CRITICAL CARE

Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest

Rinaldo Bellomo[1*], Michael Bailey[1], Glenn M Eastwood[3], Alistair Nichol[1], David Pilcher[2], Graeme K Hart[2], Michael C Reade[3], Moritoki Egi[4], D James Cooper[1], the Study of Oxygen in Critical Care (SOCC) Group

Abstract

Introduction: Hyperoxia has recently been reported as an independent risk factor for mortality in patients resuscitated from cardiac arrest. We examined the independent relationship between hyperoxia and outcomes in such patients.

Methods: We divided patients resuscitated from nontraumatic cardiac arrest from 125 intensive care units (ICUs) into three groups according to worst PaO_2 level or alveolar-arterial O_2 gradient in the first 24 hours after admission. We defined 'hyperoxia' as PaO_2 of 300 mmHg or greater, 'hypoxia/poor O_2 transfer' as either $PaO_2 < 60$ mmHg or ratio of PaO_2 to fraction of inspired oxygen (FiO_2) < 300, 'normoxia' as any value between hypoxia and hyperoxia and 'isolated hypoxemia' as $PaO_2 < 60$ mmHg regardless of FiO_2. Mortality at hospital discharge was the main outcome measure.

Results: Of 12,108 total patients, 1,285 (10.6%) had hyperoxia, 8,904 (73.5%) had hypoxia/poor O_2 transfer, 1,919 (15.9%) had normoxia and 1,168 (9.7%) had isolated hypoxemia ($PaO_2 < 60$ mmHg). The hyperoxia group had higher mortality (754 (59%) of 1,285 patients; 95% confidence interval (95% CI), 56% to 61%) than the normoxia group (911 (47%) of 1,919 patients; 95% CI, 45% to 50%) with a proportional difference of 11% (95% CI, 8% to 15%), but not higher than the hypoxia group (5,303 (60%) of 8,904 patients; 95% CI, 59% to 61%). In a multivariable model controlling for some potential confounders, including illness severity, hyperoxia had an odds ratio for hospital death of 1.2 (95% CI, 1.1 to 1.6). However, once we applied Cox proportional hazards modelling of survival, sensitivity analyses using deciles of hypoxemia, time period matching and hyperoxia defined as $PaO_2 > 400$ mmHg, hyperoxia had no independent association with mortality. Importantly, after adjustment for FiO_2 and the relevant covariates, PaO_2 was no longer predictive of hospital mortality ($P = 0.21$).

Conclusions: Among patients admitted to the ICU after cardiac arrest, hyperoxia did not have a robust or consistently reproducible association with mortality. We urge caution in implementing policies of deliberate decreases in FiO_2 in these patients.

Introduction

The majority of patients who experience cardiac arrest die at the time of the event [1,2]. Even after response to resuscitation efforts and survival to intensive care unit (ICU) admission, such patients have a short-term mortality of approximately 60% [1,2]. These dismal outcomes suggest the need for strategies to attenuate postresuscitation injury. Such injury is currently mostly

attributed to cerebral, myocardial and global ischemia-reperfusion injury [3]. Accordingly, postresuscitation therapy has focused on finding ways to diminish the intensity and consequences of ischemia-reperfusion injury.

The rapid application of therapeutic hypothermia can modify the outcomes of patients after resuscitation from cardiac arrest [4,5]. The success associated with this intervention suggests that other aspects of patient care, which may influence the course of reperfusion injury, should also be logical targets for therapeutic manipulation.

In pursuit of potential therapeutic targets, investigators from the Emergency Medicine Shock Research Network

* Correspondence: rinaldo.bellomo@austin.org.au
[1]Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, 5 Commercial Road, Prahran, Melbourne, Victoria 3181, Australia
Full list of author information is available at the end of the article

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(EMShockNet) recently explored the association between hyperoxia and in-hospital outcome in a retrospective, multicentre study [6]. They found that hyperoxia occurred in almost one-fifth of patients, that patients with hyperoxia had greater in-hospital mortality than patients with normoxia or hypoxia and that, after controlling for some confounders, hyperoxia carried a clear independent association with mortality (odds ratio (OR), 1.8). Unfortunately, these investigators used only the first set of arterial blood gases in the ICU to assess oxygenation, excluded close to 30% of patients because of lack of arterial blood gas data and did not adjust for standard illness severity scores. Their conclusion that hyperoxia is a robust predictor of mortality in patients after resuscitation form cardiac arrest was therefore potentially affected by selection bias and by insufficient adjustment for major confounders. Thus, their results are of uncertain significance and require confirmation.

The Australian and New Zealand (ANZ) Adult Patient Database (ANZ-APD) is a high-quality database [7] of all admissions to most Australian and New Zealand ICUs. Patients admitted after resuscitation from non-traumatic cardiac arrest are coded as such. The database records contain Acute Physiology and Chronic Health Evaluation II (APACHE II) and APACHE III scores as well as demographic, diagnostic and outcome factors [8]. Given the potential clinical importance of hyperoxia following cardiac arrest, we used this larger and more detailed database specifically to confirm or refute the initial findings of the EMShockNet investigators [6].

