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Letter to the Editor

Transient left ventricular dysfunction syndrome during anaphylactic shock Vasospasm, Kounis syndrome or epinephrine-induced stunned myocardium?

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ABSTRACT

Transient left ventricular dysfunction syndrome (TVLDS) has been rarely observed during anaphylactic shock and its pathophysiology remains still enigmatic. Multivessel epicardial coronary spasm or coronary microvascular impairment were suggested as primary causative mechanism. Alternatively, the release of various inflammatory mediators including histamine could induce a coronary artery spasm or erosion/rupture of an atheromatous plaque contributing to TVLDS. Challenging this paradigm, a direct catecholamine acute toxicity was recently proposed as a causative mechanism of the stunned myocardium observed in TVLDS. We report a patient with severe TVLDS during anaphylactic shock. Whilst ECG depicted a drastic ST segment elevation in the anterior leads, cardiac catheterism confirms the co-existence of severe reduction of systemic vascular resistance and normal coronary angiogram. In the absence of any documented spasm or perfusion abnormalities, the defective uptake of ¹²³I-metaiodobenzyl-guanidine (¹²³I-mIBG) in the hypocontractile LV segments suggests that epinephrine-induced stunned myocardium is the main mechanism of LV systolic dysfunction. This report highlights that excess doses of epinephrine might contribute to TVLDS through direct myocardial stunning. The possible noxious contribution of other mediators such as histamine or cytokines released in the Kounis syndrome remains to be established.

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1. Introduction

Transient left ventricular dysfunction syndrome (TVLDS) has been rarely observed during anaphylactic shock and its pathophysiology remains still enigmatic [1,2]. Multivessel epicardial coronary spasm or coronary microvascular impairment was suggested as primary causative mechanism. Alternatively, impaired coronary blood flow caused by vulnerable plaque rupture has been proposed as a direct cause of Takotsubo cardiomyopathy (TTC). The Kounis syndrome is a combination of acute coronary syndrome and anaphylactic reaction [3]. In this situation, the release of various inflammatory mediators including histamine could induce a coronary artery spasm or erosion/rupture of an atheromatous plaque contributing to TVLDS [4]. Challenging this paradigm, a direct catecholamine acute toxicity was recently proposed as a causative mechanism of the stunned myocardium observed in TVLDS [5].

We report a patient with severe left ventricular systolic dysfunction during anaphylactic shock. Whilst ECG depicted a drastic ST

segment elevation in the anterior leads, cardiac catheterism confirms the co-existence of severe decrease of systemic vascular resistance and normal coronary angiogram.

2. Case presentation

A 16-year old child (height: 172 cm, weight: 60 kg) with history of penicillin allergy was referred to our Intensive Pediatric Care Unit for anaphylactic shock and severe angio-oedema following a hymenopter bite. Sub-cutaneous epinephrine (1 mg) was initially administered before the patient's arrival to the hospital. Given the persistence of hemodynamic instability, a treatment by intravenous epinephrine (0.2 mg), methylprednisolone (120 mg) and dexchlorpheniramine (5 mg) was initiated by the Medical Mobile Intensive Care Unit. On admission, Glasgow scale score was 10, hemodynamic remains unstable with a blood pressure of 105/50 mmHg and heart rate of 100 beats per minute. First ECG showed sinus tachycardia without significant ST segment elevation, hence a treatment by epinephrine 0.05 µg/kg/min and fluid therapy (crystalloid 1500 cc) was started. Accidentally, a bolus of epinephrine was administered, producing a rapid degradation of hemodynamic with a blood pressure of 85/46 mmHg, tachycardia and alteration of consciousness. ECG documented a drastic ST elevation in the anterior leads and mirrors signs in

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the inferior leads (Fig. 1A and B). The patient underwent urgent coronarography, which showed normal vessels and no evidence of vasospasm (Fig. 1C and D). Left ventriculography revealed basal hypokinesia with left ventricular ejection fraction (LVEF) of about 35%. There was no intra ventricular gradient. At the same time, a right heart catheterism was realized using a Swan Ganz catheter. Cardiac output determined by thermodilution was slightly elevated ($7.7 \text{ L}\cdot\text{min}^{-1}$), and systemic vascular resistance were diminished at 6.9 UI Wood ($552 \text{ dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$). Treatment by epinephrine was stopped and replaced by norepinephrine enabling swift hemodynamic stabilization. On admission, laboratory tests showed a moderate elevation of serum troponin ($0.25 \mu\text{g/L}$, peak at $7.06 \mu\text{g/L}$ 18 h later), whereas CK remains on the normal range. Complete blood count revealed a white blood count cell of $17,800/\text{mm}^3$. The haemostasis and fibrinolysis parameters were also altered (INR at 59%, FV diminished at 59%, elevation of D-dimers at $2490 \mu\text{g/L}$).

