Original

Crit Care & Shock (2015) 18:61-71

Hyperoxia is associated with higher case-fatality in ventilated patients with intra-cerebral hemorrhage

Fred Rincon, Matthew Vibbert, Jacqueline Urtecho, M. Kamran Athar, William McBride, Jack Jallo, Rodney Bell

Abstract

Objectives: To test the hypothesis that hyperoxia was associated with higher in-hospital case-fatality in ventilated patients with ICH admitted to the Intensive Care Unit (ICU).

Methods: Admissions of ventilated ICH patients within 24 hours of admission to the ICU at 77 United States hospitals between 2003-2008. Patients were divided into three exposure groups: hyperoxia (PaO2≥300 mmHg), hypoxia (PaO2<60 mmHg or PaO2/FiO2 ratio ≤300), and normoxia, not defined as hyperoxia or hypoxia. The primary outcome was in-hospital case-fatality.

Results: 1,388 ventilated ICH patients. Mean age 63 years (SD 15), 47% (653/1388) female, and median GCS 5 (IQR 3-8). The overall case-fatality was 59% (812/1388). Upon admission to the ICU, 36% (492/1388) were normoxic, 47% (641/1388) were hypoxic, and 17% (238/1388) were hyperoxic on ABGt1. ABGt2 was accomplished in 780 patients, of whom 46% (352/780) were normoxic, 45% (352/780) were hypoxic, and 9% (67/780) were hyperoxic. Of the initially admitted hyperoxic patients, 15% (21/138) remained hyperoxic and had a case-fatality of 82% (18/21) as compared to 49% (67/138) who became normoxic and had a case-fatality of 46% (32/67) (crude OR 6.6, 95%CI:1.8-25, χ^2=9.4, p=0.002). In a multivariable analysis controlling for other predictors of poor outcome and hospital specific characteristics, and a propensity-score, failure to correct hyperoxia was associated with higher case-fatality (adjusted OR 2.5, 95%CI:1.1-6.1, p=0.04).

Conclusion: In ventilated ICH patients, failure to normalize hyperoxia was associated with higher case-fatality. These data underscore the need for studies of controlled re-oxygenation in ventilated ICH patients.

Introduction

Intracerebral hemorrhage (ICH) causes 10-15% strokes annually in the United States. (1) Despite ongoing attempts to find effective therapies outcomes remain poor. (1,2) Because no interventions have consistently shown to improve mortality or functional outcomes after ICH, recent basic science research, adapted from models in cerebral ischemia, (3) have concentrated on studying the effects of normobaric hyperoxia (NBO) as a treatment modality for ICH. An animal model of NBO after ICH demonstrated that this therapy neither worsen nor improved outcomes in animals exposed to high oxygen concentrations. (4) One of the proposed mechanisms by which NBO would be beneficial in ICH is related to the ability of NBO to alter the expression of matrix metalloproteinases (MMPs), which are up-regulated in areas surrounding the hematoma. (5) A recent study demonstrated that the expression of MMP-9 could be blunted by NBO. (6) However, this was a model of ischemia-reperfusion and hemorrhagic transformation, not primary ICH. (6) A major concern with NBO therapy in ICH would be related to its potential to aggravate the oxidative stress in the surrounding hematoma. (7) In addition, the toxic effects of hyperoxia may extend to other organs, which may be of importance in critically-ill populations. In support of this statement is that observational studies

From Thomas Jefferson University, Philadelphia, USA (Fred Rincon, Matthew Vibbert, Jacqueline Urtecho, M. Kamran Athar, William McBride, Jack Jallo, and Rodney Bell).

Address for correspondence:
Fred Rincon, MD, MSc, MB.Ethics
Division of Critical Care and Neurotrauma
909 Walnut Street, 3rd Floor
Philadelphia, PA 19107, USA
Tel: 215-503-7000
Fax: 215-503-7007
Email: fred.rincon@jefferson.edu

have shown an association between unnecessary hyperoxia exposure and poor outcome in stroke patients. (8-10)

Currently, there is no observational data in regards to the effect of oxygenation and ventilation strategies for ventilated ICH patients. In a preliminary study, we demonstrated that hyperoxia upon admission to the ICU was a frequent occurrence and associated with higher case-fatality in ventilated stroke patients. (10) In this follow-up study, we tested the hypothesis that failure to normalize the PaO2 and/or PaO2/FiO2 ratios in hyperoxic ventilated ICH patients would be associated with higher case-fatality.

Methods

Retrospective multi-center cohort study from prospectively collected and compiled data: the Project IMPACT (Cerner Corporation - Project IMPACT [PI], Bel Air, MD). Our methodology and description of the PI repository has been reviewed elsewhere. (11) Briefly, primary admissions of ventilated ICH patients older than 17 years at 77 US hospitals between 2003-2008.