Materials and methods

We extracted data from the ANZ Intensive Care Society (ANZICS)-APD. We used exactly same inclusion criteria as the EMShockNet investigators [6] for patients admitted at a participating centre between 2000 and 2009 after resuscitation from an out-of-hospital or in-hospital cardiac arrest. We excluded readmissions and patients for whom arterial blood gas analysis or vital status at discharge was not available. The ANZICS Centre for Outcomes and Resource Evaluation (CORE) Management Committee granted us access to the data in accordance with standing protocols. Data were collected under the Quality Assurance Legislation of the Commonwealth of Australia (Part VC Health Insurance Act 1973, Commonwealth of Australia) with government support and funding. Each hospital gives ethics approval and allows the data to be used for appropriate research, which is governed by the ANZICS CORE terms of reference and waives the need for informed consent.

Data collection for oxygen values

All arterial blood gases during the first 24 hours of ICU admission were collected and entered into a standardized data collection system which automatically selects the appropriate high and low simultaneous fraction of inspired oxygen (FiO_2) and partial pressure of arterial oxygen (PaO_2) measurements and deletes other oxygenation data. Using the APACHE II and III methodology for intubated patients with $FiO_2 \geq 0.5$, the PaO_2 associated with the arterial blood gas with the highest alveolar-arterial (A-a) gradient is selected as the index of worst oxygenation. For nonintubated patients or intubated patients with $FiO_2 < 0.5$, the lowest arterial blood gas PaO_2 level is recorded. The ratio of PaO_2 to FiO_2 (P/F ratio) is also used as an index of illness severity.

Data extraction

We recorded the sizes, types and locations of the hospitals. At the patient level, we extracted the following variables: demographics, comorbidities according to APACHE II and III classifications, hospital and ICU admission source, intubation, treatment limitation, year of admission, physiological and arterial blood gas parameters over the first 24 hours in the ICU, vital status at hospital discharge, hospital discharge destination and an APACHE III risk of death score [8]. As a marker of severity of illness independent of arterial oxygenation, we calculated an adjusted APACHE III index of illness severity (AP3no-ox), in which the oxygen component of the APACHE III scoring system was removed.

Statistical analyses

All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Continuous data are presented as means ± standard deviations or as medians with interquartile ranges (IQRs), depending on the underlying data distribution. Categorical data are reported as proportions. We categorized oxygenation levels into the same three groups as in the EMShockNet study [6], defined by the worst PaO_2 and P/F ratio obtained in the first 24 hours of ICU admission. Thus, we divided patients into three groups according to worst PaO_2 or A-a O_2 gradient in the first 24 hours after admission. We defined 'hyperoxia' as a PaO_2 300 mmHg or greater, 'hypoxia/poor O_2 transfer' as either $PaO_2 < 60$ mmHg or a P/F ratio <300, 'normoxia' as any value between hypoxia and hyperoxia and 'isolated hypoxemia' as $PaO_2 < 60$ mmHg regardless of FiO_2 level.

The primary outcome measures were in-hospital mortality and survival time, which are reported as ORs (95% confidence interval (95% CI)) or hazard ratios (HRs) (95% CI), respectively. To determine functional recovery, we also considered discharge to home as a secondary outcome. We compared outcomes between groups using the χ^2 test with the Bonferroni correction. We conducted multivariate analysis using logistic regression for mortality and Cox proportional hazards regression

for survival time, with models constructed using both stepwise selection and backwards elimination procedures. To increase robustness and model validity, we used a *P* value of 0.01 for variable inclusion. We applied several models to the statistical analysis of the independent relationship between oxygenation and patient outcome. We constructed an initial model for mortality in accordance with the EMShockNet model (see Additional file 1, Statistical appendix, Model 1) [8]. We then applied a second model to improve discriminatory power using AP3no-ox as a marker of severity (see Additional file 1, Statistical appendix, Model cluster 2). Finally, we conducted further sensitivity analysis inclusive of propensity analysis [9], Cox proportional hazards modelling, testing of different cutoff points for hyperoxia, analysis of subgroups contemporaneous with the EMShockNet cohort and assessment of PaO_2 according to deciles (Additional file 1, Statistical appendix, Model cluster 3).

As our database contained only the worst recorded oxygenation in the first 24 hours after ICU admission, we explored its relationship with that of the first PaO_2 measurement after ICU admission (as in the EMShockNet study) and the mean oxygenation on ICU admission days 1, 2 and 3 by selecting 100 of the database patients and obtaining additional data from all of their hospital arterial blood gas records during their ICU stay (see Additional file 1, Statistical appendix, Model cluster 3).

Statistical power considerations

The proportion of living patients with hyperoxia ($PaO_2 > 400$) was 5% (*n* = 280). Comprising 5,140 patients who lived and 6,968 patients who died, this study had 93% power to detect a change of 1.5% (5% versus 6.5%) in the proportion of patients with hyperoxia ($PaO_2 > 400$) with a two-sided *P* value of 0.05.

