Curtin School of Nursing

Faculty of Health Sciences

Post-resuscitation care following out-of-hospital cardiac arrest: identification of in-hospital prognostic determinants

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This thesis is presented for the degree of

Doctor of Philosophy

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Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution. To the best of my knowledge and belief, this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis includes five original manuscripts published in Resuscitation, the official journal of the European Resuscitation Council, covering research on cardiac arrest and cardiopulmonary resuscitation. As an Elsevier journal author I have the right to include the published journal articles in this thesis provided that it is not published commercially. This right extends to the posting of the thesis in the repository of Curtin University, provided that each journal article is embedded in the thesis and not separately downloadable (https://www.elsevier.com/about/policies/copyright).

The core theme of the thesis is the identification of in-hospital prognostic determinants for out-of-hospital cardiac arrest. The conception, study design, acquisition of data, analysis, interpretation and drafting of manuscripts were the principal responsibility of myself, the PhD candidate, working within the Prehospital Resuscitation and Emergency Care Research Unit (PRECRU), under the primary supervision of Professor Judith Finn and with the assistance of my other supervisors Associate Professor Kwok M. Ho and Associate Professor Janet Bray. The inclusion of co-authors in each manuscript reflects PRECRU's commitment to the development of collaborative research teams.

Ethics Approval

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007), and as updated in March 2014.

Ethics approval was granted by the Curtin University Human Research Ethics Committee (HREC) (HR 199/2014) and the relevant hospital HRECs: Sir Charles

Gairdner and Osborne Park Health Care Group HREC (Royal Perth Hospital, Sir Charles Gairdner Hospital, Fremantle Hospital, Fiona Stanley Hospital, Armadale Kelmscott District Hospital and Rockingham Kwinana District Hospital (#2012-184)); Ramsay Health Care WA/SA HREC: (Joondalup Health Campus and Peel Health Campus (#1225)); and St John of God Healthcare HREC (St John of God Hospital Midland, St John of God Hospital Murdoch, and St John of God Hospital Subiaco (#1209)). Copies of the ethics committee certificates of approval are contained in Thesis Appendix A.

Approval to access St John Western Australia (SJ-WA) Patient Care Records (both paper based and electronic) was granted by the St John Western Australia Research Advisory Group (now called the Research Governance Committee).

Access to PathWest Laboratory Medicine WA (PathWest) data was provided by PathWest, the pathology and forensic arm of the WA health system.

Nicole Frances McKenzie
22nd December 2021

Acknowledgment of Country

We acknowledge that Curtin University works across hundreds of traditional lands and custodial groups in Australia, and with First Nations people around the globe. We wish to pay our deepest respects to their ancestors and members of their communities, past, present, and to their emerging leaders. Our passion and commitment to work with all Australians and peoples from across the world, including our First Nations peoples are at the core of the work we do, reflective of our institutions' values and commitment to our role as leaders in the Reconciliation space in Australia.

Dedication

This thesis is dedicated to the memory of Professor Ian Jacobs, internationally renowned specialist in resuscitation and prehospital care and my primary PhD supervisor until his death on the 19th of October 2014. Of all the great things he achieved in life, he still took the time to help a fellow nurse embark on a path to a PhD. A path I never thought possible. Professor Jacobs, thank you for believing I could do this when I didn't believe it myself. You were an exemplary leader and teacher. I am privileged to have known you.

Abstract

Background: Cardiac arrest is an often fatal event resulting from sudden loss of heart function. When cardiac arrest occurs in the pre-hospital setting it is referred to as an out-of-hospital cardiac arrest (OHCA). In Australia, with a population of 26 million, OHCA affects an estimated 25,000 people each year; with a mortality rate of approximately 88%. A structured approach to OHCA management as defined by the 'Chain of Survival' is critical to high-quality patient outcomes. Comprised of five interconnected links, the chain of survival concept spans from early recognition of OHCA and activation of emergency medical services (first link), early CPR (second link), rapid defibrillation (third link), early advanced life support (fourth link) to standardised post-resuscitation care (fifth link). The research included in this thesis focuses on the post resuscitation care link in the chain of survival which begins with return of spontaneous circulation (ROSC).

ROSC has previously been defined as "spontaneous circulation with no further need for chest compressions for at least 20 minutes." Patients who achieve ROSC are at risk of developing post-cardiac arrest syndrome, a complex pathophysiological response to whole body ischaemia. Research suggests that early access to a post-resuscitation care bundle that includes emergent percutaneous coronary intervention (PCI), targeted management of body temperature and maintenance of normal arterial blood carbon dioxide ($PaCO_2$) and oxygen levels (PaO_2) improves survival and neurological outcomes after OHCA. However, in the absence of large randomised control trials (RCTs), there are conflicting conclusions about the survival benefit of some of the individual components of post-resuscitation care, including Emergency Medical Services (EMS) transport destination (PCI versus non PCI-capable hospital) and the optimal targets for $PaCO_2$ and PaO_2 in patients receiving mechanical ventilation. Further, there are few multicentre population-based studies that examine the impact of these factors on survival and neurological outcomes after OHCA and that assess the association between neurological outcome at hospital discharge and 12-month survival. Therefore, the broad aim of this thesis was to strengthen the evidence for optimising care in the post-resuscitation link in the chain

of survival by examining the effect of in-hospital factors on survival and neurological outcome after OHCA.

Methods: This thesis is based on a compilation of five peer reviewed manuscripts published in Resuscitation, the highest ranked journal in emergency medicine (Scimago H-Index 134) plus supporting chapters. In the first study, I conducted a multicentre retrospective cohort study of all patients (≥18 years) with OHCA from presumed medical aetiologies (presumed cardiac, or unknown, or other medical causes), who were attended by St John Western Australia (SJ-WA) paramedics in greater metropolitan Perth, WA between the 1st January 2012 and 31st December 2015 and admitted to hospital with ROSC. The aim of this study was to compare survival outcomes of OHCA patients directly transported to a PCI-capable hospital (direct transport) with patients transferred to a PCI-capable hospital via another hospital without PCI services available (indirect transport) by SJ-WA paramedics. This study used data from the prospectively collected SJ-WA database and medical chart review at each of the five hospitals included in the study. Survival to hospital discharge and survival up to 12-months after OHCA were compared between the direct and indirect transport groups using multivariable logistic regression analysis and Cox proportional hazards regression respectively, while adjusting for potential confounders.

In the second study, I performed a systematic review and meta-analysis to assess the effect of a low or high $PaCO_2$ on survival and neurological outcomes in adult patients with cardiac arrest of any aetiology. The primary outcome was survival to hospital discharge after cardiac arrest. Secondary outcomes included neurological status at the end of each study's follow-up period, hospital discharge destination and 30-day survival. Studies were included if patients had suffered an in-hospital cardiac arrest or OHCA and who had their exposure to $PaCO_2$ measured by arterial blood gas analysis (ABG). To examine this association, I searched MEDLINE, EMBASE, CINAHL and Cochrane CENTRAL databases for comparative studies published between inception and August 2015. Meta-analysis was conducted if statistical heterogeneity was low.

The findings of the meta-analysis informed my third study which included all patients with OHCA of non-traumatic aetiology transported to one of four adult tertiary intensive care units (ICUs) in Perth, Western Australia, between January 2012 and December 2017. In this study, I hypothesised that the relationship between $PaCO_2$ and survival is non-linear, and maintaining 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 improved hospital survival. Secondary outcomes were good neurological outcome at hospital discharge, as measured by Cerebral Performance Category (CPC) score of 1 or 2 and survival to 12-months. I used a four-knot restricted cubic spline function to allow for non-linearity between the mean $PaCO_2$ within the first 24 hours of ICU admission after OHCA and survival. Optimal $PaCO_2$ cut-points were identified from the shape of the spline curve to generate corresponding odds ratios in multivariable logistic regression analysis.

The methodology of the fourth study was near identical to the third and included a similar cohort of patients. In this study, I hypothesised that abnormalities in mean PaO_2 (both high and low) would be associated with decreased survival after OHCA. The primary outcome was survival to hospital discharge; secondary outcomes were CPC score at hospital discharge and 12-month survival. The potential non-linear relationship between the mean PaO_2 within the first 24-hs of ICU admission and patient outcomes was assessed by a four-knot restricted cubic spline function with adjustment for potential confounders in multivariable logistic regression analysis.

Finally, I conducted a multicentre retrospective cohort study to describe neurological and functional outcomes in adult OHCA patients (≥18 years) attended by SJ-WA paramedics in Perth, WA and admitted to hospital, between 1st January 2004 and 31st December 2019. I used multivariable logistic regression analysis to estimate the association of CPC score at hospital discharge with 12-month survival, adjusted for known prognostic variables.

Results: In the first study of 509 adults with OHCA of medical aetiology, I found that patients directly transported to a PCI-capable hospital for post-resuscitation care had

significantly increased survival to hospital discharge when compared to patients transferred via another hospital without PCI capability (adjusted odds ratio [aOR] 1.97, 95% confidence interval [CI] 1.13-3.43). Indirect transport (compared to direct transport) was also associated with an increased risk of death up to 12-months (adjusted hazard ratio 1.36, 95% CI 1.00-1.84) albeit this result did not reach statistical significance.

In the second study, nine observational studies were included in the systematic review and eight provided sufficient quantitative data for meta-analysis. I found that $PaCO_2$ has a non-linear inverted U-shaped association with survival and outcomes after cardiac arrest. Using $PaCO_2$ cut-points of <35 mmHg and >45 mmHg to define hypo- and hypercarbia, normocarbia (referred to as normocapnia elsewhere in the thesis) was associated with increased hospital survival (OR 1.30, 95% CI 1.23-1.38). Normocarbia was also associated with a good neurological outcome (CPC 1 or 2) compared to hypercarbia (OR 1.69, 95% CI 1.13-2.51). This finding is in line with international resuscitation guidelines' that normocarbia be targeted during post-resuscitation care.

Consistent with the findings of the meta-analysis, the third study concluded that a nonlinear (inverted U-shape) relationship exists between mean $PaCO_2$ in the first 24-hours of ICU admission and both hospital survival and survival to 12-months. Of the 493 patients who provided 3,769 $PaCO_2$ ABG results, I found that normocapnia was significantly associated with improved hospital survival compared to either hypocapnia (<35 mmHg) (aOR 0.45, 95% 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 11.7% of the variability in survival. The survival benefits of normocapnia extended to 12-months. Normocapnia was also significantly associated with a good neurological outcome at hospital discharge when compared to hypo- and hypercapnia.

