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Myocardial dysfunction after out-of-hospital cardiac arrest: predictors and prognostic implications

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Abstract

We aim to determine the incidence of early myocardial dysfunction after out-of-hospital cardiac arrest, risk factors associated with its development, and association with outcome. A retrospective chart review was performed among consecutive out-of-hospital cardiac arrest (OHCA) patients who underwent echocardiography within 24 h of return of spontaneous circulation at three urban teaching hospitals. Our primary outcome is early myocardial dysfunction, defined as a left ventricular ejection fraction < 40% on initial echocardiogram. We also determine risk factors associated with myocardial dysfunction using multivariate analysis, and examine its association with survival and neurologic outcome. A total of 190 patients achieved ROSC and underwent echocardiography within 24 h. Of these, 83 (44%) patients had myocardial dysfunction. A total of 37 (45%) patients with myocardial dysfunction survived to discharge, 39% with intact neurologic status. History of congestive heart failure (OR 6.21; 95% CI 2.54–15.19), male gender (OR 2.27; 95% CI 1.08–4.78), witnessed arrest (OR 4.20; 95% CI 1.78–9.93), more than three doses of epinephrine (OR 6.10; 95% CI 1.12–33.14), more than four defibrillations (OR 4.7; 95% CI 1.35–16.43), longer duration of resuscitation (OR 1.06; 95% CI 1.01–1.10), and therapeutic hypothermia (OR 3.93; 95% CI 1.32–11.75) were associated with myocardial dysfunction. Cardiopulmonary resuscitation immediately initiated by healthcare personnel was associated with lower odds of myocardial dysfunction (OR 0.40; 95% CI 0.17–0.97). There was no association between early myocardial dysfunction and mortality or neurological outcome. Nearly half of OHCA patients have myocardial dysfunction. A number of clinical factors are associated with

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Statement of human and animal rights This study was approved by the Institutional Review Board at the University of Pennsylvania.

Informed consent For this type of study, informed consent is not required.

myocardial dysfunction, and may aid providers in anticipating which patients need early diagnostic evaluation and specific treatments. Early myocardial dysfunction is not associated with neurologically intact survival.

Keywords

Cardiac arrest; Out-of-hospital; Myocardial dysfunction; Echocardiography; Neurological outcome

Introduction

Out-of-hospital cardiac arrest (OHCA) presents a considerable health burden in the United States, with an estimated incidence of 300,000 persons each year [1, 2]. Even though return of spontaneous circulation (ROSC) is achieved in 30–40% of OHCA patients, only 7% of patients receiving CPR will survive to hospital discharge, with significant geographic variability [1, 2].

Post-cardiac arrest syndrome (PCAS) is a complex constellation of multi-organ failure comprised of brain injury, systemic ischemia–reperfusion response, and post-cardiac arrest myocardial dysfunction, which contributes significantly to morbidity after cardiac arrest [2, 3]. Myocardial dysfunction is an important cause of post-resuscitation circulatory failure that may lead to early mortality after ROSC [3, 4]. It is defined as reversible global dysfunction due to stunned myocardium in the absence of coronary occlusion [5–8]. Although post-cardiac arrest myocardial dysfunction is a potentially treatable complication, the severity and duration of the myocardial dysfunction may be associated with outcome [3, 4, 7].

We aim to evaluate the incidence of post-cardiac arrest myocardial dysfunction, factors associated with its development, and its impact on outcome. Theoretically, factors that amplify ischemia–reperfusion injury should be associated with the presence and severity of post-arrest myocardial dysfunction. Therefore, we hypothesize that there would be an association between pre-hospital factors, including medical history, witnessed cardiac arrest, initial rhythm, bystander cardiopulmonary resuscitation (CPR), number of defibrillations, cumulative doses of epinephrine administered during resuscitation, total downtime, and development of myocardial dysfunction after resuscitation.

Methods

Study design

We performed a retrospective data analysis utilizing the Penn Alliance for Therapeutic Hypothermia (PATH) database. PATH is an internet-based registry focusing on post-arrest care, which is hosted by the University of Pennsylvania.

In this study, consecutive OHCA patients treated in three urban teaching hospitals between May 2005 and December 2011 were screened for inclusion. Patients were included in this study if they were over the age of 17, suffered a non-traumatic arrest, achieved ROSC, and

had a documented echocardiogram performed within 24 h of their cardiac arrest. Exclusion criteria included the initiation of extracorporeal life support or a preexisting “Do Not Resuscitate” order. Research utilizing data in PATH was approved by the University of Pennsylvania Institutional Review Board with a waiver of informed consent.

