



HAL
open science

Survival and quality of life after extracorporeal life support for refractory cardiac arrest: A case series

Amedeo Anselmi, Erwan Flécher, Hervé Corbineau, Thierry Langanay, Vincent Le Bouquin, Marc Bedossa, Alain Leguerrier, Jean-Philippe Verhoye, Vito Giovanni Ruggieri

► To cite this version:

Amedeo Anselmi, Erwan Flécher, Hervé Corbineau, Thierry Langanay, Vincent Le Bouquin, et al.. Survival and quality of life after extracorporeal life support for refractory cardiac arrest: A case series. *Journal of Thoracic and Cardiovascular Surgery*, 2015, 150 (4), pp.947–954. 10.1016/j.jtcvs.2015.05.070 . hal-01260560

HAL Id: hal-01260560

<https://univ-rennes.hal.science/hal-01260560>

Submitted on 27 Jan 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Survival and Quality-of-Life after Extracorporeal Life Support for Refractory Cardiac Arrest: A Case Series

Amedeo ANSELM^{*§}, MD PhDs, Erwan FLECHER^{*§}, MD PhD, Hervé CORBINEAU^{*§}, MD, Thierry LANGANAY^{*§}, MD, Vincent LE BOUQUIN[¶], MD, Marc BEDOSSA[†], MD, Alain LEGUERRIER^{*§}, MD, Jean-Philippe VERHOYE^{*§}, MD PhD, Vito Giovanni RUGGIERI^{*§}, MD PhD

**Division of Thoracic, Cardiac and Vascular Surgery, Pontchaillou University Hospital, Rennes, France*

§INSERM (French National Institution for Healthcare and Medical Research) Unit 1099, University of Rennes 1

¶Division of Cardiac Anesthesia, Pontchaillou University Hospital, Rennes, France

†Division of Cardiology and Cardiac Intensive Care Unit, Pontchaillou University Hospital, Rennes, France

Corresponding Author:

Amedeo Anselmi, MD

Division of Thoracic, Cardiac and Vascular Surgery, Rennes University Hospital

2, rue Henri Le Guilloux

35 033 Rennes Cedex 9

Tel : (0033) 02 99 28 24 97 ; Fax : (0033) 02 99 28 24 96

email : amedeo.anselmi@alice.it

SOURCES OF FUNDING: None.

CONFLICTS OF INTEREST: No potential conflict of interest exists.

KEY WORDS: Extracorporeal Membrane Oxygenation; Resuscitation; Outcomes; Health policy

Abstract

Objectives. Extracorporeal Life Support (ECLS) is an emerging option to treat selected patients with cardiac arrest refractory to cardiopulmonary resuscitation (CPR). Our primary objective was to determine the mortality at 30 days and at hospital discharge among adult patients receiving veno-arterial ECLS for refractory cardiac arrest. Our secondary objectives were to determine the one-year survival and the health-related quality-of-life, and to examine factors associated with 30-days mortality.

Methods. In a retrospective, single-center investigation within a tertiary referral center, we analyzed the prospectively collected data of 49 patients rescued from refractory cardiac arrest through emergent implantation of ECLS (E-CPR) (18.1% of our overall ECLS activity 2005-2013). E-CPR was implanted in-hospital and during ongoing external cardiac massage in all cases. A prospective follow-up with administration of the SF-36 questionnaire was performed.

Results. Mean age was 47.6 ± 1.6 years, out-of-hospital cardiac arrest occurred in 12% of cases, average low-flow time was 47.2 ± 33 min; causes of cardiac arrest were heart disease (61.2%), trauma (14.3%), respiratory disease (4.1%), sepsis (2%) and miscellaneous (18.4%). Primary objective: rates of survival at E-CPR explantation and at 30 days were 42.9% and 36.7%; brain death occurred in 24.5% of cases. Secondary objectives: increased SAPS score, higher serum lactates and lower body temperature at the time of implantation were associated with 30-days mortality. Bridge to heart transplantation or implantation of long-term ventricular assist device was performed in 8.2%. There were no cases of mortality during the follow-up after discharge (36.7% survival; average follow-up was 15.6 ± 19.2 months). Average Physical and Mental Component Summary scores (SF-36 questionnaire) were 45.2 ± 6.8 and 48.3 ± 7.7 among survivors.

Conclusions. E-CPR is a viable treatment for selected patients with cardiac arrest refractory to CPR. In our series, about one third of rescued patients were alive at 6 months and presented quality-of-life scores comparable to those previously observed in patients treated with ECLS.

Central Message

E-CPR can achieve 36.7% survival at mid-term in selected patients with cardiac arrest refractory to cardiopulmonary resuscitation.

Perspective

Selection of patients is pivotal to achieve adequate results with E-CPR. Among survivors, quality-of-life at follow-up was comparable than previously obtained after ECLS therapy. A multidisciplinary debate is needed to establish evidence-based protocols and justified employment of ECLS. The diffusion of ECLS needs to take into account organizational, economic, ethical and learning curve issues.

