

## Case Reports

# The Need to Develop Standardized Protocols for the Timing of Extracorporeal Membrane Oxygenation Initiation among Adult Patients in Cardiac Arrest: A Case Study

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**Abstract:** The duration of time between cardiac arrest, cardiopulmonary resuscitation (CPR), and initiation of extracorporeal membrane oxygenation (ECMO) among refractory patients is correlated with mortality. The duration of conventional CPR (CCPR) beyond which ECMO support should not be offered due to poor outcomes is not established. This case study describes a patient with heart failure with recurrent episodes of ventricular tachycardia who had a witnessed cardiac arrest in a coronary care unit. The patient received approximately 45 minutes of CCPR. Venoarterial ECMO was then initiated for extracorporeal CPR (ECPR) support. The total recorded ischemic time between CCPR and ECPR was 60 minutes. Despite aggressive medical therapy, ECMO support was discontinued 48 hours later following absence of electroencephalographic activity and no evidence of cardiac function ultimately leading to the

patient's death. This case study illustrates the possibility that prolonged ischemia resulting from duration of CCPR and time to initiate ECPR may contribute to adverse clinical outcomes. Systems of care that might reduce delays in ECMO initiation and improve patient outcomes are discussed including: 1) development of standardized protocols to allow for rapid initiation of ECMO support; 2) systematic evaluation of parameters such as biomarkers that might identify patients at risk for cardiac arrest in settings where ECMO is readily available; and 3) assessment of patient criteria to define subsets of individuals among whom late institution of ECMO, an expensive and labor-intensive mode of circulatory support, might be futile. **Keywords:** extracorporeal membrane oxygenation, cardiopulmonary resuscitation, heart failure, case report, outcomes. *JECT. 2014;46:305–309*

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Cardiac arrest occurs in approximately 3–4% of patients admitted to cardiac intensive care units (1). Adult patients in cardiac arrest who are refractory to maximal medical therapy and conventional cardiopulmonary resuscitation (CCPR), which uses noninvasive mechanical compressions to generate cardiac output, have poor outcomes (2–5). Among the 14,720 cases of in-hospital cardiac arrest reported in the National Registry of Cardiopulmonary Resuscitation, less than half of patients had return of spon-

taneous circulation (ROSC) after CCPR and 17% survived to discharge (2). Other studies have reported CCPR survival rates between 7.4 and 27% (3,4). Survival has been documented to be as low as 2% if CCPR persists beyond 10 minutes (5).

Extracorporeal cardiopulmonary resuscitation (ECPR), the use of venoarterial extracorporeal membrane oxygenation (ECMO) to provide support after CCPR has failed to restore circulation, has been shown to improve survival rates among refractory patients (1). The literature suggests that there is an inverse relation between CCPR duration prior to ECPR and survival to discharge (6). CCPR provided for less than 45 minutes prior to ECPR has been associated with a survival to discharge of 57.14% compared with an 11.5% survival rate when CCPR duration

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exceeds 60 minutes (6). These data highlight the potential for efforts to prevent prolonged duration of CCPR and to enable more rapid initiation of ECPR as a method to improve outcomes among patients undergoing cardiac arrest. The purpose of this case study is to discuss a fatal outcome in a patient who had a total ischemic time of approximately 60 minutes from cardiac arrest to initiation of ECPR. The case study highlights the need to develop systematic strategies to reduce the delay between cardiac arrest and initiation of ECPR among appropriate patients to optimize the potential for survival.

## PATIENT CHARACTERISTICS AND CLINICAL COURSE

The patient was a 66-year-old man with the following characteristics: height of 170 cm, weight of 89 kg, body surface area of 2.05 m<sup>2</sup>, and body mass index of 30.8 kg/m<sup>2</sup>. The patient's medical history included coronary artery disease, hypertension, tobacco use, posttraumatic stress disorder, and congestive heart failure. The patient's surgical history included coronary artery bypass grafting in 1989, which was redone in 1995 with the addition of an automatic implantable cardioverter-defibrillator to manage the ventricular tachycardia (VT).

