Iatrogenic Takotsubo Cardiomyopathy Following Overdose Norepinephrine Administration During Percutaneous Coronary Intervention

A Case Report

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Summary
Takotsubo cardiomyopathy (TTC) is characterized by reversible ventricular dysfunction induced by endogenous and, occasionally, exogenous catecholamine. We present a report on a patient who developed TTC and cardiogenic shock during percutaneous coronary intervention (PCI) secondary to inadvertent norepinephrine administration. His hemodynamic status and cardiac function were totally restored within 1 week after hemodynamic support using intra-aortic balloon pump without sequela. Thus, TTC should be considered once a patient presents with symptoms mimicking acute coronary syndrome (ACS) after catecholamine administration.

Key words: Stress-induced cardiomyopathy, Cardiogenic shock, Catecholamine

Takotsubo cardiomyopathy (TTC), also known as stress-induced cardiomyopathy, broken heart syndrome, or apical ballooning syndrome, is characterized by transient and reversible left ventricular dysfunction. Although TTC has been increasingly recognized in the past few decades, its exact pathophysiology and mechanism are not completely understood.1) One of the theories supported by most recent evidence is increased circulating and myocardial catecholamine levels that might induce direct myocardial injury or coronary spasm.1,2) We report a patient who developed TTC during a percutaneous coronary intervention (PCI), where supratherapeutic doses of norepinephrine were administered erroneously. The patient regained full recovery of cardiac function after hemodynamic support using intra-aortic balloon pump. This report provides the evidence that TTC could be a complication of PCI. This report also justifies support management, an effective therapy for such a critical yet transient clinical situation.

Case Report
A 54-year-old man with a medical history of hypertension, type 2 diabetes mellitus, and hyperlipidemia was admitted for an elective PCI on account of recurrent chest pain 1 year after PCI with bare metal stenting (BMS) for the left anterior descending (LAD) coronary artery.
Coronary angiography revealed in-stent intimal hyperplasia of the proximal LAD BMS with 50%-70% focal stenosis. The lesion was treated with a 3.5 × 20 mm and 3.75 × 20 mm noncompliant Euphora™ balloon catheter, followed by a 3.5 × 30 mm Pantera Lux paclitaxel-eluting balloon (PEB). However, as the patient presented with persistent chest pain and hypotension 30 seconds after PEB deflation, the physician ordered 5 mcg of intravenous norepinephrine, which is equivalent to a volume of 0.5 mL of the diluted solution (2.5 mg norepinephrine in 250 mL of saline). However, the cath lab nurse inadvertently gave 0.5 mL of undiluted norepinephrine (1 mg/1 mL) instead, which is equal to 100 times the prescribed dose. Chest pain was exacerbated with concomitant precordial lead ST-segment elevation (STE) on the hemodynamic monitor 1-2 minutes later. The systolic blood pressure initially increased from 80 to over 200 mmHg (Figure 1A) and yet dropped to 70 mmHg 5-7 minutes after norepinephrine administration (Figure 1B). A coronary angiography demonstrated no coronary artery stenosis. The operator was unaware of the nature of this situation and ordered another dose of 5 mcg norepinephrine to increase systemic blood pressure and coronary artery perfusion. The nurse staff gave the same mistaken dose as earlier, only to reproduce the same episode of high blood pressure, severe chest pain, and prominent STE, followed by profound shock and persistent ECG changes. An intra-aortic balloon bump (IABP) was then inserted to treat the cardiogenic shock before the patient was sent to ICU.

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On the first day of ICU admission, a transthoracic echocardiogram showed severe hypokinesis and akinesis in the distal half of the septal and apical segments of the left ventricle and hyperdynamic motion in the basal segments, with an ejection fraction of 15%-20% (Figure 2A and B). A 12-lead ECG on ICU admission showed atrial fibrillation and STE in precordial lead (Figure 3A). The CK, CK-MB, and troponin-I peaks were 417.1 U/L, 65.36 U/L, and 15.11 ng/mL, respectively. The patient was treated with bisoprolol and valsartan for heart failure. Another echocardiogram revealed complete resolution of wall motion abnormality and marked improvement of the LV systolic function and ejection fraction 2 days after the event; thus, IABP was removed. A follow-up ECG showed restoration of sinus rhythm from transient atrial fibrillation and diffuse symmetric T-wave inversion (Figure 3B). The patient was discharged at 3 days with minimal chest discomfort and remained symptom-free at a 1-week follow-up with an ejection fraction of 60% on echocardiography.

