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Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality

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Context Laboratory investigations suggest that exposure to hyperoxia after resuscitation from cardiac arrest may worsen anoxic brain injury; however, clinical data are lacking.

Objective To test the hypothesis that postresuscitation hyperoxia is associated with increased mortality.

Design, Setting, and Patients Multicenter cohort study using the Project IMPACT critical care database of intensive care units (ICUs) at 120 US hospitals between 2001 and 2005. Patient inclusion criteria were age older than 17 years, nontraumatic cardiac arrest, cardiopulmonary resuscitation within 24 hours prior to ICU arrival, and arterial blood gas analysis performed within 24 hours following ICU arrival. Patients were divided into 3 groups defined a priori based on PaO_2 on the first arterial blood gas values obtained in the ICU. Hyperoxia was defined as PaO_2 of 300 mm Hg or greater; hypoxia, PaO_2 of less than 60 mm Hg (or ratio of PaO_2 to fraction of inspired oxygen <300); and normoxia, not classified as hyperoxia or hypoxia.

Main Outcome Measure In-hospital mortality.

Results Of 6326 patients, 1156 had hyperoxia (18%), 3999 had hypoxia (63%), and 1171 had normoxia (19%). The hyperoxia group had significantly higher in-hospital mortality (732/1156 [63%; 95% confidence interval {CI}, 60%-66%]) compared with the normoxia group (532/1171 [45%; 95% CI, 43%-48%]; proportion difference, 18% [95% CI, 14%-22%]) and the hypoxia group (2297/3999 [57%; 95% CI, 56%-59%]; proportion difference, 6% [95% CI, 3%-9%]). In a model controlling for potential confounders (eg, age, preadmission functional status, comorbid conditions, vital signs, and other physiological indices), hyperoxia exposure had an odds ratio for death of 1.8 (95% CI, 1.5-2.2).

Conclusion Among patients admitted to the ICU following resuscitation from cardiac arrest, arterial hyperoxia was independently associated with increased in-hospital mortality compared with either hypoxia or normoxia.

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SUDDEN CARDIAC ARREST IS THE most common lethal consequence of cardiovascular disease. Even if return of spontaneous circulation (ROSC) from cardiac arrest is achieved, approximately 60% of patients will not survive to hospital discharge.[1,2] The high mortality is attributed to the postcardiac arrest syndrome, which involves global ischemia-reperfusion injury, myocardial stunning, and anoxic brain injury.[3] The recent success of therapeutic hypothermia for post-ROSC neuroprotection[4,5] has increased momentum for investigating post-ROSC factors that can improve outcomes.

In the search for modifiable post-ROSC factors, the role of supplemental oxygen, which is often administered in high concentrations to patients after cardiac arrest has come into controversy.[6] There is a paradox with oxygen when delivered to the injured brain. Too little oxygen may potentiate anoxic injury. Too much oxygen may increase oxygen free radical production, possibly triggering cellular injury and

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apoptosis.[7] Although numerous laboratory investigations support the potentially detrimental effects of hyperoxia exposure after ROSC from cardiac arrest, clinical data are lacking.

The incidence of post-ROSC hyperoxia and subsequent outcomes in patients who survived cardiac arrest to intensive care unit (ICU) admission are reported herein. The overall aim was to determine whether exposure to hyperoxia after ROSC from cardiac arrest was associated with poor clinical outcome. Specifically, for patients who survived cardiac arrest to ICU admission, the objectives were to determine (1) whether the presence of post-ROSC hyperoxia (defined as $Pa_{O_2} \geq 300$ mm Hg) was a common occurrence; (2) whether post-ROSC hyperoxia was associated with lower survival to hospital discharge; and (3) whether post-ROSC hyperoxia remained significantly associated with in-hospital death after adjustment for a predefined set of confounding variables in a multivariable analysis.

METHODS

Project IMPACT (Cerner Corporation, Kansas City, Missouri) is a large administrative database (initially developed by the Society of Critical Care Medicine) designed for critical care units across all disciplines. Adult ICUs from 131 US hospitals participate in Project IMPACT and data from more than 400 000 patients have been collected. Participating institutions upload data quarterly to a central repository. Data fields include hospital and ICU organizational characteristics, admission source (eg, emergency department vs inpatient), demographics, physiological data (including hemodynamic indices and laboratory values), procedures, complications, hospital and ICU length of stay, and outcomes. All data are collected by dedicated onsite personnel who must be trained and certified by Project IMPACT, which requires passing a written certification examination to ensure uniformity in both database definitions and entry. Onsite data collectors receive additional certification from Project IMPACT as a prerequisite to collating and uploading data. The institutional review board at Cooper University Hospital (Camden, New Jersey) approved this study.

