Iatrogenic epinephrine-induced Takotsubo cardiomyopathy in beta-blocker poisoning: case report

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SOUHRN

Kontext: Termínem stresová (takotsubo) kardiomyopatie se označuje přechodná dysfunkce levé komory s poruchou kinetiky její stěny; tento stav připomíná infarkt myokardu bez akutní formy ischemické choroby srdeční. I když patofyziologie tohoto postižení zatím nebyla zcela objasněna, bylo již publikováno několik různých hypotéz. Popisujeme případ stresové kardiomyopatie u 18letého muže vyvolané několika faktory.
Kazuistika: Dosud zdravý 18letý mladík původem ze severní Afriky byl dopraven na oddělení akutních příjmů pro otravu beta-blokátorem (propranololem). Fyzikální vyšetření prokázalo známky oběhového selhání s poruchou převodu srdečních vzruchů. Po tekutinové výzvě a infuzi adrenalinu se pacientův hemodynamický stav stabilizoval. Druhý den hospitalizace došlo u pacienta k rozvoji bolesti na hrudi a dyspnoe. Elektrokardiogram prokázal anterolaterální elevaci úseku ST při zvýšených hodnotách troponinu na 8,4 ng/ml. Transthorakální echokardiografie odhalila sníženou ejekční frakci levé komory (40 %) a akinezi apikálního segmentu. Při urgentně provedené koronární angiografii nebylo zjištěno postižení koronárních tepen; ventrikulografie prokázala apikální balonkový syndrom se zachovanými bazálními kontrakcemi; následně byla stanovena diagnóza stresové kardiomyopatie. Po podpůrné léčbě se pacientův hemodynamický stav zlepšil. Výsledkem bylo úplné vymizení symptomů a normalizace funkce levé komory.
Diskuse a závěry: Lze tedy uzavřít, že v tomto případě došlo k rozvoji stresové kardiomyopatie pravděpodobně působením tří faktorů: emocionálního stresu, infuze adrenalinu a otravy beta-blokátorem. Lékaři si musejí být vědomi možných iatrogenních spouštěčů tohoto postižení, zvláště škodlivých účinků katecholaminu na funkci srdce a/nebo otravu kardiotoxickými látkami.

Keywords:
Apical ballooning syndrome
Case report
Catecholamine cardiotoxicity
Iatrogenic disease
Poisoning
Stress-induced cardiomyopathy
Takotsubo cardiomyopathy

ABSTRACT

Background: Takotsubo cardiomyopathy is a transient left ventricular dysfunction with wall-motion abnormalities which mimics myocardial infarction without acute coronary disease. Physiopathology of this entity remains unclear and different hypotheses are given. We present a case of a multifactor induced takutsubo cardiomyopathy in a young 18-year-old man.
Case presentation: A previously healthy 18-year-old North African male presented to the emergency department for beta-blocker poisoning (propranolol). Physical examination revealed signs of circulatory failure with cardiac conduction disturbances. The patient's hemodynamic status stabilized after fluid challenge and ephedrine infusion. On second day of hospitalization, the patient developed chest pain and dyspnea. Electrocardiogram showed an anterolateral ST segment elevation and troponin was elevated at 8.4 ng/ml. Transthoracic echocardiography revealed a reduced left ventricular ejection fraction (40%) and apical akinesia. An urgent coronarography revealed normal coronary arteries and ventriculography showed apical ballooning with preserved basal contraction. The diagnosis of Takotsubo cardiomyopathy was made. Supportive therapy allowed hemodynamic improvement. The outcome was favorable with complete resolution of symptoms and normalization of left ventricular function.
Discussion and conclusions: In conclusion, Takotsubo cardiomyopathy was probably triggered in the present case by the association of three etiologies: emotional stress, epinephrine infusion and beta-blocker poisoning. Physicians should be aware of possible iatrogenic triggers of this disease, especially the harmful effects of catecholamine on heart function and/or poisoning with cardiotoxic drugs.

