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Extracorporeal Life Support during Cardiac Arrest Resuscitation in a Porcine Model of Ventricular Fibrillation

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Abstract: Implementation barriers for extracorporeal life support in out-of-hospital cardiac arrest (OHCA) include initiation delay and candidate selection. We explored ischemia duration, cardiopulmonary resuscitation (CPR) duration, and physiologic variables that discriminated animals with return of spontaneous circulation (ROSC). We instrumented eight female swine (31.9 ± 9.8 kg) with femoral artery and external jugular vein cannula. After 8 (n = 4) or 15 (n = 4) minutes ventricular fibrillation (VF), animals received 30, 40, 50, or 60 minutes of CPR and then drugs (.6 U/kg vasopressin, .1 mg/kg epinephrine, .1 mg/kg propranolol, sodium bicarbonate as indicated) after 5 minutes of CPR. Extracorporeal membrane oxygenation (ECMO) flow rate was 3 L/min ≤2 hours and then 1.5 L/min ≤2 hours before weaning. Animals were defibrillated (150 J biphasic) ≥15 minutes ECMO. Primary outcome for successful resuscitation was ROSC (organized rhythm with systolic blood pressure >80 mmHg). We measured arterial blood gas, electrolytes, mean arterial pressure (MAP), coronary perfusion pressure (CPP), and five quantitative VF waveform measures at key intervals. Continuous variables were compared with two-sample t test. All 8-minute VF animals were successfully resuscitated and had ROSC. MAP was higher at the beginning (27.0 ± 7.1 vs. 15.0 ± 4.4; p = .03) and end (31.3 ± 12.8 vs. 11.5 ± 7.3; p = .03) of CPR in animals successfully resuscitated. CPP was higher at the beginning of CPR (11.9 ± 4.6 vs. 3.3 ± 2.2; p = .01) and the end of CPR (18.5 ± 12.1 vs. .9 ± 1.4; p = .03) among animals with ROSC. Amplitude spectrum area (AMSA) was superior at the end of CPR (–2.0 ± 1.8 vs. –5.0 ± 1.4; p = .04) in animals successfully resuscitated. In a porcine OHCA model, MAP and CPP at the beginning and end of CPR were higher in animals successfully resuscitated. AMSA was superior at the end of CPR in animals successfully resuscitated. **Keywords:** cardiac arrest, ventricular fibrillation, cardiopulmonary resuscitation, extracorporeal membranous oxygenation (ECMO). *JECT. 2013;45:33–39*

Approximately 540,000 victims experience sudden cardiac death each year in the United States. Despite 57 years of refinement, advanced life support only affords 6.4% of victims survival to hospital discharge (1). A new resuscitation paradigm is needed. Regimented postresuscitation care has heralded improvements in neurologically intact survival to hospital discharge (2), but similar advances in resuscitation techniques have been lacking.

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University of Pittsburgh Institutional Animal Care and Use Committee Protocol No. 1111937.
Dr. Menegazzi is co-inventor of a patented method for analyzing the ECG, which was previously licensed to Medtronic and for which he received royalties. That agreement has been terminated and he no longer receives royalties.

Extracorporeal life support (ECLS), the incorporation of extracorporeal membranous oxygenation (ECMO) into active resuscitation, is a therapy that warrants closer investigation, because 50% of patients receiving cardiopulmonary resuscitation (CPR) never regain a pulse (3) and survival declines rapidly if CPR lasts beyond 10–15 minutes (4,5). CPR provides a "low-flow" state, approximating 25–30% of cardiac output (6), whereas ECLS can reperfuse at physiologic levels. It was introduced as a resuscitation tool in the 1960s (7) but until recently has been primarily used in pediatrics (8–10).

A 2006 systematic review of ECLS for adult, nontraumatic cardiac arrest (11) yielded 54 studies of 675 patients in a combination of case reports, case-series, or case–control studies. It found that 44.9% ± 6.7% of patients survived to hospital discharge, concluding that ECLS appeared to be an efficacious intervention. Subsequent retrospective cohort studies have further examined use in out-of-hospital cardiac arrest (OHCA), noting 10–48% neurologically intact survival to hospital discharge

and an inverse relationship between survival and collapse-to-ECLS interval (12–14).

Clinical protocols using ECLS in OHCA typically use selection criteria based on "historic" rather than "physiologic" characteristics: age, initial rhythm, delay until CPR, transport time, and total arrest time (15,16). Guidelines for patient selection are primarily expert opinion or institutional consensus.