The ICUs in Project IMPACT represent a wide scope of practice environments, including medical, surgical, and multidisciplinary ICUs. The institutions are heterogeneous in terms of hospital size, type (community vs academic; private vs public), and location (urban, suburban, or rural). Participating hospitals are not restricted to any particular geographic region.

Adult patients who sustained nontraumatic cardiac arrest and were admitted to the ICU at a participating center between 2001 and 2005 were included. Specifically, inclusion criteria were age older than 17 years, nontraumatic cardiac arrest, cardiopulmonary resuscitation within 24 hours prior to ICU arrival, and arterial blood gas analysis performed within 24 hours following ICU arrival.

The following variables were abstracted: demographics, comorbidities, preadmission functional status, site of origin prior to ICU arrival, hospital characteristics, most abnormal physiological parameters (including vital signs, other hemodynamic indices, and laboratory tests) over the first 24 hours in the ICU, first arterial blood gas result over the first 24 hours in the ICU, life-support interventions (eg, vasopressor use), vital status at hospital discharge (alive or dead), and functional status at hospital discharge. The Project IMPACT participation manual specifies that race/ethnicity data be abstracted from the registration information at the time of hospital admission. Race/ethnicity was included as a study variable because prior data have suggested an association between nonwhite race and poor outcome. Statistical analyses were conducted using SPSS software version 15.0.1 (SPSS Inc, Chicago, Illinois).

Continuous data are presented as means and standard deviations or medians and interquartile ranges (IQRs) as appropriate based on distribution of the data; categorical data are reported as proportions and 95% confidence intervals (CIs). For the purposes of this analysis, the cohort was divided into 3 exposure groups defined a priori based on Pa_{O_2} on the first arterial blood gas values obtained in the ICU. Hyperoxia was defined as Pa_{O_2} of 300 mm Hg or greater[8]; hypoxia, Pa_{O_2} of less than 60 mm Hg (or ratio of Pa_{O_2} to fraction of inspired oxygen [F_{IO_2}] <300)[9]; and normoxia, cases not classified as hyperoxia or hypoxia. These classifications were defined in a written protocol by consensus of all authors prior to querying the database or analyzing any data.

The primary outcome measure was in-hospital mortality. The occurrence of outcomes were compared between the groups using the χ^2 test or the binomial test for the difference in proportions with Bonferroni correction for multiple pairwise comparisons (ie, for 3 groups, α level of .05 divided by 3 or .017). For days to primary outcome analysis, Kaplan-Meier survival estimates and log-rank tests were used to compare the hyperoxia and normoxia groups.

Odds ratios (ORs) were calculated to determine independent predictors of mortality. Given the dichotomous outcome, multivariable logistic regression modeling was used. The analysis proceeded in 2 stages. In the first stage, significant risk factors were identified from the candidate variables; in the second stage, potential hospital effects were assessed (ie, correlation among patients sampled within hospital clusters). All patient-oriented data in TABLE 1 were considered to be potential candidate variables for the model. The regression model was run in 5 steps with in-hospital mortality as the outcome. At each step, a *P* value of less than .05 was used as the criterion for retention in the model.

Step 1 considered demographics. For entry into the model, age was coded by deciles. Step 2 included patient characteristics (other than demographics) prior to cardiac arrest. Preadmission functional status was coded as inde-

pendent or nonindependent. Site of origin prior to ICU admission was emergency department or hospital inpatient. Step 3 included preadmission comorbid conditions. Step 4 included patient physiological data after cardiac arrest. Hypotension (systolic blood pressure <90 mm Hg) on ICU admission and inotrope requirement were coded as binary (yes or no) variables. For the highest heart rate, each patient was coded as being above or below the median for the entire cohort. In the final step of the regression model, the predictive effects on in-hospital mortality were assessed for hyperoxia and hypoxia. The hyperoxia and hypoxia groups were each coded as a contrast variable against normoxia. The fifth step provides a significance test, OR, and a 95% CI around the OR for the primary covariate of interest, which was exposure to hyperoxia. The results summarize the effect and are adjusted for all other variables included in the earlier steps of the model.

Generalized estimating equations were used to account for potential correlation in mortality rates among patients sampled within hospital clusters. Three alternatives to the independence assumption (no association) were examined for within-hospital correlation. The quasi-likelihood independence criterion was used to determine the best working correlation structure assumption. First, an exchangeable (or compound symmetry) pattern was tested, assuming identical (but unknown) correlation between variables in the model and mortality over patients clustered in hospitals. Next, an unstructured pattern was tested, assuming nonidentical correlation between variables in the model and mortality over patients clustered in hospitals. Lastly, an autoregressive pattern was tested, assuming decreasing correlation between the variables in the model and mortality over patients clustered in hospitals. Compared with the independence assumption, none of these alternative correlation structures improved the model fit, suggesting that a significant hospital effect was not present in the model.