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Background

Takotsubo cardiomyopathy (TTC) is a particular reversible left ventricular (LV) dysfunction with wall-motion abnormalities which mimics an acute coronary syndrome (ACS) in the absence of occlusive coronary artery disease. The shape of LV looks like a takotsubo which is a Japanese fishing pot used for trapping octopuses.[1] This cardiomyopathy is also called "Broken-heart syndrome" or LV ballooning syndrome or stress cardiomyopathy.[2]

Knowledge about TTC had improved in the last decades but pathophysiology of this clinical entity and its different mechanisms remain unclear. One of the most plausible and sustained physiopathological theories is that this cardiomyopathy is the consequence of catecholamine's increase levels. By adrenergic induced way, many clinical situations were associated with TTC such as psychological or physical severe stress, administration of catecholamine used for hemodynamic stabilization or several drugs acting directly or indirectly as adrenergic agents especially in case of poisoning.[1]

In this paper, we present a case of a multifactor induced Takotsubo cardiomyopathy in a young 18-year-old man with no previous history of cardiac disease.

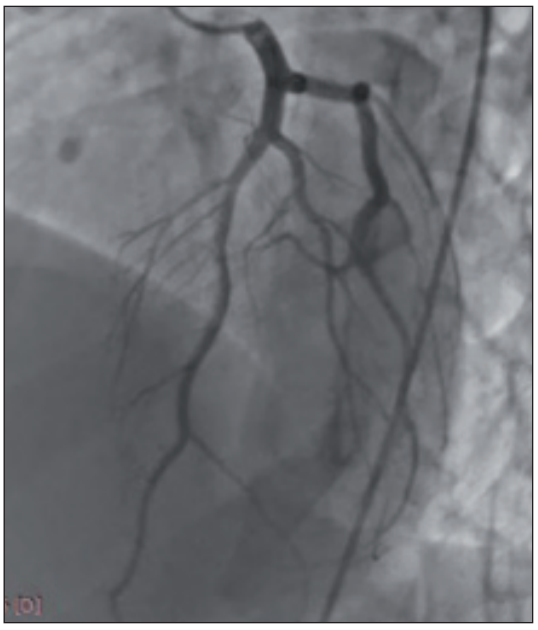

Fig. 1 – Coronarography showing normal coronary arteries.

Case presentation

A previously healthy 18-year-old North African male presented to the emergency room, 2 h after ingestion of 5 600 mg of acebutolol in autolytic attempt. Physical examination revealed an altered neurologic status with confusion and anxiety (Glasgow Coma Scale of 14/15) and a low blood pressure (BP) at 70/40 mmHg. His heart rate (HR) was 70 beats per minute (bpm) and oxygen saturation was 98%. He had no respiratory distress or signs of peripheral hypoperfusion. Glycaemia and serum potassium level were normal. An electrocardiogram (ECG) showed sinus rhythm and conduction disturbances (first-degree atrioventricular block and left bundle branch block [BBB]).

The patient received fluid loading (700 ml of isotonic saline solution) and continuous intravenous infusion of epinephrine via central venous line with the initial dose of 0.08 µg/kg/min, increased subsequently to 0.14 µg/kg/min in order to stabilize hemodynamic status. In addition, 3 mg of glucagon and 100 ml of semi molar sodium bicarbonate were administered intravenously. Neither gastric lavage nor activated charcoal were used.

Stabilization was achieved 2 h later (BP 110/70 mmHg, HR 65 bpm) and the patient was transferred to the intensive care unit (ICU).

On the third day of ICU stay, while still receiving the same dose of epinephrine, the patient complained of a retrosternal chest pain and dyspnea. Crackles were auscultated. ECG showed sinus rhythm with frequent premature ventricular complex, complete left BBB and signs of myocardial injury: significant ST segment elevation in anterolateral wall and reciprocal change in the other leads. Dysrhythmias were spontaneously reduced within 5 min. Troponin I level increased to 8.4 ng/ml at one hour (15.6 ng/ml and 10.22 ng/ml respectively at 3 and 10 h from chest pain onset).

