A rare case of takotsubo syndrome within the first day after heart transplantation

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Abstract

A 39-year-old woman underwent heart transplantation (HTx) for advanced heart failure. The donor was a 36-year-old young woman without past medical history. The first day after HTx, T-waves changes were noted. Echocardiography revealed akinesia/dyskinesia of all basal segments of the two ventricles. Coronary catheterization plus biopsy were done 7 days later showing no coronary obstruction, no rejection and complete recovery of wall motion abnormalities on echocardiogram, suggesting biventricular inverted takotsubo syndrome (TTS). This is a case of TTS during the first day after HTx, with completely denervated heart but because of the inotropic drug support it still represents a target for catecholamine-induced cardiac dysfunction.

Introduction

Takotsubo syndrome is supposed to be a disturbance of myocardial microcirculation related to increased concentration of catecholamines (*i.e.*, epinephrine, norepinephrine, and dopamine), and wall motion abnormalities with different involvement of the myocardial muscle and usually followed but complete recovery of contractility [1,2]. The most common type is the apical one with apical akinesia of the left ventricle and mid-basal hypercontractility. Catecholamines increase may be related to sympathetic overactivity caused by stress or inotropic drugs.

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Case Report

A 39-year-old woman underwent heart transplantation for New York Heart Association Class IV heart failure symptoms despite guideline-directed medical therapy. She had underlying rheumatic heart disease with mitral valve repair 10 years prior to transplantation. The donor was a 36-year-old female without significant past medical history who was declared brain-dead due to cerebral vascular accident. The donor echocardiogram that was performed 20 h prior to procurement was normal showing no wall motion abnormalities. On visual inspection during heart procurement the heart function was normal and palpation of the epicardial coronary arteries did not reveal any gross pathology, areas of atheromatous disease, or calcium. The crossmatch was negative.

An orthotopic heart transplant was carried out using the bicaval technique. The surgery was not complicated and the graft function was normal. The patient came off bypass without difficulties and she was admitted to the cardiac surgery intensive care unit intubated and on inotropic drug support. Twelve hours post-transplant, the patient developed new T-wave changes on the monitor. An echocardiogram revealed normal LV size, borderline reduce LV function (ejection fraction ~50%), presence of wall motion abnormalities characterized by akinesia of the basal septum and hypokinesia of the other septal segments, dyskinesia of all other basal segments of the LV, akinesia of the basal segment of the right ventricle and hypercontractility of the apical segments of the ventricles. In addition, also the speckle tracking of the two ventricles was significantly compromised. The patient hemodynamics were stable. Coronary angiography plus endomyocardial biopsy was done few days later showing no evidence of coronary atherosclerosis and biopsy result showed mild acute cellular rejection (ISHLT grade 1R) with no findings of antibody mediated rejection. No donor specific antibodies were detected. The echocardiogram performed in the same day showed complete recovery of the wall motion abnormalities while strain was still impaired. A final diagnosis of TTC was therefore made. The third echo done 3 weeks later confirm the complete recovery of wall motion abnormalities, showed a sig-

nificant improvement in biventricular strain although it was not normal yet (Figures 1 and 2).

Discussion

The classical clinical presentation of the TTS is similar to acute coronary syndrome (ACS) but with reversible left ventricular dysfunction that is unrelated with obstructive coronary disease [1,2]. The pathophysiology seems to be based on excessive local release of catecholamine (*i.e.*, epinephrine, norepinephrine, and dopamine) [3,4] due to sudden stress which starts at the cognitive centers of the brain, follows the hypothalamic-pituitary-adrenal axis (HPA), the thoracic nervous sympathetic system, ending on the cardiovascular apparatus (myocardium, coronary arteries and peripheral vasculature) with microvascular spasm and myocyte injury [5]. In the transplanted hearts, the heart is totally denervated in the acute phase and the stimulation of the cardiomyocyte by catecholamines has to be different from the release of norepinephine in the synaptic cleft by the thoracic sympathetic ganglia [6]. In addition, the transplanted heart has also lost inhibitory parasympathetic innervations which contribute to the exaggerated response to catecholamines. As a consequence, transplanted hearts seem to be more susceptible to non-physiologic doses of exogenous catecholamines such as dopamine, noradrenaline and adrenaline.