There were 625 patients in the data set with hyperoxia ($PaO_2 > 400$). Comprising 11,483 patients without hyperoxia, this study had 90% power to detect a difference in mortality of 7% (55% versus 62%) between groups with a two-sided *P* value of 0.05. Given an observed difference of 14% (55% versus 69%) in the EMShockNet study between hyperoxic patients ($PaO_2 > 400$) and nonhyperoxic patients, we felt that this study was adequately powered to detect a relationship between mortality and $PaO_2 > 400$. In our study, the mortality rate in the hyperoxia group ($PaO_2 > 400$) was only 0.5% higher than that in the nonhyperoxia group (54.7% versus 55.2%, *P* = 0.22).

There were 531 hyperoxia survivors ($PaO_2 > 300$). With 4,609 nonhyperoxia survivors, this study had 80% power to detect a difference between groups of 6% (64% versus 58%) regarding the proportion discharged to home with a two-sided *P* value of 0.05. Given an observed difference of

6% (38% versus 44%) in the EMShockNet study between hyperoxic survivors ($PaO_2 > 300$) discharged to home and discharged nonhyperoxic survivors, we again felt that this study was adequately powered to detect a relationship between hyperoxia and discharge to home. In our study, there was no observed difference in the proportion of patients who were discharged to home between the hyperoxia and nonhyperoxia groups.

Results

There were 12,806 patients who met the study inclusion criteria. Of these, 698 (5.4%) were excluded: 222 (1.7%) had missing arterial blood gas data, 382 (3.0%) had missing hospital mortality data and 94 (0.7%) were ICU readmissions. The remaining 12,108 patients were drawn from among 125 contributing ICUs. The median number of cardiac arrest cases per hospital was 42 (IQR, 13-148). Baseline characteristics for all groups are given in Tables 1 and 2.

The average age of patients was 64 years (SD ± 16), and 64% (7,802) were male. A total of 8,175 patients (68%) were at home prior to hospital admission and 5,756 patients (48%) were admitted to the ICU directly from the Emergency Department. One-third (3,978) of the patients had preexisting chronic comorbidities. The median APACHE III risk of death was 66% (IQR, 36%-84%). Most patients (8,904, 73.5%) had 'hypoxia/poor O_2 transfer', while 1,285 (10.6%) were hyperoxic and 1,919 (15.9%) were normoxic. Isolated hypoxemia ($PaO_2 < 60$ mmHg) was present in 1,168 patients (9.7%).

There were no significant differences in the measured physiological data between the three main oxygenation groups (Table 3). Patients had a median lowest temperature of 34.9°C, and in 33% of the patients, this value was below 34.0°C. The median ICU length of stay for survivors from ICU admission to hospital discharge was 3.8 days (IQR, 2.0 to 7.1), and for nonsurvivors it was 1.5 days (IQR, 0.5 to 3.3). The median length of hospital stay for survivors was 14.9 days (IQR, 8.2 to 27.2), and for nonsurvivors it was 3.4 days (IQR, 1.5 to 8.1).

Overall, 6,968 patients (58%) died in the hospital (Table 4). Mortality was significantly lower (*P* < 0.0001) in the normoxia group than in either the hyperoxia group or the hypoxia/poor O_2 transfer group. It was highest, however, in patients with 'isolated hypoxemia' (812 (70%) of 1,168 patients, *P* < 0.0001). The proportion of patients discharged directly to home was significantly higher in the normoxia group than in the other groups. The lowest rate of discharge to home was in patients with isolated hypoxemia (222 (19%) of 1,168 patients, *P* < 0.0001). Overall, 65% of survivors were discharged directly to home.

When the EMShockNet statistical model was replicated, 12 risk factors were significantly associated with

Table 1 Baseline characteristics of the study patients[a]

Patient characteristics	All patients (N = 12,108)	Hypoxia/poor O$_2$ exchange (n = 8,904)	Normoxia (n = 1,919)	Hyperoxia (n = 1,285)
Mean age, yr (±SD)	64 (16)	64 (16)	62 (18)	65 (17)
Male sex, n (%)	7,802 (64)	5,778 (65)	1,228 (64)	796 (62)
Indigenous Australians, n (%)	515 (5)	388 (5)	74 (4)	53 (4)
Hospital admission source from home, n (%)	8,175 (68)	5,986 (67)	1,273 (66)	916 (71)
Acute renal failure, n (%)	2,368 (20)	1,916 (22)	237 (12)	215 (17)
Chronic comorbidities, n (%)				
Cardiovascular disease, n (%)	2,395 (20)	1,821 (20)	357 (19)	217 (17)
Liver disease, n (%)	194 (2)	158 (2)	17 (1)	19 (1)
Renal disease, n (%)	668 (6)	488 (5)	100 (5)	80 (6)
Respiratory disease, n (%)	1,044 (9)	831 (9)	102 (5)	111 (9)
Cirrhosis, n (%)	195 (2)	158 (2)	18 (1)	19 (1)
Hepatic failure, n (%)	70 (1)	52 (1)	10 (1)	8 (1)
Immune suppression, n (%)	329 (3)	243 (3)	41 (2)	45 (4)
Cancer, n (%)	413 (3)	320 (4)	48 (3)	45 (4)
Markers of severity				
Median APACHE III risk of death (IQR)	66% (36 to 84)	69% (40 to 86)	50% (20 to 73)	66% (36 to 84)
Median APACHE III risk of death (no oxygen)[b] (IQR)	58% (27 to 79)	60% (29 to 80)	47% (18 to 71)	58% (29 to 80)
ICU admission source, n (%)				
Emergency department	5,756 (48)	4,123 (46)	1,035 (54)	598 (47)
Operating theatre	1,261 (10)	925 (10)	217 (11)	119 (9)
Other hospital	1,958 (16)	1,445 (16)	319 (17)	194 (15)
Ward	3,113 (26)	2,397 (27)	344 (18)	372 (29)
Treatment limitation[c]	562 (5)	429 (5)	68 (4)	65 (5)

