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Clinical paper

Surviving refractory out-of-hospital ventricular fibrillation cardiac arrest: Critical care and extracorporeal membrane oxygenation management☆

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ABSTRACT

Background: Resuscitation of refractory out-of-hospital ventricular fibrillation/ventricular tachycardia (VF/VT) cardiac arrest using extracorporeal membrane oxygenation (ECMO) establishes a complex patient population. We aimed to describe the critical care strategies and outcomes in this population.
Methods: Between December 1, 2015 and January 1, 2018, 100 consecutive adult patients with refractory VF/VT out-of-hospital cardiac arrest and ongoing CPR were transported to the cardiac catheterization laboratory. ECMO, coronary angiography, and percutaneous coronary intervention were performed. Patients achieving an organized cardiac rhythm were admitted to the cardiac intensive care unit (CICU). All patients were considered eligible for necessary intervention/surgery until declaration of death.
Results: Of 100 appropriately transported patients, 83 achieved CICU admission. 40/83 (48%) discharged functionally intact. Multi-system organ failure occurred in all patients. Cardiac, pulmonary, renal, and liver injury improved within 3–4 days. Neurologic injury caused death in 26/37 (70%) patients. Poor neurologic outcomes were associated with anoxic injury or cerebral edema on admission head CT, decline in cerebral oximetry over the first 48 h, and elevated neuron specific enolase on CICU admission. For survivors, mean time to ECMO decannulation was 3.5 ± 0.2 days, following commands at 5.7 ± 0.8 days, and hospital discharge at 21 ± 3.2 days. 41/83 (49%) patients developed infections. CPR caused traumatic injury requiring procedural/surgical intervention in 22/83 (27%) patients.
Conclusions: Multi-system organ failure is ubiquitous but treatable with adequate hemodynamic support. Neurologic recovery was prolonged requiring delayed prognostication. Immediate 24/7 availability of surgical and medical specialty expertise was required to achieve 48% functionally intact survival.

Introduction

Approximately 400,000 people in the United States suffer out-of-hospital cardiac arrest (OHCA) each year [1]. Of these, one-third present to emergency medical services (EMS) with an initial shockable rhythm (ventricular fibrillation/ventricular tachycardia [VF/VT]) [2,3]. Refractory VF/VT, defined as failure to achieve sustained return of spontaneous circulation (ROSC) after treatment with three defibrillation attempts and administration of 300 mg of amiodarone, occurs in 50% of patients [4,5]. Overall, VF/VT cardiac arrest has a functionally favorable survival rate of 29% [6], whereas refractory VF/VT reduces survival to no more than 8–15% [7–9].

Cardiac arrest results in progressive systemic injury worsening with prolonged resuscitation [10,11]. CPR-related trauma further complicates care. Successful ROSC leads to post-resuscitation syndrome with global myocardial stunning, inadequate cardiac output, and vasoplegia, reducing hemodynamic stability [12–14].

Extracorporeal cardiopulmonary resuscitation (ECPR) utilizing veno-arterial extracorporeal membrane oxygenation (ECMO) for refractory cardiac arrest provides near complete hemodynamic, oxygenation, and ventilation support [15]. The American Heart Association 2015 Guidelines incorporated consideration of ECPR for select cardiac arrest patients [16]. Refractory out-of-hospital VF/VT patients treated with ECPR represent a challenging patient population in the cardiac

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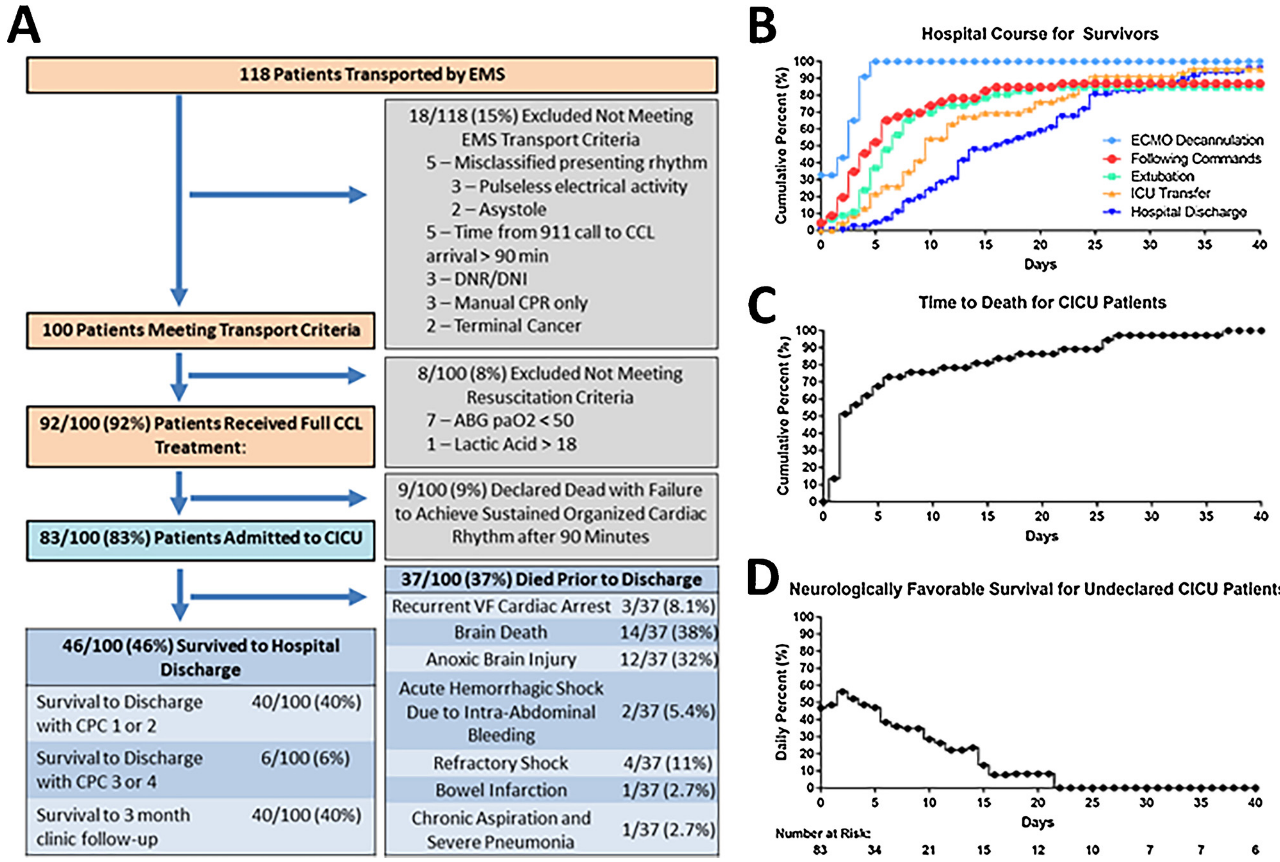


