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ORIGINAL RESEARCH

Patient and Institutional Characteristics Influence the Decision to Use Extracorporeal Cardiopulmonary Resuscitation for In-Hospital Cardiac Arrest

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BACKGROUND: Outcomes from extracorporeal cardiopulmonary resuscitation (ECPR) are felt to be influenced by selective use, but the characteristics of those receiving ECPR are undefined. We demonstrate the relationship between individual patient and hospital characteristics and the probability of ECPR use.

METHODS AND RESULTS: We performed an observational analysis of adult inpatient cardiac arrests in the United States from 2000 to 2018 reported to the American Heart Association's Get With The Guidelines—Resuscitation registry restricted to hospitals that provided ECPR. We calculated case mix adjusted relative risk (RR) of receiving ECPR for individual characteristics. From 2000 to 2018, 129 736 patients had a cardiac arrest (128 654 conventional cardiopulmonary resuscitation and 1082 ECPR) in 224 hospitals that offered ECPR. ECPR use was associated with younger age (RR, 1.5 for <40 vs. 40–59 years; 95% CI, 1.2–1.8), no pre-existing comorbidities (RR, 1.4; 95% CI, 1.1–1.8) or cardiac-specific comorbidities (congestive heart failure [RR, 1.3; 95% CI, 1.2–1.5], prior myocardial infarction [RR, 1.4; 95% CI, 1.2–1.6], or current myocardial infarction [RR, 1.5; 95% CI, 1.3–1.8]), and in locations of procedural areas at the times of cardiac arrest (RR, 12.0; 95% CI, 9.5–15.1). ECPR decreased after hours (3–11 PM [RR, 0.8; 95% CI, 0.7–1.0] and 11 PM–7 AM [RR, 0.6; 95% CI, 0.5–0.7]) and on weekends (RR, 0.7; 95% CI, 0.6–0.9).

CONCLUSIONS: Less than 1% of in-hospital cardiac arrest patients are treated with ECPR. ECPR use is influenced by patient age, comorbidities, and hospital system factors. Randomized controlled trials are needed to better define the patients in whom ECPR may provide a benefit.

Key Words: cardiopulmonary resuscitation ■ extracorporeal cardiopulmonary resuscitation ■ extracorporeal life support ■ extracorporeal membrane oxygenation ■ in-hospital cardiac arrest ■ resuscitation

Survival after extracorporeal cardiopulmonary resuscitation (ECPR) ranges widely from <15% to >50%, although most studies report ≈30%.[1–5] Some individuals have claimed that this high survival rate of ECPR patients compared with 10% to 20% for conventional cardiopulmonary resuscitation (CCPR)[6,7] has eliminated clinical equipoise.[8] However, survival rate variance between CCPR and ECPR likely reflects

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*A complete list of the American Heart Association's Get With the Guidelines—Resuscitation Investigators can be found in the Appendix.

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CLINICAL PERSPECTIVE

What Is New?

- Extracorporeal cardiopulmonary resuscitation is used in <1% of all US in-hospital cardiac arrests.
- After case mix adjustment, the decision to use extracorporeal cardiopulmonary resuscitation remains strongly influenced by patient age, sex, race, comorbidities, type, and arrest location.
- Extracorporeal cardiopulmonary resuscitation is used significantly more often in a generally younger, healthier, male cohort undergoing cardiac interventions and during the daytime.

What Are the Clinical Implications?

- Conclusions about extracorporeal cardiopulmonary resuscitation benefits and harms in observational studies are strongly influenced by this observed selective use.

Nonstandard Abbreviations and Acronyms

ECMO	extracorporeal membrane oxygenation
CCPR	conventional cardiopulmonary resuscitation
ECPR	extracorporeal cardiopulmonary resuscitation
GWTG-R	Get With The Guidelines—Resuscitation
IHCA	in-hospital cardiac arrest
IQR	interquartile range
OR	odds ratio
RR	relative risk

confounding by indication with those thought to have a high likelihood of survival preferentially receiving ECPR. Propensity-matched cases of ECPR to CCPR have shown discordant results among patients with in-hospital cardiac arrest (IHCA).[4,9] In 2 propensity-matched studies, investigators were unable to match 50% and 25% of the ECPR patients to CCPR patients, suggesting that patients receiving ECPR differ substantively from those receiving CCPR. If significant differences among patients being offered ECPR versus CCPR exist, this limits the generalizability of observational descriptions of ECPR use and survival and suggests barriers to clinical trial enrollment and randomization equipoise.

ECPR remains an uncommon therapy, even in high-volume centers.[10,11] Most previous ECPR studies of adults have been limited by sample sizes of <100 to 300 patients,[2–5,9–14] which limits comparisons across patients and hospitals. The large population studies of ECPR come from Asia and may not be reflective of US practice.[3,4,11,15] To define the characteristics that bias toward the use of ECPR, we used a large national sample spanning nearly 20 years of US IHCA patients treated at ECPR-available hospitals. The American Heart Association GWTG-R (Get With The Guidelines—Resuscitation) registry is a nationally representative, prospective, multicenter, hospital-based registry containing granular cardiac arrest details of patients with IHCA.[16] Using this data set, we sought to define hospital-level and patient-level characteristics that increase the probability of treatment with ECPR, rather than CCPR alone, for cardiac arrest. By defining the features that bias toward ECPR use, we aim to better understand which patients physicians feel may benefit from ECPR and inform future clinical trial design.

METHODS

Our analysis is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology Guidelines.[17]

Data Sharing

To facilitate research reproducibility, replicability, accuracy, and transparency, our analytic code is available in the Open Science Foundation repository (DOI: 10.17605/osf.io/u9pae; https://osf.io/U9PAE). The data that support the findings of this study are available from the American Heart Association GWTG-R investigators, which were used under license for the current study and can be requested from the American Heart Association. The code was deidentified in accordance with section 164.514 of the Health Insurance Portability and Accountability Act.

Data Source

Data were obtained from the American Heart Association GWTG-R registry.[16] Patients are identified as having an IHCA if they have lack of pulse, apnea, and unresponsiveness, without do-not-resuscitate orders, and subsequently receive chest compressions/cardiopulmonary resuscitation or defibrillation. Complete data capture is ensured through multiple case finding approaches, including a review of hospital paging system logs, centralized collection of cardiac arrest flowsheets, routine checks of code-carts, and a review of pharmacy drug-tracing records and hospital billing charges for medications.[18–20] The registry uses standard Utstein-style variable definitions.[18,21] Data are voluntarily submitted and include baseline, comorbid, prearrest, intra-arrest,

and outcome characteristics. The processes ensuring case ascertainment, data quality, and accuracy have previously been described.[22] Hospital data are available within the data set, come from the American Hospital Association Annual Survey, and were analyzed consistent with previous studies.[8,23–25] IQVIA is the data collection coordination center for the American Heart Association/American Stroke Association Get With The Guidelines programs.

Study Population

We identified cardiac arrest events from 2000 to 2018. We excluded patients younger than 18 years of age, those with out-of-hospital cardiac arrest preceding admission, those for whom the arrest occurred >4 hours before the date/time of admission, those with missing date/time values, visitors, and those whose hospital identification could not be matched to a hospital within the data set. To control for availability of ECPR, we excluded patients from hospitals with no record of ECPR use in the registry. Among hospitals that reported ECPR use for IHCA patients, we only included patients who were enrolled after the date of the first ECPR patient in the registry (Figure S1). We excluded all nonindex cardiac arrest events for each patient and all patients who were coded as brain dead on the admission Cerebral Performance Category variable. Finally, we excluded hospitals that had submitted <6 months of data or fewer than 5 cardiac arrest events (Data S1).

Study Variables and Outcomes

Our primary outcome is the receipt of ECPR during IHCA, defined within the GWTG-R as receipt of ECPR/cardiopulmonary bypass as an adjunctive therapy during resuscitation. Patient-level data available from the GWTG-R included demographics (age, sex, race), initial rhythm (ventricular fibrillation, pulseless ventricular tachycardia, pulseless electrical activity, and asystole), location of cardiac arrest (intensive care unit, nonmonitored inpatient, ambulatory, outpatient, rehabilitiation, cardiac/coronary, catheterization laboratory, operating room), time of day (work hours, 7:00 AM–2:59 PM vs. after hours, 3:00 PM–10:59 PM, 11:00 PM–6:59 AM) and day of week (weekday vs. weekend) of cardiac arrest, and use of a hospital-wide emergency response (ie, "Code Blue"). Information was obtained on comorbid conditions, including myocardial infarction; congestive heart failure; diabetes mellitus; hepatic, renal, or respiratory insufficiency; neurological status prearrest (as determined by admission Cerebral Performance Category scores)[26]; baseline evidence of cognitive, motor, or functional deficits; pneumonia; arrhythmia; acute stroke; hypotension; trauma; sepsis; metabolic or electrolyte abnormality; cancer; and therapeutic interventions in place at the time of cardiac arrest (mechanical ventilation, arterial catheters, endotracheal tubes). Moreover, information was obtained on intra-arrest characteristics, including return of spontaneous circulation, duration of arrest, and arrest treatments, including defibrillation, medication administration, and use of adjunctive therapies including the use of cardiopulmonary bypass/ECPR or induced hypothermia.

Statistical Analysis

Patient demographic, prearrest, and intra-arrest characteristics and hospital characteristics were summarized descriptively stratified by receipt of ECPR versus CCPR. Continuous variables were summarized as mean (SD) or median (interquartile range [IQR]), and categorical variables were summarized as frequency and percentage. Patient characteristics were compared with ECPR versus CCPR using mixed effects regression models to account for clustering within hospitals.

Our primary analytic goal was to measure the strength of association between individual patient and hospital characteristics and ECPR use. To account for the national sample and differences in patient complexity across hospitals, we adjusted our analyses for patient case-mix and hospital characteristics associated with differing levels of hospital care.[27] Each analysis presents an unadjusted estimate of the associations with ECPR use and 2 adjusted estimates: one adjusted for patient variables and the second adjusted for patient and hospital variables.

