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Case Report

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Takotsubo-like left ventricular dysfuction following intravenous epinephrine administration

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ABSTRACT

A 50-year old woman presented at her general practitioner following facial swelling due to an insect bite. She was treated with 100 mg Solucortef and 1 mg epinephrine of a 1: 10 000 solution intravenously. Minutes later she developed chest pain with concomitant non-specific changes in the electrocardiogram (ECG), and later significant Troponin I concentrations were demonstrated. She was treated with anticoagulants, and later a bedside echocardiography revealed reduced left ventricular ejection fraction and apical ballooning pattern as seen in Takotsubo Cardiomyopathy. During hospitalization the patient had an episode of Torsade's de pointes ventricular tachycardia and several unexplained cerebral absences. Coronary angiography revealed normal coronary arteries, and the patient exhibited normal ejection fraction one month after hospital discharge. Physicians should avoid giving high doses of epinephrine by the intravenous route and only in cases of severe anaphylaxis

INTRODUCTION

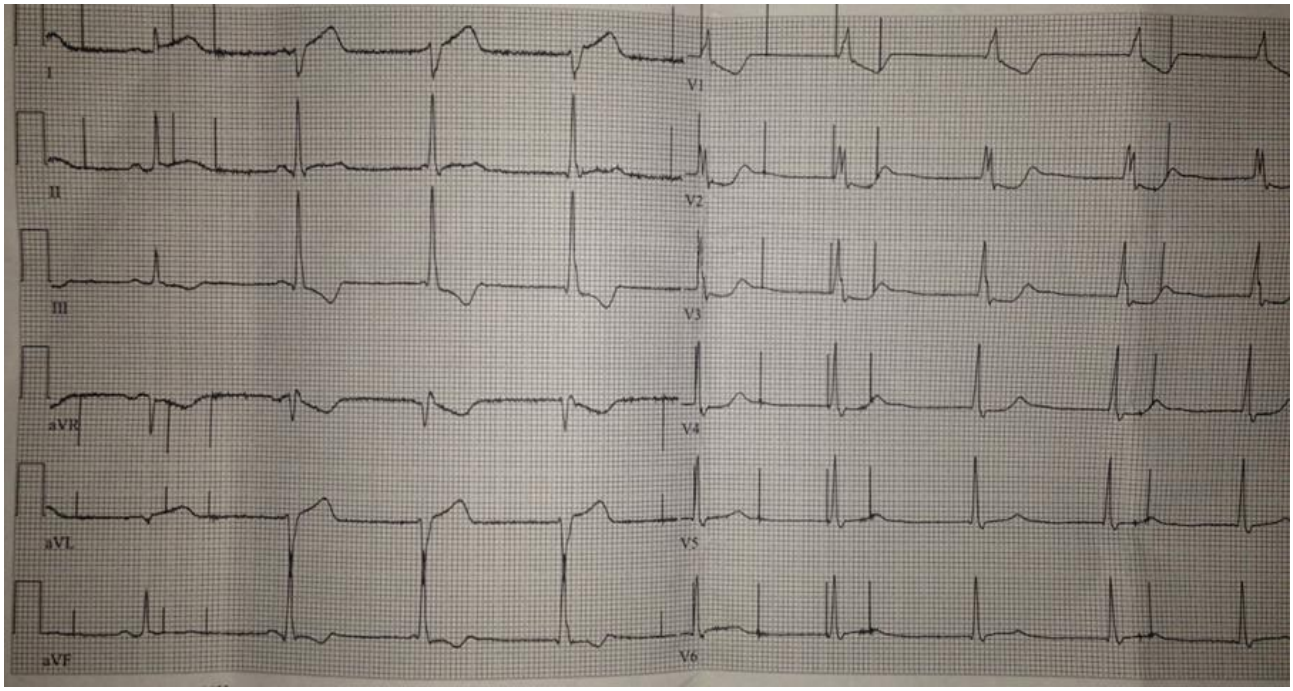
Epinephrine is considered the standard treatment in patients with severe anaphylactic reactions. The usual route for epinephrine administration in anaphylaxis is subcutaneous (S.C.), which has been considered safer than the intravenous (I.V.) route. The dosage of epinephrine is route dependent and also depends on the severity of the patient's condition-but generally 0. 1 mg I.V. or 0. 5 mg S.C. of a 1:10 000 solution is recommended [1].

