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REVIEW ARTICLE

Peripheral circulatory support in acute poisoning: 10 years' experience

Frédéric Baud[1-4], Lionel Lamhaut[1,2], Romain Jouffoy[1,2], Pierre Carli[1,2,5]

Extracorporeal life support (ECLS) has become a common technique for treating refractory cardiogenic shock and cardiac arrest induced by drug overdose. The aim of this paper is to present our group's 10-year experience (2002-2012) using ECLS to treat drug-induced, refractory cardiogenic shock and cardiac arrest. We review 112 consecutive cases of acute poisoning requiring arteriovenous ECLS. We provided ECLS with a Rotaflow pump (Jostra-Maquette). In 71 cases (63%) the patient presented with refractory cardiac arrest; 41 (37%) presented with refractory cardiogenic shock. The dose ingested was very high in all cases. Survival was strongly related to presentation (cardiogenic shock vs cardiac arrest) and the type of drug taken. Survival was highest after overdoses of β-blockers and antiarrhythmic drugs and lowest after overdoses of chloroquine, colchicine, or verapamil. Survival rates were very low in the subgroup of patients presenting with cardiac arrest who had taken hypnotics or sedatives, suggesting that the heart stopped more because of anoxia than because of a direct cardiotoxic effect. In contrast, in cardiotoxic drug-induced cardiac arrest, the survival rate of 10% was significantly higher than the rate in non cardiotoxic arrests. Survival rates in drug-induced cardiogenic shock ranged from 45% to 100%. We conclude that ECLS should be considered for the management of cardiotoxic drug overdose. Close cardiovascular monitoring should be initiated if a patient has taken a particularly high dose of a cardiotoxic drug. Severe cardiotoxicity is rare but life threatening. The use of ECLS in these cases should be based on clinical criteria. Early use of ECLS in drug-induced cardiogenic shock significantly improves survival. Delays in applying ECLS in severe drug-induced cardiotoxicity—diagnosed based on type of drug, dose, and hemodynamic effects—can lead to cardiac arrest and a worse outcome.

Keywords: Acute drug poisoning. Cardiogenic shock. Cardiac arrest. Extracorporeal life support. Extracorporeal membrane oxygenation. Cardiopulmonary bypass.

Author affiliation::
[1]Assistance Publique – Hôpitaux de Paris, France.
[2]Département d'anesthésie - Réanimation - SAMU de Paris. Hôpital Necker, Paris, Francia.
[3]Université Paris-Diderot. Paris, France.
[4]Unité UMR – Défense 8257 Cognitive Action Group, Paris, France.
[5]Université Paris Descartes, Paris, France.

Corresponding author:
Frédéric Baud
Département d'anesthésie - Réanimation - SAMU de Paris.
Hôpital Necker
Paris (France)

Email:
frederic.baud@nck.aphp.fr

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Asistencia circulatoria periférica en el curso de las intoxicaciones agudas: diez años de experiencia

El soporte vital extracorpóreo (SVEC o ECLS: *extracorporeal life support*) se ha convertido en una técnica habitual en el tratamiento del *shock* cardiogénico refractario y de la parada cardiaca inducida por una intoxicación medicamentosa. Se presenta la experiencia de nuestro grupo en el SVEC durante un periodo de diez años (2002-2012) en estas dos entidades clínicas. Se resivsan 112 intoxicaciones agudas consecutivas que requirieron un SVEC arterio-venoso. El SVEC fue llevado a cabo utilizando una bomba Rotaflow® (Jostra-Maquette). El 63% de las intoxicaciones (71 casos) se presentaron con una parada cardiaca refractaria y el 37% (41 casos) con un *shock* cardiogénico refractario. En todos los casos, la dosis ingerida fue muy elevada. La probabilidad de supervivencia estuvo muy unida al modo de presentación del intoxicado (*shock* cardiogénico o parada cardiaca) y al tipo de fármaco ingerido por el paciente. La supervivencia fue mayor en las intoxicaciones por β-bloqueantes y antiarrítmicos y menor en las intoxicaciones por cloroquina, colchicina y verapamilo. En las intoxicaciones por hipnosedantes que presentaron parada cardiaca, la tasa de supervivencia fue muy baja, indicando que dicha parada fue más el resultado de una anoxia que de un efecto cardiotóxico directo. Por el contrario, en los fármacos cardiotóxicos que indujeron parada cardiaca, la supervivencia fue alrededor del 10%, significativamente mayor que la tasa de supervivencia relacionada con una parada cardiaca de origen no tóxico. La probabilidad de supervivencia en el *shock* cardiogénico inducido por fármacos osciló entre el 45% y el 100%. Como conclusión, el SVEC ha de ser considerado como una opción terapéutica en la cardiotoxicidad por intoxicación medicamentosa. Una dosis ingerida particularmente elevada de un fármaco cardiotóxico debe motivar una estrecha monitorización cardiovascular del paciente. La toxicidad cardiaca grave no es frecuente, pero cuando se presenta pone en riesgo la vida del intoxicado. La indicación precoz del SVEC en el *shock* cardiogénico inducido por fármacos mejora de forma significativa la tasa de supervivencia. Cualquier retraso en el SVEC durante una cardiotoxicidad farmacológica grave, diagnosticada por el tipo de fármaco, la dosis y las consecuencias hemodinámicas, puede condicionar una parada cardiaca y un peor pronóstico del paciente.

Palabras clave: Intoxicación medicamentosa aguda. *Shock* cardiogénico. Parada cardiaca. Soporte vital extracorpóreo. Oxigenador de membrana extracorpóreo. Bypass cardiopulmonar.