Univariable association with receiving ECPR was assessed for each demographic, prearrest, intra-arrest, and hospital characteristic variable using a mixed effects log-binomial regression model with a log link and included a random effect for hospital. This modeling framework was used rather than simple tests because of the potential correlation of patient characteristics within hospitals. For the adjusted analysis, we selected a subset of patient and hospital characteristics based on previous associations with survival after cardiac arrest,[24,28–31] minimal missingness, and an absence of collinearity. Selected patient characteristics included age, initial pulseless rhythm, sex, race, illness category (medical vs. surgical, cardiac vs. noncardiac), event location,[23,32,33] and ethnicity. Selected hospital-level characteristics included number of cardiac intensive care unit beds, region of the country, and teaching status.[23,32] Era, categorized in 5-year increments, was included in the models as our data set spanned nearly 20 years. All variables, except ethnicity, achieved statistical significance

in univariable analyses, had minimal missingness (≤5.3%), and had no collinearity among them (variance inflation factors were all <2.5). All univariable associations with receiving ECPR were assessed for each candidate patient and hospital variable in our data set. We repeated these comparisons adjusting for both the subset of patient and hospital characteristics described previously (primary results) and adjusting for the patient characteristics alone (descriptive results) using the same modeling approach. The exponentiated model coefficients yielded relative risks (RRs) reported with their 95% CIs and *P* values. The log-binomial mixed effects model was chosen over a logistic mixed effects model for analyses reporting model coefficients because RRs are often more intuitive than odds ratios (ORs).[34] However, because ECPR cases represent about 0.8% of our data set, ORs provide a close approximation to RRs. For analyses where only *P* values were reported or where the log-binomial model could not converge, we used mixed effects logistic regression reporting ORs. These exceptions have been noted via footnotes in the tables.

Hospital characteristics were compared between ECPR-available and non-ECPR-available hospitals using chi-squared tests. Patient characteristics were compared between ECPR-available and non-ECPR-available hospitals using the log-binomial mixed effects regression modeling framework described previously.

All statistical analyses were conducted in R version 3.4.[35] Statistical significance was assessed at the 0.05 level, and all tests were 2-tailed. This study was approved by the institutional review board under No. 00091962 on September 8, 2016, with a waiver of informed consent.

RESULTS

Patient Characteristics

The final cohort included 129 736 patients (128 654 CCPR and 1082 ECPR) from 219 hospitals that offered ECPR (Table S1). Unadjusted patient characteristics are presented in Table 1. Patients were predominately 60 years of age or older (66%), male (58%), white (68%), and cardiac surgical or cardiac medical patients (40%). Arrest characteristics included 39% located in the intensive care unit, 86% witnessed, and 93% were found without a pulse, of whom 18% presented with a shockable rhythm. Patients received 2 defibrillations (IQR, 1–4) and 3 boluses (IQR, 1–5) of epinephrine after becoming pulseless and underwent a median of 15 minutes (IQR, 6–26) of resuscitation, and 70% achieved return of spontaneous circulation at some point.

Patient and Hospital Characteristics by Hospital

Hospitals offering ECPR differed from hospitals not offering ECPR (Table S2), as did the characteristics of patients treated at them (Table S3). Patients treated at non-ECPR-available hospitals were more likely to be younger than 40 years of age (7.6% vs. 5.7%; *P*<0.001) and black (22.6% vs. 19.8%; *P*<0.001) and have more comorbidities (*P*≤0.002 for all) and better neurologic function at admission (Cerebral Performance Category 1, 59.5% vs. 57.1%; *P*<0.001). Hospitals offering ECPR were larger metropolitan teaching hospitals and had higher cardiac and overall volumes (Table S2).

Adjusted Probability of Receiving ECPR

Demographic Characteristics

After adjusting for patient and hospital characteristics, patients were more likely to receive ECPR if they were younger than 40 years of age (RR, 1.5; 95% CI, 1.2–1.8; *P*<0.001), had a preceding period of hypoperfusion before their arrest (RR, 1.6; 95% CI, 1.4–1.8; *P*<0.001), and had congestive heart failure (RR, 1.3; 95% CI, 1.2–1.5; *P*<0.001) or a prior or current history of myocardial infarction (RR, 1.3; 95% CI, 1.2–1.6; *P*<0.001; and RR, 1.5; 95% CI, 1.3–1.7; *P*<0.001; respectively) (Table 2). Patients with no comorbidities were more likely to receive ECPR (RR, 1.4; 95% CI, 1.1–1.8; *P*=0.004). Correspondingly, older patients, those with 1 or more comorbidities, and patients with decreased neurologic function upon admission were all significantly less likely to be treated with ECPR. Patients of black race and women were significantly less likely to receive ECPR (RR, 0.8; 95% CI, 0.7–1.0; *P*<0.001; and RR, 0.9; 95% CI, 0.8–1.0; *P*=0.04; respectively).

Hospital Characteristics

Across hospitals offering ECPR, hospitals with a higher strata ratio of cardiac intensive care unit beds/total beds (percentage) were more likely to use ECPR (RR, 3.1; 95% CI, 1.3–7.0; *P*=0.008; for stratum 7.5 to <10%) (Table 2). At hospitals that had ECPR programs, the ECPR/CCPR ratio did not significantly change over time (Figure S2, Tables S4 and S5).

Illness Characteristics

After controlling for both patient and hospital characteristics, the presence of arterial catheters (RR, 3.1; 95% CI, 2.7–3.5; *P*<0.001), mechanical ventilation (RR, 2.0; 95% CI, 1.7–2.3; *P*<0.001), and invasive airways (RR, 1.7; 95% CI, 1.5–2.0; *P*<0.001) each increased the probability of ECPR receipt

Table 1. Descriptive Summary of Admission, Prearrest, and Arrest Characteristics

Variable	CCPR (N=127 537)	ECPR (N=1082)	All (N=128 619)	*P* Value*
Age, y, n(%)				<0.001
<40	9802 (7.7)	166 (15.3)	9968 (7.8)	···
40–59	33 189 (26)	355 (32.8)	33 544 (26.1)	···
≥60	84 546 (66.3)	561 (51.8)	85 107 (66.2)	···
Male sex, n (%)	73 928 (58)	666 (61.6)	74 594 (58)	0.035
Race, n (%)				<0.001
White	86 822 (68.2)	799 (74.1)	87 621 (68.3)	···
Black	29 351 (23.1)	168 (15.6)	29 519 (23)	···
Other	11 050 (8.7)	112 (10.4)	11 162 (8.7)	···
Hispanic ethnicity, n (%)	6088 (4.8)	55 (5.1)	6143 (4.8)	0.98
Weight, median (IQR), kg	78.9 (65–95.5)	80 (67–95.7)	78.9 (65–95.5)	0.34
Pre-existing condition, n (%)				
None	6315 (5)	86 (8)	6401 (5)	0.001
Preceding hypoperfusion	37 205 (29.3)	470 (43.6)	37 675 (29.4)	<0.001
CVA or neurologic disorder	27 086 (21.3)	100 (9.3)	27 186 (21.2)	<0.001
CHF	37 902 (29.8)	366 (33.9)	38 268 (29.8)	<0.001
Diabetes mellitus	41 897 (32.9)	246 (22.8)	42 143 (32.9)	<0.001
Hepatic insufficiency	10 531 (8.3)	53 (4.9)	10 584 (8.3)	<0.001
Major trauma	6674 (5.2)	40 (3.7)	6714 (5.25)	0.12
Cancer	15 395 (12.1)	42 (3.9)	15 437 (12)	<0.001
History of MI	19 823 (15.6)	229 (21.2)	20 052 (15.6)	<0.001
MI this hospitalization	19 981 (15.7)	289 (26.8)	20 270 (15.8)	<0.001
Renal insufficiency	45 494 (35.8)	244 (22.6)	45 738 (35.7)	<0.001
Respiratory insufficiency	59 229 (46.6)	443 (41.1)	59 672 (46.5)	0.002
Sepsis	22 446 (17.6)	87 (8.1)	22 533 (17.6)	<0.001
Admission CPC, n (%)†				<0.001
CPC 1: good cerebral performance	59 580 (60.8)	667 (78.1)	60 247 (60.9)	···
CPC 2: moderate cerebral disability	20 289 (20.7)	88 (10.3)	20 377 (20.6)	···
CPC 3: severe cerebral disability	10 859 (11.1)	39 (4.6)	10 898 (11)	···
CPC 4: coma or vegetative state	7306 (7.5)	60 (7)	7366 (7.4)	···
Duration between admission and arrest, n (%)				0.005
<24 h	120 495 (94.5)	1044 (96.5)	121 539 (94.5)	···
24 to <48 h	5268 (4.1)	29 (2.7)	5297 (4.1)	···
48 h to <1 wk	1583 (1.2)	6 (0.6)	1589 (1.2)	···
≥1 wk	191 (0.1)	3 (0.3)	194 (0.2)	···
Devices, n (%)				
Mechanical ventilation	37 626 (29.5)	556 (51.4)	38 182 (29.7)	<0.001
Invasive airway	36 726 (28.8)	531 (49.1)	37 257 (29)	<0.001
Arterial line	17 329 (13.6)	478 (44.2)	17 807 (13.9)	<0.001
Time of day of arrest, n (%)				<0.001
7 AM to 2:59 PM	44 729 (35.5)	500 (48.3)	45 229 (35.6)	···
3 PM to 10:59 PM	42 165 (33.5)	358 (34.6)	42 523 (33.5)	···
11 PM to 6:59 AM	39 052 (31)	177 (17.1)	39 229 (30.9)	···
Day of week, n (%)				
Weekday	94 290 (73.9)	896 (82.8)	95 186 (74)	<0.001
Weekend	33 247 (26.1)	186 (17.2)	33 433 (26)	···
Arrest location, n (%)				<0.001
General inpatient‡	41 134 (32.3)	100 (9.2)	41 234 (32.1)	···
Ambulatory/outpatient§	2150 (1.7)	16 (1.5)	2166 (1.7)	···
Cardiac/coronary unit	9933 (7.8)	103 (9.5)	10 036 (7.8)	···
ICU	50 229 (39.4)	402 (37.2)	50 631 (39.4)	···

(*Continued*)

