

## Review

# Clinical review: Aggressive management and extracorporeal support for drug-induced cardiotoxicity

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## Abstract

Poisoning may induce failure in multiple organs, leading to death. Supportive treatments and supplementation of failing organs are usually efficient. In contrast, the usefulness of cardiopulmonary bypass in drug-induced shock remains a matter of debate. The majority of deaths results from poisoning with membrane stabilising agents and calcium channel blockers. There is a need for more aggressive treatment in patients not responding to conventional treatments. The development of new antidotes is limited. In contrast, experimental studies support the hypothesis that cardiopulmonary bypass is life-saving. A review of the literature shows that cardiopulmonary bypass of the poisoned heart is feasible. The largest experience has resulted from the use of peripheral cardiopulmonary bypass. However, a literature review does not allow any conclusions regarding the efficiency and indications for this invasive method. Indeed, the majority of reports are single cases, with only one series of seven patients. Appealing results suggest that further studies are needed. Determination of prognostic factors predictive of refractoriness to conventional treatment for cardiotoxic poisonings is mandatory. These prognostic factors are specific for a toxicant or a class of toxicants. Knowledge of them will result in clarification of the indications for cardiopulmonary bypass in poisonings.

## Introduction

Failure of various organs may result in the death of acutely poisoned patients. In the 1960s, sedative-induced respiratory failure was the leading cause of death in Western countries. In these cases, endotracheal intubation and mechanical ventilation dramatically improved the prognosis. Similarly, renal replacement therapy with dialysis prevents deaths related to toxicant-induced acute renal failure. Even drug-induced fulminant liver failure is successfully treated in selected cases by liver transplantation. In contrast, the usefulness of temporary mechanical assistance in drug-induced cardiac failure still remains a matter of debate [1,2].

However, promising results have been obtained using a combination of percutaneous cardiopulmonary support and cardiac resuscitation [3,4]. Furthermore, a recent report of the first series of acute poisonings treated with extracorporeal life support (ECLS) [5], together with an increasing number of case reports [6-10], suggests it is necessary to define the place of this aggressive treatment for drug-induced cardiotoxicity.

## Drug-induced cardiovascular shock: a leading cause of death

Over the past 30 years, improvements in the treatment of drug-induced cardiovascular shock have been due mainly to a better understanding of the different mechanisms of shock. Routine bedside haemodynamic examinations have provided evidence of the different mechanisms of drug-induced cardiovascular shock, which has enabled the selection of drugs to address the different components of shock. Within the same period of time, indications for mechanical ventilation were extended to conscious poisoned patients presenting with severe cardiovascular shock. Consequently, the prognosis of some cardiotoxic drug poisonings improved. Indeed, in a prospective study with historical controls, the combination of epinephrine, diazepam and mechanical ventilation significantly improved the outcome of previously fatal chloroquine poisonings [11,12].

In addition to supportive treatment, a number of antidotes and specific treatments have been investigated (Figure 1). Among cardiotoxic drugs, however, only one antidote, digitalis-specific Fab fragments, has succeeded in improving the prognosis of digitalis poisoning. Digitalis-specific Fab fragments are highly efficient and should now be considered as first-line treatment for this formerly deadly poisoning [13].

AAPCC = American Association of Poison Control Centers; ACLS = advanced cardiac life support; CPB = cardiopulmonary bypass; ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; MSA = membrane stabilising activity; SSRI = selective serotonin reuptake inhibitor.

**Table 1****Drugs having 'membrane stabilising activity' with the potential for severe cardiotoxicity depending on dose**

Anti-arrhythmics class I Vaughan Williams	Flecainide, disopyramide, cibenzoline, propafenone, quinidine, lidocaine, procainamide
Beta-blockers	Propranolol, acebutolol, nadolol, pindolol, penbutolol, labetalol, oxprenolol
Polycyclic antidepressants	Imipramine, desipramine, amitriptyline, clomipramine, dosulepin, doxepin, maprotiline
Selective serotonin reuptake inhibitors	Include venlafaxine, citalopram
Dopamine and norepinephrine uptake inhibitors	Include bupropion
Anti-epileptics	Include carbamazepine, phenytoin
Phenothiazines	Include thioridazine
Opioids	Include dextropropoxyphene
Antimalarial agents	Include chloroquine and quinine
Anaesthetic-recreational agents	Include cocaine

