Arterial carbon dioxide tension has a non-linear association with survival after out-of-hospital cardiac arrest: a multicentre observational study

Nicole Mckenzie[1, 2], Judith Finn[1,3,4,5], Geoffrey Dobb[2, 6], Paul Bailey[1,3,], Glenn Arendts[6,7], Antonio Celenza[4,8], Daniel Fatovich[1,4,9], Ian Jenkins[10], Stephen Ball[1,3], Janet Bray[5], Kwok M. Ho[1, 2,11,12]

[1] Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU), Curtin University, Bentley, WA, Australia

[2] Intensive Care Unit, Royal Perth Hospital, Perth, WA, Australia

[3] St John Western Australia, Belmont, WA, Australia

[4] School of Medicine (Emergency Medicine), University of Western Australia, Crawley, WA, Australia

[5] School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

[6] Faculty of Health and Medical Sciences, University of Western Australia, Crawley, WA, Australia

[7] Fiona Stanley Hospital, Murdoch, WA, Australia

[8] Sir Charles Gairdner Hospital, Nedlands, WA, Australia

[9] Emergency Medicine, Royal Perth Hospital, Perth, WA, Australia

[10] Fremantle Hospital, Fremantle, WA, Australia

[11] Medical School, University of Western Australia, Crawley, WA, Australia

[12] School of Veterinary and Life Sciences, Murdoch University, Perth, WA, Australia

Corresponding author:

Nicole Mckenzie

Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU), School of Nursing, Midwifery, and Paramedicine, Curtin University, GPO Box U1987, Perth, WA 6845, Australia

Telephone: +61 8 9226 4182

Email: nicole.mckenzie@curtin.edu.au

ORCID ID: 0000-0002-9953-3127

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Abstract

Purpose: International guidelines recommend targeting normocapnia in mechanically ventilated out-of-hospital cardiac arrest (OHCA) survivors, but the optimal arterial carbon dioxide ($PaCO_2$) target remains controversial. We hypothesised that the relationship between $PaCO_2$ and survival is non-linear, and targeting an intermediate level of $PaCO_2$ compared to a low or high $PaCO_2$ in the first 24-hours of ICU admission is associated with an improved survival to hospital discharge (STHD) and at 12-months.

Methods: We conducted a retrospective multi-centre cohort study of adults with non-traumatic OHCA requiring admission to one of four tertiary hospital intensive care units for mechanical ventilation. A four-knot restricted cubic spline function was used to allow non-linearity between the mean $PaCO_2$ within the first 24 hours of ICU admission after OHCA and survival, and optimal $PaCO_2$ cut-points were identified from the spline curve to generate corresponding odds ratios.

Results: We analysed 3769 $PaCO_2$ results within the first 24-hours of ICU admission, from 493 patients. $PaCO_2$ and survival had an inverted U-shape association; normocapnia was associated with significantly improved STHD compared to either hypocapnia (<35 mmHg) (adjusted odds ratio [aOR] 0.45, 95% confidence interval [CI] 0.24-0.83) or hypercapnia (>45 mmHg) (aOR 0.45, 95% CI 0.24-0.84). Of the twelve predictors assessed, $PaCO_2$ was the third most important predictor, and explained >11% of the variability in survival. The survival benefits of normocapnia extended to 12-months.

Conclusions: Maintaining normocapnia within the first 24-hours of intensive care admission after OHCA was associated with an improved survival compared to those with hypocapnia or hypercapnia.

Key Words

Arterial carbon dioxide tension, out-of-hospital cardiac arrest, post-resuscitation care, survival, neurological outcome

Introduction

Despite advances in post-resuscitation care, hypoxic-ischemic encephalopathy remains a common cause of death after out-of-hospital cardiac arrest (OHCA).[1] Ischemic-reperfusion brain injury involves a number of mechanisms, including inadequate cerebral oxygen delivery and impaired autoregulation of cerebral blood flow.[2] Cerebral oxygen delivery is determined by cerebral blood flow, which in turn can be affected by numerous factors including arterial carbon dioxide tension ($PaCO_2$).[3]