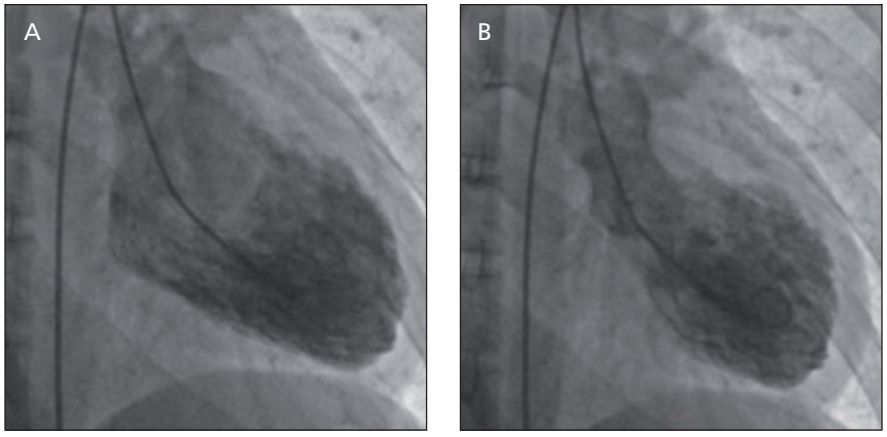

Fig. 2 – (A) End-diastole left ventriculogram in anterior oblique projection illustrating apical akinesis (ballooning). (B) End-systole left ventriculogram in anterior oblique projection illustrating apical akinesis (ballooning).

Transthoracic echocardiography showed a non-dilated LV with decreased left ventricular ejection fraction (LVEF) estimated at 40% caused by apical akinesia, without hyperdynamic basal contraction. The patient underwent urgent cardiac catheterization which showed normal and permeable coronary arteries (Fig. 1) while ventriculography revealed apical akinesia (Fig. 2A and 2B). The diagnosis of TTC was highly suspected.

Non-invasive ventilation for 48 h, diuretics and epinephrine infusion allowed hemodynamic improvement and successful weaning from catecholamine at day 5 of drug-ingestion. The outcome was favorable and the control echocardiogram at day 9 confirmed the recovery of LV function (LVEF 78%) with normal wall motion and absence of dilatation. The patient was discharged from hospital after 10 days of hospitalization.

Discussion

Takotsubo cardiomyopathy is a particular acute and transient systolic and diastolic LV dysfunction with variety of wall-motion abnormalities which mimics an ACS (chest pain, electrocardiographic changes and elevated cardiac biomarkers levels) in the absence of occlusive coronary artery disease.[1] Typically, the echocardiography shows hypokinesis or akinesis of the mid and apical segments of the left ventricle with sparing of the basal systolic function. It is almost seen in postmenopausal women. Its incidence is unknown due to its novel nature and varied presentation. It is estimated that approximately 1–2% of all patients presenting an acute myocardial infarction has TTC.[2]

This entity was first reported by Dote et al. in 1983 then individualized in Japanese population in 1991. It was called "Tako-Tsubo cardiomyopathy", because the peculiar shape on end-systolic left ventriculogram looks like a tako-tsubo (the octopus trapping pot with a round bottom and narrow neck). The typical TTC is also called the LV apical ballooning syndrome.[1,3,4]

The Mayo Clinic diagnostic criteria, based on expert consensus opinion were proposed in 2004 and revised in 2008. They are practically applied at admission set and should be widely used in both clinical practice and research field (Table 1).[4]

Table 1 – Mayo Clinic Criteria for TTC diagnosis (modified in 2008)[4]

1. Transient LV wall motion abnormalities extending beyond a single epicardial vascular distribution. A stressful trigger is often, but not always present. Optional criteria: abnormalities involving apical and/or mid-ventricular myocardial segments.
2. Evidence of ischemia/myonecrosis: new and dynamic ST-segment deviation, T-wave inversion or left BBB. Optional criteria: mild or modest increase in cardiac biomarkers
3. Exclusions of: a. Potential coronary culprit (e.g., stenosis, evidence of plaque rupture, dissection, thrombosis or spasm) b. Pheochromocytoma c. Myocarditis
All criteria must be met.

The LV dysfunction and the wall motion abnormalities are transient and generally resolved within days to weeks after initial presentation. The prognosis is generally favorable except isolated cases of death due to clinical complication such as left heart failure, cardiogenic shock, arrhythmia and valvular disease.[5]

Various triggers for TTC are described in the literature; the common etiologic feature is occurrence of severe psychological or physical stress which lead to surge in catecholamine's levels. At the normal physiological range, epinephrine results in a positive inotropic response in cardiomyocytes. At higher and supraphysiological concentrations, this condition results in cardiac dysfunction including epicardial spasm, microvascular dysfunction, hyperdynamic contractility and negative inotropic effect on myocyte contraction.[6] In an animal study, the exposure of rats to emotional stress induced a ventricular hypocontraction via activation of cardiac adrenoceptors. The administration of beta-blocker prevents this effect.[7]

The morphologic features and regional difference in TTC are explained by a higher sensitivity and greater contractile response to circulating catecholamine challenge in the apical myocardium than in the basal myocardium related to different density of beta-adrenoreceptors which decrease from base to apex.[6]

In the present case, psychiatric condition and emotional stress, subsequent to suicide attempt and ICU admission, were certainly a precipitating factor for TTC but the moment of presentation (24 h later) suggest intervention of other factors. Indeed, the close temporal association with epinephrine infusion and beta-blocker poisoning suggest a causal relationship between these factors and TTC in our patient.