Fig. 1. Hospital course for patients participating in the MRC refractory VF/VT protocol. (A) Patient flow diagram (n = 118). Overall survival, and neurologically favorable survival are shown as a proportion of patients meeting transport criteria. Causes of death for patients admitted to the CICU are shown. (B) The hospital course of patients that survived to hospital discharge is shown with cumulative proportion of patients achieving major benchmarks. Two patients had extended hospital stays transferring out of the CICU at 59 and 141 days and discharging from the hospital at 68 and 141 days. Patients with poor neurologic recovery did not follow commands and were not extubated. (C) The time to death for patients who were admitted to the CICU but did not survive to hospital discharge is shown as the cumulative proportion of patients dead at each time point. (D) Daily likelihood of neurologically favorable survival for patients who have not yet followed commands nor been declared dead at each time period after admission. The number of patients at risk at each interval of 5 days of hospital admission is shown beneath. Abbreviations: EMS, emergency medical services; CCL, cardiac catheterization laboratory; ABG, arterial blood gas; CICU, cardiac intensive care unit; CPC, cerebral performance category; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; VF, ventricular fibrillation.

intensive care unit (CICU) rarely encountered previously in the United States.

The purpose of this study was to review our critical care experience with the first 100 out-of-hospital refractory VF/VT cardiac arrest patients treated with ECPR by the Minnesota Resuscitation Consortium's (MRC) protocol [9] and describe the critical care required.

Methods

Study design

Details of the MRC refractory VF/VT protocol at the University of Minnesota (Minneapolis, MN) have been previously published [7,9]. We analyzed the first 100 consecutive patients treated from December 1, 2015 through January 1, 2018. Implemented as clinical practice, data collection was performed as part of the program's quality improvement process. The Institutional Review Board (IRB) at the University of Minnesota approved this study (IRB number 1703M11301).

MRC refractory VF/VT protocol

Patients were screened by paramedics using the following transport criteria: 1) age 18–75 years, 2) OHCA of presumed cardiac etiology, 3) initial cardiac arrest rhythm of VF/VT, 4) received 3 direct current shocks without ROSC, 5) received Amiodarone 300 mg, 6) body habitus accommodating a Lund University Cardiac Arrest System (LUCAS®) automated CPR device, and 7) estimated transfer time to the cardiac catheterization laboratory (CCL) of < 30 min [9]. Patients were transported with mechanical CPR and ongoing advanced cardiac life support (ACLS) directly to the CCL and immediately assessed for effective resuscitation on CCL arrival. Any patient with ≥1 of the following was declared dead on CCL arrival: 1) end-tidal CO_2 < 10 mmHg, 2) PaO_2 < 50 mmHg, 3) lactic acid > 18 mmol/L, and 4) time from EMS activation to CCL arrival > 90 min. Patients not meeting these criteria underwent emergent ultrasound-guided percutaneous cannulation for peripheral veno-arterial ECMO performed by interventional cardiologists. For those achieving ROSC en route with sufficient hemodynamic stability, ECMO was deferred and an intra-aortic balloon pump (IABP; Maquet Cardiovascular) was placed. Coronary angiography was performed and percutaneous coronary intervention (PCI) provided, as indicated. For ECMO patients, a 9Fr distal perfusion cannula was percutaneously placed with ultrasound guidance in the CCL. In cases of severely reduced myocardial contractility or severe coronary artery disease, an IABP or Impella CP (Abiomed) was placed in combination with ECMO. All patients received a right radial arterial line and an intravascular cooling catheter (Thermogard XP, Zoll). If an organized cardiac rhythm could not be established after 90 min of stabilized hemodynamics and treatment of reversible cardiac arrest etiologies, the patient was declared dead. All patients with an organized rhythm were admitted to the CICU [9].

Table 1
Patient and arrest characteristics for patients admitted to the CICU.