A recent meta-analysis of eight observational studies[4-11] found that both high and low $PaCO_2$ levels were associated with worse survival outcomes.[12] These findings are consistent with international guidelines that a normal $PaCO_2$ should be targeted during post-resuscitation care.[13,14] Data from existing randomized-controlled-trials targeting different $PaCO_2$ levels in adult patients after cardiac arrest are sparse.[15,16] Most of the observational studies are limited by their use of arbitrary cut-points to define an optimal $PaCO_2$, analysis of $PaCO_2$ using data from one single time point or over a limited period of time, and assuming $PaCO_2$ is linearly associated with survival.[12] Analysis assuming a linear association contradicts the results of a meta-analysis and two multi-centre cohort studies in which a non-linear association between $PaCO_2$ and patient outcome was demonstrated.[5,17]

We hypothesised that targeting normocapnia within the first 24 hours after OHCA is associated with a better chance of survival compared to hypocapnia or hypercapnia, and aimed to determine the optimal $PaCO_2$ cut-points for survival after OHCA.

Methods

Study Design and Setting

This multicentre retrospective cohort study included all patients with OHCA of non-traumatic aetiology[18] transported to one of four adult tertiary intensive care units (ICUs)[19] in Perth, Western Australia, between January 2012 and December 2017. In 2017 the Perth metropolitan area had a population 2.05 million[20]. St John Western Australia (SJWA) is the sole provider of emergency medical services in Western Australia. SJWA delivers a single tier of road-based paramedics who provide advanced life support according to SJWA Clinical Practice Guidelines[21] based on recomendations from the Australian Resuscitation Council.[22]

During the study period, all OHCA patients who had resuscitation attempted and not declared dead at the scene were transported to the nearest hospital emergency department[21] except patients with ST-segment elevation myocardial infarction who were transported directly to a hospital with the ability to perform percutaneous coronary intervention[21]. When clinically indicated, patients initially transported to the emergency department of a non-tertiary hospital were transferred to a tertiary hospital. These patients were defined as 'indirect' transport patients in this study.[23]

Participants

Adult OHCA patients (≥18 years) who achieved restoration of spontaneous circulation (ROSC) and received mechanical ventilation on arrival to one of the study centres were identified from the SJWA OHCA registry[24] and included in this study (Fig. 1).

Post-Resuscitation Care

Post-resuscitation care is standardised across the four study hospitals. At the time of this study, treatment included: hemodynamic management to maintain an adequate arterial blood pressure; protective ventilation to maintain arterial oxygen and carbon dioxide tension within normal limits; targeted temperature management (TTM) including prevention and treatment of hyperpyrexia; immediate percutaneous-coronary-intervention for patients who had ST-segment elevation myocardial infarction; and, use of multiple modalities to prognosticate neurological outcomes >72-hours after OHCA.[25]

Data Sources

Data were collected from the SJWA OHCA registry and from hospital medical records. The SJWA OHCA registry contains data on age (in years), sex (male vs female), arrest location (public vs home), OHCA witness status (paramedic vs bystander vs unwitnessed), bystander cardiopulmonary resuscitation (yes vs no), first rhythm as shockable (yes vs no), emergency medical services' response time to attend the scene (in minutes), time to tertiary ICU admission (in minutes) and transport to study centre status (direct vs indirect). This information was supplemented with data from the medical records which included all arterial blood gases (ABG) results within the first 72-hours of ICU admission, clinical interventions including percutaneous coronary intervention, mechanical ventilation, and TTM, and neurological status prior to cardiac arrest. Survival status at 12-months after OHCA was ascertained from the death registry.

Outcome Measures

The primary outcome was survival to hospital discharge (STHD). Secondary outcomes were 12-month survival and good neurological outcome at hospital discharge which was defined by Cerebral Performance Category score [26] of 1 (good cerebral performance) or 2 (moderate cerebral disability).[27]

Statistical Analyses

Continuous variables were reported as means and standard deviation (SD) or medians and interquartile range (IQR), and categorical variables as counts and percentages. Differences between groups were assesed using the t-test, Mann-Whitney-U or Kruskal-Wallis test for continuous variables, and Chi-square or Fisher's exact test for categorical variables. We adjusted for biologically plausible predictors for survival after OHCA in multivariable analysis, irrespective of their p-value in the univariate analyses.