The following variables were recorded for all patients admitted to the ICU: emergency department (ED) boarder status, demographic variables, comorbidities, most abnormal physiological parameters, and admission and hospital discharge status (alive independent, alive partially dependent, alive fully dependent, or dead) (**Table 1**). (10,11) To assess for the effect of medical complications on in-hospital mortality, we collected data on organ dysfunctions during the ICU stay according to the definitions of PI (**Table 1**). (10,11) Hospitals were divided by hospital location into urban, sub-urban, and rural; by type into community (nonacademic), academic (university-based), and public; and according to the Halpern criteria (12) into small to medium size (<300 beds), large (301-499 beds), and extra large (>500 beds). Specific data on the National Institutes of Health Stroke Scale (NIHSS), the ICH Score, or admission imaging was not available from the PI repository. We defined hyperoxia as PaO2≥300 mmHg (39.99 kPa), hypoxia as any PaO2<60 mmHg (7.99 kPa) or PaO2/FiO2 ratio ≤300, and normoxia, not hyperoxia or hypoxia (11,13) in any of first time arterial blood gas (ABGt1) or follow-up ABG (ABGt2). The primary outcome measure was in-hospital case-fatality.

Continuous data are presented as means and standard deviations (SD) or medians and interquartile ranges (IQRs) as appropriate based on distribution of the data; categorical data are reported as proportions and percentages or 95% confidence intervals (CIs). The primary outcome for the cohort as a whole was compared between exposed groups using the χ^2 test for the difference in proportions. We then calculated odds ratios (OR) and 95% CI. For days to primary outcome analysis, Kaplan-Meier survival estimates and log-rank tests were used to compare the exposure groups of interest. In a multivariable analysis, generalized estimating equations (GEE) were used to account for potential correlation in mortality rates among patients sampled within hospital clusters. We also performed a sensitivity analysis using propensity scores to test if hyperoxia remained a significant independent predictor of in-hospital case-fatality. (11,14) We fitted a logistic regression model with potential candidate variables and hyperoxia as the dependent variable. The results of our logistic regression model were used to calculate each subject's probability of being exposed to hyperoxia. The probability (i.e. propensity score) for each subject was then added to our GEE model. Finally, we tested for possible first-order interactions in those variables retained in the model. Statistical analyses were conducted using SPSS software version 20.0 (SPSS Inc., Chicago, Illinois), significance was judged when $p<0.05$. Our reporting of observational data conforms with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. (15) Based on the de-identified nature of the database, the study was exempt from full IRB review.

Results

The cohort consisted of 1,388 ventilated ICH patients. Mean age 63 years (SD 15), 47% (653/1388) were female, median GCS 5 (IQR 3-8), and primarily from hospitals in urban locations. All ICUs were non-neurological/neurosurgical models. At least 79% (1068/1388) of patients were independent at hospital admission and only 6% (83/1388) had DNR orders. The proportion of DNR orders upon admission to the ICU was higher in the non-survivor group. Additional characteristics of the cohort are presented in **Table 1**.

There were no differences in relation to hypocarbia, either on ABGt1 or ABGt2, though non-survivors tended to have higher rates of hypocarbia on ABGt1 (**Table 2**). Additional predictors of case-fatality at the univariate level were MAP<60 mmHg, fever, and hypothermia upon admission to the ICU (**Table 2**).

The overall case-fatality was 59% (812/1388). Upon admission to the ICU, 36% (492/1388) were normoxic, 47% (641/1388) were hypoxic, and 17%

(238/1388) were hyperoxic on ABGt1. ABGt2 was accomplished in 780 patients, of whom 46% (361/780) were normoxic, 45% (352/780) were hypoxic, and 9% (67/780) were hyperoxic. Of the initially admitted hyperoxic patients, 15% (21/138) remained hyperoxic and had a case-fatality of 82% (18/21) as compared to 49% (67/138) who became normoxic and had a case-fatality of 46% (32/67) (crude OR 6.6, 95%CI:1.8-25, χ^2=9.4, p=0.002). Of initially admitted normoxic patients, 8% (21/266) became hyperoxic and had a case fatality of 57% (12/21) as compared to 74% (197/266) who remained normoxic and had a case fatality of 50% (100/197) (crude OR 1.3, 95%CI:0.5-3.3, χ^2=0.3, p=0.6). Of the initially admitted hypoxic patients, 6% (22/365) became hyperoxic and had a case-fatality of 81% (18/22) as compared to 23% (85/365) who became normoxic and had a case fatality of 51% (43/85) (crude OR 4.5, 95%CI:1.4-14, χ^2=6.9, p=0.008). The case-fatality of hypoxic patients that remained hypoxic was 64% (164/258) (**Figure 1**). On Kaplan-Meier analysis, the proportion of survivors at 28-days was significantly higher in the initially admitted hyperoxic patients who became normoxic (**Figure 2**). There was no difference between normoxic patients who remained normoxic and those normoxic patients who became hyperoxic (**Figure 2**).

