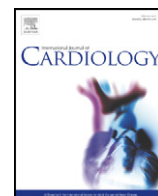




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Letter to the Editor

Iatrogenic inverted takotsubo syndrome following intravenous adrenaline injections for an allergic reaction

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Apical ballooning or takotsubo cardiomyopathy (TTC) is increasingly gaining recognition. Most commonly, the TTC is characterized by a sudden-onset, mostly reversible wall motion disturbance of the left ventricular apex, while the basal segments are normal or hyperkinetic. Notwithstanding its resemblance to acute myocardial infarction, TTC is characterized by the absence of significant epicardial coronary artery disease [1]. Postmenopausal women account for most of the cases described in the literature, but the syndrome is not restricted to any specific age or patient group.

Variant patterns of left ventricular dysfunction have been described, as some patients present with basal instead of apical hypokinesia, termed reverse or inverted TTC [2]. Considerable evidence suggests that the pathophysiologic mechanisms of the TTC involve catecholamine excess which is often caused by intense psychological or physical stress [3]. Moreover, catecholamines, either administered exogenously or secreted by neuroendocrine tumors such as pheochromocytoma, have been reported to cause TTC [4]. In this report, we present a rare case of an iatrogenic inverted takotsubo syndrome in a 49-year-old female followed by a complete recovery of the left ventricular function. This case adds to our knowledge on the potential risks of intravenous adrenaline administration and provides further evidence for the role of catecholamine toxicity in the pathophysiology of inverted TTC.

The case is a 49-year-old female, working as a children's nurse. Patient's past medical history includes asthma, atopic eczema and known anaphylaxis to milk protein. While doing recreational exercise, she developed familiar symptoms of an anaphylactic reaction,

but failed to administer adrenaline using the personal auto-injector. In the local hospital emergency room, the patient was pale and complained of abdominal pain and dyspnea. On arrival, blood pressure was 105/69 mm Hg and heart rate 94 bpm. She was given 0.1 mg adrenaline intravenously (i.v.) for the suspected anaphylactic reaction. After the injection the patient had severe chest pain and

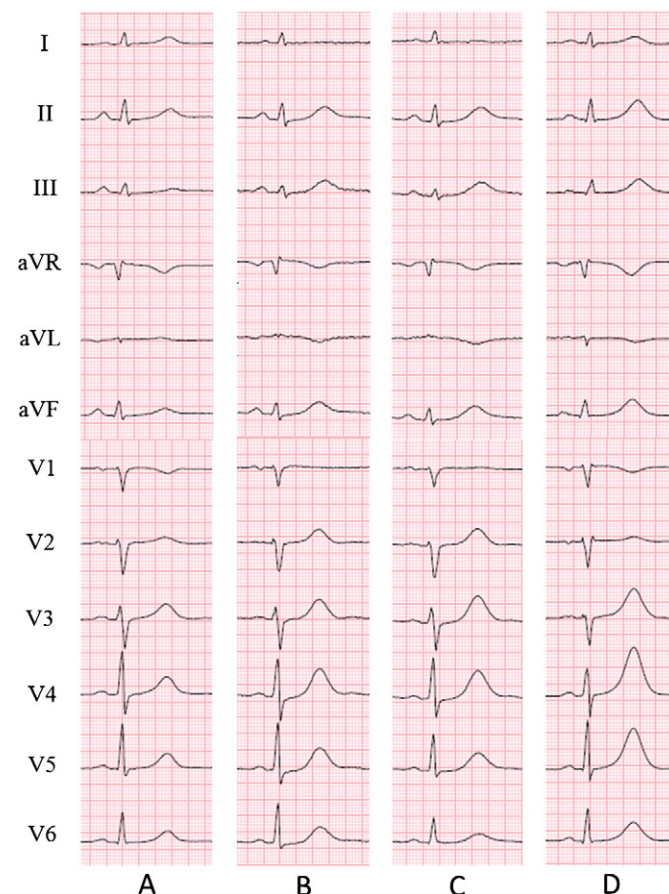


Fig. 1. 12-Lead ECG recordings from a previous visit (A), on admission (B), on day two at hospital (C) and two weeks later (D) showing the evolution of the ST/T-changes. There is progressive T-wave inversion in lead aVL with reciprocal T-wave changes in leads II, III and aVF. In leads V3–V4, there is gradual loss of R waves.

