

Refractory Anaphylactic Cardiac Arrest After Succinylcholine Administration

Antoine Baumann*

Daniela Studnicska, MD*

Gérard Audibert, MD, PhD*

Attila Bondar, MD, FCARCSI*

Yannick Fuhrer, MD*

Jean-Pierre Carteaux, MD, PhD†

Paul M. Mertes, MD, PhD*

Refractory shock from anaphylaxis can occur after induction of general anesthesia. We report two cases of fatal cardiac arrest with increased blood tryptase and immunoglobulin E values after succinylcholine administration. Tryptase and immunoglobulin E assays may help to identify anaphylactic reactions when cardiac arrest occurs at induction of anesthesia.

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Anaphylactic reactions occurring during anesthesia can be life-threatening and require urgent therapy to avoid a fatal outcome. Anaphylactic reactions presenting as cardiac arrest resistant to cardiopulmonary resuscitation (CPR) despite prompt diagnosis and appropriate treatment occur but are rarely described in medical literature. We report two cases of anaphylactic reactions with fatal cardiac arrest after succinylcholine administration.

CASE DESCRIPTION

Case 1

A 74-yr-old woman (1.70 m, 79 kg) was admitted to the hospital with acute appendicitis and scheduled for emergency surgery. Her medical history revealed dyslipidemia treated with fenofibrate and hypertension well controlled with diuretics (spironolactone and furosemide). Her surgical history consisted of two previous interventions 29 and 15 yr ago without any complications according to the patient. No atopic history or preexisting allergy was reported. General anesthesia with rapid sequence induction was planned. Anesthesia was induced with propofol (2 mg/kg), cricoid pressure applied, and succinylcholine (1 mg/kg) administered. Tracheal intubation was performed 1 min after succinylcholine injection and correct placement of the endotracheal

tube was confirmed. Four minutes after succinylcholine administration, severe bronchospasm with high airway pressure and decreased end-tidal CO₂ (ETCO₂) (from 32 to 15 mm Hg) was observed along with undetectable oxygen saturation, accompanied by hypotension (40/28 mm Hg), bradycardia (40 bpm), and no palpable carotid pulse. Despite the absence of any cutaneous signs, anaphylactic shock was immediately suspected and CPR was started without delay in accordance with international guidelines (Fig. 1)¹: 1 mg boluses of IV epinephrine were given three times at 3-min intervals and intravascular volume administration with Ringer's lactate solution (total 1500 mL over 90 min) was administered. This was followed by 2 mg and then by 5 mg boluses of epinephrine (total dose 25 mg). Chest compression was started immediately and maintained throughout CPR. Ventricular ectopy preceded ventricular fibrillation. Defibrillation using an external defibrillator was applied and repeated eight times for recurrent episodes of ventricular fibrillation. Ventricular fibrillation alternated with asystole throughout the CPR without return of spontaneous circulation. Two grams of calcium chloride and 250 mL sodium bicarbonate 8.4% were also administered. After 60 min of unsuccessful CPR, two boluses of 1 mg terlipressin at 5-min intervals were administered without any benefit. Despite 90 min continuous CPR, efficient cardiac activity was never restored, pulmonary edema occurred, and the patient died. Blood tests performed 70 min after the onset of the reaction showed a tryptase level of more than 200 µg/L (threshold: 13.5 µg/L) and a specific immunoglobulin E (IgE) for succinylcholine confirming the diagnosis of anaphylactic shock: quaternary ammonium (QA) fixation of 4.44% (>3% confirm allergic reaction) with succinylcholine inhibition of 92% (>20% confirm allergic reaction). Hemolysis of the blood sample prevented histamine measurements.

Case 2

A 49-yr-old man (1.72 m, 98 kg) was scheduled for emergency appendectomy. He had a medical history of hypertension treated with spironolactone, altizide (thiazide diuretic), and rilmenidine (α₂ blocking drug) and a congenital single kidney without renal function impairment. He had

From the *Département d'Anesthésie-Réanimation, Hôpital Central, Centre Hospitalier Universitaire, 29, avenue du Maréchal de Lattre de Tassigny, Nancy; and †Service de Chirurgie Cardiovasculaire et Transplantation, Hôpitaux de Brabois, Centre Hospitalier Universitaire de Nancy, 54500 Vandœuvre-les-Nancy, France.

