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Hyperoxia is Associated with Increased Mortality in Patients Treated with Mild Therapeutic Hypothermia after Sudden Cardiac Arrest

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Abstract

Objective—To determine if higher levels of partial pressure of arterial oxygen are associated with in-hospital mortality and poor neurologic status at hospital discharge in patients treated with mild therapeutic hypothermia after sudden cardiac arrest.

Design—Retrospective analysis of a prospective cohort study

Patients—A total of 170 consecutive patients treated with therapeutic hypothermia in the cardiovascular care unit of an academic tertiary care hospital.

Interventions—None.

Measurements and Main Results—Of 170 patients, 77 (45.2%) survived to hospital discharge. Survivors had a significantly lower maximum partial pressure of arterial oxygen (198 mmHg, IQR 152.5–282) measured in the first 24 hours following cardiac arrest compared to nonsurvivors (254 mmHg, IQR 172–363, $p = .022$). A multivariable analysis including age, time to return of spontaneous circulation, the presence of shock, bystander CPR, and initial rhythm revealed that higher levels of the partial pressure of arterial oxygen were significantly associated with increased in-hospital mortality (odds ratio 1.439, 95% confidence interval 1.028–2.015, $p = 0.034$) and poor neurologic status at hospital discharge (odds ratio 1.485, 95% confidence interval 1.032–2.136, $p = 0.033$).

Conclusions—Higher levels of the maximum measured partial pressure of arterial oxygen are associated with increased in-hospital mortality and poor neurologic status on hospital discharge in patients treated with mild therapeutic hypothermia after sudden cardiac arrest.

Keywords

therapeutic hypothermia; hyperoxia; sudden cardiac arrest; cerebral performance category; mortality; neurological outcomes

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Contributors

DRJ, RDH, and TWR conceived the study design. DRJ, RDH, and JSP collected data and DRJ and TWR analyzed the data. All authors participated in interpretation of the results. DRJ drafted the manuscript, and all authors contributed to the critical review and revision of the manuscript. All authors have seen and approved the final version of the manuscript.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

Introduction

Even in patients who achieve return of spontaneous circulation (ROSC), survival to hospital discharge after sudden cardiac arrest has been reported to range from 5% to 40% (1,2). Given such poor outcomes likely depend on the neurologic insult incurred during the arrest, recent focus has turned to potential interventions aimed at improving post-arrest neurologic function and, ultimately, mortality. Mild therapeutic hypothermia (TH) has been shown in a number of studies to improve neurologic outcomes, decrease mortality (3,4), and is now recommended for patients having suffered an out-of-hospital cardiac arrest from a ventricular arrhythmia (5,6). Because TH may modulate the systemic inflammatory response seen after cardiac arrest (7), its use in clinical practice has been extended to patients after cardiac arrest from non-ventricular arrhythmias, such as asystole and pulseless electrical activity (PEA).

Hyperoxia may play a role in the pathogenesis of the post-cardiac arrest syndrome (8) and is a potentially modifiable risk factor for poor neurologic outcomes and death in patients who achieve ROSC (9). The pathophysiologic mechanisms underlying these poor outcomes are unclear, but some evidence suggests increased formation of reactive oxygen species (ROS) resulting in lipid peroxidation of neuronal cells (10–12), impairment in cerebral oxidative energy metabolism (13), and cerebral and myocardial vasoconstriction in the setting of increased arterial oxygen tension (14, 15). TH is also thought to have protective effects against damaging ROS (16,17); however it is unknown if hyperoxia is associated with mortality or poor neurological outcomes in patients undergoing TH.

We conducted a retrospective analysis of a prospective cohort to test the hypothesis that increasing levels of the maximum measured partial pressure of arterial oxygen (PaO_2) in the 24 hours after sudden cardiac arrest is associated with an increased risk of in-hospital mortality and poor neurologic outcome in patients treated with TH.

Materials and Methods

Study Design

The study population included 173 consecutive comatose patients who were treated with mild therapeutic hypothermia following sudden cardiac arrest at Vanderbilt University Medical Center between May 15, 2007 and January 2, 2012. Patients determined by their treating physician to be suitable for mild therapeutic hypothermia were externally cooled to maintain a target temperature of 32–34 degrees Celsius for 24 hours following ROSC, after which they were rewarmed passively at a rate of 0.25 degrees Celsius per hour. After approval from the institutional review board, data were collected prospectively on these patients, including initial rhythm, time to ROSC, receipt of bystander CPR, Cerebral Performance Category (CPC) score at hospital discharge, and hospital mortality. We returned to these patients' records and retrospectively collected the highest measured PaO_2 in the first 24 hours following cardiac arrest.