Using our established porcine model of ventricular fibrillation (VF) OHCA, we aimed to 1) explore global ischemia (untreated VF) followed by clinically realistic CPR durations that could be overcome with ECLS to achieve return of spontaneous circulation (ROSC), short-term survival, and rapid weaning from ECMO; and 2) assess whether laboratory, hemodynamic, or electrophysiologic variables measured during ongoing CPR could discriminate between animals with and without ultimate ROSC.

MATERIALS AND METHODS

This study was approved by the University of Pittsburgh Institutional Animal Care and Use Committee. It was conducted in accordance with National Institutes of Health guidelines.

Animal Preparation

Female domestic swine (*Sus scrofa*) were prepared in a standardized fashion. We sedated with intramuscular ketamine (10 mg/kg) and xylazine (4 mg/kg) and then obtained intravenous (IV) access via a peripheral ear vein using a 20-gauge IV catheter. We established anesthesia using a rapid IV infusion of fentanyl (50 μg/kg) and continuous infusion (30–100 μg/kg/min).

We intubated the swine with a 5-0 cuffed endotracheal tube via direct laryngoscopy, ventilating them with FiO_2 21% using an Ohmeda 7000 ventilator (Ohmeda; BOC Health Care, Madison, WI). Ventilation was begun at a tidal volume of 15–20 mL/kg, a ventilatory rate of 12–16 breaths per minute, and an inspiration-to-expiration ratio of 40%. Ventilation was adjusted to maintain eucapnia (end-tidal CO_2 35–45 torr), which was measured with a side-stream capnometer (M-series; ZOLL, Chelmsford, MA). We measured body temperature by esophageal probe (Bi-Temp Temperature Monitor; Respiratory Supply Products, Inc., Irvine, CA) and placed three surface electrodes configured to a standard Lead II electrocardiogram (ECG). Finally, we paralyzed the animals with pancuronium (4-mg initial IV bolus; 2-mg boluses as needed).

We placed 9-Fr introducers in the left femoral artery and vein, passing 7-Fr micromanometer-tipped catheters (Mikro-Tip Catheter Transducers SPR-471A and SPC-370-S; Millar Instruments, Houston, TX) into the ascending aorta and right atrium. Positioning was confirmed by pressure tracing. Data were acquired digitally at a sampling rate of 1000 points/sec with a commercially available software package (LabChart 7; AD Instruments, Colorado Springs, CO). We analyzed an arterial blood gas when arterial access was established (Portable Clinical Analyzer, I-Stat; Heska Corp., Wakesha, WA), when ventilator settings were changed, and just before VF induction.

Extracorporeal Life Support

Cannulation for ECLS took place during instrumentation to minimize surgical misadventures during ongoing resuscitation. The ECMO circuit comprised one arterial input catheter and one venous output catheter. The right femoral artery and external jugular vein were exposed by cutdown. A 14-Fr stainless steel-tipped catheter was placed in the femoral artery and a 18-Fr coil-reinforced catheter was placed in the external jugular vein. The catheters were flushed with heparizinized .9% saline and clamped. The bypass circuit was driven by a centrifugal pump head (Bio-Medicus Bio-pump BP80; Medtronic, Inc., Brooklyn Park, MN) in line with a hollow-fiber oxygenator (Affinity NT; Medtronic, Inc.). The circuit was primed with .9% saline (700 mL), preheparinized with 225 U/kg heparin, and had 50% oxygen air mix delivered to the oxygenator. Animals did not receive heparin before the induction of VF. A water-circulating heat exchanger maintained a temperature of 34°C. Control of all circuit components was managed through a Bard CPS Cardiopulmonary Bypass System (C.R. Bard, Inc., Murray Hill, NJ).

We induced VF transthoracically with 3-second, 603Hz, 1003mA alternating current. VF was confirmed by the ECG tracing and absence of pulses in the arterial waveform. We recorded the anesthesia duration (time from initial bolus of fentanyl until VF induction).

Experimental Design

As a preliminary study, we explored the a range of VF and CPR durations that could be resuscitated with ECMO. We used a factorial, nonrandomized, sequential allocation method for each animal intended to model a clinically realistic range of times for emergency medical services dispatch, patient packaging/transportation, and preparation/initiation of ECLS. Animals 1–4 were subjected to 8 minutes of untreated VF followed by 30, 40, 50, and 60 minutes of CPR, respectively. Animals 5–8 were subjected with 15 minutes of untreated VF followed by 30, 40, 50, and 60 minutes of CPR, respectively.

