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Emergency feasibility in medical intensive care unit of extracorporeal life support for refractory cardiac arrest

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Abstract *Objective:* To report the feasibility, complications, and outcomes of emergency extracorporeal life support (ECLS) in refractory cardiac arrests in medical intensive care unit (ICU). *Design and setting:* Prospective cohort study in the medical ICU in a university hospital in collaboration with the cardiosurgical team of a neighboring hospital. *Patients:* Seventeen patients (poisonings: 12/17) admitted over a 2-year period for cardiac arrest unresponsive to cardiopulmonary resuscitation (CPR) and advanced cardiac life support, without return of spontaneous circulation. *Interventions:* ECLS femoral implantation under continuous cardiac massage, using a centrifugal pump connected to a hollow-fiber membrane oxygenator. *Measurements and results:* Stable ECLS was achieved in 14 of 17 patients. Early complications included massive transfusions ($n = 8$) and the need for surgical revision at the cannulation site for bleeding ($n = 1$). Four patients (24%) survived at medical ICU discharge. Deaths resulted from multiorgan failure ($n = 8$), thoracic

bleeding ($n = 2$), severe sepsis ($n = 2$), and brain death ($n = 1$). Massive hemorrhagic pulmonary edema during CPR ($n = 5$) and major capillary leak syndrome ($n = 6$) were observed. Three cardiotoxic-poisoned patients (18%, CPR duration: 30, 100, and 180 min) were alive at 1-year follow-up without sequelae. Two of these patients survived despite elevated plasma lactate concentrations before cannulation (39.0 and 20.0 mmol/l). ECLS was associated with a significantly lower ICU mortality rate than that expected from the Simplified Acute Physiology Score II (91.9%) and lower than the maximum Sequential Organ Failure Assessment score (> 90%). *Conclusions:* Emergency ECLS is feasible in medical ICU and should be considered as a resuscitative tool for selected patients suffering from refractory cardiac arrest.

Keywords Cardiac arrest · Cardiopulmonary resuscitation · Extracorporeal life support · Feasibility · Poisoning · Medical intensive care unit

Introduction

Cardiac arrest is a major worldwide public health concern [1]. Survival rate remains very low despite early access to emergency medical care, cardiopulmonary resuscitation (CPR), defibrillation, and advanced cardiac life support (ACLS). Extracorporeal life support (ECLS) is a well-recognized cardiac support technique in a growing number of primary cardiomyopathies and postoperative cardiac surgical cases [2]. Recently ECLS has been proposed as an ultimate rescue in prolonged cardiac arrest with failing conventional CPR [3, 4, 5]. However, the majority of out-of-hospital cardiac arrest victims are referred to intensive care units (ICUs) located

in hospitals lacking a cardiothoracic surgery department, thus prohibiting ECLS initiation in combination with CPR. To date no alternative to prolonged CPR is routinely available. Failure to obtain spontaneous circulation with continuous external cardiac massage, even with stumpers, results in death. Our aim was to assess the feasibility of emergency ECLS as an implementation technique of pre- and intrahospital ACLS in the medical ICU. We report here our experience regarding possible indications, complications and outcome of ECLS as rescue therapy in patients with refractory cardiac arrest.

Materials and methods

Our medical and toxicological ICU is located in a university hospital (Hôpital Lariboisière) which has the largest emergency department in the Paris area but does not have a cardiovascular surgery department. Each year about 950 patients are admitted to our ICU, including 450 acute poisonings and 90 cardiac arrests. Thus, following the report of Massetti et al. [6] and Babatasi et al. [7], we requested the Comité d'Evaluation et de Diffusion des Innovations Technlogiques (CEDIT), an international and independent agency examining new health technology, to assess the value of ECLS in acute cardiotoxic poisonings. The CEDIT acknowledged that ECLS should be considered as the only alternative therapy in some poisoning cases, including refractory cardiac arrests and failures (http://cedit.aphp.fr/servlet/siteCeditGB?Destination=reco&numArticle=03.03/Re1/04). Thus based on the CEDIT recommendations and in order to offer optimal treatments to patients suffering from cardiac arrest, we have decided to develop ECLS technique in our ICU.

