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Association Between Early Hyperoxia Exposure After Resuscitation From Cardiac Arrest and Neurological Disability

Prospective Multicenter Protocol-Directed Cohort Study

Editorial, see p 2125

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BACKGROUND: Studies examining the association between hyperoxia exposure after resuscitation from cardiac arrest and clinical outcomes have reported conflicting results. Our objective was to test the hypothesis that early postresuscitation hyperoxia is associated with poor neurological outcome.

METHODS: This was a multicenter prospective cohort study. We included adult patients with cardiac arrest who were mechanically ventilated and received targeted temperature management after return of spontaneous circulation. We excluded patients with cardiac arrest caused by trauma or sepsis. Per protocol, partial pressure of arterial oxygen (Pao_2) was measured at 1 and 6 hours after return of spontaneous circulation. Hyperoxia was defined as a Pao_2 >300 mm Hg during the initial 6 hours after return of spontaneous circulation. The primary outcome was poor neurological function at hospital discharge, defined as a modified Rankin Scale score >3. Multivariable generalized linear regression with a log link was used to test the association between Pao_2 and poor neurological outcome. To assess whether there was an association between other supranormal Pao_2 levels and poor neurological outcome, we used other Pao_2 cut points to define hyperoxia (ie, 100, 150, 200, 250, 350, 400 mm Hg).

RESULTS: Of the 280 patients included, 105 (38%) had exposure to hyperoxia. Poor neurological function at hospital discharge occurred in 70% of patients in the entire cohort and in 77% versus 65% among patients with versus without exposure to hyperoxia respectively (absolute risk difference, 12%; 95% confidence interval, 1–23). Hyperoxia was independently associated with poor neurological function (relative risk, 1.23; 95% confidence interval, 1.11–1.35). On multivariable analysis, a 1-hour-longer duration of hyperoxia exposure was associated with a 3% increase in risk of poor neurological outcome (relative risk, 1.03; 95% confidence interval, 1.02–1.05). We found that the association with poor neurological outcome began at ≥300 mm Hg.

CONCLUSIONS: Early hyperoxia exposure after resuscitation from cardiac arrest was independently associated with poor neurological function at hospital discharge.

Key Words: brain injuries ■ heart arrest ■ hyperoxia ■ nervous system

Sources of Funding, see page 2122

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Clinical Perspective

What Is New?

- In this prospective multicenter protocol-directed cohort study that included 280 adult patients after cardiac arrest, early hyperoxia exposure (partial pressure of arterial oxygen [Pao_2] >300 mm Hg during the first 6 hours after return of spontaneous circulation) was an independent predictor of poor neurological function at hospital discharge after adjustment for potential baseline and postcardiac arrest confounders (relative risk, 1.23; 95% confidence interval, 1.11–1.35).

What Are the Clinical Implications?

- Early hyperoxia exposure after resuscitation from cardiac arrest is independently associated with death and poor neurological function at hospital discharge. The increased risk of poor neurological function appears to begin at a Pao_2 of 300 mm Hg.

Postcardiac arrest syndrome is a unique pathophysiological condition characterized by systemic postresuscitation ischemia/reperfusion injury commonly resulting in neurological damage.[1,2] The in-hospital mortality among individuals with postcardiac arrest syndrome is >50%, and among those who survive, many are left with permanent and severe neurological disability.[3] The identification of new therapies to attenuate the ongoing brain injury in this patient population is of the utmost importance given that cardiac arrest occurs in >400 000 people each year in the United States alone.[4]

Exposure to hyperoxia (supranormal partial pressure of arterial oxygen [Pao_2] caused by high fractions of inspired oxygen [Fio_2]) after resuscitation was previously demonstrated to amplify the production of oxygen free radicals, resulting in neuronal injury and death via cellular metabolic failure and apoptosis.[5,6] Current postresuscitation guidelines recommend titrating the Fio_2 in patients after cardiac arrest to avoid hypoxia and prolonged exposure to hyperoxia (most commonly defined as Pao_2 >300 mm Hg).[7–9] Our group previously published a retrospective registry study demonstrating an association between postresuscitation exposure to Pao_2 >300 mm Hg and in-hospital mortality.[10] However, subsequent observational studies examining the associations between hyperoxia and clinical outcomes have reported conflicting results.[10–16] All previous studies have methodological limitations. They were mostly retrospective in nature; they used varying methodologies to define Pao_2 derangements; and most evaluated arterial blood gas (ABG) measurements over the first 24 hours after return of spontaneous circulation (ROSC) rather than focusing on the period immediately after ROSC when the brain is likely most susceptible to additional reperfusion injury. By their design, these previous studies were subject to measurement bias because they relied on ABG results ordered at the discretion of treating physicians, as opposed to protocol-directed ABG measurements at specific time points.

We performed a fully prospective multicenter study using protocol-directed ABG measurements in the early hours after resuscitation and protocol-directed assessments of neurological disability as opposed to chart review. Our main objective was to test the association between early postresuscitation hyperoxia and poor neurological outcome among adult patients successfully resuscitated from cardiac arrest.