CASE PRESENTATION

A 50-year old healthy, non-smoking woman not predisposed to ischemic heart disease presented at her general practitioner (GP) with facial edema involving mainly the left side of her face due to an insect bite the day before. The patient had already taken antihistamine pills at home with no beneficial effect, and her edema had accentuated over the night. The woman felt unpleasant, but was clinical stable and did not have respiratory symptoms.

The GP of the woman treated her with 100 mg Solucortef I.V. and 1 mg epinephrine of a 1:10 000 solution I.V. The woman was asked to stay in the waiting room for observation and while doing so she developed severe crushing chest paint with radiation to her left arm. She did not have shortness of breath and did not feel any arrhythmias. An ECG showed sinus-rhythm followed by junctional-rhythm with a heart rate 55 beats/min, bifascicular block (right bundle branch block (RBBB) and left posterior fascicular block(LPFB)), ST-depression in lead V1 – V3(as is normally seen in RBBB), negative T-waves in lead III and aVF, and the QT-interval was not prolonged (Figure 1). Her blood pressure dropped to 88/49 mmHg from initially 140/80 mmHg and heart rate was between 55 - 70 beats/min.

Figure 1. ECG taken several minutes after epinephrine administration when the patient arrives at the hospital at 10 am



Immediately thereafter an ambulance with a physician transferred the patient to the department of cardiology at the local hospital at 10 am. The woman was treated with I.V. morphine and her blood pressure increased following infusion of I.V. saline.

The ECG changes persisted but the chest pain was relieved following subsequent combined treated with I.V. morphine and sublingual nitroglycerine spray 0, 4 mg/dose.

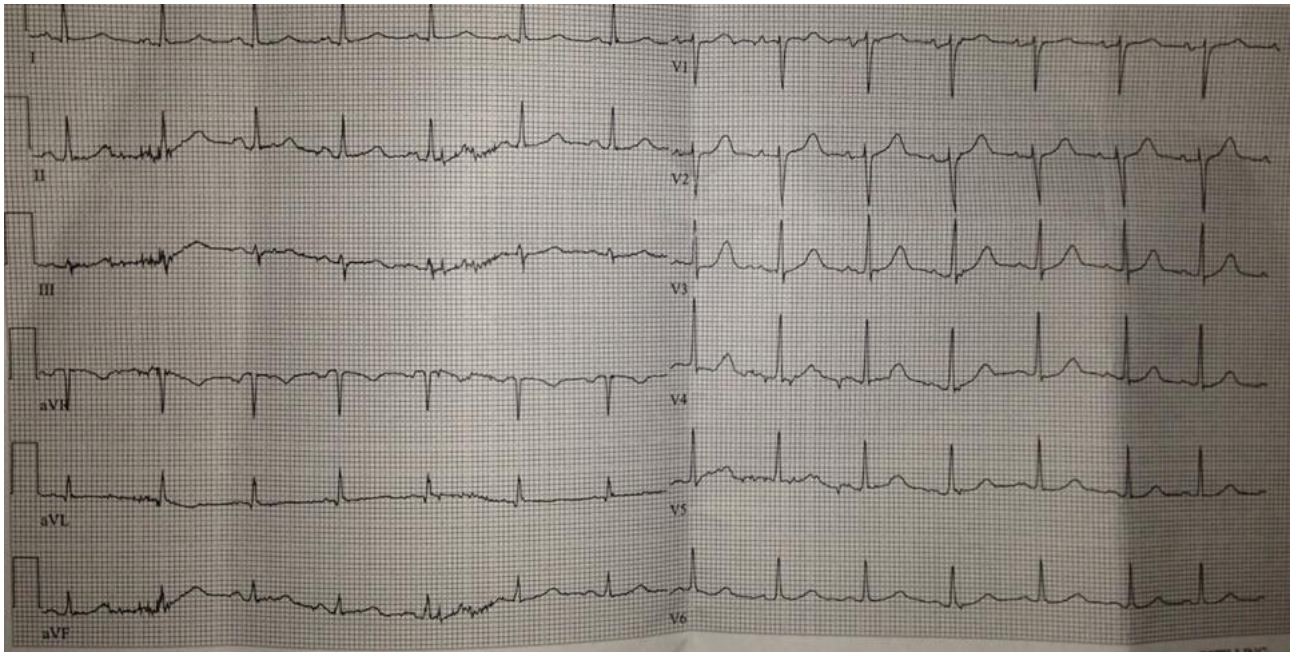
An acute bedside echocardiography showed normal ejection fraction and no valvular abnormities. A chest radiograph revealed little interstitial edema at both lung bases.