Patient and Arrest Characteristics		(n = 83)
Sex, No. (%)	Male	64 (77%)
	Female	19 (23%)
Age, No. (%), y	< 40	10 (12%)
	40–60	43 (52%)
	> 60–75	30 (36%)
Ethnicity, No. (%)	White	67 (81%)
	Black	9 (11%)
	Other	7 (8.4%)
Known Comorbidities, No. (%)	Diabetes	19 (23%)
	Hypertension	37 (45%)
	Hyperlipidemia	25 (30%)
	Smoking	21 (25%)
	Coronary artery disease	18 (22%)
	Prior coronary artery stent	10 (12%)
	Coronary artery bypass grafting	7 (8.4%)
	Congestive heart disease	12 (14%)
	Chronic Renal Failure	2 (2.4%)
	Hemodialysis	2 (2.4%)
	Alcoholism	5 (6.0%)
	History of Stroke or Dementia	4 (4.8%)
Arrest Location, No. (%)	Home	45 (54%)
	Public Place	38 (46%)
Initial Cardiac Rhythm, No. (%)	VF/VT	83 (100%)
	Other	0 (0%)
Bystander CPR, No. (%)	Yes	60 (72%)
	No	23 (28%)
Time, mean (SEM), min	911 to first responder	7.6 (1.2)
	911 to CCL arrival	56.7 (1.8)
	CCL arrival to ECMO support	8 (0.5)

Abbreviations: VT/VF, ventricular tachycardia/ventricular fibrillation; CCL, cardiac catheterization laboratory; ECMO, extracorporeal membrane oxygenation.

Post-resuscitation critical care protocol

Standard critical care measures followed guideline statements for post-cardiac arrest care [13,17,18] and ECMO management [19] with the following additions. All patients received non-contrast computerized tomography (CT) scans of the head, chest, abdomen, and pelvis on CICU admission. All patients received therapeutic hypothermia (TH) for 24 h. Goal temperature was 34 °C with increases to 35–36 °C if significant bleeding occurred. Patients were maintained in 30-degree reverse trendelenburg with the head midline. Continuous electroencephalogram and cerebral oximetry via near infrared spectroscopy (NIRS; Equanox; Nonin) were initiated within 24 h. Hemodynamics were maintained with mechanical, inotrope, pressor, and vasodilator support with goal mean arterial pressure (MAP) between 65 and 100 mmHg. ECMO flow was maximized until pressors were discontinued, then reduced, as tolerated, promoting native cardiac function. ECMO decannulation readiness was assessed daily with short weaning trials and simultaneous echocardiography. On ECMO, rest ventilator settings were used with 7–10 cmH_2O positive end-expiratory pressure at 12 breaths per minute, and tidal volumes of 6–8 mL/kg ideal body weight. Plateau pressures were maintained below 30 cmH2O. Settings were adjusted after ECMO decannulation. Continuous veno-venous hemodialysis was provided when needed. Potassium was replaced up to 3.0 mmol/L during TH and 4.0 mmol/L once rewarmed. Enteral nutrition was provided via oral-gastric (OG) or nasal-gastric (NG) access once rewarmed. All patients received five days of empiric, broad-spectrum antibiotics with narrowed coverage thereafter, as necessary. Daily surveillance blood cultures were performed while on ECMO. Blood products were provided with a goal hemoglobin > 8 g/dL, platelets > 100,000 per μL, and fibrinogen > 200 mg/dL. Heparin maintained activated clotting time (ACT) 180–200 s while on ECMO. For life-threatening bleeding, the ACT goal was reduced as low as 140–160 s. All PCI patients received aspirin 81 mg and ticagrelor by NG or OG tube.

Data classification, management, and analysis

Patient outcome was classified as: 1) Survivors (to hospital discharge), 2) Brain Death (absent brainstem reflexes and either herniation on head CT or nuclear brain perfusion scan demonstrating no cerebral flow), and 3) Other Death (patients who died of causes not meeting brain death criteria, including cerebral anoxic injury and non-neurologic causes). A Cerebral Performance Category (CPC) score of 1 or 2 was considered functionally favorable survival.

Data were placed in a REDCap database. Out-of-hospital data included review of the paramedic run report and Cardiac Registry to Enhance Survival (CARES) database. Data were exported to Excel format for biostatistical analysis.

Data are presented as mean ± standard error of the mean and percentages. Statistical analysis was performed with GraphPad Prism 7 (GraphPad Software). Continuous variables were assessed with 2-way ANOVA with multiple comparisons performed using Tukey's multiple comparisons test. Categorical variables were compared using Fisher's Exact Test.

Results

The consort diagram is shown in Fig. 1A. Participating EMS agencies encountered 292 V F/VT patients aged 18–75 with presumed cardiac etiology including 147 with ROSC. Of the refractory patients, 100 met transport criteria, 92/100 (92%) met resuscitation criteria on CCL arrival and 83/100 (83%) achieved CICU admission.

Patient and arrest characteristics of the 83 patients admitted to the CICU are shown in Table 1. Patients were predominantly male (64/83 [77%]) and white (67/83 [81%]). The mean age was 56 ± 1.3 years while 10/83 (12%) were younger than 40. Cardiac arrests occurred at home in 45/83 (54%) while 60/83 (72%) received bystander CPR. First responder response time was 7.6 ± 1.2 min and time from 911 call to arrival in the CCL (estimated CPR duration) was 57 ± 1.8 min. ECMO was inserted within 8 ± 0.5 min of CCL arrival.