To test if hyperoxia exposure remained a significant independent predictor of in-hospital death when the propensity of individuals to be exposed to hyperoxia was adjusted for, a sensitivity analysis was performed using propensity scores (the methods of the propensity score analysis appear in eMethods at http://www.jama.com). A preplanned secondary analysis also was performed that was identical to the univariable analysis but used a higher Pa_{O_2} cutoff to define hyperoxia (400 mm Hg rather than 300 mm Hg).[11-13]

Assuming a ratio of approximately 3 patients in the hypoxia group for every 1 patient in the normoxia and hyperoxia groups, the sample size that was analyzed allowed greater than

Table 1. Baseline Characteristics of the Study Patients[a]

Patient Characteristics	No. (%) of Patients[b]			
	All Patients (N = 6326)	Hypoxia (n = 3999)	Normoxia (n = 1171)	Hyperoxia (n = 1156)
Age, mean (SD), y	64 (17)	64 (16)	63 (17)	66 (16)
Female sex	2911 (46)	1766 (44)	573 (49)	572 (50)
Race/ethnicity				
White	4757 (75)	3049 (76)	850 (73)	858 (74)
Black	1041 (17)	621 (16)	223 (19)	197 (17)
Latino/Hispanic	245 (4)	153 (4)	39 (3)	53 (5)
Asian/Pacific Islander	55 (1)	33 (1)	15 (1)	7 (1)
Other[c]	228 (4)	143 (4)	44 (4)	41 (4)
Preadmission functional status[d]				
Independent	4146 (66)	2607 (65)	787 (67)	752 (65)
Partially dependent	1377 (22)	862 (22)	243 (21)	272 (24)
Fully dependent	803 (13)	530 (13)	141 (12)	132 (11)
Chronic comorbidities				
Severe cardiovascular disease[e]	732 (12)	463 (12)	124 (11)	145 (13)
Respiratory disease[f]	693 (11)	459 (11)	113 (10)	121 (11)
End-stage renal disease	545 (9)	306 (8)	106 (9)	133 (12)
Hepatic cirrhosis with portal hypertension	154 (2)	104 (3)	25 (2)	25 (2)
Cancer with metastatic disease	271 (4)	180 (5)	40 (3)	51 (4)
Active chemotherapy	127 (2)	12 (<1)	9 (1)	26 (2)
AIDS	37 (1)	19 (<1)	9 (1)	9 (1)
Hematologic malignancy	29 (<1)	24 (<1)	4 (<1)	1 (<1)
ACC at ICU admission that may be associated with oxygen status				
Acute respiratory failure	599 (9)	415 (10)	111 (9)	73 (6)
Decompensated congestive heart failure	64 (1)	54 (1)	6 (<1)	4 (<1)
Pulmonary embolism	26 (<1)	18 (<1)	5 (<1)	3 (<1)
Exacerbation of asthma or COPD	91 (1)	63 (2)	19 (2)	9 (1)
Pneumonia	112 (2)	80 (2)	17 (1)	15 (1)
Noncardiogenic pulmonary edema	18 (<1)	13 (<1)	3 (<1)	2 (<1)
Location prior to ICU arrival				
Emergency department	2747 (43)	1648 (41)	675 (58)	424 (37)
Hospital inpatient	3579 (57)	2351 (59)	496 (42)	732 (63)

Abbreviations: ACC, acute cardiopulmonary condition; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.
[a] Percentages may not equal 100 due to rounding.
[b] Unless otherwise indicated.
[c] Defined as patients whose race is known, but do not fall into any of the included race categories.
[d] Independent defined as able to live at home and requiring no assistance to complete activities of daily living (ADLs); partially dependent, able to live at home, in a group home, or in a care facility and requiring some assistance to complete ADLs; fully dependent, able to live at home or in a care facility but unable to perform ADLs so must be cared for by others. The limitations requiring assistance may be physical or mental.
[e] Defined as baseline symptoms such as angina or shortness of breath at rest or on minimal exertion (New York Heart Association class IV) plus 1 or more of the following diagnoses: severe coronary artery disease, severe valvular heart disease, or severe cardiomyopathy.
[f] Defined as chronic obstructive, restrictive, or vascular pulmonary disease resulting in severe exercise restriction, such as unable to climb stairs or perform household duties; or respirator dependency related to active respiratory disease; or documented chronic hypoxia, hypercapnia, or pulmonary hypertension (>40 mm Hg).

80% power to detect a significant difference in proportions between the groups (assuming an α level of .017 when adjusted for multiple comparisons).