Patients whose conditions required continuous CPR over at least 45 min but in whom spontaneous circulation did not return because of refractory cardiac arrest were considered candidates for ECLS support. We specifically trained our medical team and nurses to perform ECLS. In addition, we collaborated with the cardiothoracic surgery department of a neighboring hospital (Hôpital Pitié Salpétrière) to obtain a consultant list of surgeons and perfusionists. When the decision to implant an ECLS in a cardiac arrest victim admitted to our ICU was taken by a senior intensivist of our team, a senior cardiac surgeon and a perfusionist from the neighboring hospital were immediately informed and came to our ICU as soon as possible, using a devoted ambulance.

Cannulation technique

ECLS was set up using the portable centrifugal pump (Rotaflow, Jostra-Maquet, Orléans, France) with a hollow-fiber membrane oxygenator (Quadrox) and a modified circuit (BEHQV 50600) suitable for use in ICU. The entire ECLS system and all instruments for vascular approach were put on mobile carts to facilitate their transportation. Whenever a call for ECLS was received, the circuit was quickly primed with normal saline. Peripheral femorofemoral cannulation was surgically set up by a team including a senior cardiac surgeon and a senior intensivist, as previously described using a modified Seldinger technique [3]. An additional distal limb perfusion was inserted to avoid severe leg ischemia. We used femoral 15- to 17-F arterial and 23- to 29-F venous Jostra cannulas according to the patient's size and 7-F catheters for distal limb perfusion. The tip of the arterial cannula was estimated to reside at the aortic-illiac junction, whereas the tip of the venous cannula was set in the right atrium. Pump flow was initially set at 3–4 l/min. Fluid repletion, norepinephrine, and epinephrine were used to treat cardiovascular shock aiming at obtaining a mean blood pressure of at least 60 mmHg. Venous cannula position was confirmed by echocardiography during the procedure while under CPR and confirmed radiologically when a stable ECLS flow was achieved.

Patient management during ECLS in ICU

ECLS was handled by our trained ICU personnel. Extracorporeal blood flow was adjusted to maintain adequate systemic blood flow and oxygen supply as monitored by mean arterial pressure, urine output, and plasma lactate concentrations. The doses of inotropic agents used before ECLS were progressively tapered following ECLS setup. Arterial pressure tracing was strictly monitored for reappearing pulsatile systemic blood flow, indicating residual left ventricular myocardial contractility facilitating left ventricular drainage. Dobutamine (10 µg/kg per minute) was infused to facilitate left ventricular decompression, minimizing the risks of pulmonary and left ventricle blood stasis as well as intracardiac clotting. In addition, a cardiac surgeon and a perfusionist were on call for management of emergencies that could not be handled by ICU personnel.

Blood samples were sent each 2 h to the laboratory for anticoagulation monitoring. Heparin was infused as early as possible to maintain a target activated clotting time 2.0–2.5 times higher than control at full flow. Because our patients were in critical condition and were expected to have severe impairment of coagulation, no intravenous heparin bolus was provided before cannulation. Patients were mechanically ventilated with 5–6 ml/kg tidal volume and 10 cmH$_2$O positive end-expiratory pressure. The lowest possible fraction of inspired oxygen was used and guided by pulse oxymetry and radial arterial blood gas determination. Mild hypothermia was maintained during the first 24 h using a heater-cooler unit (Jostra-Maquet). Following the cannulation no further sedation was continued unless the patients showed signs of awakening. Echocardiography was used twice daily

to assess venous cannula position, to exclude significant aortic regurgitation, and to assess progressive recovery of myocardial contractility. Serial routine biological tests and electrocardiogram (ECG) findings were daily checked. Neurological status was assessed using serial electroencephalograms during ECLS while the patient remained unresponsive.

The decision to discontinue ECLS support was based upon evidence of multiorgan failure, overwhelming sepsis, or severe neurological injury. The prerequisites to wean from ECLS were echocardiography assessment of my-ocardial function (left ventricular ejection fraction > 50%) and a radial PaO_2/FIO_2 ratio greater than 150 mmHg. The pump flow was tapered, given a clotting time more than 2.5 times higher than a control, to check for the absence of any deterioration in hemodynamic status. If the patient's cardiovascular status remained stable, ECLS was withdrawn by cardiac surgeons. If irreversible damage in myocardium function was diagnosed, the patient was transferred under ECLS, accompanied by the attending physician, a cardiac surgeon, and a perfusionist to the cardiosurgical ward of the neighboring hospital, to be considered for a ventricular assist device.