In our sensitivity analysis, the following variables were predictors of hyperoxia exposure in ventilated ICH patients: GCS<8, GCS 8-12, admission to non-small or non-medium to large hospital size. No other variables were significantly associated with hyperoxia exposure (**Table 3**). In a multivariable GEE analysis controlling for, other predictors of poor outcome and hospital specific characteristics, and a propensity-score, failure to correct hyperoxia was associated with higher case-fatality (adjusted OR 2.5, 95%CI:1.1-6.1) (**Table 4**). These data indicate that failure to correct hyperoxia remained a significant independent predictor of death when adjusted for the probability of being exposed to hyperoxia. Additional factors associated with higher case-fatality were non-rural hospital admission, comorbid conditions, male sex, DNR status, GCS<8, MAP<60 mmHg, anemia, absence of ICP monitor, organ dysfunction in the ICU, and hypoxia (**Table 4**). We did not observe significant interactions in the variables retained in the GEE model.

Discussion

In this large multi-center cohort study of ventilated ICH patients, we have demonstrated that failure to correct admission hyperoxia was associated with higher in-hospital case-fatality. The effect is robust and independent of other factors associated with poor outcome including patient specific factors, hospital characteristics, and the probability of being exposed to hyperoxia. To our knowledge, this is the first observational study reporting the association between failure to normalize hyperoxia upon admission to the ICU and in-hospital case-fatality in this specific patient population, which differs from results of prior observational studies in non-medical and stroke populations. (16,17) Though our findings do not necessarily imply causation, our data support the notion that hyperoxia and failure to achieve normoxia in ventilated ICH patients, may have potential effects on in-hospital mortality. To this end, in the absence of effective therapies and meaningful outcomes in ICH, oxygenation and ventilation strategies represent an area of further research.

In a preliminary study, we demonstrated that the occurrence of hyperoxia was as high as 1:4 ventilated stroke patients admitted to the ICU and associated with higher case-fatality. (10) Our data shows that those patients in whom hyperoxia was not normalized in the ICU, therefore may have had a longer exposure time, carried the highest case-fatality as compared to hyperoxic patients that became normoxic (**Figure 2**). In support of this concept, we also found that normoxic patients that became hyperoxic did not have a significant difference in case-fatality. Unfortunately, because the PI database does not time-stamp ABG data, we can't precisely determine the exposure time required to increase this risk. Nevertheless, our data shows that hypoxic, hyperoxic, and normoxic patients that became or remained normoxic had the lowest case fatality. Of note, hypoxic patients that became hyperoxic also had a higher case-fatality (**Figure 1**). These observations suggest that hyperoxia in ventilated ICH patients, may represent a target amenable to simple correction in the ICU.

Animal studies of NBO and hyperbaric oxygen (HBO) in different models of brain injury have shown encouraging results. (3,4,18,19) Effects of NBO or HBO in these animal models are related to reduction of ischemic lesions, (3) preservation of neuronal integrity, (18) and reduction of oxidative stress. (19) An animal model of ICH, however, showed neither improvement nor worsening of outcomes related to the use of NBO. (4) Blunting the expression of MMPs, have been advocated as one of the mechanisms by which NBO may offer a beneficial effect in ICH. Several studies have shown that MMPs are up-regulated in areas surrounding the hematoma. (5) The harmful effects of MMPs are manifested by triggering of apoptotic

cellular responses, which result from cell detachment and loss of integrin signaling. (20) These effects are reduced by treatment with an endogenous inhibitor of MMPs, the tissue inhibitor of metalloproteinase (TIMP). (5) A recent study also demonstrated that the expression of MMP-9 could be blunted by NBO. (6) However, whether MMPs and TIMPs directly influence neuronal survival in ICH is still unclear. Other animal models of cerebral ischemia have shown some short-term beneficial effect of NBO as well. (3) The main concern of NBO, however, is its ability to increase oxidative stress leading to neuronal injury. (21-23) Though some studies have not found significant increase in oxidative stress in animal models of cerebral ischemia (3) or sub-arachnoid hemorrhage, (19) worsening of oxidative stress has been reported in animal models of ICH, particularly in areas surrounding the hematoma. (7) Considering the effects of NBO on oxidative stress alone may be over-simplistic, particularly because critically-ill patients are far more complex, and the effects of NBO may extend to other organs beyond the brain.