METHODS

Setting

We performed a prospective cohort study across 6 hospitals in the United States: Cooper University Hospital, Camden, NJ (coordinating center); Hospital of the University of Pennsylvania, Philadelphia; Penn-Presbyterian Medical Center, Philadelphia, PA; Methodist Hospital, Indianapolis, IN; University of Mississippi Medical Center, Jackson; and Beth Israel Deaconess Medical Center, Boston, MA. We prospectively collected 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.[17,18] Each of the participating centers had a mechanism in place for real-time notification of study personnel when a patient experiencing out-of-hospital cardiac arrest arrives in the emergency department (ED) or when a cardiac arrest occurs in hospital. This study was approved by the institutional review board at each participating institution, and each subject (or next of kin) gave written informed consent. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[19] After review and approval by the authors' study data use committee, the authors will allow other researchers who submit to the authors a protocol to have unrestricted access to their complete deidentified database in comma separated value format, together with a data dictionary.

Participants

We enrolled adult patients after cardiac arrest who were comatose after ROSC between July 2013 and March 2017. The inclusion criteria were as follows: age ≥18 years; cardiac arrest, defined as a documented absence of pulse and cardiopulmonary resuscitation (CPR) initiated; ROSC >20 minutes; mechanically ventilated after ROSC; and clinician intent to perform targeted temperature management. We decided to include patients with both in- and out-of-hospital cardiac arrest because this would generate a pragmatic study with results that could be broadly applicable to as many patients with cardiac arrest as possible. We excluded patients with presumed pathogenesis of arrest secondary to trauma, hemorrhage, or sepsis; residents of a nursing home or other long-term care facility; pregnant women; prisoners; and individuals with 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 before an ABG analysis was obtained.

Standard Care

Routine postcardiac arrest care across all sites consisted of standard elements recommended by the American Heart Association guidelines for CPR and emergency cardiovascular care and included targeted temperature management for 24 hours after ROSC; controlled rewarming to avoid hyperpyrexia with targeted temperature management; 24/7 capability for goal-directed hemodynamic support interventions; 24/7 capability for interventional cardiac catheterization (if needed); 24/7 capability for continuous electroencephalographic monitoring; and evidence-based approach to neurological prognostication, specifically waiting >72 hours after ROSC before support limitations for poor neurological prognosis.[7,20]

Data Collection

As part of our research protocol, we obtained an initial ABG 1±2 hours after ROSC and a second ABG 6±2 hours after ROSC. At the time of ABG collection, we also recorded the plateau airway pressure during an inspiratory hold on the ventilator. We recorded all additional ABG analyses ordered by the treating physician and all ventilator changes and the time the changes were made. The arterial oxygen saturation (Sao_2) and the fraction of inspired oxygen (Fio_2) were continuously monitored and recorded every 15 minutes for the initial 6 hours after ROSC. For both Sao_2 and Fio_2, the time-weighted average was calculated. To calculate the time-weighted average for each subject, we multiplied the length of time that the patient spent at a specific Sao_2 value by that Sao_2 value, added all these values together, and then divided by the total length of postresuscitation observation time.[21] We performed the same calculation for Fio_2. We prospectively captured all the components of the Sequential Organ Failure Assessment score (ie, respiratory, coagulation, hepatic, renal, cardiovascular, and neurological) during the first 24 hours after ROSC.[22] For calculation of the Sequential Organ Failure Assessment score, we used the worst value for each component during the initial 6-hour period after ROSC and excluded the neurological and respiratory components.[22–24] We abstracted clinical data from the medical record into a Research Electronic Data Capture (REDCap, Vanderbilt University, TN) database and exported them into Stata/SE 14.1 for Mac, StataCorp LP (College Station, TX) for analysis.[25]

Outcome Measures

The primary outcome was poor neurological function or death at hospital discharge, defined a priori as a modified Rankin Scale (mRS) score >3.[26] The mRS is a well-validated scale of neurological disability that is widely used to measure outcome in stroke clinical trials (0, no symptoms; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderate severe disability; 5, severe disability; 6, death). All raters were trained and certified in mRS assessment[27] and used a structured questionnaire and interview that have been shown to produce strong interobserver reliability.[28,29] Secondary outcomes were in-hospital mortality and early neurological injury defined as a Full Outline of Unresponsiveness (FOUR) score ≤6 at 72 hours after ROSC on the basis of previous literature.[30,31] The FOUR score is a well-validated scale of neurological injury for comatose patients. The FOUR score has 4 components: eye responses, motor responses, brainstem reflexes, and respiration pattern, and ranges from 0 to 16 with lower scores demonstrating worse injury.[32]

Data Analysis

Categorical variables were compared by use of the χ^2 test. Continuous variables were compared by use of the Student *t* test or Wilcoxon rank-sum test on the basis of the distribution of the data. We used the Spearman correlation coefficient (*r*) to assess the relationship between 1- and 6-hour Pao_2 and the corresponding Fio_2 and Sao_2. We used multivariable logistic regression analysis to identify what patient and management characteristics were associated with hyperoxia (see Methods in the online-only Data Supplement).

