

Relationship Between Supranormal Oxygen Tension and Outcome After Resuscitation From Cardiac Arrest

J. Hope Kilgannon, MD; Alan E. Jones, MD; Joseph E. Parrillo, MD; R. Phillip Dellinger, MD; Barry Milcarek, PhD; Krystal Hunter, MBA; Nathan I. Shapiro, MD; Stephen Trzeciak, MD, MPH; on behalf of the Emergency Medicine Shock Research Network (EMShockNet) Investigators

Background—Laboratory and recent clinical data suggest that hyperoxemia after resuscitation from cardiac arrest is harmful; however, it remains unclear if the risk of adverse outcome is a threshold effect at a specific supranormal oxygen tension, or is a dose-dependent association. We aimed to define the relationship between supranormal oxygen tension and outcome in postresuscitation patients.

Methods and Results—This was a multicenter cohort study using the Project IMPACT database (intensive care units at 120 US hospitals). Inclusion criteria were age >17 years, nontrauma, cardiopulmonary resuscitation preceding intensive care unit arrival, and postresuscitation arterial blood gas obtained. We excluded patients with hypoxia or severe oxygenation impairment. We defined the exposure by the highest partial pressure of arterial oxygen (PaO₂) over the first 24 hours in the ICU. The primary outcome measure was in-hospital mortality. We tested the association between PaO₂ (continuous variable) and mortality using multivariable logistic regression adjusted for patient-oriented covariates and potential hospital effects. Of 4459 patients, 54% died. The median postresuscitation PaO₂ was 231 (interquartile range 149 to 349) mm Hg. Over ascending ranges of oxygen tension, we found significant linear trends of increasing in-hospital mortality and decreasing survival as functionally independent. On multivariable analysis, a 100 mm Hg increase in PaO₂ was associated with a 24% increase in mortality risk (odds ratio 1.24 [95% confidence interval 1.18 to 1.31]). We observed no evidence supporting a single threshold for harm from supranormal oxygen tension.

Conclusion—In this large sample of postresuscitation patients, we found a dose-dependent association between supranormal oxygen tension and risk of in-hospital death. (*Circulation*. 2011;123:2717-2722.)

Key Words: cardiac arrest ■ heart arrest ■ cardiopulmonary resuscitation ■ resuscitation ■ oxygen ■ emergency care

The most common lethal manifestation of cardiovascular disease is sudden cardiac arrest. Although emergency interventions, such as cardiopulmonary resuscitation (CPR) and defibrillation, may be successful in restarting the heart and restoring a pulse, the majority of resuscitated patients still do not survive. A primary contributor to death and disability in these resuscitated patients is the anoxic brain injury that typically follows a severe ischemia/reperfusion insult. To date, therapeutic hypothermia is the only proven treatment for anoxic brain injury after cardiac arrest.^{1–3} However, recent evidence suggests that, in addition to body temperature, the amount of oxygen delivered to the brain after reperfusion may represent an important and modifiable factor in postresuscitation care.

Clinical Perspective on p 2722

Supplemental oxygen is routinely administered during and after CPR. It is common to deliver supplemental oxygen in maximum concentrations during the resuscitative period, but

this strategy may not be innocuous. Numerous laboratory investigations have identified a paradox relative to oxygen delivery to the injured brain. Although it is intuitive that insufficient oxygen delivery can exacerbate cerebral anoxia, excessive oxygen delivery can also be harmful by exacerbating oxygen free radical formation and subsequent reperfusion injury.^{4–11} One large-scale clinical study has examined the relationship between excessive supplemental oxygen and outcome in postresuscitation patients.¹² Postresuscitation hyperoxemia exposure, defined as a partial pressure of arterial oxygen (PaO₂) ≥300 mm Hg, was found to be an independent predictor of in-hospital death. The mortality in patients with hyperoxemia was even higher than the mortality for patients with hypoxemia. Further, hyperoxemia was associated with lower likelihood of independent functional status among patients who survived to hospital discharge.

Important questions remain about hyperoxemia exposure after resuscitation from cardiac arrest and the risk of adverse

Received October 6, 2010; accepted April 4, 2011.