In order to assess both left ventricular (LV) perfusion and myocardial sympathetic activity, the patient underwent myocardial ^{201}Tl (^{201}Tl) Gated Single Photon Emission Computed Tomography (G-SPECT) and ^{123}I -mIBG SPECT, 8 and 10 days after anaphylactic shock, respectively (Fig. 2A and B). Hypocontractile anterior mid and basal LV segments were characterized by normal perfusion but reduced uptake of ^{123}I -mIBG. Follow-up ^{123}I -mIBG SPECT was performed 3 and 7 months after the first investigation showing progressive improvement until normalization of LV sympathetic innervation (Fig. 2C). At one month follow-up, total recovery of LVEF was documented by TTE.

3. Discussion

In the present report, three main hypotheses were raised to explain the pathophysiology of the occurred transient left ventricular dysfunction syndrome: (i) epinephrine-induced vasospasm, (ii) Kounis syndrome and (iii) epinephrine-induced stunned myocardium.

- (i) Myocardial ischemia-reperfusion due to epicardial, microvascular spasm or aborted myocardial infarction and related no-reflow phenomenon, was first proposed to be a potent inducer of TLVDS [1]. In the present report, whilst ECG depicts a dramatic ST segment elevation following accidental epinephrine bolus, coronary angiography was normal and systemic vascular resistances were diminished. The possibility of a severe transient epicardial vasospasm induced by epinephrine toxicity cannot be ruled out categorically, because intravenous epinephrine has a very short half life and could have caused it before the coronary angiogram was performed. However, ST elevation was still evidenced when the angiography was performed. Although we did not evaluate coronary resistance or myocardial perfusion after physical or pharmacological stress, the rest perfusion that was assessed at the sub-acute phase by myocardial ^{201}Tl G-SPECT was normal. In the past, several authors had reported a diminished coronary flow reserve or reduced coronary flow velocity at the onset of TTC. These findings were first challenged by Abe et al. showing almost normal coronary flow reserve in TTC [6]. Other authors