Table 1. Continued

Variable	CCPR (N=127 537)	ECPR (N=1082)	All (N=128 619)	*P* Value*
Operating room/procedural/cath lab	11 160 (8.8)	421 (38.9)	11 581 (9)	···
Emergency department	12 817 (10.1)	40 (3.7)	12 857 (10)	···
Illness category, n (%)				
Medical—noncardiac	61 058 (47.9)	134 (12.4)	61 192 (47.6)	<0.001
Medical—cardiac	40 578 (31.9)	334 (30.9)	40 912 (31.8)	···
Surgical—cardiac	9731 (7.6)	528 (48.8)	10 259 (8)	···
Surgical—noncardiac	16 032 (12.6)	86 (7.9)	16 118 (12.5)	···
Witnessed, n (%)	109 519 (85.9)	1049 (97)	110 568 (86)	<0.001
Hospital resuscitation activated, n (%)	87 174 (68.4)	483 (44.6)	87 657 (68.2)	<0.001
Condition of first assessment, n (%)				0.09
Poor perfusion, lost pulses	7195 (5.6)	90 (8.3)	7285 (5.7)	···
Poor perfusion, never pulseless	2674 (2.1)	24 (2.2)	2698 (2.1)	···
Pulseless	117 603 (92.3)	968 (89.5)	118 571 (92.2)	···
Presenting rhythm status, n (%)				<0.001
Asystole	32 372 (26.8)	214 (21.2)	32 586 (26.8)	···
PEA	57 397 (47.5)	403 (40)	57 800 (47.5)	···
Pulseless ventricular tachycardia	8923 (7.4)	93 (9.2)	9016 (7.4)	···
Ventricular fibrillation	12 210 (10.1)	184 (18.3)	12 394 (10.2)	···
Palpable pulse initially	9869 (8.2)	114 (11.3)	9983 (8.2)	···
First rhythm, n (%)				<0.001
Accelerated idioventricular rhythm	201 (2)	2 (1.8)	203 (2)	···
Bradycardia	6727 (68.4)	55 (48.2)	6782 (68.1)	···
Pacemaker	300 (3)	16 (14)	316 (3.2)	···
Sinus (including sinus tachycardia)	753 (7.7)	13 (11.4)	766 (7.7)	···
Supraventricular tachyarrhythmia	249 (2.5)	1 (0.9)	250 (2.5)	···
Unknown	919 (9.3)	15 (13.2)	934 (9.4)	···
Ventricular tachycardia with pulse	692 (7)	12 (10.5)	704 (7.1)	···
Any VF/VT, n (%)	44 634 (35)	588 (54.3)	45 222 (35.2)	<0.001
Number of defibrillations, median (IQR)	2 (1–4)	3 (2–6)	2 (1–4)	<0.001
Received compressions, n (%)	125 408 (98.4)	1054 (97.4)	126 462 (98.4)	0.049
Compression method, n (%)				
Manual	100 687 (99.3)	755 (92.5)	101 442 (99.2)	<0.001
Mechanical	25 131 (24.8)	198 (24.3)	25 329 (24.8)	0.023
Open cardiac massage	722 (0.7)	154 (18.9)	876 (0.9)	<0.001
Epi boluses before pulseless, median (IQR)	3 (2–5)	4 (2–6)	3 (2–5)	0.003
Epi boluses after pulseless, median (IQR)	3 (1–5)	4 (2–8)	3 (1–5)	<0.001‖
Any ROSC, n (%)	88 686 (70.1)	861 (79.9)	89 547 (70.2)	<0.001
Total duration before durable ROSC, median (IQR)	14 (6–26)	36 (17–69.2)	15 (6–26)	<0.001
Induced hypothermia, n (%)	3477 (3.5)	114 (12.7)	3591 (3.6)	<0.001

Missing values by group: sex=6/0, race=314/3, weight (kg)=68 934/559; pre-existing condition: none=347/3, preceding hypoperfusion=347/3, CVA or neurologic disorder=347/3, CHF=347/3, diabetes mellitus=347/3, hepatic insufficiency=347/3, major trauma=347/3, cancer =347/3, history of MI=347/3, MI this hospitalization=347/3, renal insufficiency=347/3, respiratory insufficiency=347/3, sepsis=347/3, admission CPC=29 503/228; devices: mechanical ventilation=144/1, invasive airway=144/1, arterial line=144/1; time of day of arrest=1591/47; patient type=121/0; arrest location=114/0; illness category=138/0; witnessed=89/0; hospital resuscitation activated=95/0; condition of first assessment=65/0; presenting rhythm status=6766/74; first rhythm=117 696/968; any VF/VT=148/0; number of defibrillations=87 038/568; received compression?=73/0; compression method: manual=26 116/266, mechanical=26 116/266, open cardiac massage=26 116/266; Epi boluses before pulseless=123 160/1025; Epi boluses after pulseless=30 943/341; any ROSC=1079/5; total duration before durable ROSC=4353/162; induced hypothermia=27 928/184. cath lab indicates cardiac catheterization laboratory; CCPR, conventional cardiopulmonary resuscitation; CHF, congestive heart failure; CPC, cerebral performance category; CVA, cerebrovascular accident; ECPR, extracorporeal cardiopulmonary resuscitation; Epi, epinephrine; ICU, intensive care unit; IQR, interquartile range; MI, myocardial infarction; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; and VF/VT, ventricular fibrillation/ventricular tachycardia.

*Type 3 *P* values from mixed effects logistic regression model, with hospitals included as a random effect.

†CPC is defined as follows: CPC 1, good cerebral performance; CPC 2, moderate cerebral disability; CPC 3, severe cerebral disability; CPC 4, coma or vegetative state.

‡Includes adults arresting in the newborn unit.

§Includes rehabilitation and other.

‖Type 3 *P* value from linear mixed effects model regressing the variable on ECPR indicator, with hospitals included as a random effect due to a convergence issue.

Table 2. Probability of ECPR Use for Cardiac Arrest

Variable	Risk Ratio (95% CI)*	*P* Value	Risk Ratio (95% CI)†	*P* Value	Risk Ratio (95% CI)‡	*P* Value
Age, y						
40–59	Reference	···	Reference	···	Reference	···
<40	1.5 (1.3–1.8)	<0.001	1.5 (1.3–1.9)	<0.001	1.5 (1.2–1.8)	<0.001
≥60	0.6 (0.5–0.7)	<0.001	0.6 (0.5–0.7)	<0.001	0.6 (0.5–0.7)	<0.001
Sex						
Male	Reference	···	Reference	···	Reference	···
Female	0.9 (0.8–1.0)	0.034	0.9 (0.8–1.0)	0.022	0.9 (0.8–1.0)	0.044
Race						
White	Reference	···	Reference	···	Reference	···
Black	0.7 (0.6–0.8)	<0.001	0.8 (0.7–1.0)	0.013	0.8 (0.7–1.0)	0.020
Other	1.0 (0.8–1.2)	0.96	1.0 (0.8–1.3)	0.74	1.0 (0.8–1.3)	0.84
Hispanic ethnicity	1.0 (0.7–1.3)	0.96	1.0 (0.8–1.3)	0.94	1.0 (0.7–1.3)	1.00
Weight, kg	1.0 (1.0–1.0)	0.31	1.0 (1.0–1.0)	0.66	1.0 (1.0–1.0)	0.65
Pre-existing conditions						
None	1.5 (1.2–1.9)	<0.001	1.5 (1.2–1.8)	0.002	1.4 (1.1–1.8)	0.004
Preceding hypoperfusion	1.8 (1.6–2.1)	<0.001	1.6 (1.4–1.8)	<0.001	1.6 (1.4–1.8)	<0.001
CVA or neurologic disorder	0.4 (0.3–0.5)	<0.001	0.5 (0.4–0.6)	<0.001	0.5 (0.4–0.6)	<0.001
CHF	1.2 (1.1–1.4)	<0.001	1.3 (1.1–1.5)	<0.001	1.3 (1.2–1.5)	<0.001
Diabetes mellitus	0.6 (0.5–0.7)	<0.001	0.7 (0.6–0.8)	<0.001	0.7 (0.6–0.8)	<0.001
Hepatic insufficiency	0.5 (0.4–0.7)	<0.001	0.6 (0.5–0.8)	<0.001	0.6 (0.5–0.8)	0.001
Major trauma	0.8 (0.6–1.1)	0.12	0.7 (0.5–1.0)	0.06	0.7 (0.5–1.0)	0.025
Cancer	0.3 (0.2–0.4)	<0.001	0.3 (0.2–0.5)	<0.001	0.3 (0.2–0.5)	<0.001
History of MI	1.5 (1.3–1.8)	<0.001	1.4 (1.2–1.6)	<0.001	1.3 (1.2–1.6)	<0.001
MI this hospitalization	2.1 (1.8–2.4)	<0.001	1.6 (1.3–1.8)	<0.001	1.5 (1.3–1.7)	<0.001
Renal insufficiency	0.5 (0.5–0.6)	<0.001	0.6 (0.5–0.7)	<0.001	0.6 (0.5–0.7)	<0.001
Respiratory insufficiency	0.8 (0.7–0.9)	0.002	0.8 (0.7–0.9)	0.004	0.8 (0.7–0.9)	0.006
Sepsis	0.4 (0.3–0.5)	<0.001	0.5 (0.4–0.6)	<0.001	0.5 (0.4–0.6)	<0.001
Admission CPC§						
CPC 1	Reference	···	Reference	···	Reference	···
CPC 2	0.4 (0.3–0.5)	<0.001	0.5 (0.4–0.6)	<0.001	0.5 (0.4–0.6)	<0.001
CPC 3	0.3 (0.2–0.4)	<0.001	0.4 (0.3–0.5)	<0.001	0.4 (0.3–0.5)	<0.001
CPC 4	0.7 (0.6–1.0)	0.027	0.9 (0.7–1.2)	0.34	0.9 (0.7–1.2)	0.35
Hospital beds						
1–100	Reference	···	Reference	···	Reference	···
101–199	1.1 (0.3–3.9)	0.87	1.3 (0.4–4.6)	0.64	1.3 (0.4–4.4)	0.67
201–249	0.8 (0.2–2.7)	0.67	0.9 (0.3–3.2)	0.91	1.0 (0.3–3.5)	0.95
251–299	0.5 (0.2–1.7)	0.28	0.6 (0.2–2.1)	0.44	0.5 (0.2–1.7)	0.31
301–349	0.4 (0.1–1.5)	0.19	0.5 (0.1–1.5)	0.20	0.4 (0.1–1.5)	0.19
351–499	0.4 (0.1–1.3)	0.12	0.5 (0.1–1.5)	0.19	0.4 (0.1–1.3)	0.12
≥500	0.4 (0.1–1.4)	0.16	0.5 (0.2–1.6)	0.25	0.4 (0.1–1.2)	0.11
Annual admissions						
100–2499	Reference	···	Reference	···	Reference	···
2500–4999	1.8 (0.3–10.9)	0.51	2.0 (0.3–12.3)	0.44	0.9 (0.1–5.1)	0.88
5000–7499	2.7 (0.6–13.2)	0.22	3.4 (0.7–17.3)	0.13	2.6 (0.5–12.7)	0.23
7500–9999	0.7 (0.1–3.9)	0.72	0.9 (0.2–4.8)	0.89	0.6 (0.1–3.1)	0.54
10 000–14 999	0.8 (0.2–3.2)	0.72	0.9 (0.2–4.1)	0.92	0.7 (0.2–2.9)	0.60
15 000–19 999	0.7 (0.2–2.9)	0.61	0.8 (0.2–3.5)	0.76	0.5 (0.2–2.2)	0.38