The first troponin I measurements taken at 12:20 pm was elevated 468 ng/l (reference interval < 25 ng/l), and the second troponin I values taken at 19:05 pm was 490 ng/l. The blood tests revealed normal electrolytes (sodium, potassium and calcium) and normal hemoglobin.

At this stage the woman was considered having a non-ST-segment elevation myocardial infarction and was treated with Brillique (ticagrelor), Aspirin (acetylsalicylic acid) and Arixtra (fondaparinux) according to the national guidelines [2].

Later the same day at 19:00 pm the initial ECG changes had disappeared (Figure 2).

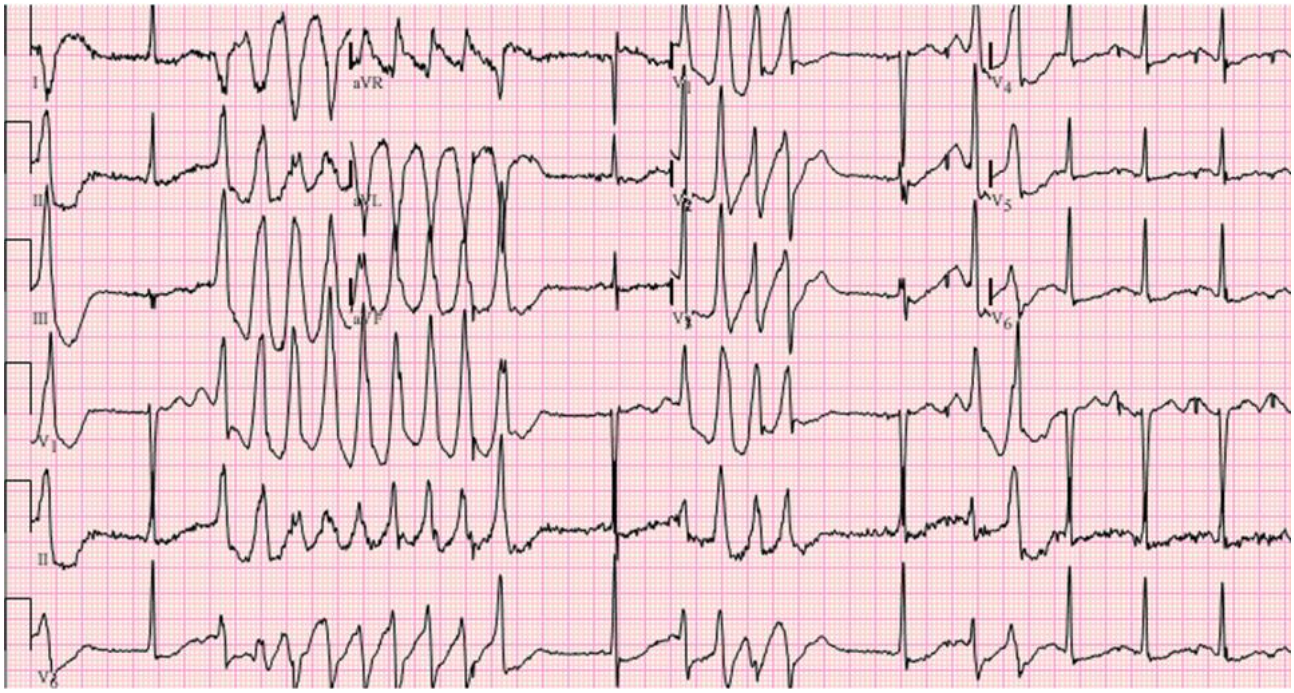
Figure 2. ECG several hours later after hospitalization at 20 pm