Using PaO_2 as the exposure variable, my fourth study also demonstrated a non-linear association with an inverted U-shape between PaO_2 and patient outcome. Analysis

of 3,764 PaO_2 results (from 491 patients) obtained within the 24-hrs of ICU admission, found that survival to hospital discharge was highest for patients with a mean PaO_2 between 100 and 180 mmHg (reference category) when compared to patients with a mean PaO_2 of <100 mmHg (aOR 0.50, 95% CI 0.30-0.84), or >180 mmHg (aOR 0.41, 95% CI 0.18-0.92). Mean PaO_2 within 24-hrs was the third most important predictor and explained 9.1% of the variability in survival to hospital discharge. Patients in the reference category also demonstrated increased survival to 12-months and good neurological outcome (CPC 1 or 2) at hospital discharge.

In the final study, I found that of the 1,062 adult OHCA patients admitted to hospital over the 16 year study period most (92.7%) were discharged with a good neurological outcome (CPC 1 or 2). Further, a CPC of 1 or 2 at hospital discharge was significantly associated with 12-month survival (aOR 3.28, 95% CI 1.69-6.39) when the cohort was restricted to WA residents.

Conclusion: The research included in this thesis suggests that a number of potentially modifiable post-ROSC factors exist that may impact upon survival and neurological outcome after OHCA. These findings have important clinical implications and RCTs are needed to confirm the effect of hospital factors on patient outcomes and to validate the optimal oxygenation and ventilation targets. Given the strong association with survival, and the excellent short and long-term outcomes in the majority of OHCA patients who survive to hospital discharge, optimising post-resuscitation care should be prioritised.

Published Manuscripts

1. McKenzie N, Williams TA, Ho KM, Inoue M, Bailey P, Celenza A, Fatovich D, Jenkins I, Finn J. Direct transport to a PCI-capable hospital is associated with improved survival after adult out-of-hospital cardiac arrest of medical aetiology. *Resuscitation*. 2018 Jul; 128:76-82. doi: 10.1016/j.resuscitation.2018.04.039. Epub 2018 May 2. PMID: 29729284.

2. McKenzie N, Williams TA, Tohira H, Ho KM, Finn J. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest. *Resuscitation*. 2017 Feb; 111: 116-126. doi: 10.1016/j.resuscitation.2016.09.019. Epub 2016 Sep 30. PMID: 27697606.

3. Mckenzie N, Finn J, Dobb G, Bailey P, Arendts G, Celenza A, Fatovich D, Jenkins I, Ball S, Bray J, Ho KM. Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study. *Resuscitation*. 2021 Jan; 158:130-138. doi: 10.1016/j.resuscitation.2020.11.021. Epub 2020 Nov 21. PMID: 33232752.

4. Mckenzie N, Finn J, Dobb G, Bailey P, Arendts G, Celenza A, Fatovich D, Jenkins I, Ball S, Bray J, Ho KM. Arterial carbon dioxide tension has a non-linear association with survival after out-of-hospital cardiac arrest: A multicentre observational study. *Resuscitation*. 2021 May; 162:82-90. doi: 10.1016/j.resuscitation.2021.01.035. Epub 2021 Feb 8. PMID: 33571603.

5. Mckenzie N, Ball S, Bailey P, Finn L, Arendts G, Celenza A, Fatovich D, Jenkins I, Mukherjee A, Smedley B, Ghedina N, Bray J, Ho KM, Dobb G, Finn J. Neurological outcome in adult out-of-hospital cardiac arrest - Not all doom and gloom! Resuscitation. 2021 Oct; 167:227-232. doi: 10.1016/j.resuscitation.2021.08.042. Epub 2021 Sep 1. PMID: 34480975.

Table of Contents

List of Tables

N.B. Tables embedded within published papers do not appear in this list with the exception of supplementary material. The table headings included in this list are identical to those used in each publication. The references included in this list refer to those within the thesis.

List of Figures

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Abbreviations and Acronyms

Abbreviation/Acronym	Definition
ABG	Arterial Blood Gas
ACS	Acute Coronary Syndrome
AOR	Adjusted Odds Ratio
ARC	Australian Resuscitation Council
Aus-ROC	Australasian Resuscitation Outcomes Consortium
CAD	Computer Aided Dispatch
CI	Confidence Interval
CO_2	Carbon dioxide
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
ECG	Electrocardiogram
ED	Emergency Department
EMS	Emergency Medical Services
ePCR	Electronic Patient Care Record
FiO_2	Fraction of inspired oxygen
HITH	Hospital in the Home
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
IHCA	In-hospital Cardiac Arrest
ILCOR	International Liaison Committee on Resuscitation
mRS	Modified Rankin Score
NHMRC	National Health and Medical Research Council
NSE	Neuron-specific Enolase (NSE)
NSTEMI	Non-ST Segment Elevation Myocardial Infarction
OHCA	Out of Hospital Cardiac Arrest
OR	Odds Ratio
$PaCO_2$	Arterial Carbon Dioxide Tension
PaO_2	Arterial Oxygen Tension

PCI	Percutaneous Coronary Intervention
PDF	Portable Document Format
PEA	Pulseless Electrical Activity
PRECRU	Prehospital Resuscitation and Emergency Care Research Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
RCT	Randomised Control Trial
ROSC	Return of Spontaneous Circulation
RR	Relative Risk
SJ-WA	St John Western Australia
SPSS	Statistical Package for Social Sciences
STEMI	ST Segment Elevation Myocardial Infarction
TTM	Targeted Temperature Management
UMRN	Unique Medical Record Number
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WA	Western Australia

Publications, Presentations and Scholarships

Other Publications Related to Cardiac Arrest Care during Candidature

1. McKenzie N, Dobb GJ. Oxygen After Cardiac Arrest: Enough Is Enough? *Circulation*. 2018 May 15; 137(20):2125-2127. doi: 10.1161/CIRCULATIONAHA.118.033620. PMID: 29760225.

2. Williams TA, **McKenzie N**, Inoue M. Does therapeutic temperature management after cardiac arrest increase the risk of bleeding? *Aust Crit Care*. 2015 Aug; 28(3):169-71. doi: 10.1016/j.aucc.2015.01.001. Epub 2015 Feb 7. PMID: 25662156.

3. Beck B, Tohira H, Bray JE, Straney L, Brown E, Inoue M, Williams TA, **McKenzie N**, Celenza A, Bailey P, Finn J. Trends in traumatic out-of-hospital cardiac arrest in Perth, Western Australia from 1997 to 2014. *Resuscitation*. 2016 Jan; 98:79-84. doi: 10.1016/j.resuscitation.2015.10.015. Epub 2015 Nov 24. PMID: 26620392.

4. Inoue M, Tohira H, Williams T, Bailey P, Borland M, **McKenzie N**, Brink D, Finn J. Incidence, characteristics and survival outcomes of out-of-hospital cardiac arrest in children and adolescents between 1997 and 2014 in Perth, Western Australia. *Emerg Med Australas*. 2017 Feb; 29(1):69-76. doi: 10.1111/1742-6723.12657. Epub 2016 Aug 23. PMID: 27554798.

5. Bray J, Cartledge S, Finn J, Eastwood G, **McKenzie N**, Stub D, Straney L, Bernard S. The current temperature: A survey of post-resuscitation care across Australian and New Zealand intensive care units. *Resuscitation Plus*. 2020; 1-2:100002

6. Majewski D, Ball S, Bailey P, **Mckenzie N**, Bray J, Morgan A, Finn J. Survival to hospital discharge is equivalent to 30-day survival as a primary survival outcome for out-of-hospital cardiac arrest studies. *Resuscitation*. 2021 Jul 24:S0300-9572(21)00275-6.

Conference Presentations

1. Mckenzie N, Finn J, Dobb G, Bailey P, Arendts G, Celenza A, Fatovich D, Jenkins I, Ball S, Bray J, Ho KM. Non-linear association between arterial oxygen tension and survival after out-of hospital cardiac arrest: a multicentre observational study.
Oral presentation at the Aus-ROC Australian and New Zealand New Investigator Symposium, online, October 2020.

2. Mckenzie N, Ho KM, Bray J, Bailey P, Celenza A, Fatovich D, Jenkins I, Arendts G, Dobb G, Ball S, Finn J. The Effect of Sex and Age on Survival and Neurological Outcome of Out-Of-Hospital Cardiac Arrest Patients Admitted to Tertiary Intensive Care Units.
Poster presentation at the Australia and New Zealand Intensive Care Society (ANZICS) 14th World Congress of Intensive Care, Melbourne, Victoria, October 2019.

3. McKenzie N, Cheetham S, Williams TA, Inoue M, Fatovich D, Celenza A, Sprivulis P, Jenkins I, Tohira H, Ho KM, Bailey P, Finn J. Neurological outcome in adult out-of-hospital cardiac arrest (OHCA) patients – Not all doom and gloom!
Poster presentation at the 11th International Spark of Life Conference, Adelaide, South Australia, May 2017.

4. McKenzie N, Williams TA, Tohira H, Ho KM, Inoue M, Bailey P, Finn J. Direct transport to a tertiary hospital improves survival from out-of-hospital cardiac arrest in adults with acute coronary syndrome.
Poster presentation at the 11th International Spark of Life Conference, Adelaide, South Australia, May 2017.

5. McKenzie N, Williams TA, Tohira H, Ho KM, Finn J. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest.
Poster presentation at the American Heart Association (AHA) Scientific Sessions, New Orleans, United States of America, 2016.

Other Presentations

1. Non-linear association between arterial oxygen tension and survival after out-of hospital cardiac arrest: a multicentre observational study.
Oral presentation at Royal Perth Hospital Research Symposium Awards Day, Perth, Western Australia, October 2020.

2. The Effect of Sex and Age on Survival and Neurological Outcome of Out-Of-Hospital Cardiac Arrest Patients Admitted to Tertiary Intensive Care Units.
Poster presentation at the 7th Emergency Medicine Society of South Africa, Cape Town, South Africa, November 2019 (presented by Prof. Finn, J).

3. Neurological outcome in adult out-of-hospital cardiac arrest (OHCA) patients – Not all doom and gloom!
Poster presentation at the Innovation and Research Week Recycle Conference Poster Display, Faculty of Health Sciences, Curtin University, Perth, Western Australia October 2017.

4. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest.
Oral presentation at the Targeted Temperature Management Trial: The Real Message Seminar, Perth, March 2017.

5. Post-resuscitation care following out-of-hospital cardiac arrest: identification of in-hospital prognostic determinants.
Oral presentation at the AUS-ROC Seminar, Melbourne, Victoria, April 2016.

6. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest.
Oral and poster presentation at Mark Liveris Seminar, Faculty of Health Sciences, Curtin University, Perth, Australia 2016.

7. Post-resuscitation care following out-of-hospital cardiac arrest: identification of in-hospital prognostic determinants.