Introduction

Extracorporeal Life Support (ECLS) therapy is an option for severe cardiac or cardiopulmonary failure. ECLS consists in an extracorporeal circulation circuit equipped with a rotary blood pump and a blood hollow-fiber oxygenator. There is cumulating evidence over the usefulness of ECLS in improving the survival of selected patients with cardiac arrest refractory to advanced cardiopulmonary resuscitation [1] (E-CPR). The survival at 30 days after ECLS implantation in such patients reportedly ranges between 24% and 36% [2, 3, 4]. Other series have reported survival rates up to 50%. Nonetheless, these studies are difficultly comparable to ours since they included also patients who received ECLS implantation not during cardiopulmonary resuscitation (CPR), or in-hospital cardiac arrest cases only [5]. Nonetheless, there are few evidence available over the clinical outcomes after hospital discharge of patients who survived refractory cardiac arrest and failed CPR thanks to ECLS therapy. This population consists of critically ill patients with major rates of severe in-hospital complications. Therefore, not only the vital status of these patients late after hospital discharge needs to be clarified, but also their quality of life. The latter information are lacking even from the analysis of major multicentre registries [6], despite they may be important in clinical decision-making and allocation of resources. Projected quality of life is evidenced in the recent European guidelines as one foremost aspect to be considered while evaluating the indication to ECLS in acute heart failure [6]. However, such judgment poses major difficulties among patients with refractory cardiogenic shock due to emergent presentation, frequent uncertainty of the extent of brain damage, and coexistence of comorbidities. The literature lacks specific information over this issue as well.

The purpose of the present investigation was twofold. The first objective was to clarify the mortality at 30 days and at hospital discharge in adult patients receiving veno-arterial

ECLS for refractory cardiac arrest (E-CPR). The secondary objective was to clarify the one-year survival and the perceived health-related quality-of-life in these patients, and to identify factors associated with 30-day mortality.

Patients and Methods

Patients' selection and technique of ECLS implantation.

Between January 2005 and October 2013, 270 patients received veno-arterial ECLS at our Institution. Of these, 49 (18.1%) were treated on an emergent basis for cardiac arrest refractory to conventional CPR. All the patients included in the present study received ECLS implantation during ongoing CPR. We excluded the patients who had ECLS in the immediate post-cardiotomy circumstances due to the impossibility to wean from cardiopulmonary bypass, and the patients receiving veno-venous ECLS for primary lung dysfunction. No patient received E-CPR out-of-hospital; nevertheless, some patients who suffered cardiac arrest out-of-hospital and received E-CPR within our center were included (N=6, 12%). The cases satisfying the above criteria were retrospectively selected from our database and served for subsequent analyses.

The indications to E-CPR were established in compliance with the current recommendations [6] by a multidisciplinary team including at least one surgeon and two physicians. We adopted the algorithm proposed by Combes and associates [7]. Briefly, E-CPR was contraindicated in case of no-flow time exceeding 5 minutes or unwitnessed cardiac arrest, in case of total expected duration of low-flow exceeding 100 minutes, in case of end-expiratory CO₂ concentration lower than 10 mmHg or of asystole on ECG. The indication to E-CPR was discussed also in perspective with the patient's known comorbidities and life expectancy. The notion of intoxication or hypothermia ($\leq 32^{\circ}\text{C}$)

represented an element in favor of the indication to E-CPR during enrollment of the present series. The implanting team included two surgeons (senior and resident), a scrub-nurse and a perfusionist. All material is available on a dedicated trailer, allowing full autonomy for prompt displacement of the team within the hospital facilities. Implantation of E-CPR was performed through longitudinal skin incision at the right groin and preparation of the anterior face of the common femoral artery and vein. The femoral vessels were neither encircled nor clamped. The percutaneous technique was never employed, in order to facilitate rapid institution of E-CPR and avoid the difficulties to appreciate pulses and backflow due to marginal hemodynamic conditions. Cannulation was performed using the Seldinger technique; arterial inflow was obtained through a 16 to 20 Fr cannula (Edwards Lifesciences Inc., Irvine, CA), and venous drainage was achieved with an 18 to 24 Fr cannula (Edwards Lifesciences Inc., Irvine, CA). In event of failed cannulation due to extensive arterial calcifications or impossibility to adequately advance the guidewires, the left groin was explored. Distal perfusion of the lower limb was assured through the superficial femoral artery using a 6-to-10 Fr cannula (Seldinger technique) connected to a side branch of the arterial inflow line. During ECLS therapy, heparin was administered through a central venous line in order to maintain an activated clotting time between 150 and 180s; in the presence of hemorrhagic complications, the dose of heparin was adjusted or the administration was temporary withheld. Efficacy of ECLS therapy was monitored by periodical assessment of arterial and central venous pressures, urine output, systemic oxygen saturation and venous lactate concentration, as reported in the current recommendations [8]. Pump speed was adjusted in order to keep the cardiac index within the 2.2-2.8 l min⁻¹ m⁻² range and to obtain adequate cardiac unloading. Patients on ECLS were evaluated on a daily basis by a multidisciplinary team including surgeons, cardiologists and anesthesiologists. Transthoracic and/or transesophageal echocardiography were employed for verification of cardiac decompression. In event of

inadequate left ventricular (LV) unloading and/or occurrence of pulmonary edema, adjustment of inotropic drugs (Dobutamine) and/or IABP therapy were adopted. Shift to central cannulation and surgical LV unloading through the right upper pulmonary vein or main pulmonary artery was considered as a further measure during the earliest part of our experience. More recently, the positioning of a transaortic axial flow pump (Impella, Abiomed Inc., Aachen, Germany) was considered. The oxygenator and the circuit were replaced in case of clot formation within the system or major haemolysis. Whether IABP therapy was already in place at the time of E-CPR implantation, it was maintained until end of ECLS. Therapeutic hypothermia was performed by at least 24 hours (target: 34°C). Weaning from ECLS was considered when partial or complete recovery from cardiac dysfunction could be demonstrated on echocardiography, associated with the presence of a stable pulsatile blood pressure waveform, and mean blood pressure remaining above 60 mmHg during a weaning trial (progressive reduction of the ECLS flow until a minimum of 1 l/min), while receiving minimal or low dose inotropic agents.