Introduction

From 1940-50 and the remarkable development of psychopharmacology, acute respiratory failure (ARF) in toxic coma became the leading cause of mortality. The application to toxicology of the principles of medical resuscitation, and in particular of intubation and mechanical ventilation (MV) in cases of respiratory distress, considerably improved the prognosis of intoxication with psychotropic drugs. Mortality decreased from 30% in psychotropic intoxications to less than 1% in patients who underwent intubation and assisted ventilation.

On the other hand, when there were cardiovascular manifestations in the form of shock or rhythm or conduction disorders, with or without inotropic decline, pharmacological treatments have shown significant but limited progress over the years. In fact, the progress made was the result of the awareness of the different mechanisms by which cardiovascular shock of toxic origin occurs, as well as the improvement in invasive or semi-invasive surveillance.

Hypovolemic shock has benefited greatly from the principles of vascular filling and rehydration. Vasoplegic shock has benefitted from standardization of norepinephrine use and maintenance of blood pressure (BP) targets. But the field in which no progress has been made, or very few advances, is cardiogenic shock of toxic origin. Numerous drugs have been tried, but the results have been disappointing, including the pharmacopoeia used in the treatment of toxic cardiogenic shock such as adrenaline, noradrenaline or dobutamine, as well as isoproterenol in case of bradycardia, not counting specific antidote treatments. In addition, three classes of drugs with a cardiac and vascular action have not been recognized for their actual practical interest, with the exception of a few anecdotal clinical cases: dopamine, phosphodiesterase inhibitors and substances that increase the availability of intracellular calcium, in particular levosimendan.

In conclusion, the conventional cardiological approach in the field of acute heart failure of toxic origin has been very disappointing and what has been learned over the last 50 years has been mainly in the field of the optimization of acute heart failure. The antidotes appeared as a novelty and their effectiveness has managed to replace the pharmacological support by specific immunotherapy in the case of digitalis intoxication; hydroxocobalamin would be another example of antidotal efficacy in cyanide poisoning; and it is also worth mentioning insulin-glucose in intoxications by calcium inhibitors, whose effectiveness is undoubtedly limited.

All this led us to reflect in 2012 on the role of mechanical heart assistance in cardiogenic shock of toxic origin, which is a priori reversible based on the elimination of the toxicant, usually a drug. The purpose of this review on circulatory assistance in severe acute poisoning is to answer a number of questions related to the problem of poisoning by cardiotoxic substances, circulatory assistance modalities, vascular approach technique, their results, complications and toxicological and cardiological indications.

Problems of cardiotoxic substance intoxication

Despite the introduction of the principles of resuscitation in the field of clinical toxicology, there is still high mortality in cardiotoxic drug intoxications, with a global death rate of more than 12%, which contrasts with the general mortality of intoxications, dominated by psychotropic drugs and non-cardiotoxic analgesics, which is 4% in our intensive care unit (ICU). Table 1 shows the mortality rate for the different intoxications in the period between 1993 and 2000, a stage that precedes the introduction of extracorporeal life support (ECLS). It should be noted that during that period there was some therapeutic progress. It is evident that the mortality rate of digoxin intoxication, which is still prescribed, was 6% lower in our unit than that found by other authors[1], but it must be taken into account that the mortality rate before the introduction of the antidigital antibodies was 17%[2]. Table 1 also shows that the substances that produced these serious poisonings had a very different profile in relation to the mortality rate. For some, such as tricyclic antidepressants, although mortality was only 2%, the high frequency of this type of poisoning resulted in 15 deaths among 600 tricyclic intoxications admitted to the ICU during the period 1995-2001. At the same time, flecainide was used very little, since it only gave rise to 10 intoxications, but had a mortality rate of 40%. Chloroquine has a disturbing record, given the frequency of this poisoning (135 cases over a period of 6 years), with a mortality rate of 14%. Finally, cocaine-related deaths appearing at the end of that period should be highlighted, with a mortality rate of 4%.

The progress in improving mortality rates in cardiotoxic poisonings, with the exception of digoxin which has a specific antibody, has mainly been the result of

Table 1. Mortality rate of cardiotropic drug poisoning during the period 1993-2001 in Paris (France)

	Intoxications (n)	Deaths (n)	Mortality rate
Mortality of cardiotropic drug intoxications (1993-2000)			
Medicines	3,579	131	3.7%
Antiarrhythmics	189	23	12.2%
Digitalis	79	5	6.3%
Chloroquine	174	22	12.6%
Among cardiotropics, agents with membrane stabilizing effect are responsible for most deaths (1995-2001) (1995-2001)			
Chloroquine	135	19	14%
Flecainide	10	4	40%
Tricyclics	612	15	2%
Cocaine	80	3	4%

withdrawal from the market of these products and, in particular, in the 1970s, of quinidine, which was present in a commercial presentation associated with phenobarbital and was prescribed for emotional tachycardia.

The restriction in the use and disappearance of numerous class I antiarrhythmics has also contributed to this decline in mortality, thanks to a 1987 study that showed high mortality in patients treated with these antiarrhythmic drugs. Quinidine, which preceded ajmaline, and was also present in a pharmaceutical specialty whose indication was emotional tachycardia, was one of the agents used by the psychologically fragile and at risk of suicide, and for whom this treatment offered a life-threatening cardiotoxic agent. In addition, it should be emphasized that in the case of ajmaline, mortality correlated closely with the amount present in each tablet[3].

Deaths from overdose of drugs that have to be prescribed by a doctor, but consumed with recreational intent or pharming, is an underestimated problem and is expanding in all countries. A recent study in the US shows that drug overdose has become the leading cause of preventable mortality, from an incidence of 6 cases / 100,000 inhabitants in 1999 to 13 cases / 100,000 inhabitants in 2013[4]. Surprisingly, data in Europe are more reassuring[5]. However, in a 12-year study (1997-2008) in 12 French ICUs, it was surprising to note that the number of intoxications had not decreased, with an average of 1,500 stays per year in ICU due to intoxication, despite the fact that some toxic drugs had been withdrawn from the market during the period.