Oral presentation at the AUS-ROC Seminar, Melbourne, April 28 2016.

8. Post-resuscitation care following out-of-hospital cardiac arrest: identification of in-hospital prognostic determinants.

Oral presentation for Candidacy, School of Nursing Midwifery and Paramedicine, Curtin University, Perth, Australia, 2015.

Scholarships

Australian Post Graduate Award (APA), Curtin University

Curtin Research Scholarship (APA-CRS)

NHMRC Australian Resuscitation Outcomes Consortium (AUS-ROC) Centre of Research Excellence PhD Scholarship

Statement of Author Contributions to Published Papers

Paper One

McKenzie N, Williams TA, Ho KM, Inoue M, Bailey P, Celenza A, Fatovich D, Jenkins I, Finn J. Direct transport to a PCI-capable hospital is associated with improved survival after adult out-of-hospital cardiac arrest of medical aetiology. *Resuscitation*.2018 Jul; 128:76-82.

Author	Total Contribution	Signature
Ms. Nicole Mckenzie	60%	v
Dr. Teresa Williams	10%	
Associate Professor Kwok Ho	5%	
Dr. Madoka Inoue	5%	
Associate Professor Paul Bailey	2.5%	
Professor Antonio Celenza	2.5%	
Professor Daniel Fatovich	2.5%	
Dr. Ian Jenkins	2.5%	
Professor Judith Finn	10%	

I, Nicole Mckenzie, was the primary author of this paper with my contribution amounting to 60%. This study was primarily conceived by myself and my supervisors Professor Judith Finn, Dr Teresa Williams and Associate Professor Kwok M. Ho. Prehospital data was sourced from the SJ-WA OHCA database by Dr Madoka Inoue, the database manager, and provided to me as de-identified data. In-hospital data was collected by myself. I conducted all data cleaning and analysis. I prepared the manuscript, which was reviewed in the first instance by my supervisors Professor Judith Finn, Dr Teresa Williams and Associate Professor Kwok M. Ho. Subsequent revisions involved all manuscript co-authors. All authors were involved in the critical

review of the article for important intellectual content and final approval of the submitted manuscript.

Paper Two

McKenzie N, Williams TA, Tohira H, Ho KM, Finn J. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest. *Resuscitation*. 2017 Feb; 111: 116-126.

Author	Total Contribution	Signature
Ms. Nicole Mckenzie	55%	
Dr. Teresa Williams	15%	
Dr. Hideo Tohira	15%	
Associate Professor Kwok Ho	5%	
Professor Judith Finn	10%	

I, Nicole Mckenzie, was the primary author of this paper with my contribution amounting to 55%. I undertook the search of the literature and selected potentially relevant papers. Dr Teresa Williams independently screened these papers to identify relevant articles for inclusion and both Dr Teresa Williams and I independently performed the risk of bias assessments. I performed the meta-analyses with the assistance of Dr Teresa Williams, Dr Hideo Tohira and Associate Professor Kwok M. Ho. I drafted the manuscript. All authors reviewed the manuscript prior to submission.

Paper Three

Mckenzie N, Finn J, Dobb G, Bailey P, Arendts G, Celenza A, Fatovich D, Jenkins I, Ball S, Bray J, Ho KM. Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study. *Resuscitation*. 2021 Jan; 158:130-138.

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Associate Professor Glenn Arrendts	2%	
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Dr Stephen Ball	10%	
Associate Professor Janet Bray	5%	
Associate Professor Kwok Ho	10%	

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Paper Four

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Paper Five

Mckenzie N, Ball S, Bailey P, Finn L, Arendts G, Celenza A, Fatovich D, Jenkins I, Mukherjee A, Smedley B, Ghedina N, Bray J, Ho KM, Dobb G, Finn J. Neurological outcome in adult out-of-hospital cardiac arrest - Not all doom and gloom! *Resuscitation*. 2021 Oct; 167:227-232.

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Chapter 1 Introduction

1.1 Background and Rationale

Cardiac arrest is an often fatal event, resulting from sudden loss of heart function and systemic circulation.[1,2] When cardiac arrest occurs in the pre-hospital setting it is referred to as an out-of-hospital cardiac arrest (OHCA).[2] OHCA is a global public health issue with significant social and economic costs; measured in terms of premature mortality, neurological injury and functional disability.[3-6]

According to global registry data, the incidence of Emergency Medical Services (EMS)-treated OHCA is high, ranging from 30.0 to 97.1 cases per 100,000 population per year and survival to hospital discharge or 30-day survival is low at between 3.1 and 20.4% across OHCA registries.[7] Substantial variations in neurological outcomes after EMS treated OHCA are also reported, with a favourable neurological outcome at hospital discharge or at 30 days estimated to be between 2.8 and 18.2%.[7] Australian OHCA registry data estimates that as many as 25,000 OHCAs occur each year with 12% of patients surviving to hospital discharge.[8]

The aetiology of OHCA is presumed to be medical when no other obvious cause is evident, for example drug overdose, submersion, trauma, asphyxia or electrocution.[1,9] OHCA of presumed medical aetiology comprised 92% of all cases in a recent registry-based observational study.[9] Regardless of the aetiology, the ultimate goal of cardiopulmonary resuscitation (CPR) is to restore the flow of oxygenated blood to the brain and heart until restoration of spontaneous circulation (ROSC) can be achieved and sustained.[10] According to internationally accepted definitions, known as the OHCA Utstein Template for Resuscitation Registries, "sustained ROSC is deemed to have occurred when chest compressions are not required for 20 consecutive minutes and signs of circulation persist (or sustained ROSC if extracorporeal circulatory support is applied)."[11]

Post-resuscitation care is started immediately after sustained ROSC to re-establish effective regional and organ tissue perfusion, diminish the severity and consequences of Post-Cardiac Arrest Syndrome and improve the likelihood of survival with a favourable neurological outcome.[12] Post-Cardiac Arrest Syndrome is a complex pathophysiological response to whole body ischaemia, comprising hypoxic-ischaemic brain injury, myocardial dysfunction, systemic ischemia/reperfusion response and persistent precipitating pathology.[12] Interventions required for post-resuscitation care are generally bundled into a care regimen and administered simultaneously.[12] These include identification and treatment of the cause of the cardiac arrest, haemodynamic, oxygenation and ventilation management, targeted temperature management (TTM), glycaemic control, seizure management and neuroprognostication.[12]

The 'Chain of Survival' concept (Figure 1.1) provides a structured approach to OHCA management from the prehospital scene to in-hospital post-resuscitation care and identifies the time-critical interventions that have been shown to improve survival and neurological outcomes in OHCA patients.[13,14] Each link is time critical and interdependent.[13,14] The sequence of events starts with recognition of the emergency and activation of the EMS (first link), early CPR (second link), rapid defibrillation (third link), (4) early advanced life support (fourth link), and (5) standardised post-resuscitation care (fifth link).[13,14] It is well recognised that the Chain of Survival is only as strong as the weakest link.[13]

Figure 1.1 The American Heart Association Chain of Survival.[15]

The variation in international OHCA survival rates reported above, is likely reflective of differences in the strength of the local chain of survival. Therefore, research into

strategies to strengthen each link has the potential to significantly improve patient outcomes across regions.[16] The research included in this thesis concentrates on the fifth link – post-resuscitation care. It addresses important knowledge gaps in the prevention and treatment of post-cardiac arrest syndrome. These include whether the direct transport of adult OHCA patients to a hospital capable of providing emergency percutaneous coronary intervention (PCI) by emergency medical services (EMS), is associated with a survival advantage when compared to patients first transported to a non-PCI capable hospital. They also include the identification of safe arterial carbon dioxide tension ($PaCO_2$) and arterial oxygen tension (PaO_2) targets in mechanically ventilated adult OHCA patients. Studies that report neurological outcome at hospital discharge and long-term survival are also required to minimise prognostic errors in decision making. In the absence of results from large randomised control trials (RCTs) investigating individual components of post-resuscitation care, observational studies such as those included in this thesis, provide the best available indication of a possible causal relation between an exposure and patient outcome.

1.2 Research Aim and Objectives

1.2.1 Research Aim

The overall aim of this thesis is to explore the effect of in-hospital factors on survival and neurological outcome after OHCA.

1.2.2 Research Objectives

In order to achieve this aim, the following research objectives will be addressed:

1. To compare survival outcomes of adults with OHCA of medical aetiology directly transported to a PCI-capable hospital (direct transport) with patients transferred to a PCI-capable hospital via another hospital without PCI services available (indirect transport) by EMS.

2. To assess the effect of a low or high $PaCO_2$ on patient outcomes after cardiac arrest by systematically reviewing the literature and by combining results from similar studies in meta-analyses.

3. To assess the associations between different levels of $PaCO_2$ over the first 24 hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of non-traumatic aetiology.

4. To assess the associations between different levels of PaO_2 over the first 24 hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of medical aetiology.

5. To describe neurological and functional outcomes among OHCA patients who survived to hospital discharge and to determine the association between neurological outcome at hospital discharge and 12-month survival.

1.3 Thesis Approach

This thesis is based on a compilation of peer reviewed publications and supporting chapters. An overview of each chapter is provided in Table 1.1.

Table 1.1 Overview of Thesis Chapters.

Chapter	Contents	Research Aims
Chapter One	Introduction	1. Describe the background and rationale of the thesis. 2. Define the aim of the thesis and research objectives. 3. Provide an overview of the structure of the thesis.
Chapter Two	Background and Context	1. Present background information about OHCA. 2. Provide context to the research presented in this thesis. 3. Outline the significance of this doctoral research.
Chapter Three	Methods	1. Provide an overview of the thesis methods. 2. Describe the data sources. 3. Describe the study definitions and measurements.
Chapter Four	The association between EMS transport destination and survival after OHCA (**Research Objective 1)**	
	Manuscript: Direct transport to a PCI-capable hospital is associated with improved survival after adult out-of-hospital cardiac arrest of medical aetiology.[17]	To compare survival outcomes of adults with OHCA of medical aetiology directly transported to a PCI-capable hospital with patients transferred to a PCI-capable hospital via another hospital without PCI services available by EMS.
Chapter Five	Systematic review and meta-analysis **(Research Objective 2)**	
	Manuscript: A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest.[18]	To assess the effect of a low or high $PaCO_2$ on patient outcomes after cardiac arrest by systematically reviewing the literature and by combining results from similar studies in meta-analyses.
Chapter Six	The association of $PaCO_2$ and survival after OHCA **(Research Objective 3)**	
	Manuscript: Arterial carbon dioxide tension has a non-	To assess the associations between different levels of $PaCO_2$ over the first

Chapter	Contents	Research Aims
	linear association with survival after out-of-hospital cardiac arrest: A multicentre observational study.[19]	24 hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of non-traumatic aetiology.
Chapter Seven	The association of PaO_2 and survival after OHCA **(Research Objective 4)**	
	Manuscript: Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study.[20]	To assess the associations between different levels of PaO_2 over the first 24 hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of medical aetiology.
Chapter Eight	Neurological outcome at hospital discharge and survival to 12-months (**Research Objective 5)**	
	Manuscript: Neurological outcome in adult out-of-hospital cardiac arrest – not all doom and gloom! [21]	To describe neurological and functional outcomes among OHCA patients who survived to hospital discharge and to determine the association between neurological outcome at hospital discharge and 12-month survival.
Chapter Nine	Discussion and conclusions	1. Summarise aims, approach and key findings of the thesis. 2. Discuss the methodological strengths and limitations of the thesis. 3. Discuss recommendations based on key findings.

