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The interaction between arterial oxygenation and carbon dioxide and hospital mortality following out of hospital cardiac arrest: a cohort study

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Abstract

Background: Outcomes following out of hospital cardiac arrest (OHCA) are poor. The optimal arterial oxygen and carbon dioxide ($PaCO_2$) levels for managing patients following OHCA are unknown. We hypothesized that abnormalities in arterial oxygenation (PaO_2/FiO_2 ratio or PaO_2) and $PaCO_2$ would be associated with hospital mortality following OHCA. We hypothesized that $PaCO_2$ would significantly modify the oxygenation–mortality relationship.

Methods: This was an observational cohort study using data from OHCA survivors admitted to adult critical care units in England, Wales and Northern Ireland from 2011 to 2018. Logistic regression analyses were performed to assess the relationship between hospital mortality and oxygenation and $PaCO_2$.

Results: The analysis included 23,625 patients. In comparison with patients with a $PaO_2/FiO_2 > 300$ mmHg, those with a $PaO_2/FiO_2 \leq 100$ mmHg had higher mortality (adjusted OR, 1.79; 95% CI, 1.48 to 2.15; $P < 0.001$). In comparison to hyperoxemia ($PaO_2 > 100$ mmHg), patients with hypoxemia ($PaO_2 < 60$ mmHg) had higher mortality (adjusted OR, 1.34; 95% CI, 1.10 to 1.65; $P = 0.004$). In comparison with normocapnia, hypercapnia was associated with lower mortality. Hypocapnia ($PaCO2 \leq 35$ mmHg) was associated with higher mortality (adjusted OR, 1.91; 95% CI, 1.63 to 2.24; $P < 0.001$). $PaCO_2$ modified the PaO_2/FiO_2–mortality and PaO_2–mortality relationships, though these relationships were complex. Patients who were both hyperoxic and hypercapnic had the lowest mortality.

Conclusions: Low PaO_2/FiO_2 ratio, hypoxemia and hypocapnia are associated with higher mortality following OHCA. $PaCO_2$ modifies the relationship between oxygenation and mortality following OHCA; future studies examining this interaction are required.

Keywords: Out of hospital cardiac arrest, Oxygen, Carbon dioxide, Interaction, Mortality, Critical care

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Introduction

In the UK, 30,000 out of hospital cardiac arrests (OHCA) occur each year [1]. Outcomes are poor; of those who survive to ICU admission, just 28.6% survive to hospital discharge [2]. Derangements in oxygenation and carbon dioxide ($PaCO_2$) following cardiac arrest (CA) may exacerbate the post-cardiac arrest syndrome [3]. Hence, there has been a recent focus on the management of arterial oxygen and $PaCO_2$ in an effort to improve outcomes [4–18]. However, definitions of hypoxemia, hyperoxemia, hypocapnia and hypercapnia vary between studies making it hard to determine thresholds for benefit or harm. Furthermore, studies typically examine the impact of either oxygenation or $PaCO_2$ on outcomes; our knowledge of their interaction is limited [18].

Arterial hypoxemia following CA is associated with higher mortality [4–7]. However, previously used criterion for hypoxemia has combined patients with low PaO_2 and those with abnormal PaO_2/FiO_2 ratios making it hard to determine whether absolute hypoxemia or abnormal gas transfer is implicated in the observed increase in mortality. In addition, this approach creates a heterogenous population where patients may have low PaO_2/FiO_2 ratios but consistently be exposed to normoxia [4–7].

Conversely, hyperoxemia may exacerbate cellular injury in CA survivors [19]. The evidence surrounding the effect of hyperoxemia is conflicting. Studies have shown an association between hyperoxemia following CA and mortality [4, 5, 8]. Whilst these studies corrected for a variety of cardiac arrest features and physiological parameters, they did not use extensively validated disease-specific scoring systems or illness severity scores. Subsequent studies which used modified Acute Physiology And Chronic Health Evaluation (APACHE) scores to correct for illness severity found no association between mortality and hyperoxemia [6].

Hypocapnia is associated with worse outcomes following CA [6, 13]. The impact of hypercapnia is more uncertain. A $PaCO_2 > 45$ mmHg has been associated with improved neurological outcomes [13, 15]. However, higher levels of hypercapnia have been associated with poor neurological outcome or higher mortality [5, 16, 17].

An interdependence exists between ventilation parameters and oxygenation [6]. However, our understanding of how interactions between arterial oxygenation and $PaCO_2$ affect outcome following CA is limited and rarely investigated [6, 15, 18]. One prospective observational study found an association between high mean $PaCO_2$ and PaO_2 in the first 24 h following CA and good neurological outcome [15]. A recent pilot study found no difference in biomarkers of cerebral injury in patients randomized to four combinations of normocapnia, hypercapnia, normoxia or hyperoxemia. In this study, elevated regional cerebral oxygen saturation was seen with

both hypercapnia and hyperoxia [18]. It is unclear whether a combination of hyperoxia and hypercapnia would overwhelm anti-oxidant systems or improve survival through increased cerebral oxygenation [18]. This is relevant as cerebral injury accounts for two thirds of deaths in patients admitted to ICU following CA [19]. Further understanding of the effects of arterial oxygenation, $PaCO_2$ and their interactions in CA survivors would guide future patient management and inform trial design.

Hypotheses

We hypothesized that abnormalities in arterial oxygenation (either abnormal PaO_2/FiO_2 ratio or PaO_2) and $PaCO_2$ would be independently associated with hospital mortality, in adult patients admitted to intensive care units (ICU) following OHCA. We also hypothesized that $PaCO_2$ would modify the relationship between oxygenation and mortality.