There is no further need for anti-arrhythmics, endocardial pacemakers or even ECLS, which had been used in the past [14,15], providing that digoxin-specific Fab fragments are available [15]. However, the future of immunotherapy in the treatment of other cardiotoxic drug poisonings still remains uncertain. Desipramine-specific Fab fragments were shown to be efficient in experimental models [16,17] but the conclusion of clinical trials is still pending [18]. Similarly, colchicine-specific Fab fragments were also shown to be efficient in experimental models [19-23] but only one life-threatening human case has benefited from this treatment due to a shortage of specific Fab fragments [24].

In spite of treatment improvement, drug-induced cardiovascular failure still remains a leading cause of death. Among 847,483 poisonings in adults over 19 years of age, cardiovascular drugs were involved in 5.8% [25]; however, cardiovascular drugs accounted for about 19% of the total 1,261 poisoning fatalities. Calcium channel blockers and beta-blockers account for approximately 40% of cardiovascular drug poisonings reported to the American Association of Poison Control Centers (AAPCC) but represent more than 65% of deaths from cardiovascular medications [26]. In the 1980s, Henry and Cassidy [27] elegantly showed that, for a pharmacological class of drugs, the mortality rate is significantly increased in poisonings involving drugs with a membrane stabilising activity (MSA) in addition to their main pharmacological activity. Since then, the increase in mortality rate induced by drugs with a MSA has been consistently confirmed [28]. Unfortunately, despite decreased use of some cardiotoxic drugs and the withdrawal of dextropropoxyphene in some countries, many widely prescribed drugs still have a MSA (Table 1), so the finding of Henry and Cassidy still holds true today [28]. Indeed, venlafaxine [29] and citalopram [30] have been shown to induce severe cardiovascular shock and, recently, high dose bupropion was shown to induce intraventricular conduction defects [31].

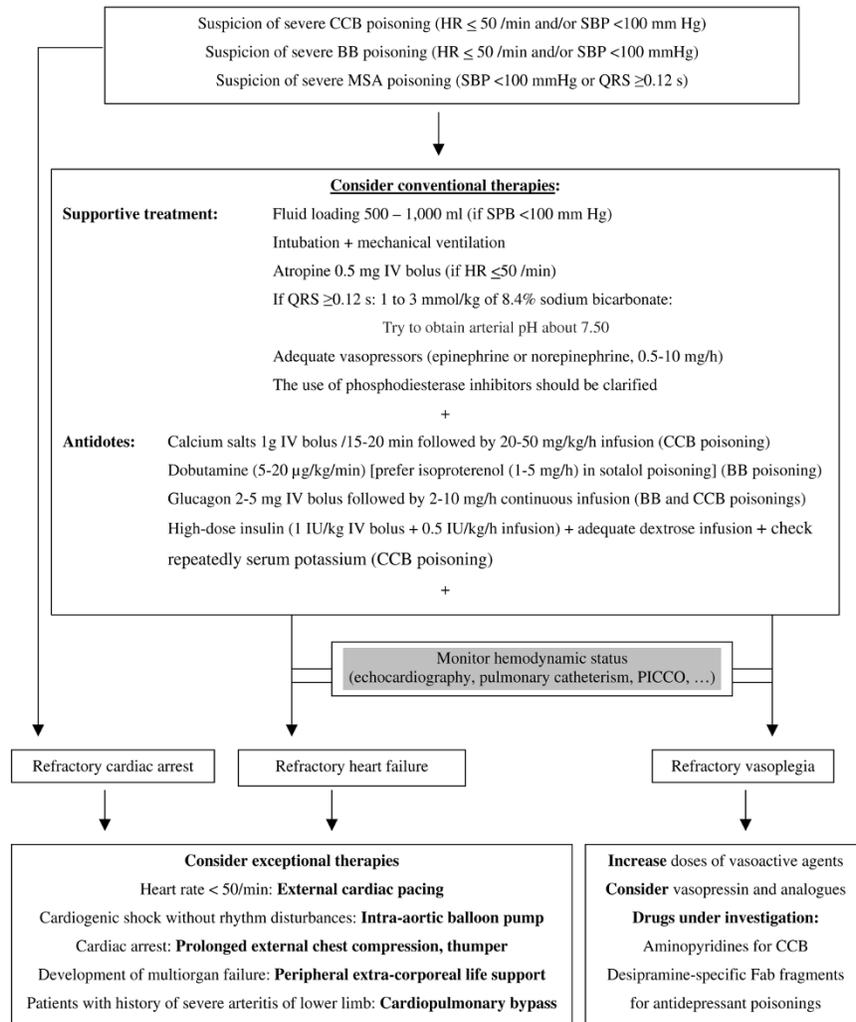
### Manifestations of severe cardiotoxicity