For the primary outcome, we calculated relative risk using multivariable generalized linear regression with a log link[33] to test whether exposure to hyperoxia during the initial 6 hours after ROSC was an independent predictor of poor neurological function at hospital discharge. We a priori defined hyperoxia as Pao_2 >300 mm Hg on ≥1 ABG analyses on the basis of previously described definition for hyperoxia.[6,7,10,13] A priori, we selected the following candidate variables for the regression model on the grounds that they were previously demonstrated to predict outcome in patients after cardiac arrest: (1) age (decile); (2) initial cardiac rhythm (asystole or pulseless electric activity versus ventricular fibrillation/pulseless ventricular tachycardia [VF/VT])[34]; (3) metabolic acidosis (defined as ≥1 recorded base deficit ≤–6 during the initial 6 hours after ROSC on the basis of previously published literature)[35]; (4) arterial hypotension (mean arterial pressure <70 mm Hg during the initial 6 hours after ROSC)[21]; (5) prearrest comorbidities (ie, Charlson comorbidities index)[36]; (6) prolonged duration of CPR (CPR duration >20 minutes)[37]; and (7) location of cardiac arrest (in versus out of hospital).[38–41] Backward elimination with a criterion of $P<0.05$ for retention in the model was used. Statistical interactions and collinearity were assessed. Goodness of fit of the model was evaluated with the deviance test. This analysis was repeated for both secondary outcomes. For the main analyses, list-wise deletion was used for missing covariables. We also report results using multiple imputation for missing covariables. These models used robust standard error and took into account the random effects at the institution (ie, site of enrollment) level.

We performed several additional preplanned sensitivity analyses for the primary outcome. First, we entered additional covariates beyond those prespecified into a multivariable generalized linear regression model with a log link. Second, we assessed whether cardiac arrest location (prehospital or in hospital) had different results. Last, we performed a sensitivity analysis limited to only patients who survived to hospital discharge (detailed description of sensitivity analyses is given in Methods in the online-only Data Supplement).

We also examined the association between Pao_2 and outcome across different thresholds to define hyperoxia (ie, Pao_2 >100, 150, 200, 250, 300, 350, and 400 mm Hg on ≥1 ABG analyses). We entered each threshold into a multivariable generalized linear regression model with a log link and calculated relative risks with 95% confidence intervals (CIs)

for poor neurological outcome, adjusting for candidate variables retained in the original model. We plotted the relative risks with 95% CIs and inspected the graph to assess whether there was a threshold signal for neurological outcome over increasing Pao_2 cut points.

To reflect the duration of hyperoxia exposure during the initial 6 hours after ROSC, we used the first Pao_2 measurement to represent the Pao_2 exposure during the time from ROSC to the first ABG measurement. We then calculated the time intervals between ABG measurements and inferred that the Pao_2 remained constant at the level observed in the earlier measurement until the time point of the subsequent measurement (ie, last value carried forward). Similar methodology to estimate Pao_2 exposure has been used previously.[16] We then added up the total time that the patients had exposure to hyperoxia during the initial 6 hours after ROSC. To test the impact of duration of hyperoxia exposure, we entered duration of exposure as a continuous variable (calibrated for 1 hour) into a multivariable generalized linear regression model with a log link, adjusting for the candidate variables retained in the original model. Given that some subjects had ABG analyses ordered by treating physicians in addition to the protocol, we adjusted the model for the total number of ABG analyses obtained during the initial 6 hours after ROSC, as well as time to first ABG.

Sample Size Calculation

We estimated the necessary sample size on the basis of the following assumptions: a predicted event (ie, survival with good neurological function) rate of 29%[21] and an estimated event (survival with good neurological function) per covariate ratio of 10:1 necessary for multivariable modeling.[42,43] To accrue the necessary 80 survivors with good neurological function, we estimated that a minimum of 276 total subjects would be necessary, and we planned to enroll 280.

RESULTS

A total of 2084 subjects were screened for inclusion, and 280 were included in the final cohort (Figure 1). We were unable to obtain informed consent for 326 patients (eg, no surrogate decision maker available or declined consent). Compared with those excluded because of a lack of informed consent, the study sample had a similar mean (SD) age of 59 (16) years versus 59 (15) years, respectively. However, we found that our study sample had a higher rate of VF/VT (37% versus 21%) and longer duration of CPR (median, 15 [interquartile range (IQR), 8–23] minutes versus 10 [IQR, 1–22] minutes). Of those included, 105 (38%) had exposure to hyperoxia and 175 (62%) had no exposure to hyperoxia during the initial 6 hours after ROSC. The median time from ROSC to the first ABG analysis was 59 (IQR, 35–103) minutes, and the median number of ABG analyses during the initial 6 hours after ROSC was 2 (IRQ, 2–3).

