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CLINICAL REPORT

Apical ballooning syndrome following perioperative anaphylaxis is likely related to high doses of epinephrine

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Abstract Apical ballooning syndrome, a reversible left ventricle dysfunction, has been reported following anaphylaxis and, during this clinical circumstance, is seemingly linked to the use of either low or high doses of epinephrine. We report a severe succinylcholine-induced IgE-mediated anaphylaxis in a 65-year-old woman, in whom the diagnosis of apical ballooning syndrome following anaphylaxis was established. As a thorough description of the clinical features and resuscitative measures could be obtained, we discuss the reasons for apical ballooning syndrome occurrence and highlight the fact that optimal care management of anaphylaxis should include a progressive titration of epinephrine.

Keywords Anaphylaxis · Anesthesia · Epinephrine · Tako-Tsubo cardiomyopathy

Introduction

Apical ballooning syndrome (ABS) or Tako-Tsubo cardiomyopathy, a reversible left ventricle dysfunction, has been reported following anaphylaxis [1–6]. Although its pathophysiology following anaphylaxis remains unclear, it may be linked to inappropriate use [7] of epinephrine as well as either low or high doses of epinephrine [1–6], a drug currently recommended by clinical guidelines as first-line therapy [8–10]. We took advantage of a documented case of ABS following succinylcholine-induced IgE-mediated anaphylaxis for which a thorough description of the clinical features and resuscitative measures, including the use of high doses of epinephrine, could be obtained to discuss the reasons for the ABS occurrence.

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Case report

A 65-year-old woman (160 cm, 57 kg) was scheduled for a surgical resection of liver metastases from colorectal cancer. She was premedicated with hydroxyzine (100 mg p.o.) the day before and 1 h before anesthesia, which was induced with sufentanil (10 μg i.v.) and propofol (130 mg i.v.). Tracheal intubation was facilitated with succinylcholine (60 mg i.v.) and mechanical ventilation initiated. Within 2–3 min following the induction, arterial hypotension (from 120/80 to 60/40 mmHg) associated with tachycardia (from 70 to 130 bpm) occurred followed by a decrease in end-tidal CO_2 concentration. No bronchospasm was observed. Cumulative doses of intravenous ephedrine up to 30 mg did not relieve the cardiovascular disturbances. Arterial pressure became non-measurable and was associated with bradycardia (40 bpm) rapidly followed by ventricular extrasystole. This prompted administration of intravenous titrated epinephrine boluses (0.02 mg + 0.01 mg + 0.01 mg + 0.01 mg followed by 0.2 mg) along with 500 ml intravascular volume expansion with hydroxyethylstarch (Voluven®, Fresenius-Kabi, Sèvres, France). Blood pressure could be restored with an additional cumulative dose of intravenous epinephrine (2 mg) along with the appearance of generalized erythema. However, two episodes of arterial hypotension associated with bradycardia subsequently occurred. Four additional doses of 1 mg intravenous epinephrine along with fluid therapy (crystalloids 500 ml, HES 2000 ml) were concomitantly administered. A continuous infusion of epinephrine (up to 0.6 μg/kg/min) was initiated because of the persistence of a vasoplegic state.

Surgery was postponed and the patient transferred to the intensive care unit where a 12-lead ECG demonstrated pathological Q waves in leads V_1–V_2. Acute pulmonary edema occurred. A transthoracic echocardiogram showed a left ventricle ejection fraction (LVEF) of 30% with significant septo-apical hypokinesis. Follow-up echocardiogram 24 h later showed a LVEF of 20% with antero-septo-apical akinesis and typical apical ballooning syndrome, whereas significant improvement was observed 48 h later (LVEF: 40%). Cardiac enzymes were increased: the initial troponin T level was 1.65 ng/ml (normal < 0.1) with a peak up to 6.18 ng/ml within 36 h. Given these persistent ECG changes, echocardiographic findings and elevated troponin levels, a cardiac catheterization was performed and showed normal coronary anatomy. Supportive treatment was continued. Epinephrine infusion was maintained for 48 h, and the patient was extubated on the same day. Further clinical outcome was uneventful with rapid improvement in LV systolic function (LVEF > 50%). The patient was discharged home 10 days after.