Materials and methods

Data source

The Case Mix Programme (CMP) is the national clinical audit for adult critical care in England, Wales and Northern Ireland; 100% of adult, general intensive care units participated in the CMP [20]. For consecutive admissions, trained data collectors collect 20 physiological parameters from the first 24 h of ICU admission. In addition, 18 non-physiological predictors of mortality are collected including sociodemographic parameters, APACHE II comorbidity status and primary reason for ICU admission [20]. The Case Mix Programme Database (CMPD) does not collect data on cardiac arrest characteristics. Diagnostic data are coded using the Intensive Care National Audit & Research Centre (ICNARC) Coding Method and are available for 99.8% of ICU admissions [21]. Data undergoes validation prior to pooling into the CMPD. Support for the collection and use of these data has been obtained under Section 251 of the National Health Service Act 2006 (approval number: PIAG 2–10(f)/2005).

Arterial blood gas (ABG) data is recorded in the CMPD. The PaO_2, $PaCO_2$, pH and FiO_2 are recorded from the ABG with the lowest PaO_2 in the first 24 h after admission to ICU. We used the worst PaO_2 in the first 24 h which has been shown to be a better discriminator of hospital mortality than other measures of oxygenation in ICU patients [22].

Study design and population

We undertook retrospective analysis of the ICNARC CMPD for the period 1 January 2011 to 31 December 2018. We included adult patients (≥ 16 years) admitted to general ICUs who had CPR in the 24-h prior to ICU

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admission. We included OHCA patients only (further details of the CA definitions used are contained in Additional file 1). We excluded unintubated patients. In keeping with other studies, we only included patients who survived beyond 24 h [9, 10, 12, 23, 24]. We excluded patients with admissions following trauma or surgery, readmissions to ICU within the same hospitalization, those with missing hospital mortality outcome and patients without ABG results.

Statistical analysis

The co-primary exposures were either PaO_2/FiO_2 ratio or PaO_2. The primary outcome was hospital mortality. We considered $PaCO_2$ as the main effect modifier in the PaO_2/FiO_2–mortality and PaO_2–mortality relationships. We report unadjusted and adjusted associations between hospital mortality and PaO_2/FiO_2 ratio, PaO_2 and $PaCO_2$.

Abnormalities of gas transfer were categorized as follows: PaO_2/FiO_2 ratio ≤ 100 mmHg, $101–200$ mmHg, $201–300$ mmHg, and > 300 mmHg. The reference category was deemed to be $PaO_2/FiO_2 > 300$ mmHg representing patients without abnormal gas transfer [25]. To assess the impact of PaO_2 on outcome, we selected three categories: $PaO_2 < 60$ mmHg (hypoxemia), $60–100$ mmHg (normoxia) and > 100 mmHg (hyperoxemia, reflecting exposure to supra-physiological levels of oxygen). Based on previous research which demonstrated a PaO_2 of $150–200$ mmHg to be associated with the lowest hospital mortality following CA, we chose hyperoxemia as the reference category [6].

We selected five $PaCO_2$ categories: ≤ 35 mmHg (hypocapnia), $36–45$ mmHg (normocapnia) and three hypercapnia categories: $46–50$ mmHg, $51–55$ mmHg and > 55 mmHg. Due to the harm associated with hypocapnia and the conflicting evidence surrounding the effect of hypercapnia, normocapnia was chosen as the reference category.

Logistic regression models with the following covariates: year of admission, age in deciles, sex, self-reported ethnicity, pre-admission dependency, presence of severe comorbidity as defined using APACHE II score, primary diagnosis categories (sepsis status, acute coronary syndrome, cardiac arrhythmias, other), maximum temperature and lowest glucose in the first 24-h and Acute Physiology Score of the APACHE II score (APS-APII) were used to examine the relationship between hospital mortality and oxygenation and $PaCO_2$. We excluded oxygenation, pH and temperature from the APS-APII score, as they were tested as exposures in our study (Supplementary Table 1, Additional file 1); a similar approach has been used in studies examining the effect of oxygenation on outcomes following CA [7].

In logistic regression model 1, we tested the effect of PaO_2/FiO_2 ratio categories on hospital mortality. In logistic regression model 2, we tested the effect of PaO_2

categories on hospital mortality. We performed a number of sensitivity analyses; we tested the effect of varying thresholds of hyperoxemia (PaO_2 $101–200$ mmHg, $201–300$ mmHg and > 300 mmHg) on hospital mortality, with PaO_2 $101–200$ mmHg chosen as the reference category [6]. We repeated all the analyses including those who had died within the first 24 h. In all models, we included $PaCO_2$ categories to test for interaction.

All logistic regression models were fitted with robust standard errors to account for clustering by ICU and were reported as odds ratios (OR) with 95% confidence intervals (CI). We used complete case analysis, which has been shown to be unbiased in logistic regression under broad assumptions regarding the missing data mechanism [26]. Reported p values are two sided, and a p value less than 0.05 was considered statistically significant. As a retrospective cohort study, all outcomes were considered hypothesis-generating only and no adjustment was made for multiple comparisons. Continuous data were summarized as mean and standard deviation (SD), where normally distributed, and median and interquartile range, where not. Categorical data were presented as frequency and percentage. All analyses were performed using Stata/SE version 14.2 (StataCorp LP, College Station, TX).