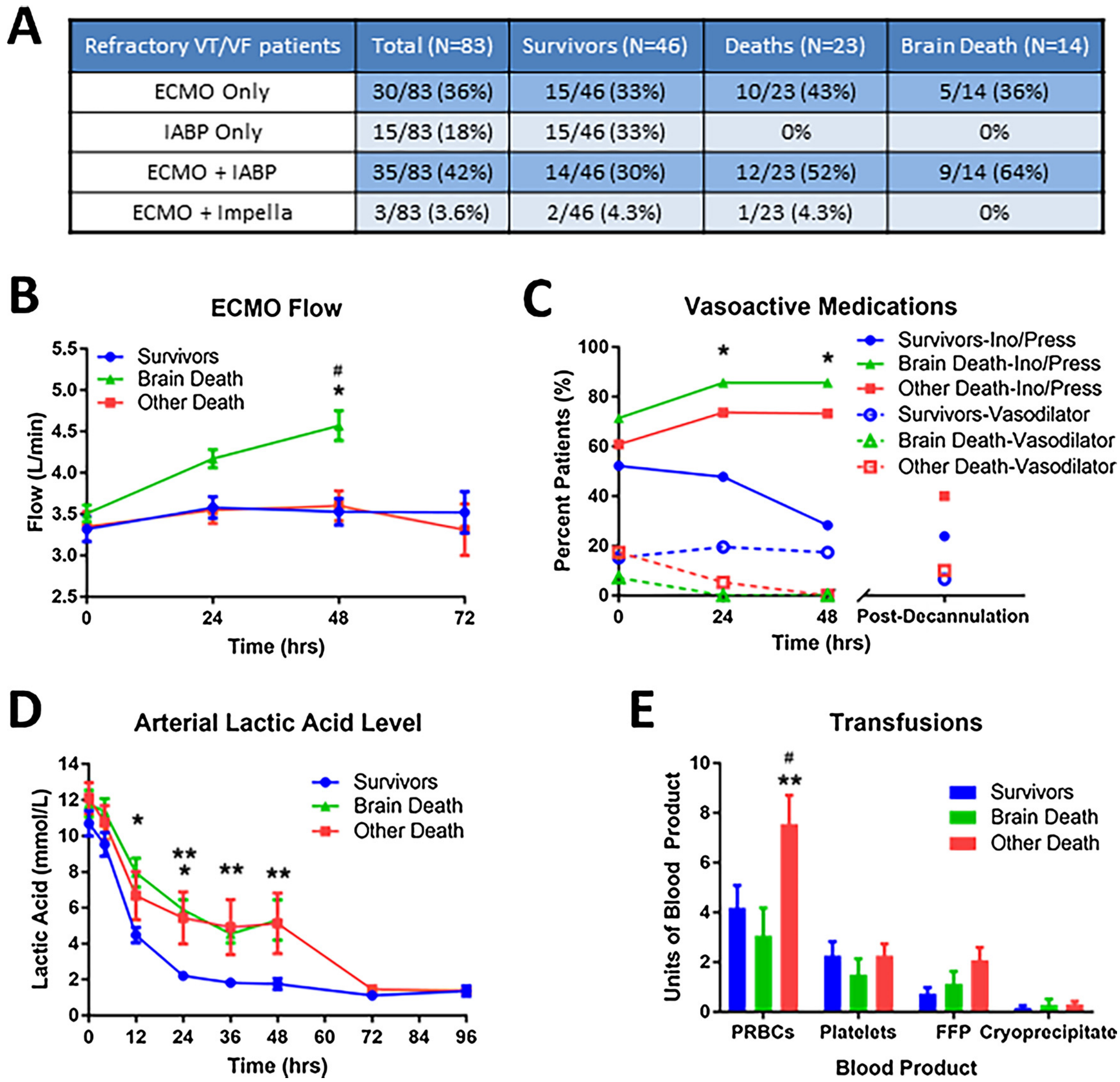
Hospital course

Of 83 patients admitted to the CICU, 46 were Survivors, 14 Brain Death, and 23 Other Death. Functionally favorable survival to hospital discharge occurred in 40/83 (48%) patients (Fig. 1A). All were alive and functionally intact (CPC = 1) at 3 months. 6/83 (7.2%) survived to hospital discharge with poor neurological function (CPC 3–4).

Time required to meet recovery benchmarks for Survivors is shown in Fig. 1B. ECMO was not required for 15/46 (33%) Survivors. Of the remaining 31/46 (67%), mean time to ECMO decannulation was 3.5 ± 0.2 days. Mean time to following commands and extubation for the 40 functionally favorable survivors was 5.7 ± 0.8 days and 7.4 ± 0.7 days, respectively. Survivors with poor neurologic recovery did not follow commands and received tracheostomy. Mean CICU duration for Survivors was 16 ± 3.2 days and hospital discharge was 21 ± 3.2 days.

Of the 37 patients who died prior to hospital discharge, mean time to death was 7.4 ± 1.5 days (Fig. 1C). Catastrophic neurologic injury caused death for 26/37 (70%) patients. Brain Death accounted for 14/37 [38%] deaths and anoxic brain injury accounted for 12/37 (32%) deaths. Non-neurologic causes included recurrent refractory VF (3/37), acute hemorrhagic shock (2/37), refractory vasoplegic shock (4/37), bowel infarction (1/37), and severe chronic aspiration pneumonia (1/37) (Fig. 1A).

