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Association Between Postresuscitation Partial Pressure of Arterial Carbon Dioxide and Neurological Outcome in Patients With Post–Cardiac Arrest Syndrome

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Background—Partial pressure of arterial CO_2 ($Paco_2$) is a regulator of cerebral blood flow after brain injury. Recent guidelines for the management of cardiac arrest recommend maintaining $Paco_2$ at 40 to 45 mm Hg after successful resuscitation; however, there is a paucity of data on the prevalence of $Paco_2$ derangements during the post–cardiac arrest period and its association with outcome.

Methods and Results—We analyzed a prospectively compiled and maintained cardiac arrest registry at a single academic medical center. Inclusion criteria are as follows: age ≥18, nontrauma arrest, and comatose after return of spontaneous circulation. We analyzed arterial blood gas data during 0 to 24 hours after the return of spontaneous circulation and determined whether patients had exposure to hypocapnia and hypercapnia (defined as $Paco_2$ ≤30 mm Hg and $Paco_2$ ≥50 mm Hg, respectively, based on previous literature). The primary outcome was poor neurological function at hospital discharge, defined as Cerebral Performance Category ≥3. We used multivariable logistic regression, with multiple sensitivity analyses, adjusted for factors known to predict poor outcome, to determine whether post–return of spontaneous circulation hypocapnia and hypercapnia were independent predictors of poor neurological function. Of 193 patients, 52 (27%) had hypocapnia only, 63 (33%) had hypercapnia only, 18 (9%) had both hypocapnia and hypercapnia exposure, and 60 (31%) had no exposure; 74% of patients had poor neurological outcome. Hypocapnia and hypercapnia were independently associated with poor neurological function, odds ratio 2.43 (95% confidence interval, 1.04–5.65) and 2.20 (95% confidence interval, 1.03–4.71), respectively.

Conclusions—Hypocapnia and hypercapnia were common after cardiac arrest and were independently associated with poor neurological outcome. These data suggest that $Paco_2$ derangements could be potentially harmful for patients after resuscitation from cardiac arrest. **(*Circulation*. 2013;127:2107-2113.)**

Key Words: anoxic brain injury ■ cardiac arrest ■ cardiopulmonary resuscitation ■ hypocapnia ■ hypercapnia ■ resuscitation ■ shock

After successful resuscitation from cardiac arrest, the majority of patients go on to die in the hospital or survive with severe neurological disability because of anoxic brain injury.[1] With the discovery that therapeutic hypothermia can reduce the degree of brain injury, it is now clear that therapeutic interventions applied after the return of spontaneous circulation (ROSC) can substantially improve clinical outcomes from cardiac arrest.[2,3] However, even with therapeutic hypothermia, the mortality of patients after cardiac arrest remains unacceptably high. Finding new approaches to further attenuate brain injury after resuscitation is a high priority for resuscitation science.

Clinical Perspective on p 2113

Partial pressure of arterial carbon dioxide ($Paco_2$) is a major regulator of cerebral blood flow after brain injury, and derangements of $Paco_2$ have been thought to worsen clinical outcomes after many forms of brain injury by altering cerebral blood flow and increasing cerebral ischemia.[4] Hypocapnia and hypercapnia have previously been demonstrated to be associated with poor clinical outcomes in traumatic brain injury[5,6] and pediatric post–cardiac arrest.[7] Hypocapnia has also been associated with poor clinical outcomes in mechanically ventilated preterm neonates[8] and adult patients who have had a stroke.[9,10] Although hyperventilation during cardiopulmonary resuscitation (CPR) has previously been demonstrated to be common and associated with poor outcome, presumably through increased intrathoracic pressure with a subsequent decrease in venous return, cardiac output, and coronary perfusion pressure, thereby lowering the chances of achieving ROSC,[11–16] it is unclear whether $Paco_2$ derangements

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after ROSC has been achieved could also potentially worsen neurological outcome. In 2010, the American Heart Association Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care recommended that during the post-ROSC period, a $Paco_2$ of 40 to 45 mm Hg should be targeted in this population of patients with brain injuries.[17] However, there is a paucity of clinical data on the subject of hypocapnia and hypercapnia during the post-ROSC period in adult patients. Specifically, it is unclear if exposure to hypocapnia and hypercapnia during the initial post-ROSC period is common and associated with neurological outcome.