Results

A total of 74,373 patients admitted following CA were identified; 50,748 met the exclusion criteria (Fig. 1). Patient demographics for 23,625 OHCA patients are shown in Table 1. ICU mortality was 48.9% and hospital mortality 59.1% (Table 1). A total of 860 patients were excluded from the final logistic regression analysis due to missing data. The crude, unadjusted and adjusted odds ratios for hospital mortality are presented in Table 2.
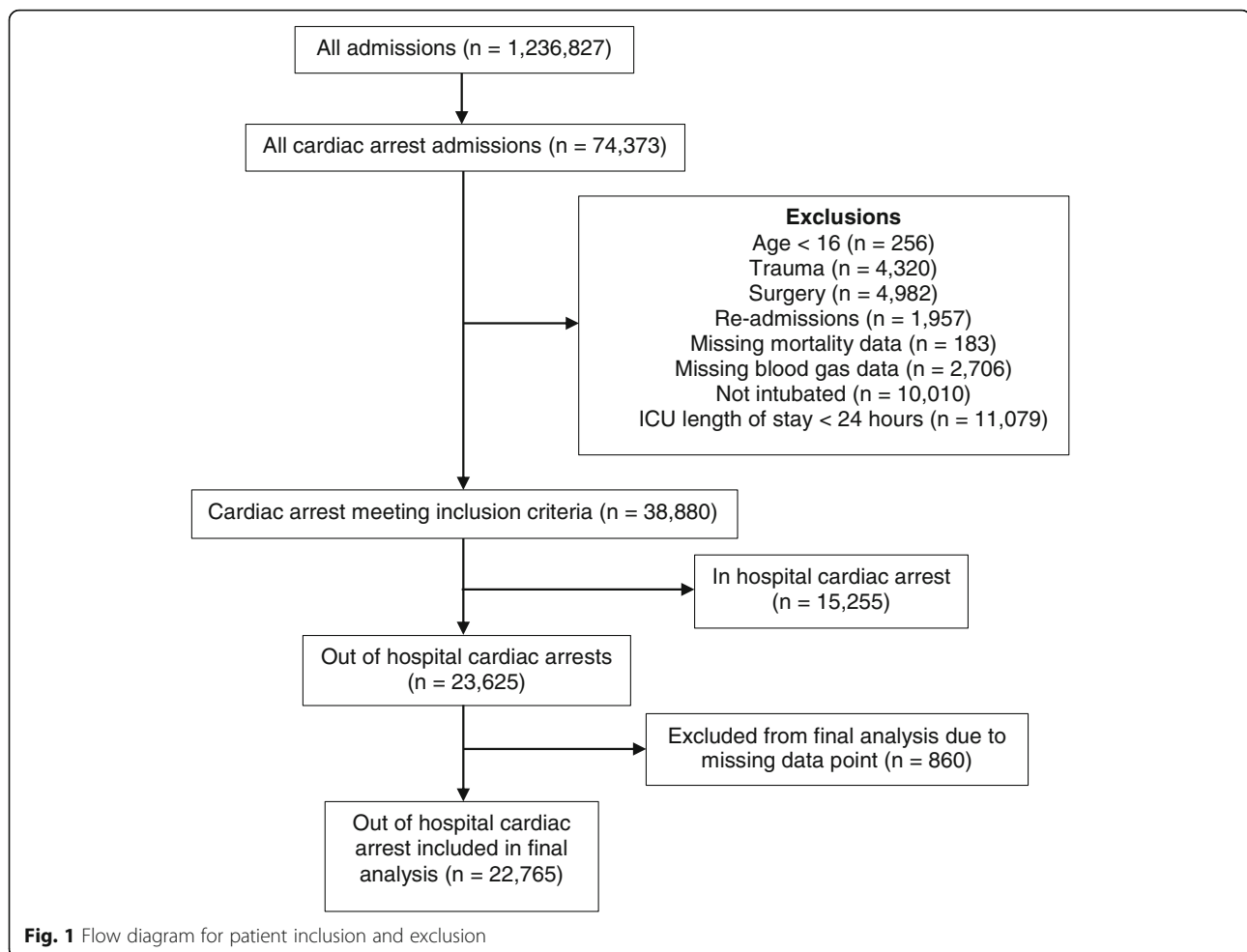
PaO_2/FiO_2–mortality relationship

The majority of patients (80.5%) had abnormal gas transfer. Crude hospital mortality was highest in those with $PaO_2/FiO_2 \leq 100$ mmHg (68.4%). Worsening PaO_2/FiO_2 ratios were associated with higher mortality (all $P < 0.001$). Patients with a $PaO_2/FiO_2 \leq 100$ mmHg had an almost twofold higher mortality than those with a PaO_2/FiO_2 ratio > 300 mmHg (Table 2).

PaO_2–mortality relationship

In comparison to the hyperoxemia group, the hypoxic group had a significantly higher mortality. There was no difference in mortality between normoxia and hyperoxemia (Table 2).

$PaCO_2$–mortality relationship

In the unadjusted analysis, the relationship between $PaCO_2$ and hospital mortality was U-shaped (Table 2).

Fig. 1 Flow diagram for patient inclusion and exclusion

In the adjusted analysis, hypocapnia was associated with higher hospital mortality, whereas a $PaCO_2$ of 46–50 mmHg and > 55 mmHg was associated with lower hospital mortality (Table 2). $PaCO_2$ modified the PaO_2/FiO_2–mortality and PaO2–mortality relationships (Figs. 2, 3, Supplementary Table 3 and 4, Additional file 1).

The impact of hypocapnia on the PaO_2/FiO_2–mortality relationship
In all PaO_2/FiO_2 categories, the presence of hypocapnia was associated with higher mortality when compared with normocapnia (Supplementary Table 3, Additional file 1).

The impact of hypocapnia on the PaO_2–mortality relationship
In patients with hypoxemia and normoxia, hypocapnia did not demonstrate a consistent effect on mortality when compared to normocapnia. In contrast, in patients with hyperoxemia, the presence of hypocapnia was associated with higher mortality when compared to normocapnia (Supplementary Table 4, Additional file 1).

The impact of hypercapnia on the PaO_2/FiO_2–mortality relationship
In all PaO_2/FiO_2 categories, hypercapnia was repeatedly associated with lower mortality. In the PaO_2/FiO_2 analysis, the lowest mortality was observed in those with a $PaO_2/FiO_2 > 300$ mmHg and a PaCO2 > 55 mmHg (adjusted OR, 0.40; 95% CI 0.23 to 0.70; $P = 0.001$) (Supplementary Table 3, Additional file 1).