[a]APACHE III, Acute Illness Severity and Chronic Health Evaluation III; IQR, interquartile range; ICU, intensive care unit; [b]APACHE III risk of death with oxygen component removed from APACHE III score; [c]treatment limitation order or coded for palliative care.

in-hospital mortality (Table 5). Data were well fitted by the model (Hosmer-Lemeshow goodness-of-fit test, P = 0.71), and the area under the curve (AUC) was 0.72. Hypoxia/poor O_2 transfer or hyperoxia were significantly associated with an increased risk of mortality in comparison to normoxia (OR 1.4 (95% CI, 1.3 to 1.6), P < 0.0001, and OR 1.5 (95% CI, 1.3 to 1.8), P < 0.0001, respectively). Once illness severity was added to the model (Table 6) (Additional file 1, Statistical appendix, Model cluster 2), the magnitude of the effect size was

markedly lower than in the original EMShockNet model (hypoxia versus normoxia: OR 1.2 (95% CI, 1.1 to 1.4), P = 0.002; hyperoxia versus normoxia: OR 1.2 (95% CI, 1.0 to 1.5), P = 0.04). This APACHE-based model showed improved discriminatory power in comparison to the EMShockNet model (AUC 0.79 when AP3no-ox was applied in isolation versus AUC 0.81 when AP3no-ox was applied in combination with other variables listed in Table 6). Data were well fitted by the model (Hosmer-Lemeshow goodness-of-fit test, P = 0.42).

Table 2 Baseline characteristics of the study hospitals

Hospital characteristics, n (%)	All patients (N = 12,108)	Hypoxia/poor O$_2$ exchange (n = 8,904)	Normoxia (n = 1,919)	Hyperoxia (n = 1,285)
Hospital size[a]				
Small to medium (≤300 beds)	2,475 (20)	1,813 (20)	361 (19)	301 (23)
Large (301 to 500 beds)	5,277 (44)	3,906 (44)	843 (44)	528 (41)
Extra large (>500 beds)	4,356 (36)	3,185 (36)	715 (37)	456 (35)
Hospital type and location				
Metropolitan community	2,670 (22)	1,988 (22)	437 (23)	245 (19)
Private	787 (6)	573 (6)	89 (5)	125 (10)
Rural	1,279 (11)	939 (11)	205 (11)	135 (11)
Tertiary academic	7,372 (61)	5,404 (61)	1,188 (62)	780 (61)

[a]Defined according to Halpern *et al.* [30].

Table 3 Abnormal vital signs in the first 24 hours in intensive care unit and interventions

Vital signs (means ± SD)	All patients (N = 12,108)	Hypoxia/poor O_2 exchange (n = 8,904)	Normoxia (n = 1,919)	Hyperoxia (n = 1,285)
Highest body temperature	37.1°C (1.5)	37.1°C (1.5)	37.1°C (1.4)	37.1°C (1.5)
Lowest body temperature	34.9°C (1.7)	34.9°C (1.7)	34.8°C (1.8)	34.7°C (1.7)
Highest heart rate, beats/min	108 (28)	109 (28)	104 (26)	108 (28)
Highest respiratory rate, breaths/min	22.0 (9.0)	22.2 (9.0)	21.4 (9.2)	21.4 (9.0)
Lowest systolic blood pressure, mmHg	88.6 (25.1)	87.3 (25.0)	94.1 (22.8)	88.9 (27.2)
Lowest mean arterial pressure, mmHg	62.3 (16.0)	61.5 (15.8)	66.2 (14.5)	62.5 (18.0)
Lowest glucose level first 24 hours	6.9 (3.9)	6.9 (4.0)	6.4 (3.1)	6.9 (3.6)
Body temperature, n (%)				
Highest temperature <34°C	860 (7)	639 (7)	90 (5)	131 (10)
Lowest temperature <34°C	4031 (33)	2918 (33)	659 (34)	454 (35)

Propensity analysis (see Additional file 1, Statistical appendix, Model cluster 3) did not alter this risk or the significance of hyperoxia. However, when the secondary outcome of discharge to home was considered, oxygenation status was no longer a statistically significant predictor (P = 0.64). Using a Cox proportional hazards regression model, we found both hyperoxia and hypoxia/poor O_2 transfer to increase the hazard of death in comparison to the normoxia group (HR 1.3 (95% CI, 1.1 to 1.4), P < 0.001, and HR 1.3 (95% CI, 1.2 to 1.4), P < 0.0001, respectively). After adjustment for the covariates described in Additional file 1, Statistical appendix, Model cluster 2, however, oxygenation status was no longer statistically significant (hyperoxia: OR 1.1 (95% CI, 1.0 to 1.2), P = 0.20; hypoxia: OR 1.1 (95% CI, 1.0 to 1.2), P = 0.01) (Table 6).