Definitions.

We defined refractory cardiac arrest as persisting beyond the 30th minute of CPR. Etiologies of cardiac arrest were categorized as follows: Cardiac disease (further divided into AMI, Cardiomyopathy, Acute myocarditis, Refractory arrhythmia, Acute pulmonary embolism), Respiratory disease, Trauma (including hypothermia, suicide attempt, drug overdose), Sepsis, and Miscellaneous (those cases which could not be categorized into the other groups). Vascular complications at the site of E-CPR implantation were the need to perform at least one additional surgical procedure to revise hemostasis at the site of cannulation for ECLS, or to reconstruct/repair the involved vessels. Lower limb ischemia was the need to perform at least one additional surgical procedure to relief ischemia and/or treat compartmental syndrome. Hemorrhagic complications on ECLS were the

need to perform at least one surgical revision for bleeding at a site different than the cannulated vessels, and/or to transfuse at least 4 units of concentrated red blood cells to treat anemia resulting from bleeding. Complications to ECLS were grouped according to the ELSO registry definitions, as follows: ECLS circuit complications, central nervous system complications, cardiac complications, pulmonary complications, infectious complications, renal complications, gastrointestinal complications, metabolic complications⁵. Brain death of patients on ECLS had to be declared by at least two intensive care medicine specialists in consensus according to the criteria fixed by the French law (abolition of all brainstem reflexes, absence of spontaneous ventilation at hypercapnia test – $P_{\text{CO}_2} > 60$ mmHg, and two electroencephalography recordings practiced with a 4-hours interval).

Patients were evaluated using the SAPS score (version 2) at the time of E-CPR implantation [9], using the calculator available online at www.sfar.org (website of the French Society of Anesthesia and Intensive Care).

Follow-up and Quality-of-Life assessment.

A follow-up program for patients receiving ECLS at our Institution was started in April 2013. Patients who were alive at the time of hospital discharge were contacted telephonically by research nurses experienced in the chronic management of patients receiving surgical treatment for heart failure. All patients could be contacted and interviewed directly. The inquiry included assessment of the functional and vital status, adverse events after discharge, and formal evaluation of quality-of-life among survivors (administration of the French Version of the Medical Outcomes Study 36-Item Short-Form Health Survey, SF-36) [10, 11, 12]. The questionnaire was administered according to recommendations [10], and provided a score for each of the following domains: physical activity, role limitation, physical pain, general health, vitality, social activity, mental health,

physical component summary and mental component summary. The SF-36 questionnaire has been previously employed in the evaluation of health-related quality-of-life in patients surviving critical illness thanks to ECLS [13], veno-venous extracorporeal membrane oxygenation [14], and in patients with advanced heart failure [15, 16, 17]. The SF-36 has been also employed to evaluate survivors to cardiac arrest who have not been treated by E-CPR [17]. Data were entered into the Rennes ECLS Registry.

Management of data and statistical analysis.

Since the beginning of the ECLS program at our Institution, the clinical data pertaining to each patient receiving such treatment are prospectively entered in an electronic database. This includes all pre- and post-implantation data, major biological and hemodynamic parameters, drug therapy and in-hospital complications. The database is regularly checked for errors and omissions by dedicated personnel. The prospectively collected data can be then retrospectively analyzed. IRB approval was obtained. Our study is declared to the CLIN online database (Commission Nationale de l'Informatique et des Libertées – French National Commission for Informatics and Freedom) according to the French law.

Continuous data are presented as mean \pm standard deviation, and categorical variables as percentages. Intergroup comparison was performed using the two-tailed Student's *t* test for continuous data, and the chi-square test for categorical data. All available baseline variables were used for intergroup comparison (about forty variables). Survival analysis was conducted according the Kaplan-Meier methodology, and the corresponding survival curves were built. Analyses were performed using the SAS software ver. 9.33 for Windows (SAS Institute Inc., Cary, NC).

Results

The study workflow is reported in Figure 1. Forty-nine patients received E-CPR (18.1% of overall ECLS activity at our Institution). The baseline features of the study population and the indications to E-CPR treatment are summarized in Table 1. Most frequently, the indication to E-CPR pertained to the Cardiac disease group; among these, AMI was prevailing (47% of the 30 patients pertaining to such group). Two patients had baseline respiratory disease, which led to anoxic refractory cardiac arrest and required E-CPR. In these patients, circulatory and myocardial failure superimposed to pulmonary failure made the use of veno-venous ECMO alone insufficient. Biological variables at the time of implantation (serum lactate concentration, pH, serum creatinine and markers of end-organ damage) underline the critical general conditions of these patients. Average no-flow time was 47.2 ± 33 minutes. Average diameter of the arterial and venous cannulae was 19.1 ± 1.5 Fr and 20.3 ± 2.6 Fr, respectively.

Twenty-one patients (42.9%) were alive at the time of explantation of ECLS; among these, the average duration of support was 6.8 ± 5.8 days. The remaining patients (57.1%) died after 2.8 ± 4 days after institution of E-CPR. Three patients deceased within the hospital after explantation of ECLS and within the 30th post-implantation day. Causes of death were: multiorgan failure in 14 cases (28.6% in the overall population), brain death in 12 cases (24.5%), and irrecoverable myocardial failure in 2 cases. No further patients died within the hospital after the 30th post-implantation day. Thus, 18 patients (36.7% of the initial population) were discharged alive from the hospital (average hospital stay: 79.1 ± 97.6 days). Thromboembolic and hemorrhagic complications were common under ECLS

(59.2% cumulative rate). Only one patient experienced an ischemic complication of the lower limb (2%). Transfusion with red blood cells, platelets units and fresh frozen plasma units was required in 79.1%, 54.2% and 61.2% of cases, respectively. Seven patients (14.3%) were concomitantly treated by IABP; among these, 3 received IABP after E-CPR implantation in order to facilitate unloading of the LV. Two patients (9.5% of survivors at explantation) were successfully bridged to heart transplantation, while two further patients received an implantable LVAD.