The objectives of this study were to determine the prevalence of hypocapnia and hypercapnia during the initial post-ROSC period and its association with neurological outcome among adult patients resuscitated from cardiac arrest. We hypothesized that hypocapnia and hypercapnia are common during the initial post-ROSC period and are both independently associated with poor neurological outcome.

Methods

Setting

We analyzed a prospectively compiled and maintained cardiac arrest registry at a single academic medical center, Cooper University Hospital in Camden, NJ.[18] We have prospectively collected data on all patients after cardiac arrest at our institution since 2009. We collect data pertaining to the index cardiac arrest event and outcomes consistent with the Utstein style for reporting cardiac arrest research, including all post-ROSC variables recommended for postresuscitation research.[19,20] To prospectively identify consecutive patients after cardiac arrest, we used a 24-hours-per-day, 7-days-per-week paging system. The paging system was activated in 1 of 2 ways: (1) a hospital-wide code blue activation anytime a cardiac arrest occurred in the hospital; (b) emergency department unit secretaries were trained to activate a page when a patient who had an out-of-hospital cardiac arrest arrived in the emergency department (or a cardiac arrest occurred in the emergency department). In each case, an on-call investigator received the page and responded to the cardiac arrest event to begin data entry. The Institutional Review Board approved this study with a waiver of written informed consent.

Participants

We included adult patients who had had both in- and out-of-hospital cardiac arrests and were comatose after ROSC between 2009 to 2011. The inclusion criteria were as follows: (1) age ≥18 years; (2) cardiac arrest, defined as a documented absence of pulse and CPR initiated; (3) ROSC > 20 minutes; and (4) neurological impairment after ROSC (defined as patient inability to follow commands [ie, Glasgow Coma Score motor <6] during the first hour after ROSC). We excluded patients with cardiac arrest related to trauma. We also excluded patients who died before an arterial blood gas analysis was obtained.

Data Collection

We abstracted the following variables: demographics, comorbidities, all arterial blood gas analyses recorded during the first 24 hours after ROSC, post–cardiac arrest interventions (eg, percutaneous coronary interventions and therapeutic hypothermia), and neurological status at hospital discharge (defined by the Cerebral Performance Category [CPC]). We entered all data into a dedicated Access database (Microsoft Corporation, WA) and exported to StatPlus version 2009 (AnalystSoft Inc) for analysis.

Outcome Measures

The primary outcome was poor neurological function at hospital discharge, defined as a CPC ≥3. The CPC is a validated 5-point scale of neurological disability and historically the most commonly used outcome measure in post–cardiac arrest research (1, good cerebral performance; 2, moderate cerebral disability; 3, severe cerebral disability; 4, coma/vegetative state; 5, death).[19,21–23] The CPC was prospectively determined for each patient at the time of hospital discharge. Patients with a CPC of 1 or 2 had sufficient cerebral function at discharge to live independently.

Data Analysis

We began the analysis with descriptive statistics. We displayed categorical data as counts and proportions. We described continuous data as mean values and standard deviation or median values and interquartile range, based on the distribution of data. For the purposes of analysis, we determined whether patients had exposure to hypocapnia and hypercapnia during the first 24 hours after ROSC. We decided a priori to define exposure to hypocapnia as one or more recorded $Paco_2$ ≤30 mm Hg and exposure to hypercapnia as one or more recorded $Paco_2$ ≥50 mm Hg, based on previously published cutoffs in studies of traumatic brain injury and pediatric post–cardiac arrest.[5,7] No exposure was defined as no recorded $Paco_2$ ≤30 or ≥50 mm Hg during the first 24 hours after ROSC. We graphed the proportion of poor neurological outcome at hospital discharge for only hypocapnia exposure, only hypercapnia exposure, both hypocapnia and hypercapnia exposure, and no exposure.