In addition, there was an increase in overall severity, as demonstrated by the Simplified Acute Physiology Score (SAPS II), which went from an average of 26 (SD: 20) in 1987 to 36 (SD: 23) in 2008. Confirming this increase in the severity of intoxications, the percentage of patients requiring MV increased from 41% to 65%, and in the same period, the percentage of intoxicated coma increased from 31% to 39%. It should also be noted that the percentage of patients who required vasoactive or cardioactive drugs rose from 12% to 22%. Finally, in the same time period, mortality in intensive care, which was 7% for drug poisoning, increased to 12%. This study concluded that there was an overall increase in morbidity and mortality of toxic origin in France.

Toxicology covers a number amount of substances, since they include medicines, addictive or recreational substances, domestic, industrial, phytosanitary products, plants and animal or vegetal toxicants. All these substances, ingested in high doses, can affect all the systems of the organism. But every toxicant, synthetic molecule or natural element has organ specificity to show its toxic effects. This toxicity is reproducible and dose dependent. The intensity of organ affectation can lead to acute functional deficiency of the target organ of the toxicant, and even to a cessation of its function. But one of the characteristics of the insufficiency of these organs, when it is the consequence of an acute intoxication, is that it is often reversible. But this reversibility is not universal, since some toxicants induce cellular damage that surpasses the capacity of repair of the organism (irreversible damage).

But when the heart stops, the question arises whether this can be reversed if it is possible to remove the toxicant present in the body or at least reduce its presence in the heart. The experience gained in more than 10 years' of circulatory assistance in poisoning allows us to affirm, to date, that it is possible to reverse them. In a large number of cases, cardiac effects observed in acute intoxications are reversible, and this is currently demonstrated for β-blockers and antiarrhythmic drugs with membrane stabilizing effect.

But this concept of complete reversibility cannot be extended to all intoxications. Thus, for example, anthracyclines and paraphenylene diamine can lead to toxic myocarditis with a virtually irreversible severe prognosis. In addition, the failures observed with chloroquine and calcium inhibitors raise the question of the mechanisms by which circulatory assistance has been unable to prevent the death of these patients. And yet, in the two examples cited, the electrical and mechanical activity of the heart had reappeared and the macro-circulation appeared to have normalized, but with evidence of serious and irreversible alterations in microcirculation.

Circulatory assistance in acute intoxications is an effective treatment that can be considered as indicated in β-blocker and antiarrhythmic intoxications with membrane stabilizing effect, but still experimental for other cases, which are many. In a recent report of severe colchicine intoxication with refractory cardiogenic shock, the patient progressed favourably under peripheral circulatory assistance[6]. This case, coupled with the one that we had treated with fragments of anticholichycin-specific antibodies, shows with near certainty that the cardiac involvement produced by colchicine is reversible in humans[7].

A systematic review of the literature focusing on circulatory assistance, very frequently arteriovenous and more rarely veno-venous, deserves reading[8]. Circulatory assistance has taught us that a heart stopped by intoxication may resume beating and that numerous toxic cardiac affections are reversible, which allows us to conclude that the phenomenon of myocardial stunning is undervalued. The existence of this stunning can be deduced by comparing the kinetics of toxicants with the evolution of myocardial function in the course of intoxications by adrenergic substances, such as caffeine and cocaine. In both cases, the intensity and brevity of the toxic effects explain the advent of atrial fibrillation (caffeine) or heart arrest in asystole (massive dose cocaine), but the duration of akinesia and subsequent myocardial hypokinesia persist for several days, are not comparable to the duration of toxic effects measured in minutes for cocaine or hours for caffeine.

Myocardial stunning of the toxic heart is undoubtedly multifactorial: myocardial exhaustion due to very intense β-adrenergic stimulation, incessant ventricular fibrillation, repeated electrical cardioversion and prolonged cardiac massage, as well as potent antiarrhythmic

agents, all of which have a negative inotropic effect, administered intravenously and at doses that may be repeated. A recent publication presents a case of acute heart failure caused by severe intoxication by tramadol, an ultra-fast metabolizer, which required ECLS, suggestive of a myocardial stunning effect induced by the inhibition of catecholamine reuptake and which generated a series of questions about the direct cardiotoxicity of tramadol[9,10].

This list of myocardial stunning factors gives rise to an additional reason for resorting to circulatory assistance. In fact, the analysis of the potential factors of this situation suggests the deleterious role of the pharmacological treatment of toxic cardiogenic shock and of ventricular malignant disorders. Excessive treatment to establish macro-circulation results in a worsening of the cardiac effects of the toxicants, rather than counteracting them. If one understands the mechanism of these vicious circles, one understands the place that ECLS occupies in the treatment of the intoxicated heart, placing it at rest and guarding against pharmacological aggression.

This new invasive treatment should not make us forget the rarity of the situations that need it, that is, cardiogenic shock of toxic origin. Masson et al. have shown that of the 2,350 intoxications admitted to resuscitation in the University Hospital Center of Lille, only 253 required the administration of catecholamines. Cardiogenic shock was observed in 62 intoxicated patients, including 52 refractory shock and 10 refractory heart arrest. In 60% of the cases, the agent responsible was an antiarrhythmic drug, being treated in 47% of these cases with a drug with membrane stabilizing effect. Intoxication was the result of a combination of cardiotropics in 73% of the cases[11].