Chapter 2 Background and Context

2.1 Introduction

The intent of this chapter is to summarise current key concepts relating to OHCA and post-resuscitation care; and to describe the context within which this doctoral research was conducted (i.e. St John Western Australia, referred to as St John WA). I also explain the significance of this research.

2.2 Background

2.2.1 Definition

OHCA is defined as the loss of functional cardiac mechanical activity in association with the absence of a detectable carotid pulse, and unresponsiveness with agonal or absent respirations occurring outside of a hospital setting.[1] OHCA is an unpredictable medical emergency and can affect anyone in the community, of any age or gender and at any time or place.[22] OHCA is a time critical emergency.[22] Within seconds of the event, reduced blood flow to the brain causes unconsciousness, and irreversible damage occurs to brain tissue within a few minutes.[22] Early activation of the chain of survival is the most important intervention to increase the likelihood of survival and reduce the severity of primary and secondary brain injury.[13]

2.2.2 Incidence

The true global incidence of OHCA has been difficult to assess due to differences in definitions and reporting.[8,23-25] The development of Utstein-style guidelines for the uniform reporting of OHCA data by the International Liaison Committee on Resuscitation (ILCOR)[1], to address this issue, has assisted in the establishment of national and regional OHCA registries.[7] These include, the Cardiac Arrest Registry to Enhance Survival (CARES)[26] in the United States, the UK Out-of-hospital Cardiac Arrest Outcomes (OHCAO)[27] in the United Kingdom, the Pan-Asian Resuscitation Outcomes Study (PAROS)[28], the European Registry of Cardiac Arrest (EuReCa ONE)[29] and the Australian and New Zealand Resuscitation Outcomes Consortium (Aus-ROC) OHCA Epistry.[8]

A recent comparison of national and regional OHCA registries, found the global incidence of EMS reported OHCA was 30.0 to 97.1 individuals per 100,000 population.[7] In comparison with other developed countries, the incidence of EMS-attended OHCA per 100,000 population in Australia was 46.8.[7] This is lower than New Zealand (50.2), United Kingdom (52.9), and the United States (62.2) but higher than Singapore (42.0).[7] Variation in OHCA incidence across countries may be explained by differences in the denominator used for population-based EMS-treated cases, case ascertainment and social determinants of health.[7,8]

The Aus-ROC Epistry (epidemiologic registry) provides a comprehensive data source to understand the epidemiology of OHCA and to explore sources of variation in incidence and outcome across Australia and New Zealand, including regional comparisons.[8] Results from the Aus-ROC Epistry estimate that around 25,000 cases of OHCA occur in Australia each year.[8]

2.2.3 Prehospital Prognostic Factors

A number of modifiable factors in the chain of survival have been identified that improve survival and neurological outcome after OHCA.[30] These include bystander CPR,[31] early defibrillation[32] and EMS response time from call to scene.[31] Non-modifiable factors associated with improved patient outcomes after OHCA include younger age[33] and female sex,[34] witnessed arrest by bystanders[30] and a shockable initial arrest rhythm.[31,35]

2.2.4 Aetiology

Historically, the cause of OHCA was presumed to be of a cardiac origin unless an obvious non-cardiac cause was identified.[9] However, a 2014 review of the Utstein-style recommendations suggested OHCA aetiology be described as medical unless it was known or likely to have been caused by trauma, drug overdose, drowning, electrocution, or asphyxia.[1] Medical aetiology (presumed cardiac, other medical causes, or unknown cause) is the most common classification, and includes up to 92% of all OHCAs.[9] However, this classification system has yet to be widely adopted by

Australian ambulance services. The term 'non-traumatic' has also been used to describe OHCA of non-medical aetiology.[9]

A common underlying pathology for adult OHCA of presumed medical aetiology is coronary artery disease,[2] with atherosclerotic plaque rupture leading to thrombus formation and partial or complete arterial blockage.[36] The resulting Acute Coronary Syndrome (ACS), further defined as ST segment myocardial infarction (STEMI), non-ST segment myocardial infarction (NSTEMI) and unstable angina, can lead to severe metabolic and electrophysiological changes that induce ventricular arrhythmias such as ventricular fibrillation (VF) or ventricular tachycardia (VT) and subsequent circulatory collapse.[37] However, OHCA of medical aetiology may also result from a diverse range of other causes, including non-atherosclerotic disease of the coronary arteries, primary arrhythmia without ischaemic heart disease, cardiomyopathy, valvular heart disease and congenital heart disease.[2] Autopsy remains the gold standard for determination of cause of death, especially in young adults where the heterogeneity of OHCA aetiology is likely increased.[38]

2.2.5 Initial Cardiac Arrest Rhythm

The initial cardiac arrest rhythm is either: (a) VF or pulseless VT causing ineffective myocardial contractions or (b) pulseless electrical activity (PEA) leading to organised electrical depolarisation of the heart without synchronous myocardial contractions or (c) asystole resulting in the absence of electrical activity and myocardial contractions.[39,40] However, it can be difficult to determine the initial arrest rhythm as the shockable rhythms of VF or VT can deteriorate with time to asystole before the first electrocardiogram (ECG) is recorded.[41,42]

Aus-ROC Epistry data reports that overall, VF is the first monitored cardiac arrest rhythm in 27.9% of EMS-attended cases.[8] In communities where the chain of survival is strong, survival rates for witnessed OHCA with VF as the presenting rhythm can reach up to 70%.[43,44] For patients with PEA or asystole as an initial arrest rhythm, the probability of survival remains low.[35,40,45,46] One Australian study reported survival to hospital discharge rates for asystole and PEA as low as 1.1% and 5.9% respectively.[45]

A second Australian study found increased mortality for patients with non-shockable (as opposed to shockable) initial arrest rhythms in the first 4-years following OHCA.[35]

2.2.6 EMS Transport Destination

It is widely accepted that early access to standardised post-resuscitation care is both feasible and associated with higher rates of neurologically intact survival in adult OHCA patients.[17,47-51] The improved patient outcomes are associated with the implementation of a post-resuscitation bundle of care that includes PCI, targeted management of body temperature and careful control of oxygenation, ventilation and haemodynamic parameters.[12] The capability of the first destination hospital has been shown to influence patient outcomes in other time critical conditions such as trauma[52] and stroke.[53] Ensuring OHCA patients arrive at the right hospital at the right time has important implications for EMS transport protocols.

National[54] and international guidelines[12,55] recommend that adult OHCA cases of presumed medical aetiology are directly transported to a PCI-capable hospital. In this respect, admission to a hospital with 24/7 PCI capability, may be considered a surrogate for a higher level of post-resuscitation care. As OHCA is frequently attributed to coronary artery disease and VF/VT is relatively common in the acute phase of STEMI,[56] coronary angiography and PCI are important elements of post-resuscitation care. Research suggests that post-resuscitation coronary angiography, with and without PCI is associated with increased survival and favourable neurological outcome in adult OHCA patients.[57-60] This observation formed the basis of **Research Objective One** in my thesis- to compare survival outcomes of adults with OHCA of medical aetiology directly transported to a PCI-capable hospital (direct transport) with patients transferred to a PCI-capable hospital via another hospital without PCI services available (indirect transport) by EMS.

2.2.7 Post-resuscitation Care

The post-resuscitation care link in the Chain of Survival commences immediately after sustained ROSC has been achieved.[12] Post-resuscitation care is time sensitive and should be commenced regardless of location. The primary aim of post-resuscitation care is to re-establish effective regional and organ tissue perfusion and diminish the

consequences of post-cardiac arrest syndrome.[61] ILCOR defines post-cardiac arrest syndrome as the collective pathophysiology that occurs with hypoxaemic/ischaemic/reperfusion injury.[61] Four components of post-cardiac arrest syndrome are described: (1) post–cardiac arrest brain injury, (2) post–cardiac arrest myocardial dysfunction, (3) systemic ischaemia/reperfusion response, and (4) persistent precipitating pathology.[61] The systemic effects of post-cardiac arrest syndrome have been described as similar to severe sepsis with organ dysfunction, hypotension and hypoperfusion[61] The severity of post-cardiac arrest syndrome depends on the underlying cause of the arrest, time to sustained ROSC and the patient's premorbid health status.[61] Patients demonstrating signs of wakefulness at, or within a short time of ROSC, are less likely to develop post-cardiac arrest syndrome than patients who remain comatose.[61]

The phases of post-cardiac arrest syndrome have been defined by time: (1) immediate post-arrest phase - first 20 minutes (2) early post-arrest phase - 20 minutes to 6 to 12 hours (3) intermediate phase – 6 to 12 hours to 72 hours and (4) recovery phase – from 72 hours onward (Figure 2.1).[61] Following early identification of the cause of arrest, international guidelines recommend that clinical interventions for post-resuscitation care are bundled into a care regimen (Figure 2.2).[12] This includes early coronary angiography for patents with presumed OHCA of medical aetiology and management of physiological goals for key parameters such as $PaCO_2$ and PaO_2 and body temperature.[12] Other clinical interventions include treatment of seizures, general intensive care management and targeting a mean arterial blood pressure to achieve adequate urine output and normal blood lactate values.[12] In the later phases of post-cardiac arrest syndrome the focus is on prognostication and rehabilitation to optimise the neurological and functional outcomes of survivors.[12] The clinical interventions most relevant to the research included within this thesis are discussed below.