Table 1 displays the baseline data for all subjects in the cohort and for subjects with and without exposure to hyperoxia. Out-of-hospital cardiac arrest with pulseless electric activity/asystole as the initial rhythm was the most common type of cardiac arrest (109 of 280, 39%), followed by out-of-hospital cardiac arrest with pulseless VF/VT as the initial rhythm (86 of 280, 31%). Initial rhythm was unclear for 23 patients (8%), and downtime was unknown for 5 patients (<2%). We found no differences in age, cardiac arrest characteristics, or comorbidities between those exposed and unexposed to hyperoxia. Table 2 displays postcardiac arrest data for all subjects. All patients were mechanically ventilated and received targeted temperature management after ROSC. Percutaneous coronary intervention was performed within the first 36 hours in 22 of 86 patients (26%) with out-of-hospital, pulseless VF/VT cardiac arrest. The median Sequential Organ Failure Assessment score was lower among subjects with exposure to hyperoxia (4; IQR, 2–7) compared with those without exposure (5; IQR, 3–7); however, this was not found to be statistically significant (Wilcoxon rank-sum

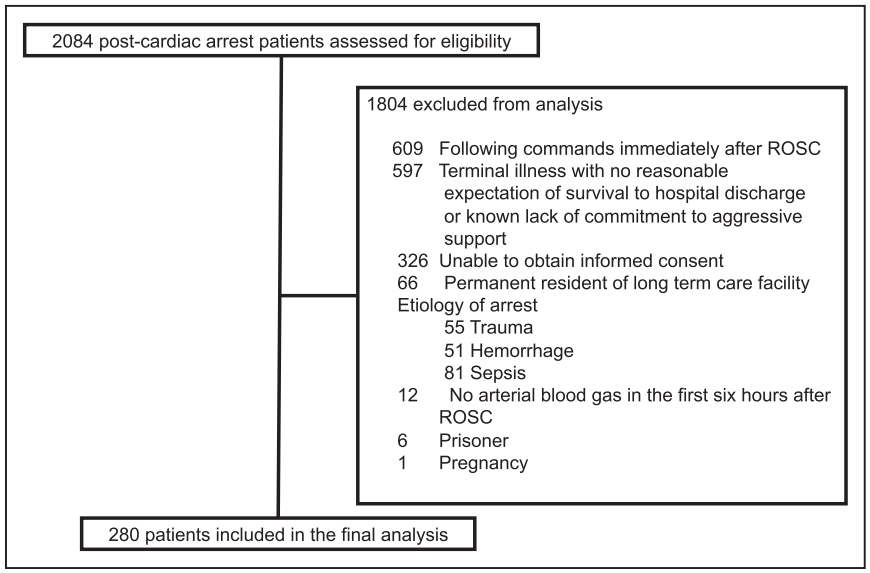

Figure 1. Study flow diagram. ROSC indicates return of spontaneous circulation.

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

Variable	All Subjects (n=280)	No Hyperoxia (n=175)	Hyperoxia* (n=105)	*P* Value
Age (SD), y	59 (15)	59 (14)	58 (16)	0.803
Female, n (%)	101 (36)	70 (40)	31 (30)	0.077
Preexisting comorbidities, n (%)				
Diabetes mellitus	68 (24)	42 (24)	26 (25)	0.886
Known coronary artery disease	75 (27)	49 (28)	26 (25)	0.554
Hypertension	183 (65)	120 (69)	63 (60)	0.144
Malignancy	20 (7)	14 (8)	6 (6)	0.472
Renal insufficiency	43 (15)	26 (15)	17 (16)	0.764
Pulmonary disease	65 (23)	39 (22)	26 (25)	0.635
Cerebral vascular disease	24 (9)	17 (10)	7 (7)	0.378
Congestive heart failure	69 (25)	42 (24)	27 (26)	0.747
Charlson comorbidity score, median (interquartile range)	1 (0–3)	1 (0–3)	1 (0–3)	0.906
Arrest location, n (%)				
Out of hospital	216 (77)	138 (79)	78 (74)	
In hospital	64 (23)	37 (21)	27 (26)	0.378
Initial arrest rhythm, n (%)				
Pulseless electric activity/asystole	154 (55)	92 (53)	62 (59)	
Ventricular fibrillation/ventricular tachycardia	103 (37)	66 (37)	37 (35)	0.389
Unknown	23 (8)	17 (10)	6 (6)	
Cardiopulmonary resuscitation duration				
Min, median (interquartile range)	15 (8–23)	15 (7–25)	15 (8–21)	0.355
>20 min, n (%)	80 (29)	54 (31)	26 (25)	0.277

*Partial pressure of arterial oxygen >300 mm Hg during the first 6 hours after return of spontaneous circulation.

test *P*=0.119). We found a poor correlation between Pao_2 and Sao_2 (*r*=0.23), as well as Pao_2 and Fio_2 (*r*=0.27). In addition, Sao_2 could not reliably rule out the presence of hyperoxia exposure, and Pao_2 as high as 295 mm Hg occurred with an Fio_2 of 0.40 (Figures I through III in the online-only Data Supplement). The only management characteristics found to be independent predictors of hyperoxia at 0 or 6 hours were Fio_2 and positive end-expiratory pressure (PEEP; odds ratios, 1.08 [95% CI, 1.05–1.11] and 0.83 [95% CI, 0.70–0.97], respectively; Table I in the online-only Data Supplement).