Figure 1 depicts the experimental timeline. After the designated interval of untreated VF, we began mechanical CPR with the LUCAS2 device (LUCAS; Jolife, Lund, Sweden) at a rate of 30:2. Manual ventilations were performed to maintain end-tidal CO_2 between 35 and 45 torr. After 5 minutes of CPR, we administered the standard drug cocktail for our porcine model (.6 U/kg vasopressin, .10 mg/kg

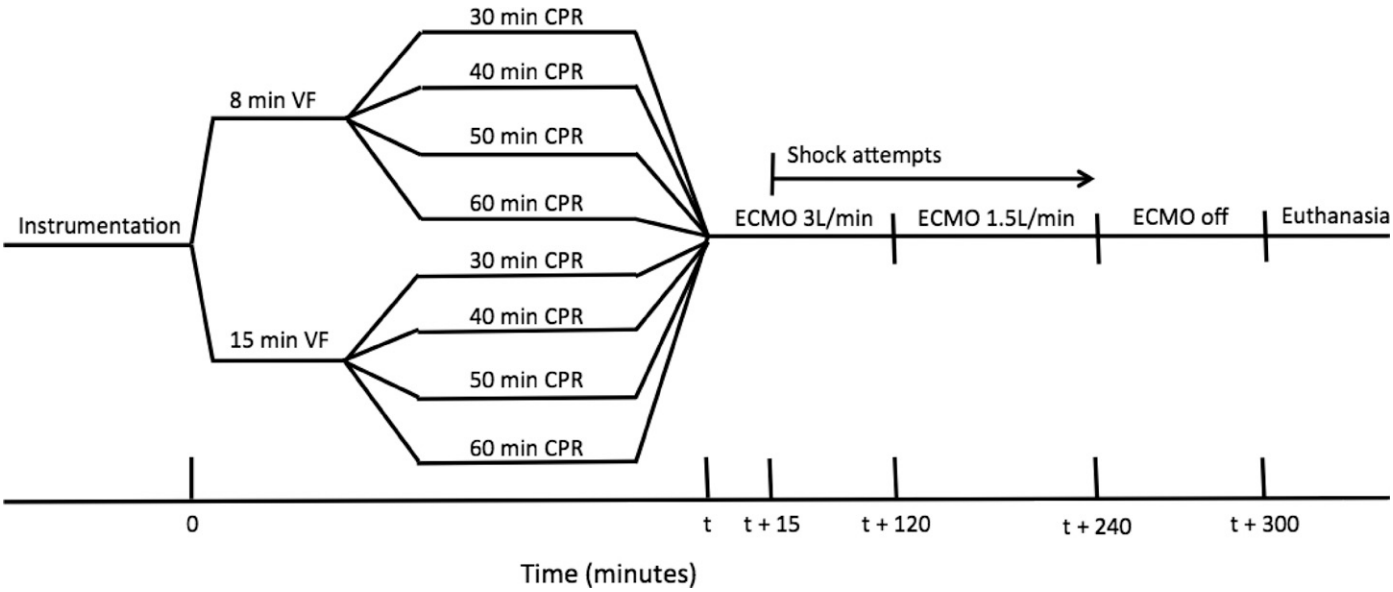

Figure 1. Timeline of the experimental protocol. VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membranous oxygenation.

epinephrine, .1 mg/kg propranolol) via the central venous catheter. Repeat doses of epinephrine (.015 mg/kg) were administered as needed to maintain coronary perfusion pressure above 30 mmHg. Acidemia was corrected with sodium bicarbonate (.3 mEq × kg × base deficit) to maintain a normal pH (7.35–7.45). After conventional resuscitation, animals were reperfused with ECMO. Oxygen flow through the oxygenator was adjusted to pO_2 100–120 mmHg. We ventilated during reperfusion to maintain alveolar expansion and prevent atelectasis. Activated clotting time was maintained above 250 seconds. The flow rate was initially 3 L/min (72–136 mL/kg), which approximates normal resting cardiac output in 31.9 ± 9.8 kg swine.

After 15 minutes of reperfusion, animals were defibrillated using biphasic 150J (M-series; ZOLL, Chelmsford, MA). If necessary for ROSC, additional epinephrine (.015 mg/kg) was administered. We defined ROSC as organized ECG with a systolic blood pressure ≥80 mmHg sustained for 20 minutes. After ROSC, norepinephrine infusion was titrated to maintain mean arterial pressure (MAP) above 60 mmHg.

Two hours after the start of reperfusion, the flow rate of the ECMO circuit was reduced to 1.5 L/min (36–68 mL/kg). Four hours after the start of reperfusion, we attempted to wean animals by titrating the norepinephrine while decreasing ECMO flow to keep the MAP above 60 mmHg.

The primary outcome for successful resuscitation was ROSC. Additional end points were successful ECMO weaning and 1-hour survival after weaning. Animals successfully weaned were euthanized 1 hour after weaning was completed. Animals unable to be weaned were euthanized 1 hour after weaning attempts were started. Animals that never achieved ROSC after 4 hours of ECLS were considered a failed resuscitation.