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palpitations, became diaphoretic and experienced a transient loss of consciousness. At this point, the patient was markedly hypotensive and vomiting with blood pressure of 67/52 mm Hg. She was given additional 0.1 mg adrenaline i.v. twice. Further medications included a fluid challenge with 1000 ml of Ringer's acetate, 125 mg methylprednisolone i.v. and several ipratropium bromide and fenoterol hydrobromide inhalations. The patient recovered slowly and was monitored overnight due to persistent mild hypotension and was discharged the next morning. The next evening she was admitted to our hospital for worsening dyspnea and chest discomfort at rest. Upon admission, blood pressure was 81/52 mm Hg and heart rate 80 bpm. She experienced dyspnea at slightest exertion. Clinical examination was unremarkable with no signs of pulmonary congestion. The electrocardiogram (ECG) (Fig. 1) showed sinus rhythm with prominent T-waves and <1 mm ST-depression in leads II, III, aVF and V4–V6. There was mild leukocytosis of 11,400/ μ l, raised sensitive troponin T of 233 ng/l (normal <15 ng/l) and hypoxemia with partial arterial oxygen pressure at 6.9 kPa. There was no lactatemia or acidosis. CT pulmonary angiography was negative for pulmonary embolism, but showed some interlobular septal thickening suggesting pulmonary congestion, supported by a mildly congestive chest X-ray. Transthoracic echocardiography showed severe hypokinesis of all the basal segments of the left ventricle with normal function in the mid and apical segments. The ejection fraction was reduced to 45% (Fig. 2). One day later the patient underwent a diagnostic coronary angiography with normal findings. Ventriculogram showed basal and mid left ventricular hypokinesis and apical hyperkinesis (Fig. 2). The patient was started on acetylsalicylic acid and an ACE-inhibitor, which was stopped by the patient due to symptomatic hypotension. At 1-week follow-up visit echocardiography was within normal limits, with no detectable wall motion abnormalities (Fig). Acetylsalicylic acid and ACE-inhibitor were discontinued, while previous medications for asthma and allergy were continued.

The cardiovascular symptoms associated with anaphylaxis, including hypotension, cardiac arrhythmia and chest pain are mediated

by catecholamines released by histamine and by the activation of the renin–aldosterone–angiotensin system. Besides the anaphylactic reaction itself [5], the exogenous catecholamines, administered as an emergency treatment for a severe reaction, can unexpectedly cause acute myocardial stunning. There are several reports on the iatrogenic apical form of TTC following exogenous catecholamine administration, but very few reports on the inverted type [6,7]. Our patient was treated for suspected anaphylaxis and the administration of i.v. adrenaline bolus caused a hemodynamic collapse. The hemodynamic status was unresponsive to i.v. fluid challenge and corticosteroids, suggesting that the hemodynamic disturbance was most probably due to myocardial stunning leading to low cardiac output. As far as we know, gradual ventricular recovery can occur within days, and thus it is possible that at the beginning of the episode the systolic dysfunction was more severe than at the time of the first echocardiography. Tachyarrhythmia inducing hemodynamic collapse seems improbable, as there was myocardial stunning lasting for days.

Post-menopausal women are at higher risk for developing the TTC. It has been hypothesized that estrogen deficiency or endothelial dysfunction might have a role [1]. Based on previous case reports [7,8] and the present case, the patients prone to develop TTC after adrenaline injection for anaphylaxis seem to be younger and the inverted type may be more common among them. The reason why some patients develop a reverse pattern of wall motion disturbance with basal akinesis is not known. The ventricular apex is thought to be more sensitive to catecholamines, perhaps due to the distribution of beta-adrenergic receptors in the myocardium. However, variable forms of left ventricular dysfunction during the clinical course of a single patient have been reported, indicating similar pathophysiologic mechanisms for both the apical and the inverted TTC [9]. Variation in the distribution or function of beta-adrenergic receptors between individuals could explain variation in phenotypes; this remains to be addressed in future studies.

