Partial pressure of arterial carbon dioxide after resuscitation from cardiac arrest and neurological outcome: a prospective multi-center protocol-directed cohort study

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Abstract

Aims: Partial pressure of arterial carbon dioxide ($PaCO_2$) is a regulator of cerebral blood flow after brain injury. We sought to test the association between $PaCO_2$ after resuscitation from cardiac arrest and neurological outcome.

Methods: A prospective protocol-directed cohort study across six hospitals. Inclusion criteria: age ≥ 18, non-traumatic cardiac arrest, mechanically ventilated after return of spontaneous circulation (ROSC), and receipt of targeted temperature management. Per protocol, $PaCO_2$ was measured by arterial blood gas analyses at one and six hours after ROSC. We determined the mean $PaCO_2$ over this initial six hours after ROSC. The primary outcome was good neurological function at hospital discharge, defined *a priori* as a modified Rankin Scale ≤ 3. Multivariable Poisson regression analysis was used to test the association between $PaCO_2$ and neurological outcome.

Results: Of the 280 patients included, the median (interquartile range) $PaCO_2$ was 44 (37-52) mmHg and 30% had good neurological function. We found mean $PaCO_2$ had a quadratic (inverted "U" shaped) association with good neurological outcome, with a mean $PaCO_2$ of 68 mmHg having the highest predictive probability of good neurological outcome, and worse neurological outcome at higher and lower $PaCO_2$. Presence of metabolic acidosis attenuated the association between $PaCO_2$ and good neurological outcome, with a $PaCO_2$ of 51 mmHg having the highest predictive probability of good neurological outcome among patients with metabolic acidosis.

Conclusion: $PaCO_2$ has a "U" shaped association with neurological outcome, with mild to moderate hypercapnia having the highest probability of good neurological outcome.

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Keywords: cardiac arrest, heart arrest, partial pressure of arterial carbon dioxide, $PaCO_2$

Introduction

Post-cardiac arrest syndrome is a devastating condition,[1, 2] with an associated mortality rate of over 50%. Among those that survive, many are left with permanent, disabling neurological injury.[3] To date there are few interventions shown to improve outcome after cardiac arrest.[4] One such potential therapy is manipulation and titration of gas exchange during mechanical ventilation.[5, 6]

Current post-resuscitation guidelines recommend titrating minute ventilation in post-cardiac arrest patients to maintain normocapnia [i.e. partial pressure of arterial carbon dioxide ($PaCO_2$) 35-45 mmHg].[7-9] However, it is currently unclear if normocapnia is the optimal $PaCO_2$ range. $PaCO_2$ is a major regulator of cerebral blood flow after brain injury.[10-13] Hypocapnia has been postulated to exacerbate brain injury by inducing cerebral vasoconstriction, decreased cerebral blood flow, and increased cerebral ischemia. [10, 11, 13] Alternatively hypercapnia induces cerebral vasodilation. This increase in cerebral vasodilation could be harmful by increasing intracranial volume with a potential increase in intracranial pressure and decreased cerebral perfusion.[5, 14, 15] However, mild hypercapnia, could result in mild cerebral vasodilation leading to improved cerebral blood flow and oxygen delivery, thereby reducing neuronal injury.[16, 17] While observational studies have consistently found hypocapnia to be associated with poor clinical outcomes after cardiac arrest,[5, 18-20] studies examining hypercapnia have conflicting results. Some studies have found hypercapnia to be associated with poor clinical outcomes,[5, 21] while others have suggested mild hypercapnia could potentially improve clinical outcomes after cardiac arrest.[19, 22] By their design, these previous studies have methodological limitations (e.g. measurement bias). Specifically, they were primarily retrospective in design and relied on arterial blood gas (ABG) results ordered at the discretion of treating physicians, as opposed to protocol-directed ABG

measurements at pre-specified time points. In addition, they used arbitrary cut points, which differed between studies, to define $PaCO_2$ ranges as opposed to analyzing the full spectrum of $PaCO_2$ as a continuous variable. Categorizing a continuous variable has several disadvantages including a loss of information.[23] We therefore conducted this study to address the existing limitations in the data.