From the Department of Emergency Medicine (J.H.K., S.T.), Department of Medicine, Division of Critical Care Medicine (J.E.P., R.P.D., S.T.), and Biostatistics Group (B.M., K.H.), Cooper University Hospital, Camden, NJ; the Department of Emergency Medicine, Carolinas Medical Center, Charlotte, NC (A.E.J.); and the Department of Emergency Medicine and Center for Vascular Biology Research, Beth Israel Deaconess Medical Center, Boston, MA (N.I.S.).

Correspondence to Stephen Trzeciak, MD, MPH, Cooper University Hospital, One Cooper Plaza, D363, Camden, NJ 08103. E-mail trzeciak-stephen@cooperhealth.edu

© 2011 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.110.001016

outcome. One question is whether supranormal oxygen tension below such an extreme value (ie, 300 mm Hg) is associated with harm.¹³ It also remains unclear if the risk of adverse outcome is a threshold effect at a specific supranormal oxygen tension or is a dose-dependent relationship.¹⁴ Addressing these knowledge gaps is necessary to permit appropriate design of clinical trials to test the efficacy of a controlled reoxygenation therapeutic strategy (ie, rapid downward titration of supplemental oxygen administration after resuscitation). We undertook the present study to better define the relationship between supranormal oxygen tension and outcome in postresuscitation patients. We hypothesized that a linear dose-dependent relationship would be present in the association between supranormal oxygen tension and in-hospital mortality.

Methods

This study was a secondary analysis of a previously published multicenter cohort study.¹² We analyzed Project IMPACT (Cerner, Kansas City, MO), a large critical-care database initially developed by the Society of Critical Care Medicine and designed for intensive care units (ICUs) across all disciplines. The Institutional Review Board at Cooper University Hospital, Camden, NJ, approved this study.

Adult ICUs from 131 US hospitals participate in Project IMPACT, and data from >400 000 patients have been entered. Participating ICUs upload patient data to a central repository. Data fields include hospital and ICU organizational characteristics, admission source (eg, emergency department versus in-patient), demographics, physiological data (including vital signs and laboratory values), procedures performed, complications, length of stay, and outcomes. All data are collected by dedicated on-site personnel who must be trained and certified by Project IMPACT in advance, a process that includes passing a written certification examination to ensure uniformity in both database definitions and entry. On-site data collectors must also be certified by Project IMPACT as a prerequisite to collating and uploading data.

Study Settings and Patients

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

We included adult patients who sustained nontraumatic cardiac arrest and were admitted to the ICU at a participating center from 2001 to 2005. Inclusion criteria were (1) age >17 years, (2) nontrauma, (3) received CPR (defined as chest compressions or defibrillation) \leq 24 hours before ICU arrival, and (4) arterial blood gas analysis performed within the first 24 hours after ICU arrival. We excluded patients with hypoxia (defined as a PaO_2 <60 mm Hg) or severe oxygenation impairment (defined as a highest PaO_2 to fraction of inspired oxygen ratio <200¹⁵). We excluded these patients on the grounds that it is already well established that hypoxemia is associated with worse outcomes, and excluding these patients would permit us to focus the analysis on a population of patients in which oxygen exposure could potentially be reduced.

Data Collection

We abstracted the following variables: demographics, comorbidities, preadmission functional status, site of origin preceding 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, arterial blood gas analyses recorded over the first 24 hours in the ICU, life support interventions (eg, vasopressor use), and vital status at hospital discharge (alive/dead). We received the data in Access (Microsoft Corp, Redmond, WA) and exported it to SPSS version 16.0.2 (SPSS, Chicago, IL) for analysis.

Data Analysis

We present continuous data as mean (SD) or median and interquartile range (IQR) as appropriate on the basis of distribution of the data, and categorical data are reported as proportions and 95% confidence intervals (CIs) where applicable. We defined the exposure by the highest partial pressure of arterial oxygen (PaO_2) over the first 24 hours in the ICU. The primary outcome measure for this study was in-hospital mortality.

We used a 2-stage approach to test the relationship between supranormal oxygen tension and outcome. In the first stage, we assessed for the presence or absence of a single PaO_2 threshold of harm. We graphed the observed (ie, unadjusted) in-hospital mortality rates across ascending ranges of oxygen tension (PaO_2 60 to 99, 100 to 199, 200 to 299, 300 to 399, and \geq 400 mm Hg). We also graphed the observed proportion of patients discharged alive and functionally independent (defined as able to live at home requiring no assistance to complete activities of daily living) across the same ranges of oxygen tension. We visually inspected the data to assess if there was a clear single threshold of increased risk of adverse outcome over ascending PaO_2 ranges. We assessed for the presence of significant linear trends in the proportions of in-hospital mortality and functional independence over ascending PaO_2 ranges using the Armitage (modified χ^2) trend test.