The primary analysis for this study was in-hospital mortality. The secondary analysis was poor neurologic outcome defined as a CPC score of 3 or greater. The Cerebral Performance Category score was developed as a measure of central nervous system function after cardiac arrest and has become the most commonly used outcome tool for this purpose (3, 4, 18). A CPC score between 3 and 5 has been recommended for use as defining a poor neurologic outcome in study patients and clinically represents a range of neurologic function from severe neurologic disability to death (18).

Inclusion/Exclusion Criteria

All patients treated with TH and who also had at least one PaO₂ measured in the first 24 hours following cardiac arrest were included. This time period was chosen because it covers the time of active cooling in TH. Patients without a PaO₂ measured in the first 24 hours following cardiac arrest were excluded.

Statistical Analysis

Univariable analyses were conducted using Wilcoxon rank sum test for continuous variables, Fisher's exact test and chi square for a trend tests for categorical variables, and Kruskal-Wallis test for ordinal variables. Median values with interquartiles were used for continuous variables and frequencies for categorical variables. Multivariable logistic regression models were developed for the outcomes of in-hospital mortality and poor neurologic outcome; explanatory variables included known risk factors for poor outcomes in this patient population and those selected using data reduction methods. Pertinent variables with p-values ≤ 0.10 in univariable analyses were included in the final multivariable regression model. In addition, shock, as defined by the requirement of vasoactive medications to maintain a mean arterial blood pressure greater than or equal to 65 mmHg, was determined a priori to be an important potential confounder and included in the regression model. IBM® SPSS® Statistics (version 19.0) was used for statistical analysis; a two-sided significance level of 0.05 was used for statistical inference.

Results

Clinical Characteristics

Of the 173 patients considered for inclusion, 170 had at least one PaO₂ measured in the first 24 hours following cardiac arrest and, therefore, defined the study population. All PaO₂ measurements included in the analysis were obtained while patients were at the target temperature of 32–34 degrees Celsius. Table 1 displays a comparison of baseline characteristics. Overall, survivors were younger, were more likely to have had a ventricular arrhythmia as the cause of their arrest, had shorter ROSC time, and had a lower median PaO₂. There was no significant difference in gender, presence of shock requiring vasoactive medications, number of patients who received bystander CPR, or the number of hours spent at the target TH temperature. The median highest PaO₂ among all patients was 226.5 mmHg (IQR 162.7–309) with a range from 54 mmHg to 608 mmHg (Figure 1a and 1b).

Mortality

Of the 170 patients included in the final analysis, 93 (54.7%) died during hospitalization. Survivors had a significantly lower maximum PaO₂ (198mmHg, IQR 152.5–282) measured in the 24 hours following cardiac arrest compared to nonsurvivors (254 mmHg, IQR 172–363, $p = 0.022$) (Figure 2).

Using data reduction methods and accounting for known risk factors for in-hospital mortality, a multivariable logistic regression model was developed to examine the association between highest measured PaO₂ and mortality. After controlling for age, time to ROSC, presence of shock, bystander CPR, and initial rhythm, higher levels of PaO₂ were significantly associated with an increased risk of in-hospital mortality (OR 1.439, 95% CI 1.028–2.015, $p = 0.034$) (Table 2) (Figure 3).

Poor Neurologic Outcome

Of the 170 patients in the final analysis, 100 (58.8%) had a poor neurologic outcome on hospital discharge, defined as a CPC greater than or equal to 3. Patients with favorable

neurologic outcomes (CPC score of 1 or 2) had a significantly lower maximum PaO₂ (197 mmHg, IQR 151.5–288.7) measured in the 24 hours following cardiac arrest compared to patients with poor neurologic outcomes (246.5 mmHg, IQR 172–357, $p = .026$)(Figure 4). After controlling for the same variables used in the mortality analysis, there was a significant association between higher levels of PaO₂ and poor neurologic outcome at hospital discharge (OR 1.485, 95% CI 1.032–2.136, $p = .033$)(Table 3).