Discussion

TTC and acute coronary syndrome (ACS) have similar clinical presentations, electrocardiographic changes, and cardiac biomarker elevation.3,4 Because patients with TTC account for 1%-2% of all suspected acute myocardial infarction cases,3,6 TTC should be considered in patients suspected of having ACS. In our case, several clinical features suggested TTC, instead of ACS, as the nature of the acute cardiac failure event. Firstly, ECG changes were limited to STE in precordial lead at the onset of symptoms without development of permanent Q waves, suggesting TTC3,7,8 rather than ischemic myocardial injury.

Secondly, the magnitude of the increase in serum cardiac biomarkers was relatively insignificant compared to ACS, and there was a discrepancy between the level of biomarker elevation and the extent of myocardial dysfunction present.3,9 Thirdly, complete resolution of cardiac wall motion abnormality was achieved 2 days after the acute event, a phenomenon not commonly seen in ischemic ACS, yet a usual evolution of TTC. TTC is typically induced by emotional or physical stress, although one-fourth of individuals experiencing TTC do not have trigger factors.10,11 Although several hypotheses have been proposed to explain the etiology of TTC, there is an agreement that TTC is characterized by increased circulating and cardiac catecholamine levels, which causes myocardial damage through possible mechanisms including direct catecholamine toxicity, microvascular dysfunction, myocardial stunning in response to excessive high wall stress, supply-demand mismatch to protect viable myocardium, and hyperdynamic contractility with mid-ventricular outflow tract obstruction.12,13 Since it is difficult for one single pathogenetic factor to fully account for the mechanism leading to TTC, various hypotheses are not mutually exclusive and may coexist to explain TTC.

Several cases of TTC triggered by exogenous catecholamines, including norepinephrine or epinephrine,
have been reported.\textsuperscript{14,15} The Table showed eight cases of TTC following exogenous norepinephrine in the past decade, with many of them caused by inadvertent administration of overdose norepinephrine. Among them, the highest dose was 4.5 mg, either as a bolus or continuous infusion. The LVEF ranged from 20\% to 40\% during acute events, but none of them required cardiopulmonary support such as IABP or ECMO, and most cases recovered completely within a couple of days, with only one mortality occurring after TTC and fatal arrhythmia.

In our case, TTC developed 3-5 minutes after undiluted norepinephrine administration for a total dose of 1 mg with the initial presentation of hypertension and tachycardia, followed by refractory cardiogenic shock. The mechanism was therefore speculated to be transient myocardial stunning caused by norepinephrine-evoked afterload and cardiac workload. The LV function fully recovered within 2 days after the acute episode, leading to the speculation that such a rapid recovery course could be due to the relatively small dose of norepinephrine administered, thus resulting in the less stunning of the myocardium.

Although TTC had been considered to have benign course, recent evidences suggest that major short-term complications, such as cardiogenic shock and mortality, are comparable or even higher in TTC than in ACS.\textsuperscript{11,16} Templin, et al.\textsuperscript{11} suggested that cardiogenic shock rate and in-hospital mortality from TTC were 9.9\% and 4.1\%, re-

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Figure 3. A: ECG taken on ICU admission in the acute stage showed atrial fibrillation and ST-segment elevation in V2-V6. B: Evolution of ECG 2 days after the acute stage revealed diffuse and deep T-wave inversion and QT prolongation.
Table. Takotsubo Cardiomyopathy Following Exogenous Norepinephrine Administration