We calculated odds ratios by using multivariable logistic regression analysis to determine whether hypocapnia exposure and hypercapnia exposure were independently associated with neurological function at hospital discharge. We selected the following candidate variables for the regression model that were previously demonstrated to be strong predictors of poor outcome in patients after cardiac arrest: initial cardiac rhythm (asystole or pulseless electric activity versus ventricular fibrillation/ventricular tachycardia) and prolonged duration of CPR (CPR duration >20 minutes).[1,24–28] To also adjust the model for the possibility that hypocapnia represented a respiratory compensation for metabolic acidosis (which may be associated with poor outcome), we also added the presence of metabolic acidosis as a variable in the regression model, defined as one or more recorded base deficit ≤ −6 (based on previously published literature).[29]

To ensure that the association between hypocapnia exposure and hypercapnia exposure remained independently associated with poor neurological outcome, after adjusting for additional candidate variables known to be predictors of poor outcome, we performed additional sensitivity analyses. Additional candidate variables included: (1) hyperoxia (defined as a Pao_2 ≥300 mm Hg on the first arterial blood gas analysis obtained after ROSC),[30,31] (2) arterial hypotension (defined as systolic blood pressure <100 mm Hg during the first 24 hours after ROSC),[32,33] and (3) a shorter duration of CPR to define prolonged downtime (CPR duration >10 minutes). To adjust for the possibility that hypercapnia represented the presence of pre–cardiac arrest pulmonary disease, we added the presence of previously documented pre–cardiac arrest pulmonary disease as a variable in the sensitivity analyses. In addition, to adjust for potential heterogeneity in the number of $Paco_2$ values assessed, we added the number of $Paco_2$ values assessed as a variable in the sensitivity analyses. Finally, to ensure we did not exclude any additional possible confounders, we performed 2 separate correlation matrixes to identify possible correlations between hypocapnia exposure and baseline variables, and hypercapnia exposure and baseline variables, that we did not adjust for in the multivariable logistic regression models, and we planned to do additional sensitivity analyses adjusting for any correlated variables.

Sample Size Calculation

To ensure adequate power to test 5 covariates in a multivariable model, we estimated the necessary sample size, based on the following assumptions: (a) a predicted survival with good neurological function rate of 28%[1] and (b) an estimated event (survival with good neurological function) per covariate ratio of 10:1 necessary for multivariable modeling.[34,35] To accrue the necessary 50 survivors with

good neurological function, we estimated that a minimum of 179 total cases would be necessary.

Results

One hundred ninety-three patients met all inclusion and no exclusion criteria. Of these, 52 (27%) had exposure to only hypocapnia, 63 (33%) had exposure to only hypercapnia, and 60 (31%) had no exposure. Eighteen (9%) patients had exposure to both hypocapnia and hypercapnia, resulting in a total of 70/193 (36%) patients with any hypocapnia exposure and 81/193 (42%) with any hypercapnia exposure. The median (interquartile range) number of Paco$_2$ assessed per patient was 2 (1–4).

Table 1 displays baseline data for all subjects in the cohort, and for patients with only hypocapnia exposure, only hypercapnia exposure, both hypocapnia and hypercapnia exposure, and no exposure, as well.[36] The majority of patients had in-hospital cardiac arrests with pulseless electric activity/asystole as the initial rhythm (128/193 [66%]), and a few patients had out-of-hospital cardiac arrests with pulseless ventricular fibrillation/ventricular tachycardia as the initial rhythm (6/193 [3%]). One hundred percent of patients were mechanically ventilated after ROSC. Therapeutic hypothermia was performed in 100% (6/6) of patients with out-of-hospital, ventricular fibrillation/ventricular tachycardia cardiac arrest (indicated population [ie, Class I recommendation]), and in 40% (77/193) of all patients. Percutaneous coronary intervention was performed in 3/6 (50%) of patients with out-of-hospital, ventricular fibrillation/ventricular tachycardia cardiac arrest and 15/193 (8%) of all patients. The overall in-hospital mortality was 68%. Table 2 displays post–cardiac arrest data for all subjects.