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Address correspondence and reprint requests to Antoine Baumann, MD, DESA, Département d'Anesthésie-Réanimation, Hôpital Central, Centre Hospitalier Universitaire, 29, avenue du Maréchal de Lattre de Tassigny, 54000 Nancy, France. Address e-mail to a.baumann@chu-nancy.fr.

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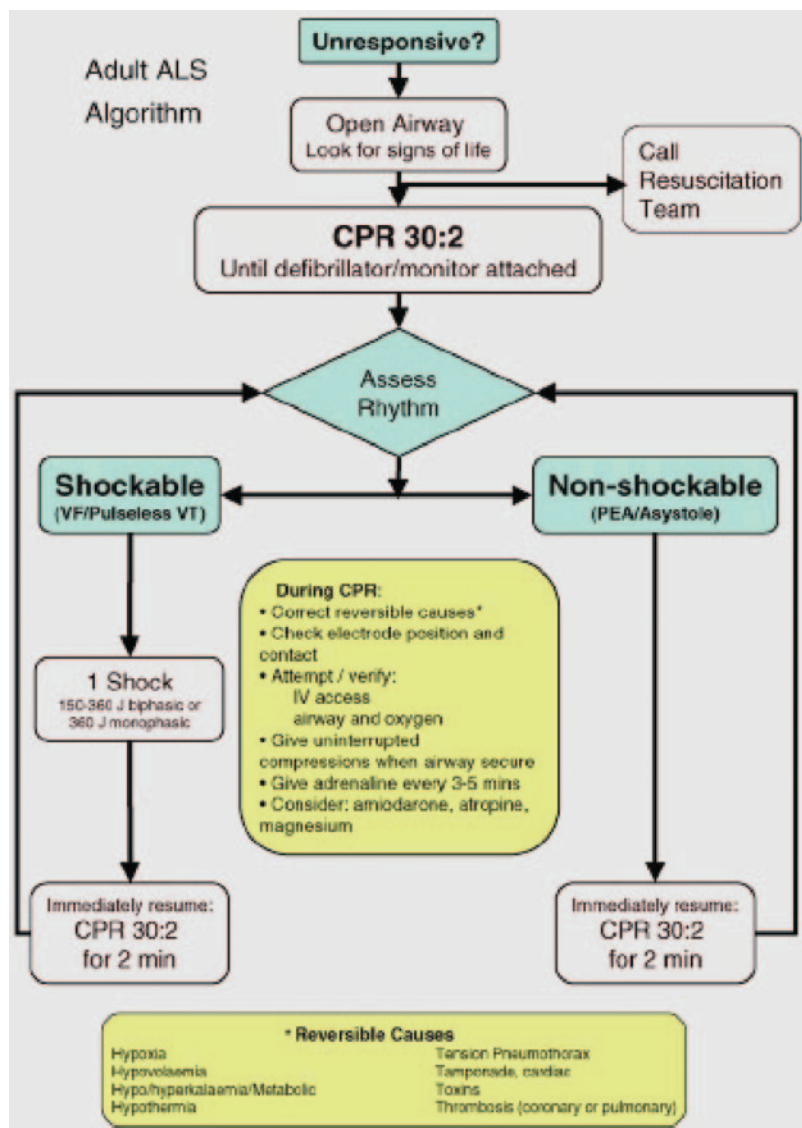


Figure 1. Advanced life support cardiac arrest algorithm.¹

no surgical history and no allergic reactions. General anesthesia was induced with propofol (2 mg/kg), cricoid pressure applied, and succinylcholine (1 mg/kg) was given to facilitate tracheal intubation. Endotracheal tube position was confirmed. A low ET_{CO}₂ (25 mm Hg) was noticed immediately and extensive erythema with piloerection appeared concomitantly. Anaphylactic shock was immediately suspected. Epinephrine was administered as a 0.2 mg IV bolus, his arterial blood pressure collapsed (50/35 mm Hg), and SpO₂ became undetectable. Pulseless electrical activity cardiac arrest occurred without any palpable carotid pulse. CPR with chest compression, rapidly increasing doses of IV epinephrine boluses (three boluses of 1 mg followed by 2 mg and then three boluses of 5 mg), and fluid administration with saline was administered¹ (Fig. 1). Two minutes later ventricular fibrillation occurred. After 15 min of CPR, including cardioversion and IV amiodarone 300 mg, two boluses of 1 mg terlipressin at 5-min intervals were administered. Twenty milligram epinephrine, 2000 mL saline, 500 mL sodium bicarbonate 8.4%, and 2 g calcium chloride were administered. Emergency circulatory support was instituted after 75 min of CPR, using extracorporeal membrane oxygenation (ECMO). The ECMO circuit consisted of a centrifugal pump (Rota Flow RF-32, Jostra Medizintechnik AG, Hirrlingen, Germany) and a hollow-fiber membrane oxygenator (Quadrox D, Jostra Medizintechnik AG). His systolic blood