At the time of ECLS explantation, a marked improvement of the biological parameters was evident: average pH was 7.4 ± 0.1 , serum lactates concentration was 2.8 ± 3.3 mmol/L. Partial recovery of end-organ damage was disclosed (average serum SGOT concentration: 82.3 ± 78.5 IU/L; serum creatinine: 116.8 ± 93 μ mol/L). Cardiac function was partially recovered as well, the average LVEF being $37\% \pm 15$. Brain death occurred in 12 cases (24.5% of the entire population, 38.7% of deceased patients). Average duration of mechanical ventilation was 7.7 ± 9.2 days. Table 2 compares the major patient-related variables among survivors and non-survivors at the 30th post-implantation day. Higher SAPS score, lower body temperature and higher lactate level at the time of ECLS implantation were statistically associated with death before explantation.

Table 3 compares the rates of bridge to urgent heart transplantation or to LVAD among patients who received E-CPR vs. the remaining patients who received veno-arterial ECLS in our Institution **during** the same time period.

Late Results.

The follow-up was 94.5% complete (one patient was lost); its average duration was 15.6 ± 19.2 months. Among the 18 patients who left the hospital alive, none of them was deceased at the latest available follow-up. The Kaplan-Meier survival curve (Figure 2)

consequently indicates stable survival after the 16th post-implantation day (timepoint of the last observed fatal event). Measures of health-related quality-of-life as obtained by the SF-36 questionnaire among the survivors at follow-up are summarized in Table 4. Our patients showed the best scores in the Physical Pain, Social Activity, Mental Health and Physical Activity domains, while the average performance was worse in the Vitality domain. Figure 3 offers a comparison of the average SF-36 scores obtained in our series vs. those previously published for survivors to ARDS through veno-venous ECMO and survivors to post-cardiotomy myocardial failure through veno-arterial ECLS. Control data are for a French age- and sex-matched population without adverse health conditions [10]. Globally, our patients showed lower average SF-36 scores than control patients, but they had also better performance than the comparator ECMO/ECLS cohorts.

Comment

Since the earliest experiences about E-CPR to rescue refractory cardiac arrest, 30-days survival in this complex patients subgroup raised from 24% [12, 19] to about 34% in recent times [20] and to 39% in selected populations (MI-related cardiac arrest [1]). Such tendency is confirmed herein. We observed a 42.9% survival at ECLS explantation and a 36.7% survival at both 30 days and hospital discharge. Our series should be compared with previously published experiences which included only patients who received ECLS during ongoing CPR. Otherwise, the interpretation of previously reported survival rates up to 50% [5] may be misleading. Yet, ECLS guarantees a survival advantage over conventional CPR if this protracts beyond 10 minutes [21]. Such amelioration may be ascribed to improved selection of candidates and growing experience of E-CPR teams. Prompt decision-making and effective organization are crucial to achieve survival of these

critically ill patients. In fact, anoxic brain death of patients treated with E-CPR appeared to be one major threaten in the published experiences [6, 23].

Causes of death on ECLS support are closely related to the major decision-making issues encountered in these patients. Despite the relatively low rate of out-of-hospital cardiac arrest in our series (12%), the rate of brain death among the E-CPR recipients remains remarkable (24.5% overall). Conversely, multiorgan failure is the most prevalent cause of death in our population: end-organ damage induced by cardiogenic shock can be reasonably considered as the triggering factor for this ominous condition. Such concept underlines the importance of prompt and effective CPR and institution of E-CPR. Concordantly, in our study survivors presented a trend towards significantly shorter average low-flow time and, additionally, absence of no-flow time. Nonetheless, ECLS itself represents a trigger for systemic inflammatory reaction: it has been associated with a 'cytokine storm' (Tumor Necrosis Factor- α , TNF- α , Interleukin 8, IL-8, IL-6) which may propagate organ injury [23]. Evidence from the animal model suggests that such mechanism may also play a role in delayed pulmonary recovery during veno-venous ECLS for severe respiratory failure [24]. Interestingly, myocardial failure itself is the less common determinant of the final outcome once ECLS has been instituted. Fatal issue due to failed electrical recovery from cardiac arrest was observed in 2 cases in our series despite effective ventricular unloading. Early termination of support was decided in these cases. Patients who present failed recovery of myocardial contractility over the later days may be bridged to urgent heart transplantation or to destination LVAD (2 cases each in our series, 9.5% of the survivors at the 30th day). Nonetheless, rational employment of transplantation and VAD resources restrain their use to patients with survivable levels of end-organ dysfunction. It has been proposed that recovery from the initial shock-related injury should be expected within the 2nd-5th postimplantation day; ECLS-related end-organ injury would

become clinically significant in the later days and render end-organ recovery unlikely [25]. Non-surviving patients presented higher SAPS score, lower body temperature and higher serum lactates at implantation compared to survivors. We observed also a trend towards longer low-flow time among non-survivors. Lower blood pH was observed among non-survivors, although significance was not attained. These data should be interpreted cautiously, since no multivariate analysis could be performed. Nonetheless, these observations suggest the importance of the degree of end-organ injury in the determinism of survival and may support the decision-making.