Hemodynamic Variables

MAP was autocalculated by the data collection software (LabChart 7; AD Instruments, Colorado Springs, CO). We determined the mean MAP for 20-second epochs at key intervals throughout the protocol.

During CPR, coronary perfusion pressure (CPP) was defined as aortic diastolic pressure – right atrial diastolic pressure immediately before the compression upsurge in pressure (i.e., end-relaxation). Custom MatLab (Mathworks, Natick, MA) code-identified, isolated, and analyzed CPP tracing segments corresponding to individual chest compressions. Mean CPP was calculated for 60-compression epochs during CPR. During ECLS, CPP was defined as aortic diastolic pressure minus right atrial diastolic pressure. Mean CPP was calculated for 20-second epochs at key intervals during ECLS.

Quantitative Electrocardiographic Waveform Measures

The ECG signal was collected from lead II configuration surface electrodes connected to a commercial signal amplifier (DAM-50; WPI, Inc., Sarasota, FL). Methods for calculating amplitude spectrum area (AMSA), median slope (MS), logarithm of absolute correlations (LAC), frequency ratio (FR), and cardioversion output predictor (COP) have been described previously (17–20). Before calculation of each measure, ECG signal was downsampled

Table 1. Outcome of resuscitation.

VF Duration (minutes)	CPR Duration (minutes)			
	30	40	50	60
8	Wean	Wean	ROSC*	Survival
15	Survival	Rhythm	Rhythm	Rhythm

Better Outcome ↑

Wean: ROSC for 1 hour after discontinuation of ECMO
Survival: ROSC for 1 hour while on ECMO
ROSC: Organized ECG with a systolic blood pressure ≥ 80 mmHg
Rhythm: Organized ECG rhythm with a systolic blood pressure ≤ 80 mmHg

*Technical difficulties with extracorporeal membranous oxygenation circuit.
VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

from 1000 Hz to 250 Hz. All calculations were made with original ECG voltages as recorded, which was not standardized, normalized, or filtered. The resulting signal was divided into sequential windows of 1250 samples (i.e., 5 seconds). All qualitative electrocardiographic waveform measures (QWMs) were calculated as the mean of three consecutive 5-second epochs at key intervals throughout the experimental protocol.

Statistical Analysis

We used Microsoft Excel 2011 (Microsoft Corporation, Redmond, WA), MatLab 7.11.0 (Mathworks, Natick, MA), and STATA 12.0 (StataCorp, College Station, TX) to record and analyze the data. Baseline characteristics (i.e., sex, weight, anesthesia duration, laboratory values) were determined with descriptive statistics. We performed two-sample *t* test with unequal variance for laboratory, hemodynamic, and QWM values at each phase of resuscitation using $\alpha = .05$. Variables that differed between groups were further analyzed to determine test performance characteristics for ultimate ROSC.

RESULTS

Eight female swine were analyzed with a mean mass of 31.9 ± 9.8 kg and mean anesthesia duration of 53.3 ± 3.9 minutes. Table 1 depicts the outcome for each animal. Outcome improved with shorter VF and CPR durations.