The objective of this prospective multicenter protocol-directed cohort study was to test the association between early $PaCO_2$ after resuscitation from cardiac arrest and neurological outcome. Based on previous post-cardiac arrest studies, we hypothesized that $PaCO_2$ has a quadratic ("U" shaped) association with neurological outcome,[5, 21] and that a $PaCO_2$ above the physiological normal range (i.e. mild hypercapnia) is associated with the highest probability of good neurological outcome.[19, 22]

Methods

Setting

We performed a prospective protocol-directed cohort study across six academic hospitals in the United States. The Institutional Review Board at each participating institution approved this study. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[24]

Participants

We included adult post-cardiac arrest patients who were comatose (defined as a Glasgow coma scale motor score < 6) after ROSC between 2013-2017. The inclusion criteria were: 1) age ≥ 18 years; 2) cardiac arrest, defined as a documented absence of pulse and initiation of cardiopulmonary resuscitation (CPR); 3) ROSC > 20 min; 4) mechanically ventilated after ROSC; and 5) clinician commitment to perform targeted temperature management. We decided *a priori* to include patients with both in- and out-of-hospital cardiac arrest, as this would generate a pragmatic study whose results could be broadly applicable to as many cardiac arrest patients as possible. We excluded patients with presumed etiology of arrest secondary to trauma, hemorrhage or sepsis; resident of a nursing home or other long-term care facility; pregnancy; prisoners; and terminal illness with no reasonable expectation to survive to hospital discharge or known lack of commitment to aggressive support by next of kin. We also excluded patients who died prior to an arterial blood gas analysis being obtained.

Data Collection

As part of our research protocol we obtained an initial ABG one-hour after ROSC and a second ABG six hours after ROSC (plus or minus two hours). We also recorded all

additional ABG analyses ordered by the treating physician. See **Supplemental Methods** for information on additional data collection.

Outcome measures

The primary outcome was good neurological function at hospital discharge, defined *a priori* as a modified Rankin Scale (mRS) ≤ 3.[25] The mRS was prospectively determined for each patient at the time of hospital discharge. All raters were trained and certified in mRS assessment [26] and used a structured questionnaire and interview, which have been shown to produce very good interobserver reliability.[27, 28]

Data Analysis

We began the analysis with descriptive statistics. We used t-test or Wilcoxon rank-sum test to compare continuous variables, based on the distribution of the data, and chi-square test or Fisher exact test to compare categorical variables.

For purposes of analysis we determined the mean $PaCO_2$ values over the initial six hours after ROSC. We chose the initial six-hour period after ROSC as this time period has been postulated to be when the brain is most likely susceptible to additional reperfusion injury.[6, 29] Our primary analysis aimed to test the relationship between mean $PaCO_2$ levels and neurological outcome. Multivariable Poisson regression analysis with robust standard error was used to calculate relative risk with 95% confidence intervals (CI) [30] for good neurological outcome entering $PaCO_2$ as a continuous variable calibrated for a rise in 5 mmHg. Based on previous post-cardiac arrest studies,[5, 21] we *a priori* hypothesized a quadratic ("U" shaped) association between $PaCO_2$ and neurological outcome (i.e. hypocapnia and severe hypercapnia would both be associated with worse neurological outcome). Therefore, we entered an interaction

term between mean $PaCO_2$ and itself (i.e. $PaCO_2$ squared) into the model in order to identify if a turning point exists in the association between $PaCO_2$ and neurological outcome. The coefficient for this interaction term describes the *change* in the association between $PaCO_2$ and good neurological outcome as $PaCO_2$ increases (i.e. nonlinear relationship). See **Supplemental Methods** for full description of the model.
Using our final model we calculated predicted probabilities with 95% CI for good neurological outcome across the spectrum of mean $PaCO_2$ and graphed the results. We used the predicted probabilities to identify the $PaCO_2$ levels with the highest probability for good neurological outcome.

We performed several *a priori* planned sensitivity analyses. First, we entered additional covariates beyond those pre-specified into our model. Second, we forced exposure to tidal volume greater than 8 mL/kg PBW during the initial six hours after ROSC, and history of chronic pulmonary disease into our model. Third, we performed an *a priori* subgroup analysis limited to patients with a metabolic acidosis. Finally, given as $PaCO_2$ increases, arterial pH decreases we performed an *ad hoc* analysis to test if pH also has a quadratic association with good neurological outcome (see **Supplemental Methods** for full description of sensitivity analyses).

It is possible that extreme $PaCO_2$ levels reflect patient populations that are more ill and thus more likely to have poor neurological outcome. To detect if mean $PaCO_2$ was a marker for severity of illness we used ordered logistic regression to test if mean $PaCO_2$ is a predictor of the six-hour Sequential Organ Failure Assessment (SOFA) score (see **Supplemental Methods**).

Protocol amendment

The initial protocol for this study stated a primary outcome of *poor* neurological outcome defined as a modified Rankin scale (mRS) ≥ 3. In order to make the outcome consistent with parallel cardiac arrest studies (clinicaltrials.gov identifiers NCT01881243 and NCT02698826), and for easier interpretation of the results, the primary outcome was changed to *good* neurological outcome defined as a mRS ≤ 3. The investigators were blinded to all data at the time of this change, which occurred in February 2016, two years before any data analysis for this study began.