Odds of functionally favorable survival decreased with increased CICU duration (Fig. 1D). Undeclared patients (those who were neither following commands nor declared dead) had a 48% rate of functionally



A

Refractory VT/VF patients	Total (N=83)	Survivors (N=46)	Deaths (N=23)	Brain Death (N=14)
ECMO Only	30/83 (36%)	15/46 (33%)	10/23 (43%)	5/14 (36%)
IABP Only	15/83 (18%)	15/46 (33%)	0%	0%
ECMO + IABP	35/83 (42%)	14/46 (30%)	12/23 (52%)	9/14 (64%)
ECMO + Impella	3/83 (3.6%)	2/46 (4.3%)	1/23 (4.3%)	0%

Fig. 2. Hemodynamic and transfusion support provided and the response of lactic acid levels. (A) The mechanical support provided to patients classified by outcome. (B) ECMO flow rates are shown over the first 72 h classified by patient outcome. (C) Percent of patients requiring inotrope/pressors and vasodilators is shown classified by patient outcome over the first 48 h of CICU admission and after ECMO decannulation. (D) The arterial blood lactic acid level is shown over the first 96 h of CICU admission classified by patient outcome. (F) The mean number of units of blood products per patient given over the course of the admission are shown for each of the blood products provided. Results are presented as mean ± SEM. Statistical significance ($p < 0.05$) is noted comparing survivors to patients with brain death (*), comparing survivors to deaths (**), or comparing deaths to brain deaths (#). Abbreviations: ECMO, Extracorporeal Membrane Oxygenation; Ino/Press, inotrope/pressor; PRBCs, Packed Red Blood Cells; FFP, Fresh Frozen Plasma.

favorable survival on CICU admission, declining to 8% at 21 days. The last patient discharged with functionally favorable survival began following commands 22 days after admission.

Hemodynamics and ECMO support

Hemodynamic support was provided as described (Fig. 2A). Eighty-two percent (68/83) of patients received ECMO while 38/68 (56%) also received an IABP or impella CP device. Only 15/83 (18%) patients achieved ROSC and sufficient hemodynamic stability to allow placement of an IABP alone.

Patients who developed brain death required significantly more hemodynamic support (Fig. 2B–C) with higher ECMO flows at 48 h compared to Survivors (4.6 ± 0.18 vs. 3.5 ± 0.16 L/min; p = 0.003) and Other Deaths (4.6 ± 0.18 vs. 3.6 ± 0.18 L/min; p = 0.014). Use of inotropes and pressors, most commonly epinephrine and vasopressin, was also higher in Brain Death patients compared to Survivors at 24 (86% vs. 48%, p = 0.015) and 48 h (86% vs. 28%, p = 0.006). Use of vasodilators, most commonly sodium nitroprusside, was similar between all groups.

Arterial lactic acid levels improved rapidly over the first 24 h. Compared to Survivors, at 24 h there was a significant delay in lactate clearance in the Other Death (5.43 ± 1.5 vs. 2.2 ± 0.25, p = 0.008) and Brain Death groups (5.9 ± 0.55 vs. 2.2 ± 0.25, p = 0.007; Fig. 2D).

Transfusion of blood products was required for 32/46 (70%) Survivors and 33/37 (89%) non-survivors (p = 0.04). Other Deaths required significantly more units of red blood cells compared to Survivors and Brain Deaths (7.6 ± 1.2 vs. 4.2 ± 0.9 [$p < 0.001$] and 7.6 ± 1.2 vs. 3.1 ± 1.1 [p = < 0.001], respectively; Fig. 2E).

Neurologic injury

Brain injury was observed on the initial head CT in 21/83 (25%) patients admitted to the CICU. Anoxic injury and cerebral edema were observed in 18% and 15% of patients, respectively (Fig. 3A). Anoxia

A

Refractory VT/VF patients Admitted to ICU		Overall (83)	Survivors (46)	Deaths (23)	Brain Death (14)
Initial Head CT	Anoxic Injury	17/83 (20%)	3/46 (6.5%)	5/23 (22%)	9/14 (64%)
	Edema	14/83 (17%)	0%	6/23 (26%)	8/14 (57%)
	Intracranial Hemorrhage	0%	0%	0%	0%
	Acute Ischemic Stroke	1/83 (1.2%)	0%	1/23 (4.3%)	0%
Continuous EEG	Convulsive Seizures	2/83 (2.4%)	2/46 (4.3%)	0%	0%
	Non-convulsive Status Epilepticus	11/83 (13%)	4/46 (8.7%)	7/23 (30%)	0%