Data collection

Patient demographics, cardiac arrest characteristics, details regarding prehospital and emergency department care, as well as patient outcomes were obtained from the PATH registry [9, 10]. Each patient record in PATH consists of 30 data elements required for quality assurance purposes from all participating institutions, and 100 additional data elements are required for research participation. Data were collected retrospectively at each of the participating institutions and entered into PATH via a secure, password-protected internet portal by a trained healthcare provider. Before entering data, these clinicians are first trained by the PATH database manager using a structured approach including mock case entry and case review. All participants are provided with a standardized data dictionary for PATH data elements and frequent telephone contact is made with each data abstracter early in registry participation. Additionally, a formal auditing process is conducted on a selection of cases to ensure data integrity, with feedback given to site abstractors for correction. The database manager has access to all entered records from each participating hospital.

Additional chart review was performed at three PATH institutions to obtain echocardiogram results, which were not available in the PATH registry. Transthoracic or transesophageal echocardiogram data were abstracted from clinical echocardiography reports interpreted by attending cardiologists by a single physician-abstractor who was trained by the principal investigator prior to the study. If there was more than one echocardiogram performed within 24 h, the final one performed within the initial 24 h period was used for analysis. The principal investigator met regularly with the data abstractor to review abstracted charts and ensure data quality. The initial 30 charts were also reviewed by the principal investigator to ensure data quality and appropriate categorization. A kappa statistic was not calculated because agreement on left ventricular ejection fraction values was 100%. The abstractor was not blinded to the study hypothesis, but was blinded to patient outcomes.

The most readily available quantitative measure of myocardial function is the left ventricular ejection fraction (LVEF). According to 2010 Heart Failure Society of America guidelines, preserved LVEF is variably defined [11]. The American Heart Association (AHA) suggests that LVEF < 40% may indicate heart failure or cardiomyopathy while an LVEF between 40 and 55% implies damage [12]. Accordingly, myocardial dysfunction is defined as LVEF < 40% in this study, and is the variable of interest.

Outcome measures

Our primary outcome is post-cardiac arrest myocardial dysfunction. Secondary outcomes include survival to hospital discharge with favorable neurological outcome. Neurological outcome is measured using the cerebral performance category (CPC) score and dichotomized into favorable versus poor outcome. Favorable neurological outcome is defined as CPC score of 1 or 2 at hospital discharge.

Statistical analyses

Descriptive statistics are used to summarize subject characteristics including median and interquartile range (IQR) for continuous variables, and number (n) and percentage (%) for categorical variables. We use Wilcoxon rank-sum test for continuous variables in univariate comparison and Chi-square tests for categorical variables. Multivariate logistic regression is then completed to adjust for variables influencing LVEF. Regression results are reported as odds ratios (ORs) with 95% confidence intervals (CI). Statistical analysis was performed using STATA 11.0 software (STATA 11.0, Statacorp, College Station, TX, USA).

Results

Between May 2005 and December 2011, 302 patients with OHCA successfully achieved ROSC and were transported to one of the three study hospitals. Nine patients (3%) were excluded because of major trauma as the cause of cardiac arrest (Fig.1). Median age in the cohort of patients with echocardiography performed within the study window is 60 years (IQR 48, 70) and 53% are male (Table 1). The majority of the cohort is black (56%). Most patients had a cardiac etiology for their arrests (78%) and a nonshockable rhythm (66%), and fewer than half received bystander CPR (47%) (Table 2). Echocardiography was performed in 221 patients (75%) and 190 (86%) of those patients had an echocardiogram performed within 24 after ROSC. A total of 83 patients (44%) had myocardial dysfunction within 24 h after ROSC. There is no difference in the median time from ROSC to echocardiogram when comparing patients with and without myocardial dysfunction (5.3 vs. 7.1 h, $p = 0.18$).

When comparing patients with and without myocardial dysfunction, there is no difference in survival or favorable neurologic outcome. Men are more likely than women to have myocardial dysfunction (65 vs. 35%, $p = 0.003$) (Table 1). Duration of resuscitation is significantly longer in patients with myocardial dysfunction (25 vs. 20 min, $p = 0.002$). Patients who have myocardial dysfunction are more likely to have a history of congestive heart failure (CHF) (63 vs. 38%, $p = 0.002$) or coronary artery disease (34 vs. 17%, $p = 0.007$). Finally, an OHCA event involving more than four defibrillations is more common in the myocardial dysfunction group (64 vs. 36%, $p = 0.001$).