When a PaO_2 of 200 mmHg or greater was used to define hyperoxia, after adjustment (Additional file 1, Statistical appendix, Model cluster 2), oxygenation status was a statistically significant predictor of outcome (P = 0.002) (hyperoxia: OR 1.3 (95% CI, 1.1 to 1.5), P = 0.01; hypoxia: OR 1.3 (95% CI, 1.1 to 1.5), P = 0.001). When a PaO_2 of 400 mmHg or greater was used in sensitivity analysis after adjustment, however (Additional file 1, Statistical appendix, Model cluster 2), oxygenation status was no longer statistically significant (P = 0.06) (hyperoxia: OR 1.0 (95% CI, 0.8 to 1.2), P = 0.71; hypoxia: OR 1.1 (95% CI, 1.0 to 1.3), P = 0.04).

When PaO_2 was divided into deciles and modelled as a predictor of hospital mortality, it was statistically

significant at a univariate level (P < 0.0001), but with only the lowest two deciles having ORs significantly greater than the norm (Figure 1). After adjustment for FiO_2 and the covariates described in Additional file 1, Statistical appendix, Model cluster 2, PaO_2 was no longer predictive of hospital mortality (P = 0.21), although those patients with isolated hypoxemia (PaO_2 < 60 mmHg) had a significantly greater risk (OR 1.2 (95% CI, 1.0 to 1.5), P = 0.03) (Figure 1). Importantly, 492 patients (42.1%) with isolated hypoxemia were receiving deliberate decreases of FiO_2 to <0.8 at the time of their hypoxemia. There was no statistical evidence that patients with higher PaO_2 levels had significantly greater risk of hospital mortality.

When the corresponding time period used by the EMShockNet study group [6] (2001 to 2005) was considered, after adjustment (Additional file 1, Statistical appendix, Model cluster 2), oxygenation was not predictive of mortality (P = 0.16) (hyperoxia: OR 1.3 (95% CI, 0.9 to 1.8), P = 0.16; hypoxia: OR 1.3 (95% CI, 1.0 to 1.6), P = 0.06). When more detailed information was obtained from a random sample of 100 patients, the worst PaO_2 value over the first 24 hours was significantly more representative of mean PaO_2 than the first PaO_2 value measured upon admission used by the EMShockNet study group [6]. This was true for the first 24 hours (Pearson's r = 0.70 versus Pearson's r = 0.50, P < 0.0001), the first 48 hours (Pearson's r = 0.63 versus Pearson's r = 0.38, P < 0.0001) and the first 72 hours (Pearson's r = 0.60 versus Pearson's r = 0.34, P < 0.0001).

Table 4 Outcomes of study patients

Patient outcomes	All patients (N = 12,108)	Hypoxia/poor O_2 exchange (n = 8,904)	Normoxia (n = 1,919)	Hyperoxia (n = 1,285)
In-hospital mortality[a], n (%) (95% CI)	6,968 (58) (57 to 58)	5,303 (60) (59 to 61)	911 (47) (45 to 50)	754 (59) (56 to 61)
Discharge destination for survivors, n	5,140	3,601	1,008	531
Home [a], n (%) (95% CI)	3,341 (28) (27 to 28)	2,350 (26) (25 to 27)	649 (34) (32 to 36)	342 (27) (24 to 29)
Rehabilitation facility	655 (5)	447 (5)	118 (6)	90 (7)
Transfer to another hospital	1,144 (9)	804 (9)	241 (13)	99 (8)

[a]P < 0.0001 for comparisons of normoxia with hyperoxia and normoxia with hypoxia in patients discharged to home.

Table 5 Multiple logistic regression model with in-hospital mortality as dependent variable using EMShockNet model variables[a]

Variable	OR (95%CI)	P value
Acute renal failure	3.3 (2.9 to 3.7)	<0.0001
Hypotension in first 24 hours[b]	1.9 (1.7 to 2.0)	<0.0001
Age, decile	1.1 (1.1 to 1.1)	<0.0001
Emergency department origin	1.6 (1.4 to 1.7)	<0.0001
High heart rate[c]	1.5 (1.3 to 1.6)	<0.0001
Hypoxia/poor O_2 exchange versus normoxia	1.4 (1.3 to 1.6)	<0.0001
Hyperoxia versus normoxia	1.5 (1.3 to 1.8)	<0.0001
Cancer	2.0 (1.5 to 2.5)	<0.0001
Cirrhosis	2.2 (1.5 to 3.1)	<0.0001
Female sex	1.2 (1.1 to 1.3)	<0.0001
Chronic renal	1.4 (1.1 to 1.6)	0.001
Chronic respiratory disease	1.3 (1.1 to 1.5)	0.002
Hepatic failure	2.7 (1.3 to 5.9)	0.01

[a]EMShockNet, Emergency Medicine Shock Research Network; OR, odds ratio; 95% CI, 95% confidence interval. The following variables (OR (95% CI), P value) were removed from the model for nonsignificance (P < 0.01): immunosuppression (1.3 (1.0 to 1.7), P = 0.04), indigenous status (1.2 (0.9 to 1.5), P = 0.13), chronic cardiovascular disease (1.1 (0.9 to 1.2), P = 0.34), chronic liver disease (0.6 (1.0 to 3.3), P = 0.56) and hospital source prior to admission being from home (1.0 (0.9 to 1.1), P = 0.61). [b]Defined as any systolic blood pressure of less than 90 mmHg in the first 24 hours; [c]indicates highest value for first 24 hours in the intensive care unit (1 = exceeds median and 0 = median or lower).