Results

Two hundred and eighty subjects met all inclusion and no exclusion criteria (exclusion flow diagram previously published).[31] The median [interquartile range (IQR)] mean $PaCO_2$ for the entire cohort was 44 (37-52) mmHg. The distribution of mean $PaCO_2$ is displayed in **Supplemental Figure 1**. The median (IQR) time to first ABG was 59 (35-103) min.

Table 1 displays baseline data for all subjects in the cohort. The most common type of cardiac arrest was out-of-hospital cardiac arrest with PEA/asystole as the initial rhythm [109/280 (39%)] and few patients were in-hospital with pulseless VT/VF as the initial rhythm [17/280 (6%)]. **Table 2** displays post-cardiac arrest data for all subjects. Several additional variables were found to be associated with neurological outcome on univariable analysis: fraction of inspired oxygen (FiO_2), positive end expiratory pressure (PEEP), history of congestive heart failure, prescribed respiratory rate and minute ventilation, airway plateau pressure, arterial pH, vasopressor use, and Charlson comorbidity index. CPR downtime was missing for four (1%) patients and mean plateau pressure was available for 85% of patients.

We did not find $PaCO_2$ to be a marker for severity of illness [linear: odds ratio, 1.04 (95% CI 0.97 - 1.11); quadratic: $PaCO_2$ odds ratio 1.10 (95% CI 0.79 - 1.52), $PaCO_2$ squared odds ratio 1.00 (0.98 - 1.01)]. The overall in-hospital mortality of the entire cohort was 55%.

Thirty percent of subjects had the primary outcome of good neurological function at hospital discharge. **Table 3** displays the results of the multivariable Poisson regression model for good neurological outcome. We found $PaCO_2$ to have a quadratic association

with good neurological outcome, relative risk for 5 mmHg rise in $PaCO_2$, 1.50 (95% CI 1.35-1.65), and $PaCO_2$ squared 0.99 (95% CI 0.99 - 0.99). These data suggest a 50% increase in the probability of good neurological outcome for every 5 mmHg increase in $PaCO_2$; however, the relative risk for $PaCO_2$ squared less than one suggests this association decreases as $PaCO_2$ increases. We found $PaCO_2$ squared significantly improved the fit of the model (Wald test $p < 0.001$). We found our results remained essentially unchanged after using multiple imputation by chained equations to impute missing co-variables (**Supplemental Table 1**). **Figure 1** displays the predicted probabilities for good neurological outcome by mean $PaCO_2$. The probability of good neurological outcome increases until a mean $PaCO_2$ of 68 mmHg after which point the probability of good neurological begins to decrease. We did not find adjusting our model for addition co-variables, including hyperoxia and exposure to tidal volume > 8 cc/kg PBW, significantly changed our results (**Supplemental Tables 2 and 3**).

On subgroup analysis of patients with metabolic acidosis, we found $PaCO_2$ had a quadratic association with good neurological outcome, relative risk for 5 mmHg rise in $PaCO_2$, 1.80 (95% CI 1.24 - 2.60), and $PaCO_2$ squared 0.97 (95% CI 0.95 - 0.99) (**Supplemental Table 4**). **Figure 2** displays the predicted probabilities for good neurological outcome by mean $PaCO_2$ among patients with metabolic acidosis. The probability of good neurological outcome increases until a mean $PaCO_2$ of 51 mmHg at which point the probability of good neurological outcome begins to decrease.

We found mean arterial pH to have a quadratic association with good neurological outcome, relative risk for 0.01 rise in pH, 4.24 (95% CI 1.76-9.57), and pH squared 0.99 (95% CI 0.99 - 0.99). **Figure 3** displays the predicted probabilities for good neurological outcome by mean arterial pH. The probability of good neurological outcome increases as

pH decreases until a pH of 7.19 after which point as the pH continues to decrease the probability of good neurological begins to decrease.

Discussion

In this prospective, multi-center study, using a standardized protocol for ABG measurements, we tested whether $PaCO_2$ exposure after resuscitation from cardiac arrest was associated with neurological function at hospital discharge. We found that $PaCO_2$ has an inverted "U" shaped association with good neurological outcome, with increasing probability of good neurological outcome as $PaCO_2$ increases up to 68 mmHg. Our results suggest a mild to moderate degree of hypercapnia is associated with improved neurological outcome. These results remained consistent even after adjusting for confounders previously associated with outcome in cardiac arrest patients, including the use of a lung protective ventilation strategy.