The ECG changes described in previous case reports of the inverted TTC showed no uniform pattern [10]. The subtle ECG

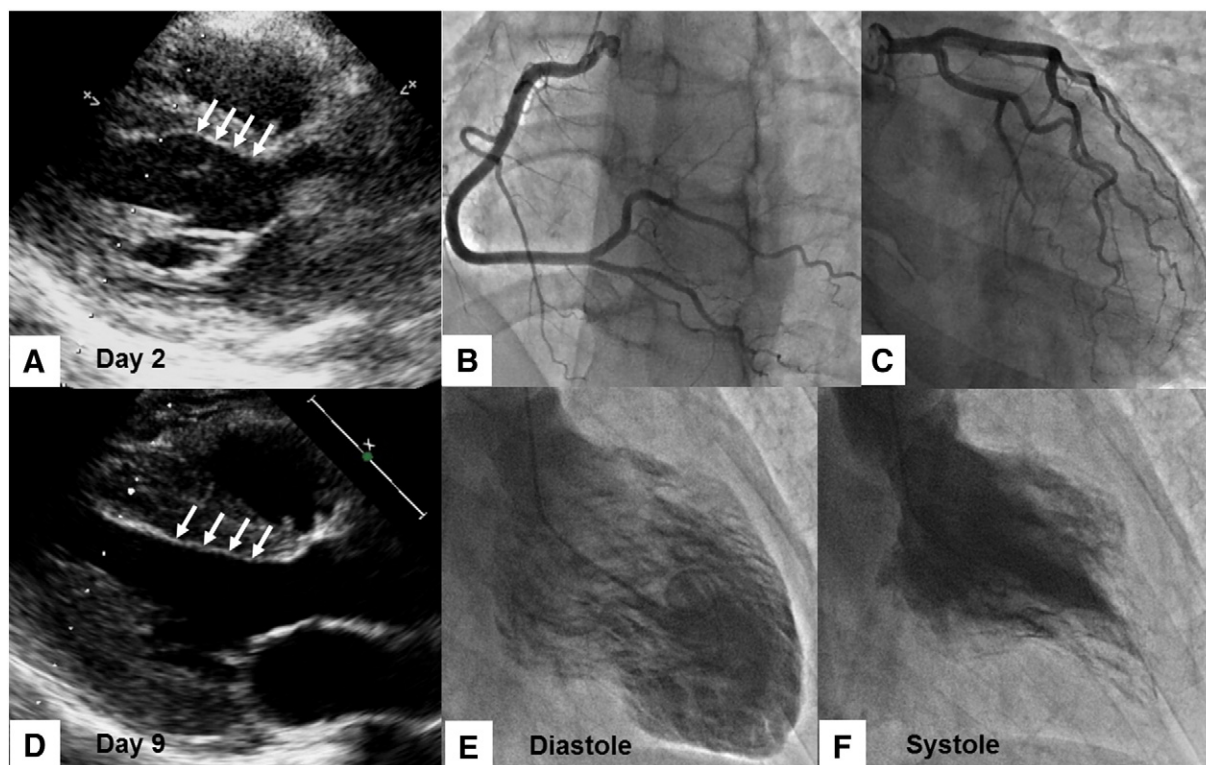


Fig. 2. Two-dimensional echocardiogram, parasternal long-axis view at baseline (A) and one week later (D), showing the recovery from basal hypokinesis (arrows marking the basal interventricular septum). Coronary angiogram, showing normal coronary arteries (B,C). Left ventricular cine-angiogram at baseline (E,F), showing basal- and mid-ventricular akinesis and apical hyperkinesis.

changes of the present case were in discrepancy to the severe, hypotensive presentation in the emergency department. Gradual development of T-wave inversion in lead aVL and loss of R waves in V3–V4 indicate myocardial damage to the basal and mid part of the left ventricle. Lead aVL reflects the basal anterolateral wall and leads V3–V4 the anterior wall. We cannot exclude a brief episode of ST elevation in these leads in our case, as no ECG was recorded during the first hours.

To conclude, our patient received aggressive treatment for incipient anaphylactic reaction. It is highly likely that the intravenous adrenaline injections induced myocardial stunning of the reverse TTC type. Fortunately, recovery was fast and without complications. Considering the serious cardiac side effects, in cases of mild anaphylaxis, intramuscular administration of adrenaline should be preferred. Intravenous adrenaline should be reserved for those not responding to intramuscular administration or to be used during resuscitation. TTC should be kept in mind in patients with long-lasting hemodynamic compromise after catecholamine administration for anaphylaxis.

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