Seventy percent of subjects had the primary outcome of poor neurological function or death at hospital discharge. Study subjects with exposure to hyperoxia had a higher incidence of poor neurological function at hospital discharge than patients with no exposure (77% versus 65%, respectively; absolute risk difference, 12%; 95% CI, 1–23; *P*=0.035). Figure 2 displays the proportion of subjects with each mRS score stratified by hyperoxia exposure (yes/no). The overall in-hospital mortality for the entire cohort was 55%. The mortality rate was 59% versus 52% among those with versus without hyperoxia exposure, respectively (*P*=0.251). Two hundred twenty-five subjects survived to 72 hours and had a FOUR score measurement. The median FOUR score at 72 hours was 8 (IQR, 3–13) for the entire cohort and 7 (IQR, 3–13) versus 10 (IQR, 4–13) among patients with versus without hyperoxia, respectively (Wilcoxon rank-sum test *P*=0.148). Forty-seven percent versus 35% had early neurological injury at 72 hours among patients with and without hyperoxia respectively (*P*=0.073). The FOUR score among those who died after 72 hours was significantly lower compared with those who survived to hospital discharge (3 [IQR, 0–7] versus 13 [IQR, 10–16]; Wilcoxon rank-sum test *P*<0.001), suggesting that those who died had significant neurological injury before death.

Table 3 displays the results of the multivariable regression models for the primary outcome and both secondary outcomes. After adjustment for potential baseline and postcardiac arrest confounders, hyperoxia was an independent predictor of poor neurological function at hospital discharge (relative risk, 1.23; 95% CI, 1.11–1.35), as well as early neurological injury. Hyperoxia was found to be associated with in-hospital mortality when multiple imputation was used (see Tables II through VII in the online-only Data Supplement for results of the full regression models).

For the first sensitivity analysis of the primary outcome, several variables were statistically different at

Table 2. Postcardiac Arrest Data for All Subjects

Variable	All Subjects (n=280)	No Hyperoxia (n=175)	Hyperoxia* (n=105)	*P* Value
Ventilator parameters				
Time-weighted average of Fio_2	0.82 (0.66 to 0.97)	0.87 (0.64 to 0.99)	0.78 (0.68 to 0.92)	0.162
Positive end-expiratory pressure, cmH_2O	5 (5 to 7)	5 (5 to 8)	5 (5 to 5)	<0.001
Tidal volume, predicted body weight, cm^3/kg	7.4 (6.7 to 8.1)	7.4 (6.8 to 8.1)	7.3 (6.7 to 8.0)	0.537
Respiratory rate, breaths/min	17 (15 to 20)	17 (15 to 21)	16 (15 to 20)	0.282
Plateau pressure, cm H_2O	20 (16 to 25)	21 (17 to 26)	20 (16 to 23)	0.241
Plateau pressure >30 cm H_2O, n (%)	42 (18)	33 (22)	9 (10)	0.016
Pao_2 at 1 h, mm Hg	201 (99 to 343)	121 (82 to 203)	406 (304 to 488)	<0.001
Pao_2 at 6 h, mm Hg	106 (75 to 193)	99 (71 to 156)	128 (88 to 238)	<0.001
Time-weighted average of Sao_2, %	98 (97 to 99)	98 (96 to 99)	99 (98 to 100)	<0.001
ROSC to first arterial blood gas, min	59 (35 to 103)	63 (39 to 122)	48 (28 to 76)	0.002
Arterial blood gases in first 6 h, n	2 (2 to 3)	2 (2 to 3)	3 (2 to 3)	0.173
$Paco_2$, mm Hg	44 (37 to 52)	45 (38 to 54)	43 (36 to 50)	0.077
pH	7.27 (7.18 to 7.34)	7.26 (7.18 to 7.34)	7.28 (7.20 to 7.35)	0.160
Base excess	−8 (−11 to −3)	−8 (−12 to −4)	−6 (−10 to −3)	0.256
Metabolic acidosis,† n (%)	202 (72)	128 (73)	74 (70)	0.630
Mean arterial blood pressure, mm Hg	94 (82 to 105)	93 (81 to 103)	95 (84 to 106)	0.209
Arterial hypotension,‡ n (%)	142 (51)	95 (54)	47 (45)	0.123
Vasopressor infusion, n (%)	150 (54)	99 (57)	51 (49)	0.194
Percutaneous coronary intervention, n (%)	31 (11)	20 (11)	11 (10)	0.806
Modified Sequential Organ Failure Assessment score	5 (2–7)	5 (3–7)	4 (2–7)	0.119

Values are median (interquartile range) when appropriate.

Fio_2 indicates fraction of inspired oxygen; $Paco_2$, partial pressure of arterial carbon dioxide; Pao_2, partial pressure of arterial oxygen; ROSC, return of spontaneous circulation; Sao_2, and arterial oxygen saturation.