Patient selection and measurements

Between July 2003 to July 2005 we prospectively collected data on all 17 patients referred to our medical ICU with a witnessed prolonged out-of-hospital or intrahospital cardiac arrest treated with ECLS (12 women, 5 men; median age 47 years, range 27–57. All included patients had a pre-sumed or identified heart-related cause of cardiac arrest (Fig. 1). Cardiac arrest occurred either out of the hospital ($n = 9$), including at home ($n = 5$), in the ambulance ($n = 2$), on the street ($n = 1$), and in a public place ($n = 1$), or in our hospital ($n = 8$), including in the emergency room ($n = 2$), the labor room ($n = 1$), and a medical ward ($n = 5$). Toxic causes of cardiac arrest ($n = 12$) included acute acebutolol ($n = 3$), flecainide ($n = 2$), chloroquine ($n = 2$), verapamil ($n = 2$), propranolol ($n = 1$), dextropropoxyphen ($n = 1$), and colchicine ($n = 1$) poisonings. Nontoxic causes included pulmonary embolism ($n = 3$), cardiomyopathy-related ventricular arrhythmia ($n = 1$), and amniotic embolism ($n = 1$). ECG showed persistent asystole ($n = 13$) or electromechanical dissociation with enlarged ventricular complexes ($n = 4$). Massive pulmonary edema ($n = 5$) occurred during CPR. Before connection to ECLS median arterial pH was 7.15 (10–90 percentiles 6.92–7.49), PaO_2/FIO_2 ratio 259 mmHg (51–516), $PaCO_2$ 38 mmHg (25–70), serum bicarbonate concentration 17.0 mmol/l (7.2–31.8), plasma lactate concentration 17.6 mmol/l (6.4–39.0), and serum creatinine concentration 128 μmol/l (86–339). The initial admission coagulation profile was the following: prothrombin time 36% (10–59%, expressed as a percentage of normal value), activated clotting time 2.0 (1.8–8.0) times higher than control, fibrinogen 1.70 g/l (0.50–2.47), and platelets 112 G/l (68–195).

Fig. 1 Outcome of cardiopulmonary resuscitation (*CPR*) refractory cardiac arrest victims who were admitted and treated with extracorporeal life support (*ECLS*) in a medical intensive care unit (*ICU*)
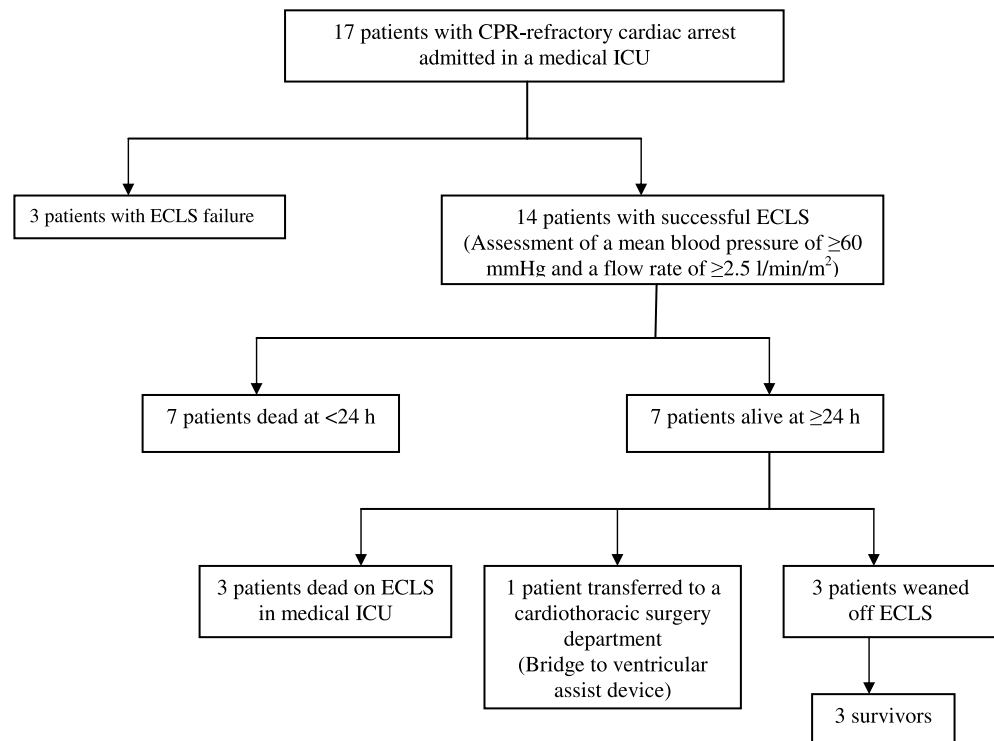
CPR and advanced life-support were performed according to the standard guidelines currently recommended [8, 9]. Regarding out-of-hospital arrest, CPR was initiated by either bystanders or first responders and then continued at the scene and during patient transportation to hospital by the emergency medical service personnel (mobile medical team, ambulance crews, or firefighters). Cardiac arrest was considered refractory if no return of spontaneous circulation was obtained within 45 min despite continuous cardiac massage. This study was conducted according to the principles established in Helsinki. The study was approved by our institutional investigation review board. When possible, verbal consent was obtained from next of kin, provided with information regarding the purposes and risks of ECLS procedure.