In multivariate analysis, a number of factors are associated with myocardial dysfunction, including history of CHF, male gender, witnessed arrest, more than three doses of epinephrine, more than four defibrillations, longer duration of resuscitation, and therapeutic hypothermia (Fig. 2). CPR immediately initiated by health professional personnel is associated with better myocardial function. In addition, there is a significant interaction between duration of resuscitation and more than three doses of epinephrine used during resuscitation (OR 0.95; 95% CI 0.9–1.0).

Bystander CPR, immediate CPR from a healthcare professional, witnessed arrest, and shockable rhythm are associated with favorable neurologic outcome on multivariable analysis (Fig. 3). Advanced age, administration of epinephrine during resuscitation and longer duration of resuscitation are associated with poor outcome. There is no association between early myocardial dysfunction and neurological outcome.

Discussion

We perform a cohort study of 190 patients after out-of-hospital cardiac arrest to examine predictors of post-arrest myocardial dysfunction and its association with outcome. We find associations between the following variables and myocardial dysfunction: male gender, history of CHF, witnessed arrest, longer duration of resuscitation, more than three doses of epinephrine, more than four defibrillations, and therapeutic hypothermia. CPR immediately initiated by a health professional is associated with a better LVEF. Mortality and neurological outcome are not significantly different when comparing patients with and without myocardial dysfunction.

Classically, post-cardiac arrest myocardial dysfunction is a transient global dysfunction that starts within minutes of arrest, becomes clinically apparent around 7 h after ROSC, and potentially recovers fully within 48–72 h [4, 5, 7, 8, 13, 14]. Our results confirm findings from previous studies that initial post-arrest myocardial dysfunction is not associated with neurologic outcome [4, 14].

Few studies have looked at clinical factors associated with post-arrest myocardial dysfunction. A previous study assessing hemodynamics in OHCA survivors reports that the amount of epinephrine used during CPR is associated with post-arrest instability, but not neurologic outcome [4]. Another study reports high doses of epinephrine as an independent predictor of post-resuscitation myocardial dysfunction, but demonstrates no association with neurologic outcome [14]. We find that a high epinephrine dose during CPR, as well as the duration of resuscitation, is associated with post-arrest myocardial dysfunction, and that there is an interaction between these two variables. Catecholamine excess has been described as a cause of myocardial dysfunction in other disease states, such as stress-induced cardiomyopathy and subarachnoid hemorrhage [15, 16]. Because epinephrine dose and duration of resuscitation are tightly associated, it is difficult to determine if this is truly a pharmacologic effect, or simply related to prolonged ischemia and amplified reperfusion after ROSC.

We also find that repeated defibrillation is associated with myocardial dysfunction. The adverse effect of repeated defibrillation on myocardial function has been reported in laboratory studies [7, 8, 17–19]. The mechanism is not well understood, but may be related to increased intra-myocardial temperature causing myocardial damage, potentiated excitation–contraction uncoupling, dose-dependent release of free radicals, and waveform-specific effects on mitochondrial function [20]. This finding, along with high doses of epinephrine and longer duration of resuscitation, suggests that individuals who develop post-cardiac arrest myocardial dysfunction may have had more difficult, intervention-intensive resuscitative efforts prior to ROSC. It is also possible that both epinephrine dose and repeated defibrillation attempts are simply markers for prolonged resuscitation, which has itself been associated with post-arrest myocardial dysfunction.

In this study, we also compare predictors of neurological outcomes to those of post-cardiac arrest myocardial dysfunction. We find that factors traditionally associated with better neurological outcome may not reliably predict preserved myocardial function. Witnessed

cardiac arrest, as an independent predictor of favorable neurological outcome in multiple studies, is associated with myocardial dysfunction in our study [21]. Prior investigators demonstrate that patients with a cardiac etiology for their arrest are more likely to be witnessed, and have a higher prevalence of pre-existing cardiovascular disease, including congestive heart failure, previous myocardial infarction, angina pectoris, and hypertension [22]. In our study, there is a trend toward an increased prevalence of cardiac etiology among patients with witnessed arrest when compared with patients whose arrest was not witnessed (81 vs. 72%), but this did not reach statistical significance. It is possible that because more patients with witnessed arrest have a primary cardiac etiology or pre-existing cardiovascular disease, they are more likely to develop post-arrest myocardial dysfunction.