In the second stage, we used a multivariable logistic regression model of relative risk of in-hospital mortality adjusted for patient-specific risk factors and PaO_2 as a continuous variable. This analysis used generalized estimating equations to account for potential hospital effects (ie, clustering of patients within hospitals). As shown in Tables 1 and 2, the model considered demographics, prearrest patient characteristics (eg, preadmission functional status [independent versus nonindependent]), comorbid conditions, site of origin preceding ICU admission (emergency department versus inpatient), time of admission to the ICU (day versus night), and postcardiac arrest physiological data (eg, arterial hypotension on ICU admission). For vital signs such as heart rate, we coded patients as being above or below the median for the entire cohort. We entered PaO_2 as a continuous variable in the regression model and calculated an OR for in-hospital death for PaO_2 that was calibrated for a rise in PaO_2 of 25 mm Hg. This provided a significance test, OR, and a 95% CI for the OR on the covariate of primary interest, increase in PaO_2 . Results summarize the effect adjusted for all other variables in the model. To further support the assumption of a linear effect of PaO_2 on mortality, we calculated ORs for in-hospital death using different increments of PaO_2 up to 100 mm Hg, and we graphed the ORs and 95% CIs for increasing PaO_2 increments.

To account for potential within-hospital correlation, we considered multiple alternatives to the independence assumption (ie, no association). We used the quasi-likelihood independence criterion to identify the covariance structure that provided the best fit of data to the model. An autoregressive pattern, reflecting decreasing correlation between risk factors and mortality with increasing number of eligible patients (hospital size) showed a slight improvement in the quasi-likelihood independence criterion residual as compared to the independence assumption, and was used as the working correlation matrix for model fit.

Results

Of the 6326 patients that met inclusion criteria, 1867 were excluded because of the presence of the exclusion criteria of hypoxia or severe oxygenation impairment, leaving 4459 patients in the study sample. The patients came from 120 different hospitals. The median number of cases per hospital was 30 (IQR 10 to 50). Baseline characteristics appear in Table 1. Patients were predominantly white and came from large community (nonacademic) hospitals. The most common comorbid condition was severe cardiovascular disease (eg, New York Heart Association class IV; $n=512$). Data pertaining to vital signs and life support interventions over the first 24 hours in the ICU appear in Table 2. Approximately half of

Table 1. Baseline Characteristics of the Study Patients and Hospital Characteristics

	All Patients (n=4459)
Age, y, mean (SD)	65 (16)
Female sex, n (%)	2099 (47)
Race, n (%)	
White	3308 (74)
Black	756 (17)
Latino/Hispanic	181 (4)
Asian/Pacific Islander	45 (1)
Other	169 (4)
Preadmission functional status, n (%) [*]	
Independent	2843 (64)
Partially dependent	974 (22)
Fully dependent	564 (13)
Chronic comorbidities, n (%)	
Severe cardiovascular disease†	512 (12)
Respiratory disease‡	491 (11)
End-stage renal disease	389 (9)
Hepatic cirrhosis (with portal hypertension)	104 (2)
Cancer with metastatic disease	168 (4)
Active chemotherapy	80 (2)
Acquired immune deficiency syndrome	29 (1)
Hematologic malignancy	16 (<1)
Site of origin immediately preceding ICU arrival, n (%)	
Emergency department	1988 (45)
Inpatient	2471 (55)
Time of ICU admission, n (%)	
Night, 23:00 to 06:59 hours	1238 (28)
Day or evening, 07:00 to 22:59 hours	3221 (72)
Hospital characteristics, n (%)	
Hospital size, n %	
Small to medium (<300 beds)	688 (15)
Large (301–500 beds)	1925 (43)
Extra large (>500 beds)	1846 (41)
Hospital type, n (%)	
Community, nonacademic	3555 (80)
Academic, university-based	775 (17)
Public	101 (2)
Military	28 (<1)
Hospital location, n (%)	
Urban	2307 (52)
Suburban	1444 (32)
Rural	708 (16)

^{*}Defined as: Independent, able to live at home requiring no assistance to complete activities of daily living; partially dependent, able to live at home, in a group home, or in a care facility and requiring some assistance to complete activities of daily living; the limitation(s) requiring assistance may be physical or mental; and fully dependent, able to live at home or in a care facility and unable to perform activities of daily living; must be cared for by others; the limitation(s) requiring assistance may be physical or mental.