Serum tryptase concentration measured 2 h after the clinical reaction showed a dramatic increase (142 μg/l; normal < 13.5) followed by a further decrease over time at 10 μg/l, 24 h after the clinical reaction. The level of specific IgEs against succinylcholine (ImmunoCAP, Phadia SAS, Uppsala, Sweden) was increased (5.66 kU/l, normal < 0.1). Specific serum IgEs against latex remained undetectable.

With the patient's consent, skin tests were performed 3 weeks later. Prick-test with succinylcholine was positive. No cross-reactivity was found with the other neuromuscular blocking agents (NMBAs). Skin tests remained negative in response to propofol, sufentanil and latex solutions. Basophil activation test (BAT) was analyzed using a FACSCanto II flow cytometer (Becton-Dickinson, Rungis, France). Succinylcholine showed CD63 and CD203c upregulation, confirming basophil sensitization by specific IgE towards succinylcholine. Both activation markers were negative for the other tested NMBAs. Surgery was therefore scheduled a few weeks later and anesthesia conducted with propofol, sufentanil and atracurium. Anesthesia and surgery remained uneventful.

Discussion

In our patient, the onset of succinylcholine-induced IgE-mediated anaphylaxis was confirmed by the clinical, biological and allergological evidence. The combined persistent ECG changes, elevated troponin levels, echocardiographic findings and normal coronary anatomy established the diagnosis of ABS [11] following this anaphylactic event. Additionally, during ABS, the most common abnormality on the electrocardiogram is ST-segment elevation. Nevertheless, transient pathological Q waves may also be observed, as in the present case [12].

Anaphylaxis is a clinical syndrome that varies in severity. The clinical signs are described according to the adapted *Ring and Messmer* four-step grading scale [13]. Grade I reactions involve mucocutaneous signs and grade II correspond to moderate clinical features, which may be associated with mucocutaneous, cardiovascular or respiratory signs. While the cardinal sign of grade III reactions is cardiovascular collapse, which may be associated with mucocutaneous signs or bronchospasm, cardiac arrest is associated with grade IV reactions. During severe clinical presentation, intravenous epinephrine undoubtedly remains the first-line treatment of anaphylaxis. Although the therapeutic range of epinephrine plasma concentrations associated with successful anaphylaxis treatment remains unknown, epinephrine doses should be adapted to the clinical presentation, with boluses of 0.1–0.2 mg recommended

in cases of grade III, while doses of 0.01–0.02 mg are adequate for grade II. High doses of intravenous epinephrine (i.e., 1–3 mg over 3 min) are only recommended during cardiac arrest (grade IV) [8–10, 13]. Accordingly, epinephrine is characterized by a narrow therapeutic index [14], and pulmonary edema, ventricular dysrhythmias, myocardial and cerebral infarctions or deaths have been reported following overdose of epinephrine during anaphylaxis. This highlights the need for practitioners to precisely determine the appropriate epinephrine dose according to the clinical picture of anaphylaxis [9, 13, 15].

In the present case, the three predictive criteria associated with the severity of the ongoing anaphylactic reaction were present, including: (1) the speed of onset of the clinical reaction after allergen exposure; (2) the absence of inaugural cutaneous signs which secondarily appeared following restoration of blood pressure; (3) initial tachycardia rapidly followed by bradycardia [13]. As reported in approximately 10% of patients with perioperative anaphylaxis, considering the sudden decrease in peripheral resistance associated with decreased venous return, the occurrence of bradycardia may have been triggered in order to preserve cardiac filling despite profound hypovolemia [13]. In such a clinical form, changes in vascular permeability during anaphylaxis might lead to a 50% transfer of the intravascular fluid into the interstitial space within 10 min [9]. Large fluid therapy followed by epinephrine administration (i.e., 0.1–0.2 mg renewed every 1–2 min according to the hemodynamic response, and if necessary followed by a continuous infusion) should thus be initiated [9, 13].