We also demonstrate that the use of therapeutic hypothermia (TH) is associated with myocardial dysfunction. The association between TH and myocardial function is complex, and should be interpreted cautiously. Therapeutic hypothermia as part of a standardized treatment for comatose survivors of cardiac arrest is recommended by the AHA due to its beneficial effect on both survival and neurological outcomes, but its effect on post-resuscitation myocardial function remains unclear [23]. One study documents moderately reduced myocardial function among OHCA patients at the time of admission that increases upon induction of TH [24]. Animal models show that moderate TH preserves myocardial function, stabilizes hemodynamics, and decreases myocardial damage; others have not demonstrated such effects [25–30]. A sub-analysis of a recent, large randomized trial demonstrates a decrease in cardiac index in patients treated with TH at 33 °C compared with 36 °C that is entirely attributable to heart rate; myocardial systolic function is not different between the groups [31]. In our study, one possible explanation for the association between TH and myocardial function is that patients who receive TH are different from those who do not. A total of 11 patients did not receive TH because they regained sufficient neurologic function shortly after ROSC; these patients will generally fare better than comatose patients with regard to neurologic outcome, survival, and, likely, myocardial function. In fact, only three of these patients had documented myocardial dysfunction.

Post-cardiac arrest myocardial dysfunction is a common component of PCAS, which can lead to early death [4, 32, 33]. In a recent large randomized trial, 46% of patients who died did so before thorough neurologic prognostication could occur because of a cardiac or hemodynamic cause [34]. These findings reinforce the need for early, aggressive hemodynamic evaluation and support. In a small pilot study, our group shows that early goal-directed hemodynamic optimization combined with TH is feasible and is associated with improved outcomes when compared to historical controls [35]. Other authors have suggested that every patient admitted to the ICU after ROSC should be screened for post-cardiac arrest myocardial dysfunction because of its significant treatment implications, and because it can be easily identified with appropriate monitoring tools [36]. Echocardiography is a safe, widely available, and relatively inexpensive clinical tool, which can provide both anatomical and functional information. The AHA guideline for post-cardiac arrest care suggests performing echocardiographic evaluation within 24 h to help guide therapeutic decisions [23]. It is possible that patients with risk factors for post-arrest myocardial dysfunction, as identified in this manuscript, might benefit from even more aggressive, earlier screening and early treatment [36–38]

Limitations

This study has several limitations. Because this is a retrospective cohort registry study, the quality of data mainly relies on the accuracy of existing documentation, which may be incomplete or incorrect. We define myocardial dysfunction according to left ventricular function, so it is possible that patient with other forms of myocardial dysfunction, namely right ventricular dysfunction, were missed. Another factor is the limited availability of documentation of pre-arrest myocardial function in these individuals, which precludes the ability to account for baseline myocardial dysfunction. It is possible that some patients may have already had a low LVEF before their arrest. One study finds that LVEF decreases approximately 25% among in-hospital cardiac arrest survivors within 72 h regardless of their LVEF before cardiac arrest [37]. Importantly, we adjusted for a history of CHF in the multivariate analysis to control for a potential difference in baseline function. We also were unable to obtain follow up echocardiograms on all patients, so we could not demonstrate whether post-cardiac arrest myocardial dysfunction is transient or sustained. All patients in this study were treated at tertiary centers with comprehensive post-arrest care. Finally, selection bias may exist because patients who have echocardiographic evaluation after resuscitation may be significantly different from those who do not.

Conclusions

In survivors of out-of-hospital cardiac arrest, myocardial dysfunction is common in the early post-resuscitation phase. In our study, early myocardial dysfunction is not associated with survival or neurologic outcome. Systematic screening for post-arrest myocardial dysfunction should be considered to improve knowledge of this potentially dangerous sequela, and provide evidence to direct future management of these patients.