As expected we found the presence of a metabolic acidosis to attenuate the association between $PaCO_2$ and neurological outcome, with the highest probability of good neurological outcome occurring at a lower $PaCO_2$ among patients with a metabolic acidosis (i.e. metabolic acidosis shifts the quadratic curve to the left). It is reasonable to infer from these results that the quadratic association between $PaCO_2$ and neurological outcome is at least partially influenced by arterial pH. As $PaCO_2$ increases it may lower the arterial pH to a point at which the harmful effects of acidemia negate any potential benefit from hypercapnia. As we found, this point would be expected to occur at a lower $PaCO_2$ in the setting of a concomitant metabolic acidosis given an elevated $PaCO_2$ typically results in a lower arterial pH in the setting of a concomitant metabolic acidosis compared to a similar $PaCO_2$ level in a patient without a concomitant metabolic acidosis. This is further supported by our results, which found the probability of good neurological outcome to increase as arterial pH decreases to 7.19, below which probability of good neurological outcome begins to decrease. This suggests allowing hypercapnia up to a $PaCO_2$ of 68 mmHg or until pH decreases to 7.19 may be a potential therapeutic target.

Our finding of a quadratic association between $PaCO_2$ and neurological outcome has biological plausibility. $PaCO_2$ is a major regulator of cerebral blood flow after brain injury.[12] Thus, hypocapnia may induce cerebral vasoconstriction resulting in decreased cerebral blood flow and increased cerebral ischemia potentially exacerbating anoxic brain injury.[10, 11, 13] Alternatively, hypercapnia may decrease cerebrovascular resistance and increase blood flow, offering a potential benefit in patients suffering from ischemic brain injury.[11, 32] Consistent with our findings, a recent study of post-cardiac arrest subjects found induced mild hypercapnia during the early post-resuscitation period resulted in increased cerebral tissue oxygen saturation compared to normocapnia.[17] A small feasibility randomized control trial of mild hypercapnia versus normocapnia among post-cardiac arrest patients found mild hypercapnia attenuated the rise in neuron-specific enolase (a serum biomarker for neuronal injury), but not S100b protein (a biomarker of glial injury).[16] In addition to potential cerebrovascular benefits, hypercapnia has also been demonstrated to decrease key components of inflammatory pathways,[33, 34] and is associated with survival to hospital discharge among patients with sepsis-induced respiratory failure requiring mechanical ventilation.[31]

Although mild to moderate hypercapnia may induce improvement in cerebral blow flood and potentially confer benefit, it remains possible that severe hypercapnia could result in excessive cerebral vasodilation resulting in increased intracranial pressure and decreased cerebral perfusion, thus conferring harm.[14, 15] In addition, severe hypercapnia can result in a significant arterial acidosis, which may be harmful. On univariable analysis we found lower arterial pH to be associated with poor neurological outcome. However, when adjusted for $PaCO_2$ and metabolic acidosis in our sensitivity model, arterial pH was no longer found to be associated with neurological outcome, suggesting pH may be on the causal pathway. In addition, when we tested arterial pH in

our model without $PaCO_2$ we found an arterial pH below 7.19 was associated with decreased probability of good neurological outcome. These results are also supported by recent studies of non-cardiac arrest patients with acute respiratory distress syndrome admitted to the intensive care unit, which found severe hypercapnia to be independently associated with in-hospital mortality.[35, 36]

This current study has several strengths. First, to our knowledge this is the first fully prospective, multi-center study using protocol-directed ABG measurements in the early hours following resuscitation, as well as protocol-directed assessments of neurological disability, testing the association between $PaCO_2$ and neurological outcome. Second, we tested $PaCO_2$ as a continuous variable as opposed to using arbitrary cut points to define $PaCO_2$ ranges. Categorizing a continuous variable has several important disadvantages; there is a loss of information and statistical power, as well as potential concealment of any non-linear relationships between the variable and outcome.[23] Thus, by keeping $PaCO_2$ as a continuous variable we were able to identify its quadratic relationship with neurological outcome. Third, previous studies did not investigate the interaction between $PaCO_2$ and metabolic acidosis. In this study we found metabolic acidosis to be an important effect modifier of the relationship between $PaCO_2$ and neurological outcome, which could help explain the conflicting results between previous studies. Our findings demonstrating a “U” shaped relationship between $PaCO_2$ and neurological outcome are consistent with our previous work as well as results from studies of multiple forms of cerebral injury (e.g. traumatic brain injury, post-cardiac arrest syndrome, and stroke).[5, 37]

We acknowledge that this study has important limitations to consider. First, this was an observational study and thus we can only report association rather than infer causation.