In 2013 the patient was admitted to a major academic medical center after a failed ablation in a catheterization laboratory at an outside institution. The patient underwent another unsuccessful ablation, experienced a series of VT episodes, and was transferred to the coronary care unit (CCU) to manage the VT and symptoms of heart failure. In the CCU, the patient required maximal inotropic and vasopressor support and was elevated to 1A status on the United Network for Organ Sharing heart transplant list. After 2 weeks in the intensive care unit, the patient's pacemaker failed to capture at 0530 hours and the patient went into pulseless electrical activity while attempting to rise from bed. The arrest was witnessed and CCPR was performed for approximately 45 minutes. Heparin (10,000 IU) was administered; the patient was cannulated with a 15-Fr Biomedicus femoral cannula in the femoral artery and a 21-Fr Biomedicus femoral cannula in the femoral vein. Venoaerterial ECMO support was initiated at 0625 hours.

The patient was immediately cooled to 34°C to protect his neurological function. The gas flow was tripled (up to 7 L/min) and the flow rate was increased (up to 4.1 LPM) to compensate for the patient's progressive acidosis. A distal perfusion catheter was placed in the left superficial femoral artery to prevent distal limb ischemia, and an Impella 2.5 was inserted to decompress the left ventricle. The day after the arrest, the patient developed renal and liver failure complicated by anemia (hemoglobin 6 g/dL) and thrombocytopenia (platelet count 33,000/ $\mu$ L). Despite multiple packed red blood cell and fresh-frozen plasma transfusions, the patient's bleeding worsened. The heparin drip was stopped and a disseminated intravascular coagulopathy panel was ordered. Continuous venovenous hemodialysis was started in an attempt to correct a lack of urine output, hyperkalemia, and hypernatremia. Antibiotic therapy was begun for a positive blood culture. The patient was rewarmed from 34–36°C to mitigate coagulopathy.

After 48 hours of ECMO support, the patient's status continued to deteriorate. Despite aggressive fluid replacement, there were multiple decreases in ECMO flows. The patient developed refractory coagulopathy and lost native cardiac contractility and electrical activity. His mean arterial pressure could not be maintained above 50 mmHg, venous saturation rose to 93%, hemoglobin fell below 5 g/dL, lactate measured 18 mmol/L, and blood gas and electrolyte status became highly abnormal. The patient was withdrawn from ECMO support after a duration of 2 days 7 hours as a result of multisystem organ failure including complete absence of neurological and cardiac electrical activity. The patient's blood test results are recorded in Tables 1 through 4 documenting the patient's physiological and hemostatic deterioration leading up to the discontinuation of ECMO support.

## DISCUSSION

This case study illustrates a fatal outcome in a patient with a witnessed cardiac arrest in a CCU who received CCPR and ECPR therapy. The patient experienced unrecoverable organ failure possibly related to prolonged ischemia up to 60 minutes. Although it cannot be determined that the prolonged duration of CCPR before initiation of

**Table 1.** Blood composition report leading up to discontinuation of ECMO support.

Date, Time	Na <sup>+</sup> (mEq/L)	K <sup>+</sup> (mEq/L)	Cl <sup>-</sup> (mEq/L)	HCO <sub>3</sub> <sup>-</sup> (mEq/L)	Blood Urea Nitrogen (mg/dL)	Creatine (mg/dL)	Glucose (mg/dL)	Calcium mg/dL
Day 2, 1000	150	5.4	98	16	58	2.79	42	7.8
Day 3, 0300	166	9.8	94	18	56	2.91	361	8.4
Day 3, 1100	163	10.6	96	16	44	2.58	45	6.9

ECMO, extracorporeal membrane oxygenation; Na<sup>+</sup>, ionized sodium; K<sup>+</sup>, ionized potassium; Cl<sup>-</sup>, ionized chloride; HCO<sub>3</sub><sup>-</sup>, bicarbonate; Calcium, total serum.