Discussion
Key findings
We conducted a large, multicentre, cohort study of patients admitted to ICUs in ANZ after resuscitation from cardiac arrest to examine the relationship between hyperoxia and patient outcome. We initially found that hyperoxia was relatively uncommon and had only a weak relationship with risk of death. This relationship was significantly reduced by the addition of illness severity scores. In addition, once Cox proportional hazards modelling of survival, sensitivity analyses using deciles of hypoxemia, time period matching and defining

hyperoxia in keeping with experimental studies [10-13] as PaO_2 > 400 mmHg, hyperoxia had no independent association with mortality. Finally, after adjustment for FiO_2 and relevant covariates, PaO_2 was no longer predictive of hospital mortality. Thus, hyperoxia was relatively uncommon, and it had no robust and consistently reproducible independent relationship with mortality.
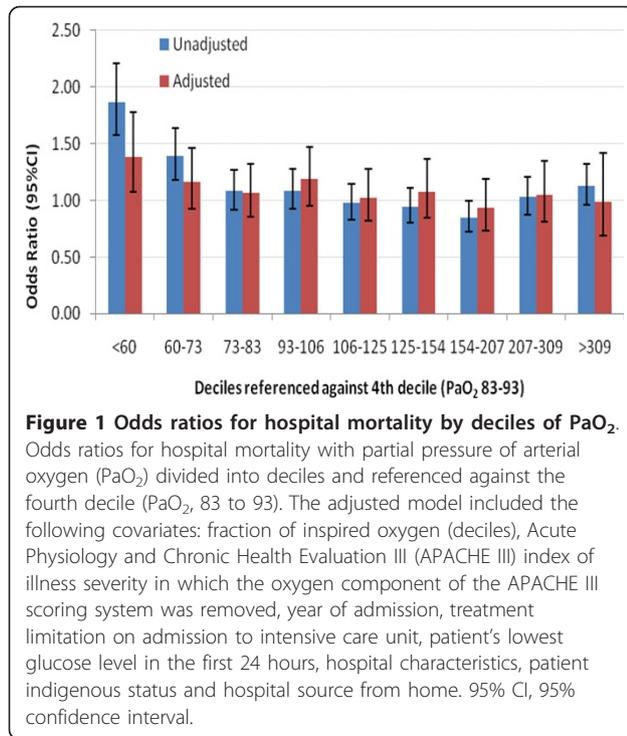
Comparison with other studies
Until very recently, concerns about the possible risks associated with hyperoxia during and after recovery from cardiac arrest were based on animal experiments [10-13]. In this regard, several experimental studies have suggested that hyperoxia can increase oxidative stress [14], induce more severe histopathological changes [10] and worsen neurological injury [15]. On the other hand, two studies have failed to confirm such findings [16,17], and two other often-quoted major studies did not actually assess animals after cardiac arrest [10,12]. Nonetheless, despite the lack of human data, the International Liaison Committee on Resuscitation moved to advocate the avoidance of arterial hyperoxia. The committee instead advocated the targeting of arterial oxygen saturation not exceeding 94% to 96% [18]. In response to these issues, in June 2010, the EMShockNet investigators reported that, in a cohort of 6,326 USA patients who had survived nontraumatic cardiac arrest and were admitted to the ICU, hyperoxia was independently associated with increased risk (OR 1.6) of in-hospital mortality. This was the largest clinical study to date of the association between hyperoxia after cardiac arrest and mortality. Our findings should therefore be evaluated in direct comparison to the EMShockNet study and have been specifically configured to facilitate such comparison.

Several important observations emerge from such comparison. First, the baseline characteristics of the U.S. and ANZ patients appear almost identical, although no information was available on the APACHE scores for

Table 6 Multiple regression models for in-hospital mortality and survival time using an APACHE III-based marker of severity[a]

Variable	Hospital mortality OR (95% CI)	P value	Time to death HR (95% CI)	P value
AP3no-ox[b]	1.5 (1.5 to 1.6)	<0.0001	1.2 (1.2 to 1.2)	<0.0001
Treatment limitation[c]	5.3 (3.8 to 7.2)	<0.0001	1.7 (1.5 to 1.8)	<0.0001
Year of admission	0.9 (0.9 to 0.9)	<0.0001	0.97 (0.96 to 0.98)	<0.0001
Lowest glucose in first 24 hours	1.1 (1.1 to 1.1)	<0.0001	1.02 (1.02 to 1.03)	<0.0001
Hospital admission from home	1.3 (1.1 to 1.4)	0.0002	1.1 (1.0 to 1.1)	0.02
Hypoxia/poor O_2 exchange versus normoxia	1.2 (1.1 to 1.4)	0.002	1.1 (1.0 to 1.2)	0.01
Hyperoxia versus normoxia	1.2 (1.0 to 1.5)	0.04	1.1 (1.0 to 1.2)	0.20

[a]APACHE III, Acute Illness Severity and Chronic Health Evaluation III; OR, odds ratio; 95% CI, 95% confidence interval; HR, hazard ratio; AP3no-ox, APACHE III score with oxygenation component removed; [b]APACHE III risk of death with oxygen component removed from calculation algorithm; [c]treatment limitation order or palliative care coded for the patient. Indigenous status was removed from both models for nonsignificance (P < 0.01): (OR 1.3 (95% CI, 1.0 to 1.8), P = 0.04), (HR 1.1 (95% CI, 0.9 to 1.1) P = 0.89).