Severe cardiotoxicity may be evident, either at the time of presentation or during the course of poisoning, by the sudden onset of high degree atrio-ventricular block, asystole, pulseless ventricular tachycardia or ventricular fibrillation. However, the most frequent presentation of severe cardiotoxicity is hypotension and even cardiovascular shock.

The delay in onset of life-threatening events depends on the toxicant and its galenic formulation, the ingested dose, the duration of QRS length on echocardiogram for the MSA, and the occurrence of mixed cardiotoxic poisonings. The delay is up to two hours after ingestion for class I anti-arrhythmics [32] and of about six hours for polycyclic antidepressants [33], chloroquine [12] and beta blockers [34]. It should be noted that, in one case series, beta-blocker-induced cardiopulmonary arrest did not develop until patients were in the care of health care personnel in 59% of cases [35]. As in our personal experience, beta-blocker-induced cardiovascular shock may slowly progress after admission to hospital. In these cases, there is a misleading moderate increase in plasma lactate concentration, probably related to the protective effect of beta-blockers on glycolysis and lactate production in comparison with other cardiotoxic poisonings, while there is a severe impairment of microcirculation assessed by a decreasing urine output, an increased serum creatinine concentration, and a progressive alteration in liver function and coagulation tests. The delays in onset with calcium channel blockers have been clarified recently [36]. Asymptomatic patients are unlikely to develop symptoms if the interval between ingestion and the call is greater than six hours for immediate-release products, 18 hours for modified-release products other than verapamil, and 24 hours for modified-release verapamil.

It should be noted that drug-induced cardiovascular shock does not always result from a decrease in cardiac

**Figure 1**



Proposed algorithm for the treatment of severe calcium-channel-blocker (CCB), beta-blocker (BB), and membrane-stabilizing agent (MSA) poisoning. This algorithm is based on series and case reports. HR, heart rate; SBP, systolic blood pressure.

contractility. Many cases of drug-induced shock result from a combination of relative hypovolemia and arterial vasodilation. This point is well recognized for calcium channel blockers and more especially for dihydropyridines, including nifedipine [26]. It is less known for polycyclic antidepressants and chloroquine, while it can be underestimated for labetalol poisoning. Therefore, in drug-induced cardiovascular shock with apparent refractoriness to conventional treatment, it is mandatory to perform a haemodynamic examination using either right heart catheterization or echocardiography to assess the mechanisms of shock. Finally, only a few cases of shock result from cardiogenic shock refractory to conventional treatment. In a series of 137 consecutive cases admitted in our department of severe poisoning with a drug with MSA requiring catecholamine administration for shock in addition to specific treatments, the mortality rate was 28% (unpublished data). These data suggest two conclusions:

first, 72% of severe patients had a favourable outcome in association with optimization of conventional treatment (Figure 1); and second, there is a need for more aggressive treatment in the subset of patients not responding to optimal conventional treatment. As stated in the Toxicologic-oriented advanced cardiac life support (TOX-ACLS) guidelines, evidence supports the use of circulatory assist devices such as intra-aortic balloon pumps (IABPs) and emergency cardiopulmonary bypass (CPB) in the management of drug-induced cardiovascular shock refractory to maximal therapy [1].

### Experimental evidence of the efficiency of extracorporeal life support in cardiotoxic drug poisonings

Three experimental studies with control groups performed in various species, including dogs and swine, poisoned with

membrane stabilising agents support the hypothesis that ECLS is life-saving in comparison with ACLS-treated animals. It is quite interesting to note that, among the large spectrum of cardiotoxic drugs, the authors of the experimental studies selected only drugs having MSA.