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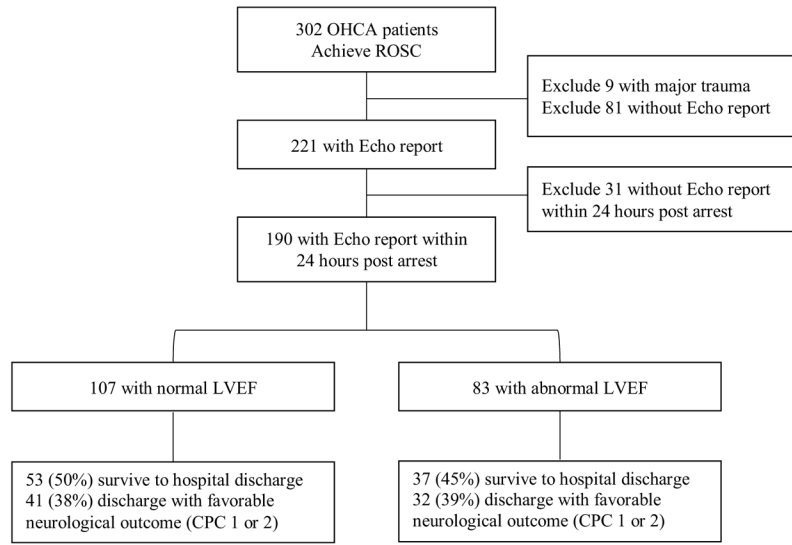


Fig. 1. Flow diagram of patient enrollment, exclusions, and outcomes. *OHCA* out of hospital cardiac arrest, *ROSC* return of spontaneous circulation, *Echo* echocardiography, *LVEF* left ventricular ejection fraction

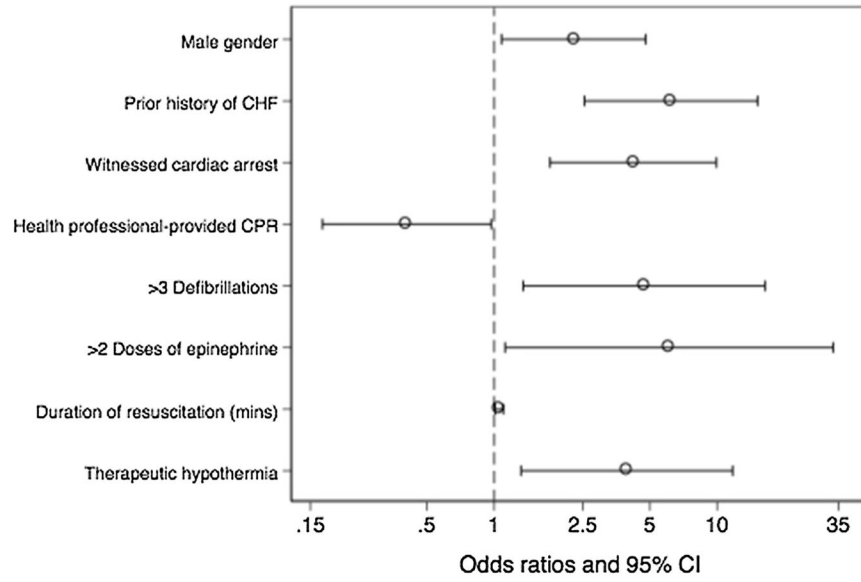


Fig. 2. Factors significantly associated with myocardial dysfunction within 24 h post-arrest (multivariable analysis). Odds ratio > 1 indicates increased likelihood of myocardial dysfunction and odds ratio < 1 indicates decreased likelihood. *CHF* congestive heart failure, *CPR* cardiopulmonary resuscitation, *mins* minutes, *CI* confidence interval