Figure 2.1 Phases of Post Cardiac Arrest Syndrome.[61]

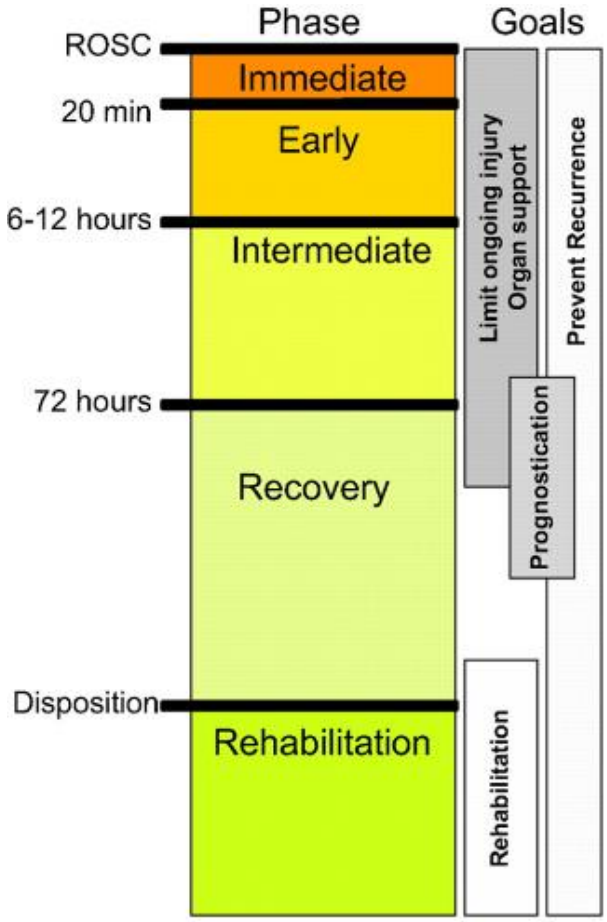
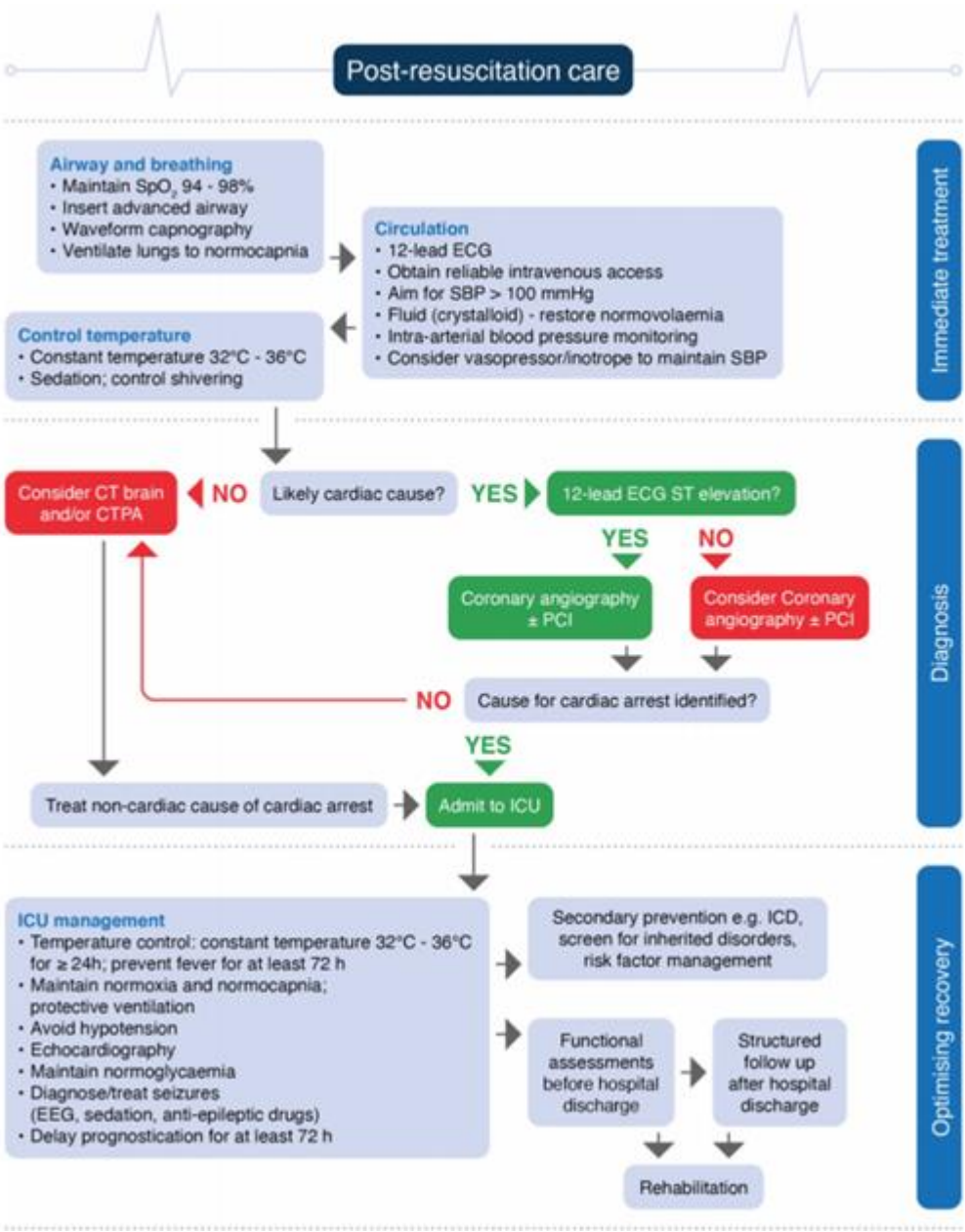


Figure 2.2 European Resuscitation Council and European Society of Intensive Care Medicine Post Resuscitation Care Algorithm.[12]



Abbreviations indicate as follows: SBP; systolic blood pressure, PCI; percutaneous coronary intervention, CTPA; computed tomography pulmonary angiogram, ICU; intensive care unit, EEG; electroencephalography, ICD; implanted cardioverter defibrillator.

Coronary Angiography

Patients with OHCA of medical aetiology have a high incidence of ACS.[12,62] The clinical management of ACS depends on whether the underlying cause is STEMI, NSTEMI or unstable angina, as defined by ECG criteria.[62] STEMI results from complete occlusion of a coronary artery whereas NSTEMI and unstable angina occur if the occlusion is partial (incomplete).[62] NSTEMI may be further distinguished from unstable angina by the presence of elevated cardiac biomarkers that reflect myocardial damage.[62] Early coronary angiography to determine the need for PCI in selected patients following resuscitation from OHCA has been shown to improve survival and neurological outcomes.[63] A 2017 meta-analysis of 23 observational studies found that coronary angiography performed within 24 hours of OHCA was associated with improved survival and neurological outcomes (compared with angiography performed more than 24 hours later or not at all).[63]

Control of Ventilation

A significant proportion of adult OHCA patients will remain unconscious after ROSC and will require endotracheal intubation and mechanical ventilation in an ICU to ensure adequate ventilation and removal of carbon dioxide from the lungs.[64] $PaCO_2$ is inversely proportional to minute alveolar ventilation and a direct reflection of gas exchange in the lungs. Abnormalities in $PaCO_2$ within the first 24 hours of ICU admission after OHCA are common.[64,65] Irrespective of the underlying cause of the arrest and post-ROSC factors, clinical interventions that slow metabolism such as the targeted management of body temperature may contribute to abnormalities in $PaCO_2$.[66] High $PaCO_2$ levels associated with insufficient carbon dioxide removal (hypoventilation) may result in vasodilation of cerebral blood vessels with a subsequent rise in intracranial pressure. Conversely low $PaCO_2$ levels associated with excessive carbon dioxide removal (hyperventilation) can induce cerebral vasoconstriction and exacerbate post-cardiac arrest brain injury.[67]

Observational studies examining the association between $PaCO_2$ and survival after OHCA suggest that a low $PaCO_2$ in the post-ROSC period (compared to a normal $PaCO_2$) is associated with worse patient outcomes.[68-71] While international guidelines

recommend targeting normal $PaCO_2$ levels in mechanically ventilated OHCA patients,[12] the optimal $PaCO_2$ target remains controversial. There are few RCTs targeting different levels of $PaCO_2$ in adult OHCA patients[66,72] and many of the existing observational studies have methodological limitations.[64,69-71,73-77] For example, using $PaCO_2$ data from a single time point[64,69,73] or limiting the number of $PaCO_2$ samples included in the analysis.[71,76,77]

These observations formed the basis of the following research objectives in my thesis: **Research Objective Two** - To assess the effect of a low or high $PaCO_2$ on patient outcomes after cardiac arrest by systematically reviewing the literature and by combining results from similar studies in meta-analysis; and **Research Objective Three** - To assess the associations between different levels of $PaCO_2$ over the first 24 hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of non-traumatic aetiology.

Control of Oxygenation

Supplemental oxygen is routinely given to patients after OHCA to increase PaO_2 and improve tissue hypoxia.[78] Inadvertent arterial hyperoxaemia (defined as supranormal PaO_2) may occur in the pre-hospital setting as poor peripheral perfusion during OHCA limits the accuracy of pulse oximetry and therefore the ability of the clinician to titrate oxygen to normal arterial blood levels.[79] In this instance, hyperoxaemia may not be detected until the first blood gas sample is analysed in the emergency department (ED) or ICU. Although the functional and pathological effects of prolonged hyperoxaemia are well established in animals[80] and neonates[81,82] the impact of post-ROSC hyperoxaemia on survival and neurological outcomes in adults remains unclear. It is thought that hyperoxaemia in adults potentiates secondary brain injury through haemodynamic changes resulting in vasoconstriction and reduced cardiac output and inflammatory changes producing oxygen free radical production triggering cell injury and apoptotic activity.[83]

Oxygen delivery and consumption can be optimised by maintaining PaO_2 within a target range in patients requiring mechanical ventilation after OHCA.[12] While international guidelines recommend targeting normoxaemia, the optimal PaO_2 target range is unknown. There are few RCTs[72,84] comparing different PaO_2 targets during the early post-resuscitation period, and results from observational studies are inconsistent and have substantial methodological limitations. For example, using a single PaO_2 data point as a measure of oxygen exposure, such as the first recorded PaO_2,[78] the highest PaO_2[85,86] or worst PaO_2[70,79] is unlikely to reflect overall oxygen exposure during the early to intermediate post-resuscitation phase. Further, studies investigating the association between PaO_2 and survival have often assumed PaO_2 has a linear effect on survival rather than allowing the data to be modelled in a non-linear fashion when such a relationship exists. This observation formed the basis of **Research Objective Four** in my thesis- to assess the associations between different levels of PaO_2 over the first 24 hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of medical aetiology.

