Extracorporeal Life Support in a Case of Fatal Flecainide and Betaxolol Poisoning Allowing Successful Cardiac Allograft

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Use of cardiac allograft for transplantation from donors after acute poisoning is a matter of debate because of potential toxic organ injuries, especially if death results from massive ingestion of cardiotoxic drugs. We report successful allograft cardiac transplantation from a brain-dead patient after severe flecainide and betaxolol self-poisoning requiring extracorporeal life support. Extracorporeal life support was initiated in the emergency department because of a refractory cardiac arrest caused by the cardiotoxicants' ingestion and continued after the onset of brain death to facilitate organ donation of the heart, liver, and kidneys. Forty-five months later, each organ recipient was alive, with normal graft function. [Ann Emerg Med. 2010;56:409-412.]

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INTRODUCTION

The number of patients awaiting allograft transplantation is constantly growing and now exceeds the number of organs available for transplantation.[1] Organ donors are generally young healthy individuals who die of trauma, cerebral hemorrhage, or sudden cardiac arrest. Whereas the use of allografts for transplantation from donors after acute poisoning is still a matter of debate because of potential toxic organ injuries and secondary toxic effects in recipients, limited knowledge in organ-specific toxicity may lead to the premature exclusion of organ procurement.[2,3] Elsewhere, the context of the donor suicide may induce ethical questions for the physicians about organ donation, and medicolegal issues must also be considered. Finally, circulating toxicants such as psychotropic agents may be confounding factors for the diagnosis of brain death.[4] However, several donations from poisoned cerebrally dead patients have been reported, mainly involving the kidney and liver. Reported cases of poisonings followed by heart transplantation after brain stem death remain rare, especially if death results from ingestion of cardiotoxic drugs.[5]

Extracorporeal life support may lead to survival without neurologic sequelae in a selected subset of immediately and adequately resuscitated patients.[6,7] By treating the severe cardiac dysfunction, maintaining adequate liver metabolism, and renal elimination of the cardiotoxic agent, extracorporeal life support may allow complete recovery of cardiac function. Because of delayed or nonoptimal initial cardiopulmonary resuscitation, significant brain anoxia or death occurs in the majority of cases. To the best of our knowledge, we report here the first case describing extracorporeal life support use for refractory antiarrhythmic poisoning-related cardiac arrest resulting in brain death and finally allowing multiple organ harvesting, including the heart.

CASE REPORT

A 40-year-old woman called the emergency medical services about 9 AM because of flecainide (12,000 mg)-betaxolol (400 mg) self-poisoning performed 10 hours earlier. She was immediately transferred by first aid providers to the emergency department (ED) of a general hospital. However, on arrival she was unconscious, with a Glasgow Coma Scale score of 6 (E1,V1, M4), without focal neurologic sign. The blood pressure was 70/50 mm Hg, pulse rate was 32 beats/min, the respiratory rate was 14 breaths/min, and SpO_2 was undetectable under 15 L/min oxygen with facial mask. ECG revealed a broad complex bradycardia (QRS duration 0.32 seconds) with a type 1 Brugada pattern, compatible with sodium-channel blockade (Figure 1A). Intubation was complicated by 2 successive asystolic cardiac arrests requiring, respectively, 8 and 12 min of cardiopulmonary resuscitation (CPR), with epinephrine (9 mg), glucagon (3 mg), and 8.4% sodium bicarbonate (250 mL) administration. After return of spontaneous circulation, the patient developed cardiogenic shock (blood pressure 69/44 mm Hg, pulse 43 beats/min, undetectable SpO_2) refractory to continuous epinephrine infusion (6 mg/hour). Because an intra-aortic balloon pump was not available, the decision was made to start extracorporeal life support in the ED. Before arrival of the surgical team from another hospital, a third asystolic cardiac arrest occurred. Dobutamine infusion (20 μg/kg per minute)