Excess intravenous exogenous epinephrine (0.75 mg) [16] can lead to global left ventricular dysfunction (likely secondary to coronary spasm), but may also account for ABS. Acute emotional or physical stress, high concentrations of endogenous catecholamines produced by a tumor with chromaffine tissue or exogenous epinephrine have all been implicated in the occurrence of ABS [12, 17]. However, catecholamine-mediated microvascular dysfunction, direct toxic effects of catecholamines on cardiac myocytes and catechol *O*-methyltransferase genotype patient profiles may also be involved in the left ventricle dysfunction [4, 5, 11]. Thus, epinephrine either at pharmacologic or supra-pharmacologic doses can be sufficient to induce Tako-Tsubo cardiomyopathy [4, 6, 18].

ABS may occur during anaphylaxis. The role of enhanced sympathetic activity in response to anaphylaxis itself cannot be ruled out [6, 11], but epinephrine overdosage is most likely implicated [1–6]. ABS has been observed following either perioperative anaphylaxis [2, 6] or in patients with anaphylaxis outside the intraoperative period [1, 3–5]. In one case of perioperative anaphylaxis, a single bolus of 1 mg intravenous epinephrine was injected despite a grade III reaction [6]. Our patient received more than 6 mg epinephrine during the initial phase of shock, suggesting that this high dose might have caused ABS. It is possible that lower doses would have been enough, as suggested by the fact that cutaneous signs indicating restoration of peripheral perfusion were observed after the first 2 mg cumulated epinephrine dose. Although we did not measure plasma epinephrine levels, the role of presumably high plasma levels of catecholamines could be the main trigger when considering the high doses of administered epinephrine. Litvinov et al. [4] indeed reported an increased epinephrine plasma level of 798 pmol/l (normal range 120–600 pmol/l) 8 h following a 5 mg intramuscular epinephrine administration. Interestingly, low doses of intravenous epinephrine have also been associated with the occurrence of ABS. In one case, the two last boluses of intravenous epinephrine (0.1 mg each) were injected after generalized cutaneous signs had appeared, suggesting that tissue perfusion had been restored. These injections were immediately followed by ventricular fibrillation [2]. Altogether these case reports, including ours, suggest that epinephrine administration needs to be carefully reevaluated in patients in whom cutaneous signs are initially absent and appear during resuscitation. In other words, one could reasonably assume that the appearance of cutaneous signs would therefore be indicative of a restored cutaneous perfusion, thus suggesting that subsequent epinephrine administration might no longer be necessary.

Acute coronary syndromes associated with mast cell activation, also called allergic angina or allergic myocardial infarction or Kounis syndrome, have been reported [19]. Two variants are described. Variant I concerns patients without risk factors in coronary artery disease in whom the allergic reaction triggers either coronary artery spasm without cardiac enzyme increase or myocardial infarction. Variant II occurs in patients with predisposing factors where the allergic reaction induces plaque erosion or rupture and myocardial infarction. Finally, if epinephrine overdosage is most likely involved in cases of Tako-Tsubo cardiomyopathy occurring following anaphylaxis, Kounis syndrome seems to be secondary to the release of inflammatory mediators induced by the activation of various inflammatory cells [20].

In conclusion, even though epinephrine remains the cornerstone of severe anaphylaxis care, practitioners should be aware of the potential deleterious effects of high doses of epinephrine. The optimal care management of perioperative anaphylaxis should therefore be conducted on a case-by-case basis, including a progressive titration of epinephrine. Finally, although the short-term outcomes are good, there are no data analyzing long-term prognosis in patients with previous ABS, suggesting the need for prospective studies.

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