To the best of our knowledge this is the first report of TTS, with inverted and biventricular involvement of the heart beyond a single coronary artery territory, in a young woman 24-hour post HTx.

Upon literature review, there are 6 case reports of TTS peri or post HTx (Table 1). Chinali *et al.* [7] reported a case of TTS following angry debate in a 21-year-old woman with HTx done 10 years back. The patient complained reduced tolerance to physical activity and fatigue. Behnes *et al*. [8] reported the case of a 64-year-old man with HTx done 9 years earlier. Few days after an acute coronary syndrome (ACS), the patient developed sudden dyspnea. Another case [9] was a 69-year-old man who had an orthotopic HTx 6 years back who presented respiratory distress and hypotension 30 min after total shoulder arthroplasty. In all of these cases the clinical scenario was dyspnea and congestive heart failure but not chest pain where the most likely explanation is that the sympathetic re-innervation had already occurred, usually happens within the first years, while the nociceptive sensory afferences probably had not. In addition, Gastwirth *et al*. [10] reported a case of a 55-year-old woman who had HTx 1 year early from a 19-year-old donor who had a dobutamine stress echocardiography and at peak stress and during recovery, images showed significant wall motion abnormalities and severe left ventricular dysfunction which normalized within 5 days. The patient remained always asymptomatic. The authors hypothesized that the high dose of dobutamine on the denervated heart could be the cause. The use of donors with TTS have been reported in the literature. Redfors *et al.* [11] reported the case of a patient with subarachnoid hemorrhage, suitable for organ donation. Pre HTx coronary angiography revealed normal coronary arteries but midventricular akinesia with reduced EF confirmed by echocardiography. The diagnosis of TTS was made and the heart was used for transplant. One month after HTx, the patient's left ventricular function was normal. The authors hypothesized that the process of brain death could have elicited significant somatic stress and a catecholamine surge. A second case [12] described an apical left ventricular ballooning in the donor's cardiac heart that was probably affected by the intense physiologic stress caused by the fatal motor vehicle accident.

In our case we hypothesize, since the postganglionic sympathetic nerve fibers to the heart were excluded, TTS was caused by the release of catecholamines from the adrenal gland through the hypothalamic-pituitary-adrenal axis and lower-spinal cord sympathetic pathway activation and by the inotropic drugs given to the patient. In addition to the increased blood stream catecholamine