Specifically, we are unable to determine if hypocapnia and severe hypercapnia cause harm or are the result of an intrinsic characteristic of the subject (e.g. more acidotic patients having an increased intrinsic respiratory rate resulting in lower $PaCO_2$ or more severe lung injury resulting in higher $PaCO_2$). However, our results remained consistent after adjusting for metabolic acidosis, alveolar dead space, and airway plateau pressure. In addition, we found important differences in patient characteristics, such as age, initial rhythm, and duration of CPR between patients with good vs. poor neurologic outcome; however, our results remained consistent after adjusting for these variables. Second, unlike Beitler, *et al*, we did not find lower tidal volumes to be associated with improved neurological outcome.[38] However, this previous study tested the association between tidal volume over the first 48 hours after ROSC, while we adjusted our model for the tidal volume over the first six hours (time frame of $PaCO_2$ exposure tested). The presumed mechanism by which higher tidal volumes causes cerebral injury is through mechanical lung injury that propagates systemic inflammation.[38] It is possible that the development of this systemic inflammation requires a prolonged time at high tidal volumes (i.e. greater than six hours). Alternatively, higher $PaCO_2$ levels, secondary to lower tidal volumes, may account for some of the association previously found between lower tidal volumes and improved neurological outcome. Third, in contrast to some resuscitation clinical investigations we *a priori* decided to include patients with both in- and out-of-hospital cardiac arrest. We felt this was warranted to allow for a more pragmatic study, in which the results can be applicable to the largest possible patient population. It is possible that there were unmeasured confounders such as time to initiation of CPR and quality of basic life support in the out-of-hospital setting. However, in this study, arrest location was not associated with outcome and $PaCO_2$ remained an independent predictor of neurological outcome after adjusting for cardiac arrest location. Fourth, it remains possible that hypocapnia and severe hypercapnia reflect patient populations that are

more ill and thus more likely to have poor neurological outcome. However, we did not find $PaCO_2$ to be associated with the six-hour SOFA score, which suggests this is not the case.

Conclusion

In summary, $PaCO_2$ has a quadratic association with neurological outcome, with mild to moderate hypercapnia having the highest predicted probability for good neurological outcome. Randomized controlled trials are warranted to further determine whether manipulation of $PaCO_2$ to target mild hypercapnia after resuscitation from cardiac arrest improves outcomes.

Availability of data

After review and approval by our study data use committee, we will allow other researchers who submit to us a protocol to have unrestricted access to our complete de-identified database in comma separated value format, together with a data dictionary.

Conflicts of interest

Dr. Jones is an investigator on unrelated studies sponsored by Roche Diagnostics, AstraZeneca, Janssen, and Hologic, which provide research funding to the Department of Emergency Medicine at Cooper University Hospital. None of the other authors have potential financial conflicts of interest to disclose.

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Authors' contributions

All authors have made substantial contributions to this paper: BWR supervised all aspects of the study and takes responsibility for the paper as a whole. BWR, ST, and JHK conceived this study. All authors took part in acquiring the data. JHK, BWR, and LS managed the data. BWR and ST analyzed the data and interpreted results. BWR and ST drafted the manuscript and all authors contributed substantially to its revision. All authors approved the manuscript in its final form.

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Figure 1: Predicted probability* of good neurological function at hospital discharge [defined as a modified Rankin Scale (mRS) ≤ 3 at hospital discharge] in relation to mean partial pressure of arterial carbon dioxide ($PaCO_2$) during the first six hours after return of spontaneous circulation. Shaded area, 95% confidence intervals.

*Predicted probabilities calculated using Poisson regression model with robust standard errors adjusting for initial cardiac arrest rhythm, age, airway dead space (corrected minute ventilation for normal $PaCO_2$), metabolic acidosis (yes/no), mean arterial blood pressure, and percutaneous coronary intervention (yes/no).