RESULTS

There were 8736 patients that met the first 3 inclusion criteria of age older than 17 years, nontraumatic cardiac arrest, and cardiopulmonary resuscitation prior to ICU arrival. There were 2410 patients who did not have arterial blood gas values obtained within the first 24 hours in the ICU and were thus excluded from the study. The remaining 6326 patients were from 120 hospitals. The median number of cardiac arrest cases per hospital was 41 (IQR, 17-72). Baseline characteristics for all groups appear in Table 1 and TABLE 2. Patients were predominantly white and from community, nonacademic hospitals. Sixty-six percent (n=4146) of patients were living independently prior to hospital admission and 43% (n=2747) were admitted to the ICU from an emergency department. The most common comorbid condition was severe cardiovascular disease (eg, New York Heart Association class IV; n=732 patients). Of the 6326 patients, 1156 were in the hyperoxia group (18%), 3999 were in the hypoxia group (63%), and 1171 were in the normoxia group (19%).

Table 2. Baseline Characteristics of the Study Hospitals[a]

Hospital Characteristics	No. (%) of Patients			
	All Patients (N = 6326)	Hypoxia (n = 3999)	Normoxia (n = 1171)	Hyperoxia (n = 1156)
Hospital size[b]				
Small to medium (≤300 beds)	979 (16)	594 (15)	198 (17)	187 (16)
Large (301-500 beds)	2685 (42)	1737 (43)	490 (42)	458 (40)
Extra large (>500 beds)	2661 (42)	1668 (42)	483 (41)	510 (44)
Hospital type				
Community (nonacademic)	5023 (79)	3130 (78)	939 (80)	954 (83)
Academic (university-based)	1116 (18)	740 (19)	206 (18)	170 (15)
Public	144 (2)	97 (2)	20 (2)	27 (2)
Military	43 (1)	32 (1)	6 (1)	5 (<1)
Hospital location				
Urban	3300 (52)	2091 (52)	583 (50)	626 (54)
Suburban	1976 (31)	1194 (30)	392 (34)	390 (34)
Rural	1050 (17)	714 (18)	196 (17)	140 (12)

[a]Percentages may not equal 100 due to rounding.
[b]Defined according to the criteria from Halpern et al.[10]

Table 3. Abnormal Vital Signs in the First 24 Hours in the Intensive Care Unit and Interventions

	All Patients (N = 6326)	Hypoxia (n = 3999)	Normoxia (n = 1171)	Hyperoxia (n = 1156)
	Mean (SD)			
High temperature, °C	38 (3)	38 (3)	38 (1)	38 (3)
Low temperature, °C	36 (3)	36 (1)	36 (1)	36 (3)
High heart rate, beats/min	117 (25)	119 (25)	114 (24)	117 (26)
High respiratory rate, breaths/min	26 (9)	24 (8)	24 (8)	25 (6)
Low systolic blood pressure, mm Hg	85 (22)	83 (22)	91 (21)	83 (23)
Low mean arterial pressure, mm Hg	60 (16)	58 (16)	65 (15)	58 (16)
	No. (%)			
Hemodynamic support				
Vasopressor agent[a]	3789 (60)	2574 (64)	513 (44)	702 (61)
Dobutamine	591 (9)	412 (10)	83 (7)	96 (8)
Ventilator support[b]	6123 (97)	3842 (96)	1150 (98)	1131 (98)

[a]Defined as initiation of a continuous infusion of dopamine, norepinephrine, epinephrine, or phenylephrine.
[b]Indicates presence of mechanical ventilation when index arterial blood gas in the intensive care unit was obtained.

Physiological data over the first 24 hours in the ICU for all groups are displayed in TABLE 3. Sixty percent of patients required a vasopressor agent (eg, continuous infusion of dopamine, norepinephrine, epinephrine, or phenylephrine); the overall mean (SD) for lowest systolic blood pressure was 85 (22) mm Hg. For all patients, the mean (SD) high temperature was 38°C (3°C) and for low temperature was 36°C (3°C). The median ICU length of stay for survivors to hospital discharge was 4 days (IQR, 2-8 days) and for nonsurvivors was 2 days (IQR, 1-5 days). The median hospital length of stay for survivors was 12 days (IQR, 7-22 days) and for nonsurvivors was 4 days (IQR, 1-11 days).

Overall, 56% of patients (n=3561) met the primary outcome of in-hospital mortality (TABLE 4). Mortality was highest in the hyperoxia group (732/1156; 63% [95% CI, 60%-66%]) compared with the hypoxia group (2297/3999; 57% [95% CI, 56%-59%]) and the normoxia group (532/1171; 45% [95% CI 43%-48%]). The hyperoxia group had significantly higher in-hospital mortality compared with the normoxia group (proportion difference, 18% [95% CI, 14%-22%]; $P<.001$). Mortality also was significantly higher in the hyperoxia group compared with the hypoxia group (proportion difference, 6% [95% CI, 3%-9%]; $P<.001$). On Kaplan-Meier analysis, the survival fractions for the hyperoxia and normoxia groups diverged significantly over time (log-rank $P<.001$; FIGURE). In addition, among hospital survivors, patients with hyperoxia had a significantly lower proportion of discharges from the hospital as functionally independent compared with patients with normoxia (29% vs 38%, respectively; proportion difference, 9% [95% CI, 3%-15%]; $P=.002$; Table 4).