Over the night the woman had intermittent chest pain which was relieved by sublingual nitroglycerin together with I.V. morphine.

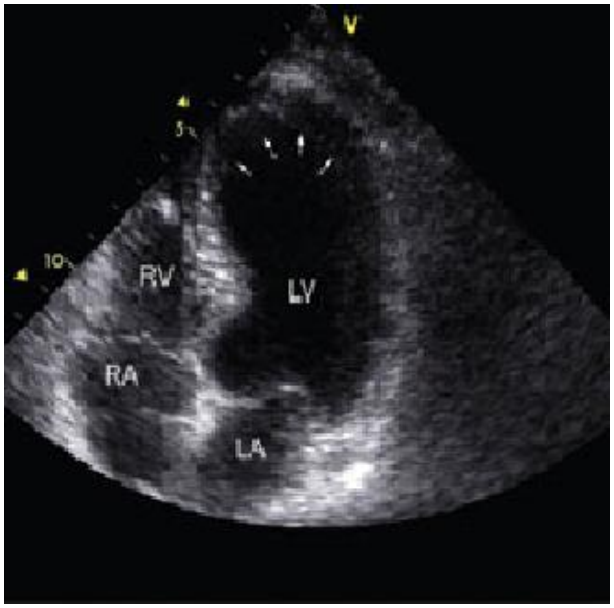
The next morning at 8 am the patient collapsed during a walk in the department but spontaneously gained conscious after less than 10 seconds. Continues heart rate monitoring, revealed Torsade's de pointes ventricular tachycardia at the time of the black-out episode (Figure 3).

Figure 3. Illustration of torsade's de pointes on ECG records



A new bedside echocardiography, this time performed by a cardiology consultant, revealed depressed contractile function of the mid and apical segments of the left ventricle together with hyperkinesis of the basal walls, producing a pattern of apical ballooning. The ejection fraction was estimated to be 35 - 40 % (Figure 4).

Figure 4. Apical four-chamber view during transthoracic echocardiography performed the second day of hospitalization, revealing apical ballooning (arrows)



The woman subsequently had several unexplained cerebral absences during the next 12 hours, but no concomitant arrhythmias were observed on continues heart rate monitoring. During the cerebral episodes the patient's consciousness was impaired, and the patient was starring on the room wall and could not be brought to reaction by talking to or physical stimulation. Each of the cerebral absences lasted from seconds up to 1-2 minutes, and thereafter the patient regained full consciousness but had amnesia for the episodes. No pareses or muscle spasms were observed. The patient's blood pressure was normal during the cerebral episodes.

Subsequently the patient was acutely transferred to the Regional University Hospital and underwent coronary angiography, which revealed normal coronary arteries and the treatment with anticoagulants was stopped. However, apical ballooning pattern was observed during the coronary angiography procedure.

The patient had a brain computer tomography performed, which excluded stroke or other cerebral abnormities including bleeding. These cerebral symptoms disappeared later the same day.