In light of worse results, there is controversy over the opportunity of employing E-CPR outside the referral Institution for out-of-hospital cardiac arrest [1, 26, 27]. Not only clinical factors, but also organizational, public healthcare, economic and ethical issues are involved in such controversy. The possibility of sudden cardiac arrest everywhere in the territory and the prognostic importance of prompt initiation of support when indicated, suggests the diffusion of ECLS equipment and techniques in all peripheral hospital who have an ICU available. This model would better guarantee a uniform respect of the citizens' right to access lifesaving care, even though the cardiac arrest occurs far away from a tertiary referral center. On the other hand, the need for surgical and intensive care expertise, the non-negligible learning curve and the major social costs support the reservation of this technique to tertiary centers. The concept of territorial network (several peripheral hospitals depending on one tertiary center) is part of this debate. As ECLS is at the frontier between cardiology, cardiac surgery and intensive care medicine, professionals involved in all these specialties are expected to contribute and develop shared recommendations.

Interestingly, it emerged from our experience that the rate of bridge to heart transplantation is comparable among patients receiving E-CPR vs. the remainder veno-arterial ECLS

cases at our Institution (Table 3). The rate of long-term VAD implantation was even higher among refractory cardiac arrest patients. Such analysis is limited by low sample size and should be interpreted keeping in mind the heterogeneous composition of the non-cardiac arrest population (including patients receiving ECLS for early graft failure and post-cardiotomy myocardial failure) and the different average age (younger among the E-CPR patients). Nevertheless, this information suggests that urgent transplantation and long-term VAD are as effective among rescued-cardiac arrest individuals as in the general ECLS population. Therefore, the E-CPR patients should be submitted to the same decisional criteria than conventional ECLS patients, although particular attention must be devoted to the assessment of brain death and nonsurvivable end-organ injury.

One major finding of the present work consists in the demonstration of stable survival at the mid-term follow-up among patients who were discharged from the hospital. Concerning the assessment of quality-of-life, better scores were observed for Mental Health and related domains; lower scores were observed for the General Health and Vitality domains. This may be interpreted as the consequences at the early- to mid-term follow-up of long-term hospitalization and ICU stay. The subtending disease, ICU-related neuropathy, hyponutrition and the high rate of complications may explain such finding. It is reasonable to expect improvements in these domains and more complete recovery at later intervals. Survivors to cardiac arrest using E-CPR showed herein worse health-related quality-of-life scores than the normal matched French population, as the expression of severe disease and prolonged hospitalization. Interestingly, our E-CPR patients presented better average scores in all SF-36 domains compared to previous studies over ECLS patients [13], venovenous ECMO patients of the CESAR study [14] and survivors to post-cardiotomy myocardial failure through ECLS [13] (Figure 3). Such finding may be attributed to different characteristics of the comparator populations. Namely, patients on venovenous ECMO are particularly likely to experience particularly long and debilitating hospitalization in

critical care environment. The patients enrolled in the study by Wang and associates all presented post-cardiotomy myocardial failure and structural heart disease, with inherent negative prognostic significance [13]. Collectively, our data suggest that survivors to acute events thanks to E-CPR may attain satisfactory health-related quality-of-life compared to similar populations of critical care patients. Similarly, the SF-36 Mental and Physical summary scores were comparable to those obtained among survivors to cardiac arrest without E-CPR treatment [18]. The present paper reports for the first time measures of quality-of-life among patients surviving refractory cardiac arrest thanks to E-CPR. Therefore, the practice of E-CPR is justified by the possibility to achieve good functional results in the survivors.

The present investigation is limited by retrospective analysis of data; such limitation is partially offset by the prospective inclusion of patients' information into a dedicated database. Another limitation is the lack of a control group (survivors to cardiac arrest who did not receive E-CPR). On the other hand, we limited the inclusion to patients who received E-CPR during ongoing external cardiac massage. This allows focusing on a more selected population than previous reports [5]. As a further minor limitation, the rate of thromboembolic and hemorrhagic complications is given in aggregate form.

Conclusions.

Use of E-CPR is an effective strategy which allows saving lives in a population of severely compromised patients. This is probably the most challenging domain within an ECLS program. The survival at ECLS explantation reported herein is among the highest published so far. Patients who survive the initial cardiac arrest injury thanks to E-CPR may subsequently enter the same decision-making algorithm than patients who received ECLS

during non-cardiac arrest circumstances. Nonetheless, high rates of brain death and non-survivable end-organ injury are common among patients rescued from cardiac arrest, and may preclude bridging to urgent transplantation or VAD in a significant proportion of cases. Overall, about one third of patients in our experience survived at both discharge and mid-term follow-up. Remarkably, survival tends to remain stable after discharge. Health-related quality-of-life among survivors is better or comparable than in previous investigations over ECLS / ECMO recipients or cardiac arrest survivors. These findings support the practice of E-CPR, provided that adequate patients' selection is performed in order to avoid unjustified employment of hospital resources.

Acknowledgements.

The Authors are grateful to Pascale Roualt, Veronique Desriac and to Anne Ingels for their invaluable contribution in data collection and analysis.