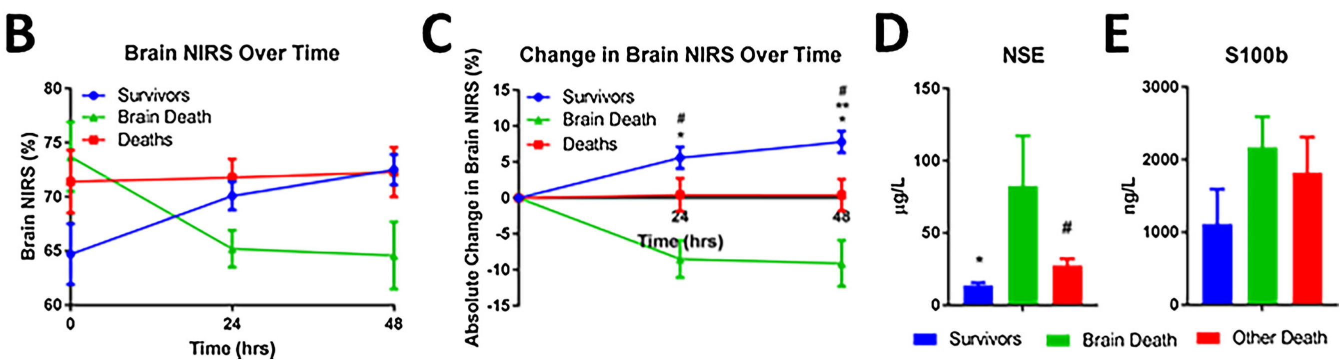


Fig. 3. Neurologic injury identified on CICU admission and during recovery. (A) Head CT results assessed on CICU admission and the results of continuous EEG monitoring initiated on CICU admission. EEG monitoring was continued until neurologic function improved or death occurred. (B) Non-invasive cerebral perfusion monitoring with NIRS over the first 48 h of CICU admission. (C) Absolute change in NIRS over the first 48 h. (D) Serum neuron specific enolase values on CICU admission classified by patient outcome. (E) Serum S100B levels on CICU admission classified by patient outcome. Results are presented as mean ± SEM. Statistical significance ($p < 0.05$) is noted comparing survivors to patients with brain death (*), comparing survivors to deaths (**), or comparing deaths to brain deaths (#). Abbreviations: CT, computerized tomography; EEG, electroencephalogram; NIRS, near infrared spectroscopy; NSE, neuron specific enolase.

and edema were present significantly more in the Brain Death and Other Death groups compared to Survivors ($p < 0.001$). Of patients with anoxic injury or cerebral edema on the initial head CT, 86% died prior to discharge.

Convulsive seizures occurred in 2% of patients and both survived (Fig. 3A). In contrast, non-convulsive status epilepticus occurred in 7/23 (30%) Other Deaths and 4/46 (8.7%) Survivors. These occurred at mean hospital day 7 with a range from day 3–13 with 64% occurring while the patient was still receiving sedation. All patients with non-convulsive status epilepticus died or discharged with poor neurologic function.

There were no significant differences in absolute cerebral oximetry value as measured by NIRS (Fig. 3B). However, there was a significant difference in the change in NIRS from baseline between all groups at 48 h. NIRS values increased for Survivors over the first 48 h whereas, the Other Death group had stable NIRS and the Brain Death group demonstrated declining NIRS (Fig. 3C).

Neurologic biomarkers were collected upon CICU admission. Neuron specific enolase (NSE) was significantly increased in patients with Brain Death compared to Survivors or Other Deaths (82.5 ± 35 vs. 13.7 ± 1.8 [$p < 0.001$] and 82.5 ± 35 vs. 27.6 ± 4.6 [$p = 0.006$], respectively). There were no significant differences in S100B between groups.

End-organ dysfunction

Left ventricular function was severely compromised in all patients for the first 48 h requiring continued ECMO/IABP support (Fig. 4A). Significant recovery was observed within 5 days. Mean left ventricular ejection fraction was 15.3% at 24 h, 28% at 48 h, 37% at 4 days, and 44% at hospital discharge.

Markers of injury to the heart (Fig. 4B), kidneys (Fig. 4C), and liver (Fig. 4D) peaked within 24–48 h with improvement thereafter. Severity of end-organ injury was associated with survival. When compared to Survivors, Brain Death patients had significantly higher mean serum troponin levels as early as 4 h (132 ± 20 vs. 49 ± 10 ng/mL; $p < 0.001$) and higher mean creatinine levels at 24 h (2.2 ± 0.22 vs. 1.1 ± 0.1 mg/dL; $p < 0.001$). Creatinine was the only marker of injury that differed between Other Deaths and Survivors (2.0 ± 0.20 vs. 1.1 ± 0.1, respectively, at 24 h; $p = 0.001$). Overall, 10/83 (12%) patients required dialysis. Five were Survivors and five died prior to discharge. Two patients were receiving outpatient dialysis prior to the cardiac arrest; both died. No survivor required dialysis after discharge.