Studies in healthy subjects have shown that hyperoxia is associated with a decrease in cerebral blood flow. (24,25) It is possible that in brain injury, high oxygen concentrations are associated with decrease in delivery of oxygen as well. (26) Observational studies in critically-ill non-brain-injured patients, have demonstrated that hyperoxia is also associated with higher morbidity and mortality. (27) Excessive oxygen concentrations may be deleterious for cardiac output, peripheral vascular resistances, cerebrovascular flow, and lung function. (26,28) The vasoconstricting effects of hyperoxia or hyperoxia-induced hypocapnia may not be widely recognized as potential adverse effects in brain injured patients. (29,30) If cerebral perfusion decreases more than arterial oxygen content increases during hyperoxia exposure, then regional oxygen delivery may also decrease. This mechanism, and not just that attributed to reactive oxygen species, may contribute to the worse outcomes in ICH patients that may routinely be exposed to hyperoxia. (31)

At the clinical level, NBO therapy was associated with partial improvement in ischemic lesions seen in magnetic resonance imaging (MRI) but without meaningful effect on outcomes. (32,33) The National Institute of Neurological Disorders and Stroke (NINDS) sponsored NBO Therapy in Acute Ischemic Stroke Trial was terminated in 2009 after 85 patients with AIS were enrolled. Although an external safety monitoring board considered the excess mortality to be unrelated to NBO, these results are important as this was the largest randomized clinical trial investigating NBO as a treatment for AIS with negative results. (33)

There is currently no data on the use of NBO in patients with ICH. Our results suggest that hyperoxia may be associated with poorer outcomes in ventilated ICH patients. Our data also adds to the growing body of literature suggesting that unnecessary excess oxygen may cause adverse effects in critically-ill patients. (8-11,33,34) Though it is possible that NBO or HBO may have a role in the treatment of specific types of brain injury, (35) careful patient selection, timing, and appropriate dosing may need to be further determined.

The strengths of our study are related to the methodology used to test our hypothesis, the multicenter basis of the cohort ascertainment, and our sensitivity analysis to investigate our internal validity. We also acknowledge the limitations of this study. First, our analysis is observational in nature, limiting the inferences that can be made about causal relationships. Second, the inherent nature of the database used to perform our analysis, which was designed from an ICU perspective rather than to collect prospective data and endpoints specific to outcome research related to ICH. This suggests the possibility of some residual confounding. Specifically, we were not able to determine the characteristics of ICH or onset of hematoma growth based on imaging. However, our multivariable analysis is robust and included classic factors that have been associated with poor outcome in ICH such as age, sex, comorbid conditions, GCS, DNR status, ED boarder status, and organ dysfunctions (including coagulopathy) among others. Third, our study used a priori definitions of hyperoxia as suggested by animal (13) and observational studies. (11) Though our study suggests an effect of hyperoxia on in-hospital case-fatality, we were unable to define the precise PaO2 level at which the maximal risk for death would occur. We were also unable to explore the time of exposure to hyperoxia as ABGs in PI were not time-stamped. Fourth, we could not examine or link case-fatality data beyond the hospital admission, which may be more important for public health. Fifth, we did not know the attributable cause of death, which would have explained the effect of hyperoxia on case-fatality based on specific organ dysfunctions. Sixth, our data are limited by the quality of the PI repository. The advantages of our robust sample size are potentially offset by our inability to audit the data elements. Seventh, our analysis may have been subjected to selection bias in the sense that our sample may not be representative of the whole

population of ICH or ICUs in the United States. Specifically, we included ventilated ICH patients for which our case-fatality was higher than overall ICH in-hospital mortality, (2) so our results should be interpreted with this in mind. Finally, because the study focuses on non-neurological/neurosurgical ICUs in the United States, our results may not be generalizable to other settings where management of ventilated ICH patients and patient characteristics may differ substantively.

In summary, ventilated ICH patients admitted to the ICU, arterial hyperoxia was independently associated with higher case-fatality. These results underscore the need for studies and clinical trials of controlled re-oxygenation in ventilated critically-ill ICH patients. In the absence of results from clinical trials, unnecessary oxygen delivery should be avoided in ventilated ICH patients.

Acknowledgements

Dr. Rincon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors would like to thank Andrew Kramer, PhD and the Cerner Corporation for permitting access to the Project IMPACT database. Neither funding sources nor Cerner Corporation had a role in the design of this study or in the decision to submit it for publication.

Sources of funding

Dr. Rincon has received salary support from the American Heart Association (AHA 12CRP12050342).

Dr. Jallo has received grant support from the Department of Defense (DOD#110398).

Disclosures and conflicts of interest

Dr. Rincon has received non-financial research support from the Cerner Corporation.