(*Continued*)

Table 2. Continued

Variable	Risk Ratio (95% CI)*	*P* Value	Risk Ratio (95% CI)†	*P* Value	Risk Ratio (95% CI)‡	*P* Value
20 000–29 999	0.6 (0.1–2.5)	0.48	0.7 (0.2–3.0)	0.62	0.4 (0.1–1.9)	0.27
30 000–39 999	0.5 (0.1–2.0)	0.31	0.6 (0.1–2.6)	0.48	0.3 (0.1–1.4)	0.12
≥40 000	0.7 (0.2–2.8)	0.56	0.8 (0.2–3.6)	0.76	0.4 (0.1–1.9)	0.26
Cardiac ICU beds						
≥31	Reference	···	Reference	···	Reference	···
0	1.6 (1.0–2.7)	0.054	1.7 (1.0–2.7)	0.032	1.7 (1.1–2.8)	0.027
1–5	1.4 (0.5–4.2)	0.50	1.2 (0.4–3.8)	0.72	1.0 (0.3–3.3)	1.00
6–10	1.2 (0.7–2.0)	0.57	1.1 (0.6–1.8)	0.77	1.1 (0.7–1.8)	0.73
11–15	0.9 (0.5–1.5)	0.56	0.9 (0.5–1.5)	0.64	0.9 (0.5–1.4)	0.56
16–20	1.4 (0.8–2.4)	0.21	1.3 (0.8–2.1)	0.35	1.1 (0.7–1.8)	0.78
21–30	1.7 (1.0–2.8)	0.06	1.6 (1.0–2.6)	0.07	1.6 (1.0–2.6)	0.053
Cardiac ICU beds/total beds (%)						
0.1 to <2.5	Reference	···	Reference	···	Reference	···
0	1.7 (1.1–2.8)	0.026	1.8 (1.1–2.8)	0.013	2.0 (1.3–3.2)	0.003
2.5 to <5	1.2 (0.8–1.8)	0.40	1.1 (0.8–1.7)	0.52	1.1 (0.8–1.7)	0.50
5 to <7.5	1.5 (0.9–2.5)	0.09	1.5 (0.9–2.3)	0.11	1.6 (1.0–2.5)	0.052
7.5 to <10	2.7 (1.1–6.5)	0.025	2.8 (1.2–6.3)	0.017	3.1 (1.3–7.0)	0.008
≥10	1.3 (0.5–3.4)	0.61	1.2 (0.5–3.0)	0.74	1.3 (0.5–3.3)	0.58
Geographic region of United States						
North/Mid Atlantic	Reference	···	Reference	···	Reference	···
South Atlantic and Puerto Rico	0.6 (0.4–0.9)	0.008	0.6 (0.4–1.0)	0.035	0.7 (0.4–1.0)	0.06
North Central	0.9 (0.6–1.3)	0.49	0.9 (0.6–1.4)	0.75	1.0 (0.6–1.5)	0.86
South Central	0.8 (0.5–1.2)	0.27	0.9 (0.6–1.5)	0.79	1.1 (0.7–1.7)	0.78
Mountain/Pacific	1.1 (0.7–1.8)	0.61	1.2 (0.8–1.9)	0.41	1.3 (0.8–2.2)	0.25
Intensivist services on site	1.5 (0.8–2.6)	0.19	1.3 (0.7–2.3)	0.35	1.1 (0.6–2.0)	0.65
Urban/rural location						
Urban	Reference	···	Reference	···	Reference	···
Rural	0.7 (0.3–1.7)	0.49	0.8 (0.4–1.8)	0.59	0.8 (0.4–1.7)	0.55
Teaching status						
Major teaching	Reference	···	Reference	···	Reference	···
Minor teaching	0.7 (0.5–1.0)	0.050	0.8 (0.6–1.0)	0.07	0.7 (0.5–1.0)	0.025
Nonteaching	0.9 (0.5–1.5)	0.65	0.9 (0.6–1.5)	0.75	0.8 (0.5–1.3)	0.36
Medicare days						
0	Reference	···	Reference	···	Reference	···
1–1500	12.4 (3.5–43.4)	<0.001	8.6 (2.6–28.5)	<0.001	8.2 (2.4–27.4)	<0.001
1501–5000	6.8 (0.9–50.8)	0.06	2.7 (0.4–17.9)	0.31	2.7 (0.4–18.7)	0.32
5001–20 000	1.3 (0.4–4.3)	0.64	1.1 (0.3–3.3)	0.93	0.9 (0.3–2.7)	0.80
>20 000	0.7 (0.2–1.8)	0.42	0.5 (0.2–1.4)	0.21	0.5 (0.2–1.2)	0.12

Risk ratio and 95% CI were estimated using mixed effects log-binomial model with hospital included as a random effect. Because ECPR is a rare event (0.8%), the odds ratio is an approximation to the risk ratio. We reported the unadjusted risk ratio (column 1), with the risk ratio adjusting for patient variables (age, sex, race, Hispanic origin, presenting rhythm status, subject type, and event location; column 2) and the risk ratio adjusting for patient and hospital variables (cardiac ICU beds, area type, teaching status, and admission period [2000–2004, 2005–2009, etc]; column 3). For the variables hospital beds, annual admission, and cardiac ICU beds/total beds (%), we did not adjust for cardiac ICU beds. CHF indicates congestive heart failure; CPC, cerebral performance category; CVA, cerebrovascular accident; ECPR, extracorporeal cardiopulmonary resuscitation; ICU, intensive care unit; and MI, myocardial infarction.

*Unadjusted risk ratio.

†Risk ratio adjusting for patient variables.

‡Risk ratio adjusting for patient and hospital variables.

§CPC is defined as follows: CPC 1, good cerebral performance; CPC 2, moderate cerebral disability; CPC 3, severe cerebral disability; CPC 4, coma or vegetative state.

during the cardiac arrest (Table 3). The probability of ECPR treatment increased in ambulatory/outpatient settings such as same-day procedural areas (RR, 3.1; 95% CI, 1.8–5.2; *P*<0.001) and inpatient cardiac units (RR, 4.0; 95% CI, 3.0–5.3; *P*<0.001), intensive care units (RR, 2.8; 95% CI, 2.2–3.5; *P*<0.001), and operating rooms (RR, 12.0; 95% CI, 9.6–15.2; *P*<0.001) compared with general inpatient units (Figure 1). Correspondingly, cardiac medical and cardiac surgical patients were more likely to be treated with ECPR (RR, 4.3; 95% CI, 3.5–5.4; *P*<0.001; and RR, 24.1; 95% CI, 19.5–29.6; *P*<0.001; respectively).

Arrest Characteristics

Arrest characteristics associated with the use of ECPR included the presence of ventricular fibrillation (RR, 1.5; 95% CI, 1.2–1.8; *P*<0.001), witnessed arrest (RR, 4.5; 95% CI, 3.1–6.5; *P*<0.001), or any return of spontaneous circulation (RR, 1.5; 95% CI, 1.3–1.8; *P*<0.001) during the arrest (Tables 3 and 4). Features associated with decreased ECPR use included arrests occurring after 3 PM or before 7 AM (RR, 0.8; 95% CI, 0.7–1.0; *P*=0.02; and RR, 0.6; 95% CI, 0.5–0.7; *P*<0.001; respectively) and on weekends (RR, 0.7; 95% CI, 0.6–0.9; *P*<0.001) (Table 3, Figure 2). Increased duration of resuscitation (RR, 1.02 per minute; 95% CI, 1.02–1.03;

Table 3. Risk Ratio of Getting ECPR for Prearrest Characteristics

Variable	Risk Ratio (95% CI)*	*P* Value	Risk Ratio (95% CI)†	*P* Value	Risk Ratio (95% CI)‡	*P* Value
Duration between admission and arrest						
<24 h	Reference	···	Reference	···	Reference	···
24 to <48 h	0.6 (0.4–0.9)	0.007	0.7 (0.5–1.0)	0.07	0.7 (0.5–1.0)	0.06
48 h to <1 wk	0.4 (0.2–0.8)	0.018	0.5 (0.2–1.0)	0.07	0.5 (0.2–1.1)	0.08
≥1 wk	1.4 (0.5–4.3)	0.57	1.3 (0.4–4.1)	0.62	1.4 (0.4–4.1)	0.59
Devices						
Mechanical ventilation	2.6 (2.3–3.0)	<0.001	2.0 (1.7–2.3)	<0.001	2.0 (1.7–2.3)	<0.001
Invasive airway	2.4 (2.2–2.7)	<0.001	1.8 (1.5–2.0)	<0.001	1.7 (1.5–2.0)	<0.001
Arterial line	4.8 (4.2–5.4)	<0.001	3.2 (2.8–3.6)	<0.001	3.1 (2.7–3.5)	<0.001
Time of day of arrest						
7 AM to 2:59 PM	Reference	···	Reference	···	Reference	···
3 PM to 10:59 PM	0.8 (0.7–0.9)	<0.001	0.9 (0.7–1.0)	0.021	0.8 (0.7–1.0)	0.020
11 PM to 6:59 AM	0.4 (0.3–0.5)	<0.001	0.6 (0.5–0.7)	<0.001	0.6 (0.5–0.7)	<0.001
Day of week						
Weekday	Reference	···	Reference	···	Reference	···
Weekend	0.6 (0.5–0.7)	<0.001	0.7 (0.6–0.9)	<0.001	0.7 (0.6–0.9)	<0.001
Arrest location						
General inpatient§	Reference	···	Reference	···	Reference	···
Ambulatory/outpatient‖	3.0 (1.7–5.0)	<0.001	3.0 (1.8–5.1)	<0.001	3.1 (1.8–5.2)	<0.001
Cardiac/coronary unit	4.0 (3.0–5.3)	<0.001	3.7 (2.8–5.0)	<0.001	4.0 (3.0–5.3)	<0.001
ICU	3.2 (2.6–4.0)	<0.001	2.9 (2.3–3.6)	<0.001	2.8 (2.2–3.5)	<0.001
Operating room/procedural/cath lab	14.0 (11.3–17.4)	<0.001	12.1 (9.7–15.2)	<0.001	12.0 (9.6–15.2)	<0.001
Emergency department	1.4 (0.9–2.0)	0.09	1.3 (0.9–1.8)	0.23	1.2 (0.8–1.8)	0.37
Illness category						
Medical—noncardiac	Reference	···	Reference	···	Reference	···
Medical—cardiac	3.8 (3.1–4.6)	<0.001	4.3 (3.5–5.3)	<0.001	4.3 (3.5–5.4)	<0.001
Surgical—cardiac	21.5 (17.7–26.0)	<0.001	23.8 (19.5–29.2)	<0.001	24.0 (19.5–29.6)	<0.001
Surgical—noncardiac	2.3 (1.8–3.0)	<0.001	2.5 (1.9–3.3)	<0.001	2.6 (1.9–3.4)	<0.001
Witnessed	4.7 (3.4–6.7)	<0.001	4.3 (3.0–6.2)	<0.001	4.5 (3.1–6.5)	<0.001

cath lab indicates cardiac catheterization laboratory; ECPR, extracorporeal cardiopulmonary resuscitation; and ICU, intensive care unit.
*Unadjusted risk ratio.
†Risk ratio adjusting for patient variables.
‡Risk ratio adjusting for patient and hospital variables.
§Includes adults arresting in the newborn unit.
‖"Ambulatory/outpatient" includes rehabilitation unit.

