Hyperoxia in the intensive care unit and outcome after out-of-hospital ventricular fibrillation cardiac arrest

Joshua F Ihle, Stephen Bernard, Michael J Bailey, David V Pilcher, Karen Smith and Carlos D Scheinkestel

ABSTRACT

Background: Laboratory and clinical studies have suggested that hyperoxia early after resuscitation from cardiac arrest may increase neurological injury and worsen outcome. Previous clinical studies have been small or have not included relevant prehospital data. We aimed to determine in a larger cohort of patients whether hyperoxia in the intensive care unit in patients admitted after out-of-hospital cardiac arrest (OHCA) was associated with increased mortality rate after correction for prehospital variables.

Methods: Data from the Victorian Ambulance Cardiac Arrest Registry (VACAR) of patients transported to hospital after resuscitation from OHCA and an initial cardiac rhythm of ventricular fibrillation between January 2007 and December 2011 were linked to the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS-APD). Patients were allocated into three groups (hypoxia [$Pa_{O_2} < 60$ mmHg], normoxia [Pa_{O_2}, 60–299 mmHg] or hyperoxia [$Pa_{O_2} \geqslant 300$ mmHg]) according to their most abnormal Pa_{O_2} level in the first 24 hours of ICU stay. The relationship between Pa_{O_2} and hospital mortality was investigated using multivariate logistic regression analysis to adjust for confounding prehospital and ICU factors.

Results: There were 957 patients identified on the VACAR database who met inclusion criteria. Of these, 584 (61%) were matched to the ANZICS-APD and had hospital mortality and oxygen data available. The unadjusted hospital mortality was 51% in the hypoxia patients, 41% in the normoxia patients and 47% in the hyperoxia patients ($P = 0.28$). After adjustment for cardiopulmonary resuscitation by a bystander, patient age and cardiac arrest duration, hyperoxia in the ICU was not associated with increased hospital mortality (OR, 1.2; 95% CI, 0.51–2.82; $P = 0.83$).

Conclusions: Hyperoxia within the first 24 hours was not associated with increased hospital mortality in patients admitted to ICU following out-of-hospital ventricular fibrillation cardiac arrest.

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Sudden out-of-hospital cardiac arrest (OHCA) is common and carries a high mortality rate.[1] Most OHCA patients who are successfully resuscitated and transported to hospital remain comatose due to the anoxic brain injury and may be admitted to the intensive care unit for mechanical ventilation and haemodynamic support. It has long been known that age, emergency medical service (EMS) response time, initial cardiac rhythm and duration of cardiac arrest are important predictors of outcome. In addition, postresuscitation factors such as therapeutic temperature management, early cardiac catheterisation and management at a cardiac arrest centre have been shown to influence outcomes.[2]

There are also compelling laboratory data suggesting that hyperoxia in the early postarrest period is associated with increased neurological injury.[3] In a systematic review of animal studies, six studies showed that treatment with 100% oxygen resulted in a significantly worse neurological deficit score than oxygen administered at lower concentrations. In four of five studies looking at histological findings, there was increased neuronal damage present in animals that received 100% oxygen therapy. The mechanism for this is uncertain but may relate to an increase in the generation of oxygen free radicals known to be toxic to injured neurones.[4]

In addition to these laboratory data, two observational clinical studies have found an association between a high arterial oxygen concentration and adverse outcome at hospital discharge.[5,6] A third observational study could not find such an association.[7] However, two of these observational studies did not include data on important baseline factors that are known to effect outcomes, such as initial cardiac rhythm, whether bystander chest compressions were performed and total cardiac arrest time.[5,7] The third study included prehospital data but was a single-centre study and limited to 170 patients.[6]

In Victoria, Australia, the Victorian Ambulance Cardiac Arrest Registry (VACAR) contains information on all episodes of OHCA attended by ambulance since 1999. The Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS-APD) contains patient data for all patients admitted to an Australian or a New Zealand ICU, and includes physiological data for the first 24 hours of ICU stay as well as chronic health data and ICU and hospital outcomes.

We linked these two datasets to identify patients admitted to an ICU after resuscitation from an OHCA in which the initial cardiac rhythm was ventricular fibrillation (VF), and we determined the hospital mortality after dividing patients into three oxygen groups. We hypothesised that there would be an association between hyperoxia in the first 24 hours in the ICU and hospital mortality, after

adjusting for prehospital variables and severity of illness on admission to the ICU.