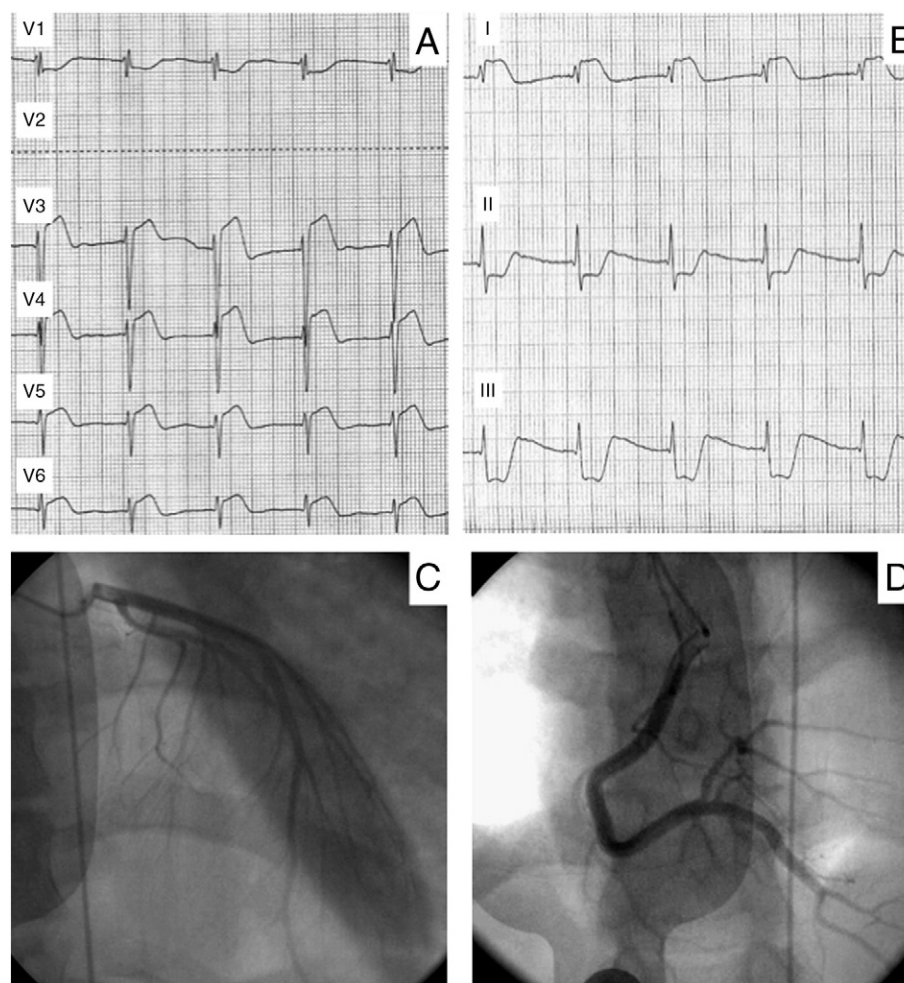


Fig. 1. Drastic ST elevation in the anterior leads (A) and mirrors signs in the inferior leads (B) following epinephrine administration. Urgent angiography showed normal coronary vessels and no evidence of vasospasm (C, D).

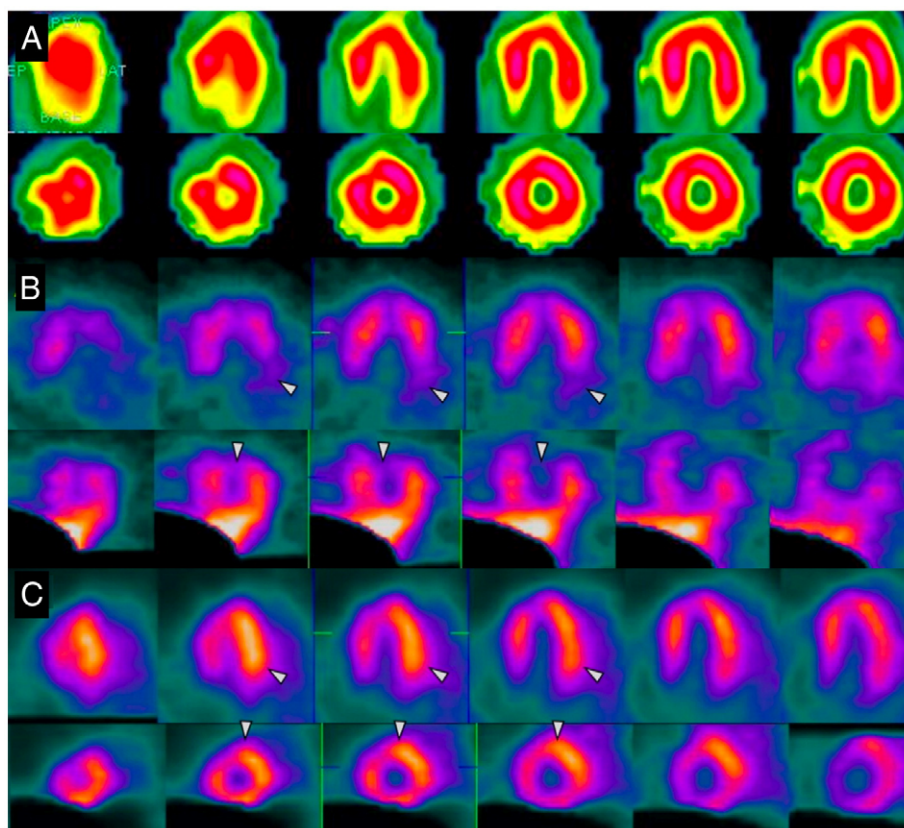


Fig. 2. Results of ^{201}Tl and ^{123}I -mIBG SPECT performed in a 16-year old patient with iatrogenic epinephrine-induced TLVDS during anaphylactic shock. In the sub-acute phase (8–10 days after shock), the hypocontractile anterior mid and basal LV segments were characterized by normal perfusion (A) but reduced uptake of ^{123}I -mIBG (B). Follow-up ^{123}I -mIBG SPECT, which was performed 3 and 7 months after the first investigation, showed progressive improvement until normalization of LV sympathetic innervation (C).

have also reported severe reduction of myocardial fatty acid or glucose metabolism coexisting with normal or minimally reduced perfusion in the apex or mid-ventricle region [7]. Overall, it is unlikely that a limited alteration of myocardial perfusion observed in the TTC could provide a unifying mechanism explaining the very large extent of myocardial transient dysfunction.