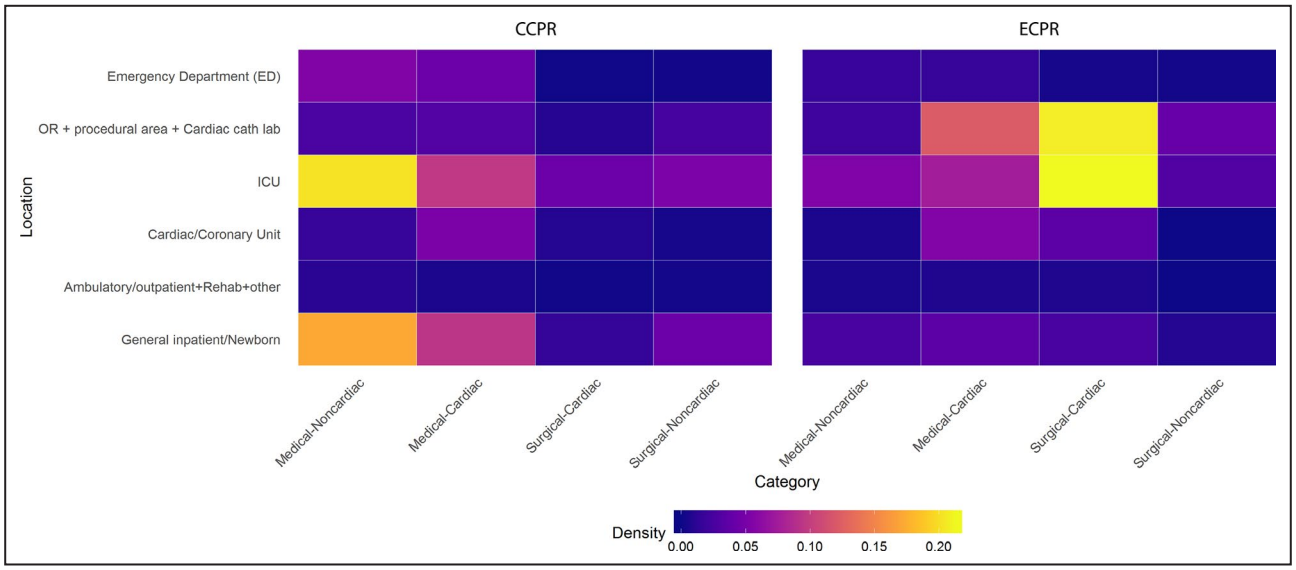

Figure 1. Comparison of CCPR vs ECPR use within hospitals (patient type and physical location).
CCPR indicates conventional cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; and ICU, intensive care unit.

P<0.001) and use of post-arrest-induced hypothermia (RR, 3.2; 95% CI, 2.7–3.9; *P*<0.001) were both associated with ECPR use.

DISCUSSION

In this large, multicenter, observational study of ECPR as an adjunctive treatment of IHCA, we determined that the decision to offer ECPR is highly influenced by patient and arrest characteristics. Patients who received ECPR were younger, more likely to have cardiac-specific conditions, and less likely to have other pre-existing conditions. Patients whose arrest occurred during daytime and weekdays and in procedural areas (operating room, coronary catheterization laboratory) were more likely to be offered ECPR. This

Table 4. Risk Ratio of Getting ECPR for Arrest Characteristics/Management

Variable	Risk Ratio (95% CI)*	*P* Value	Risk Ratio (95% CI)†	*P* Value	Risk Ratio (95% CI)‡	*P* Value
Hospital resuscitation activated	0.3 (0.3–0.4)	<0.001	0.5 (0.4–0.6)	<0.001	0.5 (0.4–0.6)	<0.001
Presenting rhythm status						
Asystole	Reference	···	Reference	···	Reference	···
PEA	1.0 (0.8–1.2)	0.83	0.9 (0.8–1.1)	0.43	0.9 (0.8–1.1)	0.45
Pulseless VT	1.4 (1.1–1.7)	0.012	1.2 (1.0–1.6)	0.11	1.2 (0.9–1.5)	0.15
VF	2.0 (1.6–2.4)	<0.001	1.6 (1.3–1.9)	<0.001	1.5 (1.2–1.8)	<0.001
Palpable pulse initially	1.4 (1.1–1.8)	0.005	1.2 (0.9–1.5)	0.14	1.2 (0.9–1.5)	0.23
Any VF/VT	2.1 (1.9–2.4)	<0.001	2.0 (1.7–2.2)	<0.001	1.9 (1.7–2.2)	<0.001
Compression method						
Manual	0.073 (0.054–0.098)§	<0.001	0.139 (0.101–0.191)§	<0.001	0.137 (0.099–0.189)§	<0.001
Mechanical	1.3 (1.0–1.5)	0.023	1.3 (1.0–1.6)	0.017	1.5 (1.1–2.1)	0.006
Open cardiac massage	20.1 (17.1–23.8)	<0.001	18.349 (14.718–22.876)§	<0.001	18.026 (14.399–22.566)§	<0.001
Any ROSC	1.6 (1.4–1.9)	<0.001	1.5 (1.3–1.7)	<0.001	1.5 (1.3–1.8)	<0.001
Total duration before durable ROSC	1.024 (1.023–1.026)§	<0.001	1.024 (1.023–1.026)§	<0.001	1.024 (1.023–1.026)§	<0.001
Induced hypothermia	3.5 (2.9–4.3)	<0.001	3.2 (2.7–3.9)	<0.001	3.2 (2.7–3.9)	<0.001

ECPR indicates extracorporeal cardiopulmonary resuscitation; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; and VT, ventricular tachycardia.
*Unadjusted risk ratio.
†Risk ratio adjusting for patient variables.
‡Risk ratio adjusting for patient and hospital variables.
§A mixed effects logistic model was used because of convergence issues, and the reported odds ratio is an approximation to the risk ratio.

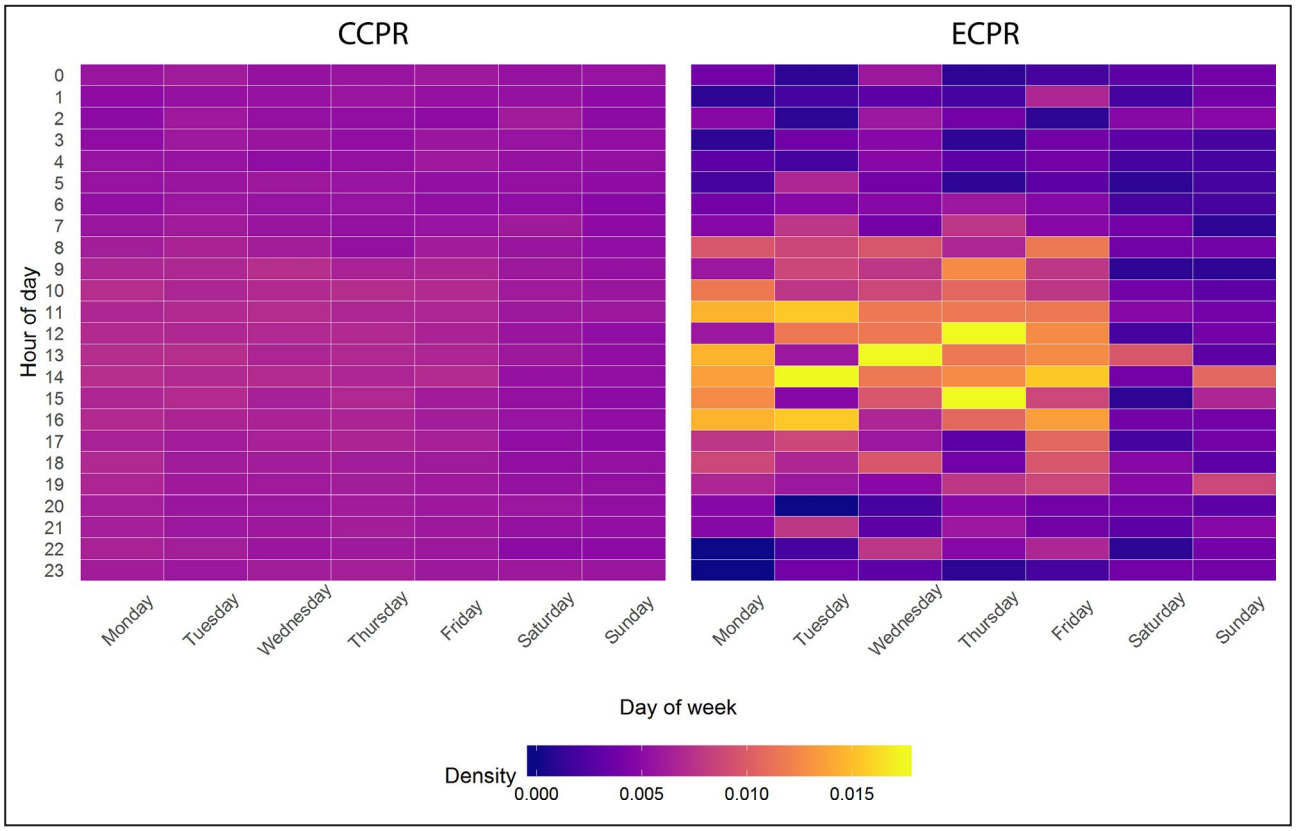

Figure 2. Temporal relationship of CCPR vs ECPR use.
CCPR indicates conventional cardiopulmonary resuscitation; and ECPR, extracorporeal cardiopulmonary resuscitation.