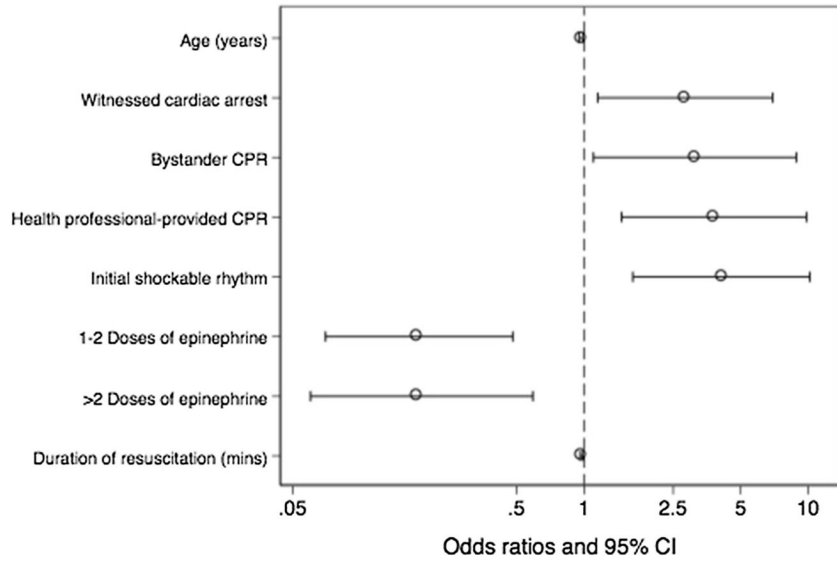


Fig. 3. Factors significantly associated favorable neurological outcome after out of hospital cardiac arrest (multivariable analysis). Odds ratio > 1 indicates increased likelihood of myocardial dysfunction and odds ratio < 1 indicates decreased likelihood. Favorable neurological outcome is defined as Cerebral Performance Category score of 1 or 2. *CHF* congestive heart failure, *CPR* cardiopulmonary resuscitation, *mins* minutes, *CI* confidence interval

Table 1

Demographic characteristics and co-morbidities

	All patients (<i>n</i> = 190)	LVEF < 40% (<i>n</i> = 83)	LVEF 40% (<i>n</i> = 107)	<i>p</i> value
Gender, <i>n</i> (%)				0.003
Male	101 (53)	55 (65)	46 (43)	
Female	90 (47)	29 (35)	61 (57)	
Age, median (IQR), years	60 (48, 70)	60 (48, 70)	60 (48, 71)	0.811
Race, <i>n</i> (%)				0.22
Black	105 (56)	48 (58)	57 (54)	
White	72 (38)	31 (38)	41 (39)	
Other	11 (6)	3 (4)	8 (7)	
Preexisting conditions, <i>n</i> (%)				
Previous CHF	48 (25)	30 (36)	18 (17)	
Coronary artery disease	46 (24)	28 (33)	18 (17)	0.003
Previous MI	22 (12)	12 (14)	10 (9)	0.008
Hypertension	94 (49)	35 (42)	59 (55)	0.288
Arrhythmia	6 (14)	12 (14)	14 (13)	0.064
Diabetes mellitus	65 (34)	24 (29)	41 (38)	0.81
Stroke	14 (7)	6 (7)	8 (7)	0.158
Renal insufficiency	35 (18)	14 (17)	21 (20)	0.93

LVEF left ventricular ejection fraction, CHF congestive heart failure, MI myocardial infarct, IQR interquartile range

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Table 2

Out-of-hospital cardiac arrest event characteristics and post-arrest care

	All patients (n = 190)	LVEF < 40% (n = 83)	LVEF ≥ 40% (n = 107)	p value ^a
Cardiac etiology				0.088
Yes	148 (78)	69 (84)	79 (74)	
No	41 (22)	13 (16)	28 (26)	
Witnessed event				0.131
Yes	130 (68)	62 (74)	68 (64)	
No	61 (32)	22 (26)	39 (36)	
Location				0.266
Health care facility	58 (30)	22 (26)	36 (34)	
Non-healthcare facility	133 (70)	62 (74)	71 (66)	
CPR				0.173
Bystander	41 (21)	21 (25)	20 (19)	
Health Professional	61 (32)	21 (25)	40 (37)	
No	89 (47)	42 (50)	47 (44)	
First pulseless rhythm, n (%)				0.079
Shockable	65 (34)	34 (40)	31 (29)	
Non-shockable	126 (66)	50 (60)	76 (71)	
Number of defibrillations				0.016
No	81 (45)	28 (36)	53 (52)	
1–4	48 (27)	20 (26)	28 (28)	
> 4	50 (28)	30 (38)	20 (20)	
Epinephrine				0.17
No dose	47 (25)	16 (19)	31 (29)	
1–3 doses	74 (39)	31 (38)	43 (40)	
> 3 doses	68 (36)	30 (43)	33 (31)	
Duration of resuscitation, median (IQR), min	21 (13,41)	25 (18, 47)	20 (10, 34)	0.001
Hypothermia				0.067
Yes	160 (84)	75 (89)	85 (79)	
No	31 (16)	9 (11)	22 (21)	
Duration of ROSC to echo median (IQR), h	6.25 (3.80, 11.38)	5.28 (3.18, 13.25)	7.07 (4.1, 11.22)	0.198

LVEF left ventricular ejection fraction, CPR cardiopulmonary resuscitation, IQR interquartile range, ROSC return of spontaneous circulation, Echo echocardiography

^aComparing patients with LVEF < 40% to those with LVEF ≥ 40%