**Table 2.** Additional test results leading up to discontinuation of ECMO support.

Date, Time	Mg <sup>2+</sup> (mEq/L)	Anion Gap (mEq/L)	White Blood Cell Count ( $\times 10^3/\mu\text{L}$ )	Hemoglobin (g/dL)	Hematocrit (%)	Platelets ( $\times 10^9/\text{L}$ )	Albumin (g/dL)	Lactate (mmol/L)
Day 2, 1000	3.4	36	4.3	7.1	21.7	67	1.5	—
Day 3, 0300	4.7	54	3.2	5.7	18	33	—	39.4
Day 3, 1100	4.5	— <sup>1*</sup>	3.8	4.9	15.4	33	1.7	—

\*Value unable to be measured by an EPOC blood gas analyzer.  
ECMO, extracorporeal membrane oxygenation; Mg<sup>2+</sup>, ionized magnesium.

ECPR was causal, the negative outcome underscores the need to establish national standards for the timing of initiation of ECPR that are evidence-based and can be tailored to institutional capabilities.

The duration of CCPR after which a patient develops unacceptable neurological status and poor clinical outcomes once transitioned to ECPR is not firmly established; however, published data suggest a significant association between increased CPR duration and increased mortality (2–6). There are case reports of patients that have survived up to 90 and 250 minutes of CCPR with good recovery and no significant cerebral insult after being transitioned to ECMO (7,8). However, these case studies represent outliers (e.g., use of partial support devices and noncontinuous CCPR) and are not representative of typical CCPR to ECPR experiences. In these circumstances, the assessment of true ischemic time is more challenging.

Chen et al. (6) showed a significant improvement in survival to discharge among patients who had CCPR for 45 minutes or less before ECPR compared with those who had CCPR greater than 45 minutes and found survival dropped precipitously after 60 minutes. A meta-analysis revealed that survival was decreased when ECMO was initiated after 30 minutes of CCPR (9); additional data also suggest early initiation of CPR and ECPR is critical to improve patient outcomes (9,10). A mortality rate as high as 70% was observed when CCPR exceeded 60 minutes (11). These data could inform the development of standardized protocols for the timing of initiation of ECPR.

Improved standardization of patient selection based on the duration CCPR may help prevent the “bridge to nowhere” phenomenon in which expensive resources are used to resuscitate unrecoverable patients. One challenge

**Table 3.** Coagulation and liver test results leading up to discontinuation of support.

Date, Time	PT (sec)	PTT (sec)	INR	Bilirubin (mg/dL)	AST (U/L)	ALT (U/L)	ALKPhos (U/L)
Day 2, 1000	52.6	73.5	6.3	2.7	6392	3713	97
Day 3, 0300	63	97.8	8	2.1	6012	3073	191
Day 3, 1100	36.2	82.6	3.8	2.3	7041	3194	298

PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; Bilirubin, total; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALKPhos, alkaline phosphatase.

to creating evidenced-based ECPR protocols is that the time period between arrest and ECPR initiation is not always accurately or systematically recorded as a result of the emergent nature of cardiac arrest and variation in documentation procedures. Lack of accurate measurements of CCPR duration may be one possibility why research has shown inconsistent associations between duration of CCPR before ECPR and survival. This challenge could be addressed with creation of standardized cardiac arrest forms that are developed collaboratively with nursing and contain information vital to ECPR research. In 2013, the institution where this study was conducted updated its Department of Nursing Manual to improve documentation and to clarify responsibilities for completion of paper and electronic cardiac arrest flow sheets. Electronic records may be used to identify and to validate the exact time of arrest (electrocardiographic asystole) and reperfusion (mean arterial pressure recovery). The adequacy of perfusion during the arrest period needs to be better measured and studied to determine when patients are refractory to CCPR and when it is appropriate to switch over to ECPR.