Epinephrine is a life-saving medication but its use exposes to possible severe adverse effects. Adrenaline infusion is an iatrogenic inducing factor for TTC which was already reported in the literature. Several cases provided evidence that iatrogenic catecholamine administration, especially epinephrine, at therapeutic and supra-therapeutic doses, can be the trigger factor of TTC by inducing coronary spasm and/or direct myocardial stunning.[8] 41 cases of cardiomyopathies induced by exogenous catecholamines were reported.[9] These TTC occurred mostly in young and female patients who received intravenously epinephrine at doses often used in routine clinical practice. Prognosis was generally good and recovery was complete in most of cases.

The present case was admitted in ICU for beta-blocker poisoning which probably have synergistic effect with epinephrine rise levels (from both endogenous and exogenous origin). Among the broad family of beta-blockers, acebutolol is a cardioselective with intrinsic sympathomimetic activity and membrane stabilizing effect. The peak plasma is obtained between 2–3 h and the overdose appears 20–60 min after ingestion. First hepatic passage has a moderate effect and allows its transformation into active metabolites (diacetolol) which prolongs global action's duration. The half-life of acebutolol is 7 h and that of the diacetolol is longer. In case of poisoning, a decrease in hepatic metabolism and biliary and renal elimination have been described. It is secondary to hepatic

microsomal saturation and hemodynamic complications which decrease hepatic and renal blood flow.[10,11]

Time of TTC's occurrence suggest that gradual attenuation of the beta-blocking effect of toxic poisoning has allowed recuperation of the sensitivity of adrenergic receptors and at consequence a higher impact of catecholamine systemic perfusion on cardiac function. The occurrence of TTC in poisoned patients has already been reported but remains rare. It was associated to several clinical situations in poisoning patients such as drug withdrawal and poisoning with direct or non-direct sympathomimetic drugs. In a retrospective French study, the incidence of TTC was 0.5% in ICU. Only 5 patients of the 973 poisoning patients included have met the echocardiographic criteria for TTC diagnosis. A beta-blocker (propranolol) was identified as a toxic agent in two cases in which TTC was associated with severe shock requiring extracorporeal life support. In different models of multivariate analysis, poisoning with beta-blockers was associated with the occurrence of TTC. Among the possible suggested hypotheses, metabolism dysfunctions were advocated as potential mechanism. Indeed, fatty acid metabolism, which is the major heart's source of energy, can be impaired in beta-blocker poisoning.[1]

Many questions concerning etiology and physiopathology of TTC remain unanswered. The present case demonstrates that TTC can occur even in young poisoning patients with cardiotoxic agents, especially those needing catecholamine infusion as complementary therapy. In case of cardiac symptoms mimicking ACS, indeed, toxic induced cardiomyopathy itself, clinician should be aware of possible iatrogenic triggers of TTC especially harmful effects of catecholamine on heart function. Echocardiography may suggest the TTC diagnosis but can't exclude an ACS. Therefore, early coronarography remains necessary to rule out existing coronary artery disease.[12]

Conclusions

TTC is a particular acute cardiomyopathy which occurs in particular circumstances. This entity still underrecognized and often misdiagnosed. Etiologies and mechanisms remain incompletely known. It is important to consider this diagnosis in ICU patients presenting cardiac symptoms because of myriad of possible conditions leading to this disease.

In the present case, TTC was probably triggered by association of three factors: intensive emotional distress, epinephrine infusion for hemodynamic support and beta-blocker poisoning.

Further researches are warranted to understand this disease and to identify its mechanisms and features in order to better guide preventive and therapeutic interventions.

Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary info.

Authors' contributions
MO, HK and MS cared of the patient (emergency department, intensive care unit and cardiology). HM acquired and analyzed case data. AA, HK and MO conceived of, drafted different sections and revised the whole manuscript critically for important intellectual content. MB revised the final manuscript. All authors have read, correct and approved the final manuscript.

Conflict of interest
The authors declare that they have no competing interests.

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Ethical statement
Authors state that the research was conducted according to ethical standards.

Informed consent
Written informed consent for publication and accompanied images was obtained from the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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