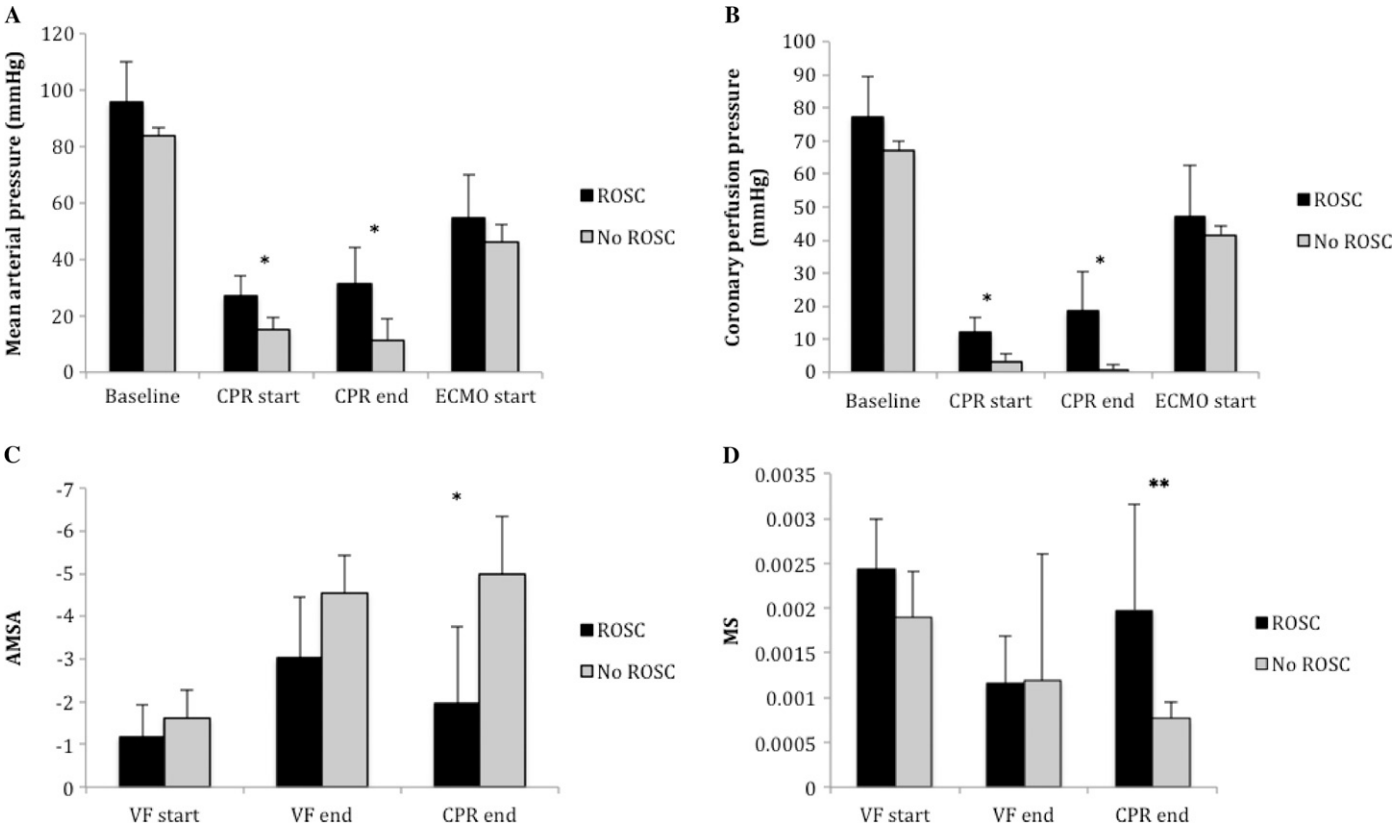

Figure 2. Mean and standard deviation mean arterial pressure (**A**), coronary perfusion pressure (**B**), AMSA (**C**), and MS (**D**) at key intervals throughout the experimental protocol. AMSA, amplitude spectrum area; MS, median slope; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membranous oxygenation; VF, ventricular fibrillation; ROSC, return of spontaneous circulation. *$p < .05$. **$p < .10$.

The most prolonged successful resuscitation occurred 1 hour 27 minutes after VF onset.

Neither weight (ROSC 28.1 ± 1.7; no ROSC 41.5 ± 17.4; p = .10) nor anesthesia duration (ROSC 52.8 ± 3.9; no ROSC 54.5 ± 4.9; p = .72) differed between groups. There were clinically insignificant differences in baseline sodium (ROSC 141.8 ± 1.0 mEq/L; no ROSC 137.5 ± .7 mEq/L; p = .01), baseline potassium (ROSC 3.5 ± .3 mEq/L; no ROSC 4.0 ± .1 mEq/L; p = .03), and ionized calcium at the start of CPR (ROSC 1.4 ± .1 mEq/L; no ROSC 1.5 ± .1 mEq/L; p = .04). Otherwise, laboratory values did not differ between animals with or without ROSC.

MAP and CPP at each phase of resuscitation are given in Figure 2A–B. MAP was higher at the beginning of CPR (ROSC 27.0 ± 7.1; no ROSC 15.0 ± 4.4; p = .03) and the end of CPR (ROSC 31.3 ± 12.8; no ROSC 11.5 ± 7.3; p = .03) among animals resuscitated. CPP was higher at the beginning of CPR (ROSC 11.9 ± 4.6; no ROSC 3.3 ± 2.2; p = .01) and the end of CPR (ROSC 18.5 ± 12.1; no ROSC .9 ± 1.4; p = .03) among animals successfully resuscitated. Of these four variables, CPP at the end of CPR perfectly predicted ROSC with a cutoff of 2.2 mmHg. The other three variables predicted ROSC with sensitivity 80%, specificity 67%, positive predictive value (PPV) 80%, negative predictive value (NPV) 67%, and area under the ROC curve (AUROC) .93 (Figure 3).