The impact of hypercapnia on the PaO_2–mortality relationship
In patients with hypoxemia or normoxia, those with hypercapnia had a higher mortality when compared to those with normocapnia. In contrast, in those with hyperoxemia, all categories of hypercapnia were associated with significantly lower mortality which followed a dose-dependent pattern: $PaCO_2$ 46–50 mmHg (adjusted OR, 0.61; 95% CI, 0.41 to 0.89; $P = 0.011$), $PaCO_2$ 51–55 mmHg (adjusted OR, 0.53; 95% CI, 0.33 to 0.86; $P = 0.010$) and $PaCO_2 > 55$ mmHg (adjusted OR, 0.42; 95% CI, 0.26 to 0.63; $P < 0.001$). The lowest mortality overall

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Table 1 Patient characteristics

Characteristic	Entire cohort, n = 23,625
Male (%)	16,352 (69.2%)
Age (years), mean ± SD	60.6 ± 16.6
Self-reported ethnicity, n (%)	
White	20,750 ((87.8%)
Mixed	137 (0.6%)
Asian	961 (4.1%)
Black	458 (1.9%)
Other	344 (1.5%)
Not stated	975 (4.1%)
Pre-admission dependency, n (%)	
Able to live without assistance	18,716 (80.1%)
Some (minor/major) assistance with daily activities	4454 (19.1%)
Total assistance with all daily activities	183 (0.8%)
Severe co-morbidity[a], n (%)	
No	21,469 (90.9%)
Yes	2156 (9.1%)
APACHE II Acute Physiology Score, mean ± SD	14.3 ± 6.3
Primary diagnosis category, n (%)	
Sepsis	998 (4.2%)
Acute coronary syndrome	9166 (38.8%)
Cardiac arrhythmia	9155 (38.8%)
Other	4306 (18.2%)
FiO$_2$ (from ABG with lowest PaO$_2$), median (IQR) (data missing on n = 1)	0.35 (0.3–0.5)
Central temperature (°C), mean ± SD	
Maximum temperature in first 24 h (data missing on n = 1)	36.7 ± 1.3 °C
Minimum temperature in first 24 h (data missing on n = 1)	34.0 ± 1.6 °C
Glucose (mmol/L), mean ± SD	
Highest glucose in first 24 h (data missing on n = 1926)[b]	12.0 ± 5.2
Lowest glucose in first 24 h (data missing on n = 591)	6.5 ± 2.5
Treatment withdrawal after 24 h (%)	
No	14,820 (62.7%)
Yes	8805 (37.3%)
ICU outcome, n (%)	
Survived	12,064 (51.1%)
Died	11,561 (48.9%)
ICU length of stay (days), median (IQR)	
All patients	4.0 (2.4–7.1)
ICU survivors	5.2 (3.0–9.9)
ICU non-survivors	3.2 (1.9–5.1)
Hospital outcome, n (%)	
Survived	9649 (40.8%)
Died	13,976 (59.1%)
Hospital length of stay (days), median (IQR)	
All patients	7 (3–17)
Hospital survivors	19 (11–34)
Hospital non-survivors	4 (2–7)

[a]See Supplementary Table 1, Additional file 1. For definitions of APACHE II severe co-morbidities
[b]In patients where only one glucose is recorded, ICNARC CMPD records this as the lowest glucose; this results in a greater number of patients with missing highest glucose values

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Table 2 Impact of PaO_2/FiO_2, PaO_2 and $PaCO_2$ on hospital mortality

Variable	Incidence, **n** (%)	Hospital mortality, **n** (%)	Unadjusted odds ratio for hospital mortality (95% CI)	Adjusted odds ratio for hospital mortality (95% CI)
PaO_2/FiO_2[a]				
≤ 100 mmHg	3314/23,624 (14.0%)	2268/3314 (68.4%)	2.18 (1.98–2.39), $P < 0.001$	1.79 (1.48–2.15), $P < 0.001$
101–200 mmHg	8393/23,624 (35.5%)	5304/8393 (63.2%)	1.72 (1.60–1.85), $P < 0.001$	1.63 (1.45–1.84), $P < 0.001$
201–300 mmHg	7313/23,624 (31.0%)	4105/7313 (56.1%)	1.28 (1.19–1.38), $P < 0.001$	1.36 (1.21–1.53), $P < 0.001$
> 300 mmHg	4604/23,624 (19.5%)	2298/4604 (49.9%)	1 (Reference category)	1 (Reference category)
PaO_2[b]				
Hypoxemia	4135/23,625 (17.5%)	2704/4135 (65.4%)	1.61 (1.45–1.80), $P < 0.001$	1.34 (1.10–1.65), $P = 0.004$
Normoxia	17,480/23,625 (74.0%)	10,187 / 17,480 (58.3%)	1.19 (1.09–1.31), $P < 1.001$	1.15 (0.98–1.35), $P = 0.082$
Hyperoxemia	2010/23,625 (8.5%)	1085/2010 (54.0%)	1 (Reference category)	1 (Reference category)
$PaCO_2$[a]				
≤ 35 mmHg	5554/23,625 (23.5%)	3621/5554 (65.2%)	1.44 (1.34–1.54), $P < 0.001$	1.91 (1.63–2.24), $P < 0.001$
36–45 mmHg	9910/23,625 (41.9%)	5605/9910 (56.6%)	1 (Reference category)	1 (Reference category)
46–50 mmHg	3444/23,625 (14.6%)	1906/3444 (55.3%)	0.95 (0.88–1.03), $P = 0.215$	0.69 (0.55–0.86), $P = 0.001$
51–55 mmHg	1958/23,625 (8.3%)	1079/1958 (55.1%)	0.94 (0.86–1.04), $P = 0.237$	0.74 (0.53–1.04), $P = 0.079$
> 55 mmHg	2759/23,625 (11.7%)	1765/2759 (64.0%)	1.36 (1.25–1.49), $P < 0.001$	0.40 (0.23–0.70), $P = 0.001$

[a]Reported using logistic regression model 1, data missing on $n = 1$
[b]Reported using logistic regression model 2

was observed in patients with hyperoxemia and $PaCO_2 >$ 55 mmHg (Supplementary Table 4, Additional file 1).