References

1. Demondion P, Fournel L, Golmard JL, Niculescu M, Pavie A, Leprince P. Predictors of 30-day mortality and outcome in cases of myocardial infarction with cardiogenic shock treated by extracorporeal life support. *Eur J Cardiothorac Surg* 2014;45:47-54.
2. Chen Y, Chao A, Yu H, Ko WG, Wu IH, Chen R et al. Analysis and results of prolonged resuscitation in cardiac arrest patients rescued by extracorporeal membrane oxygenation. *J Am Coll Cardiol* 2003;41:197-203.
3. Ruttman E, Weissenbacher A, Ulmer H, Muller H, Hofer D, Kilo J et al. Prolonged extracorporeal membrane oxygenation-assisted support provides improved survival in hypothermic patients with cardiocirculatory arrest. *J Thorac Cardiovasc Surg* 2007;134:594-600.
4. Megarbane B, Leprince P, Deye N, Resiere D, Guerrier G, Rettab S et al. Emergency feasibility in medical intensive care unit of extracorporeal life support for refractory cardiac arrest. *Intensive Care Med* 2007;33:758-64.
5. Chen J, Ko W, Yu H, Lai L, Huang S, Chi N et al. Analysis of the outcome for patients experiencing myocardial infarction and cardiopulmonary resuscitation refractory to conventional therapies necessitating extracorporeal life support rescue. *Crit Care Med* 2006;34:950-7.

6. Thiagarajan R, Brogan T, Scheurer M, Laussen P, Rycus P, Bratton S. Extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in adults. *Ann Thorac Surg* 2009;87:778-85.
7. Combes A, Leprince P, Luyt CE, Trouillet JL, Chastre J. Extracorporeal membrane oxygenation (ECMO) for cardiopulmonary support (Assistance cardiorespiratoire par extracorporeal membrane oxygenation (ECMO). *Réanimation* 2009;18:420-7.
8. Beckmann A, Benk C, Beyersdorf F, Haimerl G, Merkle F, Mestres C et al; ECLS working group. Position article for the use of extracorporeal life support in adult patients. *Eur J Cardiothorac Surg* 2011;40:676-80.
9. Brinkman J, Bakhshi-Raiez F, Abu-Hanna A, de Jonge E, Bosman RJ, Peelen R et al. External validation of Acute Physiology and Chronic Health Evaluation IV in Dutch intensive care units and comparison with Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology Score II. *J Crit Care* 2011;26:e11-8.
10. Leplège A, Ecosse E, Verdier A, Perneger T. The French SF-36 Health Survey: translation, cultural adaptation and preliminary psychometric evaluation. *J Clin Epidemiol* 1998;51:1013-23.
11. Aaronson NK, Acquadr C, Alonso J, Apolone G, Bucquet D, Bullinger M et al. International Quality of Life Assessment (IQOLA) Project. *Qual Life Res* 1992;1:349-51.
12. Doll N, Kiaii B, Borger M, Bucerius J, Kramer K, Schmitt V et al. Five-years results of 219 consecutive patients treated with extracorporeal membrane oxygenation for refractory postoperative cardiogenic shock. *Ann Thorac Surg* 2004;77:151-7.
13. Wang J, Han J, Jia Y, Zeng W, Shi J, Hou X et al. Early and intermediate results of rescue extracorporeal membrane oxygenation in adult cardiogenic shock. *Ann Thorac Surg* 2009;88:1897-93.

14. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;17:374:1351-63.
15. Kugler C, Malehsa D, Tegtbur U, Guetzlaff E, Meyer A, Bara C et al. Health-related quality of life and exercise tolerance in recipients of heart transplants and left ventricular assist devices: A prospective, comparative study. *J Heart Lung Transplant* 2011;30:204-10.
16. Freitas P, Haida A, Bousquet M, Richard L, Mauriège P, Giraud T. Short-term impact of a 4-week intensive cardiac rehabilitation program on quality of life and anxiety-depression. *Annals of Physical and Rehabilitation Medicine* 2011;54:132–3.
17. Maclver J, Ross H. Quality of life and left ventricular assist device support. *Circulation* 2012;126:866-74.
18. Graf J, Muhlhoff C, Doig S, Reinartz S, Bode K, Dujardin R, Koch CK et al. Health care costs, long-term survival, and quality of life following intensive care unit admission after cardiac arrest. *Critical Care* 2008, 12:R92 (doi:10.1186/cc6963).
19. Schwarz B, Mair P, Margreiter J, Pomaroli A, Hoerman C, Bonatti J et al. Experience with percutaneous venoarterial cardiopulmonary bypass for emergency circulatory support. *Crit Care Med* 2003;31:758-64.
20. Haneya A, Philipp A, Diez C, Schopka S, Bein T, Zimmermann M et al. A 5-year experience with cardiopulmonary resuscitation using extracorporeal life support in non-postcardiotomy patients with cardiac arrest. *Resuscitation* 2012;83:1331-7.
21. Chen Y, Lin J, Yu H, Ko W, Jerng JS, Chang WT et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet* 2008;372:554-61.