QWM at each phase of resuscitation are given in Table 2. COP, FR, and LAC did not differ among animals, whereas AMSA and MS at the end of CPR were superior in animals successfully resuscitated (Figure 2C–D). AMSA was superior at the end of CPR (ROSC –2.0 ± 1.8; no ROSC –5.0 ± 1.4; p = .04) in animals resuscitated. MS trended toward superiority at the end of CPR (ROSC $2.0 \times 10^{-3} \pm 1.2 \times 10^{-3}$; no ROSC $.8 \times 10^{-3} \pm .2 \times 10^{-3}$; p = .08). AMSA at the end of CPR also predicted ROSC with a sensitivity 80%, specificity 67%, PPV 80%, NPV 67%, and AUROC .93 (Figure 3).

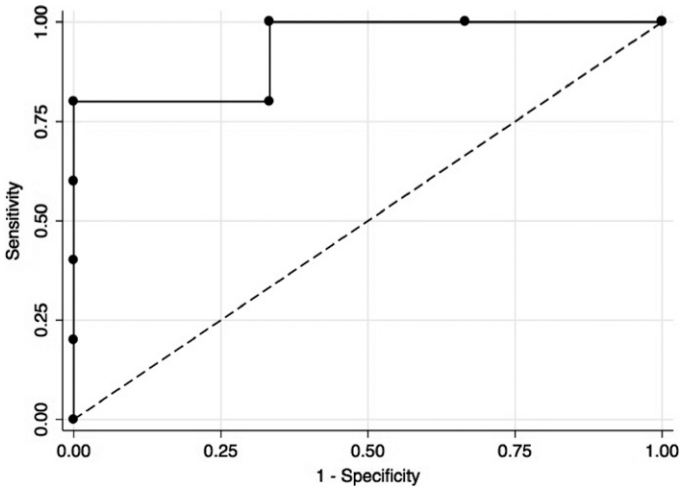

Figure 3. Receiver operating characteristic (ROC) curve for unadjusted predictors of return of spontaneous circulation with an area under the ROC curve = .933.

Table 2. Mean and standard deviation for QWM values between animals with and without return of spontaneous circulation (ROSC).

	No ROSC (n = 3)	ROSC (n = 5)	p Value
Start of VF			
COP	$-5.0 \times 10^{9} \pm 9.9 \times 10^{8}$	$-4.9 \times 10^{9} \pm 1.6 \times 10^{9}$	.95
AMSA	–1.6 ± .7	–1.2 ± .7	.44
FR	41.9 ± 19.4	53.4 ± 39.7	.60
MS	$1.9 \times 10^{-3} \pm 5.1 \times 10^{-4}$	$2.4 \times 10^{-3} \pm 5.6 \times 10^{-4}$	.23
LAC	–2.9 ± .2	–2.6 ± .4	.27
End of VF			
COP	$-1.3 \times 10^{10} \pm 8.1 \times 10^{9}$	$-1.1 \times 10^{10} \pm 7.5 \times 10^{9}$	.68
AMSA	–4.5 ± .9	–3.0 ± 1.4	.12
FR	1.2 ± .8	7.6 ± 11.4	.28
MS	$1.2 \times 10^{-3} \pm 1.4 \times 10^{-3}$	$1.2 \times 10^{-3} \pm 5.2 \times 10^{-4}$	.98
LAC	–3.7 ± .3	–3.4 ± .5	.41
End of CPR			
COP	$-1.8 \times 10^{10} \pm 7.3 \times 109$	$-.8 \times 10^{10} \pm 6.3 \times 10^{9}$	.14
AMSA	–5.0 ± 1.4	–2.0 ± 1.8	.04
FR	.4 ± .3	10.2 ± 17.4	.28
MS	$.8 \times 10^{-3} \pm .2 \times 10^{-3}$	$2.0 \times 10^{-3} \pm 1.2 \times 10^{-3}$	.08
LAC	–3.7 ± .6	–2.9 ± .6	.14

QWM, waveform measures; VF, ventricular fibrillation; COP, cardioversion output predictor; AMSA, amplitude spectrum area; FR, frequency ratio; MS, median slope; LAC, logarithm of absolute correlations.

DISCUSSION

ECLS may represent the next paradigm shift in OHCA treatment. The 2010 International Liaison Committee on Resuscitation guidelines recommend consideration of ECLS for patients in cardiac arrest when it is readily available and the condition leading to cardiac arrest is reversible or amenable to other therapy (21).

We successfully resuscitated animals with ECLS across clinically realistic ischemia (8 or 15 minutes) and CPR duration (30–60 minutes). A 2010 Japanese clinical series of ECLS in OHCA reported a median interval of 1 minute (interquartile range [IQR], 1–8 minutes) from collapse to start of CPR and a median interval of 59 minutes (IQR 45–65) from collapse to reperfusion (15). A different 2010 Japanese clinical series reported a median interval of 10 minutes (IQR, 8–13) from collapse to EMS arrival with 55% receiving bystander CPR (13).