After two more days of observation the ECG was still normal and the woman did not develop new episodes of chest pain, cerebral absences, seizures or arrhythmias and was discharged with tablet metoprolol 50 mg daily as the only treatment.

One month and three months later echocardiographic examinations revealed normal left ventricular function and no wall motion abnormalities. The patient had not experienced any cardiac nor neurological symptoms during the follow up period.

DISCUSSION

In the present case I.V. administration of epinephrine resulted in a clinical picture of Takotsubo Cardiomyopathy. This was supported by the echocardiographic and coronary angiographic findings together with the reversible left ventricular dysfunction observed in our patient.

Our patient had non-specific ECG changes on admission to the hospital, however patients with Takotsubo Cardiomyopathy do not necessarily present with the typical ST-segment elevation in the anterior leads on the ECG, as is frequently associated with this condition. These patients may present with different and non-specific ECG changes, and sometimes even with a normal ECG [3, 4, 5]. Therefore ECG changes alone cannot be used to either confirm or dismiss the diagnosis of Takotsubo Cardiomyopathy.

Within the following 24 hours the condition was complicated by Torsade's de pointes ventricular tachycardia and intermittent cerebral absences not associated with arrhythmias.

Previously, a few reports have suggested an association between epinephrine administration and the development of Takotsubo Cardiomyopathy [6, 7, 8]. In these earlier case reports, however, the patients did not exhibit potential lethal ventricular arrhythmias or neurological symptoms as in our case.

Khoueiry et a.l [6] recently reported a 44-year old woman with known hypertension, who developed reverse Takotsubo Cardiomyopathy

following intravenous administration of 1 mg epinephrine during anaphylaxis. The diagnosis was confirmed by echocardiographic findings, the presence of unspecific ECG changes and significantly increased troponin I values. Echocardiography showed an ejection fraction around 35 %. Three weeks later a control echocardiographic examination revealed normal left ventricular function and an elective coronary angiography demonstrated normal coronary arteries.

Härle et al. [7] published a case of a 39-year old woman who developed Takotsubo Cardiomyopathy following accidental administration of 1 mg epinephrine intravenously. Again the patient had reduced ejection fraction which was reversible. Cardiac magnetic resonance-scan revealed midventricular ballooning and apical hypercontractility. The patient was known with Crohn's disease and in treatment with immunosuppressive medicine including corticosteroids.

Volz et al. [8] reported a case of a young drug abusive man, not predisposed to ischemic heart disease, who developed a reverse Takotsubo Cardiomyopathy following self-injection of 2 mg epinephrine intravenously. However, in none of these prior case reports no association between Takotsubo Cardiomyopathy and subsequent severe ventricular arrhythmias or cerebral symptoms have been described.

Indeed these findings suggest that I.V. administration of epinephrine may cause different complications in different patients.

Previously, there have also been some reports addressing I.V. and S.C. administration of epinephrine resulting in an acute myocardial infarction [9, 10]. As an example Shaver et al. [9] reported on a 29-year old woman, smoker and positive family history of premature coronary artery disease with anaphylaxis. The woman was treated with administration of 0,1 mg of a 1:10 000 solution of epinephrine I.V. and developed chest pain with anterior ST-segment elevation on the ECG and a significant elevation of troponin concentrations. Both echocardiography and CT-coronary angiography were normal.

According to the authors the mechanism leading to the myocardial infarction most likely was coronary vasospasm following epinephrine administration.

Saff et al. [10] published data on a 30 year old man heavily predisposed to ischemic heart disease, and who used an epinephrine auto injector containing 0.3 mg epinephrine S.C., which resulted in myocardial infarction. In this case the man's ECG revealed ST-segment deviations and his concentrations of troponin I were significantly elevated. Thus, in both reports linking epinephrine administration to a subsequent myocardial infarction lower dosages of epinephrine have been used [9, 10] compared with the dosages used in the Takotsubo Cardiomyopatihy cases [6, 7, 8].