Modalities of ECLS in intoxications

The review of the literature on this subject differentiates two classic models of circulatory assistance: veno-venous for syndromes of severe acute respiratory distress and arteriovenous for cardiogenic shock and heart arrest refractory to conventional treatment.

The venous-venous circulatory assistance used in respiratory distress of toxic origin is fundamentally applied for its ability to restore haematosis, ensuring an always limited oxygenation, but which has the great advantage of being stable, safeguarding the patient from serious accidents linked to episodes when the ventilator circuits are manipulated, whether for tracheal aspiration, fiberoptic bronchoscopy or other care.

Hypoxemia is corrected in extracorporeal circulation of the veno-venous system. At the same time a very important extraction of carbon dioxide is carried out, which results in the correction of the arterial pH, where endogenous or exogenous catecholamines are effective. Hence the term "extracorporeal membrane oxygenation" (ECMO) is perfectly applicable. ECMO has some historical indications, particularly in massive petroleum hydrocarbon intakes, especially in children[8] and the inhalation of smoke from fires[12].

In our experience, there are two additional indications of veno-venous ECMO: bronchoaspiratory pneumonitis of toxic coma that is the cause of a very severe adult respiratory syndrome and refractory to recruitment and supine manoeuvres, and respiratory distress in the context of intoxication by membrane stabilizing drugs or by calcium inhibitors. In both cases, there is severe delayed-onset IRA, between 36 and 48 hours after major cardiac events. In these circumstances, it is possible to consider passing from an arteriovenous ECMO for early cardiac care to a venous ECMO in the secondary phase of intoxication, based on the predominant respiratory distress and the harmful role of retrograde arterial flow of the femoro-femoral arteriovenous circulatory assistance, which considerably increases left ventricular afterload, which adds a factor of hemodynamic pulmonary edema in an existing context of pulmonary edema lesion.

Harlequin syndrome due to coping with debits, the patient's own and the one provided by the pump, is observed in the course of the above-mentioned intoxications. It is in this context that the possible passage from an arteriovenous to a veno-venous assistance is discussed, if the restoration of the systolic function allows it, by decreasing the afterload of the left ventricle, especially in cases of prolonged myocardial stunning.

In the second mode of circulatory assistance, with arterial and venous cannulas, this is fundamentally cardio-circulatory assistance, but in which the flow of blood from the right heart to the left heart or, more accurately, the right heart that replaces the left heart, needs the use of a gas exchanger. However, the fundamental parameter assured is hemodynamic, in the form of BP and cardiac output. In these indications, we find a technique where the term ECLS insists on the aspect of support for insufficient cardiac function.

The two major conditions that could benefit from ECLS are cardiogenic shock and heart arrest refractory to conventional treatments and optimized according to current recommendations. In acute intoxications, ECLS will ensure recovery of lung function and cardiac function. It should be noted that the habitual evolution of the intoxicated patient towards total recovery of the cardiac function largely explains the success of this circulatory assistance in some toxicological indications.

A new indication that we have just discovered refers to intoxications in which an antidote exists, but is not available; in these cases, it is possible to propose ECLS as a bridge to the antidote, an aspect that will be discussed later. On the contrary, the option of the bridge to transplantation has never been proposed in acute poisonings treated by our group.

Toxicological indications of ECLS

Table 2 shows the results of a review of the literature, and indicates the toxicants that have been re-

Table 2. Intoxications in which extracorporeal circulatory assistance has been described in the medical literature[8]

Toxic agent	Number of cases	Toxic agent	Number of cases
Acebutolol	7	Fluoxetine	1
Aconitine	1	Phosphine	1
Amiodarone	1	Unspecified hydrocarbon	1
Amlodipine	1	Ibuprofen	1
Tricyclic antidepressants		Imipramine	1
(Others)	2	Lidocaine	1
Arsenic	1	Mepivacaine	1
Atenolol	1	Meprobamate	6
Betaxolol	3	Methadone	2
Bupropion	1	Metoprolol	1
Carbamazepine	1	Carbon monoxide	1
Cibenzoline	2	Paracetamol	1
Citalopram	1	Paraquat	2
Clomipramine	1	Paroxetine	2
Chloroquine/ Hydroxychloroquine	5	Pyrilamine	1
Zinc Chloride	1	Prajmalin	1
Cocaine	1	Propafenone	2
Colchicine	1	Propranolol	9
Radiographic Contrast	1	Quetiapine	1
Desipramine	1	Quinidine	2
Dextropropoxyphene	2	Sotalol	3
Diphenhydramine	1	Taxus	1
Diltiazem	1	UTIHA*	1
Disopyramide	4	Tramadol	3
Fenitrotion/Malathion	1	Venlafaxine	1
Fentanyl (patch)	1	Verapamil	10
Flecainide	4	Zotepine	1

*Unspecified toxicant in heart arrest.

ported up to 2013, which have benefited from peripheral circulatory assistance. Apart from hydrocarbon poisoning, where insufficiency is exclusively pulmonary and requires veno-venous assistance, the vast majority of the other assistances cited in this table are arteriovenous[8]. The list is not closed, since the cardiotoxicity of the drugs is often discovered at the time of massive overdose. ECLS is an exceptional technique in relation to the frequency of presentation of intoxications.

As shown in Table 1, digoxin does not appear despite the fact that in 1998 a case of massive intoxication was reported to be unsuccessfully treated with peripheral circulatory assistance and administration of Fab fragments of anti-digoxin antibodies[18]. Our group recently treated a 20 mg digoxin intoxication, in which ECLS was started as soon as heart arrest occurred, allowing equimolar neutralization of antibodies administered during treatment with ECLS according to the protocol of Schaumann[19], i.e. half the dose of antibodies perfused for one hour, followed by a continuous infusion over 6 hours. This protocol results in a larger fraction of Fab fragments deleted in the urine and bound to digoxin, reducing the amount of free Fab unnecessarily removed by urine. It was found that the patient had an electromechanical dissociation during treatment with ECLS. Finally, at 7 hours after infusion of anti-digoxin antibodies, a difference appeared between systolic and diastolic pressures.