Temperature Control

International guidelines recommend the targeted management of body temperature in adult OHCA patients who remain unresponsive after ROSC, irrespective of initial arrest rhythm.[12] However, this recommendation is based on weak evidence from RCTs with many methodological limitations. The results of the recent TTM2 Trial,[87] which has overcome some of these limitations, found no survival benefit associated with targeted hypothermia (33° Celsius) over targeted normothermia (37.8° Celsius) in 1,861 randomised patients. While these results support active temperature management in comatose post-ROSC patients, the optimal target temperature for different subgroups of OHCA patients remains unknown.[87]

2.2.8 Survival and Neurological Outcomes

The global survival rate to hospital discharge after OHCA has increased over the last four decades, probably due to an increased frequency of bystander CPR, early

defibrillation[88] and advances in post-resuscitation care.[12] A 2020 meta-analysis of 141 studies reporting survival rates of OHCA patients who received CPR, estimated the global survival rate to hospital discharge and 12 months to be 8.8% and 7.7% respectively.[88] The review found significant variability in survival across regions, with the highest survival rates observed in Western countries.[88] Research suggests that patients who experience a bystander-witnessed, shockable cardiac arrest (as defined by Utstein Criteria) have increased survival rates.[1] In 2019, Seattle and King County Medic One/EMS system, considered the gold standard for OHCA survival by the international resuscitation community, reported a survival rate of 56% for patients.[89] While early CPR and defibrillation make a difference, in-hospital post-resuscitation care is also important and further clinical research is essential to improve survival and neurological and functional outcomes.

Research assessing the neurological and functional status of survivors after OHCA is important for evaluating the outcomes of post-resuscitation care.[90] A number of scoring systems have been developed to measure neurological and functional outcomes after OHCA. These include the modified Rankin Score (mRS)[91] and the Cerebral Performance Category (CPC) score.[92,93] While ILCOR recommends use of the mRS over CPC scores, due to substantial interrater reliability and increased sensitivity in discriminating between mild and moderate disability,[94] most OHCA studies reporting neurological outcomes use the CPC scoring system.[12]

The CPC is a five category scale which ranges from unimpaired survival to severe dependence and death.[92,93] The scores are described as follows: CPC1: full recovery; CPC2: moderate disability; CPC3: severe disability; CPC4: coma or vegetative state; and CPC5: death. OPC scores at hospital discharge, ranged from OPC1 (capable of normal life) to OPC5 (death). CPC scores of ≤ 2 (moderate cerebral disability) suggest good neurological recovery.[1] Often used in conjunction with the CPC score, the overall performance category (OPC) score provides a measure of functional recovery after OHCA (Table 2.1). This type of evaluation is well suited to retrospective cohort studies as it is not restricted to a specific time point, does not require direct patient

contact and the scores can usually be determined by medical record or chart review.[90] CPC and OPC scores are most commonly assessed at hospital discharge.[90]

A recent survey of nine national and seven regional registries reported that for patients with EMS treated OHCA, a good neurological outcome at hospital discharge or 30 days was estimated to be between 2.8 to 18.2%.[7] This increased to between 9.9 to 33.3% for the subpopulation of patients with bystander witnessed shockable OHCA.[7] However, this survey also reported significant variations across regions,[7] suggesting further studies describing neurological and functional outcomes are required. This would assist in identifying reasons for variation in outcomes of care, support neurological prognostication and ensure that families and surrogate decision makers have realistic expectations of patient treatment and outcomes. This observation formed the basis for **Research Objective Five** in my thesis- to describe neurological and functional outcomes among OHCA patients who survived to hospital discharge and to determine the association between neurological outcome at hospital discharge and 12-month survival.

Table 2.1 Outcome of Brain Injury: The Glasgow-Pittsburgh Cerebral Performance and Overall Performance Categories.[95]

Cerebral Performance Categories	Overall Performance Categories
CPC1. Good Cerebral Performance Conscious, alert, able to work, might have mild neurologic or psychologic deficit.	**OPC1. Good Overall Performance** Healthy, alert and capable of normal life (CPC1).
CPC2. Moderate Cerebral Disability Conscious, sufficient cerebral function for independent activities of daily life. Able to work in a sheltered environment.	**OPC2. Moderate Overall Disability** Conscious (CPC2) or moderate disability from non-cerebral organ systems dysfunction alone (CPC1) or both. Performs independent activities of daily life but is disabled for competitive work.
CPC3. Severe Cerebral Disability Conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia and paralysis.	**OPC3. Severe Overall Disability** Conscious (CPC3) or severe disability from non-cerebral organ systems dysfunction alone (CPC1 or 2), or both. Dependent on others for daily support.
CPC4. Coma or Vegetative State Any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/wake cycles. Cerebral unresponsiveness.	**OPC4. Coma or Vegetative State** Same as CPC4.
CPC5. Brain Death Apnoea, areflexia, ECG silence etc.	**OPC5. Brain Death** Same as CPC5.

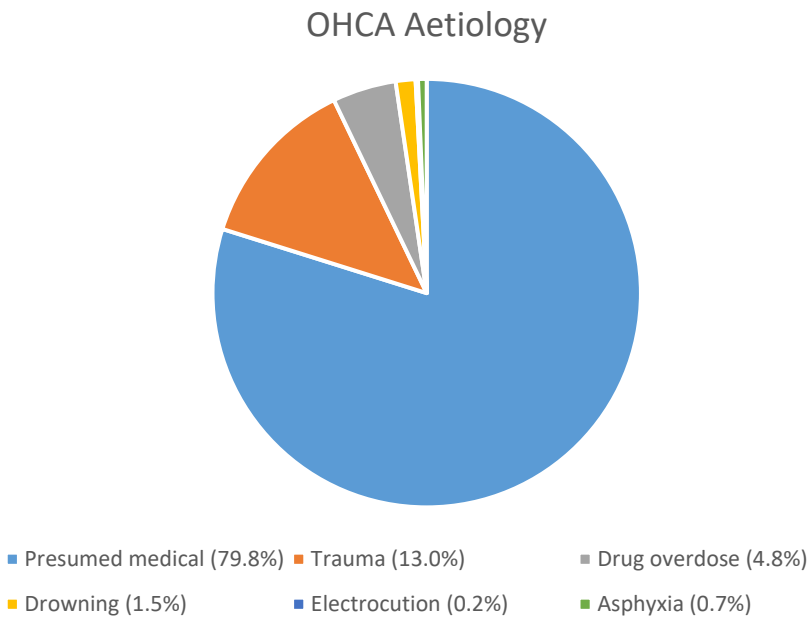
2.3 Context

2.3.1 Overview of OHCA in WA

The first OHCA registry in the Australia/New Zealand region was established with vision and foresight by Professor Ian Jacobs in 1996.[96] Following his death in 2014, responsibility was transferred to Professor Judith Finn, Director of the Pre-hospital, Resuscitation and Emergency Care Research Unit (PRECRU) Curtin University Perth, WA. The OHCA Database is now managed by the PRECRU Deputy Director Dr Stephen Ball with assistance from Ms Alani Morgan, Ms Sheryl Gallant, Ms Lyndall Finn and myself, the PhD Candidate. Data from the SJ-WA OHCA Database was used to inform the research included in this thesis.

In 2019, there were 1096 EMS-treated OHCA cases in WA.[97] This equates to 3 cases per day in this state alone.[96] In the same year, patients who had resuscitation attempted by SJ-WA paramedics had an OHCA of presumed medical aetiology in 79.8% of cases (unpublished data provided by Dr. S Ball; PRECRU Deputy Director 30th of July 2021). The aetiology of OHCA in WA during 2019 is further described in Figure 2.3. SJ-WA reported a survival to hospital discharge rate of 12% for patients who had resuscitation attempted by paramedics.[98] The survival rate increased to 35.1% for patients who experienced a bystander witnessed shockable arrest as defined by Utstein criteria.[98] In 2019, most patients who survived to hospital discharge had a good neurological outcome (CPC 1 or 2) at hospital discharge.[21]

Figure 2.3 The aetiology of OHCA in WA during 2019.



Data source: SJ-WA OHCA Database (unpublished data provided by Dr. S Ball; PRECRU Deputy Director 30th of July 2021)

2.3.2 Geography and Demography of Metropolitan Perth

Western Australia is Australia's largest state, spanning 2,527,013 square kilometres.[99] Perth (the capital city of WA) is located in the south-western corner of the state on the traditional lands of the Whadjuk Noongar Aboriginal People.[100] Over the study period (2004 to 2019), the Perth population increased from 1.49 to 2.0 million people representing an actual change of 35.5%.[101] In the 2016 Census there were 1,943,858 people in the Perth metropolitan area: 49.6% were male and 50.4% were female. Aboriginal and/or Torres Strait Islander people comprised 1.6% of the population.[102]

2.3.3 SJ-WA EMS Overview

SJ-WA is a not for-profit humanitarian organisation contracted by the WA Department of Health to provide emergency and non-emergency road based ambulance services across the state of WA. As the primary provider of emergency ambulance services, SJ-WA services a population of 2.5 million people geographically dispersed over 2.5 million square kilometres.[103] This is the largest area covered by a single ambulance provider in the world.[103] Of the 194 ambulance depots operating in WA, 34 are located within the Perth metropolitan area.[104] Of these, 30 are

operational 24 hours a day, 7 days a week and four provide day ambulance services only.[104] Metropolitan ambulance depots are staffed by a single tier of paramedics who provide advanced life support skills according to SJ-WA Clinical Practice Guidelines.[105] Clinical support paramedics provide clinical leadership and support to operational ambulance personnel. They also carry specialised equipment such as mechanical chest compression devices and extrication and lifting equipment.

The SJ-WA Clinical Practice Guidelines are consistent with recommendations by the Australian Resuscitation Council[106] for the life support management of adult OHCA. These include, high quality CPR and manual defibrillation, advanced airway management (endotracheal intubation, laryngeal mask or surgical airway [Cricothyrotomy]), needle thoracocentesis for tension pneumothorax, intravenous access for medication and fluid administration.[105] Paramedics are authorised to terminate resuscitation and declare life extinct when resuscitation efforts are considered futile, for example, if the initial arrest rhythm is asystole, non-paramedic witnessed and 20 minutes of continuous CPR is performed without ROSC.[105] Where there are obvious signs of death, such as injuries incompatible with life, resuscitation is withheld.[105]

In Australia, emergency ambulance services are activated by a call for help using the 24/7 triple zero (000) telephone number.[107] In WA, these calls are transferred to the SJ-WA State Operations Centre, where communication officers use Medical Priority Dispatch System (MPDS)[108] via ProQA software to undertake case entry and key questioning to determine dispatch priority and response time target and provide instructions to implement first aid or CPR.[107] This process is supported by Computer Aided Dispatch (CAD) software that provides geographical and incident information to identify the closest available ambulance crew.[107] Where OHCA is suspected, SJ-WA will dispatch at least two 2-person Priority 1 (potentially life threatening emergency) ambulances with 'lights and siren' to the scene with a response time target of less than 15 minutes.[107]

SJ-WA Clinical Practice Guidelines in place during the PhD study period, stated that OHCA patients who had resuscitation attempted by paramedics and not ceased in the field be transported to the nearest ED. Subsequent inter-hospital transfer occurred when the patient required a higher level of post-resuscitation care or access to another specialty service. Patients directly transported from scene to a PCI-capable hospital were defined as 'direct' transport patients. Patients transferred to a PCI-capable hospital via another hospital where PCI was not available to a PCI-capable hospital within 24 hours of EMS call were defined as 'indirect' transport patients.

