubo CM, derived from the Japanese
Figure 2. Echocardiogram (A) on hospital day 2; (B) 6 months later. ES, end-systole; ED, end-diastole.

Figure 3. LV angiogram (A) showed apical ballooning during systole, but coronary angiogram (B) showed no significant stenosis. LV, left ventricle; ES, end-systole; ED, end-diastole; LCA, left coronary artery; RCA, right coronary artery.
words *tako*, meaning octopus, and *tsubo*, meaning bottle[1,2]. Doctors also named this disease ampulla or amphora CM[2].

Despite the striking initial manifestations closely resemble AMI, the minimal changes of cardiac enzymes are not consistent with the extent of LV change in acute stage and the complete normalization of the unusual LV morphology within several weeks in most cases[6-8]. Furthermore, the changes on ECG are different from those in anterior AMI. In patients with Takotsubo CM, the ECG in acute stage shows ST-segment elevation, usually in leads V₃₋₆ and often concave in shape, with less dynamic change for days followed by T wave inversion and resolved in approximately 2–3 weeks[6,9] associated with QTₙ prolongation[9]. The abnormal Q wave and reciprocal changes are rarely seen[9].

Ogura et al[9] found the ratio of ST-segment elevation in leads V₄₋₆ to V₁₋₃ was significantly higher in patients with Takotsubo CM than in those with anterior AMI. The combination of the absence of reciprocal change and a ΣST V₄₋₆/V₁₋₃ ≥1 had a 100% specificity and 91% overall accuracy[9]. Our reported case is a typical one. Clinical course of the present case as described in above section is same as to the literatures reported cases[3-8]. Also, the ECG on presentation in our case shows a concave-shaped ST-segment elevation in leads II, III, a VF and V₃₋₆ (ΣST V₄₋₆/V₁₋₃ =4) with no reciprocal change, which is same as to the cases in the literatures review[6,9].

The etiology of Takotsubo CM is still not clear although Japanese doctors have reported more than 250 cases[10]. Stunned myocardium has long been known as a prolonged postischemic LV dysfunction after brief myocardial ischemia and presents a reversible LV dysfunction[11]. Because normal or nonsignificant stenosis on CAG with only mild elevation of cardiac enzyme in these patients accompanied with broad area of LV dysfunction beyond one vessel territory on LV angiogram in acute phase when chest discomfort is ongoing and ST-segment is elevated; thus, thrombotic occlusion followed by spontaneous recanalization on a single epicardial coronary artery is not a possible etiology. Recently, the largest and observational study in the United States by Scott et al[8] including 22 elderly women with this disease from a community-based practice used cardiac magnetic resonance (CMR) imaging for evaluation. The result showed myocardial viability with neither necrosis, loss of cellular integrity nor scar formation in patients with Takotsubo CM. CMR also detected diffusely allocated wall-motion abnormalities that covered LV
myocardium beyond any single vascular territory in 95% and in the vascular distribution of all 3 coronary arteries in 90% of cases. The authors confirmed the disease is not AMI and excluded a single epicardial vessel involvement. Moreover, many clinical and histologic findings excluded the possibility of myocarditis[6,8,13]. Thus, the potential causes are epicardial multivessel coronary spasm[12], microvascular multivessel coronary spasm[12] and catecholamine-induced cardiotoxicity[4]. Epicardial multivessel coronary spasm is very rare[14]. Moreover, absence of spasm during CAG in acute phase indicated that spasm is not likely[6,8,10]. Indeed, Ergonovine provocative test proved positive in only one fifth of cases in the Japan multicenter registry (JMR) by Tsuchihashi et al[6], though only 55% of the patients tested and not in acute phase (88 cases was enrolled, 48 cases had provocation and 10 showed positive)[6]. Moreover, Abe et al[13] investigated a prospective study in 17 patients and performed provocation in 7 of 9 during CAG. Five of 7 showed positive result, however, the authors found dissociations between the hypokinetic area and provocation-induced coronary artery territories. Epicardial multivessel coronary spasm is not likely from above findings. Microvascular spasm-induced stunned myocardium is a possible etiology. It is well known that Takotsubo CM often occurred shortly after a severe emotional and/or physical stress (35~90% of cases)[3-6] as in the present case with jet syndrome, exacerbated bronchial asthma, drinking 3 cups of coffee and taking a sauna for more than one hour while JMR[6] documented that 70% of patients had. It is proposed that stunned myocardium from multiple microvascular coronary spasm[8,15,16] induced by cardiac adrenergic denervation, i.e., excessive catecholamine release due to intense stress, is a possible cascade. Kurisu et al[16] assessed myocardial perfusion and fatty acid metabolism[3] in patients with Takotsubo CM using thallium-201 (TI) and I-123-beta-methyl-iodophenyl pentadecanoic acid (BMIPP) single-photon emission computed tomography (SPECT), respectively. Reduced uptake of BMIPP is related to transiently reduced function of myocytes in various disease conditions including ischemia[3]. The investigators found uptake of BMIPP was higher than that of TI in apex during acute phase and this discrepancy improved during follow-up. The authors concluded that impaired multivessel coronary microcirculation is involved as an etiology. However, intracoronary Doppler flow wire, a new tool for confirming the patency of coronary microcirculation
showed controversial results. Ako et al[15] found impaired coronary microcirculation, but Abe et al[13] did not. Moreover, Tsuchihashi et al[6] stated some autopsy cases by Kawai et al[2] did not show ischemic findings. Catecholaminergic or adrenoceptor-hyperactive myocardial toxicity as the finding in cases of neurogenic stunned myocardium has been presented as another possible mechanism[6,13,17,18]. It is believed that in some cases excessive catecholamine release due to foregoing severe psychological and/or bodily stresses resulted in cardiac dysfunction, though catecholamine levels are not inevitably elevated[3,10]. Plasma norepinephrine level may increase immediately and only transiently after attack[18]. Adrenergic nerve endings can uptake radiolabeled I-123 metaiodobenzyl-guanidine (MIBG)[19]. Owa et al[3] showed prolonged absence of MIBG accumulation in the apex of LV which indicated a cardiac adrenergic denervation in Takotsubo CM. In addition, exposure to high temperature might be a trigger for increasing adrenergic activity. Wakino et al[20] reported a heat stroke patient with transient ST-segment elevation on ECG and reversible diffuse hypokinesis on echo and considered due to a catecholamine cardiotoxicity. The reversible LV dysfunction is considered to be a short burst of powerful sympathetic discharge like the cases after head injury[21] and subarachnoid hemorrhage[22]. Adachi et al[23] reported a case of crush syndrome with reversible LV dysfunction who was buried for 24 hours during the Kansai earthquake. The MIBG images showed continual defects and TI images showed a notable recovery 1 month later in this patient. The authors suggested the earthquake-induced catecholamine release resulted in a transient LV dysfunction. Animal study by Ueyama[5] showed immobilizing stress-induced ECG and LV changes in rats normalized by combined blockade of α- and β-adrenoceptors. The animal model features resembled the Takotsubo CM in human beings. Moreover, molecular study revealed blocking α- and β-adrenoceptors will remove the upregulation of immediate early genes (IEG) induced by stress; conversely, α- and β-agonists upregulated IEG in the perfused heart. The sequential gene expression might be a stress-adaptive reaction. The author[5] concluded that emotional stress triggers activation of α- and β-adrenoceptors to yield the cardiac damage. However, definitely etiologic explanation is still deficient because investigators studied each of these potentially causative mechanisms in very limited number of patients. We did not consider an ischemic event in our reported
case because the CK-MB level did not increase while the AMI-like elevated ST-segment continued for more than 24 hours with a wide LV involvement. We did not perform radiounclide study nor examine catecholamine level. However, we suspect the activity of adrenergic nerve might incongruously increase in the patient who was under an acute and vigorous stress.