Freedman and colleagues [37] poisoned dogs with a 30 mg/kg bolus dose of lidocaine. In the control group, dogs were treated with antiarrhythmics, vasopressors, and cardioversion. Of the 8 animals, 6 died within 30 minutes after lidocaine infusion. In the ECLS group, none of the eight animals died. Furthermore, the total body clearance of lidocaine in the ECLS group was comparable to that in animals having received a non-toxic dose of lidocaine,  $39.75 \pm 4.16$  ml/kg/minute and  $38.29 \pm 8.6$  ml/kg/minute, respectively.

Martin and colleagues [38] poisoned 12 dogs with intravenous 1 mg/kg/minute desipramine until they arrested in spite of aggressive supportive care. Six were treated with up to two hours of ACLS with a thumper and six with ECLS. Dogs achieving return of spontaneous circulation to a sufficient degree to wean them from the thumper or ECLS were observed for one hour further. Return of spontaneous circulation occurred in one of six dogs in the thumper group and all six dogs in the ECLS group. Furthermore, the surviving dogs from the thumper and ECLS groups required a mean of 60 mg/kg versus 31 mg/kg norepinephrine and 2.2 mg versus no epinephrine, respectively, during the period of observation. In this model of severe desipramine toxicity, resuscitation with ECLS was superior to ACLS with a thumper.

Larkin and colleagues [39] poisoned 20 swine with intravenous amitriptyline 0.5 mg/kg/minute until systolic blood pressure dropped below 30 mmHg for 1 minute. The control group received supportive treatment, including intravenous fluids, sodium bicarbonate, and vasopressors. Control animals failing to respond to supportive measures after 5 minutes were given open-chest cardiac massage for 30 minutes or until return of spontaneous circulation. The ECLS group received only mechanical support by ECLS for 90 to 120 minutes. No sodium bicarbonate, antiarrhythmics, or cardiotoxic agents were provided to the ECLS group during this resuscitation. All 20 animals experienced cardiac conduction delays, dysrhythmias and progressive hypotension within 30 minutes of receiving amitriptyline. Only one of the ten animals in the control group could be resuscitated. In contrast, the ten animals in the ECLS group had complete correction of the dysrhythmias, cardiac conduction abnormalities, and hypotension related to amitriptyline. Nine of these ten swine were easily weaned off bypass without any pharmacological intervention; however, one required norepinephrine to be weaned. The authors concluded that ECLS improved survival in this swine model of severe amitriptyline poisoning.

## Temporary mechanical assistance of the poisoned failing heart

When evaluating the medical literature on this topic, it should be emphasized that different extracorporeal techniques have been used [40,41]. Unfortunately, the same word is used with different meanings.

Extracorporeal membrane oxygenation (ECMO) is used to treat refractory hypoxemia induced by the acute respiratory distress syndrome, and it has been used in a limited number of cases of severe drug-induced hypoxemia [7-9,42]. It is a venous-venous method providing oxygenation of venous blood; thus, there is no circulatory support. The use of ECMO for respiratory failure following ingestion or inhalation has the same limited indications as for other patients with respiratory failure [43]. It should be emphasized that data supporting an improvement in outcome are not available.

An IABP is an arterial device aimed at decreasing left ventricular afterload. It provides limited support of cardiac output, increasing it by about 20%. IABPs are the first choice for mechanical circulatory support and do play a certain beneficial role in the management of cardiogenic shock [44]. They have been used alone to treat life-threatening toxic manifestations induced by quinidine [45], propranolol [46], dextropropoxyphene [47], antihistamine [48] poisonings, and a combination of verapamil and atenolol [49] poisonings. Furthermore, an IABP has been used in combination with ECLS in a case of organophosphate poisoning [50]. However, IABPs do not work in patients with cardiac arrest. When dealing with cardiotoxic poisonings, this is a major limitation as major events of cardiotoxic poisonings are ventricular tachycardia and fibrillation as well as electromechanical dissociation and refractory asystole.