2.3.4 WA Hospital System

The WA hospital system operates as a hybrid model with a mix of public, private and private-public hospital partnerships.[109] There are more than 80 hospitals, servicing 2.5 million people, spread across an area of 2.5 million square kilometres.[109] The public system ensures that all Australians, permanent residents of Australia and some overseas visitors, have access to free treatment as a public patient in a public hospital or private-public partnership hospital, paid for by the universal health insurance scheme Medicare.[110] In addition to Medicare, the purchase of private health insurance for in-hospital treatment provides access to both public and private hospitals.[110]

OHCA patients who were transported to hospital in the Perth metropolitan area during the study period (2004 to 2019), were transported to one of 11 hospitals with an ED that provided 24 hour emergency services: seven public hospitals: four tertiary and three general hospitals, one private hospital and three private-public partnership hospitals. Of these, six hospitals (four tertiary, one private and one private public partnership hospital) were PCI-capable as they had an onsite cardiac catheterisation laboratory and the ability to perform PCI. Of the four PCI-capable tertiary hospitals, two had restricted operating periods; Fremantle Hospital was downgraded to a non-teaching hospital in February 2015 and Fiona Stanley Hospital commenced operations in February 2015. The private-public partnership hospital with PCI capability (St John of God Midland Hospital) operated from November 2012 (Table 2.2). The few patients admitted to the private hospital were excluded from

this study as I did not seek Human Research Ethics Committee (HREC) approval from that hospital.

Table 2.2 Metropolitan Perth hospitals stratified by hospital type, PCI capability and operating restrictions.[109]

Hospital Name	Hospital Type	PCI-capable	Operating restrictions
Royal Perth Hospital	Tertiary	Yes	Unrestricted
Sir Charles Gairdner Hospital	Tertiary	Yes	Unrestricted
Fiona Stanley Hospital	Tertiary	Yes	Restricted- opened February 2015
Fremantle Hospital	Tertiary	Yes	Restricted- downgraded February 2015
Armadale Health Service	General	No	Unrestricted
Rockingham Hospital	General	No	Unrestricted
Swan District Hospital	General	No	Restricted- closed November 2015
St John of God Murdoch	Private	Yes	Unrestricted
Joondalup Health Campus	Private Public Partnership	Yes	Unrestricted
St John of God Midland	Private Public Partnership	No	Restricted- opened November 2012
Peel Health Campus	Private Public Partnership	No	Unrestricted

2.4 Significance of Doctoral Research

There is growing evidence that advances in post-resuscitation care have led to improvements in survival rates and neurological morbidity following OHCA.[12] Certainly, the individual and combined components of post-cardiac arrest syndrome may be treatable if the patient is managed appropriately with coordinated, collaborative care and resources. However, in the absence of high-certainty evidence from large RCTs,[12] well designed observational studies, such as those included in this thesis, are required to inform international guidelines for post resuscitation care.

In the first retrospective cohort study, I investigated whether direct transport to a PCI-capable hospital for post-resuscitation care is associated with a survival advantage for adults with OHCA of medical aetiology.[17] EMS transport protocols should now be informed by studies such as this, comparing patient characteristics and outcomes following OHCA between those patients transported to hospitals with or without PCI-capability. Also, this PhD study was included in a systematic review of 17 observational studies and one RCT, that addressed the question as to whether post resuscitation care at a cardiac arrest centre, compared to care in a hospital not designated as a cardiac arrest centre, is associated with a better patient outcomes.[51] This systematic review informed ILCOR guidelines, that state wherever possible, adult OHCA patients with medical aetiology should be cared for in a hospital with 24/7 PCI capability.[111]

In the second and third retrospective cohort studies included in this thesis, I assessed the associations between different levels of $PaCO_2$[19] and PaO_2[20] over the first 24 hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of non-traumatic aetiology. An ILCOR systematic review investigating oxygen and ventilation targets after cardiac arrest, (based on 36 observational studies and seven RCTs) concluded that point estimates of individual studies generally favoured normoxemia and normocapnia when compared to hypo and hyperoxaemia and hypo and hypercapnia.[112] However, many of the included studies were limited by an excessive

risk of bias and did not reach statistical significance.[112] Given the quality of this evidence, studies addressing the limitations of previous analyses are required to identify optimal $PaCO_2$ and PaO_2 targets after OHCA. Many of these limitations were identified in my systematic review and meta-analysis investigating the association between $PaCO_2$ and outcome after cardiac arrest.[18] This information was used to inform the methodology of the retrospective cohort studies included in this thesis which importantly did not assume a linear relationship between $PaCO_2$ and PaO_2 and outcome after OHCA. This in turn identified U-shaped relationships between mean $PaCO_2$ and PaO_2 for periods up to 72 hours after ICU admission for OHCA and identified target ranges for $PaCO_2$ and PaO_2 associated with optimum outcomes that should be maintained over this time period. These studies should now be incorporated into evidence to inform international guideline recommendations.

In the fourth retrospective cohort study included in this thesis, I described neurological and functional outcomes of adult OHCA patients admitted to hospital and estimated the association of CPC score at hospital discharge with 12-month survival, adjusted for known prognostic variables.[21] International guidelines acknowledge that the CPC score is the most widely used outcome measure after cardiac arrest.[12] This study provides additional information about the association between CPC score at hospital discharge and survival to 12-months that can inform prognostic decision making. It may also help to reduce the risk of premature withdrawal of life sustaining therapy in patients who have a chance of meaningful neurological recovery.

2.5 Conclusion

This chapter provided background and context to the research included in this thesis. It also outlined the significance of this doctoral research. The next chapter presents the methodology used to conduct the four multicentre retrospective cohort studies presented in this thesis.

Chapter 3 Methods

3.1 Overview

This chapter provides an overview of the methods used to undertake the four retrospective multicentre cohort studies included in this thesis. The chapter describes the research ethics, study design and setting, inclusion and exclusion criteria, data sources, patient outcomes and statistical methods used to analyse the data in each study. Further details of the methods used in each study are described in the publications incorporated into the subsequent chapters. The methods for the systematic review and meta-analysis are presented separately in Chapter Five.

3.2 Research ethics

The research presented in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014.

This PhD research project sits under an overarching study titled "Functional status of survivors of out-of-hospital cardiac arrest in Perth Western Australia". This study has been approved by the HREC of the lead site Sir Charles Gairdner Hospital (RGS0000001631 2012-184). The PhD Candidate has been listed as a co-investigator on this study and has been employed as the primary data collector since July 2013. Ethics approval was granted by the Curtin University Human Research Ethics Committee (HREC) (HR 199/2014) and the relevant hospital HRECs: Sir Charles Gairdner and Osborne Park Health Care Group HREC (Royal Perth Hospital, Sir Charles Gairdner Hospital, Fremantle Hospital, Fiona Stanley Hospital, Armadale Kelmscott District Hospital and Rockingham Kwinana District Hospital (#2012-184)); Ramsay Health Care WA/SA HREC: (Joondalup Health Campus and Peel Health Campus (#1225)); and St John of God Healthcare HREC (St John of God Hospital Midland, St John of God Hospital Murdoch, and St John of God Hospital Subiaco (#1209)). Copies of the ethics committee certificates of approval are contained in Thesis Appendix A.

Approval to access St John Western Australia (SJ-WA) Patient Care Records (both paper based and electronic) was granted by the St John Western Australia Research Advisory Group (now called the Research Governance Committee). This data was managed at PRECRU (Curtin University) and protected by robust data security protocols.

Access to PathWest Laboratory Medicine WA (PathWest) data was provided by PathWest, the pathology and forensic arm of the WA health system.

I was required to sign a confidentiality agreement with PRECRU, SJ-WA, the WA Department of Health and PathWest prior to accessing any patient identified data. I am also a Registered Nurse and patient confidentiality is a required agreement with the registering body Australian Health Practitioner Regulation Agency (Ahpra). All data was de-identified prior to statistical analysis and confidentiality is ensured as published data is aggregate.

3.3 Study design and setting

This thesis includes four observational studies designed to examine post-resuscitation care factors associated with survival and neurological outcome after OHCA. These were all retrospective cohort studies. A summary of each study including the study design is provided in Table 3.1 and further information is included in each manuscript. The study setting was greater metropolitan Perth, WA. The study setting has previously been described in Chapter 2.3.

Table 3.1 Overview of the design of each multicentre retrospective cohort study included in this thesis.

Chapter	Study information
Chapter Four	**Manuscript:** Direct transport to a PCI-capable hospital is associated with improved survival after adult out-of-hospital cardiac arrest of medical aetiology.[17] Study design: Multicentre retrospective cohort study Study period: 2012 to 2015 (4 years) **Data sources:** 1. SJ-WA OHCA Database 2. The WA Registry of Births, Deaths and Marriages 3. Medical chart review
Chapter Six	**Manuscript:** Arterial carbon dioxide tension has a non-linear association with survival after out-of-hospital cardiac arrest: A multicentre observational study.[19] Study design: Multicentre retrospective cohort study Study period: 2012 to 2017 (6 years) **Data sources:** 1. SJ-WA OHCA Database 2. The WA Registry of Births, Deaths and Marriages 3. Medical chart review 4. PathWest Laboratory Medicine WA
Chapter Seven	**Manuscript:** Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study.[20] Study design: Multicentre retrospective cohort study Study period: 2012 to 2017 (6 years) **Data sources:** 1. SJ-WA OHCA Database 2. The WA Registry of Births, Deaths and Marriages 3. Medical chart review 4. PathWest Laboratory Medicine WA
Chapter Eight	**Manuscript:** Neurological outcome in adult out-of-hospital cardiac arrest - Not all doom and gloom![21] Study design: Multicentre retrospective cohort study Study period: 2004 to 2019 (16 years) **Data sources:** 1. SJ-WA OHCA Database

Chapter	Study information
	2. The WA Registry of Births, Deaths and Marriages 3. Medical chart review

3.4 Data sources

Four separate data sources were used to complete the research included in this thesis:

1. SJ-WA OHCA Database
2. The WA Registry of Births, Deaths and Marriages
3. Medical chart review (electronic and paper based)
4. PathWest Laboratory Medicine WA

Each of these data sources are described in more detail below.