†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, and severe cardiomyopathy.

‡Defined as chronic obstructive, restrictive, or vascular pulmonary disease resulting in severe exercise restriction, such as inability to climb stairs or perform household duties; respirator dependency related to active respiratory disease; or documented chronic hypoxia, hypercapnia, or pulmonary hypertension (>40mm Hg).

ICU indicates intensive care unit.

the patients were treated with vasopressor agents or combined vasopressor/inotropic agents (ie, phenylephrine, nor-epinephrine, epinephrine, or dopamine), and 8% were treated with a pure inotropic agent (ie, dobutamine). Ninety-eight percent of patients were on mechanical ventilation when the exposure variable (PaO₂) was measured.

The median postresuscitation PaO₂ among all patients was 231 (IQR 149 to 349) mm Hg. Overall, 2399/4459 (54%) of patients suffered the primary outcome of in-hospital death. Figure 1 displays the proportion of in-hospital deaths over ascending ranges of oxygen tension. The proportion of in-hospital deaths was 41% for patients with a PaO₂ in the range of 60 to 99 mm Hg, and rose to 65% for patients with a PaO₂ in the range ≥400 mm Hg. We observed no clear single threshold of increased risk of death over ascending PaO₂ ranges. In addition, we found a significant linear trend for the increase in mortality rates over ascending PaO₂ ranges ($P<0.0001$).

The proportion of patients who were discharged alive with independent functional status is also displayed in Figure 1. This proportion decreased over ascending ranges of oxygen tension, from 23% for patients with a PaO₂ in the range of 60 to 99 mm Hg to 9% for patients with a PaO₂ in the range ≥400 mm Hg. We found a significant linear trend for the decrease in functional independence over ascending PaO₂ ranges ($P<0.0001$).

Results of the multivariable logistic regression analysis using generalized estimating equations appear in Table 3. Odds ratios are presented for the 8 factors that were independently and significantly associated with increased risk of in-hospital death. These are: age, emergency department origin, nonindependent functional status preceding admission, chronic renal failure, active chemotherapy, higher than median heart rate, arterial hypotension on ICU arrival, and PaO₂. A 25 mm Hg increase in PaO₂ was associated with a 6% increase in relative risk of death (OR 1.06 [95% CI 1.05 to 1.07]). This effect is estimated independent of risks associated with all other factors included in the model. Figure 2 projects increases in mortality risk for different increments of rise in PaO₂. For example, a 100 mm Hg increase in PaO₂ was associated with a 24% increase in relative risk of death (OR 1.24 [95% CI 1.18 to 1.31]).

Discussion

In this large multicenter cohort study of patients admitted to an ICU after resuscitation from cardiac arrest, we identified a significant linear relationship between supranormal oxygen tension and risk of in-hospital death, consistent with a dose-dependent interpretation. The observed association between PaO₂ and mortality was adjusted for various patient-oriented covariates and potential hospital effects. We observed no evidence supporting a single threshold for harm from supranormal oxygen tension. These results differ from previously published data in human subjects resuscitated from cardiac arrest.¹² Using PaO₂ as a continuous variable in the multivariable logistic regression model, with generalized estimating equations, provided improved granularity in analyzing the relationship between supranormal oxygen tension and associated risk of death. We found that the association between supranormal oxygen tension and increased mortality was not limited to extreme oxygen tension values. A rela-

Table 2. Most Abnormal Vital Signs in the First 24 Hours in the ICU and Life Support Interventions

	All Patients (n=4459)
Temperature, high, °C, mean (SD)	37.9 (0.9)
Temperature, low, °C, mean (SD)	35.9 (1.2)
Heart rate, high, bpm, mean (SD)	117 (20)
Respiratory rate, high, breaths/min, mean (SD)	25 (6)
Systolic blood pressure, low, mm Hg, mean (SD)	86 (17)
Mean arterial pressure, low, mm Hg, mean (SD)	60 (12)
Hemodynamic support, n (%)	
Vasopressor agent*	2486 (56)
Dobutamine	365 (8)
Ventilator support,† n (%)	4355 (98)

*Defined as initiation of a continuous infusion of any of the following drugs: dopamine, norepinephrine, epinephrine, or phenylephrine.