Table 1. Demographic characteristics of the cohort of ventilated ICH patients

Characteristics	Total	Survivor	Non-survivor	p
	(N=1388)	(N=576)	(N=812)	
Age, mean (SD), years	63 (15)	60.2 (15)	63.6 (14)	<0.0001
Female, N (%)	742 (53)	307 (53)	435 (53)	0.9
Race/ethnicity, white (N=1338), N (%)	949 (71)	388 (70)	561 (72)	0.2
[a]Pre-admission functional status				0.0005
Independent	1068 (79)	468 (83)	600 (77)	
Partially dependent	140 (10)	61 (11)	79 (10)	
Fully dependent	138 (10)	37 (7)	101 (13)	
DNR/No CPR/limited intervention	83 (6)	12 (2)	71 (8)	<0.0001
ED boarder	65 (5)	25 (4)	40 (5)	0.6
Hospital size, N (%)				0.5
Extra large	612 (44)	244 (42)	368 (45)	
Large	661 (48)	324 (56)	471 (58)	
Small to medium	115 (8)	41 (7)	46 (6)	
Hospital location, N (%)				0.02
Urban	898 (65)	357 (62)	541 (67)	
Sub-urban	258 (19)	102 (18)	156 (19)	
Rural	232 (17)	117 (20)	115 (14)	
Hospital type, N (%)				0.5
Academic	506 (36)	211 (37)	295 (36)	
Community non-academic	795 (57)	324 (56)	471 (58)	
Public	87 (6)	41 (7)	46 (6)	
Glasgow Coma Scale, N (%)				<0.0001
GCS<8	1039 (75)	315 (55)	724 (89)	
GCS 8-12	205 (15)	150 (26)	55 (7)	
GCS>12	144 (10)	111 (19)	33 (4)	
Median (IQR)	5 (3-8)	7 (5-11)	4 (3-6)	<0.0001
[b]Comorbidities, >1, N (%)	186 (13)	69 (12)	117 (14)	0.2
[c]Organ dysfunction, >1, N (%)	638 (46)	216 (38)	422 (52)	<0.0001
ICP monitor (N=1378), N (%)	432 (31)	233 (41)	199 (25)	<0.0001

Legend: Data presented as N (%), mean (SD); DNR=do not resuscitate; CPR=cardio-pulmonary resuscitation; GCS=Glasgow Coma Scale; ICP=intracranial pressure; ED=Emergency Department.
[a] the definition of functional status in the PI database is: independent (the patient is living at home requiring no assistance in completing activities of daily living, which includes people who are homeless, or who are incarcerated, but otherwise physically and mentally functional); partially dependent (the patient is living at home, in a group home or in a care facility and requires some assistance in completing the activities of daily living and the limitation(s) requiring assistance may be physical or mental); and fully dependent (the patient is living at home or in a care facility and is unable to perform the activities of daily living; must

be cared for by other(s); the limitations requiring assistance may be physical or mental).
[b] co-morbidities: cardiovascular disease (defined as baseline symptoms such as angina or shortness of breath at rest or on minimal exertion, NYHA class IV, plus one or more of the following diagnoses: severe coronary artery disease, severe valvular heart or severe cardiomyopathy), respiratory disease (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 mmHg), cirrhosis, chronic renal disease or end-stage renal disease, human immunodeficiency virus (HIV) status, and cancer.
[c] organ dysfunction in ICU: cardiovascular (systolic blood pressure [SBP] <90 mmHg, or MAP <70 mmHg, or vasopressor requirement to keep SBP >90 mmHg or MAP >70 mmHg, and duration >1 hr), metabolic (lactic acidosis >2.0 mmol/dL), respiratory (acute lung injury [ALI] PaO2/FiO2≤300 [39.99 kPa] or PEEP>5 cmH2O), renal (serum creatinine [Cr] increased >1 mg/dL from baseline despite fluid resuscitation or Cr >2 mg/dL regardless of baseline), hepatic (acute elevation of serum bilirubin >2 mg/dL), hematologic (platelet count <100,000/mm3 or PT/PTT >1.5 times baseline), and neurologic (onset delirium or Glasgow Coma Scale <12).

Table 2. Significant physiological and laboratory characteristics of ventilated ICH patients upon admission to the ICU

Characteristics	Total (N=1388)	Survivor (N=586)	Non-survivor (N=812)	p value
PaCO2<35 mmHg ABGt1	465 (50)	172 (46)	293 (52)	0.09
PaCO2<35 mmHg ABGt2	286 (49)	112 (47)	174 (50)	0.4
MAP≥120 mmHg	620 (45)	253 (45)	367 (45)	0.6
MAP<60 mmHg	370 (27)	85 (15)	285 (35)	<0.0001
Fever (temp >37.5 °C)	403 (29)	146 (25)	257 (32)	0.008
Hypothermia (temp <36.0 °C)	379 (28)	112 (19)	267 (33)	<0.0001
Anemia (Ht<30%)	275 (21)	100 (18)	175 (24)	0.006
Arterial pH (ABG) (<7.35 or >7.45)	526 (56)	198 (53)	328 (58)	0.1

Legend: Data presented as N (%). PaCO2=partial arterial pressure of CO2; ABG=arterial blood gas; MAP=mean arterial pressure; Ht=hematocrit.