Methods

The study was undertaken in Victoria, where there were two ambulance services before June 2008, and a single ambulance service after that time. Since 2007, all ambulance patient data have been collected via an electronic patient care record. Patients who have had an OHCA are able to be identified and their data loaded into the VACAR. EMS operational data and hospital data (outcome, discharge destination and diagnosis) are also entered into the registry. The VACAR data are subject to quality control procedures including mandatory fields, range validations, cardiac rhythm confirmation from a printed electrocardiogram, and audit (by a senior ambulance paramedic) of key cases, such as patients who received cardiac defibrillation. The registry is based on data variables and definitions that follow the Utstein criteria, and contains over 60 000 patient episodes.[8]

The ANZICS-APD database collects de-identified data from all ICUs in Australia and New Zealand and has data on over 1.2 million patient admissions. The dataset includes baseline demographics (age, postcode and sex), diagnosis leading to ICU admission, and outcome. Data quality is maintained through built-in validation rules and onsite audits of contributing hospitals. The data identify all patients who had a cardiac arrest in the 24 hours before admission to an ICU separately from the diagnosis that leads to an ICU admission. The severity-of-illness score used is the Acute Physiological and Chronic Health Evaluation version III (APACHE III).[9]

Data collection for oxygen

All blood gas data in the first 24 hours of admission are collected and entered into local software that selects the most "abnormal" Pa_{O_2} by analysis of simultaneous recordings of the fraction of inspired oxygen (F_{IO_2}) and the partial pressure of arterial oxygen (Pa_{O_2}). This value is based on the following criteria: for intubated patients with an $F_{IO_2} \geq 0.5$, the Pa_{O_2} associated with the arterial blood gas with the highest arterial–alveolar gradient is selected. For non-intubated patients, or intubated patients with an $F_{IO_2} < 0.5$, the lowest arterial blood gas Pa_{O_2} is selected.[10]

Data matching

For our study, the VACAR was searched for patients between January 2007 and December 2011 who met the following criteria: age ⩾ 18 years, initial cardiac rhythm of VF, and transport to hospital with a return of spontaneous circulation (ROSC). Probabilistic linkage using hospital, age, sex, date of hospital admission and residential postcode was used to match patients from the VACAR to de-identified ANZICS-APD records during the 5-year period.

During the study period, the ANZICS-APD received data on 126 382 admissions to Victorian ICUs, of which 4732 were recorded as having had a cardiac arrest in the 24 hours before ICU admission. During the same period, 957 patients were identified on the VACAR who met the inclusion criteria. Of these patients, 609 (64%) were matched to the ANZICS-APD and 584 (61%) had complete mortality and oxygen data available. These patients formed the final study cohort. Figure 1 shows the reasons for exclusion of patients.

The 584 study patients were divided into three groups according to their APACHE III Pa_{O_2} level:

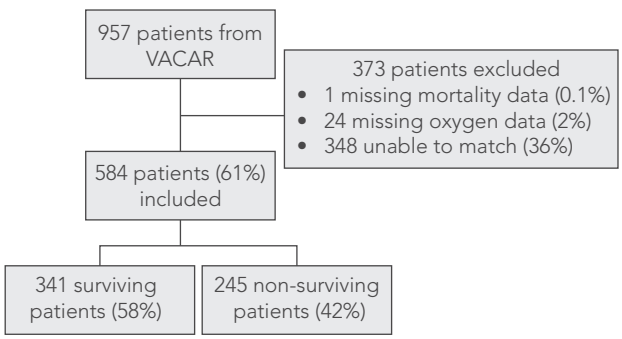
- hypoxia ($Pa_{O_2} < 60$ mmHg)
- normoxia ($Pa_{O_2} = 60$–299 mmHg)
- hyperoxia ($Pa_{O_2} \geq 300$ mmHg).

The primary outcome measure was hospital mortality. We compared survivors to those who died to identify confounders that might influence the relationship between Pa_{O_2} and mortality. We then adjusted for these confounders to determine if there was an independent association between Pa_{O_2} and outcome.

Statistical analysis

Statistical analyses were performed using SAS 9.2 (SAS Institute) and Stata 12.0 (StataCorp). Continuous data were presented as means and SDs, or medians and interquartile ranges (IQRs), depending on the distribution of the data. Univariate analyses were conducted using χ^2 tests for equal proportion, student *t* tests and analyses of variance for normally distributed data, and Wilcoxon rank-sum and Kruskal–Wallis tests were used otherwise. Multiple logistic regression analysis using stepwise and backward elimination techniques were performed to identify variables independently associated with mortality, with results presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). Oxygenation status and variables which met univariate significance at a level of $P = 0.1$ and below were included in the multivariate analysis. To create a marker of illness severity independent of oxygenation status,

Figure 1. Path of patient exclusion and inclusion in study



VACAR = Victorian Ambulance Cardiac Arrest Registry.

the oxygen component of the APACHE III risk of death was removed. The study was approved by the human research and ethics committee at the Alfred Hospital (project number 269/12).