†Indicates presence of mechanical ventilation when index arterial blood gas in the ICU was obtained.

ICU indicates intensive care unit.

tively small increase in PaO₂, 25 mm Hg, was associated with a 6% increase in relative risk of death. Relatively larger increases in PaO₂ projected larger increases in mortality risk. For example, a 100 mm Hg increase in PaO₂ was associated with a 24% increase in relative risk of death. Given that the median postresuscitation PaO₂ in this sample was 231 (IQR 149 to 349) mm Hg, it appears that a high proportion of adult patients resuscitated from cardiac arrest have exposure to supranormal oxygen tension. Considering the linear increase in risk of death associated with PaO₂, these results suggest a need for clinical trials of a controlled reoxygenation therapeutic strategy after resuscitation from cardiac arrest.

Patients resuscitated from cardiac arrest are subjected to global ischemia/reperfusion injury, with potentially devastating neurological consequences. There is ample preclinical experimental evidence that excessive supplemental oxygen adminis-

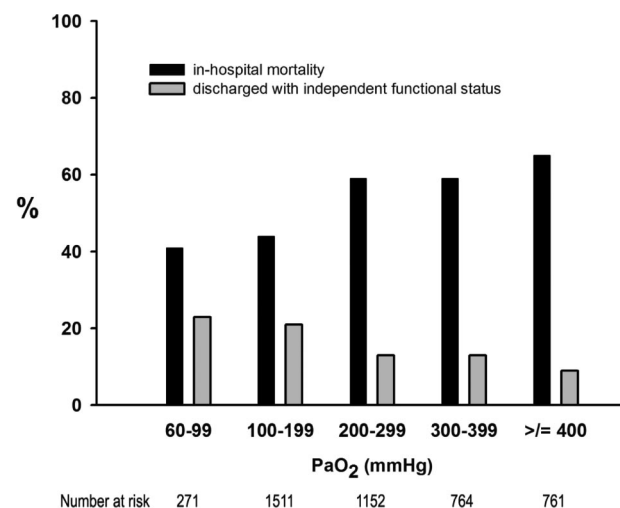


Figure 1. Oxygen tension and outcomes. Over ascending ranges of oxygen tension, we found significant linear trends of increasing in-hospital mortality and decreasing survival with functional independence (Armitage χ^2 trend $P<0.0001$). PaO₂ indicates partial pressure of arterial oxygen.

Table 3. Multiple Logistic Regression Model With In-Hospital Mortality as the Dependent Variable

Variable	OR [95% CI]	P
Age, decile	1.13 [1.10–1.16]	<0.001
Emergency department origin	1.35 [1.20–1.52]	<0.001
Nonindependent functional status on admission	1.15 [1.04–1.27]	0.008
Chronic renal failure	1.38 [1.17–1.63]	<0.001
Active chemotherapy	1.99 [1.23–3.23]	0.005
Heart rate in ICU, high*	1.63 [1.48–1.79]	<0.001
Arterial hypotension on ICU arrival†	1.56 [1.42–1.71]	<0.001
PaO ₂ , rise of 25 mm Hg	1.06 [1.05–1.07]	<0.001

Arterial partial pressure of oxygen is treated as a continuous variable in the model and the OR is calculated for an increase of 25 mm Hg in PaO₂. For example, for an increase in PaO₂ of 25 mm Hg, the relative risk of death rises on average by 6% (OR 1.06; 95% CI 1.05–1.07).

Covariates retained in the model but not meeting statistical significance (ie, $P<0.05$): Female sex (OR 1.08 [95% CI 0.98–1.20]; $P=0.131$); admission to the ICU at night (defined as 23:00–06:59 hours; OR 1.07 [95% CI 0.95–1.21]; $P=0.266$); chronic respiratory disease (OR 0.86 [95% CI 0.70–1.05]; $P=0.134$); and human immunodeficiency virus (OR 1.62 [95% CI 0.80–3.27]; $P=0.182$).