CPB basically provides circulatory support, although it collects venous oxygen-desaturated blood in the right atrium and, thus, always requires an oxygenator, which is integrated within the circuitry. CPB requires sternotomy and both atrial and aortic cannulations. Thus, it is a surgical procedure whose use must be restricted to the operating room. CPB has been performed in cases of aconite [51], diltiazem [6], and verapamil [52] poisonings, and has been used in combination with an IABP in a case of prajmalinum poisoning [53]. CPB is an invasive method resulting in a number of potentially life-threatening complications. In one case of massive diltiazem poisoning treated with CPB, the procedure was prematurely terminated after 48 hours because of uncontrollable mediastinal haemorrhage (21 litres over 30 hours) [6]. Coagulopathy and extensive blood loss from mediastinal drains were reported during the course of aconite poisoning as well as further tamponade, necessitating evacuation of mediastinal haematoma [51].

ECLS (or CPB support or percutaneous cardiopulmonary support or extracorporeal circulation) also provides circula-

tory support. In contrast with CPB, ECLS can be performed using peripheral cannulations of both arterial and venous vessels. In adults, femoral vessels are the most frequently used. In infants, other vessels have also been used, including the carotid artery and internal jugular vein [54]. As for CBP, ECLS requires ECMO. ECLS may result in blood flows ranging from 1.5 to 6 l/minute, thus providing a complete supplementation of a failing or even arrested heart. The preferred method for cannulation remains a matter of debate. Percutaneous cannulation of femoral vessels is used. However, a blinded approach of vessels may cause laceration resulting in severe occult local bleeding. Furthermore, due to the size of the arterial cannula of about 15 to 17 F gauge, the occlusion of the vessel lumen by the cannula may result in arterial ischemia. A peripheral femoro-femoral shunt was shown able to prevent this severe complication of ECLS [5]. Cases in which ECLS has been used include imipramine [55], desipramine [54,56], carbamazepine [10], propranolol [57], acebutolol [58], disopyramide [59], quinidine [60], flecainide [54,61,62], verapamil [63], digoxin [15], and chloroquine [64] poisonings. Peripheral ECLS has been used in combination with an IABP in a case of organophosphate poisoning [50]. Babatasi and colleagues [5] and Massetti and colleagues [65] published a series of seven consecutive severe poisonings involving cardiotoxic drugs and treated with ECLS using the peripheral bypass to prevent limb ischemia. Circulation in the cannulated limb was provided by a tube inserted distally into the superficial femoral artery and connected to the side port of the ECLS arterial line [65]. In contrast to other case reports, in this series the majority of poisonings resulted from mixed poisonings involving a combination of sotalol and verapamil in one case, acebutolol and meprobamate in two cases, propranolol, verapamil and betaxolol in one case, and various psychotropic drugs in one case; the single drug poisoning resulted from disopyramide ingestion [5].

ECLS is, however, an invasive method and may also result in life-threatening complications [2]. In a case of flecainide poisoning, ECLS was discontinued after ten hours because of persistent haemorrhage at the cannulation site [61]. Coagulopathy may result in severe bleeding requiring multiple transfusions despite the use of aprotinin infusion [62]. Femoral nerve palsy [62] and deep venous thrombosis [62] have also been reported. In this critical condition, severe haemorrhage has also been reported at sites other than the cannulation site. Auzinger and Scheinkestel [54] reported extensive diffuse retroperitoneal haemorrhage, attributable to a femoral catheter inserted under resuscitation conditions. In addition to haemorrhagic complications, ischemia of the cannulated limb may occur. In the series of seven poisoned patients reported by Massetti and colleagues [65], the first three patients had severe ischemic complications of the distal leg; two patients died and one patient underwent fasciotomy for a lower leg compartment syndrome. Furthermore, severe hypotension four hours after ECLS cessation has been

reported in one patient [2]. Pulmonary oedema may require emergency decompression of the left atrium during an ECLS procedure [66]. However, to our knowledge, emergency decompression of the left atrium during ECLS has not been reported in poisoned patients treated with ECLS.