In an effort to determine if there is a threshold PaO₂ level at which the CPC score significantly worsens, maximum PaO₂ levels in the first 24 hours after cardiac arrest were divided into quartiles and CPC scores in each quartile were compared. Overall, there was no statistically significant association between increasing PaO₂ and a change in CPC score ($p = 0.08$); however there were significant differences in CPC score between the first PaO₂ quartile (54–163 mmHg) and second PaO₂ quartile (164–227 mmHg) compared to the fourth quartile (310–608 mmHg)($p = .038$ and $.018$, respectively)(Figure 5).

Discussion

In this retrospective analysis of a prospective cohort, there was a significant association between the maximum PaO₂ measured, in-hospital mortality, and poor neurologic status on hospital discharge in victims of sudden cardiac arrest undergoing therapeutic hypothermia. These findings are similar to associations found in previous studies of patients with out-of-hospital cardiac arrest (9, 19), chronic obstructive pulmonary disease (20, 21), and acute myocardial infarction (22).

It is unclear what specific effects of hyperoxia result in poor neurologic outcomes and mortality. One proposed mechanism is hyperoxia-induced increase in the generation of reactive oxygen species (ROS) and their subsequent peroxidation of neuronal lipid membranes (11–12). To our knowledge, this study is the first to examine the effects of increasing PaO₂ levels in patients undergoing TH and demonstrates an association between hyperoxia and worse outcomes in this population (19). Our study is unable to answer whether TH may still provide some protection against the oxidative effects of hyperoxia or if there is a threshold PaO₂ above which exposure is more deleterious. In addition, we chose to account for the maximum PaO₂ measured in the first 24 hours after cardiac arrest rather than using the first PaO₂ measured as hyperoxia at any time point during TH should, theoretically, be harmful to patients and deleterious to the benefit of 24 hours of TH. This study is also unique in that we chose to analyze PaO₂ as a continuous variable rather than dividing groups into hyperoxia and normoxia, adding strength to our statistical findings and biologic plausibility to our hypothesis. Hyperoxia has been shown to cause vasoconstriction (14, 15), potentially severe enough to actually reduce overall oxygen delivery to vital tissues like the heart and brain, even despite suprathreshold arterial oxygen concentrations. Although not addressed in our study, if the deleterious effects of hyperoxia are mediated via a mechanism other than ROS, such as vasoconstriction, it is not surprising that TH may fail to lessen these effects.

Our study has a number of limitations. First, this is a retrospective analysis of a prospectively collected, observational cohort that only allows us to suggest associations rather than causation. Non-invasive measurement of arterial oxygen saturation is inaccurate in the setting of hypotension and can be associated with the practitioner's response of increasing the inspired oxygen, creating a situation where hyperoxia is a marker of shock rather than a true risk for poor outcomes. It is difficult to account for this aspect of bedside management in this analysis; however there was no difference in the incidence of shock between groups and shock was not significantly associated with either mortality or poor neurologic outcome in multivariable analysis, while maximum PaO₂ remained significantly

associated with both. Since acute physiology and chronic health evaluation (APACHE) scores have not been validated and may be inaccurate in cardiac arrest and therapeutic hypothermia populations (23) and have not been used in previous landmark studies (3, 4, 24–26), we chose not to control for APACHE score in our regression model. We tried to control for severity of illness by including shock in our model. However, omission of a more conventional severity of illness score such as APACHE allows the possibility that patients who were more ill were also more likely to receive higher FiO_2 . We did not have data on the FiO_2 administered at the time of blood gas analysis to control for this additional, potential confounder. Finally, our analysis prohibits commentary on whether the associated outcomes are a result of one elevated PaO_2 level or if the underlying pathogenesis involves a dose-response relationship.

Our results differ from a recent, large cohort study that found the association between hyperoxia and worse mortality was lost in multivariable analysis when severity of illness was included in the regression model (27). However, that study used worst alveolar-arterial (A-a) gradient and not PaO_2 . A-a gradient does not correlate in a linear fashion with the PaO_2 as fraction of inspired oxygen increases (28, 29). Furthermore, the oxygen levels in their cohort were considerably lower than the hyperoxia seen in our and other studies. The mean PaO_2 in their study was 112 mmHg compared to 248 mmHg in our study and the lowest end of their highest quartile of PaO_2 starts around 187 mmHg while ours starts at 363 mmHg.