Sensitivity analysis

The results of the sensitivity analyses are presented in Supplementary Tables 5 to 11, Additional file 1. In the PaO_2 five-category model, the number of patients with a PaO_2 201–300 mmHg or $PaO_2 > 300$ mmHg was small ($n = 40$ and $n = 31$, respectively). There was no statistically significant difference in mortality between a PaO_2 201–300 mmHg or $PaO_2 > 300$ mmHg and the reference category of PaO_2 101–200 mmHg (Supplementary Table 5 and 6, Additional file 1).

Sensitivity analyses including patients who died within the first 24 h were performed.

Crude, adjusted and unadjusted analysis produced near identical results to the main analysis (Supplementary Tables 7–9, Additional file 1). However, when those who died within the first 24 h were included, a $PaO_2 >$ 300 mmHg was associated with higher mortality (Supplementary Table 10 and 11, Additional file 1).

Analysis of the performance of the logistic regression model

Of the components included in the logistic regression analysis (Supplementary Table 1, Additional file 1), pH had the greatest influence on outcome, with acidosis being associated with increased mortality (Supplementary Table 2, Additional file 1). Variance inflation factors indicated there was no co-linearity between any of the ABG values used in our analysis.

Discussion

In this large retrospective study of patients admitted to ICU following OHCA, we found a significant association between hypoxemia and worsening PaO_2/FiO_2 ratios and mortality. This is in keeping with the other large CA databases [4–7, 12]. This has biological rationale as hypoxemia is a marker for pulmonary pathology and exacerbates myocardial dysfunction and cerebral injury [27]. No association between hyperoxemia and mortality was observed. Importantly, we found $PaCO_2$ modified the PaO_2/FiO_2–mortality and PaO_2–mortality relationships.

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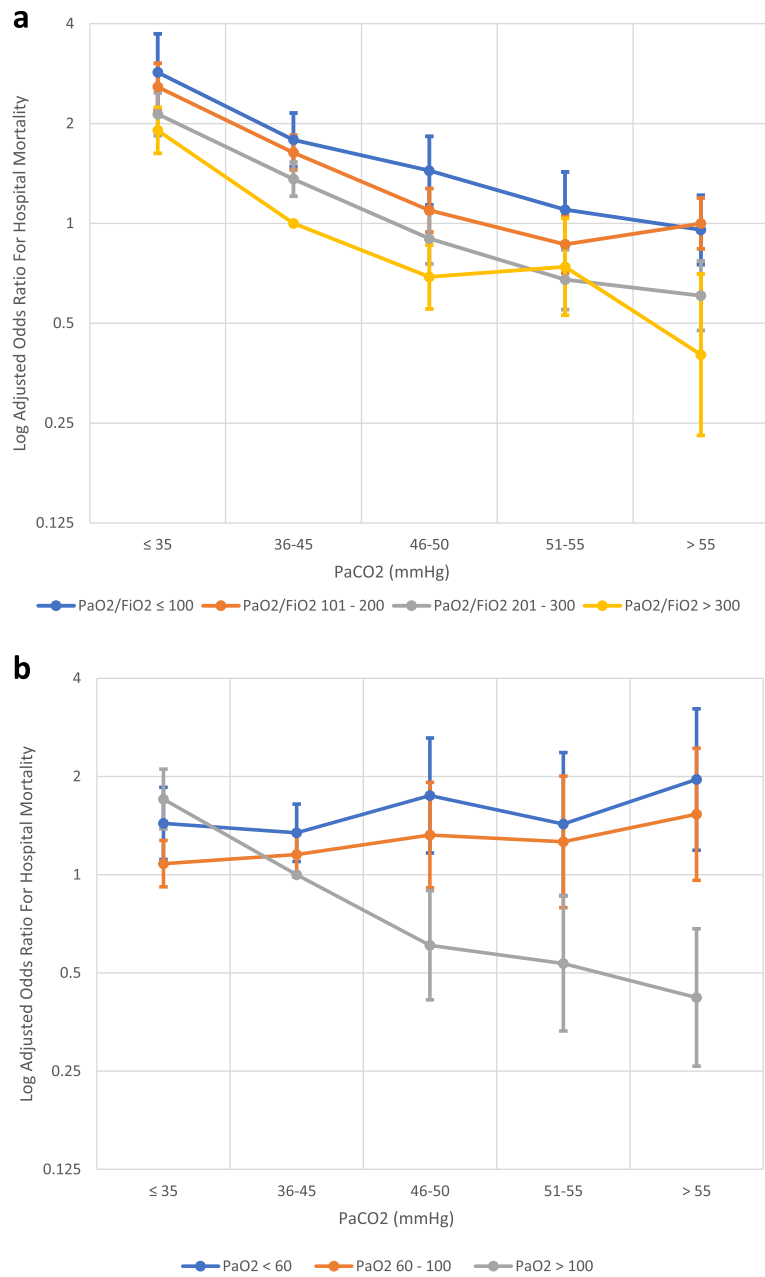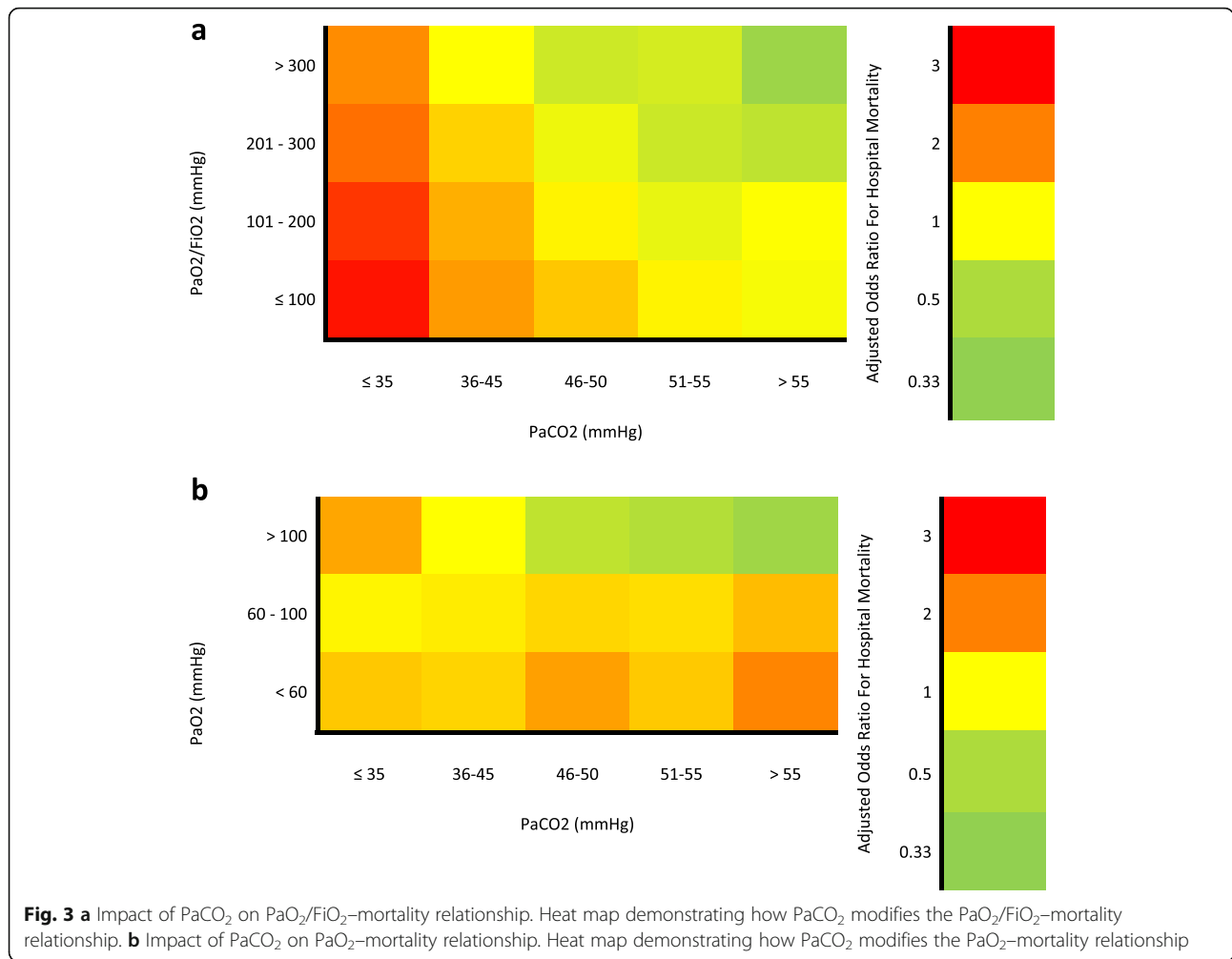
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Fig. 2 a Adjusted odds ratio for mortality PaO$_2$/FiO$_2$ versus PaCO$_2$ derived using logistic regression model 1. Presented using a semi-logarithmic scale. **b** Adjusted odds ratio for mortality PaO$_2$ versus PaCO$_2$ derived using logistic regression model 2. Presented using a semi-logarithmic scale