Nine risk factors proved to be significantly associated with in-hospital death on multivariable logistic regression analysis. Significant demographic and other factors prior to cardiac arrest included age, nonindependent preadmission functional status, emer-

gency department origin, active chemotherapy, and chronic renal failure. Significant physiological factors included hypotension on ICU arrival, tachycardia, and hypoxia. Exposure to hyperoxia was found to be a significant predictor of in-hospital death (OR, 1.8 [95% CI, 1.5-2.2]; TABLE 5). This is an independent effect that persists after adjusting for all other significant risk factors. In the sensitivity analysis adjusting the model for propensity scores, the OR and 95% CIs for hyperoxia exposure did not change (see eResults and eTable 1 at http://www.jama.com).

In the secondary analysis using a PaO_2 of 400 mm Hg or greater to define the hyperoxia group, mortality was even greater in the hyperoxia group (377/549; 69% [95% CI, 65%-72%]) compared with the hypoxia group (2297/3999; 57% [95% CI, 56%-59%]) and the normoxia group (887/1778; 50% [95% CI, 48%-52%]). The hyperoxia group had significantly higher in-hospital mortality compared with the normoxia group (proportion difference, 19% [95% CI, 14%-24%]; $P<.001$). Mortality also was significantly higher in the hyperoxia group compared with the hypoxia group (proportion difference, 12% [95% CI, 8%-16%]; $P<.001$).

Table 4. Outcomes of Study Patients

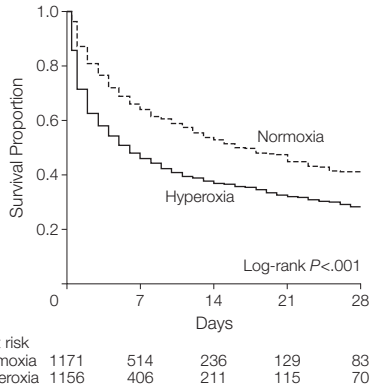
	All Patients (N = 6326)	Hypoxia (n = 3999)	Normoxia (n = 1171)	Hyperoxia (n = 1156)
In-hospital mortality, No. (%) [95% CI][a]	3561 (56) [55-58]	2297 (57) [56-59]	532 (45) [43-48]	732 (63) [60-66]
Survivors, No. (%)	2765 (44)	1702 (43)	639 (55)	424 (37)
Independent functional status at hospital discharge, No. (%) [95% CI][b]	939 (34) [32-36]	570 (33) [31-36]	245 (38) [35-42]	124 (29) [25-34]
Discharge destination, No. (%)				
Home	1203 (44)	746 (44)	294 (46)	163 (38)
Rehabilitation facility	405 (15)	248 (15)	87 (14)	70 (17)
Nursing home	759 (27)	462 (27)	162 (25)	135 (32)
Transfer to another acute care hospital	91 (3)	64 (4)	13 (2)	14 (3)
Other or unknown	307 (11)	182 (11)	83 (13)	42 (10)

[a] $P<.001$ for both comparison of hyperoxia with normoxia and for hyperoxia with hypoxia.
[b] Defined as able to live at home and requiring no assistance to complete activities of daily living. $P=.002$ for comparison of hyperoxia with normoxia and $P=.10$ for comparison of hyperoxia with hypoxia.

COMMENT

In this large multicenter cohort study of patients admitted to an ICU after resuscitation from cardiac arrest, we found that post-ROSC exposure to hyperoxia was a common occurrence, as evidenced by the first arterial blood gas values obtained after ICU arrival. In this cohort, post-ROSC hyperoxia was associated with the lowest survival rate to hospital discharge among all patients, including those who had hypoxia. After controlling for a predefined set of confounding variables in a multivariable analysis, we found that exposure to hyperoxia was an independent predictor of in-hospital death. This effect remained robust in sensitivity analyses that adjusted for hospital factors and propensity of hyperoxia exposure. Additionally, we found that among hospital survivors, hyperoxia was associated with a lower likelihood of independent functional status at hospital discharge compared with normoxia. To our knowledge, this is the first large multicenter study documenting the association between post-ROSC hyperoxia and poor clinical outcome. While we acknowledge that association does not necessarily imply causation, these data support the hypothesis that high oxygen delivery in the postcardiac arrest setting may have adverse effects.