The implications of these findings are significant for the care of patients and generation of future research. First, hyperoxia is a potentially cost-free, modifiable risk factor that, in this analysis, seems to be detrimental to a therapy (TH) that is not only used to improve outcomes (3, 4), but is also expensive and labor intensive (30). The avoidance of hyperoxia after cardiac arrest promises to be a simple and attractive strategy in achieving better outcomes in patients treated with TH. Although current guidelines recommend use of 100% inspired oxygen during resuscitation (31), normoxic resuscitation or rapid titration of inspired oxygen after ROSC to a goal PaO_2 of normoxia promises improvement in neurologic outcomes (12, 32) and warrant study in humans. Any future therapeutic interventions must also be weighed against the fact that hypoxia is clearly harmful in all patient populations and must be avoided. As our study is in agreement with past investigations (9) suggesting that the potential harm generated with exposure to increasing levels of PaO_2 occurs above a level of 300 mmHg, it seems prudent and safe to avoid these high levels and, if encountered, to act with a sense of urgency to return the patient to normoxia.

Conclusions

Sudden cardiac arrest is associated with high hospital mortality and poor neurologic outcomes. Hyperoxia in the post-arrest setting is also a risk for the same outcomes. We found that with increasing levels of the maximum PaO_2 measured in the 24 hours following cardiac arrest there is an association with increased hospital mortality and poor neurologic status on hospital discharge. Given the growing evidence suggesting the harm of hyperoxia and now the potential deleterious effects hyperoxia may have on the benefits of therapeutic hypothermia, large, randomized, controlled trials should be undertaken to confirm these findings. Additionally, more specific oxygenation goals are needed in the post-resuscitation care of victims of sudden cardiac arrest.

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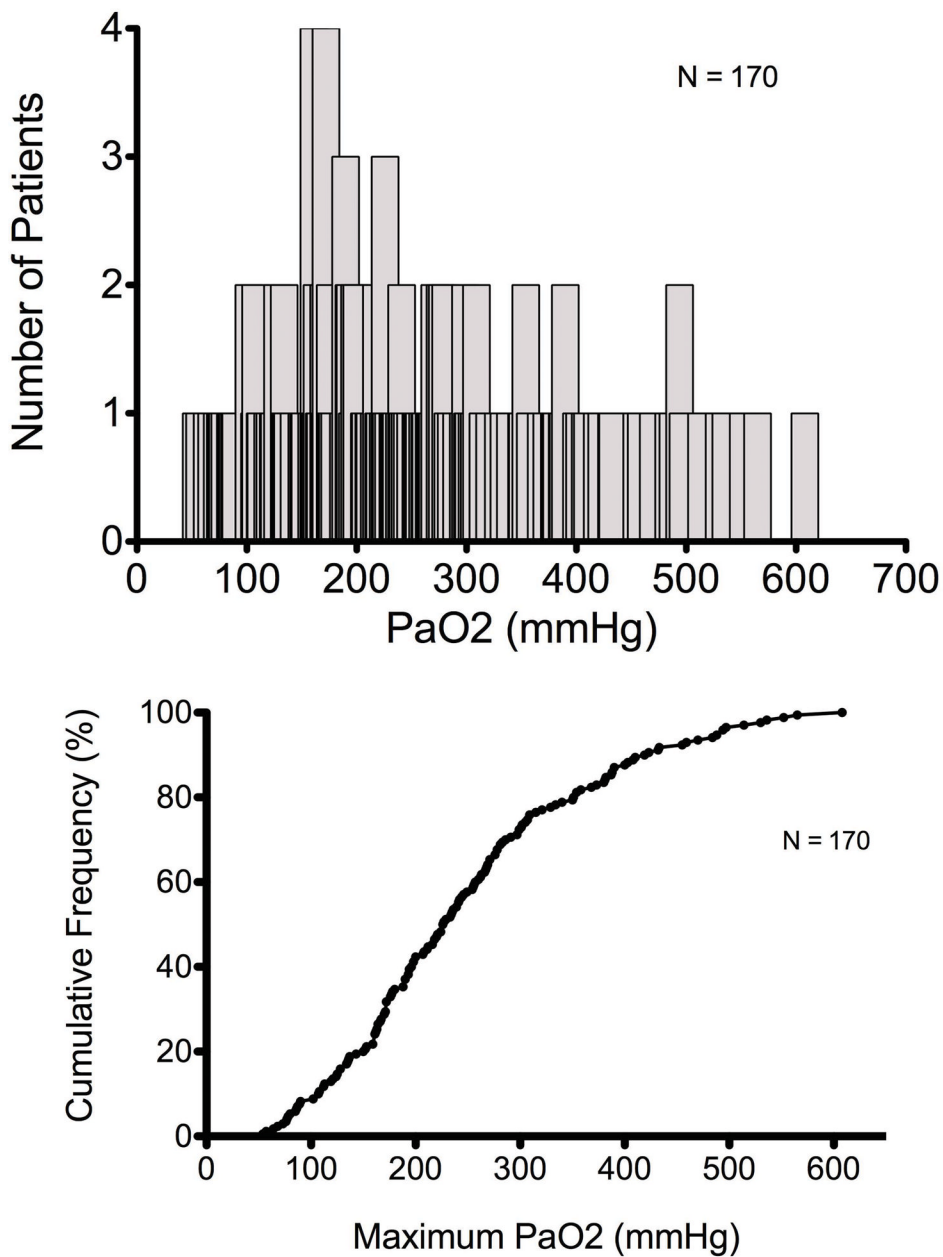