We used a four-knot restricted cubic spline function[28] to allow for the possibility of a non-linear relationship between $PaCO_2$ and outcome. Optimal $PaCO_2$ cut-points were then identified based on the shape of the spline curve to generate corresponding odds ratios (ORs) using multivariable logistic regression. We assessed the relative importance of mean $PaCO_2$ to other predictors in explaining the variability in observed hospital mortality by each predictor's Chi Square contribution (or incremental improvement in the area under the receiver-operating-characteristic curve) in the multivariable logistic model[29]. Finally, we conducted two sensitivity analyses examining whether the mean $PaCO_2$ during the first 48 and 72-hours in ICU after OHCA remained associated with survival.

All analyses were two sided tests and conducted using SPSS for Windows (version 24.0, IBM, USA) and S-PLUS (version 8.2, 2010; TIBCP Software Inc., USA), and a $p < 0.05$ was considered statistically significant.

Ethics approval

Ethics approval was granted by the Curtin University Human Research Ethics Committee (HREC) (HR 199/2014) and each study hospital's HREC: Royal Perth Hospital (13-044), Sir Charles Gairdner Hospital (2012-184), Fremantle Hospital (AR-13-96) and Fiona Stanley Hospital (2015-091).

Results

Selection of the study population and its characteristics

Between January 2012 and December 2017, SJWA paramedics attended 8016 patients with non-traumatic OHCA. Of these, 3997 (49.9%) had resuscitation commenced by paramedics and 2812 (70.4%) were transported to a hospital emergency department (954; 33.9% with ROSC). Of the 887 (31.5%) patients who survived to emergency department discharge, 728 (82.1%) were admitted (directly or indirectly) to a tertiary hospital with 502 (69.0%) to the ICU. Nine patients (1.8%) were excluded because two were not ventilated on admission to ICU, four did not have an ABG within the first 6 hours of ICU admission or three had missing $PaCO_2$ data. Of the 493 patients included in this study, 232 (47.1%) survived to hospital discharge, a majority of them (n=210, 91.0%) with a good neurological outcome; 225 (97%) hospital survivors remained alive at 12-months (Fig. 1).

Table 1 summarises the characteristics of the study patients. Hospital survivors were younger (57 vs 63 years-old), more likely to be male (78.4% vs 65.1%), had bystander cardiopulmonary resuscitation (77.6% vs 63.2%), ventricular fibrillation or tachycardia as the initial arrest rhythm (83.6% vs 44.1%), and ROSC on arrival to the first emergency department (93.1% vs 76.6%) compared to non-survivors. With respect to in-hospital factors, hospital survivors were more likely to have a diagnosis of ST-segment elevation myocardial infarction (27.1% vs 16.9%), received percutaneous coronary intervention within 24-hours of OHCA (35.8% vs 22.6%) and TTM in the ICU (88.4% vs 75.1%) compared to non-survivors.

The association between mean $PaCO_2$ within the first 24 hours and survival

A total of 3769 ABG samples were collected within the first 24-hours and the median number of ABG samples per patient was 7 (IQR 5-10). Fig. 2 shows individual $PaCO_2$ values within the first 24-hours of ICU admission stratified by patients' hospital survival status. Without allowing the mean $PaCO_2$ to be modelled as a non-linear predictor, it had no significant association with STHD (p=0.62) while adjusting for other predictors of survival (listed in Table 2) (Supplementary Fig. 1). Conversely, after allowing $PaCO_2$ to be associated with STHD in a non-linear and non-monotonic fashion, we observed an inverted U-shaped relationship between the mean $PaCO_2$ and STHD (Fig. 3), with the predicted and observed probabilities of STHD closely matched each other (Supplementary Fig 2). The inverted U-shaped association between the mean $PaCO_2$ and survival to 12-months was similar to STHD (Fig 3).