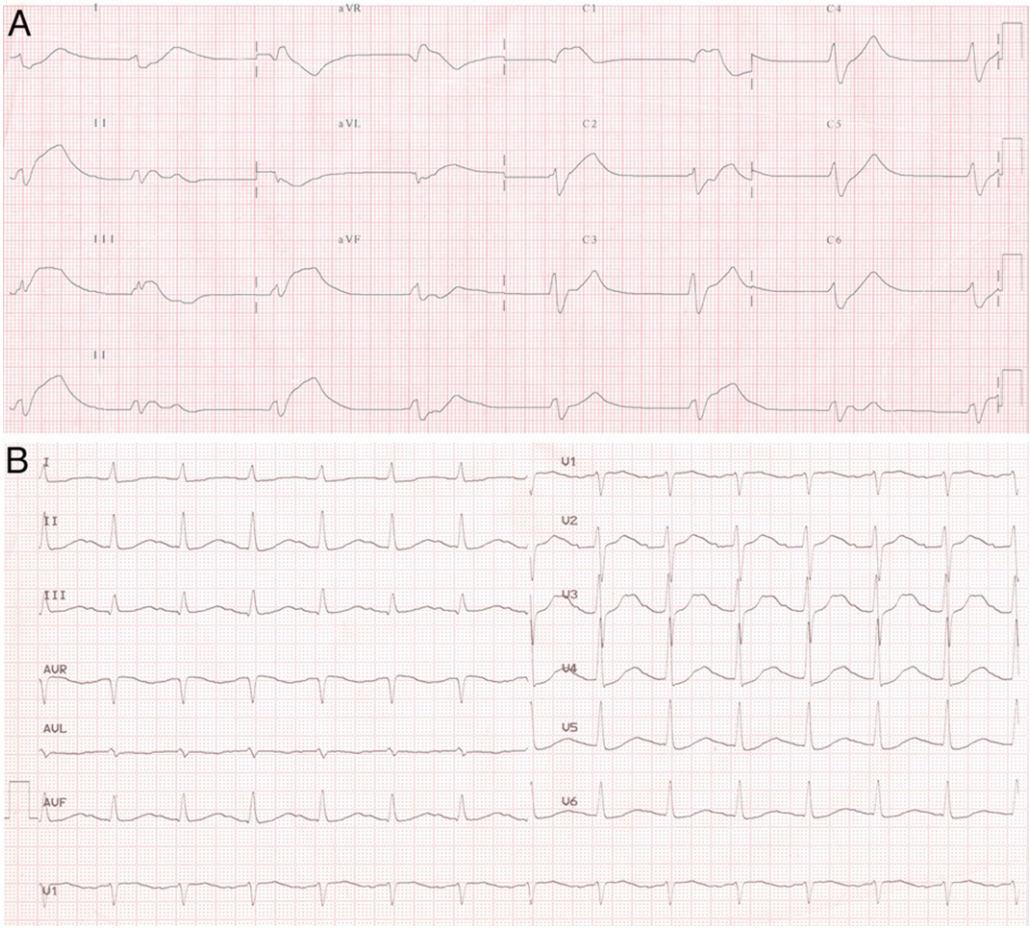

Figure 1. *A,* Twelve-lead ECG on admission in the ED, showing bradycardia with broad QRS complexes and a type 1 Brugada pattern. *B,* Twelve-lead ECG on day 2 after ICU admission before organ harvesting, showing a significant improvement in cardiac conduction.