This observation suggests that ECLS may also be a means of bridging to the antidote, allowing the physician facing severe intoxication to have more time to obtain the antidote and to administer it optimally.

Results of ECLS in the course of acute poisoning

The first series in the medical literature was published by the Caen Hospital surgeons, who reported on 6 patients with a mean age of 34 years (range 17-55 years) who on admission presented heart arrest as a result of massive dose intoxication[13]. The first two patients died in a context of multiorgan failure related to delayed care. The other four survived without sequels. The mean duration of ECMO was 59.25 (SD: 2 h) (range 48-71 h). Table 3 indicates the substances supposedly ingested by these 6 patients[13].

These first results were confirmed by a study in our department, with ten consecutive patients who presented severe intoxication by cardiotropic drugs with membrane stabilizing effect, treated with early ECLS and whose indication was performed according to the algorithm described in Figure 1. Table 4 shows the demographic characteristics and circumstances of the acute intoxication of these ten patients, as well as the drugs and doses responsible for the state of shock, to emphasize the massive nature of the doses supposedly ingested.

A mass dose should alert us to the possible indication of ECLS, although this factor is not the only one to be taken into account for its application to the patient. Table 5 shows the severity of the hemodynamic status at the time of ECLS activation. It should be emphasized that this was indicated when the adrenaline dose reached 3 mg / h, which was progressively increased up to 10 mg / h at the start of ECLS, demonstrating the refractory nature and irreversible aggravation of the patient who was under pharmacological treatment. The 10 patients had a very serious cardio-circulatory state and two of them were cannulated when in refractory heart arrest. There was an alteration of the level of consciousness and a widening of the QRS complexes, which testifies to the membrane stabilizing effect on the one hand and the low cerebral blood flow on the other. Despite the severity of these intoxicated patients, evolution was favourable in 7 patients (Table 6).

From the statistical point of view, the survival threshold for asserting the efficacy of ECLS was equal to or greater than 40%, while the theoretical survival rate expected from the intoxicated condition was less than 10%. From this study carried out in these 10 patients, it was possible to conclude that ECLS was effective in treating refractory shock states. It is important to note that all these patients had one or more complications directly related to ECLS, of which the most frequent was early bleeding at the site of vascular access, thus showing the need for collaboration with cardiac surgeons. Another contribution of these cases with refractory heart arrest that were treated with ECLS is that their survival rate was 10%, significantly higher than that ob-

Table 3. Suspected toxicants in 6 cases of heart arrest treated with extracorporeal circulatory assistance in the Caen series[13]

Age	Medications
40	Sotalol (4.8 g), isoptine (7.2 g calcium antagonist)
36	Disopyramide (10 g), meprobamate (10 mg)
18	Acebutolol (10 g), aspirin (15 g), meprobamate (4 g)
37	Fluoxetine, escitalopram, zolpidem (4 g)
17	Propranolol (4 g), betaxolol (6.8 g), isoptine (1.2 g)
22	Acebutolol (8 g), meprobamato (5 g)

served in refractory heart arrest due to non-toxic causes, which is equal to or less than 2%[16].

A retrospective comparative study performed in two centres, Hospital de Lille (which does not have circulatory assistance) and the Caen Hospital (which does), has shown a significant improvement in the overall survival of severe cardiotropic intoxications due to circulatory assistance[11]. This study was carried out in 62 patients in severe cardiogenic shock of toxic origin, of whom 14 benefited from circulatory assistance and 48 from conventional treatment. The survival rate was 86% with circulatory assistance (12 of the 14 cases), while with the conventional treatment the survival rate was 48% (23 out of 48 cases), a statistically significant difference ($p < 0.02$). It should also be noted that the survival of heart arrest patients in the absence of circulatory assistance was 0% in Lille, while the survival rate of toxic refractory heart arrest in Caen was 100%. These results confirm the extraordinary effectiveness of circulatory assistance in two types of cardiotropic poisoning: on the one hand, membrane stabilization poisonings (survival rate in Caen of 100% and in Lille of 30%) and, on the other hand, poisonings by beta-blocker (survival in Caen was 90% and in Lille 40%).

Our experience, acquired over 10 years with the application of ECLS in cardiotropic drug poisoning, has reached 112 cases. It should be noted that 71 of them (63%) had refractory heart arrest at the time of the indication of ECLS (Table 7). The place where this arrest occurred was out of hospital in 45 cases (63% of all heart arrests) and in hospital in 26 cases (37%). A retrospective analysis of these data suggests a very late indication of ECLS. Our results are in addition to the known ones of beta-blocker intoxications, where about 40% suffer heart arrest after hospitalization, thus showing the need for very close monitoring of cardiotropic intoxication[20].

Regarding the time interval between cardiorespiratory arrest and ECLS start-up, it was possible to accurately measure this in 36 patients, with the mean of 145 ± 50 min (median 136 min, range 59-381 min). It should be noted that these intervals are particularly prolonged. In fact, circulatory assistance was performed in an average of 100 min after heart arrest. There is no doubt that these intervals could be improved with an awareness of the potential severity of heart arrest of toxic origin, which in the medical literature is often considered to have a "good prognosis". This prognostic concept related to toxic heart arrests deserves to be

Table 4. Demographic and toxicological description of 10 patients treated with extracorporeal circulatory assistance

Sex	
Female	8/10
Men	2/10
Age (median and rank)	42 years (18-50)
History of depression	10/10
History of attempted suicide	6/10
Intake-intake interval (median and range)	5.5 hours (2-27)
Type of medication and dose	
Acebutolol	34 g delayed release
Acebutolol	4 g
Carbamazepine	332 g delayed release
Cybenzoline	3.9 g
Chloroquine	10 g
Chloroquine	9 g
Disopyramide	6 g
Propafenone	9 g
Propranolol	2.24 g
Propranolol	2 g delayed release

reviewed in the light of the results presented, since they may lead to delay in the implementation of circulatory assistance and, consequently, the results considerably altered.