likely reflects the schedule of planned procedures, familiarity with the patient, and an increased numbers of proceduralists required to provide ECPR in house. As an example of this, nonshockable rhythms are not traditionally considered an inclusion criteria for ECPR programs given their lower observed survival[2,10,36,37]; despite this, >60% of ECPR patients had a nonshockable rhythm initially. Given 48.9% of ECPR patients were located in a procedural area at the time of arrest, the inclusion of nonshockable rhythms likely reflects the proceduralist's familiarity with the patient at the time of the arrest and therefore willingness to use ECPR. ECPR increased if patients had witnessed arrests, shockable initial rhythms, or intermittent/temporary return of spontaneous circulation. Overall, the 1% of patients who receive ECPR for IHCA are characteristically different than CCPR patients, which likely effects the survival and quality of survival for these patients with "favorable" arrest characteristics.[38]

ECPR series have shown heterogenous survival, underscoring the critical importance of randomized clinical trials for this invasive and expensive therapy[1–5]; yet ECPR use has dramatically increased during the previous 2 decades.[39,40] Some have opined that the growing clinical use of ECPR may reflect a lack of equipoise among some providers for certain patients.[41] Others have stated that extracorporeal membrane oxygenation (ECMO) "is a heroic measure that involves high cost, invasive procedures, and exposes the patients to a series of potential complications."[42] Both of these opinions are likely correct. Unequivocally, the use of ECMO is an ethically complex topic that has generated significant discussion and controversy for more than 30 years.[41–46] The addition of patients in acute cardiopulmonary arrest to the pool of potential ECMO candidates has only added to this controversy. We believe this simultaneously emphasizes the need for randomized controlled trials of ECPR to define outcomes from unbiased patient selection and the difficulty in their design and recruitment. To adequately enroll patients, trials will need to select patients for whom there is a willingness to perform ECPR yet for whom there remains equipoise across diverse regions, hospitals, providers, and patients. Our study fills a previous knowledge gap in that it defines the features that favor ECPR use for IHCA. By identifying these patients, clinical trials may have a target population for enrollment.

Limitations

The data set is voluntary and captures fewer than 10% of US hospitals. Despite this, the use of this large data set enabled us to perform the largest published analysis of ECPR arrest characteristics contributing to generalizability. Some variables, such as admission Cerebral Performance Category, had a high degree of missingness (>15%) (Table 1), which may influence the findings for these variables. Previous analyses have demonstrated that the ECPR variable within the data set may not capture all instances of ECPR.[47] As the ratio of ECPR to CCPR was <1%, we feel the amount of miscoded ECPR cases within the CCPR cohort is below a meaningful level. Finally, ECMO support details were not collected.

CONCLUSIONS

ECPR is increasing in use for IHCA and out-of-hospital cardiac arrest; however, reported outcomes are heterogenous and influenced by favorable patient selection. Randomized controlled trials are needed to define the best use of this technology to rescue patients after cardiac arrest. As enrollment in randomized controlled trials is a major barrier to trial feasibility,[48] the success of future randomized controlled trials of ECPR depends on defining patients, providers, and clinical illnesses for whom there is both equipoise and a low barrier to trial implementation.[49] Our findings identify and define the characteristics that bias toward use of ECPR. Physicians are willing to place younger patients who have primarily a cardiac history with few other comorbidities on ECPR. This may be a group to target for enrollment in future trials.

ARTICLE INFORMATION

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Author contributions: J.E. Tonna had full access to all the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the integrity of the submission as a whole, from inception to published article. J.E. Tonna, R.R. Thiagarajan, A.P. Presson, and H.T. Keenan conceived study design; J.E. Tonna, A.P. Presson, C. Zhang, R.R. Thiagarajan, S. Girotra, L.B. Becker, C.H. Selzman, and H.T. Keenan contributed to data analysis; J.E. Tonna, C. Zhang, A.P. Presson, and H.T. Keenan drafted the work. All authors revised the article for important intellectual content, had final approval of the work to be published, and agreed to be accountable for all aspects of the work.

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Disclosures

Dr Tonna received modest support from LivaNova as a speaking honorarium relevant to cardiac arrest. The remaining authors have no disclosures to report.

Supplementary Materials

Appendix S1
Data S1
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Supplemental Material

Appendix

Adult Resuscitation Task Force Members:

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Data S1.

Supplemental Methods and Results

Data Filtering

Sample size

Step	N.events	N.admissions	N.eCPR
Raw data	359107	300649	1303
Exclude all admissions with OOH_ARREST==1	344837	289833	1250
Excluding events occurred more than 4 hrs before admission	344667	289726	1250
Excluding events occurred prior to admission (EVT_DT< ADM_DT) if ADM_DTM is missing	344653	289714	1250
Excluding events with SUBJ_TY=7 (visitors..)	344159	289248	1250
Excluding events with ILL_CAT=8 (visitors..)	344007	289248	1249
Excluding events from hospitals that could not be matched to the hospital data	343870	288998	1249
Removing all events from non-eCPR hospitals	218823	182764	1249
Removing all events before the first eCPR of the hospital	156547	130035	1249
Keeping only the first event per admission	130035	130035	1098
Remove patients with admission CPC =Brain death	129963	129963	1097
Remove additional hospitals with no eCPR patients left	128809	128809	1097
Excluding hospitals with <5 events or duration for provided events shorter than 6 months	128619	128619	1082

Table S1. Descriptive summary of hospital characteristics at hospital level.

Variable*	Summary (N=219)
Hospital Beds	
1-100	3 (1.4%)
101-199	16 (7.4%)
201-249	13 (6%)
251-299	26 (12%)
301-349	21 (9.7%)
351-499	57 (26.4%)
≥500	80 (37%)
Annual Admissions	
100-2,499	2 (0.9%)
2,500-4,999	4 (1.9%)
5,000-7,499	8 (3.7%)
7,500-9,999	6 (2.8%)
10,000-14,999	40 (18.5%)
15,000-19,999	49 (22.7%)
20,000-29,999	54 (25%)
30,000-39,999	34 (15.7%)
≥40,000	19 (8.8%)
Cardiac ICU Beds	
0	43 (20.9%)
1-5	6 (2.9%)
6-10	31 (15%)
11-15	37 (18%)
16-20	32 (15.5%)
21-30	30 (14.6%)
≥31	27 (13.1%)
Cardiac ICU Beds/Total Beds (%)	
0	43 (20.9%)
0.1 to <2.5	38 (18.4%)
2.5 to <5	76 (36.9%)
5 to <7.5	36 (17.5%)

Variable*	Summary (N=219)
7.5 to <10	7 (3.4%)
≥10	6 (2.9%)
Geographic Region of US	
North / Mid Atlantic	38 (17.4%)
South Atlantic and Puerto Rico	52 (23.9%)
North Central	48 (22%)
South Central	44 (20.2%)
Mountain/Pacific	36 (16.5%)
Intensive Services on site	180 (90.9%)
Urban/Rural Location	8 (3.8%)
Teaching Status	
Major teaching	71 (32.6%)
Minor teaching	121 (55.5%)
Non-teaching	26 (11.9%)
Medicare Days	
0	5 (2.3%)
1-1,500	7 (3.2%)
1,501-5,000	1 (0.5%)
5,001-20,000	13 (6%)
>20,000	190 (88%)

*Number (percent, %)

Missing values: Hospital Beds=3, Annual Admissions=3, Cardiac ICU beds=13, Cardiac ICU beds/total beds (%)=13, Geographic Region of US=1, Intensive Services on site=21, Urban/Rural Location=9, Teaching Status=1, Medicare Days=3.

ICU = intensive care unit, US = United States

Table S2. Hospital characteristics by ECPR Available and Non ECPR Available*.

Variable†	Non ECPR Available* Hospital Dropped (N=594)	ECPR Available Hospital Kept (N=219)	P-value
Hospital Beds			<0.001
1-100	88 (15.5%)	3 (1.4%)	-
101-199	161 (28.3%)	16 (7.4%)	-
201-249	63 (11.1%)	13 (6%)	-
251-299	50 (8.8%)	26 (12%)	-
301-349	52 (9.2%)	21 (9.7%)	-
351-499	73 (12.9%)	57 (26.4%)	-
≥500	81 (14.3%)	80 (37%)	-
Annual Admissions			<0.001
100-2,499	37 (6.5%)	2 (0.9%)	-
2,500-4,999	81 (14.3%)	4 (1.9%)	-
5,000-7,499	99 (17.4%)	8 (3.7%)	-
7,500-9,999	61 (10.7%)	6 (2.8%)	-
10,000-14,999	106 (18.7%)	40 (18.5%)	-
15,000-19,999	78 (13.7%)	49 (22.7%)	-
20,000-29,999	59 (10.4%)	54 (25%)	-
30,000-39,999	27 (4.8%)	34 (15.7%)	-
≥40,000	20 (3.5%)	19 (8.8%)	-
Cardiac ICU Beds			<0.001
0	279 (57.5%)	43 (20.9%)	-
1-5	13 (2.7%)	6 (2.9%)	-
6-10	63 (13%)	31 (15%)	-
11-15	45 (9.3%)	37 (18%)	-
16-20	30 (6.2%)	32 (15.5%)	-
21-30	35 (7.2%)	30 (14.6%)	-

Variable†	Non ECPR Available* Hospital Dropped (N=594)	ECPR Available Hospital Kept (N=219)	P-value
≥31	20 (4.1%)	27 (13.1%)	-
Cardiac ICU Beds/Total Beds (%)			<0.001
0	279 (57.5%)	43 (20.9%)	-
0.1 to <2.5	58 (12%)	38 (18.4%)	-
2.5 to <5	93 (19.2%)	76 (36.9%)	-
5 to <7.5	32 (6.6%)	36 (17.5%)	-
7.5 to <10	10 (2.1%)	7 (3.4%)	-
≥10	13 (2.7%)	6 (2.9%)	-
Geographic Region of US			0.81
North / Mid Atlantic	92 (15.9%)	38 (17.4%)	-
South Atlantic and Puerto Rico	139 (24.1%)	52 (23.9%)	-
North Central	127 (22%)	48 (22%)	-
South Central	104 (18%)	44 (20.2%)	-
Mountain/Pacific	115 (19.9%)	36 (16.5%)	-
Site in GWTG_R	594 (100%)	219 (100%)	1.00
Intensive Services on site	347 (75.8%)	180 (90.9%)	<0.001
Urban/Rural Location			<0.001
Urban	483 (87%)	202 (96.2%)	-
Rural	72 (13%)	8 (3.8%)	-
Teaching Status			<0.001
Non-teaching	192 (33.5%)	26 (11.9%)	-
Major teaching	83 (14.5%)	71 (32.6%)	-
Minor teaching	298 (52%)	121 (55.5%)	-
Medicare Days			<0.001

Variable†	Non ECPR Available* Hospital Dropped (N=594)	ECPR Available Hospital Kept (N=219)	P-value
0	33 (5.8%)	5 (2.3%)	-
1-1,500	14 (2.5%)	7 (3.2%)	-
1,501-5,000	22 (3.9%)	1 (0.5%)	-
5,001-20,000	188 (33%)	13 (6%)	-
>20,000	313 (54.9%)	190 (88%)	-

* ECPR occurred at some “Non-ECPR available” hospitals. “Non-ECPR available” was defined for the purposes of this analysis as hospitals had done no ECPR cases, or hospitals that had submitted < 5 cardiac arrests events or <6 months of data.