Results

The mean age of the 584 patients was 63.3 years (SD, 14.2 years) and 464/584 (80%) were men. In 81% of patients, cardiac arrest was witnessed by a bystander, and 71% received bystander cardiopulmonary resuscitation (CPR). The median time from emergency call to ambulance arrival at the scene was 7.9 minutes, and time to first shock was 11.0 minutes. The median number of defibrillations was three (IQR, two to six). The mean time from emergency call to ROSC was 25.7 minutes (SD, 12 minutes). The overall survival was 341/584 (58%) and most of the survivors were discharged home (61%). Of the patients who died, most died in the ICU (82%).

Baseline demographics of patients in the hypoxia, normoxia and hyperoxia groups are shown in Table 1. Patients with hypoxia had a higher APACHE III predicted risk of death, even when the oxygen component was removed. There was a non-significantly (P= 0.07) higher proportion of patients with cardiovascular disease in the hypoxia (29%) and normoxia (21%) groups, compared with the hyperoxia group (9%).

Table 2 shows the outcomes of patients. The hospital mortality was not significantly different between the three groups (51% for the hypoxia group, 41% for normoxia and 47% for hyperoxia [P=0.28]). The hypoxia group had a shorter length of stay (5.1 v 8.9 v 7.6 days, respectively [P=0.013]).

Table 3 shows the prehospital and APACHE III factors associated with survival at hospital discharge. This confirms that bystander CPR, a shorter duration of cardiac arrest and younger age are associated with improved survival. Non-survivors were administered higher F_{IO_2} (73% for non-survivors v 63% for survivors [P<0.001]) but had a non-significantly lower Pa_{O_2} (P=0.31).

Although there was a significant difference between the number of shocks in survivors versus non-survivors, we did not adjust for this (Table 4), as it did not appear to be independently predictive of mortality (OR, 1.05 [95% CI, 0.98–1.12]; P=0.15) primarily because of the strong relationship between the number of shocks and the time from the emergency call to ROSC (Spearman ρ=0.58; P<0.0001). To avoid issues with collinearity, "total shocks" was subsequently excluded from the final model.

Table 1. Univariate comparisons of baseline characteristics of patients in the three oxygen groups

Characteristic	Hypoxia	Normoxia	Hyperoxia	*P*
Number of patients	55	494	35	–
Mean age, years (SD)	64 (15)	63 (14)	65 (14)	0.35
Male, % (*n*)	80 (44)	80 (395)	74 (26)	0.67
Witnessed, % (*n*)	82 (45)	82 (405)	77 (27)	0.79
Bystander CPR applied, % (*n*)	71 (39)	72 (356)	74 (26)	0.94
Median time from emerg. call to first shock, minutes (IQR)	11 (9–14)	11 (9–13)	11 (10–12)	0.32
Median time from emerg. call to ROSC, minutes (IQR)	25 (17–34)	23 (17–31)	21 (16–27)	0.46
Cardiovascular disease, % (*n*)	29 (16)	21 (105)	9 (3)	0.07
Liver disease, % (*n*)	0 (0)	0.4 (2)	0 (0)	0.83
Renal disease, % (*n*)	2 (1)	2 (10)	3 (1)	0.94
Respiratory disease, % (*n*)	4 (2)	5 (22)	3 (1)	0.88
Cancer, % (*n*)	0 (0)	1.4 (7)	0 (0)	0.53
Immunosuppressed, % (*n*)	0 (0)	0.6 (3)	3 (1)	0.91
Mean APACHE III score (SD)	124 (30)	103 (29)	105 (30)	0.003
Mean, median APACHE III risk of death (no oxygen),* % (IQR)	68, 71 (54–85)	55, 60 (36–75)	57, 65 (36–77)	0.002

CPR = cardiopulmonary resuscitation. ROSC = return of spontaneous circulation. APACHE III = Acute Physiology and Chronic Health Evaluation III. * APACHE III risk of death with oxygen component removed from APACHE III score.

Table 2. Univariate comparison of outcomes in the three oxygen groups

Outcome	Hypoxia	Normoxia	Hyperoxia	*P*
Number of patients	55	494	35	–
ICU mortality, % (*n*)	49 (27)	32 (153)	35 (12)	0.042
Hospital mortality, % (*n*)	51 (28)	41 (194)	47 (16)	0.28
Median hospital LOS, days (IQR)	5.1 (2.2–12)	8.9 (4.2–16.9)	7.6 (2.8–12.2)	0.013

ICU = intensive care unit. LOS = length of stay. IQR = interquartile range.