Actually Sampson et al. [11] previously have suggested that I.V. epinephrine administration should only be used in severe anaphylaxis, because of potential severe complications including cardiac arrhythmias. Indeed, Richardson et al. [12] reported a case of epinephrine induced Torsade's de pointes ventricular tachycardia in a child with long QT syndrome. Also, Lee et al. [13] have published a case in which a 35 year old male developed ventricular tachycardia and cardiac arrest following a submucosal injection of a 1:100.000 solution of epinephrine during nasal septoplasty operation.

Our case differs from these earlier publications in more aspects. First, our patient was not known with long QT-syndrome prior to the acute event. Second, the ventricular tachycardia in our patient occurred late - almost 24 hours after epinephrine administration. Epinephrine is rapid in onset and of short duration with a half-life of approximately 5-10 minutes after I.V. administration [14].

We believe that the Torsade's de pointes ventricular tachycardia observed in our case is a result of the temporary myocardial dysfunction inherent in the epinephrine induced Takotsubo Cardiomyopathy.

Apical ballooning and regional wall motion abnormalities that extend beyond a single epicardial vascular distribution is described in patients suffering Takotsubo Cardiomyopathy; a condition believed to be triggered by stress and increased levels of biological catecholamines in the body. In this condition the reduced ejection fraction is reversible [15]. Thus, from a theoretical

point of view, the I.V. administration of a high dosage of epinephrine in our patient may have simulated the increased levels of catecholamines associated with the endogenous stress induced production supposed to take place in patients Takotsubo Cardiomyopathy. Our patient developed a reversible reduction in ejection fraction and signs of apical ballooning on echocardiography. This supports the theory that increased stress and increased endogenous levels of catecholamines in otherwise healthy people without earlier cardiovascular disease can lead to development of Takotsubo Cardiomyopathy.

Wittstein et al. [4] have proposed that serum catecholamine levels in Takotsubo patients 1 – 2 days after symptom debut are higher than those in patients, who suffer myocardial infarction with pulmonary oedema. Epinephrine levels returns to myocardial infarction levels 7 – 9 days later.

It has also been proposed that catecholamine storms in patients with pheochromocytomas can precipitate Takotsubo Cardiomyopathy [16]. Recently, Paur et al. [17] suggested that the mechanism underlying epinephrine induced Takotsubo Cardiomyopathy is the direct effect of epinephrine on the B2 receptors in the hearts apical region, while myocardial infarctions following epinephrine administration is in many cases believed to be a result of coronary vasospasm [9, 10].

Our patient, in addition to Takotsubo Cardiomyopathy and self-limiting Torsade's de pointes ventricular tachycardia, had several unexplained episodes of cerebral absences in the 12 hours following the ventricular tachycardia episode. The patient had never before experienced similar symptoms, and she had no history of epileptic attacks of any kind. A potential explanation for these episodes could be that the patient had developed a transitoric cerebral attack following the Torsade's de pointes ventricular tachycardia. The reduced myocardial contractility potentially could have resulted in mural thrombi, which might have embolized to the patient's cerebral arteries following the spontaneous conversion to sinus rhythm from ventricular tachycardia. The presence of mural thrombus is a well-known complication following acute myocardial infarction. Small brain embolisms or early cerebral infarction may be undetectable on an acute brain computer tomography scan [18]. As the cerebral symptoms disappeared within 12 hours of onset, no other radiology imagining tests of the patient's brain or heart where performed. For the same reason anticoagulation was not considered.

CONCLUSION

In the present case of a healthy 50-year old woman not predisposed to ischemic heart disease I.V. administration of epinephrine resulted in a clinical picture of Takotsubo Cardiomyopathy. Within the following 24 hours the condition was complicated by Torsade's de pointes ventricular tachycardia and intermittent cerebral absences not associated with arrhythmias. One month later left ventricular function had normalized. Physicians should avoid giving high doses of epinephrine by the intravenous route and only in cases of severe anaphylaxis.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this article.

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