The post-cardiac arrest syndrome is characterized by a widespread ischaemia/reperfusion response [28]. Post-ischaemic tissue is susceptible to oxygen free radical damage, resulting in reduced left ventricular function, coronary artery vasoconstriction and myocardial ischaemia [29]. Hyperoxemia may exacerbate oxygen free radical-mediated damage in the brain and promote pulmonary inflammation [4, 30]. In contrast, a recent porcine model of CA demonstrated a reduced incidence of low brain tissue oxygenation in swine treated with a

FiO$_2$ of 1.0 and a 20-mmHg increase in mean arterial pressure (MAP) from baseline compared to those treated with a SpO2 target of 94–98% and a MAP target of > 65 mmHg [31]. This may help explain our finding of a lower mortality associated with hyperoxia. Previous studies which demonstrated an association between hyperoxemia and mortality following CA did not use validated scores to correct for illness severity [4, 5]. Our study, derived from a high-quality database, demonstrated no association between mortality and

Fig. 3 a Impact of $PaCO_2$ on PaO_2/FiO_2–mortality relationship. Heat map demonstrating how $PaCO_2$ modifies the PaO_2/FiO_2–mortality relationship. **b** Impact of $PaCO_2$ on PaO_2–mortality relationship. Heat map demonstrating how $PaCO_2$ modifies the PaO_2–mortality relationship

hyperoxemia or $PaO_2/FiO_2 > 300$ mmHg and is in keeping with similar studies [6]. Indeed, we found patients with hyperoxemia to have the lowest mortality. A sensitivity analysis examining different thresholds of hyperoxia found no association between hyperoxia and mortality. Following CA, the risk of exposure to hyperoxia falls with time, hence the low number of patients with a lowest $PaO_2 > 300$ mmHg [10]. However, the risk of a type II error is high. In sensitivity analyses including those who died within the first 24 h, a $PaO_2 > 300$ mmHg was associated with a higher mortality. Two thirds of patients who do not survive the first 24 h following OHCA have withdrawal of life-sustaining therapy based on pre-existing co-morbidities or perceived poor neurological prognosis [32]. Thus, for the majority of deaths within the first 24 h, the risk of mortality is unrelated to exposure to oxygenation or $PaCO_2$. As the risk of exposure to hyperoxia falls with time during the first 24 h following OHCA [10], those who die within the first 24 h have a disproportionate risk of having a lowest PaO_2 in the hyperoxia range. In our study, these patients were

excluded to avoid this important potential confounding variable.