† Number (%)

ECPR = extracorporeal cardiopulmonary resuscitation, CCPR = conventional cardiopulmonary resuscitation, ICU: Intensive Care Unit; GWTG-R: Get With The Guidelines—Resuscitation; US: United States

Missing values by group: Hospital Beds=26/3, Annual Admissions=26/3, Cardiac ICU beds=109/13, Cardiac ICU beds/total beds (%)=109/13, Geographic Region of US =17/1, Intensive Services on site=136/21, Urban/Rural Location=39/9, Teaching Status=21/1, Medicare Days=24/3.

Table S3. Patient characteristics by ECPR Available vs. Non ECPR Available* hospitals†.

Variable‡	Non ECPR Available* Hospital Dropped (N=110775)	ECPR Available Hospital Kept (N=178223)	P-value§
Age			<0.001
<40	6270 (5.7%)	13590 (7.6%)	-
40-59	25794 (23.3%)	46325 (26%)	-
≥60	78711 (71.1%)	118308 (66.4%)	-
Male Sex	64488 (58.2%)	103102 (57.9%)	0.027
Race			<0.001
White	77230 (70.1%)	120863 (68%)	-
Black	21619 (19.6%)	40311 (22.7%)	-
Other	11281 (10.2%)	16593 (9.3%)	-
Hispanic Ethnicity	6330 (5.7%)	9623 (5.4%)	0.86
Weight(kg) ‖	77 (63.5, 93)	78 (64.5, 95)	0.09
Pre-Existing Condition			
None	8452 (7.7%)	9547 (5.4%)	0.003
Preceding Hypoperfusion	25640 (23.2%)	49340 (27.8%)	<0.001
CVA or Neurologic Disorder	19573 (17.7%)	36387 (20.5%)	<0.001
CHF	31160 (28.2%)	51883 (29.2%)	<0.001
Diabetes Mellitus	34509 (31.2%)	57006 (32.1%)	<0.001
Hepatic Insufficiency	7687 (7%)	14067 (7.9%)	<0.001
Major Trauma	3403 (3.1%)	9015 (5.1%)	0.15
Cancer	12372 (11.2%)	21471 (12.1%)	<0.001
History of MI	15457 (14%)	27566 (15.5%)	<0.001
MI this Hospitalization	16247 (14.7%)	27793 (15.6%)	<0.001
Renal Insufficiency	36737 (33.3%)	61992 (34.9%)	<0.001
Respiratory Insufficiency	44263 (40.1%)	78969 (44.4%)	0.013

Variable‡	Non ECPR Available* Hospital Dropped (N=110775)	ECPR Available Hospital Kept (N=178223)	P-value§
Sepsis	18181 (16.5%)	29963 (16.9%)	<0.001
Admission CPC			<0.001
CPC 1: Good cerebral performance	46289 (57.1%)	82750 (59.5%)	
CPC 2: Moderate cerebral disability	19871 (24.5%)	30388 (21.9%)	
CPC 3: Severe cerebral disability	10036 (12.4%)	15698 (11.3%)	
CPC 4: Coma or vegetative state	4716 (5.8%)	10132 (7.3%)	
CPC 5: Brain death	102 (0.1%)	99 (0.1%)	

*ECPR occurred at some “Non-ECPR capable” hospitals. “Non-ECPR capable” was defined for the purposes of this analysis as hospitals had done no ECPR cases, or hospitals that had submitted < 5 cardiac arrests events or <6 months of data.

†Exclusion criteria like keeping events after 1st ECPR, dropping brain dead patients were not applied here.

‡Number (percent, %)

§Type 3 p values from mixed effects logistic regression model, with hospitals included as a random effect.

||Median (interquartile range, IQR)

CPC Defined as: CPC 1: Good cerebral performance, CPC 2: Moderate cerebral disability, CPC 3: Severe cerebral disability, CPC 4: Coma or vegetative state

ECPR = extracorporeal cardiopulmonary resuscitation, CCPR = conventional cardiopulmonary resuscitation, CVA = cerebrovascular accident, CHF = congestive heart failure, MI = myocardial infarction, CPC = cerebral performance category

Missing values by group: Sex=19/10, Race=645/456, Weight(kg)=50246/85640, Pre-existing condition: None=338/479, Preceding hypoperfusion=338/479, -CVA or Neurologic Disorder=338/479, -CHF=338/479, -Diabetes Mellitus=338/479, -Hepatic Insufficiency=338/479, -Major Trauma=338/479, -

Cancer =338/479, -History of MI=338/479, -MI this Hospitalization=338/479, -Renal Insufficiency=338/479, -Respiratory Insufficiency=338/479, -Sepsis=338/479, Admission CPC=29761/39156.

Table S4. Summary of #ECPR, #CCPR, and their ratio for 23 hospitals that had eCPR cases in 2010.

Year	#ECPR	#CCPR	#ECPR/#CCPR ratio	Fraction of all ECPRs represented by these 23 hospitals
2010	48	2327	0.021	1
2011	20	2872	0.007	0.645
2012	20	2607	0.008	0.357
2013	32	2675	0.012	0.36
2014	42	2663	0.016	0.368
2015	34	2608	0.013	0.296
2016	48	2717	0.018	0.425
2017	30	2506	0.012	0.288
~~2018~~	~~0~~	~~49~~	~~0~~	~~0~~

Table S5. Comparing ECPR patient characteristics between two eras.

Variable*	2000-2008 (N=357)	2009-2018 (N=725)	P -value†
Age			0.95
<40	47 (13.2%)	119 (16.4%)	-
40-59	113 (31.7%)	242 (33.4%)	-
≥60	197 (55.2%)	364 (50.2%)	-
Sex			0.24
Male	212 (59.4%)	454 (62.6%)	-
Female	145 (40.6%)	271 (37.4%)	-
Race			0.30
White	272 (76.6%)	527 (72.8%)	-
Black	42 (11.8%)	126 (17.4%)	-
Other	41 (11.5%)	71 (9.8%)	-
Hispanic Ethnicity	18 (5%)	37 (5.1%)	0.76
Weight(kg) ‡	80.0 (67.5, 95.5)	80.0 (65.6, 96.9)	0.52
Pre-existing condition			
None	16 (4.5%)	70 (9.7%)	0.39
Preceding hypoperfusion	166 (46.5%)	304 (42.1%)	0.78
CVA or Neurologic Disorder	32 (9%)	68 (9.4%)	0.42
CHF	124 (34.7%)	242 (33.5%)	0.57
Diabetes Mellitus	61 (17.1%)	185 (25.6%)	0.29
Hepatic Insufficiency	12 (3.4%)	41 (5.7%)	0.23
Major Trauma	14 (3.9%)	26 (3.6%)	0.49
Cancer	12 (3.4%)	30 (4.2%)	0.62
History of MI	99 (27.7%)	130 (18%)	0.036
MI this Hospitalization	130 (36.4%)	159 (22%)	0.16
Renal Insufficiency	55 (15.4%)	189 (26.2%)	0.001
Respiratory Insufficiency	107 (30%)	336 (46.5%)	<0.001
Sepsis	17 (4.8%)	70 (9.7%)	0.08

Variable*	2000-2008 (N=357)	2009-2018 (N=725)	P -value†
Admission CPC§			0.44
CPC 1: Good cerebral performance	224 (76.2%)	443 (79.1%)	-
CPC 2: Moderate cerebral disability	41 (13.9%)	47 (8.4%)	-
CPC 3: Severe cerebral disability	16 (5.4%)	23 (4.1%)	-
CPC 4: Coma or vegetative state	13 (4.4%)	47 (8.4%)	-
Duration between Admission and Arrest:			0.52
<24h	347 (97.2%)	697 (96.1%)	-
24 - <48h	8 (2.2%)	21 (2.9%)	-
48h - 1wk	1 (0.3%)	5 (0.7%)	-
≥1wk	1 (0.3%)	2 (0.3%)	-
Devices in place at arrest			
Mechanical Ventilation	205 (57.4%)	351 (48.5%)	0.27
Invasive Airway	197 (55.2%)	334 (46.1%)	0.38
Arterial Line	162 (45.4%)	316 (43.6%)	0.44
Time of Day of arrest			
7am-3pm	170 (50.4%)	330 (47.3%)	0.72
3pm-11pm	118 (35%)	240 (34.4%)	-
11pm-7am	49 (14.5%)	128 (18.3%)	-
Day of Week	53 (14.8%)	133 (18.3%)	0.16
Arrest location			0.29
General inpatient‖	29 (8.1%)	71 (9.8%)	-
*Ambulatory/outpatient***	7 (2%)	9 (1.2%)	-
Cardiac/Coronary Unit	16 (4.5%)	87 (12%)	-
ICU	129 (36.1%)	273 (37.7%)	-
OR + procedural area + Cardiac catheterization lab	163 (45.7%)	258 (35.6%)	-
Emergency Department	13 (3.6%)	27 (3.7%)	-
Illness Category:			0.35
Medical-Noncardiac	35 (9.8%)	99 (13.7%)	-