The key question is why Takotsubo CM involves the apex only. Washout rate of MIBG myocardial scintigraphy reflects cardiac adrenergic activation[24]. Moriya et al[17] followed-up Takotsubo CM and found persistent difference between apical and total washout rate for 6 months in MIBG image. The researchers inferred not all people after acute catecholamine overload showed an apical ballooning and suggested who had uneven distribution of adrenergic innervations in apical and basal regions might result in this particular pattern of LV change during acute phase.

Takotsubo CM must be considered in the differential diagnosis of patients with prolonged chest pain although the mortality rate in Takotsubo CM (near 1%) is far less than that of AMI, long-term prognosis does not change by drug therapy and the recurrent rate is 2-5%[6]. Several clinical implications are noted: (1) Differential diagnosis between Takotsubo CM and stenotic AMI is important when considering use of intravenous thrombolytic therapy. In fact, clinicians diagnosed many cases retrospectively and it is often difficult to differentiate from stenotic AMI in daily practice. Takotsubo CM is likely when minimal elevated or even normal CK-MB level associated with an AMI-like extensive elevated ST-segment for more than 24 hours and widespread LV apical involvement on echo. (2) Identification of transient LV outflow obstruction may be important because this finding may predispose apical ischemia with eventually forming an apical infarct although Tsuchihashi et al[6] and Abe et al[13] reported 18% and 0% of patients had this phenomenon. The traditional strategies to treat ischemia, including nitrate and afterload vasodilator may exacerbate the outflow tract obstruction and deteriorate the patient with Takotsubo CM. Beta-blocking agent and intravenous fluid may be helpful and life saving[25]; (3) There are two quite important unanswered clinical problems: should aspirin be administrated indefinitely and can minor tranquilizer prevent the attack?. Again, we do not know how many cases in these 250 reported cases[10] in Japan are typical Takotsubo CM. However, in face of establishing a completely novel disease or syndrome the diagnostic criteria should be strict, the definition should be of narrow
sense and it should be finished with gene study.

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老年女性在時差症候群後之壺狀心肌病變
—病歷報告及文獻回顧

邱啟勝 1 張念中 1 施俊明 1 畢偉楓 1 黃群耀 1 賴志洋 1 林美淑 2

摘   要

壺狀心肌病變在台灣仍屬罕見。吾等報告一位74歲台灣人之女性案例。病患發作之一週前由旅居之海外歸國，發生持續、嚴重之時差症候群。她在發作前有呼吸道感染合併氣喘惡化，在喝下三杯咖啡及洗三溫暖一小時多以後胸痛發作。住院時，心電圖的第Ⅱ、Ⅲ、aVF及V3-6導程有ST段上昇，而心肌酶只有少許上昇。發作當天心臓超音波檢查有左心室收縮期之廣範圍心尖部壺狀變化。第二天當胸痛仍持續且心電圖仍呈ST段上昇時進行冠狀動脈攝影，發現冠狀動脈尚稱正常。心電圖第三天出現反向T波；6個月後心電圖及左心室異常現象完全恢復正常。此一新型心臟症候群之誘因被推測因病人之左心室心尖部有較多交感神經之分佈，當有急性及嚴重之壓力發生時導致心肌交感神經之活化有關。

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1 台北醫學大學附設醫院內科部心臓內科  2 台大醫院藥劑部
通訊作者：張念中
通訊處：台北市吳興街252號
E-mail: ncchang@tmu.edu.tw