The patient in this case study may have endured prolonged ischemia during CCPR given that even the best performed CPR provides inadequate cardiac output, ranging from 25% to 40% of what may be considered optimal. (12). The duration of ischemia might have been reduced if the call for ECPR had been made earlier. In centers that have the appropriate staff available 24/7, the call for ECPR can be made early such that emergent cannulation and ECPR support can be initiated after there has been no ROSC within a specified timeframe. For example, French guidelines suggest that a CCPR duration of 30 minutes without ROSC is considered refractory (13). The use of

**Table 4.** Patient arterial blood gas after ECMO initiation and hours before death.

Date, Time	pH	pCO <sub>2</sub> (mmHg)	pO <sub>2</sub> (mmHg)	HCO <sub>3</sub> <sup>-</sup> (mEq/L)	BE	SaO <sub>2</sub> (%)	Lactate (mmol/L)
Day 1, 0915	7.06	80	453	22.7	-7.9	100	9.3
Day 3, 0814	7.34	28	539	15	-10	100	>18

pCO<sub>2</sub>, partial pressure of carbon dioxide; pO<sub>2</sub>, partial pressure of oxygen; HCO<sub>3</sub><sup>-</sup>, bicarbonate; BE, base excess; SaO<sub>2</sub>, arterial saturation.

CCPR for less than 15 minutes has been suggested as a contraindication to ECPR to avoid cannulation when ROSC is still possible.

The American Heart Association recommends the consideration of ECPR when the time without blood flow is brief and the condition leading up to the cardiac arrest is reversible or amenable to heart transplantation or revascularization (14). The details of what is considered a brief period of no flow needs to be more clearly defined if national guidelines are to be helpful in clinical settings. Age and specific patient pathology should be considered when evaluating the resilience of the patient to periods of no or little flow. Physicians must make a rapid on-scene assessment of the patient's recoverability and, in some cases, with limited knowledge of the patient. Circumstances that may exclude a patient from ECPR include those conditions that are exacerbated by the therapy or are irreversible, including history of severe neurological damage, current intracranial hemorrhage, terminal malignancies, irreversible organ failure, a CCPR duration of less than 15 minutes, aortic dissection, severe peripheral vascular disease, and a do-not-resuscitate order (15). Protocols that take into consideration duration of CCPR and patient factors, such as reversibility of the condition, could help inform and standardize decisions about when to call for ECPR.

A recent review suggests the following inclusion criteria for ECPR, including conditions such as medical intoxication, hypothermia, and patient pathology correctable by angioplasty, surgery, or transplantation (15). Additionally, patients younger than 75 years of age, those patients who have endured less than or equal to 15 minutes between the arrest and the initiation of CCPR, and those patients who have not had a ROSC within 20 minutes of CCPR should be considered when deciding on institution of ECPR. The French Cardiopulmonary Council has created an algorithm for the institution of ECPR, incorporating the duration of no or low flow, the reversibility of the condition, and comorbidities that would prohibit invasive techniques such as ECPR (13).

In the United States, ECPR protocols could provide the time at which the call should be made for ECPR based on national standards that are adapted to local needs and resources. For example, placement of a primed ECMO circuit in or near intensive care units may reduce the response time when the call for ECMO initiation is made. Stored primed ECMO circuits are not likely to be a source of infection (16) and the oxygenator can remain functional up to 2 weeks (17). The availability and proximity of surgical and ECMO staff should also be considered, suggesting that national guidelines incorporate proper timing of ECMO initiation while recognizing that individual institutions may need to adapt based on local resources.

A number of factors have been shown to independently predict survival and neurological status after ECPR. Age

and subsequent coronary or surgical intervention were independently associated with survival and neurological status in a 2-year follow-up study (18). In a pediatric population, improved survival was associated with lower pre-ECPR phosphorous and creatinine concentrations (19). Others have shown a reduced survival with higher serum lactate levels before ECPR, renal failure after ECPR (20), and a pH <7.00 post-ECPR initiation (21). Prearrest renal insufficiency, metabolic or electrolyte abnormalities, and intervention with sodium bicarbonate/tromethamine have also been associated with decreased survival after ECPR (22). Prognostic markers of poor neurological outcome after cardiac arrest may include somatosensory-evoked potentials (23,24), neuron-specific enolase, and S-100b (25). Future prospective studies are needed to determine the efficacy of biomarkers in predicting outcomes for ECPR patients.