Variable*	2000-2008 (N=357)	2009-2018 (N=725)	P -value†
Medical-Cardiac	102 (28.6%)	232 (32%)	-
Surgical-Cardiac	190 (53.2%)	338 (46.6%)	-
Surgical-Noncardiac	30 (8.4%)	56 (7.7%)	-
Witnessed	346 (96.9%)	703 (97%)	0.89
Hospital resuscitation activated	143 (40.1%)	340 (46.9%)	0.58
Condition of 1st assessment			0.54
Poor perfusion, lost pulses	27 (7.6%)	63 (8.7%)	-
Poor perfusion, never pulseless	6 (1.7%)	18 (2.5%)	-
Pulseless	324 (90.8%)	644 (88.8%)	-
Presenting rhythm status			0.08
Asystole	88 (26.7%)	126 (18.6%)	-
PEA	106 (32.2%)	297 (43.7%)	-
Pulseless Ventricular Tachycardia	29 (8.8%)	64 (9.4%)	-
Ventricular Fibrillation	73 (22.2%)	111 (16.3%)	-
Palpable pulse initially	33 (10%)	81 (11.9%)	-
First Rhythm			0.62
Accelerated idioventricular rhythm	0 (0%)	2 (2.5%)	-
Bradycardia	11 (33.3%)	44 (54.3%)	-
Pacemaker	9 (27.3%)	7 (8.6%)	-
Sinus (including sinus tachycardia)	3 (9.1%)	10 (12.3%)	-
Supraventricular tachyarrhythmia	1 (3%)	0 (0%)	-
Unknown	4 (12.1%)	11 (13.6%)	-
Ventricular Tachycardia with a pulse	5 (15.2%)	7 (8.6%)	-
Any VF/VT	195 (54.6%)	393 (54.2%)	0.74
Number of defibrillations‡	3.0 (2.0, 6.0)	3.0 (2.0, 6.0)	0.74
Received compressions	344 (96.4%)	710 (97.9%)	0.35
Compression Method			
Manual	98 (92.5%)	657 (92.5%)	0.26

Variable*	2000-2008 (N=357)	2009-2018 (N=725)	P -value†
Mechanical	101 (95.3%)	97 (13.7%)	<0.001
Open Cardiac Massage	16 (15.1%)	138 (19.4%)	0.52
Epi boluses before pulseless‡	3.0 (1.8, 5.0)	4.0 (2.0, 6.0)	0.64
Epi boluses after pulseless‡	4.0 (2.0, 5.0)	5.0 (3.0, 9.0)	0.004
Any ROSC	257 (72.8%)	604 (83.4%)	0.12
Total duration before durable ROSC ‡	39.0 (17.2, 85.0)	35.5 (17.0, 65.0)	0.046
Induced Hypothermia	26 (11.4%)	88 (13.2%)	0.49

* Number (percent, %)

† Type 3 p values from mixed effects logistic regression model, with hospitals included as a random effect.

‡ Median (interquartile range, IQR)

§ CPC Defined as: CPC 1: Good cerebral performance, CPC 2: Moderate cerebral disability, CPC 3: Severe cerebral disability, CPC 4: Coma or vegetative state

|| Includes adults arresting in the newborn unit

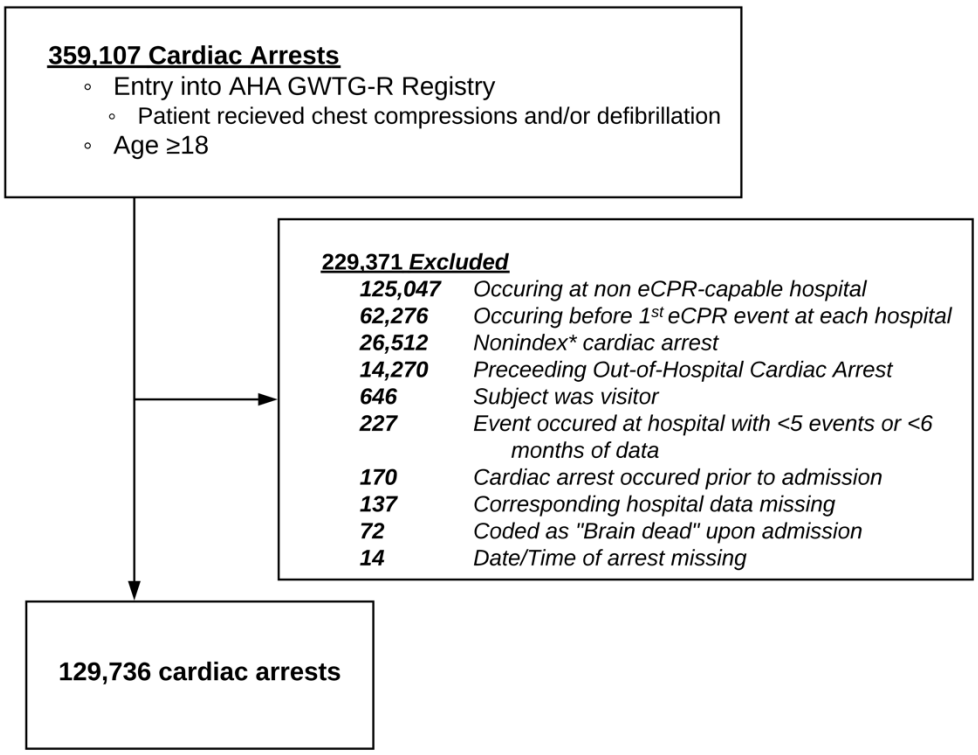
** Includes rehabilitation and other

ECPR = extracorporeal cardiopulmonary resuscitation, CCPR = conventional cardiopulmonary resuscitation, CVA = cerebrovascular accident, CHF = congestive heart failure, MI = myocardial infarction, CPC = cerebral performance category, h = hours, wk = week, VF/VT = ventricular fibrillation/ventricular tachycardia, Epi = epinephrine, ROSC = return of spontaneous circulation

Missing values by group: Race=2/1, Weight(kg)=38/521, Pre-existing condition-None=0/3, -Preceding hypoperfusion=0/3, -CVA or Neurologic Disorder=0/3, -CHF=0/3, -Diabetes Mellitus=0/3, -Hepatic Insufficiency=0/3, -Major Trauma=0/3, -Cancer =0/3, -History of MI=0/3, -MI this Hospitalization=0/3, -Renal Insufficiency=0/3, -Respiratory Insufficiency=0/3, -Sepsis=0/3, Admission CPC=63/165, Devices - Mechanical Ventilation=0/1, Devices - Invasive Airway=0/1, Devices - Arterial Line=0/1, Time of Day of

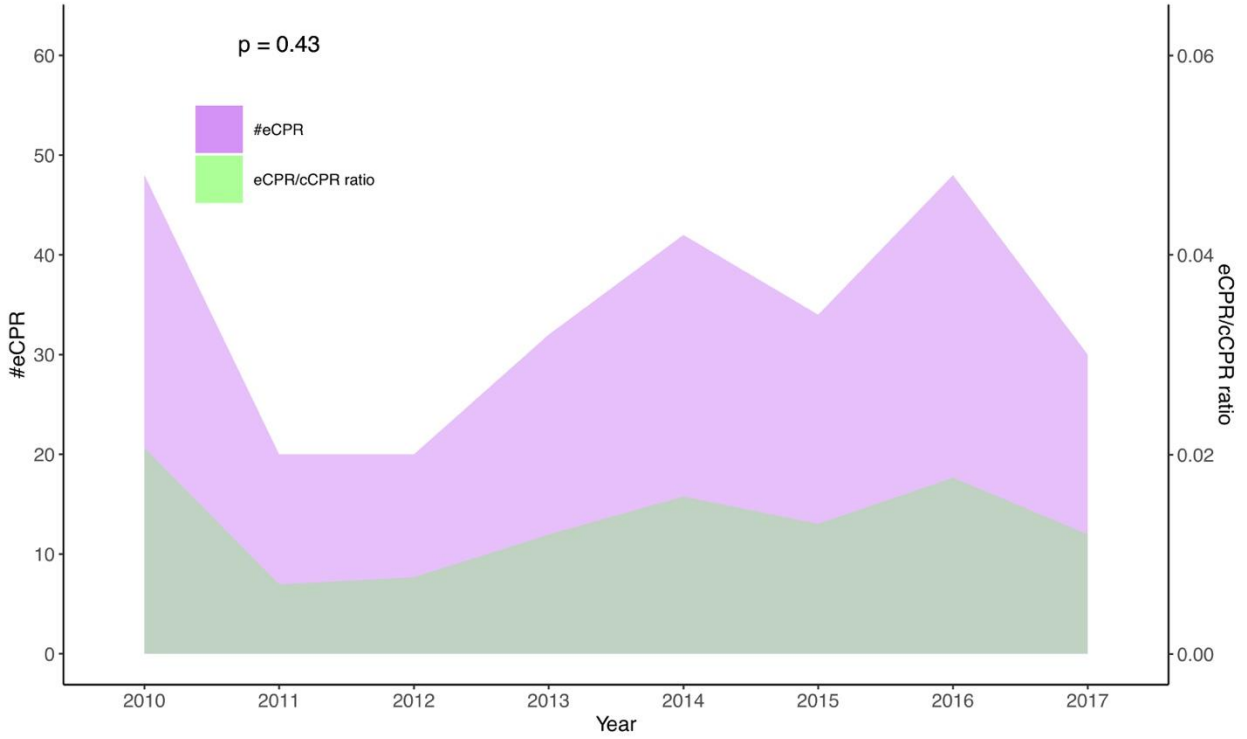
arrest=20/27, Presenting rhythm status=28/46, First Rhythm=324/644, Number of defibrillations=204/364, Compression method-Manual=251/15, Compression method-Mechanical=251/15, Compression method-Open Cardiac Massage=251/15, Epi boluses before pulseless=349/676, Epi boluses after pulseless=165/176, Any ROSC=4/1, Total duration before durable ROSC=71/91, Induced Hypothermia=128/56.

Figure S1. Study enrollment flowchart.



eCPR = extracorporeal cardiopulmonary resuscitation

Figure S2. Number and percent of ECPR cases over time among hospitals that had an ECPR program in 2010.



Data from 2018 incomplete so dropped from Figure S2. (*See Table S5*)

Cochran Armitage trend p value reported.

ECPR = extracorporeal cardiopulmonary resuscitation, CCPR = conventional cardiopulmonary resuscitation