In keeping with other studies, we found hypercapnia to be associated with lower mortality [13–15]. Hypercapnia modified both the PaO_2/FiO_2–mortality and PaO_2–mortality relationships. The mortality benefit was seen in all PaO_2/FiO_2 categories but was confined to hyperoxic patients in the PaO_2–mortality model.

Following CA, cerebral vasoconstriction and a loss of cerebral autoregulation have been demonstrated [33, 34]. Hypercapnia may increase cerebral blood flow, improve cerebral oxygenation, exhibit direct neuroprotective effects, reduce pulmonary and systemic inflammation and reduce oxygen free radical-mediated tissue injury [13, 15, 35–40]. In CA survivors, hypercapnia may attenuate oxygen free radical production. Alternatively, the observed benefit of hypercapnia over normocapnia may be attributable to injurious ventilation strategies used to achieve normocapnia [3].

Hypercapnia was repeatedly associated with lower mortality in the PaO_2/FiO_2 model. However, hypercapnia was not associated with lower mortality in the setting

of hypoxemia or normoxia in the PaO_2–mortality model. This may represent a sick cohort of patients with respiratory failure and poor pulmonary compliance not fully corrected for in the PaO_2–mortality model [41]. Hypercapnic acidosis causes pulmonary hypertension, right ventricular strain, reduced coronary blood flow and cerebral oedema [42, 43]. These effects are accentuated by hypoxemia [44, 45].

Hypocapnia was associated with higher mortality in all categories in the PaO_2/FiO_2–mortality model and in patients with hyperoxemia. Hyperoxemia and hypocapnia both cause cerebral vasoconstriction reducing cerebral blood flow [46–48]. Hypocapnia shifts the oxygen dissociation curve impairing oxygen delivery [47]. Together, these may exacerbate cerebral ischaemia.

The ability of $PaCO_2$ to modify outcomes depended on whether a PaO_2/FiO_2 or PaO_2 model was used. In addition, $PaCO_2$ had limited influence on outcomes in patients with hypoxemia and normoxia. It is likely that hypoxemia is the overwhelming factor determining mortality and $PaCO_2$ has a limited ability to modify this outcome. However, our understanding of the pathophysiology of the modifying impact of $PaCO_2$ is poor.

Our observational study has a number of strengths. We investigated the association between PaO_2/FiO_2 and absolute PaO_2 on mortality separately and unlike in other studies tested for interaction with $PaCO_2$. The cohort was larger than other studies in this area [4–18, 42]. Thus, allowing us to treat $PaCO_2$ as a categorical variable and investigate whether a threshold existed beyond which hypercapnia became harmful. Our cohort was derived from a high-quality database allowing correction for confounding variables. Our findings are supported by sensitivity analyses. We used the Acute Physiology Score component of the APACHE II score to correct for illness severity having excluded oxygenation, pH and temperature as they were tested as primary exposures in our model. The Acute Physiology Score has previously been demonstrated to have a better positive predictive value in predicting mortality following cardiac arrest than the APACHE II score [49]. The use of modified APACHE scores to correct for illness severity when examining the association between oxygenation and carbon dioxide and outcomes following cardiac arrest is well established [6, 7, 13, 15] but not universally applied [4, 5, 7, 9–11, 16, 17]. The APACHE II score has previously been shown to have a similar ability to predict mortality following OHCA as the disease-specific OHCA score [50].

Our study has a number of limitations. As a cohort study, causality cannot be inferred. It is possible that residual confounders remain. No data was available on intra-arrest characteristics. Hence, we have been unable to account for presenting rhythm, bystander CPR or defibrillation or duration of delay to ROSC, all of which

significantly impact on patient outcomes [51]. For OHCA patients, APACHE III scores showed a modest ability to predict mortality, whereas delay to ROSC showed a good ability to predict mortality [52]. We acknowledge that intra-arrest characteristics, including the delay to ROSC, are better predictors of outcome following cardiac arrest than illness severity scores. Unfortunately, no such data was collected within the ICNARC-CMPD. During our study period, there may have been temporal changes in cardiac arrest management including temperature control post-cardiac arrest; to account for this, we adjusted for year of admission [53]. Our outcome measure was hospital mortality; no data was available on longer-term mortality or neurological outcomes.

Previous studies have demonstrated an association between hyperoxemia on admission to ICU and mortality following CA [4, 5]. We cannot exclude that exposure to derangements in oxygenation and $PaCO_2$ in the immediate post-ROSC period is more prognostically significant than derangements as recorded in the ICNARC database. However, this is unlikely, as the worst PaO_2 in the first 24 h predicts ICU mortality more accurately than PaO_2 on the first ABG in a general ICU population [22]. Additionally, cumulative exposure to hyperoxemia over the first 24 h following CA has also been associated with mortality; the ICNARC-recorded ABG provides a surrogate for cumulative oxygen exposure during the first 24 h [10].

It could be argued that the ABG data collected may not be truly representative of an individual's exposure to derangements in oxygenation following CA. However, the ICNARC-recorded ABG uses methods similar to the APACHE methodology. The PaO_2 recorded using the APACHE methodology is more representative of the mean PaO_2 in the first 24, 48 and 72 h following CA than an ABG taken on admission to ICU [4, 7]. A further limitation is the use of the ICNARC-recorded $PaCO_2$; however, the $PaCO_2$ recorded using similar APACHE methodology correlates closely with $PaCO_2$ in the first 24 h in CA survivors [13].