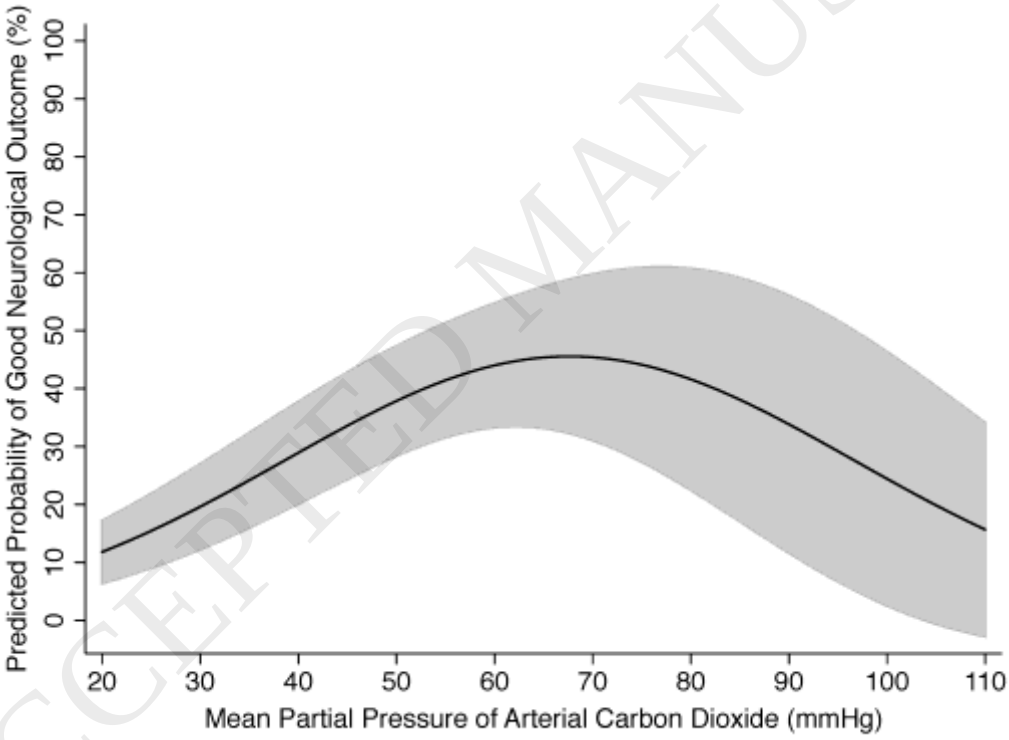

Figure 2: Predicted probability* of good neurological function at hospital discharge [defined as a modified Rankin Scale (mRS) ≤ 3 at hospital discharge] in relation to mean partial pressure of arterial carbon dioxide ($PaCO_2$) during the first six hours after return of spontaneous circulation among patients with a metabolic acidosis (defined as one or more recorded base deficit ≤ -6 during the initial six hours after ROSC). Shaded area, 95% confidence intervals.

*Predicted probabilities calculated using Poisson regression model with robust standard errors adjusting for initial cardiac arrest rhythm, age, airway dead space (corrected minute ventilation for normal $PaCO_2$), mean arterial blood pressure, and percutaneous coronary intervention (yes/no).

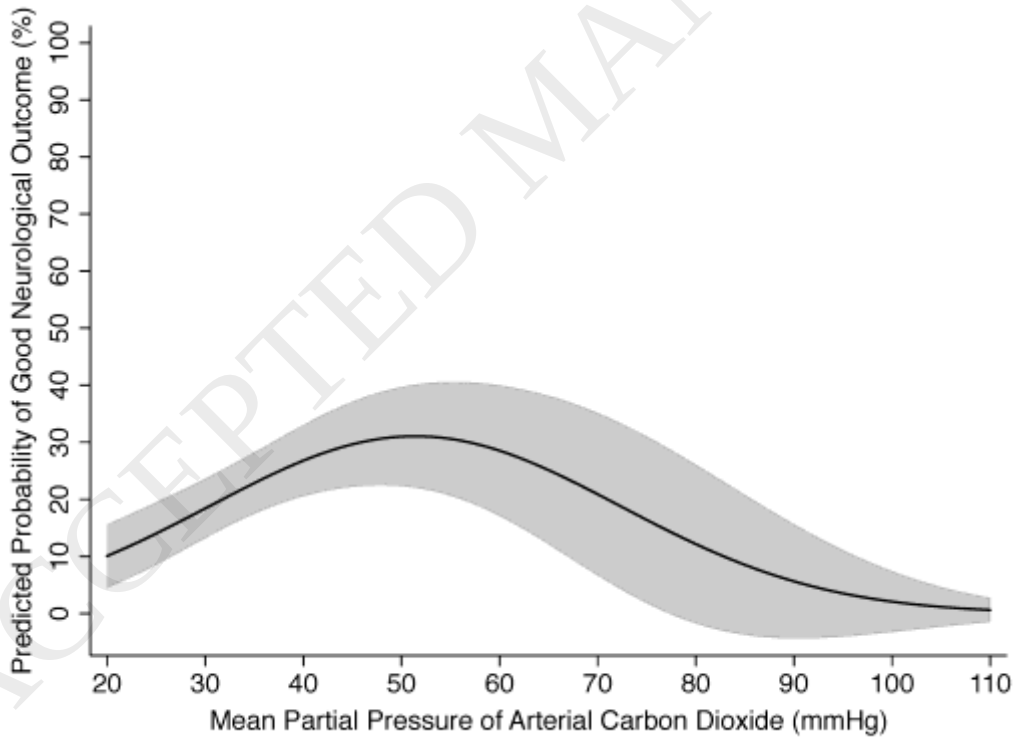

Figure 3: Predicted probability* of good neurological function at hospital discharge [defined as a modified Rankin Scale (mRS) ≤ 3 at hospital discharge] in relation to mean arterial pH during the first six hours after return of spontaneous circulation. Shaded area, 95% confidence intervals.

*Predicted probabilities calculated using Poisson regression model with robust standard errors adjusting for initial cardiac arrest rhythm, age, airway dead space (corrected minute ventilation for normal $PaCO_2$), metabolic acidosis (yes/no), mean arterial blood pressure, and percutaneous coronary intervention (yes/no).