The duration of ECLS start-up in the resuscitation service, i.e. outside the cardio-surgical environment, could be accurately determined in 36 patients. The mean duration of placement was 48 minutes (SD: 26 min, median 41 min, range 13-175 min). The ICU discharge survival rate for out-of-hospital heart arrest was 11% (5 out of 45 cases), while the in-hospital survival rate was only 14% (3 of 26 cases). These results are surprising, since in the hospitalized patient with shorter delays in specialized care, a better prognosis was expected. All this suggests, once again, an underestimation of heart arrest of toxic origin.

Unfavourable evolution to death occurs in two different ways: on the one hand, a capillary leak, which results in the need for continuous and ineffective vascular filling, which leads to deformation of the patient's body image with significant weight gain and, on the other hand, multiorgan failure. Very few patients develop post-anoxic encephalic death, since the function of the different organs had been well preserved and the initial alterations related to heart arrest were corrected during the ECLS period. Of the 4 patients with brain death, organ transplantation was performed in 3 patients, representing 4% of out-of-hospital refractory heart arrest (3 of 45 cases) and 4% of in-hospital refractory heart arrest (1 of 26 cases).

Refractory cardiogenic shock of toxic origin, preceded or not by transient heart arrest, has been the indication of ECLS in 41 cases during this 10-year period, which means that 37% of intoxicated patients have benefited from this technique (Table 8). Surprisingly, refractory cardiogenic shock occurred in only 3 of the 41 cases treated extra-hospital (7%) and in 38 of the 41 hospital cases (93%). Therefore, the delay in the refractory presentation of cardiogenic shock should be underlined, as opposed to heart arrest, since this has been observed essentially in 60% of cases in prehospital care,

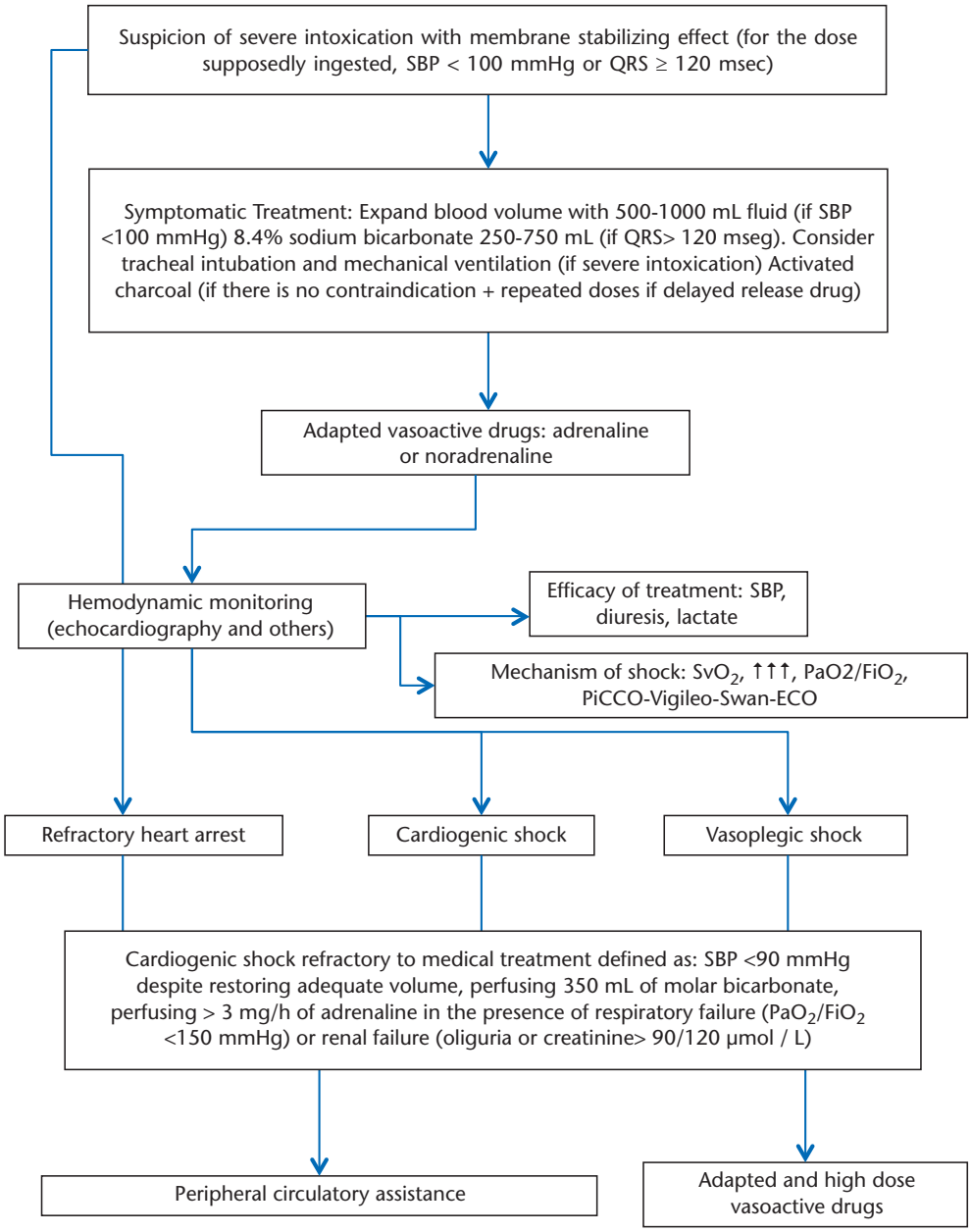

Figure 1. Indication for extracorporeal life support after ingestion of drugs with membrane stabilizing effect, treated using this algorithm.