| Author                  | Year | Age | Gender | Indication for norepinephrine administration | Dose | Symptoms/manifestation | TS location | Complications | Treatment                     | Recovery/ time available |
|-------------------------|------|-----|--------|-----------------------------------------------|------|------------------------|-------------|---------------|-------------------------------|-------------------------|
| Lainez, et al.          | 2009 | 61  | F      | SAS and subsequent hypotension mistaken for anaphylactic shock during anesthesia for urinary tract neoplasm surgery |      | High-dose adrenaline and noradrenaline | LBBB in the ECG followed by TWI in V1-V6 | Mid-apical | No                           | Interrupting inotropic drugs | Yes/1 month             |
| Subramaniam, et al.     | 2010 | 26  | F      | Hypotension after diarrhea and vomiting       |      | Hypertension, AF with RVR, STD in V3-V5 | Inverted TTC, LVEF: 35% | Hypotension | Infusion of norepinephrine and epinephrine | Yes/7 weeks             |
| Redfors, et al.         | 2012 | 18  | M      | Prevent hypotension due to sepsis             |      | STD and ventricular arrhythmia | Mid-apical, LVEF: 20%-30% | VF, heart failure, cardiogenic shock, death | Fluid supplement, inotropics | No/died                  |
| Quick, et al.           | 2013 | 59  | F      | Septic shock during treatment for Guillain-Barré syndrome |      | N/A | VT, STE in precordial leads | Mid-apical, LVEF: 25% | No                           | VT | N/A | N/A | Yes/1 week             |
| Vailas, et al.          | 2016 | 51  | M      | Hypotension after renal transplantation       |      | 4 µg/kg/minute | Chest pain, sinus tachycardia, mild hypotension, STE consistent with anterolateral MI | Mid-apical, LVEF: 30% | No                           | Cease of NE | Yes/1 week             |
| Ouerghi, et al.         | 2016 | 17  | M      | Septic shock                                  |      | An accidental bolus of 2 mg | Chest pain, dyspnea; STD in apico-lateral leads | Mid-apical, LVEF: 40% | Required noninvasive ventilation for 48 hours | Dobutamine infusion | Yes/1 week             |
| Sherif, et al.          | 2016 | 76  | F      | Eroneously replace furosamide with norepinephrine after blood transfusion |      | An accidental bolus of 4 mg | Chest pain, dyspnea, respiratory distress, tachycardia; ECG: NSSTTC | Mid-apical, LVEF: 25% | No                           | Beta-blocker, ACE-I, aldosterone antagonist | Yes/6 months            |
| Vieira, et al.          | 2018 | 82  | F      | Shock due to adrenal crisis mistaken for septic shock |      | 0.8 µg/kg/minute | N/A | Mid-apical, LVEF: 25% | Correct adrenal insufficiency and taper NE | Yes/11 days            |

TS indicates Takotsubo syndrome; SAS, subclavian artery stenosis; LBBB, left bundle branch block; TWI, T-wave inversion; AF, atrial fibrillation; RVR, rapid ventricular response; STD, ST-segment depression; TTC, Takotsubo cardiomyopathy; VF, ventricular fibrillation; STE, ST-segment elevation; NE, norepinephrine; and NSSTTC, nonspecific ST- or T-wave changes.
spectively, which is comparable to ACS. By contrast, exogenous catecholamine-triggered (either norepinephrine or epinephrine) TTC had a cardiogenic shock rate of 30.8% and in-hospital mortality of 2.6%.14–16 Currently, there is no established guideline or randomized clinical trials available to guide specific treatment for TTC, neither in acute phase nor in long-term management. The main goal of treatment focuses on supportive care and prevention of complications until cardiac function is restored.17 Di Vece, et al.18 reported that patients with TTC and cardiogenic shock who received cardiac mechanical support, including intra-aortic balloon pump, Impella, and extracorporeal membrane oxygenation, as a bridge to recovery, had a lower in-hospital mortality rate than those without cardiac mechanical support (5 of 39 [12.8%] versus 45 of 159 [28.3%], P = 0.046). These data illustrated the extremely devastating scenarios of iatrogenic TTC and justify the roles of mechanical cardiac support for such patients to survive this potentially fatal serious event.

Conclusion
Iatrogenic TTC could be a complication of administration of inadvertent supratherapeutic dose of undiluted norepinephrine during PCI, which yet could be treated with cardiac support using IABP and completely recovered within 1 week. This is, to our knowledge, the first case of TTC induced by exogenous norepinephrine during PCI. This finding raises the importance of strict training of cath lab nursing staff about accurate administration of potentially harmful catecholamine agents and alerts physicians to recognize the development of such a drug-induced TTC if unexpectedly happening.

Disclosure
Conflicts of interest: None.

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