A biventricular assist device was used in one case of scombroid poisoning with refractory myocardial dysfunction [67]. The rationale of the authors to use a biventricular assist device rather than ECLS was pulsatile and adequate blood flow provided by the biventricular device with efficient unloading of the ventricle, and less circuit-related complications. However, the costs of both methods were not compared.

A review of the literature shows that temporary mechanical assistance of poisoned heart is feasible. Furthermore, the largest reported experience has resulted from the use of peripheral ECLS. However, an analysis of the medical literature dealing with extracorporeal assistance of poisoned failing heart does not allow one to draw any conclusions regarding the efficiency or the indications for this invasive method [2]. Regarding the different mechanisms of shock that may be observed in poisoned patients, it should be noted that ECLS should not be considered in shock related to arterial vasodilation. The global survival rate of poisoned patients having benefited from ECLS is about 79%, including many patients that experienced transitory or prolonged cardiac arrest. However, as the majority of cases were single case reports, it is reasonable to assume that failure of ECLS to allow recovery of poisoned patients has been under-reported while the lack of availability and access of patients to this treatment has been ignored. Interestingly, in the international Extracorporeal Life Support Registry Report of 2004, poisonings were not individualized as a cause of cardiac failure in adults [68]. Furthermore, the need to clarify the indications of aggressive management of cardiotoxic toxicity is further supported by the recent report of the AAPCC's toxic exposure database. Indeed, in 2005, 676 poisoned patients received cardiopulmonary resuscitation. In contrast, ECMO was performed in only six poisoning cases [25].

Methodology to assess the efficiency of a new treatment is well known in clinical toxicology. The first step is to determine prognostic factors. It should be outlined that prognostic factors are specific for a toxicant or a class of toxicants. Thereafter, knowledge of prognostic factors of a poisoning of interest allows a clinical trial to be performed in a subset of patients with poor prognostic factors. This method was shown to be efficient in digitalis [69,70], chloroquine [11], and colchicine [24] poisonings. Unfortunately, prognostic factors able to predict refractoriness to conventional treatment of cardiotoxic drugs are unknown, except for digitalis [71]. Therefore, the true need for ECLS in the previously reported cases of cardiotoxic drug poisonings cannot be assumed. There is an urgent need to clarify these

prognostic factors in order to advance understanding of both the indications as well as the efficiency of this invasive treatment. The report by Massetti and colleagues [65] on seven consecutive patients suggests that ECLS is promising in cardiotoxic poisoned patients. However, in this series, cardiotoxic drugs belonged to different toxicological classes, precluding any broad conclusion. Finally, peripheral ECLS permits one to institute ECLS outside the operating room and to begin immediate cardiopulmonary perfusion [72].

Several pre-requisites should be considered for the development of ECLS in a medical intensive care unit. There is a need to establish a close collaboration with a department of cardiac surgery [73]. Indeed, depending on local facilities, cardiac surgeons may decide whether ECLS will be performed inside the department of cardiac surgery, requiring the patient to be transferred to the surgical intensive care unit in a hospital with a cardiac surgery facility, or will be performed in the medical intensive care unit. The latter solution requires training of intensivists to some degree regarding the surgical approach of the femoral vessels at the Scarpa, while additional physicians and nurses have to be trained in the priming and handling of ECLS. Facilities must exist for coagulation tests as well as emergency blood supply. Cardiac surgeons must be available on a 24 hour a day basis to: discuss the indications for ECLS; insert the cannulae and start ECLS; provide local hemostasis; cope with local complications, including local bleeding and lower limb ischemia; address any complication related to the pump and membrane oxygenation; and withdraw the cannulae and perform vascular repair in case of favourable outcome.

## Conclusion

The renewed interest regarding the efficiency and safety of temporary mechanical assistance of the poisoned heart has highlighted the frequency and high mortality rate of cardiotoxic drugs. There is a need for more aggressive treatment in the subset of patients not responding to conventional treatment. Experimental studies support the hypothesis that ECLS is life-saving in comparison with ACLS-treated animals. In contrast, the majority of human cases are single case reports, except for one series. Appealing clinical results have been reported supporting the assumption that further studies are needed to clarify prognostic factors of cardiotoxic drug poisonings and, therefore, the indications and usefulness of peripheral ECLS.

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## Competing interests

The authors declare that they have no competing interests.

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