Visual inspection of the inverted U-shape of relationship between $PaCO_2$ and STHD suggested that the best cut-points for $PaCO_2$ to differentiate survival were <35mmHg (n=78), 35-45mmHg (n=332) and >45 mmHg (n=83), in line with how hypocapnia, normocapnia and hypercapnia, respectively, were defined in other studies.[5,8-10] Patients in the normocapnia group were more likely to be male, have VF/VT as an intial arrest rhythm, and ROSC on arrival to the first emergency department compared to the hypo- and hypercapnia groups. The differences in patient characteristics between different $PaCO_2$ groups are described in Supplementary Table 1.

Maintaining normocapnia ($PaCO_2$ 35-45 mmHg) was significantly associated with a higher odds of STHD compared to either hypocapnia (adjusted odds ratio [aOR] 0.45; 95% CI 0.24-0.83) or hypercapnia (aOR 0.45; 95% CI 0.24-0.84) (Table 2). We observed a similar result between $PaCO_2$ and survival to 12 months for hypocapnia (aOR 0.37 (0.19-0.69) and hypercapnia (aOR 0.42 0.22-0.79) (Supplementary Table 2). Normocapnia was also significantly associated with a good neurological outcome at hospital discharge when compared to hypo- and hypercapnia. (Supplementary Fig. 4).

Relative importance of $PaCO_2$ on survival compared to other predictors

Initial rhythm that was shockable, witnessed arrest and mean $PaCO_2$ in the first 24-hours of ICU admission were the three most important predictors of survival, explaining 50.5%, 13.6% and 11.7% of the variability in STHD, respectively (Fig. 4). We noted that $PaCO_2$ was also more important than mean arterial oxygen tension within the first 24-hours (which explained 5.2% of the variability in STHD).

Sensitivity analysis

When compared to normocapnia, both hypocapnia (aOR 0.44; 95% CI 0.24-0.79) and hypercapnia (aOR 0.31; 95% CI 0.14-0.67) within the first 48-hours were associated with a reduced odd of survival (Supplementary

Table 3); this result remained similar when hypocapnia (aOR 0.44; 95% CI 0.24-0.80) and hypercapnia (aOR 0.28; 95% CI 0.13-0.62) within the first 72-hours were assessed (Supplementary Table 4).

Discussion

This multicentre cohort study found that maintaining normocapnia during the first 24-hours of ICU admission was associated with a significantly higher odd of survival compared to hypocapnia (<35 mmHg) or hypercapnia (>45 mmHg), and was the third most important predictor of OHCA survival. These results are clinically relevant and require careful consideration.

Our findings are consistent with a recent meta-analysis of eight observational studies including 23,434 patients, in which the relationship between $PaCO_2$ and survival and neurological outcome after cardiac arrest is found to be in a U-shaped and that normocapnia (35-45 mmHg) is associated with improved patient outcomes compared to hypo- or hypercapnia in the post-resuscitation phase.[12] They are also in line with international guidelines for post-resuscitation care that recommend protective lung ventilation targeting normocapnia by monitoring end-tidal carbon dioxide and ABG analyses.[13,14]

The existing observational studies that were used to inform international guidelines for post-resuscitation care after cardiac arrest have methodological limitations. These include a lack of serial ABG analyses within the first 24-hours of ICU admission, with some studies reporting results from using a single[5,6,8,10,11,30] measurement or at best only a limited number of ABG analyses[9,17,31]. For example, based on the results of a single ABG (with worst oxygenation data) during the first 24-hours in ICU admission, Helmerhorst et al.,[5] described a curvilinear relationship between $PaCO_2$ and survival after OHCA. Previous studies are also limited by using different, often arbitrary, $PaCO_2$ cut-points to define normocapnia (from >30 mmHg[4,6,7,32] to <50 mmHg[6,7]), making it difficult for clinicians to decide the optimal $PaCO_2$ range for OHCA patients[12]. Observational studies examining the association between $PaCO_2$ and survival after OHCA are limited[4,5,30,31], but suggest that hypocapnia in the post-ROSC period is associated with worse patient outcomes compared to normocapnia. As for hypercapnia, McGuigan et al.[30] found that hypercapnia was associated with a lower hospital mortality compared to normocapnia[30], but this study only used data from a single ABG associated with the lowest PaO_2 in the first 24-hours of ICU admission. Surely, a single $PaCO_2$ measurement would not fully capture the potential impact of $PaCO_2$ on the brain during the vulnerable period after OHCA. Clinicians might also have altered the ventilation subsequently without repeating ABG analyses, potentially inducing classification errors in determining whether a patient has been (mostly) exposed to hypocapnia, normocapnia or hypercapnia. Another important limitation in some existing studies is that they analyzed $PaCO_2$ as a linear predictor and as expected, these studies did not confirm the importance of normocapnia similar to our results when non-linearity of $PaCO_2$ was not allowed (Supplementary Fig. 1).