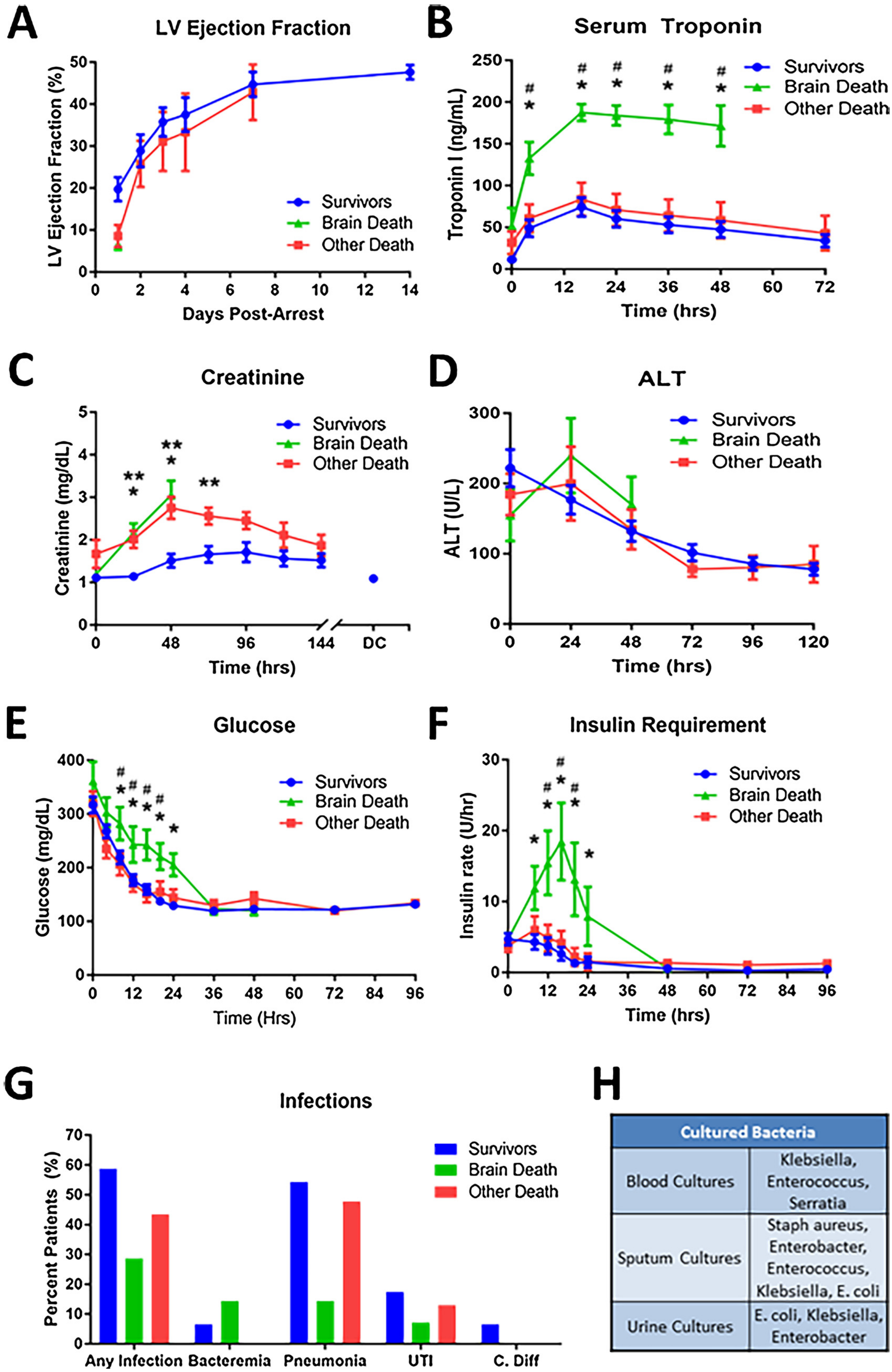
Glucose was severely elevated in all patients requiring continuous insulin infusions (Fig. 4E–F). Brain Death patients had persistently elevated glucose compared to Survivors (242 ± 28 vs. 160 ± 9.5 mg/dL at 16 h; $p = 0.001$) requiring increased insulin doses (18.5 ± 5.4 vs. 2.6 ± 0.94 U/hr at 16 h; $p < 0.001$).

Infections and inflammation

Culture positive infections occurred in 41/83 (49%) patients including pneumonia 38/83 (46%), bacteremia 5/83 (6%), and urinary tract infections 12/83 (14%). Pneumonia was most commonly associated with bacteria associated with aspiration (Fig. 4G–H).

Trauma

Prolonged CPR caused substantial trauma: 27/83 (33%) had rib fractures, 6/83 (7%) had pneumothorax, 2/83 (2%) required a chest



Cultured Bacteria	
Blood Cultures	Klebsiella, Enterococcus, Serratia
Sputum Cultures	Staph aureus, Enterobacter, Enterococcus, Klebsiella, E. coli
Urine Cultures	E. coli, Klebsiella, Enterobacter

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tube, 8/83 (11%) had intra-thoracic bleeding, 1/83 (1%) had hemopericardium due to a ruptured right ventricle, and 5/83 (6%) had intraperitoneal bleeding. Traumatic injury required urgent or emergent procedural/surgical intervention in 22/83 (27%) patients including 14/40 (35%) functionally intact survivors. Throughout hospitalization, 36/83 (43%) patients including 23/46 (50%) Survivors required an

Fig. 4. Markers of end-organ dysfunction during recovery and resuscitation-induced injury complicating recovery. (A) Left ventricular ejection fraction as determined by transthoracic echocardiography over the first 14 days of the CICU admission classified by patient outcome. Patients with brain death were only assessed at day 1. (B) Serum troponin I values over the first 72 h of CICU admission classified by patient outcome. (C) Serum creatinine levels over the first 144 h of CICU admission and upon discharge classified by patient outcome. (D) Serum ALT levels classified by patient outcome over the first 120 h of CICU admission. (E) Serum glucose levels classified by patient outcome over the first 96 h of CICU admission. (F) Insulin requirements as delivered by a continuous insulin infusion as needed during the first 96 h of CICU admission classified by patient outcome. (G) Incidence of bacterial culture-positive infections classified by patient outcome. The source of infection is delineated. (H) List of cultured microorganisms from the infections encountered. Results are presented as mean ± SEM. Statistical significance ($p < 0.05$) is noted comparing survivors to patients with brain death (*), comparing survivors to deaths (**), or comparing deaths to brain deaths (#). Abbreviations: LV, left ventricular; ALT, alanine aminotransferase; DC, discharge; UTI, urinary tract infection.

Table 2
Complications and the invasive procedures performed after CICU admission.