Seventy-four percent of all patients were found to have the primary outcome of poor neurological function at hospital discharge (CPC 1, 43/193 [22%]; CPC 2, 8/193 [4%]; CPC 3, 8/193 [4%]; CPC 4, 4/193 [2%]; CPC 5, 130/193 [68%]). The Figure displays the poor neurological function at hospital discharge in relation to only hypocapnia exposure, only hypercapnia exposure, both hypocapnia and hypercapnia exposure, and no exposure, during the first 24 hours after return of spontaneous circulation. Patients with only hypocapnia exposure, only hypercapnia exposure, and both hypocapnia and hypercapnia exposure had a higher prevalence of poor neurological function at hospital discharge than patients with no exposure (83%, 78%, 89%, and 57%, respectively).

Table 3 displays the results of the multivariable logistic regression model with poor neurological function at hospital discharge as the dependent variable. After adjusting for initial cardiac rhythm, prolonged duration of CPR, and metabolic acidosis, both hypocapnia exposure and hypercapnia exposure were found to be independent predictors of poor neurological function at hospital discharge, odds ratio 2.43 (95% confidence interval, 1.04–5.65) and 2.20 (95% confidence interval, 1.03–4.71), respectively. Table 4 displays sensitivity analyses. Both hypocapnia exposure and hypercapnia

Table 1. Baseline Data for All Subjects at the Time of Cardiac Arrest

	All Subjects	Only Hypocapnia Exposure	Only Hypercapnia Exposure	Both*	No Exposure
	n = 193	n = 52	n = 63	n = 18	n = 60
Age, y (SD)	64 (18)	63 (19)	61 (17)	66 (15)	66 (15)
Female sex, n (%)	83 (43)	30 (58)	28 (44)	5 (28)	20 (33)
Preexisting comorbidities, n (%)					
Diabetes mellitus	79 (41)	21 (40)	29 (46)	5 (28)	24 (40)
Known coronary artery disease	40 (21)	13 (25)	10 (16)	2 (11)	15 (25)
Hypertension	99 (51)	23 (44)	26 (41)	11 (61)	39 (65)
Malignancy	35 (18)	12 (23)	5 (8)	5 (28)	13 (22)
Renal insufficiency	50 (26)	15 (29)	15 (24)	4 (23)	16 (26)
Pulmonary disease	45 (23)	8 (15)	25 (40)	3 (17)	9 (15)
Cerebral vascular disease	11 (6)	3 (6)	4 (6)	1 (6)	3 (5)
Congestive heart failure	34 (18)	10 (19)	7 (11)	1 (6)	16 (27)
Charlson comorbidity score[36] (SD)	2.8 (2.3)	2.7 (1.8)	3.0 (2.7)	2.9 (2.1)	2.7 (2.3)
Arrest location, n (%)					
Out-of-hospital	33 (17)	10 (19)	12 (19)	4 (22)	7 (12)
In-hospital	160 (83)	42 (81)	51 (81)	14 (78)	53 (88)
Initial arrest rhythm, n (%)					
PEA/asystole	154 (80)	40 (77)	58 (92)	13 (72)	43 (72)
VF/VT	38 (19)	12 (23)	5 (8)	5 (28)	16 (27)
Unknown	1 (1)	0	0	0	1 (1)
CPR duration > 10 min, n (%)	81 (42)	23 (44)	26 (41)	9 (50)	23 (38)
CPR duration > 20 min, n (%)	19 (10)	5 (10)	4 (6)	4 (22)	6 (10)

CPR indicates cardiopulmonary resuscitation; PEA, pulseless electric activity; SD, standard deviation; VF, ventricular fibrillation; and VT ventricular tachycardia.
*Exposure to both hypocapnia and hypercapnia during the first 24 hours after the return of spontaneous circulation.