Figure 1 Odds ratios for hospital mortality by deciles of PaO$_2$. Odds ratios for hospital mortality with partial pressure of arterial oxygen (PaO$_2$) divided into deciles and referenced against the fourth decile (PaO$_2$, 83 to 93). The adjusted model included the following covariates: fraction of inspired oxygen (deciles), Acute Physiology and Chronic Health Evaluation III (APACHE III) index of illness severity in which the oxygen component of the APACHE III scoring system was removed, year of admission, treatment limitation on admission to intensive care unit, patient's lowest glucose level in the first 24 hours, hospital characteristics, patient indigenous status and hospital source from home. 95% CI, 95% confidence interval.

the USA cohort. Despite such similarities, there were striking differences in the lowest body temperatures recorded (ANZ 34.9°C, USA 36°C). These differences may reflect greater uptake of therapeutic hypothermia in ANZ and make the observations from our cohort more relevant to current recommended practice [4,5]. However, we cannot determine whether greater use of therapeutic hypothermia accounts for the difference in the proportion of survivors discharged to home (65% in ANZ as compared to 44% in the USA, approximately a 50% relative increase in favourable outcome).

In the ANZ cohort, hyperoxia occurred in only 10.6% of patients as compared with 18% in the USA, and mortality in the hyperoxic group was identical to that in the hypoxia/poor O$_2$ transfer group, instead of being much greater. Importantly, the relationship between hyperoxia and in-hospital mortality appeared much weaker using the same modelling used by the EMShockNet investigators. Even more importantly, this relationship could not be confirmed when a different threshold for hyperoxia was applied which mimicked that reported in experimental studies [11-13] (rather than using a seemingly arbitrary cutoff point of 300 mmHg), when a Cox proportional hazards model was used, when PaO$_2$ was split into deciles, when FiO$_2$ was taken into account or when the same time period (2000 to 2005) was used for analysis. In the aggregate, these observations suggest that the relationship between hyperoxia and mortality is dependent on the individual healthcare system, the statistical

model used, the time period examined and the definitions used. Such features are not consistent with a robust and reproducible biological phenomenon.

Study significance

Our findings imply that it is incorrect and premature to conclude that hyperoxia is an independent risk factor for mortality in patients resuscitated from nontraumatic cardiac arrest. In particular, we contend that hyperoxia implies the administration of high FiO$_2$ fractions, making it more likely for hyperoxia to actually be a marker of illness severity than a biological toxin. This notion is supported by the significant decrease in ORs for mortality once APACHE scores were added to the model and the disappearance of significant ORs once FiO$_2$ was added to the model. Moreover, the definition of 'hypoxia' used by the EMShockNet investigators (reproduced here to facilitate comparison under the term 'hypoxia/poor O$_2$ transfer') included patients with a P/F ratio <300, together with patients with PaO$_2$ < 60 mmHg. This approach conflates physiologically relevant lack of oxygen at the tissue level (true hypoxia) with a gas transfer problem. When we examined isolated hypoxemia (PaO$_2$ < 60 mmHg), we found that it was nearly as frequent as hyperoxia. The risks of cerebral injury associated with hypoxemia are well known [19-21], and hypoxemic patients in our cohort had particularly poor outcomes. Importantly, after adjustment for FiO$_2$ and relevant covariates, PaO$_2$ was no longer predictive of hospital mortality. These observations suggest that the association seen in the models that do not include FiO$_2$ may simply reflect the fact that hyperoxia is an indirect marker of higher FiO$_2$ (that is, the higher the FiO$_2$, the greater the PaO$_2$) and that a higher FiO$_2$ is a marker of illness severity (that is, the sicker the patient is perceived to be, the greater the FiO$_2$ administered in an emergency situation). However, the link between FiO$_2$ and outcome is independent of APACHE score. Thus, FiO$_2$ cannot be considered simply a marker of disease severity. The physician can lower PaO$_2$ and FiO$_2$ levels at the same time and avoid inducing hyperoxia. Only interventional studies can clarify whether the association between oxygenation and outcome is truly a causal relationship.

All the above observations have potential clinical relevance. For example, emergency responders may not have access to pulse oximetry or blood gas analysis, or such techniques may be unreliable immediately following cardiac arrest because of decreased peripheral perfusion. If fear of hyperoxia led emergency responders, in the absence of adequate monitoring, to limit FiO$_2$ levels, logically more people would likely be exposed to the risk of hypoxemia. In our study, >40% of patients with hypoxemia might have had correction of their hypoxemia had a higher FiO$_2$ level been induced. Thus, if concerns about the alleged ill effects of hyperoxia or high

FiO_2 administration were taken into the clinical arena to avoid a condition whose association with mortality is uncertain, more patients might be exposed to a condition whose adverse cerebral effects are well established. Given our findings, we counsel against implementing policies of deliberately induced decreases in FiO_2 unless accurate continuous pulse oximetry monitoring is in place. Importantly, in no way do we advocate, promote or justify hyperoxia in this setting. However, lowering FiO_2 is justified only if good transcutaneous or arterial oxygenation monitoring is available.