ECLS feasibility in ICU was assessed with respect to time from cardiac arrest to ECLS initiation and to the percentage of successful procedures. ECLS was considered as successful if a mean blood pressure of 60 mmHg or higher and a flow rate of at least 3 l/min were obtained. Patients were evaluated for survival and morbidities. Outcome was evaluated according to survival at 24 h, ICU discharge, and ultimately at 1-year follow-up after hospital discharge. ECLS-attributable complications were documented. Capillary leak syndrome was defined as a generalized edema with persistent hypovolemia despite repeated vascular repletion.

Results of routine blood tests (including plasma lactate level), ECG, and toxicological screening were collected on admission (out-of hospital patients) or at the time of cardiac arrest (in-hospital patients), before connection to ECLS. Physiological variables measured at admission were used to calculate the Simplified Acute Physiology Score (SAPS) II [10]. The maximum Sequential Organ Failure Assessment (SOFA) score was defined by the highest score achieved during the entire ICU stay [11]. At 1-year follow up the Glasgow-Pittsburgh Cerebral Performance Category (CPC) was determined for the survivors [12].

Statistical analysis

For data analysis the patient population was split into two groups according to the cause of cardiac arrest: acute cardiotropic poisonings ("toxic group") and other primary cardiac causes ("nontoxic group"). Results are presented as median and 10–90 percentiles. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables or Fisher's exact test for categorical variables. Significance level was set at $p \leq 0.05$. Statistical software (Statview, SAS, N.C., USA) was used for data analysis.

Results

Patients' median SAPS II was 79 (42–94), and maximum SOFA score 18.0 (17.0–20.0). CPR duration before ECLS initiation (120 min, 60–180) was prolonged, considering the delay needed for the cardiothoracic surgeon to arrive from the neighboring hospital to our ICU. Femoral arterial and venous cannulation was successful in all patients. Targeted extracorporeal flow was achieved in 14 of the 17 patients, with a duration of 40 h (3–154). Early complications included the need for surgical revision at the cannulation site for continuous bleeding ($n = 1$) and massive transfusions ($n = 8$, more than five packs in the first 24 h). Seven patients (41%) were alive at 24 h and 4 (24%) survived at ICU discharge. In our ICU deaths resulted from multiorgan failure ($n = 8$), catheter- and CPR-related thoracic bleeding ($n = 2$), severe sepsis ($n = 2$), and brain death ($n = 1$). A major capillary leak syndrome ($n = 6$) and a persistence of the hemorrhagic pulmonary edema ($n = 5$) were observed

Table 1 Comparison of extracorporeal life support (*ECLS*) management and outcome according to the cause of the refractory cardiac arrest (*SAPS II* Simplified Acute Physiology Score II, *SOFA* Sequential Organ Failure Assessment)

	Toxic cardiac arrest ($n = 12$)	Nontoxic cardiac arrest ($n = 5$)	p
Age (years)	49 (33–59)	29 (20–49)	0.02
SAPS II value on admission	79 (38–94)	83 (53–94)	0.9
Maximal SOFA score	18.5 (15.8–20.3)	18.0 (17.0–20.0)	0.9
Place of cardiac arrest occurrence (out-of vs. intrahospital)	8/4	1/4	0.1
Duration of continuous external cardiac massage (min)	120 (45–180)	135 (120–185)	0.2
Plasma lactate concentration (mmol/l)	17.3 (5.3–39.3)	22.5 (10.5–29.6)	0.8
Serum creatinine concentration (μmol/l)	141 (83–369)	128 (92–173)	0.6
PaO$_2$/FIO$_2$ ratio (mmHg)	271 (41–557)	76 (71–358)	0.3
ECLS success (%)	83	80	0.9
ECLS duration (h)	56 (5–108)	14 (5–129)	0.5
24-h survival (%)	50	20	0.3
Hospital discharge (%)	25	0	0.5

among the eight patients who died with multiorgan failure. In these patients ECLS termination was decided based on our conviction of irreversible signs of cellular damage, including probable brain death.