In examining PaO_2/FiO_2 and PaO_2 separately, we have demonstrated that derangements in both were associated with higher mortality [4–7]. Despite a large number of patients with abnormal gas transfer, patients were typically normoxic; this may reflect titration of FiO_2 and adherence to ILCOR guidelines [3, 54]. However, it may have contributed to the different behaviour of the PaO_2/FiO_2 and PaO_2 models in relation to the modifying impact of $PaCO_2$. In our PaO_2/FiO_2 model, we were unable to differentiate between low PaO_2/FiO_2 ratios due to ARDS, pulmonary oedema or pre-existing lung pathology. Whilst we corrected for the presence of APACHE II-defined severe respiratory co-morbidity, residual confounding due to pre-existing respiratory pathology may have remained.

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Finally, in choosing $PaO_2 > 100$ mmHg as the threshold for hyperoxemia, we may have missed harm associated with a higher threshold [55]. To address this, we presented a sensitivity analysis. There are several reasons to justify our threshold of 100 mmHg; a $PaO_2 > 100$ mmHg is rarely observed in health (hence, patients where the lowest PaO_2 is > 100 mmHg have been exposed to supraphysiological levels of oxygenation over a 24-h period and are by definition hyperoxemic), a PaO_2 of 150-200 mmHg has been associated with the lowest hospital mortality in a post-cardiac arrest population, a similar threshold has previously been used when investigating hyperoxemia in a general ICU population and choosing this threshold identified a large hyperoxic patient cohort reducing the risk of a type II error [6, 32]. However, conclusions from our sensitivity analysis are limited by the small number of patients in the hyperoxemia categories, resulting in a risk of a type II error.

Conclusions

We found an association between hypoxemia, low PaO_2/FiO_2 ratios and hypocapnia and mortality following OHCA. As hypothesized, $PaCO_2$ modifies the relationship between oxygenation and mortality, though the relationships are complex. Our study emphasizes the need for future studies examining the interaction of PaO_2 and $PaCO_2$ in OHCA survivors.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13054-020-03039-6.

Additional file 1: The interaction between arterial oxygenation and carbon dioxide and hospital mortality following out of hospital cardiac arrest; a cohort study. Provides details on variables used in the logistic regression analysis and of how $PaCO_2$ modified the PaO_2/FiO_2 – mortality and PaO_2 – mortality relationships. Sensitivity analyses are presented examining the effects of varying thresholds of hyperoxia on mortality and the effect of including those who died in the first 24 hours. **Table 1** Variables used in logistic regression analysis Model-1 and Model-2. [a]APACHE II severe co-morbidities include the following: 1. Liver: biopsy proven cirrhosis with portal hypertension, previous upper gastrointestinal bleeding secondary to portal hypertension, previous hepatic encephalopathy or failure. 2. Cardiovascular: New York Heart Association Classification IV. 3. Respiratory: pulmonary disease resulting in severe exercise limitation, chronic hypoxemia or hypercapnia, severe pulmonary hypertension or ventilator dependency. 4. Renal: Dialysis dependent renal failure. 5. Immunocompromised: either drug or disease induced. **Table 2** Odds ratio for mortality for six pH categories used in logistic regression analysis Model-1. Table 3 Adjusted odds ratio for mortality PaO_2/FiO_2 versus $PaCO_2$ derived using logistic regression Model-1. Table 4 Adjusted odds ratio for mortality PaO_2 versus $PaCO_2$ derived using logistic regression Model-2. Table 5 Sensitivity analysis; Impact of varying thresholds of hyperoxia on hospital mortality. Five PaO_2 categories were chosen to examine the impact of alternative thresholds of hyperoxemia on mortality. **Table 6** Sensitivity analysis; Adjusted odds ratio for mortality for varying thresholds of PaO_2 versus $PaCO_2$. Five PaO_2 categories were chosen to examine the impact of alternative thresholds of hyperoxemia on mortality, $PaCO_2$ categories were included to test for interaction. [a]Due to the small number of patients in this subcategory of the sensitivity analysis (all of whom died), the interaction term has been dropped from the model

and the category therefore has the same OR for mortality as the reference category. **Table 7** Sensitivity analysis; Impact of PaO_2/FiO_2, PaO_2 and $PaCO_2$ on hospital mortality including those who died within the first 24 hours. **Table 8** Sensitivity analysis; Adjusted odds ratio for mortality PaO_2/FiO_2 versus $PaCO_2$ including those who died within the first 24 hours. **Table 9** Sensitivity analysis; Adjusted odds ratio for mortality PaO_2 versus $PaCO_2$ including those who died within the first 24 hours. Here, the ability of $PaCO_2$ to modify mortality relationships is attenuated. **Table 10** Sensitivity analysis; Impact of varying thresholds of hyperoxia on hospital mortality including those who died within the first 24 hours. Five PaO_2 categories were chosen to examine the impact of alternative thresholds of hyperoxemia on mortality including those who died within the first 24 hours. **Table 11** Sensitivity analysis; Adjusted odds ratio for mortality for varying thresholds of PaO_2 versus $PaCO_2$ including those who died within the first 24 hours. Here, the ability of $PaCO_2$ to modify mortality relationships is attenuated. [a]Due to the small number of patients in this subcategory of the sensitivity analysis (all of whom died), the interaction term has been dropped from the model and the category therefore has the same OR for mortality as the reference category.

Abbreviations

ABG: Arterial blood gas; APACHE: Acute physiology and chronic health evaluation; APS-APII: Acute physiology score of acute physiology and chronic health evaluation II score; CA: Cardiac arrest; CI: Confidence intervals; CMPD: Case Mix Programme database; CPR: Cardiopulmonary resuscitation; ICNARC: Intensive Care National Audit & Research Centre; ICU: Intensive care units; IHCA: In-hospital cardiac arrest; ILCOR: International Liaison Committee on Resuscitation; OHCA: Out of hospital cardiac arrests; OR: Odds ratio; $PaCO_2$: Arterial partial pressure of carbon dioxide; PaO_2: Arterial partial pressure of oxygen; PaO_2/FiO_2: Ratio of arterial partial pressure of oxygen divided by fraction of inspired oxygen; ROSC: Return of spontaneous circulation

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