By summarising *all* serial measurements of $PaCO_2$ (over up to 72 hours) and allowing $PaCO_2$ to be modelled as a non-linear continuous predictor (Fig. 2), our results suggest that maintaining $PaCO_2$ of 5 mmHg above or below the 35-45mmHg range may have an important influence on patient outcome. Our results provide another piece of robust evidence to support the latest resuscitation guidelines that maintaining normocapnia (35-45mmHg) after OHCA is important to patient survival with a good neurological outcome. Because $PaCO_2$ can be titrated relatively easily by varying the ventilator settings, maintaining normocapnia potentially represents one of the most important therapies to optimize the survival of patients after OHCA.

Study strengths and limitations

This multi-centre cohort included all adult OHCA patients transported to four adult tertiary hospitals in Perth over six years with extensive data on $PaCO_2$ results up to 72-hours after ICU admission (Supplementary Tables 3 and 4), making our results more representative of the true exposure to $PaCO_2$ during the critical post-ROSC time period. We were also able to adjust for both pre-hospital and in-hospital variables that may impact survival, and allowed $PaCO_2$ to vary non-linearly with survival.

Our study has limitations. First, this was a retrospective observational study and we do not assert causality. Two recent small randomized-controlled-trials have examined the relationship between $PaCO_2$ and outcome after OHCA;[15,16] these studies were, however, limited by their small sample size and only used biomarkers as an outcome. The Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest (TAME) study[33] is a phase III clinical trial aiming to determine whether targeted therapeutic mild hypercapnia ($PaCO_2$ 50-55 mmHg) for 24 hours following randomization would improve neurological outcome at 6 months compared to standard care ($PaCO_2$ 35-45 mmHg) for adult OHCA patients. This study is estimated to complete in December 2022.

Second, a proportion of OHCA patients who survived their emergency department stay (17.9%) were not transferred to a tertiary hospital and were not included in our study. Because most of these patients did not require tertiary intensive care therapy, excluding these patients was logical and would not have altered our results. Third, protocols for post-resuscitation care varied between study centres in the timing and frequency of

ABG analyses and the temperature target for TTM. While the effects of hypothermia on $PaCO_2$ have not been directly considered, all sites used protective ventilation strategies. Fourth, it is unclear whether the ABGs were corrected to the patient's body temperature (pH-stat) or not (alpha-stat) and this may have had a small impact on the patients $PaCO_2$ grouping. Finally, we have no information on $PaCO_2$ before ICU admission.

Conclusions

Compared to hypocapnia (<35 mmHg) and hypercapnia (>45 mmHg), maintaining normocapnia (35-45mmHg) within the first 24-hours of ICU admission after OHCA was associated with a significantly greater chance of survival to hospital discharge and at 12 months. Our results support the existing international guidelines, and have important implication on how OHCA patients should be managed within the first 24 hours after ICU admission.

Conflicts of interest

None

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Authors' contributions

Nicole Mckenzie, Judith Finn and Kwok M. Ho contributed to the study conception and design. Material preparation, and data collection was performed by Nicole Mckenzie, Geoffrey Dobb and Stephen Ball. Data analysis was performed by Nicole Mckenzie and restricted cubic spline analysis was conducted by Kwok M. Ho. The first draft of the manuscript was written by Nicole Mckenzie and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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