was started while epinephrine infusion (6 mg/hour) and saline serum infusion (3,000 mL) were continued. After peripheral femorofemoral cannulation, the centrifugal pump (Rotaflow®, Jostra-Maquet, Orléans, France) connected to a hollow-fiber membrane oxygenator (modified BEHQV-50600 circuit, Jostra-Maquet, Orléans, France) enabled the restoration of a cardiac output of about 3 L/minute. The duration of this third cardiac arrest was 90 minutes until start of extracorporeal life support. No other intervention or investigation could be done while CPR and cannulation were simultaneously performed. The patient was then transferred by a SAMU mobile emergency unit to a specialized toxicologic ICU. On admission, the patient presented with multiple organ failure and severe global hypokinesia (echocardiography-measured spontaneous cardiac output was 1.5 L/minute, with 20 μg/kg per minute dobutamine infusion, whereas epinephrine infusion had been stopped since extracorporeal life support was started), pulmonary hemorrhage, and anuria. Neurologic examination without sedation revealed a Glasgow Coma Scale score of 3 without focal sign and a bilateral nonreactive mydriasis, but some spontaneous head movements with inspiratory efforts were observed. Chest radiography showed bilateral alveolar edema. Laboratory tests revealed a plasma lactate concentration of 15.6 mmol/L, potassium 3.1 mmol/L, pH 7.36, HCO_3^- 12 mmol/L, serum creatinine concentration 165 μmol/L, PaO_2/FiO_2 ratio 250 mm Hg, and disseminated intravascular coagulation with prothrombin time less than 10%, factor V at 3%, and fibrinogen less than 1 g/L. Plasma flecainide concentration was 7.89 μmol/L (therapeutic range 0.50 to 1.45 μmol/L). Measurement of betaxolol concentration was not available. Although a first electroencephalogram (EEG) was isoelectric, extracorporeal life support was continued because of the likelihood of reversibility of cardiac flecainide toxicity. However, dialysis was not performed because anuria rapidly resolved and also because both flecainide and betaxolol are weakly dialyzable. The cardiogenic shock progressively resolved, with significant improvement in echocardiography parameters and ECG (Figure 1B), enabling stopping of extracorporeal life support within 48 hours. Organ function recovered in parallel with the decrease of plasma flecainide concentration (Figure 2).

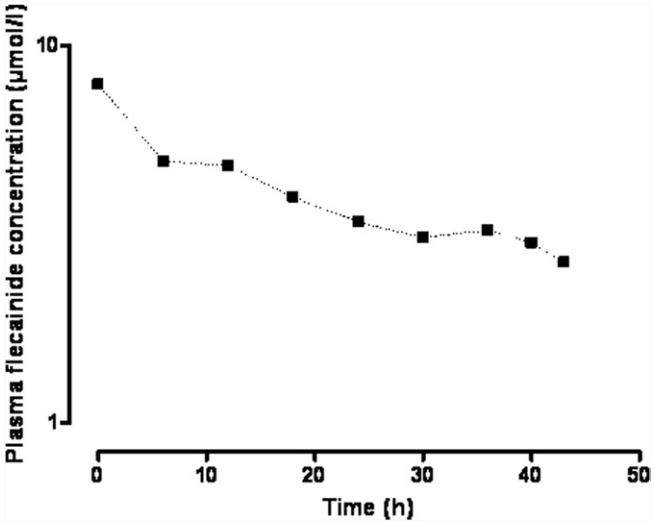

Figure 2. Time course of plasma flecainide concentrations in a severely poisoned patient treated with extracorporeal life support, finally evolving to brain death and allowing organ donation.

Brain death was diagnosed 3 days after admission according to 2 isoelectric EEG and cerebral computed tomography–angiography. At that time, a screening result for psychotropic drugs was negative. On day 4, according to the patient's wish assessed during a meeting between her family and ICU physicians, heart, liver, and kidneys were harvested for organ donation. At that time, plasma flecainide concentration was 2.66 μmol/L and shortening fraction was 47% on echocardiography. The cardiac transplantation was uneventful, without necessity for mechanical assistance in the recipient and a rapid weaning of his inotropic support. Ejection fraction was greater than 60% on the first day after transplantation. Forty-five months later, each organ recipient was alive, with normal graft function.