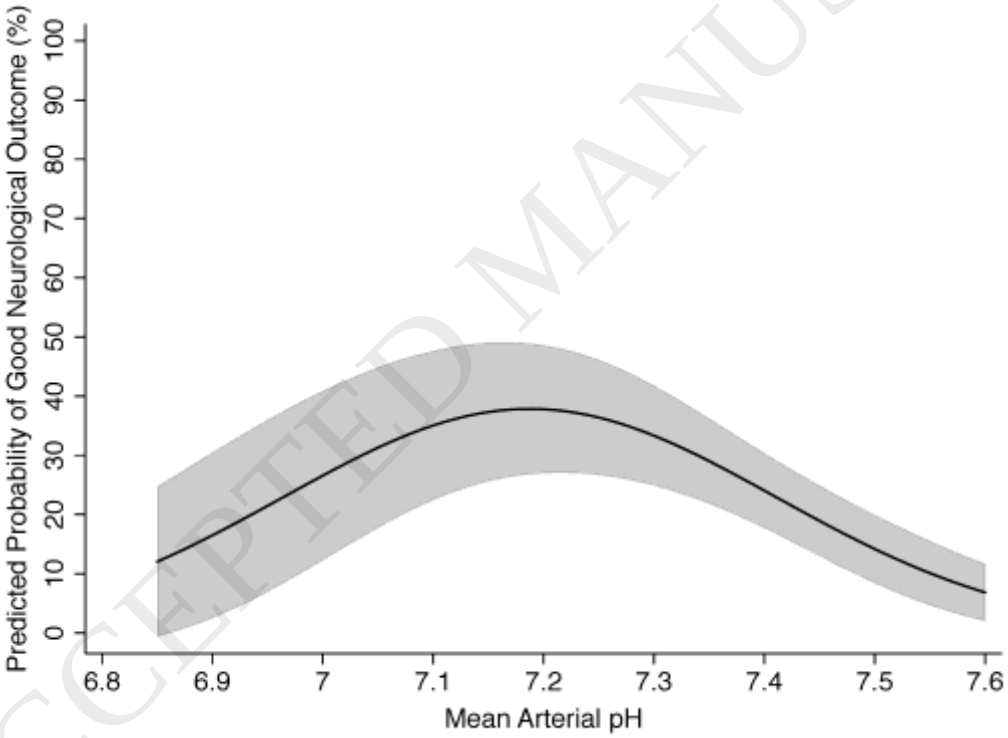

Table 1: Baseline data for all subjects at the time of cardiac arrest.

* Defined as a Modified Rankin Scale ≤ 3 at hospital discharge. † Defined as a Modified Rankin Scale > 3 at hospital discharge.

BMI, body mass index; CPR, cardiopulmonary resuscitation; IQR, interquartile range; mRS, modified Rankin Scale; PEA, pulseless electrical activity; SD, standard deviation; VF, ventricular fibrillation; VT ventricular tachycardia

Variable	All Subjects	Good Neurological Outcome*	Poor Neurological Outcome†	p-value
	n = 280	n = 85	n = 195	
Age [years (SD)]	59 (15)	55 (13)	60 (15)	0.002
Female gender [n (%)]	101 (36)	33 (39)	29 (35)	0.527
BMI [median (IQR)]	29 (24-34)	30 (24-32)	30 (25-34)	0.553
Pre-existing comorbidities [n (%)]				
Diabetes	68 (24)	20 (24)	48 (25)	0.846
Known coronary artery disease	75 (27)	20 (24)	55 (28)	0.417
Hypertension	183 (65)	51 (60)	132 (68)	0.214
Malignancy	20 (7)	4 (4)	16 (8)	0.449
Renal insufficiency	43 (15)	10 (12)	33 (17)	0.271
Pulmonary disease	65 (23)	15 (18)	50 (26)	0.145
Cerebral vascular disease	24 (9)	6 (7)	18 (9)	0.551
Congestive heart failure	69 (25)	14 (16)	55 (28)	0.036
Charleson comorbidity score	1 (0-3)	1 (0-2)	1 (0-3)	0.005

Arrest location [n (%)]				
Out-of-hospital	216 (77)	68 (80)	148 (76)	0.452
In-hospital	64 (23)	17 (20)	47 (24)	
Initial arrest rhythm [n (%)]				
PEA/asystole	154 (55)	27 (32)	127 (65)	
VF/VT	103 (37)	49 (58)	54 (28)	<0.001
Unknown	23 (8)	9 (11)	14 (7)	
CPR duration [median (IQR)]	15 (8-23)	10 (5-17)	17 (9-28)	<0.001

Table 2: Post-cardiac arrest data for all subjects. All values are median (interquartile range) unless otherwise noted.