*Highest value for first 24 hours in ICU (1=exceeds median; 0=median or lower).

†Defined as systolic blood pressure <90 mm Hg within 1 hour of ICU arrival.

OR indicates odds ratio; CI, confidence interval; ICU, intensive care unit; and PaO₂, arterial partial pressure of oxygen.

tration after return of spontaneous circulation can worsen reperfusion injury in the brain.^{4–11} The major mechanisms for these deleterious effects include oxidative impairment of mitochondrial respiration, oxidation of brain lipids, and promotion of cellular inflammatory reactions, all of which are byproducts of a persistently hyperoxic environment that drives an increase in reactive oxygen species. Multiple clinically relevant animal models of global cerebral ischemia/reperfusion injury from

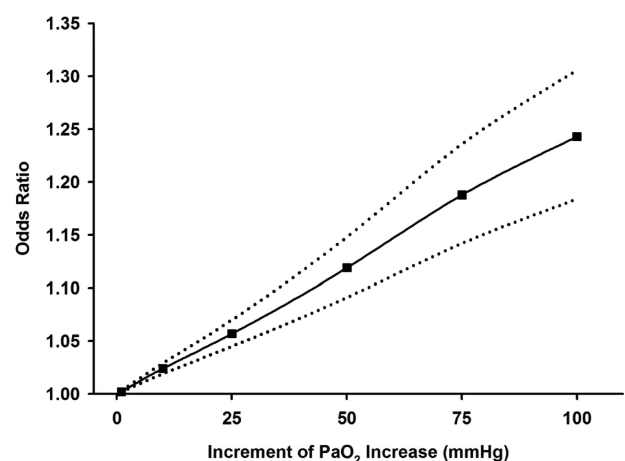


Figure 2. Odds ratios (square data points) for in-hospital death and associated 95% confidence intervals (dotted lines) for increments of rise in PaO₂. A 25 mm Hg increase in PaO₂ was associated with a 6% increase in relative risk of death (odds ratio, 1.06 [95% confidence interval, 1.05 to 1.07]). A 100 mm Hg increase in PaO₂ was associated with a 24% increase in mortality risk (odds ratio, 1.24 [95% confidence interval, 1.18 to 1.31]). The change of odds ratio for increasing values of PaO₂ assumes that all the other covariates in the model are constant. PaO₂ indicates partial pressure of arterial oxygen.

cardiac arrest demonstrate that excessive supplemental oxygen administration after resuscitation worsens neurological deficits,^{6,7,11} confirmed by brain histopathological changes,^{4,10} and worsens survival.⁸ The clinical data in this report support the concept that postresuscitation supranormal oxygen tension could also be harmful in human subjects.

We submit that the information in the present study has important implications for the future design of clinical trials of controlled reoxygenation after cardiac arrest. One concern about attempting to limit supplemental oxygen in the postresuscitation period has been related to safety and the possibility of precipitating hypoxic events,¹⁴ given that the majority of patients resuscitated from cardiac arrest do require some level of supplemental oxygen.¹² However, if only extreme values of supranormal oxygen tension (eg, PaO₂ of 300 mm Hg) were associated with adverse outcome, then perhaps a less aggressive approach to titrating FiO₂, one that would only aim to avoid extremes of oxygen tension rather than a marked reduction, would be an optimal therapeutic target for a clinical trial because of a lower likelihood of inducing hypoxic events. On the contrary, the present study indicates that there is a significant association between relatively small increments of supranormal oxygen tension and risk of poor outcome, suggesting that limiting supplemental oxygen as much as possible could be beneficial. Therefore, we submit that the recently postulated goal of an arterial oxygen saturation of 94% to 96%³ is in fact a reasonable therapeutic target for the design of clinical trials of controlled reoxygenation after cardiac arrest. In addition to testing the efficacy of this therapeutic strategy, rigorous clinical trials would be needed to test the safety of such an aggressive approach.¹⁴