Table 2. Post–Cardiac Arrest Data for All Subjects

	All Subjects	Only Hypocapnia Exposure	Only Hypercapnia Exposure	Both*	No Exposure
	n = 193	n = 52	n = 63	n = 18	n = 60
Metabolic acidosis,† n (%)	132 (68)	48 (92)	43 (68)	12 (67)	29 (48)
Hyperoxia,‡ n (%)	46 (24)	18 (35)	12 (19)	2 (11)	14 (23)
Arterial hypotension,§ n (%)	173 (90)	47 (90)	56 (89)	16 (89)	54 (90)

*Exposure to both hypocapnia and hypercapnia during the first 24 hours after the return of spontaneous circulation.
†Defined as a base deficit ≤ −6 during the first 24 hours after return of spontaneous circulation.
‡Defined as a Pa_{O_2} ≥ 300 mm Hg on the first arterial blood gas analysis obtained after the return of spontaneous circulation.
§Defined as systolic blood pressure < 100 mm Hg during the first 24 hours after the return of spontaneous circulation.

exposure remained independently associated with poor neurological function at hospital discharge after adjusted for additional variables known to be predictors of poor outcome (ie, hyperoxia, arterial hypotension, know pre–cardiac arrest pulmonary disease, and different durations of CPR). With the use of correlation matrixes, the only additional baseline variable we found to have a statistically significant correlation with hypocapnia or hypercapnia was between hypercapnia and congestive heart failure (Table I in the online-only Data Supplement). Both hypocapnia exposure and hypercapnia exposure remained independently associated with poor neurological function at hospital discharge after adjusted for the number of $Paco_2$ values assessed and congestive heart failure (Table II in the online-only Data Supplement).

Discussion

In this study, we prospectively identified adult patients after cardiac arrest and determined the prevalence of hypocapnia exposure and hypercapnia exposure during the first 24 hours after ROSC. Our objective was to test whether post-ROSC exposure to hypocapnia and hypercapnia was associated with poor neurological function at hospital discharge. We found that 36% of patients had any hypocapnia exposure, and 42% had any hypercapnia exposure. By the use of multivariable logistic regression, including multiple sensitivity analyses, we found that both hypocapnia exposure and hypercapnia exposure after ROSC were independent predictors of poor neurological function at hospital discharge. These findings suggest that both hypocapnia and hypercapnia are common during the initial post-ROSC period and are independently associated with poor neurological outcome.

The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care recommend that ventilation should be titrated to achieve a $Paco_2$ of 40 to 45 mm Hg during the post-ROSC period.[17] However, at the present time, we are unaware of any previous clinical research studies on the subject of hypocapnia and hypercapnia during the post-ROSC period in adult patients. Specifically, it has been unclear if exposure to hypocapnia and hypercapnia during the initial post-ROSC period is common and independently associated with neurological outcome. To our knowledge, this is the first report that both hypocapnia and hypercapnia during the post-ROSC period could be potentially harmful in adult patients resuscitated from cardiac arrest.

$Paco_2$ is a major regulator of cerebral blood flow after brain injury. Although hyperventilation during CPR has previously been found to be associated with poor outcome, it is thought to be more related to increased intrathoracic pressure with subsequent decrease in venous return and cardiac output, and decreased coronary perfusion pressure during CPR, thereby lowering the chances of achieving ROSC, as opposed to an effect of hypocapnia itself.[11–16] Hypocapnia has been postulated to be detrimental during the post-ROSC period secondary to hypocapnia-induced cerebral vasoconstriction resulting in decreased cerebral blood flow and increased cerebral ischemia potentially exacerbating anoxic brain injury.[4,37,38] Cerebral blood flow has been demonstrated to decrease ≈3% for every 1 mm Hg decrease in $Paco_2$ in patients with traumatic brain injury.[39] Although it has been suggested that this degree of reactivity to $Paco_2$ may be blunted during this initial post-ROSC period,[40–42] recent literature suggests it remains intact.[4,43,44] Hypocapnia has also been suggested to worsen ischemic/reperfusion injury by increasing cerebral oxygen demand through increased neural excitability, and increasing cerebral oxygen demand could be deleterious in anoxic brain injury.[45,46]

Hypocapnia has been demonstrated to be associated with poor clinical outcomes in patients who have traumatic brain injury,[5,6] mechanically ventilated preterm neonates,[8] and