Figure 1. Figures 1a and 1b. Distribution and Cumulative Frequency Distribution Curves of Maximum PaO₂ in the first 24 hours Following Sudden Cardiac Arrest.

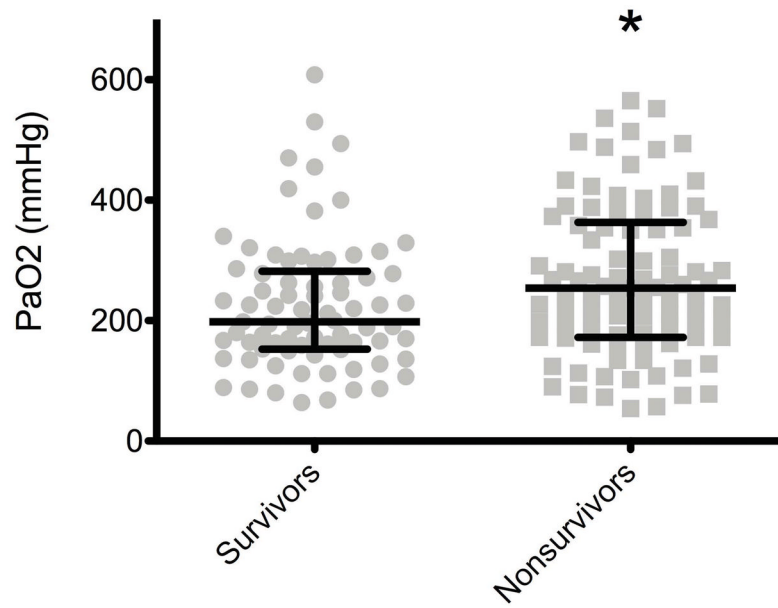


Figure 2. Maximum PaO₂ and In-Hospital Mortality

Survivors had a significantly lower maximum PaO₂ (198 mmHg) in the first 24 hours than non-survivors (254 mmHg)($p = 0.022$)*. Values are medians (middle long horizontal line) and interquartile ranges (IQR: upper and lower caps).