Table 3. Multivariable analysis of factors associated with exposure to hyperoxia in ventilated ICH patients upon admission to the ICU

Variable	OR	Low	High	p value
Glasgow coma scale (ref. GCS>12)				
• GCS<8	1.6	1.01	2.9	0.04
• GCS 8-12	1.9	1.03	3.7	0.03
Hospital size (ref. extra-large)				
• Large	0.6	0.3	0.9	0.04
• Small-medium	0.6	0.4	0.9	0.01

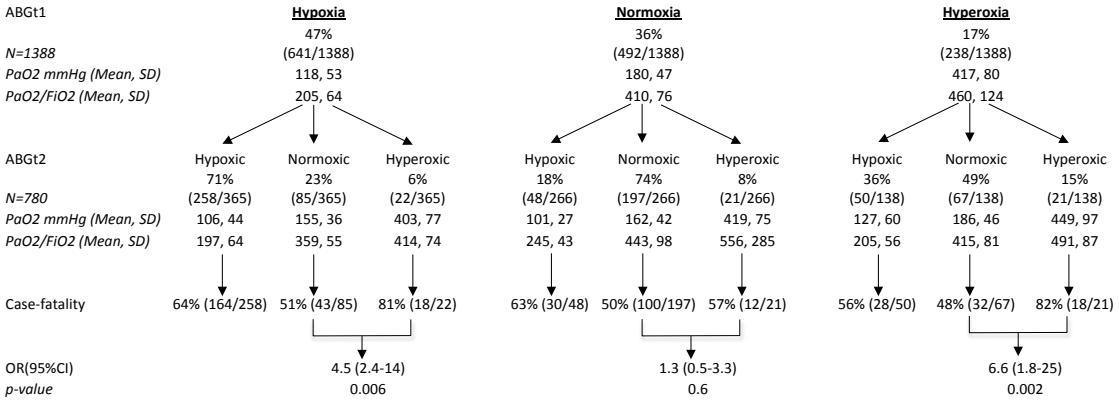
Legend: GCS=Glasgow coma scale.
Model also adjusted for the following variables: female sex (OR 0.7, 95%CI:0.5-1.0), non-white race (OR 1.2, 95%CI:0.8-1.7), ABGt1 hypocarbia (OR 0.8, 95%CI:0.6-1.1) or ABGt1 hypercarbia (OR 1.1, 95%CI:0.6-1.8), MAP<60 mmHg (OR 0.8, 95%CI:0.6-1.2), MAP>120 mmHg (OR 0.9, 95%CI:0.6-1.2), anemia (OR 0.9, 95%CI:0.6-1.4), which were removed from the table based on non-significant p values.

Table 4. Multivariable analysis of factors associated with in-hospital mortality in ventilated ICH patients upon admission to the ICU

Variable	OR	Low	High	p
Hospital location (ref. urban)				
• Sub-urban	0.8	0.4	1.5	0.6
• Rural	0.5	0.2	0.9	0.01
Sex, female	0.4	0.3	0.7	<0.0001
Co-morbidities (ref. none)				
• One	1.2	0.6	2.6	0.6
• Two or more	25.3	6.1	106.2	<0.0001
DNR order	4.2	1.5	12.2	0.008
Glasgow Coma Scale (ref. GCS>12)				
• GCS<8	21.2	8.0	60.1	<0.0001
• GCS 8-12	2.4	0.9	7.1	0.1
Admission MAP (ref. normotension)				
• MAP>120 mmHg	1.2	0.9	1.7	0.5
• MAP<60 mmHg	2.0	1.4	3.1	0.003
Anemia (Ht<30%)	1.9	1.1	3.5	0.02
ICP monitor placement	0.5	0.3	0.7	0.003
Organ dysfunction (ref. none)	1.7	1.1	2.5	0.04
Oxygen exposure (ref. normoxia)				
• Hyperoxia ABGt2 (PaO2≥300 mmHg)	2.5	1.1	6.1	0.04
• Hypoxia ABGt2 (PaO2<60 mmHg or PaO2/FiO2<300)	1.9	1.2	3.3	<0.0001
Probability of hyperoxia exposure (per quintile)	1.3	1.01	1.6	0.04