*Pao_2 >300 mm Hg during the first 6 hours after ROSC.

†Defined as a base deficit ≤−6 during the first 6 hours after ROSC.

‡Defined as mean arterial blood pressure <70 mm Hg during the first 6 hours after ROSC.

P<0.10 when the hyperoxia and no hyperoxia groups were compared: sex, mean PEEP, plateau airway pressure >30 cmH_2O, time-weighted average Sao_2, time from ROSC to first ABG analysis, and mean arterial partial pressure of carbon dioxide during the initial 6 hours after ROSC. After adjustment for these identified potential confounders, hyperoxia remained an independent predictor of poor neurological outcome (relative risk, 1.23; 95% CI, 1.05–1.44; Table VIII in the online-only Data Supplement). We did not find evidence that the association between hyperoxia and poor neurological outcome differed between cardiac arrest locations (Table IX in the online-only Data Supplement). Among patients who survived to hospital discharge, 33% had poor neurological outcome at hospital discharge. Hyperoxia remained an independent predictor of poor neurological outcome among survivors to hospital discharge (relative risk, 1.42; 95% CI, 1.09–1.87; Table X in the online-only Data Supplement).

Figure 3 displays the adjusted relative risks with 95% CIs for poor neurological outcome across ascending cut points used to define hyperoxia. Only Pao_2 cut points of ≥300 mm Hg were found to be significantly associated with poor neurological outcome.

During the initial 6 hours after ROSC, after adjustment for potential baseline and postcardiac arrest confounders and total number of ABG analyses, a 1-hour-longer duration of hyperoxia exposure was associated with a 3% increase in risk of poor neurological outcome (relative risk, 1.03; 95% CI, 1.02–1.05; Table XI in the online-only Data Supplement).

DISCUSSION

In this prospective multicenter study, using a standardized protocol for ABG measurements, we tested whether exposure to hyperoxia after resuscitation from cardiac arrest was associated with poor neurological function at hospital discharge. We found that 38% of patients had exposure to hyperoxia during the early hours after resuscitation and that hyperoxia exposure after ROSC was an independent predictor of poor neurological function at hospital discharge. Our results suggest that the association between supranormal levels of Pao_2 and poor

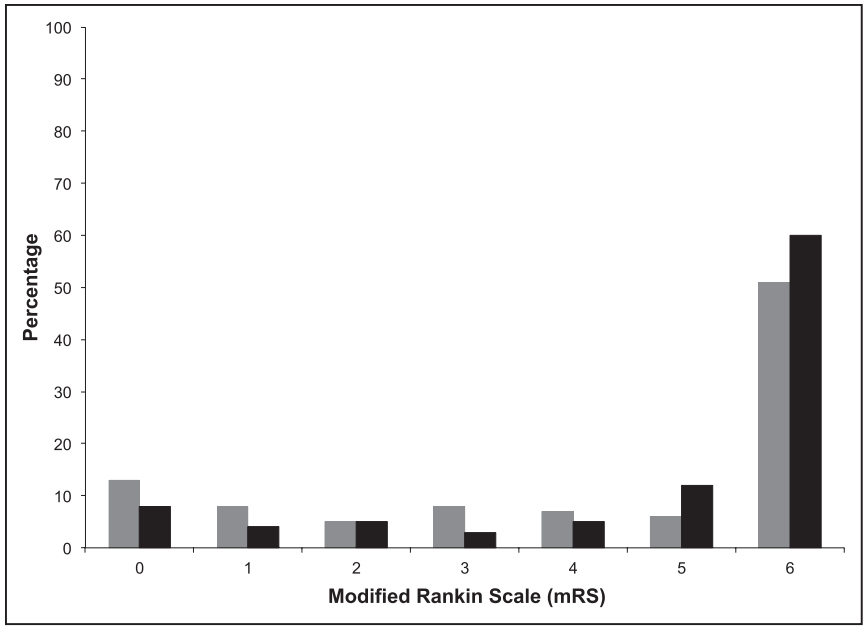

Figure 2. mRS score at hospital discharge stratified by no hyperoxia (gray columns) and hyperoxia (black columns). An mRS score of 0 indicates no symptoms; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderate-severe disability; 5, severe disability; and 6, death.

neurological outcome begins at a Pao_2 of ≥300 mm Hg. In addition, we found an association between duration of hyperoxia exposure and neurological outcome. In our multivariable models, we also found hyperoxia to be independently associated with early neurological injury, and our results suggest that hyperoxia is associated with in-hospital mortality. Early neurological injury was common among subjects who died in hospital, suggesting that neurological injury was a major factor for mortality. Thus, it is reasonable to infer that the association of hyperoxia with mortality is mediated by early neurological injury. Last, we found that Sao_2 and Fio_2 levels could not reliably rule out exposure to hyperoxia; therefore, frequent ABG measurements may be needed to avoid hyperoxia exposure. Although we found a weak correlation between Fio_2 and Pao_2 on univariable analysis, with adjustment for other ventilator settings and patient characteristics, we found that higher Fio_2 was a predictor of hyperoxia exposure. We also found higher PEEP to have a negative association with hyperoxia exposure. Higher PEEP strategies are often used in patients with lung injury who have higher oxygen requirements. Thus, elevated PEEP may be a marker for patients who are more difficult to oxygenate and thus less likely to develop hyperoxia. In summary, in this prospective multicenter study using protocol-directed ABG measurements, we found that hyperoxia during the early period after ROSC is associated with poor neurological outcome.