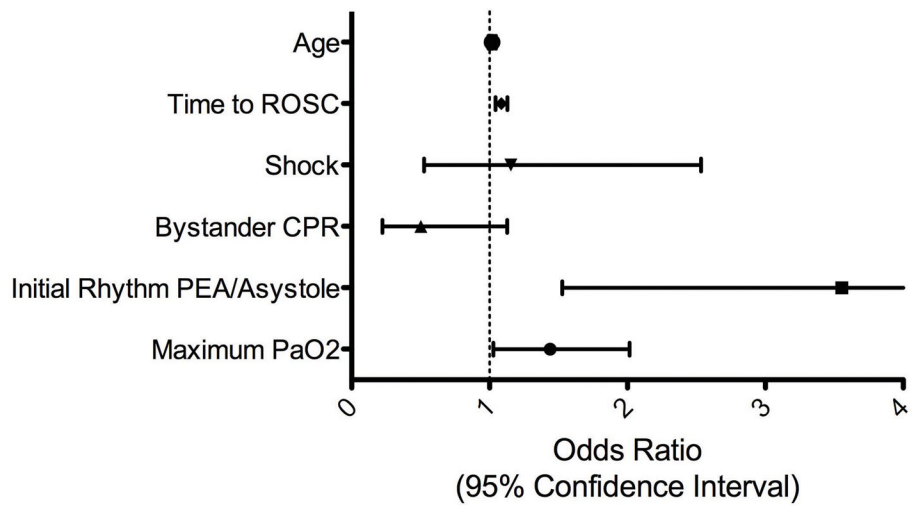


Figure 3. Risk of In-Hospital Mortality associated with Maximum PaO₂
 Odds ratio adjusted for age, time to ROSC, shock, bystander CPR, and initial rhythm. The odds ratio for maximum PaO₂ is for an increment of every 100mmHg above 54 mmHg. Shock = requirement of vasoactive medications to maintain a mean arterial blood pressure greater than or equal to 65 mmHg.

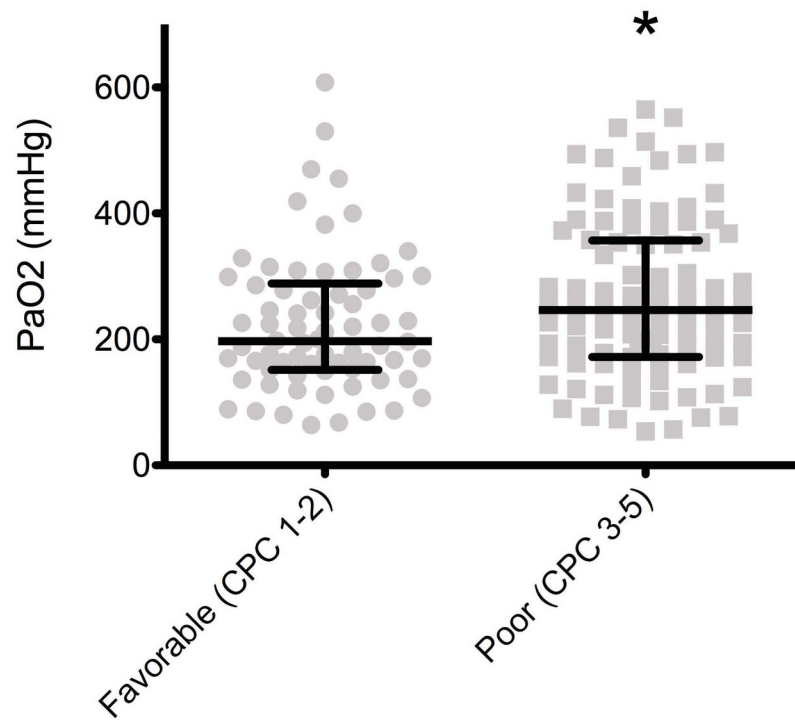


Figure 4. Maximum PaO₂ and Neurologic Status at Hospital Discharge

Patients with favorable neurological outcomes had significantly lower maximum PaO₂ (197 mmHg) in the first 24 hours than patients with poor neurological outcomes (246.5 mmHg)($p = 0.026$)* at hospital discharge. Values are medians (middle long horizontal line) and interquartile ranges (IQR: upper and lower caps).