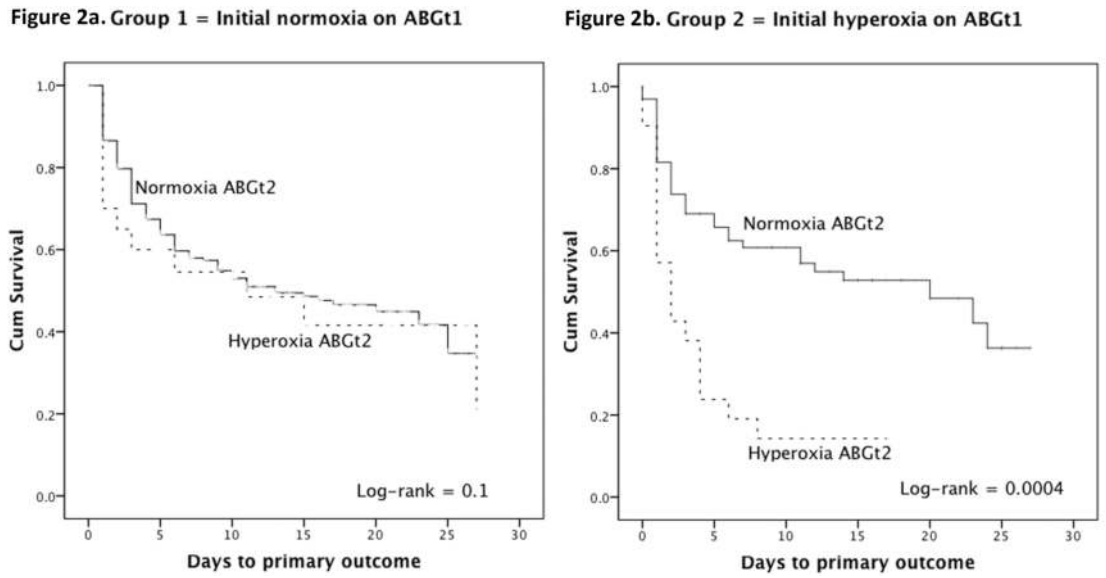
Legend: DNR=do not resuscitate; GCS=Glasgow Coma Scale; MAP=mean arterial pressure; ICP=intracranial pressure; ABG=arterial blood gas.
Model also adjusted for the following variables: age (OR 1.01, 95%CI:1.0-1.02), non-white race (OR 1.1, 95%CI:0.7-1.7), fully dependent admission status (OR 1.7, 95%CI:0.9-3.1), ED boarder status (OR 0.7, 95%CI:0.3-1.6), hospital type (community non-academic [OR 0.8, 95%CI:0.5-1.4], public [OR 1.1, 95%CI:0.8-1.6]), and hospital size (small [OR 1.1, 95%CI:0.8-1.5]; large [OR 0.8, 95%CI:0.4-1.9]), hypothermia (OR 1.6, 95%CI:1.0-2.6) and fever (OR 0.6, 95%CI:0.4-1.0) on admission to ICU, abnormal pH (arterial pH<7.35 or >7.45 [OR 0.9, 95%CI:0.6-1.3]), ABGt1 hypoxia (OR 1.3, 95%CI:0.6-1.5) or ABGt1 hyperoxia (OR 1.1, 95%CI:0.7-1.7), which were removed from the table based on non-significant p values. We used generalized estimated equations (GEE) under a robust estimation technique assuming an independent working correlation matrix.

Figure 1. Breakdown of exposure groups based on ABGt1 and ABGt2



Legend: For comparison of the primary end-point (case-fatality), we adjusted our p value using a Bonferroni correction. In this case, for three exposure groups or three pair-wise comparisons, a p value of less than 0.05÷3 or 0.017 was judged as significant.

Figure 2. Kaplan-Meier analysis of 28-day case-fatality between hyperoxia and normoxia on ABGt2 stratified by ABGt1



Legend: Group 1=Initial normoxia evidenced on ABGt1; Group 2=Initial hyperoxia on ABGt1.
There is no significant difference in survival in those normoxic patients that became hyperoxic. Those hyperoxic patients on ABGt1 that remained hyperoxic on ABGt2 had lower survival (log-rank=0.0004).