Standardized patient selection criteria for this resource-intensive intervention are lacking. Criteria currently used tend to select patients based on historical case data rather than real-time physiological data. A 2010 Japanese series included patients with ages 18–74 years, ventricular fibrillation present on ECG, an estimated interval of <15 minutes from collapse to CPR, a presumed cardiac or cor

pulmonale etiology, and the inability to achieve ROSC with 20 minutes of conventional resuscitation (13). A recent U.S. case series of emergency department-initiated ECLS included patients with persistent cardiac arrest despite resuscitative efforts, excluding those asystolic on initial evaluation, without CPR initiated within 10 minutes of arrest, with prehospital transport time >10 minutes, with a total arrest duration >60 minutes, clinically suspicious for septic or hemorrhagic shock, or with pre-existing severe neurological disease (16).

Nagao et al. reported the optimal ROC cutoff of collapse-to-reperfusion interval as 55.5 minutes with classification accuracy of 85.4% for identifying favorable neurologic outcome. Additionally, the optimal reperfusion-to-34°C interval was 21.5 minutes with classification accuracy of 89.5% for identifying favorable neurologic outcome (13).

Mégarbane et al. evaluated routine laboratory studies in 66 adult victims of in-hospital and OHCA just before cannulation for ECMO. They measured serum potassium, creatinine, aminotransferases, platelet count, prothrombin index, activated clotting time, fibrinogen, peripheral venous oxygen saturation ($SpvO_2$), arterial blood gases, and lactate. In multivariate analysis, precannulation $SpvO_2$ predicted early multiple organ failure and premature ECMO discontinuation within the first 24 hours. $SpvO_2$ < 8% maximized PPV of failure at 1, whereas $SpvO_2$ > 80% maximized NPV for failure at 1. The optimal cutoff to maximize both sensitivity (.68) and specificity (.81) of failure was $SpvO_2$ 33% (22).

Several of the hemodynamic and electrophysiologic variables we preliminarily explored in this small series discriminated between animals with and without ultimate ROSC. The intervals at which we measured (e.g., end of untreated VF, start of CPR, end of CPR) represent potential key decision points during evaluation of a candidate for ECLS. We envision a model for OHCA resuscitation that features prehospital identification of ECLS candidates via noninvasive real-time physiologic feedback. Potential measures include $SpvO_2$, QWM, $EtCO_2$, tissue oximetry, cerebral oximetry, and pupillometry (23–28). These patients could be expediently transported to a cardiac arrest center with continuous mechanical chest compressions en route as a bridge to extracorporeal reperfusion. Hospital personnel could then begin a phased intervention (16) during a more invasive evaluation of hemodynamics.

Limitations

We analyzed young healthy swine whose physiology may not reflect that of typical human patients with cardiac arrest. We placed the ECMO catheters during initial instrumentation to minimize surgical misadventures. However, we have demonstrated the ability to cannulate during ongoing CPR (29). Our discussion of resuscitation hemodynamics is limited to CPP, which is a product of coronary blood flow and vascular resistance. We use a closed-chest model of young swine, which do not have any known coronary artery disease that would limit myocardial blood flow. Typical patients with cardiac arrest have a burden of cardiovascular disease with increased coronary vascular resistance, adversely affecting the translation of pressure into flow. VF was electrically induced.

CONCLUSION

In our porcine model of out-of-hospital VF cardiac arrest, ROSC is achievable with ECLS after bridging with 30–60 minutes of mechanical CPR. In a clinically realistic mixture of heterogeneous VF and CPR durations, MAP and CPP at the beginning and end of CPR were higher in animals successfully resuscitated (RSOC). AMSA was superior at the end of CPR in animals resuscitated.