We acknowledge important limitations. First, this was an observational study, and thus we can only identify association rather than causation. In addition, although the preponderance of laboratory data to date has been focused on brain injury, we acknowledge that hyperoxemia-induced exacerbation of reperfusion injury could also potentially affect other organ systems. The mode of death was not measured in our study, and thus we cannot comment on the relative contribution of brain injury to the outcome versus other potential organ system injuries. Another consideration is timing of the exposure. We defined the exposure on the basis of the highest PaO₂ value recorded in the first 24 hours after ICU admission, and thus it is possible that some of the oxygen tension measurements were not obtained early after reperfusion. Some laboratory data have supported the concept that exposure to supranormal oxygen tension immediately after return of spontaneous of circulation worsens reperfusion injury, whereas later exposure does not.¹⁶ However, we point out that if delayed oxygen tension measurements were included in our study this would bias the results toward the null (ie, no association with increased mortality). It is also important to recognize that we determined the presence of the exposure in this study but not the duration.

We also acknowledge that the ICU registry we used for this study was designed from a critical care perspective, and thus it does not capture variables in the typical Utstein format¹⁷ (eg, initial cardiac rhythm and no-flow time) specific to the cardiac arrest event that preceded the ICU admission. However, dedicated Utstein-style CPR registries may not include data on oxygen tension after return of spontaneous circula-

tion, and thus we submit that the ICU perspective makes this registry a valuable resource to study this topic. We also acknowledge that our study did not explicitly capture whether or not a therapeutic hypothermia strategy was attempted. However, only 6% of patients in this study 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. Given that multiple published practice surveys have indicated slow adoption of therapeutic hypothermia and low penetration into clinical practice in the United States during the time frame of this study, we are not surprised by the low proportion of patients with body temperature in the range of mild therapeutic hypothermia. We also acknowledge that our results are not adjusted for the arterial partial pressure of carbon dioxide (Paco₂) or pH. The relationship between Paco₂ and outcome is potentially confounded by the presence and/or degree of metabolic acidosis, and pH was not available for all subjects. We found no correlation between Paco₂ and PaO₂ (Pearson correlation coefficient = -0.0005; *P*=0.98). This indicates that the observed association between supranormal oxygen tension and outcome is not a function of collinearity with hypocarbia.

We also acknowledge that the ORs for increases in PaO₂ are only applicable to the range of PaO₂ values in the dataset. In addition, a number of potential subjects were excluded from this study because of hypoxia or severe oxygenation impairment. This was our a priori design, on the grounds that it avoided potential confounding over the presence and/or degree of acute lung injury in postresuscitation patients. Excluding these patients also permitted us to focus on a population of patients in which postresuscitation oxygen exposure could potentially be reduced.

Conclusions

In this large, representative sample of postresuscitation patients, we observed a linear dose-dependent relationship in the association between supranormal oxygen tension and relative risk of in-hospital mortality. We observed no evidence supporting a single threshold for harm from supranormal oxygen tension. Clinical trials are warranted to test the safety and efficacy of a controlled reoxygenation strategy as part of postcardiac arrest care.

Sources of Funding

The investigators' effort to this project was supported by a career development grant from the Emergency Medicine Foundation (to Dr Kilgannon), by grants from the National Institutes of Health/National Institute of General Medical Sciences (GM76652 to Dr Jones, GM076659 to Dr Shapiro, and GM83211 to Dr Trzeciak), and a grant from the National Institutes of Health, National Heart, Lung and Blood Institute (HL091757 to Dr Shapiro). No sponsor had a role in the design and conduct of the study; data collection, management, analysis, and interpretation; or preparation, review, and approval of the manuscript.

Disclosures

None.