Figure. In-Hospital Death Between Hyperoxia and Normoxia



Reperfusion after an ischemic insult is associated with a surge of reactive oxygen species, which may overwhelm host natural antioxidant defenses.[15-17] The oxidative stress from the reactive oxygen species formed after reperfusion may lead to increased cellular death by diminishing mitochondrial oxidative metabolism, disrupting normal enzymatic activities, and damaging membrane lipids through peroxidation.[7] In clinically relevant experimental models of cardiac arrest, hyperoxia has been shown to worsen the severity of oxidative stress, causing a greater loss of pyruvate dehydrogenase complex,[18] impairment of oxidative energy metabolism,[11] and higher oxidation of brain lipids,[19] culminating in more severe brain histopathologic changes and worse neurological deficits.[12,19,20] In addition, recent preclinical data suggest that early postischemic hyperoxic reperfusion may worsen brain injury via cellular inflammatory reactions in the neurons or their microenvironment (eg, activation of microglia and astrocytes).[21] After the burst of reactive oxygen species that occurs in the initial minutes after reperfusion, oxidant stress can be perpetuated in a persistently hyperoxic environment. Analogous to the concept that hyperoxia exposure may be associated with harm in the resuscitation of

Table 5. Multiple Logistic Regression Model With In-Hospital Mortality as the Dependent Variable[a]

Variable	OR (95% CI)	*P* Value
Age decile	1.1 (1.1-1.2)	<.001
Emergency department origin	1.5 (1.3-1.7)	<.001
Nonindependent functional status at admission	1.3 (1.1-1.4)	<.001
Chronic renal failure	1.6 (1.3-1.9)	<.001
Active chemotherapy	2.8 (1.8-4.6)	<.001
High heart rate in ICU[b]	1.9 (1.7-2.1)	<.001
Hypotension at ICU arrival[c]	2.1 (1.9-2.3)	<.001
Hypoxia exposure	1.3 (1.1-1.5)	.009
Hyperoxia exposure	1.8 (1.5-2.2)	<.001

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio.
[a] Event rates (mortality) for each variable and for the relevant reference group appear in eTable 2 at http://www.jama.com. The following variables were removed from the model because of nonsignificance: female sex, OR, 1.1 (95% CI, 1.0-1.2; *P*=.29); chronic respiratory disease, OR, 1.3 (95% CI, 1.0-1.6; *P*=.05); human immunodeficiency virus, OR, 1.9 (95% CI, 1.0-3.7; *P*=.06); and requiring inotropic therapy, OR, 1.1 (95% CI, 0.9-1.3; *P*=.19).
[b] Indicates the highest value for first 24 hours in the ICU (1=exceeds median; 0=median or lower).
[c] Defined as any systolic blood pressure of less than 90 mm Hg within 1 hour of ICU arrival.[14]

neonates,[22] the ongoing oxidant stress associated with hyperoxic reperfusion may be capable of worsening anoxic brain injury in adult patients with postcardiac arrest syndrome.

Current American Heart Association guidelines for adult cardiopulmonary resuscitation advocate 100% inspired oxygen during resuscitative efforts because this may maximize the likelihood of achieving ROSC.[23] However, after circulation is successfully restored, clinicians frequently maintain high FIO_2 for variable periods.[24] Our study quantifies the incidence of postcardiac arrest hyperoxia. Nearly 1 in 5 patients had exposure to hyperoxia (PaO_2 ≥300 mm Hg) postcardiac arrest and almost half of these patients had PaO_2 of 400 mm Hg or greater. Therefore, arterial hyperoxia appears to be a common occurrence in patients resuscitated from cardiac arrest. These data provide insight into a potential large-scale problem in postcardiac arrest care.

A recent consensus statement on the treatment of postcardiac arrest syndrome by the International Liaison Committee on Resuscitation advocated the avoidance of unnecessary arterial hyperoxia and a controlled reoxygenation strategy targeting an arterial oxygen saturation not to exceed 94% to 96%.[24] However, the consensus statement acknowledged that this recommendation was based solely on preclinical data and identified the role of post-ROSC oxygenation as a critical knowledge gap for resuscitation science.[24] The present study provides important data to help fill this knowledge gap. Although it may be intuitive that adequate oxygenation is vital (and persistent hypoxia should be avoided) after resuscitation from cardiac arrest, the present study questions whether a more is better strategy for post-ROSC oxygenation is actually harmful as opposed to beneficial. In fact, these data support the hypothesis that both hyperoxia and hypoxia are harmful and underscore the need for clinical trials of controlled reoxygenation in adults resuscitated from cardiac arrest.