Scientific challenges limiting the creation of evidence-based ECPR protocols include lack of randomized trials, inconsistent recordkeeping/data collection, and suboptimal methods to measure the efficacy of CCPR and ECPR. Most of the research done on ECPR has been confined to small observational studies and retrospective analyses. Observational studies have inherent limitations and are subject to inconsistent reporting regarding circumstances of arrest, the time and duration of CCPR, and the timing and duration of ECPR. Documentation of these variables can be assisted by review of vital data contained within electronic records. An additional challenge for the creation of ECPR protocols is that prior literature has focused on a narrow scope of outcomes, primarily survival to discharge. More expansive outcomes and systematic collection of parameters that predict important outcomes may help to guide decisions regarding ECPR. For example, the collection of quantitative data from oximetry pads and end-tidal CO<sub>2</sub> may help justify earlier institution of ECPR. An end-tidal CO<sub>2</sub> <10 mmHg after 20 minutes of CCPR has been associated with poor neurological outcomes (26). Incorporation of such data may help predict endpoints important to patients and their families such as neurologic status and quality of life.

As the practice of ECPR evolves, information from registries and collaboration should be used to update research that can help to establish evidence-based strategies for ECPR initiation. National standards of care will become increasingly important because the availability of ECMO will likely expand beyond tertiary care centers through ECMO networks. In 2009 the Italian Health Authorities were successful in improving survival by using a referral network for patients with H1N1 (27). Such networks may place patients on ECMO in the emergency departments of primary centers and then transfer patients for advanced care to tertiary hospitals. Individual institutions may not have the resources to develop protocols for ECMO



initiation and ongoing management; therefore, national guidelines that are adaptable to local needs will be of vital importance. Improved documentation, quality assurance, and evaluation of outcomes that are meaningful for patients will help to shape and to refine guidelines. Future research should address the effectiveness of ECPR guidelines in selecting appropriate candidates and improving patient outcomes and survival.