REFERENCES

1. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300:1423–31.
2. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardized treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation. 2007;73:29–39.
3. Hostler D, Everson-Stewart S, Rea TD, et al. Effect of real-time feedback during cardiopulmonary resuscitation outside hospital: Prospective, cluster-randomised trial. BMJ. 2011;342:d512.
4. Cummins RO, Eisenberg MS, Hallstrom AP, Litwin PE. Survival of out-of-hospital cardiac arrest with early initiation of cardiopulmonary resuscitation. Am J Emerg Med. 1985;3:114–8.
5. Pionkowski RS, Thompson BM, Gruchow HW, Aprahamian C, Darin JC. Resuscitation time in ventricular fibrillation—A prognostic indicator. Ann Emerg Med. 1983;12:733–8.
6. Barsan WG, Levy RC. Experimental design for study of cardiopulmonary resuscitation in dogs. Ann Emerg Med. 1981;10:135–7.
7. Kennedy JH. The role of assisted circulation in cardiac resuscitation. JAMA. 1966;197:615–8.
8. Thiagarajan RR, Laussen PC, Rycus PT, Bartlett RH, Bratton SL. Extracorporeal membrane oxygenation to aid cardiopulmonary resuscitation in infants and children. Circulation. 2007;116:1693–700.
9. Haines NM, Rycus PT, Zwischenberger JB, Bartlett RH, Undar A. Extracorporeal Life Support Registry Report 2008: Neonatal and pediatric cardiac cases. ASAIO J. 2009;55:111–6.
10. 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.
11. Nichol G, Karmy-Jones R, Salerno C, Cantore L, Becker L. Systematic review of percutaneous cardiopulmonary bypass for cardiac arrest or cardiogenic shock states. Resuscitation. 2006;70:381–94.
12. Tanno K, Itoh Y, Takeyama Y, Nara S, Mori K, Asai Y. Utstein style study of cardiopulmonary bypass after cardiac arrest. Am J Emerg Med. 2008;26:649–54.
13. Nagao K, Kikushima K, Watanabe K, et al. Early induction of hypothermia during cardiac arrest improves neurological outcomes in patients with out-of hospital cardiac arrest who undergo emergency cardiopulmonary bypass and percutaneous coronary intervention. Circ J. 2010;74:77–85.

14. Morimura N, Sakamoto T, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: A review of the Japanese literature. Resuscitation. 2011;82:10–4.
15. Kagawa E, Inoue I, Kawagoe T, 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.
16. Bellezzo JM, Shinar Z, David DP, et al. Emergency physician-initiated extracorporeal cardiopulmonary resuscitation. Resuscitation. 2012;83:966–70.
17. Povoas HP, Weil MH, Wanchun T, Bisera J, Klouche K, Barbatsis A. Predicting the success of defibrillation by electrocardiographic analysis. Resuscitation. 2002;53:77–82.
18. Neurauter A, Eftestol T, Kramer-Johansen J, et al. Prediction of countershock success using single features from multiple ventricular fibrillation frequency bands and feature combinations using neural networks. Resuscitation. 2007;73:253–63.
19. Sherman LD, Rea TD, Waters JD, Menegazzi JJ, Callaway CW. Logarithm of the absolute correlations of the ECG waveform estimates duration of ventricular fibrillation and predicts successful defibrillation. Resuscitation. 2008;78:346–54.
20. Sherman LD. The frequency ratio: An improved method to estimate ventricular fibrillation duration based on Fourier analysis of the waveform. Resuscitation. 2006;69:479–86.
21. Cave DM, Gazmuri RJ, Otto CW, et al. Part 7: CPR techniques and devices. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;22:S720–8.
22. Mégarbane B, Deye N, Aout M, et al. Usefulness of routine laboratory parameters in the decision to treat refractory cardiac arrest with extracorporeal life support. Resuscitation. 2011;82:1154–61.
23. Reynolds JC, Salcido DD, Menegazzi JJ. Correlation between coronary perfusion pressure and quantitative ECG waveform measures during resuscitation of prolonged ventricular fibrillation. Resuscitation. 2012;83:1497–502.
24. Salcido DD, Kim YM, Sherman LD, et al. Quantitative waveform measures of the electrocardiogram as continuous physiologic feedback during resuscitation with cardiopulmonary bypass. Resuscitation. 2012;83:505–10.
25. Kolar M, Krizmaric M, Klemen P, Grmec S. Partial pressure of end-tidal carbon dioxide successful predicts cardiopulmonary resuscitation in the field: A prospective observational study. Crit Care. 2008;12:R115.
26. Frisch A, Suffoletto BP, Frank R, Martin-Gill C, Menegazzi JJ. Potential utility of near-infrared spectroscopy in out-of-hospital cardiac arrest: An illustrative case series. Prehosp Emerg Care. 2012;16:564–70.
27. Ito N, Nanto S, Nagao K, Hatanaka T, Nishiyama K, Kai T. Regional cerebral oxygen saturation on hospital arrival is a potential novel predictor of neurological outcomes at hospital discharge in patients with out-of-hospital cardiac arrest. Resuscitation. 2012;83:46–50.
28. Behrends J, Niemann CU, Larson MD. Infrared pupillometry to detect the light reflex during cardiopulmonary resuscitation: A case series. Resuscitation. 2012;83:1223–8.
29. Menegazzi JJ, Salcido DD, Housler GJ, Logue ES. Feasibility of initiating extracorporeal life support during mechanical chest compression CPR: A porcine pilot study. Resuscitation. 2012;83:130–3.