Among the four patients alive at medical ICU discharge the patient who suffered from severe cardiomyopathy, died in relation to hospital-acquired pneumonia 14 days after ECLS initiation and 2 days after her transfer under ECLS to the cardiothoracic surgery ward. Three poisoned patients (18%, out-of-hospital cardiac arrest, CPR duration 30, 100, and 180 min, respectively) were successfully weaned and left ICU at day 12, 13, and 14, respectively. The ingested toxicants [doses, plasma concentrations (therapeutic concentrations)] were flecainide [40 mg, 6.0 mg/l (0.2–0.6)] plus acebutolol [2 g, 1.8 mg/l (0.2–1.5)], acebutolol (40 g, 41.1 mg/l), and acebutolol (sustained-release preparation, 34 g, 40.2 mg/l), respectively. Two of the three survivors developed ventilator-acquired pneumonia successfully treated with antibiotics. No patient experienced limb ischemia. One survivor developed a scar infection. No significant technical incident occurred during ECLS, and no significant cannulation-related injuries of femoral vessels were reported. At 1-year follow-up, all three survivors were symptom-free, presenting no significant cardiac or neurological sequelae (CPC 1). ECLS was associated with a significantly lower ICU mortality rate than that expected from the resultant SAPS II (91.9%, $p = 0.02$) and lower than maximum SOFA score (> 90%).

Comparison of the "toxic" and "nontoxic" groups showed no significant differences except for the age (Table 1). The median CPR duration before ECLS was not significantly different according to survival at ICU discharge (110 min in the four survivors vs. 138 min in the 13 nonsurvivors, $p = 0.4$). Similarly, the median lactate level before ECLS initiation was not significantly different in relation to ICU survival (16.2 vs. 17.6 mmol/l, $p = 0.8$). Interestingly, the flecainide/acebutolol-poisoned patient survived with a very elevated plasma lactate concentration on presentation (39 mmol/l).

Discussion

Over a 2-year period 17 witnessed and CPR-refractory cardiac arrests were managed using ECLS in our ICU. We recorded a long-term survival of 18%. Our results clearly suggest that ECLS implementation using femoral cannulation is feasible in a medical ICU, with limited complications and hopeful results. The delay to ECLS implementation [120 min (60–180) median duration vs. 105 ± 44 min average time of cardiac massage] and the patient survival rate (3/17 vs. 8/40) were comparable with those previously reported [3]. However, the hemorrhagic risk of this invasive technique remains an important concern as it may offset ECLS potential benefits. In three of our patients massive transfusions were related to local or thoracic bleedings (cardiac massage and/or prehospital attempts to insert a venous catheter); in five others they resulted from hemorrhagic pulmonary edema, major capillary leaking syndrome, and venous congestion.

Experience with cardiopulmonary bypass during cardiac arrest remains limited with variable survival rates (0–64%) [3, 4, 6, 7, 13, 14, 15, 16, 17, 18]. Differences in outcome are related to the small number of patients, causes of cardiac arrest, variable delay until onset of circulatory support, and varying experience with this technique. In our series, in contrast to that of Massetti et al. [3], definitive survival was obtained only in poisonings. Cardiotoxic intoxication and severe hypothermia are the two accepted indications for ECLS in cardiac arrest [3, 4]. Our results clearly support that irreversibility of the underlying cardiac pathology and cerebral ischemic injury after prolonged CPR is a serious limitation for emergency ECLS.