Table 4 shows the multiple logistic regression analysis. This shows that, after correction for prehospital baseline variables, there was no significant detriment with hyperoxia compared with normoxia.

Discussion

We found no association between oxygenation status during the first 24 hours of ICU admission and survival at hospital discharge, after adjustment for prehospital variables that affect outcome. Our study did, however, confirm previous data showing an association between bystander CPR, patient age and duration of cardiac arrest, and outcomes.

The findings of our study differ from the study by Kilgannon et al.[5] In their study, a critical care database of ICUs at 120 United States hospitals between 2001 and 2005 was examined. Of 6326 patients, 1156 had hyperoxia (18%), 3999 had hypoxia (63%) and 1171 had normoxia (19%).

The hyperoxia group had a significantly higher inhospital mortality (63%) compared with the normoxia group (45%) and the hypoxia group (57%). After controlling for age, preadmission functional status, comorbid conditions, vital signs in ICU and other physiological indices in ICU, hyperoxia exposure had an OR for death of 1.8 (95% CI, 1.5–2.2). However, this study did not have prehospital data known to influence the outcomes of these patients.

More recently, Janz et al reviewed the association between hyperoxia and outcome at hospital discharge in 170 consecutive patients treated with therapeutic hypothermia in an academic tertiary care hospital following resuscitation from an OHCA.[6] Of these 170 patients, 77 (45.2%) survived to hospital discharge. Survivors had a significantly lower maximum Pa_{O_2} of 198 mmHg measured in the first 24 hours following cardiac arrest, compared with non-survivors (254 mmHg) ($P = 0.022$). A multivariate analysis including age, time from emergency call to ROSC, bystander CPR and initial cardiac rhythm revealed that higher levels of Pa_{O_2} in the ICU were significantly associated with increased inhospital mortality (OR, 1.4; 95% CI, 1.0–2.0; $P = 0.034$). However, this study was from a single centre with a relatively small number of patients.

On the other hand, a study by Bellomo et al, of patients in Australia admitted to an ICU after both inhospital cardiac arrest and OHCA, using the ANZICS-APD, did not find a consistent relationship between hyperoxia and increased hospital mortality.[7] This study found that of 12 108 patients admitted to an ICU after cardiac arrest, 1285 (10.6%) had hyperoxia, 8904 (73.5%) had hypoxia, and 1919 (15.9%) had normoxia. The hyperoxia group had a mortality rate of 59%, the normoxia group had a mortality rate of 47% and the hypoxia group mortality rate was 60%. The association between hyperoxia and mortality was dependent on the statistical method used to adjust for confounding variables. This study also did not have prehospital data known to influence the outcomes of these patients. Furthermore, Bellomo et al found other confounders that influenced outcome, such as acute renal failure (ARF). Because the effects of ARF are embedded within the calculation of the APACHE III risk of death, and APACHE III risk of death was included in the multivariate model, the effects of ARF were indirectly controlled for in this study. Finally, the rate of hypoxia in these patients appeared to be very high compared with the previous two observational studies.

It is also of interest that in our study, 80% of the patients were men but in the other studies discussed above[5-7] only 60%–65% were men. We postulate that this is due to a greater incidence of ischaemic heart disease in men, which manifests as VF and leads to a greater proportion of men in this study, when compared with the other studies that did not restrict their final cohort to VF cardiac arrests.

Table 3. Factors associated with survival at hospital discharge

Factor	Survivor	Non-survivor	*P*
Number	341	245	–
Mean age, years (SD)	60.2 (14.9)	67.5 (12)	< 0.0001
Male, % (*n*)	82 (278)	78 (190)	0.23
Pre-hospital factors			
Cardiac arrest witnessed, % (*n*)	82 (279)	80 (197)	0.54
Bystander CPR applied, % (*n*)	75 (256)	66 (161)	0.014
Median time from emergency call to scene, minutes (IQR)	7.8 (6.2–9.5)	8.1 (6.7–9.9)	0.08
Median time from emergency call to first shock, minutes (IQR)	10 (9–12)	11 (9–13)	0.07
Median number of shocks (IQR)	3 (1–6)	4 (2–7.5)	< 0.0001
Median time from emergency call to ROSC, minutes (IQR)	20 (15–29)	27 (24–35)	< 0.0001
APACHE III factors, % (*n*)			
Cardiovascular	18.7 (64)	23.3 (57)	0.18
Liver	0.3 (1)	1.2 (3)	0.31
Renal	1.8 (6)	2.4 (6)	0.56
Respiratory	2.9 (10)	5.3 (13)	0.14
Immunosuppression	0.6 (2)	0.8 (2)	1.00
Cancer	1.2 (4)	1.2 (3)	1.00
Mean APACHE III score (SD)	94 (28)	119 (27)	< 0.0001
Oxygen data			
Median Pa_{O_2} (IQR)	105 (77–162)	97 (78–138)	0.31
Mean F_{IO_2} % (SD)	63 (27)	73 (26)	< 0.0001
Mean A–a gradient* (SD)	373 (158)	395 (151)	0.15