DISCUSSION

Flecainide acetate, a Vaughan Williams class 1C antiarrhythmic agent, acts by blocking the fast inward sodium channel during phase 0 of the action potential, resulting in a marked depression of atrial and ventricular conduction and contractility.[8] Betaxolol is a cardioselective β-blocker agent without intrinsic sympathomimetic and membrane stabilizing activity, resulting in marked bradycardia and atrioventricular conduction blockade. Both toxicants are functional, ie, recovery of cardiac conduction and function are expected with the elimination of the toxicant, unless there is prolonged coronary hypoperfusion resulting in myocardial injury.

Extracorporeal life support is an alternative therapeutic method for patients who present with refractory cardiac failure or arrest of reversible cause such as poisoning with cardiotoxic agents.[6,7,9-12] By providing adequate flow, extracorporeal life support restores vital organ perfusion, allowing drug metabolism and elimination and thus resulting in termination of cardiac toxicity. Redistribution of the intoxicant from its cardiac target tissue is a prerequisite for any improvement in heart function and conduction. Nevertheless, before considering extracorporeal life support, adequate resuscitation maneuvers remain essential to prevent definitive hypoxic cerebral damage.[6,7] Indeed, because the brain is the organ most vulnerable to metabolic damage, brain death may occur after intoxication while other organ systems maintain their function.[5]

In our patient, extracorporeal life support was initiated after refractory toxic cardiac arrest. Extracorporeal life support was continued after brain death to facilitate multiple organ donation. We observed a 66% decrease in plasma flecainide concentration during extracorporeal life support for 48 hours, allowing time for drug redistribution but resulting in a significant slowing of flecainide elimination in comparison with normal pharmacologic conditions (elimination half-lives 7 to 22 hours).[13] However, 48 hours of support allowed elimination of enough drug to restore sufficient cardiac function. We presume that the harvested heart still contained flecainide because of significant blood concentrations at donation. In 2 extracorporeal life support–treated flecainide-poisoned patients, plasma flecainide concentrations decreased from 43.3 to 3.4 μmol/L during 32 hours[11] and from 11.3 to 2.9 μmol/L over 10 hours.[14] Interpretation of pharmacokinetic measures during extracorporeal life support should always be cautious, bearing in mind the increased volume of distribution caused by the large amounts of exogenous fluids required for circuit priming and blood flow maintenance, as well as prolonged drug elimination.[15] Additional factors may affect drug disposition during extracorporeal life support, including alteration in renal and liver function, as well as drug sequestration from adhesion to the circuit components.

The use of extracorporeal life support in brain-dead patients with cardiac failure or arrest could considerably expand the donor pool for organ transplantation.[16,17] Toxic deaths usually involve healthy and young patients; however, they represent less than 1% of organ donors. The suicidal origin of poisoning should not be a major concern for organ harvesting because victims of other forms of suicide-related brain death (head trauma, gunshots, hanging) are commonly considered as donors. Nevertheless, the decision to use organs from poisoned patients is complicated because of the concerns about potential injuries to the organs and recipients resulting from the toxicants involved. Limited knowledge in organ-specific toxicity may lead to the premature exclusion of organ procurement.[2] Conversely, several successful transplantations with organs from acutely poisoned patients have been reported, generally with good long-term survival. To date, there are only a few case reports of heart transplantation after poisoning with cardiotoxicants, and only 1 involved antiarrhythmic drugs.[5] Nevertheless, Tenderich et al[5] reported that hearts from poisoned donors, even if poisoned by cardiotoxicants, could be transplanted in selected cases, provided that the organ donors were not hemodynamically compromised.[5] To our knowledge, our case is the first one describing the use of extracorporeal life support for refractory

cardiac arrest caused by antiarrhythmic poisoning, finally enabling cardiac allograft transplantation.

Organ donation should be considered after brain-death assessment in extracorporeal life support–treated poisoned patients who have experienced prolonged cardiac arrest because the toxic effects on heart function induced by the majority of drugs are reversible.

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