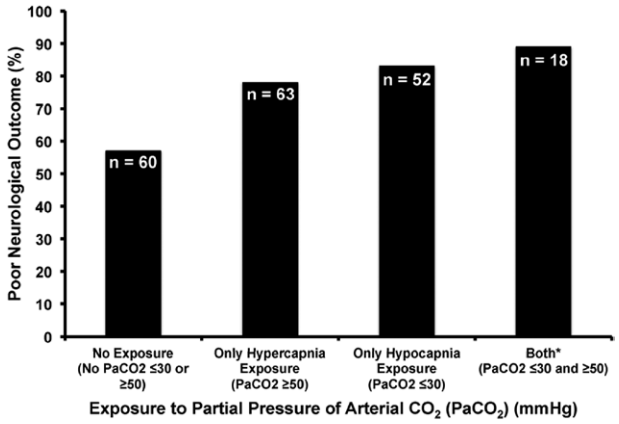

Figure. Proportion of patients with poor neurological function at hospital discharge (defined as a Cerebral Performance Category [CPC] ≥ 3) in relation to no exposure, only hypercapnia exposure, only hypocapnia exposure, and both hypocapnia and hypercapnia exposure during the first 24 hours after return of spontaneous circulation. $Paco_2$ indicates partial pressure of arterial CO_2.

Table 3. Multivariate Logistic Regression Model With Poor Neurological Outcome (Defined as Cerebral Performance Category [CPC] ≥3 at Hospital Discharge) as the Dependent Variable

Variable	β	Standard Error	Odds Ratio	95% LCI	95% UCI	*P* Value
Hypocapnia*	0.89	0.43	2.43	1.04	5.65	0.040
Hypercapnia†	0.79	0.39	2.20	1.03	4.71	0.042
Metabolic acidosis‡	1.05	0.38	2.85	1.35	5.99	0.006
PEA/asystole initial rhythm	0.78	0.44	2.17	0.91	5.18	0.080
CPR > 20 min	1.32	0.81	3.74	0.76	18.46	0.105

CPR indicates cardiopulmonary resuscitation; LCI, lower confidence interval; PEA, pulseless electric activity; and UCI, upper confidence interval.
*Defined as exposure to a partial pressure of arterial CO_2 ≤30 mm Hg during the first 24 hours after the return of spontaneous circulation.
†Defined as exposure to a partial pressure of arterial CO_2 ≥50 mm Hg during the first 24 hours after the return of spontaneous circulation.
‡Defined as a base deficit ≤ −6 during the first 24 hours after return of spontaneous circulation.

pediatric patients after cardiac arrest.[7] In a post–cardiac arrest animal model, cerebral blood flow promotion, through induced hypertension, mild hemodilution, and normocapnia, along with therapeutic hypothermia, was shown to improve neurological outcome in comparison with combined hypocapnia, normotension, and normothermia.[44] Also, in a recent clinical study, ventilation titrated to maintain Paco$_2$ 37.6 to 45.1 mm Hg, as a part of a bundle with multiple other goals (including hypothermia, arterial oxygen saturation optimization, and blood pressure goals), was associated with increased survival in patients after cardiac arrest.[47] However, the independent effects of Paco$_2$ control itself cannot be determined from these 2 studies.

Conversely, hypercapnia has been demonstrated to decrease cerebrovascular resistance and increase blood flow, suggesting a potential benefit in patients with ischemic brain injury;[4,48] however, studies of traumatic brain injury and pediatric post–cardiac arrest syndrome have demonstrated that hypercapnia is associated with poor clinical outcomes.[5,7] The association between hypercapnia and poor outcome has been suggested to be secondary to hypercapnia-induced cerebral vasodilation and increased intracranial volume, resulting

Table 4. Results of Sensitivity Analyses: Multivariate Logistic Regression Models With Poor Neurological Outcome (Defined as Cerebral Performance Category [CPC] ≥ 3 at Hospital Discharge) as the Dependent Variable