Continuous variables reported are the mean value for each subject over the initial six hours after return of spontaneous circulation. *Defined as a Modified Rankin Scale ≤ 3 at hospital discharge. †Defined as a Modified Rankin Scale > 3 at hospital discharge. ‡Exposure to a set tidal volume > 8 cc/kg PBW at any point during this initial six hours after return of spontaneous circulation. §Defined as exposure to PaO_2 > 300 mmHg on at least one arterial blood gas during the initial six hours after ROSC. **Estimated using corrected minute ventilation for normal partial pressure of arterial carbon dioxide. ††Defined as a base deficit ≤ -6 on one or more arterial blood gas analyses during the first six hours after return of spontaneous circulation. ‡‡Defined as exposure to mean arterial pressure < 70 mmHg during the initial six hours after ROSC

FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PBW, predicted body weight; PEEP, positive end expiratory pressure; MAP, mean arterial blood pressure; PCI, percutaneous coronary intervention; SOFA, sequential organ failure assessment.

Variable	**All Subjects**	**Good Neurological Outcome***	**Poor Neurological Outcome†**	**p-value**
	n = 280	n = 85	n = 195	
Ventilator parameters				
FiO_2	0.82 (0.66-0.97)	0.78 (0.60-0.95)	0.84 (0.68-0.98)	0.077
PEEP (cmH_2O)	5 (5-7)	5 (5-5)	5 (5-7)	0.043
Set tidal volume (cc/kg PBW)	7.4 (6.7-8.1)	7.5 (6.8-8.1)	7.3 (6.7-8.1)	0.813

Set tidal volume > 8 cc/kg PBW‡ [n (%)]	91 (34)	26 (31)	65 (35)	0.483
Set respiratory rate (breaths/min)	17 (15-20)	16 (14-18)	18 (15-21)	<0.001
Set minute ventilation (cc/kg*min)	125 (106-153)	120 (105-137)	129 (106-166)	0.015
Plateau airway pressure (cmH_2O)	20 (16-25)	19 (16-22)	22 (17-26)	0.004
PaO_2	175 (109-268)	157 (108-254)	177 (109-274)	0.194
PaO_2/FiO_2 ratio	237 (145-337)	237 (153-299)	237 (142-348)	0.665
Hyperoxia§ [n (%)]	105 (38)	24 (28)	81 (42)	0.034
Alveolar dead space** (l/min)	9 (7-12)	8 (7-10)	10 (7-12)	0.003
Arterial pH	7.27 (7.18-7.34)	7.28 (7.22-7.36)	7.26 (7.17-7.33)	0.007
Base deficit	-7 (-11- -3)	-6 (-10 to -2)	-8 (-12 to -4)	0.009
Metabolic acidosis†† [n (%)]	202 (72)	49 (58)	153 (78)	<0.001
MAP (mmHg)	94 (82-105)	100 (91-109)	89 (81-101)	<0.001
Hypotension‡‡ [n (%)]	142 (51)	27 (32)	115 (59)	<0.001
Vasopressor infusion [n (%)]	148 (53)	30 (35)	118 (61)	<0.001
PCI [n (%)]	31 (11)	15 (18)	16 (8)	0.021
Time to target temperature (min)	166 (73-257)	170 (90-285)	155 (70-241)	0.256
Modified SOFA score	7 (5-10)	7 (5-10)	7 (5-10)	0.408

Variables	Relative Risk	95% CI	p-value
Mean $PaCO_2$	1.50	1.35 - 1.65	<0.001
Mean $PaCO_2$ squared	0.99	0.99 - 0.99	<0.001
VT/VF	2.06	1.69 - 2.50	<0.001
Age*	0.84	0.77 - 0.92	<0.001
Alveolar dead space† (L/min)	0.90	0.84 - 0.97	0.004
Metabolic Acidosis‡	0.60	0.45 - 0.82	0.001
Mean arterial blood pressure (mmHg)	1.02	1.01 - 1.02	<0.001
Percutaneous coronary intervention	1.62	1.26 - 2.09	<0.001

Table 3: Multivariable Poisson regression model with good neurological outcome [defined as modified Rankin Scale (mRS) ≤ 3 at hospital discharge] as the dependent variable. Mean partial pressure of arterial carbon dioxide ($PaCO_2$) during the initial six hours after return of spontaneous circulation entered as a continuous variable calibrated for rise in 5 mmHg.

*Calibrated for a rise in 10 years; †Estimated using corrected minute ventilation for normal $PaCO_2$. ‡Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation.

CI, confidence interval; VT/VF, ventricular tachycardia/ventricular fibrillation.

Model has good fit: Deviance test p = 1

Removed for non-significance: cardiac arrest location (p = 0.607); and duration of cardiopulmonary resuscitation (p = 0.500).