We acknowledge important limitations in this study. First, this was a purely observational study; therefore, we can only identify association rather than causation. Next, we defined hyperoxia as PaO_2 of 300 mm Hg or greater based on PaO_2 levels from a previously published experimental study,[8] but the precise PaO_2 level associated with maximal risk is unknown. In addition, our definition for the hypoxia group was not based on PaO_2 alone but rather included the ratio of PaO_2 to FIO_2 as a component of the definition. This was necessary because a patient with normal PaO_2 may have required a high FIO_2 to achieve the observed PaO_2 value (ie, PaO_2 of 65 mm Hg on a FIO_2 of 1.0), and such a patient would be at high risk of death, similar to patients with a PaO_2 of less than 60 mm Hg. Although our exposure variable is based on the first PaO_2 value measured over the first 24 hours after arrival in the ICU, the arterial blood gas data in Project IMPACT are not precisely time stamped. Thus, it is possible that some of the PaO_2 measurements were not obtained early during the postresuscitation period; specifically, we did not capture intraarrest arterial blood gas data. Laboratory data indicate that early exposure to hyperoxia after reperfusion worsens ischemia-reperfusion injury; however, hyperoxia exposure at later time points may not.[25] In this context, the limitation of this study that later PaO_2 measurements may be included in our sample would be expected to bias the results toward the null (ie, no association between hyperoxia exposure and increased mortality).

We also recognize that the Project IMPACT database was designed from an ICU perspective, and thus it does not capture variables in the Utstein style[26] (eg, initial cardiac rhythm, no-flow time, cardiopulmonary resuscitation quality) specific to the cardiac arrest event that preceded the admission to the ICU. However, the ICU perspective makes Project IMPACT a valuable source of information on this topic because cardiopulmonary resuscitation registries may not collect PaO_2 data after ROSC. Another limitation worthy of note is that our study did not capture whether or not therapeutic hypothermia was attempted. However, only 6% of patients had a lowest body temperature under 34°C in the first 24 hours after arrival in the ICU, indicating that therapeutic hypothermia was not widely applied in this cohort. Although the postulated scientific basis for the association between hyperoxia exposure and outcome is related to the degree of anoxic brain injury, we also acknowledge that hyperoxia could potentially be associated with extracerebral deleterious consequences that were not ascertained in our study. In addition, Project IMPACT does not capture airway pressure measurements

from the ventilators that could be a surrogate for barotrauma (such as peak or plateau airway pressure or positive end-expiratory pressure). Finally, there may have been unmeasured confounders that may have influenced the association between oxygenation status and mortality.

CONCLUSIONS

In this large multicenter cohort of adult patients admitted to the ICU after resuscitation from cardiac arrest, we found that exposure to hyperoxia is a common occurrence and an independent predictor of in-hospital mortality. These data support the hypothesis that postresuscitation hyperoxia could be harmful and provide scientific rationale for clinical trials of controlled reoxygenation during the postresuscitation period.

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Study concept and design: Kilgannon, Jones, Shapiro, Angelos, Parrillo, Trzeciak.
Acquisition of data: Trzeciak.
Analysis and interpretation of data: Kilgannon, Jones, Shapiro, Milcarek, Hunter, Parrillo, Trzeciak.
Drafting of the manuscript: Kilgannon, Trzeciak.
Critical revision of the manuscript for important intellectual content: Kilgannon, Jones, Shapiro, Angelos, Milcarek, Hunter, Parrillo, Trzeciak.
Statistical analysis: Kilgannon, Jones, Shapiro, Milcarek, Hunter, Trzeciak.
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Titrating Oxygen During and After Cardiopulmonary Resuscitation

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SEVERAL INVESTIGATIONS HAVE REKINDLED IMPORtant concern that administration of 100% oxygen during and early after resuscitation from experimental cardiopulmonary arrest might be deleterious to the brain. In a canine model of ventricular fibrillation cardiopulmonary arrest, use of 100% oxygen compared with use of room air early during resuscitation was associated with increased neuronal death in selectively vulnerable brain regions and worse neurological outcome.[1] Several studies have focused on oxidative injury to key mitochondrial enzymes (such as pyruvate dehydrogenase or manganese superoxide dismutase) or mitochondrial lipids (such as cardiolipin) in mediating these deleterious effects.[2-4]

Concern about the use of 100% oxygen in resuscitation is not new. In neonatal resuscitation, detrimental effects of 100% oxygen have been described in case reports and randomized controlled trials.[5] However, infants have compromised antioxidant defenses and age-related differences in endogenous defenses against hypoxemia, including fetal hemoglobin, among others.[6] Thus, the potential risk of 100% oxygen and the potential benefit of room air may be greatly magnified in neonates compared with adults.