- (ii) Described in 1991 as the syndrome of allergic angina, the “Kounis syndrome” is defined as the concomitant occurrence of chest pain and allergic reactions associated with clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during anaphylactic degranulation [3]. This so-called “allergic angina” can ultimately lead to acute myocardial infarction. During anaphylaxis, several inflammatory and vasoconstricting mediators are released locally or in the peripheral circulation. For instance, cardiac mast cell-derived histamine can produce a constriction of atherosclerotic coronary artery and activation of sensitive nerve endings. Alternatively, the profound depression of cardiac systolic function observed during anaphylaxis could result in a direct inotropic negative effect of $\text{TNF-}\alpha$ or $\text{IL-1}\beta$, which are released by activated mast cells [2]. In the past, experimental data have demonstrated that cardiac damage is a primary event during anaphylaxis. Indeed, in isolated perfused heart, impairment of contractility, increased of end-diastolic left ventricular pressure and ECG signs of myocardial ischemia were triggered by anaphylactic reaction [8]. Other authors have suggested that histamine H_3 activation contribute to cardiovascular collapse by inhibiting adrenergic neural norepinephrine release during anaphylactic shock [2,3].
- (iii) In our patient, the collapse was immediately preceded by an accidental bolus infusion of excess doses of epinephrine. This

observation is in line with a recent description of a prolonged cardiogenic shock caused by intravenous high dose dopamine administration in a patient with TTC [9]. In the absence of any documented spasm or perfusion abnormalities, the defective uptake of ^{123}I -metalodoBenzyl-Guanidine (^{123}I -mIBG) in the hypocontractile LV segments suggests that epinephrine-induced stunned myocardium is the main mechanism of LV systolic dysfunction. The reduced ^{123}I -mIBG myocardial uptake could be the result of an enhanced sympathomimetic activity, associated to an increased norepinephrine release and competitive inhibition of ^{123}I -mIBG reuptake. Alternatively, the ^{123}I -mIBG uptake defect could be explained by the impairment of uptake-1 function at nerve endings, an adenosine triphosphate-required system that is altered in the failing heart. We have recently shown the close relationship between ^{123}I -mIBG and ^{18}F -FDG (as a marker of glucose metabolism) uptake abnormalities as well as their common temporal evolution during TLVDS [7]. According to Lyon et al., high levels of epinephrine of endogenous or exogenous origins could trigger a switch in intracellular trafficking in cardiomyocytes from G_s protein to G_i protein signalling via the β_2 receptor, which is negatively inotropic. On a finalistic point of view, this switch to β_2 receptors- G_i protein could be viewed as beneficial by protecting against the proapoptotic effects of intense activation of β_1 -adrenoreceptors whereas β_2 mediated G_i signalling induces the activation of Akt pathway, which has an anti-apoptotic effect [5]. Our observation is also in line with experimental data. In dogs, if it is administered immediately after anaphylactic shock, the bolus-epinephrine does not accelerate recovery but it is responsible for LV function impairment [10]. Moreover, during anaphylaxis, coronary vasodilation rather than coronary vasoconstriction was

observed, and evidence of myocardial ischemia as assessed by altered myocardial lactate metabolism was not found [11]. Apart from the iatrogenic administration of excess doses of epinephrine, other mechanisms could contribute to the endogenous release of catecholamines during anaphylaxis. Indeed, anaphylaxis is also characterized by a rapid movement of intravascular fluid into the extravascular space which can trigger the stimulation of the rennin–angiotensin–aldosterone system and contribute to acute catecholamine release [2]. In addition, histamine, could stimulate the release of catecholamines by a direct action on adrenal medulla [2,3]. Altogether, we could not rule out the possible contribution of the Kounis syndrome. In this particular case, histamine and other systematically released cytokines related to mast cell degranulation might act as direct or indirect cofactors of epinephrine toxicity.

4. Conclusion

Although epinephrine is considered to be the drug of choice for anaphylactic shock, excess doses might contribute to transient left ventricular dysfunction syndrome through direct myocardial stunning. The possible noxious contribution of other mediators such as histamine or cytokines released in the Kounis syndrome remains to be established.

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The authors certify that they comply with the principles of ethical publishing in the International Journal of Cardiology [12].

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