Strengths and limitations

This study has several strengths. It involved more than 12,000 patients from 125 ICUs in two countries, making it the largest study of its type conducted so far and making its findings reflective of all ICUs in ANZ [22,23]. It included a multifaceted assessment of the independent relationship between hyperoxia and outcome using multiple models and adjusting for illness severity. However, like other studies of association using a large database, it is limited by the nature of the data available and by the fact that no causal inferences can be drawn. The assessment of oxygenation status in the first 24 hours was based on the 'worst' possible arterial blood gas result, while the EMShockNet study used the 'first' ICU arterial blood gas measurement for evaluation. Thus, patients may have been exposed to hyperoxia and may not have been identified in our study. However, using a random sample of 100 patients, we found that the measurement used in our study was more closely representative of overall mean oxygenation status in ICU patients during the first 24 to 48 hours after admission (when reperfusion injury occurs) than the first set of blood gas measurements obtained in the ICU. In our study, data were missing for only 5.4% of patients compared with 27.6% in the EM ShockNet study, making selection bias in our study less likely. One-third of patients had a lowest body temperature <34°C. Clinical knowledge (confirmed by the EMShockNet data) that such severe spontaneous hypothermia is uncommon suggests that many patients were therefore treated with induced hypothermia as is common in ANZ [24-28]. This finding distinguishes our study from the US investigation because it is in keeping with current recommendations. Unfortunately, however, our database does not enable us to identify which patients had induced versus spontaneous hypothermia. Finally, we are unable to comment on the causes of death or consider other potential confounding variables that were not collected as part of the ANZICS-APD.

Future studies

More investigations appear necessary, perhaps using other national databases [29]. Prospective investigations with focused data collection are also needed. If such studies confirmed a postive association, interventional strategies should be tested; if not, interventional studies would not seem justified.

Conclusions

In a large, multicentre, cohort study of patients admitted to the ICU after resuscitation from cardiac arrest, we found that hyperoxia was relatively uncommon. On the basis of initial multivariable analysis, it had only a weak independent relationship with mortality. This relationship could not be confirmed on the basis of sensitivity analysis, adjusted Cox proportional hazards modelling, after taking FiO_2 into account or after adjusting for time period, making it unlikely that it represents a reproducible biological phenomenon. Our findings support arguments against implementing policies of deliberate decreases in FiO_2 unless accurate and reliable pulse oximetry monitoring is available.

Key messages

- When the worst set of arterial blood gases is used for assessment, hyperoxia is uncommon in the first 24 hours after ICU admission in patients resuscitated from cardiac arrest.
- Using the same approach, isolated hypoxemia is just as common.
- Hyperoxia in these patients has a weak, model-dependent and nonreproducible association with mortality.
- Unless accurate and reliable pulse oximetry is available to prevent hypoxemia, a policy of reducing FiO_2 to avoid possible hyperoxia is not justified and may not be prudent.

Additional material

Additional file 1: Statistical appendix with details of multiple statistical models linking oxygen status with outcome.

Abbreviations
ANZ: Australia and New Zealand; ANZICS: Australian and New Zealand Intensive Care Society; APACHE III: Acute Physiology and Chronic Health Evaluation III; CORE: Centre for Outcomes and Resource Evaluation; FiO_2: inspired fraction of oxygen; PaO_2: arterial oxygen tension.

Author details
[1]Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, 5 Commercial Road, Prahran, Melbourne, Victoria 3181, Australia. [2]Australia New Zealand Intensive Care Society (ANZICS) Clinical Outcomes and Resource Evaluation (CORE) Centre, 10 Ievers Terrace, Carlton, Melbourne, Victoria 3053, Australia.

[3]Department of Intensive Care, Austin Hospital, 145 Studley Road, Heidelberg, Melbourne, Victoria 3084, Australia. [4]Department of Anesthesiology and Resuscitology, Okayama University Medical School, 5-1 Shikata-Cho 2-Chome, Okayama 700-8558, Okayama, Japan.

Authors' contributions

RB conceived the study in conjunction with the other authors and wrote the initial draft of the manuscript. MB conceived the study in conjunction with the other authors and performed the statistical analysis. GME conceived the study in conjunction with the other authors and reviewed and modified the final manuscript. AN conceived the study in conjunction with the other authors and reviewed and modified the final manuscript. DP conceived the study in conjunction with the other authors and reviewed and modified the final manuscript. GKH conceived the study in conjunction with the other authors and reviewed and modified the final manuscript. MCR conceived the study in conjunction with the other authors and reviewed and modified the final manuscript. ME assisted with the study and obtained and provided information on arterial blood gases in a selected cohort of cardiac arrest patients. DJC conceived the study in conjunction with the other authors and reviewed and modified the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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