22. Massetti M, Tasle M, Le Page O, Dereck R, Babatasi G, Buklas D et al. Back from irreversibility: extracorporeal life support for prolonged cardiac arrest. *Ann Thorac Surg* 2005;79:178-84.
23. Risnes I, Wagner K, Ueland T, Mollnes T, Aukrust P, Svennevig J. Interleukin-6 may predict survival in extracorporeal membrane oxygenation treatment. *Perfusion* 2008;23:173-8.
24. Shi J, Chen Q, Yu W, Shen J, Gong C, He J et al. Continuous renal replacement therapy reduces the systemic and pulmonary inflammation induced by venovenous extracorporeal membrane oxygenation in a porcine model. *Artif Organs* 2013 Dec 11 in press. doi: 10.1111/aor.12154.
25. Pagani FD, Aaronson KD, Dyke DB, Wright S, Swaniker F, Bartlett RH. Assessment of an extracorporeal life support to LVAD bridge to heart transplant strategy. *Ann Thorac Surg* 2000;70:1977-84.
26. Kagawa E, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Kurisu S et al. Assessment of outcomes and differences between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal life support. *Resuscitation* 2010;81:968-73.
27. Le Guen M, Nicolas-Robin A, Carreira S, Raux M, Leprince P, Riou B et al. Extracorporeal life support following out-of-hospital refractory cardiac arrest. *Crit Care* 2011;15:R29.
28. Flécher E, Anselmi A, Corbineau H, Langanay T, Verhoye JP, Félix C et al. Current aspects of extracorporeal membrane oxygenation in a tertiary referral centre: determinants of survival at follow-up. *Eur J Cardio-Thorac Surg* 2014;46:665-71.

Figure Legends

Figure 1. Study design. VA: Veno-Arterial.

Figure 2. Actuarial (Kaplan-Meier) survival curve for patients receiving ECLS for refractory cardiogenic shock; in-hospital mortality is included. The grey interrupted lines depict the confidence limits for the estimate.

Figure 3. Comparison of SF-36 scores observed among patients enrolled in our study (red line, E-CPR) with the corresponding SF-36 scores obtained from patients who survived ARDS through veno-venous ECMO (CESAR study ECMO cohort from reference 14; yellow interrupted line, ECMO-CESAR), patients who survived post-cardiotomy myocardial failure through veno-arterial ECLS (from reference 13; green interrupted line, ECLS-postcardiotomy). Comparison with normal age- and sex-matched French population is offered (blue continuous line, Control). PA: Physical Activity. RL: Role Limitation. PP: Physical Pain. GH: General Health. VT: Vitality. SA: Social Activity. MH: Mental Health.

Central Picture Legend

Survival curve for patients receiving E-CPR (follow-up: 15.6 ± 19.2 months).

Table 1. Descriptors of the study population. LVEF: Left Ventricular Ejection Fraction. SGOT: Serum Glutamic Oxaloacetic Transaminase. *Refers to any LVEF measurement available on the day of E-CPR implantation, including LVEF immediately after institution of support. [§]Refers to catecholamines administered while on support, excluding those administered during cardiopulmonary resuscitation.

| Characteristic | |
|-------------------------------------|---------------------|
| Age (years) | 47.6 ± 16 |
| Gender: Male/Female | 30/19 (61.2%-38.8%) |
| Body Surface Area (m ²) | 1.89 ± 0.23 |
| <u>Site of cardiac arrest</u> | |
| - In-hospital | 43 (88%) |
| - Out-of-hospital | 6 (12%) |
| <u>Site of E-CPR implantation</u> | |
| - Operative theater | 24 (49%) |
| - ICU | 18 (36.7%) |
| - Catheterization room | 2 (4.1%) |
| - Other | 5 (10.2%) |
| <u>Indication to E-CPR ECLS</u> | |
| - Cardiac disease | 30 (61.2%) |
| - Respiratory disease | 2 (4.1%) |
| - Trauma | 7 (14.3%) |
| - Sepsis | 1 (2%) |
| - Miscellaneous | 9 (18.4%) |
| LVEF* (%) | 22.8 ± 15.3 |
| No-flow time (min) | 1.1 ± 2.9 |
| Low-flow time (min) | 47.2 ± 33 |
| <u>Inotropes[§]</u> | |
| - Dobutamine >5 μ g/kg/min | 18 (36.7%) |
| - Adrenaline >1 mg/h | 16 (32.6%) |
| - Noradrenaline >1 mg/h | 25 (51%) |
| pH | 7.2 ± 0.3 |
| Lactate (mmol/l) | 11.7 ± 6 |

| | |
|--|-----------------|
| Serum Creatinine ($\mu\text{mol/L}$) | 144 \pm 53 |
| SGOT (IU/L) | 637 \pm 961 |
| Troponin T | 472 \pm 1188 |
| SAPS Score | 61.1 \pm 29.2 |

ACCEPTED MANUSCRIPT

Table 2. Survivors vs. non-survivors at 30 days after implantation of E-CPR ECLS: univariate intergroup comparison of patient-related variables at the time of start of support.