CPR = cardiopulmonary resuscitation. IQR = interquartile range. ROSC = return of spontaneous circulation. APACHE = Acute Physiology and Chronic Health Evaluation. * Arterial–alveolar gradient.

Table 4. Logistic regression model for in-hospital mortality*

Characteristic	Odds ratio (95% CI)	*P*
Time from emergency call to ROSC (minutes)	1.04 (1.03–1.06)	< 0.001
APACHE III risk of death (no oxygen)†	1.03‡ (1.02–1.04)	< 0.001
Age (years)	1.02 (1.00–1.04)	0.007
Bystander CPR applied	0.62 (0.40–0.95)	0.03
Cardiac arrest witnessed by bystander	1.09 (0.66–1.79)	0.73
Oxygenation status	–	0.83
Hypoxia v normoxia	0.93 (0.47–1.87)	–
Hyperoxia v normoxia	1.20 (0.51–2.82)	–

ROSC = return of spontaneous circulation. APACHE = Acute Physiology and Chronic Health Evaluation. CPR = cardiopulmonary resuscitation. * Area under receiver operating characteristic = 0.80. † APACHE III risk of death with oxygen component removed from APACHE III score. ‡ Odds ratio associated with a 1% increase.

Limitations and strengths

Our study has several limitations. First, it is a retrospective study and thus there is likely to be bias in the allocation of patients into the different groups. For example, it is possible that more unstable patients remain on a high F_{IO_2} in the ICU. Second, the true incidence of hyperoxia is uncertain given that the ANZICS-APD records no more than two oxygen samples in the first 24 hours. It is possible that patients spend a considerable time on a high fraction of inspired oxygen early in the ICU admission without an arterial blood gas measurement. Third, the F_{IO_2} and Pa_{O_2} before ICU admission is not recorded. Fourth, an association between hyperoxia may still be present but not detectable by this study as it may have been underpowered. Equally, hypoxia didn't carry an independent association with outcome after correction for prehospital variables. It is likely that the time to ROSC, bystander CPR and severity of illness all have a stronger association with mortality, but the amount of oxygen administered is one factor we can control after admission to hospital.

The total patient cohort is relatively small compared with two of the previous studies. Only 609 of the 957 patients identified on VACAR were identified among the 4732 patients listed on the APD with a diagnosis of any cardiac arrest. This may represent VACAR patients admitted to hospital who died in the emergency department; were a direct admission to a general ward for palliation; were extubated and admitted to a coronary care bed; or had had a non-VF cardiac arrest. The impact and extent of an inability to match patients who should be represented on both datasets is unknown.

This study has several strengths. Both datasets used are large, established databases with quality controls and few items of missing data. Also, a previous study has demonstrated the reliability of matching the de-identified data in the ANZICS-APD to other databases.[11] The multivariate analysis highlights prehospital variables associated with an improvement in outcome, including shorter time to ROSC, younger age and bystander CPR.

Conclusion

We could not find a significant association between hyperoxia in the first 24 hours of ICU admission and hospital mortality in patients admitted following out-of-hospital ventricular fibrillation cardiac arrest, when prehospital and other ICU factors were taken into account.

Competing interests

None declared.

Author details

Joshua F Ihle, Intensivist[1]
Stephen Bernard, Intensivist and Professor[1-3]
Michael J Bailey, Statistician[4]
David V Pilcher, Intensivist,[1] Associate Professor,[3,4] and Chair[5]
Karen Smith, Manager Research and Evaluation,[2] Senior Research Fellow,[3] and Associate Professor[6]
Carlos D Scheinkestel, Director of ICU,[1] and Professor[3]

1 Intensive Care Unit, The Alfred Hospital, Melbourne, VIC, Australia.
2 Ambulance Victoria, Melbourne, VIC, Australia.
3 Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia.
4 Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia.
5 Centre for Outcome and Research Evaluation, Australian and New Zealand Intensive Care Society, Melbourne, VIC, Australia.
6 Emergency Medicine, University of Western Australia, Perth, WA, Australia.

Correspondence: joshihle@yahoo.com

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