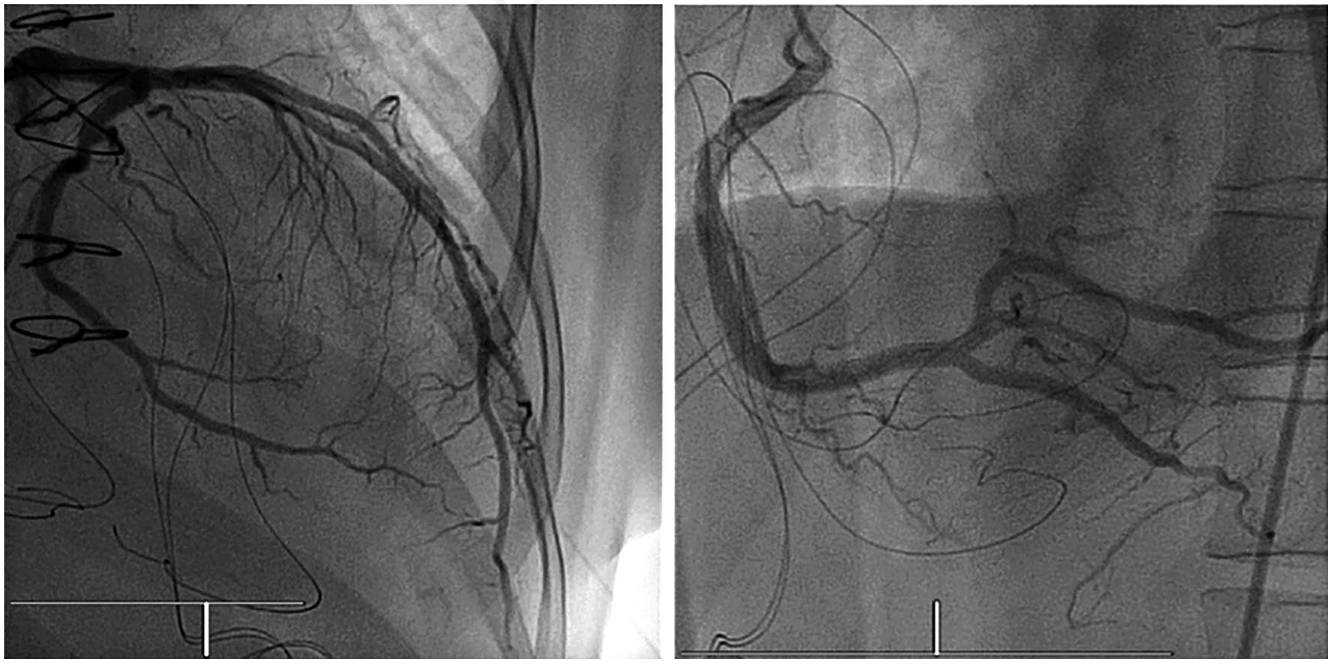

Figure 1. Coronary angiogram showing normal coronary arteries.

concentration, also a higher sensitivity to catecholamines by the denervated heart might play a role and most likely also a decreased re-uptake capacity from the pre-synaptic neural endings. This patient had the involvement of the basal segments of both ventricles, which goes along with the younger age [13] and the epinephrine sensitivity after the heart denervation [14]. Although there was the involvement of the right ventricle, the patient had no intra or extra hospital complications related to TTS even though the prognosis of patients with the right ventricle involvement is reported to be worse [15].