Table 5. Hemodynamic, electrocardiographic and neurological status at the time of extracorporeal circulatory assistance (n = 10)

Systolic blood pressure (mean and range)	60 mmHg (0-113)
Heart rate (mean and range)	45 min (0-135)
Level of consciousness assessed by the Glasgow scale (average and rank)	4 points (3-15)
QRS amplitude (mean and range)	150 msec (110-250)
ECG	
Persistent asystole	2/10
Ventricular fibrillation	3/10
Aortic-ventricular block	4/10
Brugada ECG	2/10

Table 6. Evolution of 10 patients intoxicated with membrane stabilizing drugs and treated with extracorporeal circulatory assistance

Discharge without neurological sequelae	7/10 (at 28 days of admission)
Brain death	2/10 (in both cases, cardiorespiratory arrest prior to initiation of treatment)
Septic shock death	1/10 (at 14 days of admission)
Complications	4/10 major bleeding 1/10 extensive thrombosis 1/10 lymphedema 8/10 nosocomial infection 2/10 laryngeal edema

Table 7. Frequency, place of care and prognosis of refractory heart arrest during 112 severe intoxications treated with peripheral circulatory assistance

Place	Survival rate at discharge from intensive care unit
Refractory cardiorespiratory arrest (n = 71)	
Out-of-hospital (n = 45.63%)	5/45 (11%)
Intra-hospital (n = 26.37%)	3/26 (14%)
Organ donation for transplantation (n = 4))	
Out of hospital (n = 3.7%)	Not applicable
In hospital (n = 1.4%)	Not applicable

Table 8. Frequency, place of care and prognosis of refractory cardiogenic shock in the course of 112 severe intoxications treated with peripheral circulatory assistance

Place	Survival rate at discharge from intensive care unit
Refractory cardiogenic shock (n = 41), preceded or not by a recovered heart arrest	
Out of hospital (n = 3. 7%)	3/3 (100%)
In hospital (n = 38.97%)	18/38 (47%)

while in the case of cardiogenic shock, this was present in only 7% of the cases in the prehospital environment. These results show, once again, the need for very close monitoring of all cardiotropic substance intoxications.

In contrast to the bleak prognosis of refractory heart arrest of toxic origin, the survival rate at ICU discharge of patients with refractory cardiogenic shock has been markedly improved by ECLS. This survival rate was 100% (3 out of 3 cases) for refractory cardiogenic shock in the outpatient setting, whereas it was 47% (18 out of 38 patients) in the hospital setting. These results underscore the dramatic efficacy of circulatory care in refractory cardiogenic shock of toxic origin.

Table 9 shows that the impact of ECLS on survival depends greatly on the type of drug involved. Medications seen in the table generated at least three serious poisonings requiring ECLS in this 10-year period. We did not think it appropriate to present the survival rates for drugs in which there was only one case of intoxication. The efficacy of circulatory assistance is particularly high in β-blocker poisonings and in particular with propranolol and acebutolol, where the survival rate reached 55%. Circulatory assistance is also very effective in poisoning by antiarrhythmic membrane stabilizing drugs, most notably flecainide, cibenzoline, propafenone and disopyramide. A survival rate of 30-60% is usually observed in these severe intoxications, which are the cause of refractory cardiogenic shock, with or without transient heart arrest.

But one cause of repeated failure has been and is chloroquine. In Paris, chloroquine poisoning has been the main toxicological indication during the study period, but unfortunately the rate of survival has been only 10%, specifically 2 of the 19 patients. The recent restriction on access to packs of 10 g of chloroquine has caused the number of intoxications by this product to fall. Therefore, ECLS cannot be considered to have resolved the cardio-circulatory problem induced by severe chloroquine poisoning, but this is not a reason to reject the indication of ECLS in severe chloroquine intoxication, but is an additional reason to indicate ECLS with maximum precocity. This failure probably is due to two factors: on the one hand, the frequency and severity of initial heart arrest induced by chloroquine and, on the other hand, the multiorgan involvement induced by this toxicant, particularly evident at the cardiocirculatory level, but which could underestimate the involvement in other organs, as evidenced by the hyperlactacidemia that we observed, even though the hemodynamic state was preserved, thus demonstrating diffuse tissue affectation unrelated to hemodynamic alteration.

Likewise, in the case of verapamil poisonings, despite the use of ECLS, the survival rate is only 14%. The retrospective analysis of our results suggests the mechanisms that could explain the failure of this technique in this indication. In fact, the initial phase of verapamil intoxication induces a decrease in contractility and disturbances of the rhythm and sinoatrial and ventricular atrial conduction, which are associated with important arterial vasoplegia. ECLS can only respond to the cardiogenic part of the intoxication, but not to the arterial vascular toxic effects. The evolutionary profile to death of verapamil intoxicated patients undergoing treatment with ECLS demonstrates that this technique allows a very high cardiac output to be obtained at the same time as keeping diastolic BP very low, always below 40 mmHg and even below 30 mmHg. In fact, these patients may develop systolic hypertension during treatment with ECLS and noradrenaline, but this drug is unable to correct arterial vasoplegia. In our opinion, verapamil induces a phase of cardiogenic shock followed by a phase that could be described as "diastolic shock" which cannot be treated with ECLS and noradrenaline at high doses, and in which a high cardiac output does not prevent eventual multiorgan failure.