Cardiotoxic poisoning-related death occurs in relation to sudden ventricular tachycardia or fibrillation as well as myocardial contractility incompetence [19]. In some cases return of spontaneous circulation may be achieved with CPR alone, suggesting a reversible pathophysiology [20]. However, massive drug ingestions may be associated with refractory cardiac failure, which reversibility makes ECLS promising despite prolonged arrest (grade C recommendation) [1, 3, 6, 7, 21]. In selected patients, cardiopulmonary bypass may be life-saving, provided that the patient has not sustained hypoxic cerebral damage due to prolonged no or low flow prior to its initiation. Once implemented, the purpose of ECLS is to take over heart function until recovery can occur, thus minimizing myocardial work, improving organ perfusion, and maintaining the renal and biliary elimination of the toxicant [22, 23, 24].

Long-term survival was shown to be possible after emergency ECLS in patients with underlying cardio-circulatory diseases amenable to immediate corrective intervention, such as angioplasty, surgery, and transplantation [4]. In patients experiencing myocardial infarction with either cardiac arrest or refractory shock ECLS afforded a better chance of survival [5]. Up to 50% survival rates have been obtained in patients resuscitated in the controlled environment of the catheter laboratory [25]. In our series no myocardial infarction was included. However, three patients suffered from pulmonary embolism with refractory cardiac arrest despite thrombolysis and one from amniotic fluid embolism. All cases were evidenced by necropsy. Mortality related to pulmonary embolism remains high [26]. Similarly, amniotic fluid embolism is associated with poor maternal and neonatal survival, when cardiac arrest occurs [27].

The decision to withhold resuscitation is generally based upon presumed prolonged anoxia, with existing advisory rules for termination [28, 29]. In the majority of victims transportation to emergency departments remains

inappropriate, futile, and ethically unacceptable [9]. However, in immediately resuscitated victims our results suggest the necessity of early medical recognition of potential reversible causes, such as poisoning, for a rapid transport with continuing CPR to ECLS-equipped hospitals. In these candidates for ECLS rescue the quality of prehospital CPR remains, as for all cardiac arrest victims [30], the critical step for neurological outcome.

Survival from cardiac arrest is critically related to the delay of initiation of basic and ACLS [31]. High lactate levels (> 16.3 mmol/l) were generally associated with unfavorable neurological recovery, with a 100% specificity [32]. However, based on our observations this value assessed to predict outcome appears questionable in immediately resuscitated poisoning-related cardiac arrest victims. In our series at least two poisoned patients with high lactate levels (20.0 and 39.0 mmol/l) completely recovered. Moreover, there were no significant differences in lactate concentration on admission according to survival. However, although a weak association between cardiac arrest duration and admission lactate levels has been shown [32], functional neurological recovery is more likely to be unfavorable with increasing concentrations. In a multivariate analysis lactate level at 48 h was an independent predictor for mortality and unfavorable neurological outcome [33]. In our two survivors ECLS allowed rapid decrease in lactate concentrations (2.2 and 3.2 mmol/l at 48 h, respectively).

Long delays to return of spontaneous circulation are compatible with good cognitive outcome, confirming that duration should not limit CPR efforts [34]. Good outcome-contributing factors include immediate and skilled basic and ACLS, ventricular fibrillation as the primary and persistent rhythm, age under 70 years, absence of previous medical diseases, and highly aggressive postresuscitation care [35]. However, although guidelines exist to avoid futile efforts [36], early criteria of no recovery despite ECLS and potential interest of the recently marketed CPR assist devices remain to be determined. Moreover, future research should evaluate ECLS to provide both systemic cooling and hemodynamic support in cardiac arrest.

Several limitations to this single center study exist. The number of patients remained insufficient to yield any persuasive statistically significant findings. Otherwise, due to the specificity of our center, there is a selection bias regarding the number of poisonings. Inclusion of various causes of cardiac arrest with various degrees of heart dysfunction reversibility also limits definitive comparisons. Moreover, decision to stop CPR and not to transport patients under cardiac massage to our ICU was independent of our team, making difficult any estimation of the proportion of refractory cardiac arrest victims that should have benefited from ECLS. Another limitation of ECLS performed in a medical ward would be its yearly incidence. The threshold bellow which ECLS practice would be of concern is unknown.

In conclusion, ECLS instituted in medical ICU in close collaboration with a cardiosurgical ward is feasible and effective for the hemodynamic resuscitation of ACLS-unresponsive cardiac arrest. Based on our experience, ECLS should be considered as an emergency resuscitative tool, providing the ability for rapid intervention of cardiac surgeon to control ECLS-related complications. Thus ECLS remains to date an investigational and compassionate treatment until further studies assess its efficiency in refractory cardiac arrest from nontoxic origin.

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