References

1. Hypothermia After Cardiac Arrest (HACA) Investigators. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549–556.

2. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563.
3. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, Kern KB, Laurent I, Longstreth WT Jr, Merchant RM, Morley P, Morrison LJ, Nadkarni V, Peberdy MA, Rivers EP, Rodriguez-Nunez A, Sellke FW, Spaulding C, Sunde K, Vanden Hoek T. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication: a consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation*. 2008;118:2452–2483.
4. Danilov CA, Fiskum G. Hyperoxia promotes astrocyte cell death after oxygen and glucose deprivation. *Glia*. 2008;56:801–808.
5. Fiskum G, Danilov CA, Mehrabian Z, Bambrick LL, Kristian T, McKenna MC, Hopkins I, Richards EM, Rosenthal RE. Postischemic oxidative stress promotes mitochondrial metabolic failure in neurons and astrocytes. *Ann NY Acad Sci*. 2008;1147:129–138.
6. Hazelton JL, Balan I, Elmer GI, Kristian T, Rosenthal RE, Krause G, Sanderson TH, Fiskum G. Hyperoxic reperfusion after global cerebral ischemia promotes inflammation and long-term hippocampal neuronal death. *J Neurotrauma*. 2010;27:753–762.
7. Liu Y, Rosenthal RE, Haywood Y, Miljkovic-Lolic M, Vanderhoek JY, Fiskum G. Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome. *Stroke*. 1998;29:1679–1686.
8. Mickel HS, Vaishnav YN, Kempinski O, von Lubitz D, Weiss JF, Feuerstein G. Breathing 100% oxygen after global brain ischemia in Mongolian Gerbils results in increased lipid peroxidation and increased mortality. *Stroke*. 1987;18:426–430.
9. Richards EM, Fiskum G, Rosenthal RE, Hopkins I, McKenna MC. Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism. *Stroke*. 2007;38:1578–1584.
10. Vereczki V, Martin E, Rosenthal RE, Hof PR, Hoffman GE, Fiskum G. Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death. *J Cereb Blood Flow Metab*. 2006;26:821–835.
11. Zwemer CF, Whitesall SE, D'Alecy LG. Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerbates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs. *Resuscitation*. 1994;27:159–170.
12. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, Parrillo JE, Trzeciak S. Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010;303:2165–2171.
13. Kochanek PM, Bayir H. Titrating oxygen during and after cardiopulmonary resuscitation. *JAMA*. 2010;303:2190–2191.
14. Trzeciak S, Kilgannon JH, Jones AE. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. *JAMA*. 2010;304:1441.
15. Abraham E, Matthay MA, Dinarello CA, Vincent JL, Cohen J, Opal SM, Glauser M, Parsons P, Fisher CJ, Repine JE. Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: time for a reevaluation. *Crit Care Med*. 2000;28:232–235.
16. Rosenthal RE, Silbergleit R, Hof PR, Haywood Y, Fiskum G. Hyperbaric oxygen reduces neuronal death and improves neurological outcome after canine cardiac arrest. *Stroke*. 2003;34:1311–1316.
17. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, Cassan P, Coovadia A, D'Este K, Finn J, Halperin H, Handley A, Herlitz J, Hickey R, Idris A, Kloeck W, Larkin GL, Mancini ME, Mason P, Mears G, Monsieurs K, Montgomery W, Morley P, Nichol G, Nolan J, Okada K, Perlman J, Shuster M, Steen PA, Sterz F, Tibballs J, Timmerman S, Truitt T, Zideman D. International Liaison Committee on Resuscitation. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation*. 2004;110:3385–3397.

CLINICAL PERSPECTIVE

Historically, the administration of supplemental oxygen has been considered a cornerstone of cardiopulmonary resuscitation for victims of cardiac arrest. However, laboratory experiments and recent clinical data suggest that after a pulse is restored, excessive supplemental oxygen could be harmful. Supranormal oxygen tension can exacerbate oxygen free radical formation and subsequent reperfusion injury. However, it is unclear if the risk of poor outcome is a threshold effect at a specific supranormal oxygen tension, or is a dose-dependent association. The authors studied patients admitted to an intensive care unit after resuscitation from cardiac arrest at 120 US hospitals. After excluding patients with hypoxia, there were 4459 patients in the sample. The authors tested the association between postresuscitation arterial partial pressure of oxygen and in-hospital mortality. The median postresuscitation arterial partial pressure of oxygen was 231 (interquartile range 149–349) mm Hg. Fifty-four percent of the patients died. Over ascending ranges of oxygen tension, the authors found significant linear trends of increasing in-hospital mortality and decreasing survival as functionally independent. On multivariable analysis adjusted for patient-oriented covariates and potential hospital effects, a 100 mm Hg increase in postresuscitation arterial partial pressure of oxygen was associated with a 24% increase in relative risk of death. The authors observed no evidence supporting a single threshold for harm from supranormal oxygen tension. In this large sample of postresuscitation patients, the authors found that the association between supranormal oxygen tension and risk of in-hospital death is a linear dose-dependent relationship. These data provide further support that supranormal oxygen tension may be harmful in patients resuscitated from cardiac arrest.