We have attempted to understand why the pharmacological treatment of refractory cardiogenic shock, consisting essentially of optimization of vascular filling and administration of catecholamines which have not only a β-mimetic but also α-mimetic effect, could have A deleterious effect. The answer, we believe, has come from the observation, during a period of 4 years, of 5 cases of severe cardiotropic poisoning that presented mesenteric ischemia. At the same time, 17 patients had been hospitalized with a suspicion on admission of mesenteric infarction, in the absence of any toxicological insult. The population of the group with primitive mesenteric infarction was significantly older than those of the intoxicated group and had vascular risk factors, which were absent in the intoxication group. Mesenteric infarction was the cause of admission in the first group, while signs suggestive of infarction appeared delayed in the second group, some 48 h after admission (percentile 25-75: 36-60 h). Toxicants included calcium antagonists, beta blockers, dextropropoxyphene, cyclic antidepressants and hydroxyzine. The median dose of catecholamines in the

Table 9. Survival rate of intoxicated patients with circulatory insufficiency and those treated with extracorporeal assistance, depending on the type of toxicant

Toxicant (n)	Survival rate
Cybenzyl (3)	66%
Propranolol (9)	55%
Acebutolol (9)	55%
Flecainide (7)	28%
Verapamil (7)	14%
Chloroquine (19)	10%
Venlafaxine (5)	0%
Colchicine (4)	0%
Meprobamate (3)	0%
Ciamemazine (3)	0%
Cocaine (3)	0%
Clomipramine (3)	0%

intoxication group was 15.5 (4.5-30) mg / h for norepinephrine and 6 (4.9-6.3) mg / h for adrenaline. The length of the resected intestine was also different, with a mean of 90 cm in the intoxicated group (range 36-227 cm) versus 375 cm (range 66-500 cm) in the group with primary mesenteric infarction, which was a very significant difference, as was the location: in the group of intoxications, ischemia was only ileal in 20% of cases, while in the remaining 80% it was mainly jejunal; by contrast, 100% of the primary mesenteric infarcts had ileal ischemia. Regarding mortality, this was 90% in the group with primary mesenteric infarction and 20% in the intoxicated group. In the latter, there was a close correlation between the extent of the resected intestine and the cumulative amount of catecholamines administered. These results suggest that the prolonged administration of high doses of vasoconstrictor catecholamines allows one to maintain macro-circulation at the price of a serious alteration of the microcirculation, particularly in the intestine, leading to ischemia that allows bacterial translocation and the onset of multiorgan failure. The early start-up of ECLS allows the catecholamine administration to be significantly reduced, even stopped, thus avoiding the establishment of a vicious circle.

Complications of ECLS in the course of cardiotropic poisoning

A review of the literature showed that all local and general ECLS complications observed in our department had already been described in the context of ECLS for intoxication in other cases[8]. High prevalence of early bleeding at the place of cannulation placement should be noted.

From toxicological indications to cardiological indications

The success of the ECLS comes from the demonstration that during these 10 years, although the initial indication was cardiogenic shock and toxic heart arrest, very quickly cardiology became a demander of this type of assistance for cardiogenic shock due to cardiac disease, especially in the acute phase of myocardial damage. This has resulted in 10 years (2002-2012) of practical experience with ECLS, in which we performed a total of 332 arteriovenous and venous-venous circulatory assists. But a toxic cause as the source of acute heart failure has only been the reason for the indication in 112 cases, that is, 34% of all circulatory assistance made during these 10 years in our department. In other words, two-thirds of the circulatory assistance has been performed for cardiological reasons, and in this case, the problems of circulatory assistance are much more complex than in the case of intoxications.

We would like to mention one fact in the history of medicine, clinical toxicology and intensive care. In fact, since its inception, clinical toxicology has benefited more from the principles of medicine and intensive medicine than vice-versa. But clinical toxicology has also been able to make its own contribution to intensive care medicine in two respects: first, intoxications are a common cause of organ failure, often reversible, as far as drugs are concerned; and, second, there are antidotes that facilitate and even make supportive treatment unnecessary, being the only treatment that guarantees success, as with N-acetylcysteine in paracetamol intoxication. But with the advent of arteriovenous ECLS in cardiotropic poisonings, clinical toxicology has been the medium in which this mode of care has been developed and extended to acute non-toxic heart failure in a setting outside the cardiac surgery operating room.

Conclusions

ECLS, implemented in an environment outside cardiac surgery, is feasible. Close collaboration between the medical and surgical departments is a prerequisite for the success of the project, since even if a trained doctor can implement ECLS, only a surgeon will be able to solve the complications.

ECLS should be integrated in the treatment of severe poisoning by cardiotoxic drugs. But circulatory assistance only represents the treatment of the cardiogenic part of the shock and absolutely not of the vasoplegic part.

Two classes of drugs can benefit from ECLS: on the one hand, Vaughan-Williams class I antiarrhythmics with membrane stabilizing effect and, on the other hand, β-blockers. The early initiation of ECLS is a prognostic factor of great importance in cardiogenic shock and even more in refractory heart arrest, where every minute lost significantly aggravates the prognosis.

Heart arrest may occur in the course of psychotropic poisoning and this group of drugs may also have cardiac toxicity. But ECLS should be indicated only when cardiac failure is of cardiotoxic origin and not the result of cerebral anoxia.

Awareness of the severity of heart arrest of toxic origin should lead to shortening the times of indication and placement of ECLS.

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Conflicting interests

The authors declare no conflict of interest in relation to this article.

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