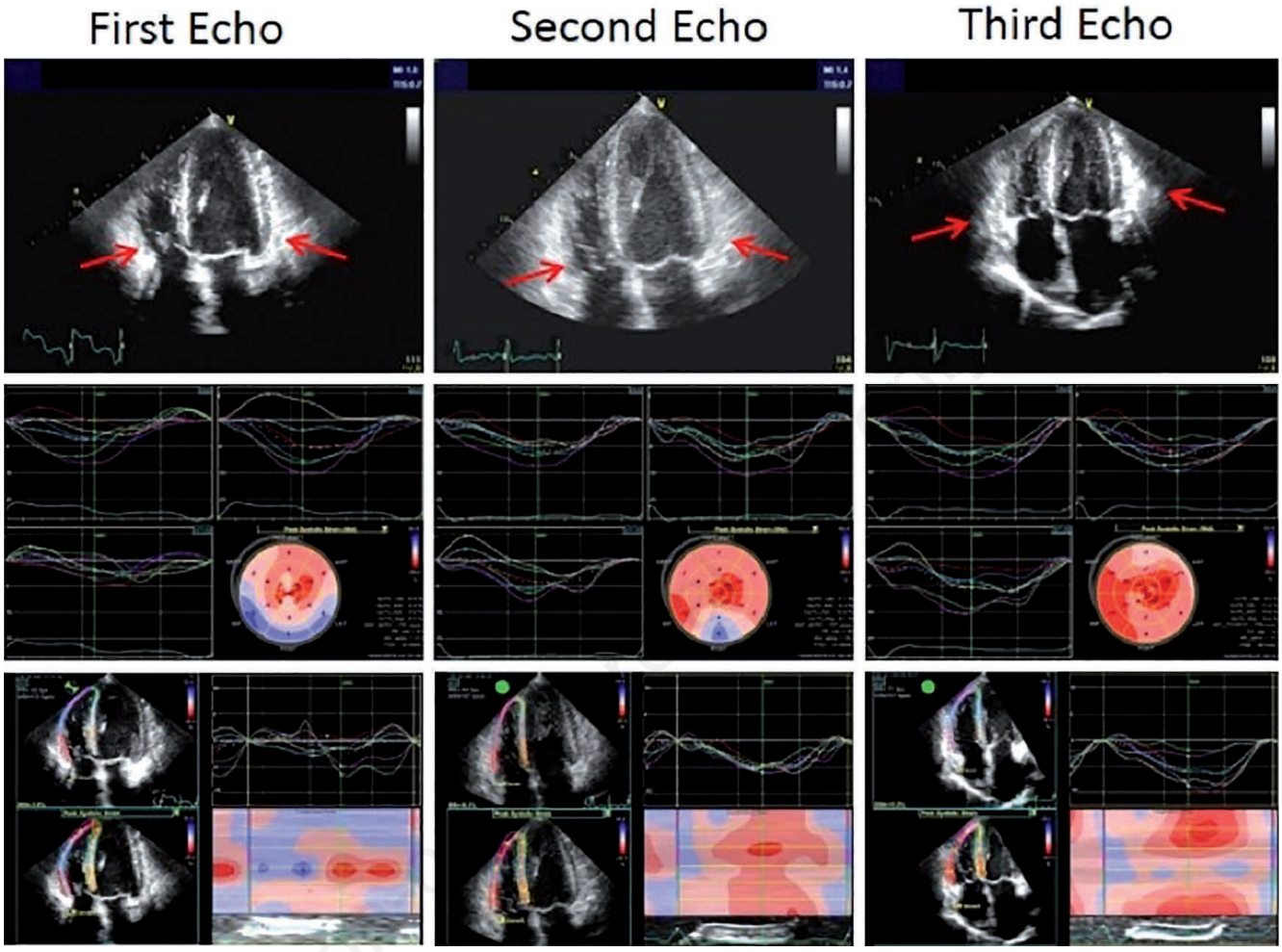

Figure 2. Echocardiogram in 4CH view at day 1, 7 and 21 showing the regional involvement of the basal segments of the LV and RV. The 2D strain of the LV and RV at day 1, 7 and 21 is represented.

Table 1. Reports of TTS peri or post HTx in literature.

Author	Sex	Age	Type of TTS	Immunosuppression Rx	Time after HTx	Possible triggers	Time of recovery
Behnes (2018) [8]	Male	64	Biventricular	Cyclosporine, Mycophenolate mofetil, and low-dose steroids	After 9 years	1 week after PCI to lcx for NSTEMI	10 days
Chinali (2018) [7]	Female	21	Apical left ventricle	Not mentioned	After 10 years	After angry debate	20 days
Gastwirth (2009) [10]	Female	55	Apical left ventricle	Tacrolimus, Sirolimus and Azathioprine	After 1 year	After dobutamine stress echocardiography	5 days
Cunanan (2013) [9]	Male	69	Apical left ventricle	Tacrolimus	6 years	Hypotension after total shoulder arthroplasty	10 days
Ravi (2018) [12]	Female (donor)	17	Apical left ventricle	-	Donor Peri HTx	Motor vehicle accident	3 days
Redfors (2015) [11]	Male (donor)	50	Apical left ventricle	-	Donor Peri HTx	Subarachnoid hemorrhage	30 days

Conclusions

This is a rare case of TTS that happened within the first 24 hours after heart transplantation, when the heart is completely denervated. We hypothesized that the present case of TTS was related to the drug inotropic support and the endogenous catecholamines released by the adrenal medulla as response to stressful clinical setting.

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