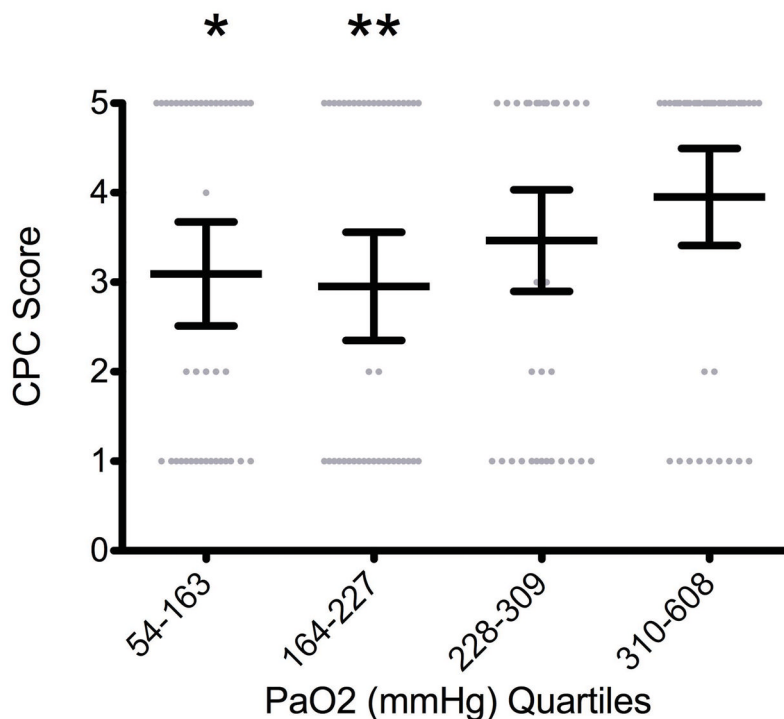


Figure 5. CPC Score at Hospital Discharge by PaO₂ Quartiles

There was no statistically significant association between increasing PaO₂ and a change in CPC score ($p = 0.08$); however quartiles 1 and 2 had significantly better CPC scores at discharge than quartile 4 ($p = 0.038^*$ and 0.018^{**} , respectively). Values are means (middle long horizontal line) and standard deviations (SD: upper and lower caps).

Table 1

Baseline Characteristics

Characteristic	Survivors (n = 77)	Nonsurvivors (n = 93)	p-value	Overall
Age (years)	57 (49, 64)	62 (54, 71)	0.002	60.5 (51.7, 69)
Male (%)	51 (66.2%)	60 (64.5%)	0.872	111 (65.3%)
Presence of Shock requiring vasopressors (%)	29 (37.7%)	46 (49.5%)	0.162	75 (44.1%)
Initial Rhythm Vtach/Vfib (%)	60 (77.9%)	43 (46.2%)	<0.001	103 (60.6%)
Out-of-hospital Arrest (%)	63 (81.8)	72 (77.4%)	0.569	135 (79.4%)
Received bystander CPR (%)	45 (58.4%)	42 (45.2%)	0.092	87 (51.2%)
Time to ROSC (minutes)	15 (9, 18)	25 (15, 37.5)	<0.001	18 (12, 30)
Time spent at target temperature of 32–34 degrees Celcius (hours)	17 (15, 22)	20 (16, 23.5)	0.071	18 (16, 23)
Highest PaO2 (mmHg)	198 (152.5, 282)	254 (172, 363)	0.022	226.5 (162.7, 309)
CPC score at hospital discharge	1 (1, 1.5)	5 (5, 5)	<0.001	5 (1, 5)
Poor Neurologic Outcome (%)	7 (9.1%)	93 (100%)	<0.001	100 (58.8%)

Data given as median (25th percentile, 75th percentile) or number (percentage) of patients.

Vtach = Ventricular Tachycardia; Vfib = Ventricular Fibrillation; CPR = Cardiopulmonary Resuscitation

Table 2

Logistic Regression Model for In-Hospital Mortality

Characteristic	Odds Ratio	95% Confidence Interval	<i>p</i> -value
Age (years)	1.019	0.991–1.047	0.182
Time to ROSC (minutes)	1.086	1.044–1.130	<0.001
Shock	1.154	0.525–2.534	0.722
Bystander CPR	0.502	0.223–1.128	0.095
Initial Rhythm PEA/Asystole	3.554	1.527–8.275	0.003
Maximum PaO ₂ (mmHg)	1.439	1.028–2.015	0.034

The odds ratio for maximum PaO₂ is for an increment of every 100mmHg above 54 mmHg.

ROSC = Return of Spontaneous Circulation; CPR = Cardiopulmonary Resuscitation; PEA = Pulseless Electrical Activity; Shock = requirement of vasoactive medications to maintain a mean arterial blood pressure greater than or equal to 65 mmHg.

Table 3

Logistic Regression Model for Poor Neurological Status at Hospital Discharge

Characteristic	Odds Ratio	95% Confidence Interval	<i>p</i> -value
Age (years)	1.02	0.991–1.049	0.185
Time to ROSC (minutes)	1.121	1.065–1.181	<0.001
Shock	1.24	0.539–2.854	0.612
Bystander CPR	0.509	0.215–1.203	0.124
Initial Rhythm PEA/Asystole	4.975	1.953–12.673	0.001
Maximum PaO ₂ (mmHg)	1.485	1.032–2.136	0.033

The odds ratio for maximum PaO₂ is for an increment of every 100 mmHg above 54 mmHg. Poor neurological status is defined as CPC 3.

ROSC = Return of Spontaneous Circulation; CPR = Cardiopulmonary Resuscitation; PEA = Pulseless Electrical Activity; Shock = requirement of vasoactive medications to maintain a mean arterial blood pressure greater than or equal to 65 mmHg.