pressure remained low (60 mm Hg) and pulmonary edema occurred. The patient died 12 h later from refractory shock and multiple organ failure, including acidosis, renal failure, rhabdomyolysis, and coagulopathy. Blood tests performed 50 min after the onset of the reaction showed a tryptase level over 200 µg/L and specific IgE against succinylcholine confirming the diagnosis of anaphylactic shock: QA fixation of 29.96% and succinylcholine inhibition of 36%.

DISCUSSION

The risk of immediate hypersensitivity reaction during anesthesia is estimated to be between 1/10,000 and 1/20,000 anesthesia,^{2,3} and neuromuscular blocking drugs are the most frequently involved substances (50%–70% of cases), succinylcholine being involved in the majority of cases.⁴ The mortality of anesthesia-related anaphylaxis ranges from 5% to 10%.^{5,6}

Our two cases document the potential acuteness, suddenness, and severity of cardiovascular events in anaphylaxis, which can be refractory to epinephrine and vasopressin analogs even with prompt treatment. In our two cases ET_{CO}₂ collapse was the first sign

preceding cardiac arrest. Several authors have underlined the value of this early clinical sign for the suspicion of anaphylactic shock, even in the absence of any cutaneous manifestations.⁷

Epinephrine-resistant anaphylactic shock is a strong incentive to search for possible alternative treatments.⁸ Methylene blue,⁹ glucagon,¹⁰ and α -agonists¹¹ have recently been proposed as alternative therapeutic options. Successful results have also been reported using arginine-vasopressin¹² or vasopressin analogues (terlipressin)¹³ in epinephrine-resistant anaphylactic shock resuscitation. Arginine-vasopressin is not available in France, therefore we used terlipressin. Cardiopulmonary bypass and extracorporeal support have also been successfully used in one case after 60 min of futile resuscitation.¹⁴ However, prompt resuscitation, use of terlipressin, and circulatory support were ineffective in our cases.

Tryptase is a marker of mast cell activation,¹⁵ with a specificity exceeding 93% for the diagnosis of anaphylaxis during anesthesia when a 20 $\mu\text{g/L}$ threshold is used.¹⁶ Its use for the postmortem diagnosis of anaphylaxis has been questioned because of the possibility of nonspecific mast cell activation during resuscitation.¹⁷ However, one should emphasize that this nonspecific increase is very limited during resuscitation. Therefore, vastly increased serum tryptase levels as observed in our cases support the strong argument in favor of an allergic reaction.^{18,19}

Identification of the causal agent is possible using specific IgE measurement, even when these tests are performed at the time of reaction.²⁰ In our cases, the presence of specific QA IgE was investigated by the University Laboratory of Medical Biochemistry using radioimmunoassay based on coupling of a choline analog to Sepharose (quaternary ammonium Sepharose-radioimmunoassay, positive threshold 1.5%). The sensitivity and specificity of these assays have been estimated to be 88% and 97%, respectively.²¹ A combination of high tryptase and high IgE values allowed us to conclude definitively the diagnosis of anaphylaxis to succinylcholine.

In anaphylaxis with early cardiac arrest, direct myocardial injury has been suggested.²² Several clinical observations and experimental studies support this hypothesis.^{23,24} Myocardial injury could be related to a high myocardial mast cell infiltration in these patients.²⁵ Unfortunately, in our patients the degree of cardiac mast cell infiltration could not be investigated because of the refusal of autopsy. In conclusion, despite the immediate diagnoses and prompt therapy, anaphylaxis can be lethal. Anaphylactic reactions to succinylcholine have been described. We postulate that a direct deleterious effect of the various mediators on myocardial function is a potential cause of the refractory cardiac arrest.²⁵ The failure of promptly instituted epinephrine, vasopressin analog, and even ECMO to treat these patients once again emphasizes the need for further studies on the mechanism of

severe anaphylaxis to identify possible alternative treatments to epinephrine. In case of unexpected death or cardiac arrest at induction of general anesthesia, blood tryptase and IgE measurements may help to identify possible anaphylactic reactions to neuromuscular blocking drugs.

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