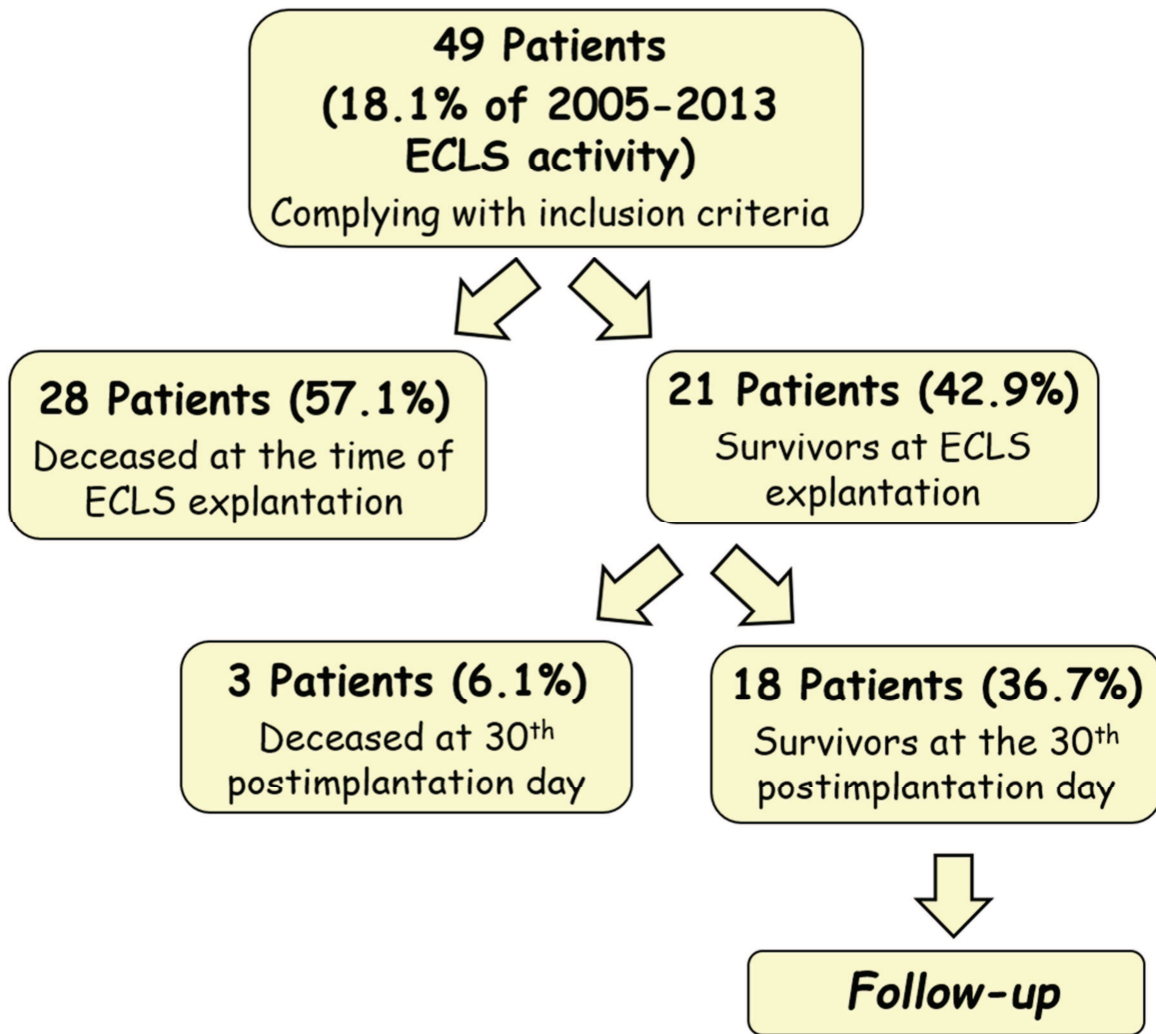
| Characteristic | Survivors (N=18) | Non-survivors (N=31) | p |
|---|------------------|----------------------|-------|
| Gender: male | 13 (72.2%) | 17 (54.8%) | 0.2 |
| Age (years) | 44.9 ± 17.3 | 48.8 ± 15.3 | 0.2 |
| <u>Site of implantation</u> | | | |
| - Operative theater | 11 (61%) | 13 (41.9%) | 0.19 |
| - Other | 7 (39%) | 18 (58.1%) | |
| SAPS Score | 43.5 ± 21.5 | 70.3 ± 28.8 | 0.006 |
| Body temperature at E-CPR implantation (°C) | 36 ± 1.9 | 34.7 ± 2.2 | 0.02 |
| Serum creatinine (µmol/L) | 139 ± 53 | 148 ± 53 | 0.5 |
| Serum lactates (mmoL/L) | 8.6 ± 4.4 | 12.8 ± 6.6 | 0.04 |
| pH | 7.28 ± 0.3 | 7.2 ± 0.2 | 0.4 |
| Low-flow time | 33.4 ± 15.6 | 52.9 ± 36.6 | 0.09 |
| No-flow time | 0 | 1.6 ± 3.3 | 0.16 |

Table 3. Rates of bridge to urgent heart transplantation or to VAD implantation: patients receiving E-CPR vs. those receiving veno-arterial ECLS during the same period under non-cardiac arrest circumstances. * $p < 0.001$ (mean age comparison among cardiac arrest vs. non-cardiac arrest patients).

| Characteristic | E-CPR patients | ECLS patients – no cardiac arrest at implantation |
|--|----------------|---|
| <i>Overall series</i> | | |
| - Urgent Heart Transplantation | 4.1% | 4.8% |
| - VAD | 4.1% | 1.9% |
| - Any | 8.2% | 6.7% |
| <i>Survivors at ECLS explantation only</i> | | |
| - Urgent Heart Transplantation | 9.5% | 9.8% |
| - VAD | 9.5% | 3.8% |
| - Any | 19.4% | 13.6% |
| Age (years) | 47.6 ± 16* | 55.5 ± 13.9* |

Table 4. Results of Quality-of-Life scores assessment among survivors at the average 15.6 months follow-up. SD: Standard deviation. 100: best possible score.

| Characteristic | Mean \pm SD |
|----------------------------|---------------------------------|
| Physical Activity score | 70.8 \pm 27.4 |
| Role Limitation score | 63.6 \pm 23.2 |
| Physical Pain score | 81.3 \pm 23.6 |
| General Health score | 62.7 \pm 16 |
| Vitality score | 56.5 \pm 18.8 |
| Social Activity score | 74 \pm 23 |
| Mental Health score | 71.4 \pm 17 |
| Physical Component Summary | 45.2 \pm 6.8 |
| Mental Component Summary | 48.3 \pm 7.7 |



ACCEPTED