Complications Requiring a Procedure or Operation				
Complication	**Procedure**	**Total Patients**	**Survivors**	**Deaths**
CPR-Associated Ruptured RV/Tamponade	Emergent Pericardiocentesis, Sternotomy, and RV Repair	1	1	0
Unable to Wean from ECMO	Durable Left Ventricular Assist Device Implantation	2	2	0
Ischemic Lower Extremity/ Hemodynamically Stable	Decannulation of Peripheral ECMO	2	2	0
Ischemic Lower Extremity/ Hemodynamically Unstable	Decannulation of Peripheral ECMO and Central Cannulation	1	1	0
Spontaneous RP Bleed	Endovascular Embolization of Lumbar Artery	1	0	1
CPR-Associated Pneumothorax	Chest Tube Insertion	2	2	0
Late Occurrence Pneumothorax	Chest Tube Insertion	2	1	1
Large Hemothorax	Chest Tube Insertion	1	0	1
Recurrent VF	Impella Insertion	1	1	0
Recurrent Cardiogenic Shock	Intra-Aortic Balloon Pump Insertion	1	1	0
Recurrent VF	Defibrillation	4	1	3
Indication for ICD (non-ischemic VF or recurrent VF)	ICD Insertion	10	9	1
Tachy-Brady Syndrome	Permanent Pacemaker Insertion	1	1	0
Bradycardia/Heart Block	Temporary Pacemaker Insertion	3	2	1
Poor Neurologic Recovery/ Unable to Protect Airway	Tracheostomy/Gastro-jejunal Tube Insertion	6	5	1
Prolonged respiratory failure	Tracheostomy Insertion	3	3	0
Acute Renal Failure	Dialysis Catheter Insertion	8	5	3
Chronic Renal Failure	Dialysis Catheter Insertion	2	0	2
Pleural Effusion	Thoracentesis	1	1	0
Hypoxia	Bronchoscopy	10	8	2
Upper Gastrointestinal Bleed	Endoscopy	1	1	0
Hemodynamically Significant Atrial Fibrillation	Cardioversion	2	0	2
Ankle Fracture	Splint	1	1	0

Abbreviations: CPR, cardiopulmonary resuscitation; RV, Right Ventricle; ECMO, extracorporeal membrane oxygenation, RP, retroperitoneal, VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator.

invasive/surgical procedure. Complications, procedures, and patient outcome are shown in Table 2.

Three patients had ECMO-related lower extremity ischemia due to thrombosed distal perfusion catheters. Resolution occurred in two patients following ECMO decannulation. One patient converted to central ECMO for continued ECMO support. Retroperitoneal bleeding was present in 4/83 (5%).

Nine patients required tracheostomy due to severe pneumonia or altered mental status. Of these, 3/9 patients survived with functionally favorable status. Five patients were discharged with poor neurologic recovery. One patient died prior to discharge.

Discussion

Refractory out-of-hospital VF/VT patients treated with mechanical CPR, ECMO, and PCI represent a challenging CICU patient population rarely seen in the United States. Comprehensive critical care resulted in functionally intact survival in 48% of patients admitted to the CICU.

Several unique features of the CICU care deserve attention. All patients were considered viable and eligible for any necessary intervention or surgery until definitive declaration of death. This approach allowed determination of an achievable functionally intact survival rate without confounding of physician-advocated early withdrawal of life sustaining therapy.

CICU care of this patient population required a wide range of immediately available, emergent, surgical and medical interventions and expertise including trauma surgery, cardiothoracic surgery, vascular surgery, otolaryngology, general surgery, interventional cardiology, electrophysiology, neurology, nephrology, pulmonary medicine, gastroenterology, and interventional radiology. This immediately available expertise significantly contributed to survival. Highly sophisticated resuscitation hospitals are likely necessary to provide the emergent, life-saving interventions required.

Neurologic prognostication began no earlier than 72 h following normothermia unless evidence of brain death was present [13,17]. After 72 h, all prognostic factors and family wishes were used to inform decision-making. Nonetheless, only 52% of survivors were following commands within 5 days. The last patient surviving functionally intact began following commands at 22 days. Thus, more than 72 h of comprehensive support was necessary to capture all survivors.

All patients suffered severe multi-system organ failure. Neurologic injury was the most common cause of death with anoxic injury or cerebral edema on the initial head CT, non-convulsive status epilepticus on EEG, declining cerebral NIRS, and elevated serum NSE predicting poor neurologic outcomes [20–28]. Severity of cardiac and renal injury was also associated with patient outcome [29–31]. Severe myocardial dysfunction and hemodynamic compromise were present in all patients requiring sustained ECMO/IABP treatment for 3–4 days [12,32,33]. Despite routine use of antibiotics, pneumonia was common, most often caused by resuscitation-related aspiration [34,35]. Infections did not appear to impact mortality.

Compared to prior studies, the transfusion rate was similar and ECMO complications were less common, likely due to placement of distal perfusion cannulas [36–39]. CPR-induced trauma was common and may become more apparent with ECMO because: 1) ECMO extends survival, allowing recognition of underlying trauma, and 2) ECMO requires anticoagulation, exacerbating traumatic bleeding [40]. A thorough trauma evaluation and immediate intervention was crucial to survival.

The possibility of survival with residual neurological impairment is an important concern. This initial experience is reassuring with 40/46 (87%) survivors functionally intact (CPC = 1) at 3 months. The rate of unfavorable functional survival (6/83 [7.2%]) is comparable or lower than with current therapy [8]. Nonetheless, the risk/benefit ratio of this approach warrants continued assessment.

This study has several limitations. It is subject to limitations of observational studies including selection, information, and confounding bias. Although selection bias cannot be excluded, data were derived from a consecutive case series. While this remains the largest published study in the United States, the limited size of the patient population reduces statistical power of inter-group comparisons, possibly underestimating significance of some differences. Generalizability of this approach and cost effectiveness deserve study.

Conclusions

Refractory VF/VT out-of-hospital cardiac arrest represents a new critical care patient population. Multi-system organ failure was ubiquitous but treatable with adequate hemodynamic support. Neurologic recovery was prolonged requiring delayed prognostication. Immediate 24/7 availability of a spectrum of surgical and medical specialty expertise in a sophisticated medical/trauma center was required to provide frequent emergent life-saving interventions and achieve a 48% functionally intact 3-month survival rate.

Conflicts of interest

None of the authors have any financial or personal relationships with people or organizations that could have inappropriately influenced this work.

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