Hyperoxia is postulated to cause harm in the context of reperfusion injury by increasing the formation of reactive oxygen species, resulting in oxidative impairment of mitochondrial respiration and cerebral energy metabolism. Oxidative modification of mitochondrial proteins may disable brain pyruvate dehydrogenase complex activity,[44] the only bridge between anaerobic and aerobic metabolism. In addition, oxidative stress activates the mitochondrial permeability transition pore to release NAD(H) into the cytosol, depleting a vital metabolic cofactor.[45] Metabolic failure may ensue, resulting in decreased cerebral consumption of glucose and oxygen, increased production of lactate, and delayed neuronal cell death.[46,47] Furthermore, increased reactive oxygen species may impair electron transport chain activity by forming mitochondrial membrane pores that release cytochrome c into the cytosol,[45] resulting in caspase-dependent apoptosis. Increased reactive oxygen species may also cause oxidation of brain lipids (ie, lipid peroxidation), which may have physiological (eg, alteration

Table 3. Adjusted Relative Risks for Hyperoxia (Pao_2 >300 mm Hg) for the Primary and Secondary Outcomes

Outcome	Relative Risk	95% Confidence Interval	*P* Value
Primary outcome: poor neurological outcome*			
List-wise deletion	1.23	1.11–1.35	<0.001
Multiple imputation	1.24	1.13–1.35	<0.001
Secondary outcomes:			
In-hospital mortality			
List-wise deletion	1.24	0.99–1.55	0.060
Multiple imputation	1.25	1.01–1.54	0.040
Early neurological injury†			
List-wise deletion	1.32	1.03–1.69	0.026
Multiple imputation	1.39	1.11–1.74	0.004

Results of the full models are displayed in the online-only Data Supplement. Pao_2 indicates partial pressure of arterial oxygen.

*Defined as modified Rankin Scale score >3 at hospital discharge.

†Defined as a Full Outline of Unresponsiveness score ≤6 at 72 hours after return of spontaneous circulation.

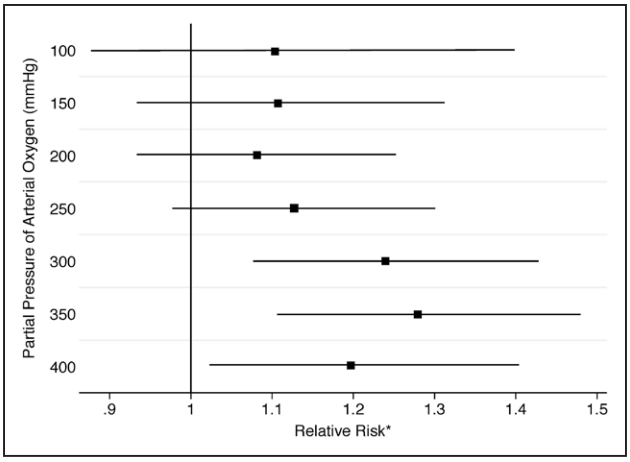

Figure 3. Adjusted relative risks (squares) with 95% confidence intervals (horizontal lines) for poor neurological outcome (defined as modified Rankin Scale [mRS] score >3) across ascending cut points to define hyperoxia.

*Relative risks were calculated with multivariable linear regression analysis (with a log link) with adjustment for age, initial cardiac rhythm, metabolic acidosis, arterial hypotension, prearrest comorbidities, and prolonged duration of cardiopulmonary resuscitation.

of blood flow, neutrophil chemoattraction) and cellular (eg, excitotoxicity, neurodegeneration) toxic effects[48,49] and promote cellular inflammatory reactions, specifically the activation of microglia and astrocytes in the neuronal microenvironment, leading to increased neuronal cell death.[50] In addition, hyperoxia may have a direct vasoconstrictor effect, which may reduce cerebral blood flow after ROSC, exacerbating ischemic injury.[51,52]

Preclinical studies support the hypothesis that hyperoxia after ROSC worsens brain damage, as evidenced on functional neurological testing[48,50,53] and histopathology,[47,54] and decreases survival.[49] A recent randomized clinical trial of patients with acute myocardial infarction found no decrease in mortality at 1 year with the use of supplemental oxygen compared with room air.[55] In addition, a randomized clinical trial of supplemental oxygen versus no supplemental oxygen in patients with ST-segment–elevation myocardial infarction found that supplemental oxygen increased the risk of recurrent myocardial infarction and cardiac arrhythmias and increased myocardial infarct size at 6 months, suggesting that higher Pao_2 levels worsen myocardial reperfusion injury.[56]