Variable	β	Standard Error	Odds Ratio	95% LCI	95% UCI	*P* Value
Analysis 1						
Hypocapnia*	0.90	0.42	2.45	1.08	5.56	0.032
Hypercapnia†	0.77	0.38	2.16	1.03	4.52	0.041
Metabolic acidosis‡	1.05	0.37	2.85	1.38	5.86	0.004
PEA/asystole initial rhythm	0.57	0.43	1.77	0.77	4.10	0.182
Hyperoxia§	0.05	0.43	1.05	0.45	2.42	0.911
Analysis 2						
Hypocapnia*	1.25	0.42	3.49	1.54	7.90	0.003
Hypercapnia†	1.00	0.40	2.73	1.25	5.95	0.011
Arterial hypotension‖	1.37	0.58	3.92	1.26	12.14	0.018
Pulmonary disease¶	0.38	0.46	1.46	0.59	3.62	0.410
CPR > 20 min	1.26	0.79	3.52	0.75	16.53	0.110
Analysis 3						
Hypocapnia*	1.22	0.42	3.40	1.51	7.68	0.003
Hypercapnia†	1.03	0.40	2.80	1.28	6.15	0.010
Arterial hypotension‖	1.38	0.57	3.96	1.29	12.12	0.016
Pulmonary disease¶	0.34	0.46	1.40	0.57	3.47	0.466
CPR > 10 min	0.12	0.36	1.12	0.55	2.29	0.748

CPR indicates cardiopulmonary resuscitation; LCI, lower confidence interval; and UCI, upper confidence interval.
*Defined as exposure to a partial pressure of arterial CO_2 ≤ 30 mm Hg during the first 24 hours after the return of spontaneous circulation.
†Defined as exposure to a partial pressure of arterial CO_2 ≥ 50 mm Hg during the first 24 hours after the return of spontaneous circulation.
‡Defined as a base deficit ≤ −6 during the first 24 h after the return of spontaneous circulation.
§Defined as a Pa_{O_2} ≥300 mm Hg on the first arterial blood gas analysis obtained after the return of spontaneous circulation.
‖Defined as systolic blood pressure < 100 mm Hg during the first 24 hours after the return of spontaneous circulation.
¶Documented pre–cardiac arrest chronic obstructive pulmonary disease or asthma.

in increased intracranial pressure and decreased cerebral perfusion.[49,50]

We sought to perform this study because we believe that, if titrating ventilation to maintain an ideal $Paco_2$ during the post-ROSC period is shown to improve patient neurological outcome, this would potentially allow for a simple therapeutic approach to help attenuate the brain injury associated with post–cardiac arrest syndrome. In this observational study, we showed that both hypocapnia and hypercapnia exposure were common and were independently associated with poor neurological function at hospital discharge. Our findings suggest that post-ROSC $Paco_2$ derangements may be harmful, and we provide a scientific rationale for further research to determine the optimal target $Paco_2$ range during the initial post-ROSC period.

We acknowledge that this study has important limitations to consider. First, we did not measure cerebral blood flow in patients, and, therefore, we were unable to determine the direct effects of $Paco_2$ derangements on cerebral blood flow during the post-ROSC period. Second, although we used multivariable logistic regression analyses to adjust for cardiac arrest characteristics known to predict in-hospital mortality, the potential of unmeasured confounders still exists. It is noteworthy that we did not find hyperoxia to have a statistically significant association with poor neurological outcome in our cohort. This may be secondary to the fact that this study had a much smaller sample size than previous hyperoxia studies[30] (n=193 versus n=6326) and thus was not powered to identify such an association. Third, this study was limited to 1 center, and it is possible that a study of larger scope could have found different results. Fourth, this was an analysis of a prospectively compiled and maintained cardiac arrest registry; therefore, there was no predefined protocol for obtaining arterial blood gases potentially resulting in heterogeneity in timing and number of arterial blood gases obtained for each patient. Fifth, although we believe the association between hypercapnia and poor neurological outcome is secondary to increased intracranial pressure, the possibility exists that hypercapnia is a reflection of lung injury and poor pulmonary compliance, which may be associated with poor outcome. Sixth, we defined hypocapnia as $Paco_2 \leq 30$ mm Hg and hypercapnia as $Paco_2 \geq 50$ mm Hg based on $Paco_2$ levels from previously published studies[5,7]; thus the exact $Paco_2$ levels associated with potential harm are unknown. Last, this was an observational study, and, thus, we can only report association rather than infer causation.