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125:e2-e220.
2. Rincon F, Mayer SA. The Epidemiology of Intracerebral Hemorrhage in the United States from 1979 to 2008. Neurocrit Care 2013;19: 95-102.
3. Singhal AB, Wang X, Sumii T, Mori T, Lo EH. Effects of normobaric hyperoxia in a rat model of focal cerebral ischemia-reperfusion. J Cereb Blood Flow Metab 2002;22:861-8.
4. Fujiwara N, Mandeville ET, Geng X, Luo Y, Arai K, Wang X, et al. Effect of normobaric oxygen therapy in a rat model of intracerebral hemorrhage. Stroke 2011;42:1469-72.
5. Power C, Henry S, Del Bigio MR, Larsen PH, Corbett D, Imai Y, et al. Intracerebral hemorrhage induces macrophage activation and matrix metalloproteinases. Ann Neurol 2003; 53:731-42.
6. Sun L, Zhou W, Mueller C, Sommer C, Heiland S, Bauer AT, et al. Oxygen therapy reduces secondary hemorrhage after thrombolysis in thromboembolic cerebral ischemia. J Cereb Blood Flow Metab 2010;30:1651-60.
7. Nakamura T, Keep RF, Hua Y, Hoff JT, Xi G. Oxidative DNA injury after experimental intracerebral hemorrhage. Brain Res 2005; 1039:30-6.
8. Rusyniak DE, Kirk MA, May JD, Kao LW, Brizendine EJ, Welch JL, et al. Hyperbaric oxygen therapy in acute ischemic stroke: results of the Hyperbaric Oxygen in Acute Ischemic Stroke Trial Pilot Study. Stroke 2003;34:571-4.
9. Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. Stroke 1999;30:2033-7.
10. Rincon F, Kang J, Maltenfort M, Vibbert M, Urtecho J, Athar MK, et al. Association between hyperoxia and mortality after stroke: a multicenter cohort study. Crit Care Med 2014; 42:387-96.
11. Rincon F, Kang J, Vibbert M, Urtecho J, Athar MK, Jallo J. Significance of arterial hyperoxia and relationship with case fatality in traumatic brain injury: a multicentre cohort study. J Neurol Neurosurg Psychiatry 2014;85:799-805.
12. Halpern NA, Pastores SM, Thaler HT, Greenstein RJ. Changes in critical care beds and occupancy in the United States 1985-2000: Differences attributable to hospital size. Crit Care Med 2006;34:2105-12.
13. Douzinas EE, Patsouris E, Kypriades EM, Makris DJ, Andrianakis I, Korkolopoulou P, et al. Hypoxaemic reperfusion ameliorates the histopathological changes in the pig brain after a severe global cerebral ischaemic insult. Intensive Care Med 2001;27:905-10.
14. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res 2011;46:399-424.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-7.
16. Eastwood G, Bellomo R, Bailey M, Taori G, Pilcher D, Young P, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. Intensive Care Med 2012;38:91-8.
17. Young P, Beasley R, Bailey M, Bellomo R, Eastwood GM, Nichol A, et al. The association between early arterial oxygenation and mortality in ventilated patients with acute ischaemic stroke. Crit Care Resusc 2012;14:14-9.
18. Wang GH, Zhang XG, Jiang ZL, Li X, Peng LL, Li YC, et al. Neuroprotective effects of hyperbaric oxygen treatment on traumatic brain injury in the rat. J Neurotrauma 2010;27: 1733-43.
19. Ostrowski RP, Colohan AR, Zhang JH. Neuroprotective effect of hyperbaric oxygen in a rat model of subarachnoid hemorrhage. Acta Neurochir Suppl 2006;96:188-93.
20. Felberg RA, Grotta JC, Shirzadi AL, Strong R, Narayana P, Hill-Felberg SJ, et al. Cell death in experimental intracerebral hemorrhage: the "black hole" model of hemorrhagic damage. Ann Neurol 2002;51:517-24.
21. Haelewyn B, Chazalviel L, Nicole O, Lecocq M, Risso JJ, Abraini JH. Moderately delayed post-insult treatment with normobaric hyperoxia reduces excitotoxin-induced neuronal degeneration but increases ischemia-induced brain damage. Med Gas Res 2011;1:2.
22. Mickel HS, Vaishnav YN, Kempski 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;18:426-30.
28. Yusa T, Beckman JS, Crapo JD, Freeman BA. Hyperoxia increases H2O2 production by brain in vivo. J Appl Physiol (1985) 1987;63:353-8.
29. Johnston AJ, Steiner LA, Gupta AK, Menon DK. Cerebral oxygen vasoreactivity and cerebral tissue oxygen reactivity. Br J Anaesth 2003;90:774-86.
30. Floyd TF, Clark JM, Gelfand R, Detre JA, Ratcliffe S, Guvakov D, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. J Appl Physiol (1985) 2003;95:2453-61.
31. Lodato RF. Decreased O2 consumption and cardiac output during normobaric hyperoxia in conscious dogs. J Appl Physiol (1985) 1989; 67:1551-9.
32. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care 2008;12:R156.
33. Zwemer CF, Whitesall SE, D'Alecy LG. Hypoxic cardiopulmonary-cerebral resuscitation fails to improve neurological outcome following cardiac arrest in dogs. Resuscitation 1995;29:225-36.
34. Bulte DP, Chiarelli PA, Wise RG, Jezzard P. Cerebral perfusion response to hyperoxia. J Cereb Blood Flow Metab 2007;27:69-75.
35. Rossi S, Stocchetti N, Longhi L, Balestreri M, Spagnoli D, Zanier ER, et al. Brain oxygen tension, oxygen supply, and oxygen consumption during arterial hyperoxia in a model of progressive cerebral ischemia. J Neurotrauma 2001;18:163-74.
23. Rousseau A, Tesselaar E, Henricson J, Sjoberg F. Prostaglandins and radical oxygen species are involved in microvascular effects of hyperoxia. J Vasc Res 2010;47:441-50.
24. Singhal AB, Benner T, Roccatagliata L, Koroshetz WJ, Schaefer PW, Lo EH, et al. A pilot study of normobaric oxygen therapy in acute ischemic stroke. Stroke 2005;36:797-802.
25. National Institute of Neurological Disorders and Stroke (NINDS). Normobaric oxygen therapy in acute ischemic stroke trial. [Online]. 2010 [cited 2013 Aug 10]. Available from: URL:http://clinicaltrials.gov/ct2/show/results/NCT00414726
26. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 2010;303:2165-71.
27. Rockswold SB, Rockswold GL, Zaun DA, Liu J. A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. J Neurosurg 2013;118: 1317-28.