Current postresuscitation guidelines recommend that if the Sao_2 is >98% during the early period after cardiac arrest, the Fio_2 should be titrated down to avoid prolonged exposure to hyperoxia.[7–9] However, the current data on hyperoxia after resuscitation from cardiac arrest have significant limitations and are mostly from retrospective cohort studies with conflicting results.[10–16,57,58] Interpreting the current literature is difficult secondary to heterogeneity in methodologies used to define Pao_2 derangements and outcomes. In addition, none of these previous studies used protocol-directed ABG measurements at specific time points, causing concern for measurement bias. A recent systematic review and meta-analysis of observational studies found hyperoxia to be associated with in-hospital mortality; however, the authors of this meta-analysis warn that these results should be interpreted with caution because there was significant heterogeneity between studies.[59]

A recent cohort study with historical controls found that initiating conservative oxygen therapy targeting an Sao_2 of 88% to 92% using the lowest possible Fio_2 among patients after cardiac arrest admitted to the intensive care unit was feasible, decreased intensive care unit length of stay, but did not improve survival to hospital discharge.[60] Of note, all patients in both the titrated and the conventional oxygen therapy groups in this previous study had Pao_2 levels <200 mm Hg; thus, these results do not help inform the effects of Pao_2 >200 mm Hg. To date, 2 randomized controlled trials have evaluated the effects of supranormal Pao_2 levels after resuscitation from cardiac arrest. One study randomized 28 subjects to an Fio_2 of 0.30 versus 1.0 and found that conservative oxygen therapy was safe.[61] This trial found no difference in serum neuron-specific enolase, a marker of neuronal injury, in the entire cohort but found that use of 0.30 oxygen was associated with a decreased level of neuron-specific enolase at 24 hours in patients not treated with targeted temperature management. A second study in the prehospital setting randomized 18 subjects to standard care (highest possible oxygen flow rate) versus oxygen titration (targeting Sao_2 90%–94%).[62] This trial was terminated early because of increased hypoxia episodes in the oxygen titration group. These data suggest that titration of Fio_2 is perhaps more appropriately managed in the hospital setting.

The results in the present study prospectively validate our previous findings that a Pao_2 >300 mm Hg is associated with poor clinical outcomes.[10] These findings, in conjunction with the current body of literature evaluating the association between Pao_2/supplemental oxygen and clinical outcomes during reperfusion injury, support current postcardiac arrest guideline recommendations to avoid prolonged exposure to hyperoxia. This study has important implications for future design of clinical trials aimed at identifying an optimal Pao_2 after ROSC. Specifically, given the current evidence of an association with harm and no evidence to suggest any potential benefit, such trials should focus on testing varying Pao_2 ranges <300 mm Hg because at this time there is currently insufficient equipoise to ethically randomize subjects to a Pao_2 >300 mm Hg.

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. Second, although we used multivariable linear regression with a log link and multiple sensitivity analyses to adjust for potential confounders, the potential of unmeasured confounders still exists. Third, in contrast with some resuscitation clinical investigations, we included patients with both in- and out-of-hospital cardiac arrest. We felt that this was necessary to allow a more pragmatic study, the results of which can be applicable to the largest possible patient population. In the present study, arrest location was not associated with outcome. In addition, in sensitivity analysis, we did not find evidence that the association between hyperoxia and poor neurological outcome differs between arrest locations (ie, arrest location was not an effect modifier). Fourth, 326 subjects were excluded secondary to inability to obtain informed consent. Although we found similar mean ages between our study sample and those subjects excluded because of lack of informed consent, we found that our study population had a higher rate of VF/VT and longer duration of CPR, suggesting some difference between our study sample and those excluded because of lack of informed consent, potentially introducing selection bias. Of note, 29% of subjects screened for inclusion who underwent CPR for cardiac arrest were excluded secondary to a known lack of commitment to aggressive support. These patients likely underwent CPR secondary to the treatment team being unaware of the patient's wishes (ie, unavailable or no advanced directive), or the family made the decision to withdraw care shortly after ROSC. Fifth, we found discordance between the measured Pao_2 and corresponding Sao_2. This discordance, likely secondary to poor Sao_2 sensing, demonstrates the limitations of pulse oximetry and underscores the importance of obtaining an ABG for Pao_2 monitoring. Sixth, for estimating the duration of hyperoxia exposure, we assumed that the Pao_2 level remained constant between ABG analyses. It is possible that the Pao_2 level varied during this time, allowing potential measurement bias. Last, it remains possible that hyperoxia reflects a patient population that is more ill and therefore has a higher likelihood to have poor neurological outcome. However, we did not observe any significant differences in the duration of CPR, postresuscitation Sequential Organ Failure Assessment score, incidence of postresuscitation arrest hypotension or vasopressor administration, or degree of metabolic acidosis between the 2 groups, suggesting that this was not the case.

CONCLUSIONS

Early hyperoxia exposure after resuscitation from cardiac arrest is independently associated with death and poor neurological function at hospital discharge. The increased risk of poor neurological function appears to begin at a Pao_2 of 300 mm Hg.

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Disclosures

None.

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