Conclusions

In this sample of adult patients resuscitated from cardiac arrest, we found that both hypocapnia and hypercapnia exposure after ROSC were common and were independently associated with poor neurological function at hospital discharge. These data suggest that $Paco_2$ derangements could be potentially harmful in patients resuscitated from cardiac arrest. Future research to determine the optimal target $Paco_2$ range after ROSC is warranted.

Disclosures

None.

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CLINICAL PERSPECTIVE

Partial pressure of arterial CO_2 is a major regulator of cerebral blood flow after brain injury. The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care recommend that ventilation should be titrated to achieve a partial pressure of arterial CO_2 of 40 to 45 mm Hg after return of spontaneous circulation from cardiac arrest. However, at the present time, we are unaware of any previous clinical research studies on the subject of hypocapnia and hypercapnia during the post–return of spontaneous circulation period in adult patients. Specifically, it has been unclear if exposure to hypocapnia and hypercapnia during the initial post–return of spontaneous circulation period is common and independently associated with neurological outcome. In this observational study, both hypocapnia and hypercapnia exposure were common and were independently associated with poor neurological function at hospital discharge. Future research is needed to determine the optimal partial pressure of arterial CO_2 range after the return of spontaneous circulation.

SUPPLEMENTAL MATERIAL

Online Data Supplement 1: Correlations between hypocapnia exposure and hypercapnia exposure, and baseline variables.

		Hypocapnia	Hypercapnia
Age	Correlation Coefficient	*0.022*	*-0.091*
	p-value	*0.764*	*0.210*
Female Gender	Correlation Coefficient	*0.104*	*-0.034*
	p-value	*0.153*	*0.642*
Charleson Comorbidity score[36]	Correlation Coefficient	*-0.020*	*0.067*
	p-value	*0.784*	*0.356*
Diabetes	Correlation Coefficient	*-0.062*	*0.023*
	p-value	*0.396*	*0.749*
Coronary artery disease	Correlation Coefficient	*0.011*	*-0.121*
	p-value	*0.879*	*0.093*
Hypertension	Correlation Coefficient	*-0.045*	*-0.090*
	p-value	*0.532*	*0.215*
Malignancy	Correlation Coefficient	*0.119*	*-0.125*
	p-value	*0.101*	*0.083*
Renal insufficiency	Correlation Coefficient	*0.019*	*-0.044*
	p-value	*0.794*	*0.543*
Cerebral vascular disease	Correlation Coefficient	*0.000*	*0.019*
	p-value	*0.995*	*0.794*
Congestive heart failure	Correlation Coefficient	*-0.040*	*-0.171*
	p-value	*0.586*	*0.018*
In-hospital cardiac arrest	Correlation Coefficient	*-0.056*	*-0.063*
	p-value	*0.437*	*0.385*

Online Data Supplement 2: Results of sensitivity analyses: Multivariate logistic regression models with poor neurological outcome [defined as Cerebral Performance Category (CPC) ≥ 3 at hospital discharge] as the dependent variable.

Variable	Beta	Standard Error	Odds Ratio	95% LCI	95% UCI	p-value
Hypocapnia*	1.16	0.40	3.19	1.44	7.05	0.004
Hypercapnia†	0.85	0.38	2.33	1.10	4.92	0.027
Number of $PaCO_2$ assessed	0.04	0.07	1.04	0.90	1.19	0.612

Variable	Beta	Standard Error	Odds Ratio	95% LCI	95% UCI	p-value
Hypocapnia*	0.98	0.37	2.66	1.28	5.52	0.009
Hypercapnia†	1.23	0.40	3.43	1.56	7.55	0.002
Congestive heart failure	0.47	0.47	1.60	0.64	3.98	0.313

*Defined as exposure to a partial pressure of arterial CO_2 ≤ 30 mmHg during the first 24 hours after return of spontaneous circulation; †Defined as exposure to a partial pressure of arterial CO_2 ≥ 50 mmHg during the first 24 hours after return of spontaneous circulation; $PaCO_2$, partial pressure of arterial carbon dioxide