## REFERENCES

- Chai PJ, Jacobs JP, Dalton HJ, et al. Extracorporeal cardiopulmonary resuscitation for post-operative cardiac arrest: Indications, techniques, controversies, and early results—What is known (and unknown). *Cardiol Young*. 2011;21(Suppl 2):109–17.
- Peberdy MA, Kaye W, Ornato JP, et al. Cardiopulmonary resuscitation of adults in the hospital: A report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. *Resuscitation*. 2003;58:297–308.
- Krittayaphong R, Saengsung P, Chawaruechai T, et al. Factors predicting outcome of cardiopulmonary resuscitation in a developing country: The Siriraj cardiopulmonary resuscitation registry. *J Med Assoc Thai*. 2009;92:618–23.
- Nadkarni VM, Larkin GL, Peberdy MA, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA*. 2006;295:50–7.
- Schultz SC, Cullinane DC, Pasquale MD, et al. Predicting in-hospital mortality during cardiopulmonary resuscitation. *Resuscitation*. 1996;33:13–7.
- Chen YS, Chao A, Yu HY, 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.
- Chiu CW, Yen, HH. Prolonged cardiac arrest: Successful resuscitation with extracorporeal membrane oxygenation. *Amer J Emerg Med*. 2013;1627.e5-1627e6.
- Cohen DO, Shubjeet K. Duration of CPR: How long is too long? A positive outcome after 90 minutes of CPR. Department of Anesthesiology at the University of Massachusetts Medical School. Presented at the Annual Meeting of the American Society of Anesthesiologists, Washington, DC, October 2012.
- Cardarelli MG, Young AJ, Griffith B. Use of extracorporeal membrane oxygenation for adults in cardiac arrest (E-CPR): A meta-analysis of observation studies. *ASAIO J*. 2009;55:581–6.
- Hajbaghery MA, Mousavi G, Akbari H. Factors influencing survival after in-hospital cardiopulmonary resuscitation. *Resuscitation*. 2005;66:317–21.
- Chen YS, Yu HY, Huang SC, et al. Extracorporeal membrane oxygenation support can extend the duration of cardiopulmonary resuscitation. *Crit Care Med*. 2008;36:2529–35.
- Andreka P, Frenneaux MP. Hemodynamics of cardiac arrest and resuscitation. *Curr Opin Crit Care*. 2006;12:198–203.
- Riou B, Adnet F, Baud F, et al. Guidelines for indications for the use of extracorporeal life support in refractory cardiac arrest. *Ann Fr Anesth Reanim*. 2009;28:182–90.
- ECC Committee, Subcommittees and Task Forces of the American Heart Association. American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2005;112:S1–203.
- Lazzeri C, Bernardo P, Sori A, et al. Venous-arterial extracorporeal membrane oxygenation for refractory cardiac arrest: A clinical challenge. *Eur Heart J*. 2013;2:118–26.
- Bistrussu S, Beeton A, Castaldo G, et al. Are extracorporeal membrane oxygenation circuits that are primed with Plasmalyte and stored a likely source of infection? *J Clin Microbiol*. 2004;42:3906.
- Karimova A, Robertson A, Cross N, et al. A wet-primed extracorporeal membrane oxygenation circuit with hollow-fiber membrane oxygenator maintains adequate function for use during cardiopulmonary resuscitation after 2 weeks on standby. *Crit Care Med*. 2005;33:1572–6.
- Shin TG, Jo IJ, Slim MS, et al. Two year survival and neurological outcome of in-hospital cardiac arrest patients rescued by extracorporeal cardiopulmonary resuscitation. *Int J Cardiol*. 2013;168:3424–30.
- Kelly RB, Harrison RE. Outcome predictors of pediatric extracorporeal cardiopulmonary resuscitation. *Pediatr Cardiol*. 2010;31:626–33.
- Huang SC, Wu ET, Chen YS, et al. Extracorporeal membrane oxygenation rescue for cardiopulmonary resuscitation in pediatric patients. *Crit Care Med*. 2008;36:1607–13.
- Kane DA, Thiagarajan RR, Wypji D, et al. Rapid-response extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in children with cardiac disease. *Circulation*. 2010;122(Suppl):S241–8.
- Raymon TT, Cunyngham CB, Thompson MT, et al. Outcomes among neonates, infants, and children after extracorporeal cardiopulmonary resuscitation for refractory in-hospital pediatric cardiac arrest: A report from the National Registry of Cardiopulmonary Resuscitation. *Pediatr Crit Care Med*. 2010;11:362–71.
- Cheliout-Heraut F, Rubinsztajn R, Lous C, et al. Prognostic value of evoked potentials and sleep recordings in the prolonged comatose state of children. Preliminary data. *Neurophysiol Clin*. 2001;31:283–92.
- Mewasingh LD, Christophe C, Fonteyne C, et al. Predictive value of electrophysiology in children with hypoxic coma. *Pediatr Neurol*. 2003;28:178–83.
- Bottiger BW, Moles S, Glatzer R, et al. Astroglial protein S-100 is an early and sensitive marker of hypoxic brain damage and outcome after cardiac arrest in humans. *Circulation*. 2001;103:2694–8.
- Levine RL, Wayne MA, Miller CC. End-tidal carbon dioxide and outcome of out-of-hospital cardiac arrest. *N Engl J Med*. 1997;337:301–4.
- Patroniti N, Zangrillo A, Pappalardo F, et al. The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: Preparation for severe respiratory emergency outbreaks. *Intensive Care Med*. 2011;37:1447–57.