In this issue of *JAMA*, Kilgannon et al[7] report the results of an important multicenter cohort study generated from a critical care database of intensive care units (ICUs) in 120 US hospitals. The authors studied 6326 adults with nontraumatic cardiopulmonary arrest and analyzed the relationship between in-hospital mortality and hypoxia (Pa_{O_2} <60 mm Hg), normoxia (Pa_{O_2} <300 mm Hg), or hyperoxia (Pa_{O_2} ≥300 mm Hg) as assessed on the first ICU arterial blood gas. Hyperoxia was associated with a significantly increased mortality rate compared with normoxia (proportion difference, 18%; 95% confidence interval [CI], 14%-22%). Moreover, the hyperoxia group showed increased mortality vs the hypoxia group (proportion difference, 6%; 95% CI, 3%-9%). In a model controlling for a predefined set of confounders, hyperoxia exposure had an odds ratio for death of 1.8 (95% CI, 1.5-2.2).

See also p 2165.

In this study, 18% of the patients had hyperoxia based on the first arterial blood gas determination in the ICU. Given the rather conservative definition of hyperoxia (Pa_{O_2} ≥300 mm Hg), the true incidence of more moderate levels of hyperoxia is likely to be quite high. Even though mechanisms producing secondary deleterious effects after cardiac arrest can be successfully manipulated (as evidenced by the use of induction of mild hypothermia), this finding underscores the possibility that further meaningful improvements in outcome might result from careful attention to appropriately titrating basic aspects of extracerebral physiology at the bedside, such as prevention of hyperoxia.

The authors acknowledge the limitations of this observational study. For instance, it would have been informative to have provided an assessment of the temporal relationship of hyperoxia with outcomes because experimental work suggests the possibility that early hyperoxia rather than delayed postresuscitation hyperoxia is deleterious to the brain.[1,8] The first Pa_{O_2} value in this study was obtained within 24 hours of ICU arrival, precluding assessment of the temporal effects of hyperoxia. Moreover, cause of death and neurological outcome were both lacking in the database, limiting any inferences regarding the contribution of cerebral vs extracerebral effects to the reported findings. The authors suggest putative deleterious effects of hyperoxia on pulmonary function, but (based on experimental data) tissue hyperoxia early postreperfusion also could adversely affect other organ systems.

This study also showed an association between hypoxia and mortality after cardiopulmonary arrest. Many underlying pathologies that may require high levels of fraction of inspired oxygen to achieve normal arterial saturation can either cause or represent comorbidities in adults with cardiopulmonary arrest, such as drowning or pulmonary embolism. This complicates the ability to make sweeping recommendations against the use of 100% oxygen early in resuscitation. Similarly, it is not clear that arterial hyperoxia necessarily results in brain tissue hyperoxia. As

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experimental and clinical data on putative detrimental effects of arterial hyperoxia are emerging in the setting of cardiopulmonary arrest, the pendulum has shifted in the opposite direction regarding use of oxygen for patients with severe traumatic brain injury. Specifically, there has been a resurgence in the administration of supplemental oxygen related to the use of brain tissue oxygen (ie, brain tissue oxygenation; $PbtO_2$) tension monitoring—and titration of fraction of inspired oxygen and other therapies to achieve target $PbtO_2$ values above critical thresholds ranging from 10 mm Hg to 20 mm Hg.[9] Monitoring of $PbtO_2$ has rarely been used in adults with cardiopulmonary arrest,[10] likely related to the use of anticoagulation in many of these patients. Whether arterial saturation or $PbtO_2$ represents the optimal target to achieve favorable long-term outcome in adults with cardiopulmonary arrest remains unexplored.

The study by Kilgannon et al[7] also supports the potential value of translational research using experimental models that carefully mimic the clinical condition. For instance, Balan et al[11] demonstrated the benefits of titrating oxygen therapy to arterial oxygen saturation in the early postresuscitation phase in experimental cardiopulmonary arrest. In addition, the current International Liaison Committee on Resuscitation guidelines[12] advocate a controlled reoxygenation strategy targeting an arterial saturation of 94% to 96% once spontaneous circulation has been restored. Important issues involve whether to recommend that more meticulous care be given to titrating oxygenation after cardiac arrest and whether an alarm threshold should be set for arterial saturation in patients with cardiac arrest after return of spontaneous circulation. To date, however, randomized controlled trial data on which to make evidence-based recommendations are lacking.

Experimental evidence suggests that the risk of oxidative injury may be greatest early in resuscitation,[13] possibly related to the initial burst of reperfusion. Accordingly, unconventional resuscitation strategies that were considered but heretofore unproven (such as intermittent, controlled, or even delayed reperfusion) are being explored in the laboratory with promising results in some cases.[14,15] Such an approach might be particularly important in the setting of prolonged cardiac arrest. With the upcoming 50th anniversary of the birth of cardiopulmonary resuscitation,[16] the work of Kilgannon et al[7] provides an impetus for better defining the use of oxygen in all settings of cerebral resuscitation, in further exploring these revolutionary approaches to resuscitation, and in examining other strategies such as the combination of 100% oxygen with antioxidant therapy or the use of targeted mitochondrial antioxidants.[17]

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