3.4.1 SJ-WA OHCA Database

The SJ-WA OHCA Database contains prospectively collected data for all OHCA cases attended by SJ-WA paramedics in metropolitan Perth since inception and state-wide since 2014.[96] The variables included in the database are based on internationally recognised definitions outlined in the 'Utstein' template from ILCOR.[1] In this context an OHCA patient is defined as "…someone with no signs of circulation - specifically the absence of a carotid pulse, in combination with unconsciousness /unresponsiveness, and agonal/absent breathing; with the event occurring outside of hospital."[96] The case inclusion and exclusion criteria for this database are described in Table 3.2.[96]

The SJ-WA OHCA Database captures information from two sources; the CAD System Database and the electronic patient care record (ePCR) (paper based prior to 2011).[96] CAD data provides geographical and incident information for each emergency call including the date, location of the incidence and critical time stamps (activation, response, on-scene and transport intervals).[96] The CAD Database assigns a unique 'case number' to each ambulance or emergency vehicle dispatched to an emergency call. Where multiple ambulances or emergency vehicles attend the same incident, an

'incident number' is generated to link each 'case number'. CAD data is interrogated on a routine basis to identify OHCA cases and the results are reviewed manually by PRECRU clinical staff to ensure the accuracy and completeness of data before inclusion in the SJ-WA OHCA Database.[96]

The ePCR is a confidential medico-legal document that includes administrative, demographic and clinical data for each patient attended by SJ-WA. The primary ePCR is completed by the paramedic providing the majority of patient treatment. Administrative data includes prefilled crew, location information and time data. It also includes the problem urgency and problem code that best describes the patient condition. OHCA is usually identified as Problem Code 418 (cardiac arrest) or 419 (post cardiac arrest). A list of SJ-WA Problem Codes is included in Thesis Appendix B.

Demographic information includes patient sex, date of birth, residential address and contact details. Clinical information includes vital sign monitoring, interventions and medications. The minimum requirements for vital sign monitoring include respiratory rate, heart rate, blood pressure, oxygen saturation, pain score and level of consciousness (Glasgow Coma Scale). Patients may also have an ECG, end-tidal carbon dioxide, oxygen saturation, dyspnoea, pain scores and blood glucose levels recorded.

Prehospital variables collected in the SJ-WA Database and abstracted for this study included geographic location of the event (rural versus metropolitan), whether resuscitation was attempted by paramedics (yes/no), OHCA aetiology (cardiac versus non-cardiac) patient age and sex, location of arrest (home, public place, other), witness status (paramedic, bystander, unwitnessed), performance of bystander CPR (yes/no), initial arrest rhythm (unknown classified as non-shockable), asystole or VF ever reported and any prehospital ROSC (yes/no).

Date and time variables were also abstracted including date and time of the arrest, day of arrest (weekday versus weekend), time of the arrest (night versus day), median EMS response time (using time interval from EMS call to arrival on scene), median

time to first ED (using time interval from EMS call to arrival at first ED) and median time to PCI-capable hospital (using time interval from EMS call to arrival in cardiac catheterisation laboratory). Where multiple ambulance crews attended the arrest, I preferentially selected data captured by the primary crew.

Table 3.2 Inclusion/exclusion criteria for the SJ-WA OHCA Database.[96]

Inclusion criteria: all of the following	Exclusion Criteria: any of the following
All patients (of any age) who suffer a cardiac arrest in an out-of-hospital setting (including residential care facilities).	Any patient who suffers a cardiac arrest in a hospital facility where SJ-WA may be in attendance but are not the primary care providers.
Occurred in the State of Western Australia and were attended by SJ-WA	Any patient who suffers a cardiac arrest during an inter-hospital transfer where SJ-WA may be providing transport but are not the primary care providers
a. All unconscious patients who are also pulseless with either agonal or no breathing on arrival of SJ-WA OR b. All patients who become unconscious and pulseless with either agonal or no breathing in the presence of SJ-WA (so called EMS witnessed/paramedic/witnessed arrests) OR c. Patients who have a pulse on arrival of SJ-WA following successful defibrillation provided by a bystander prior to arrival of SJ-WA.	Any patient where bystander/lay person suspected a cardiac arrest, but the patient is not in cardiac arrest on arrival of SJ-WA, and no defibrillation has occurred.
	Patients with brief episodes of pulselessness who DO NOT receive CPR or defibrillation from SJ-WA

3.4.2 WA Registry of Births, Deaths and Marriages

In accordance with WA legislation, the WA Registry of Births, Deaths and Marriages creates and preserves records of births, deaths and marriages occurring within the state. Under agreement with PRECRU, the Registry provides confidential death information for medical research purposes. These data were used to determine

patient survival to 30 days and 12-months. If there was no record of the patient in the Registry at 30 days or 12-months it was assumed that the patient was still alive.

3.4.3 Medical chart review

Retrospective medical chart review was conducted at each study hospital to abstract the in-hospital variables. Where patients were transferred between hospitals, I reviewed the medical charts at both the referring hospital and receiving hospital. Of the hospitals included in the study, only two hospitals (Fiona Stanley Hospital and St John of God Midland Hospital) had implemented an electronic clinical information system. I used Statistical Package for Social Sciences (SPSS) software to create an electronic abstraction form. This form included a combination of free text and coded responses for data entry. All data were collected by experienced research nurses who had received training in the electronic data abstraction form.

The medical chart consisted of a complete record of the patient's key clinical data and medical history, such as demographics, past medical history, ED and hospital discharge diagnoses, clinical interventions, vital signs, medications, treatment plans, radiology and cardiac catheterisation images. For patients admitted to ICU, the medical chart also included a critical care flow sheet. Each flow sheet was reviewed to capture clinical observations, interventions, medications and pathology results.

3.4.4 PathWest Laboratory Medicine WA

PathWest Laboratory Medicine WA provided the ABG data used in the multicentre cohort studies examining the association between $PaCO_2$ and PaO_2 and survival after OHCA. $PaCO_2$ and PaO_2 values in the first 72 hours of ICU admission was abstracted from each ABG result to provide information on the patients' ventilation and oxygenation status respectively. ABG analysis is the internationally recognised gold standard method for assessment of pulmonary gas exchange and acid base homeostasis in critically ill patients.[113] The machines used for point-of care testing for ABG analysis are owned by PathWest and form part of their overall laboratory services. ABG data from PathWest was cross checked against the patient ICU flow sheets to ensure accuracy and completeness of the dataset.

PathWest has a comprehensive schedule of internal and external audits as part of a quality assurance and improvement program.[114] The organisation also participates in proficiency testing programs provided by the Royal College of Pathologists of Australasia and other external providers.[114] PathWest testing facilities are routinely accredited by the following organisations:

- National Association of Testing Authorities (NATA): international standards ISO 15189 (Medical Testing), and ISO/IEC 17025 (Biological Testing) including Media Preparation and Forensic Biology.
- Therapeutic Goods Administration (TGA): sterility testing of pharmaceutical products, serological testing of human tissue and cell therapy donations, microbial contamination testing of human tissue and cell therapy donations and products and In house In Vitro Devices (IVDs) used for human diagnosis and treatment.
- Royal College of Pathologists (RCPA): Pathologist Accreditation and ongoing professional development.[114]

3.5 Data Linkage

Deterministic data linkage was conducted to combine death data from the WA Registry of Births, Deaths and Marriages with the SJ-WA OHCA Database. Data linkage was conducted by PRECRU Director Professor Judith Finn or Deputy Director Dr Stephen Ball. I also used deterministic data linkage to link PathWest ABG data with my PhD study database using a unique hospital unit medical record number (UMRN). Any patient with a missing UMRN was linked on date of birth and first and last name. Patients in the datasets were de-identified before the data were provided for analysis.

3.6 Inclusion and exclusion criteria

The inclusion and exclusion criteria varied across the four observational studies included in this thesis. In the first study,[17] investigating the association between EMS transport destination and survival OHCA, I included all patients (≥18 years) with OHCA of medical aetiology (presumed cardiac or unknown, other medical causes) who were attended by SJ-WA paramedics in in greater metropolitan Perth, WA between 1

January 2012 and 31 December 2015 (4 years) and who were admitted to a study hospital with ROSC. I excluded patients whose ED attendance could not be verified from medical chart review and those with missing medical charts. A medical chart was determined to be 'missing' if it could not be located after three separate requests to the admitting hospital. I decided *a priori* to exclude patients if they had a second OHCA within 7 days of hospital discharge due to the potential influence on pre-CPC and OPC scores. I also excluded patients admitted to the Hospital in the Home' (HITH) program, as they were already receiving acute hospital level care in the community.

In the second[19] and third[20] studies investigating the association of $PaCO_2$ and PaO_2 and survival after OHCA, I included all patients (≥18 years), with OHCA of presumed non-traumatic aetiology and medical aetiology respectively, who were attended by SJ-WA paramedics in greater metropolitan Perth, WA between 1 January 2012 and 31 December 2017 (six years) and who were admitted to a study hospital with ROSC. In line with the first study,[17] I excluded patients with missing medical records and those admitted from HITH. I also excluded patients who did not receive mechanical ventilation on admission to ICU, those who did not have an ABG recorded within the first six hours of ICU admission and any patient who did not have a $PaCO_2$ or PaO_2 value recorded during their ICU admission.

In the final study, describing neurological and functional outcomes among OHCA patients who survived to hospital discharge, I included adults with OHCA of any aetiology who had resuscitation attempted by SJ-WA paramedics, in greater metropolitan Perth, and who survived to hospital discharge at one of eleven hospitals between 1st January 2004 and 31st December 2019 (16 years). I excluded patients with missing medical charts and interstate/overseas visitors from the multivariable logistic regression analysis (to minimise loss to follow-up).

3.7 Patient outcomes

There is variation in the patient-centred outcomes used in the four retrospective cohort studies included in this thesis. For clarification, the cohort definition and outcome used in each study is described in Table 3.3 below.

Table 3.3 Cohort definition and patient-centred outcomes included in each study.

Chapter	Study information
Chapter Four	**Manuscript:** Direct transport to a PCI-capable hospital is associated with improved survival after adult out-of-hospital cardiac arrest of medical aetiology.[17] **Cohort:** All cases of adult OHCA (>18years) of presumed medical aetiology resuscitated by SJ-WA paramedics and admitted to a PCI-capable hospital with ROSC. **Outcomes:** There is one primary and three secondary outcomes in this study: 1. Survival to hospital discharge (primary outcome) 2. 30-day survival (secondary outcome) 3. 12-month survival (secondary outcome) 4. Good neurological outcome at hospital discharge (secondary outcome)
Chapter Six	**Manuscript:** Arterial carbon dioxide tension has a non-linear association with survival after out-of-hospital cardiac arrest: A multicentre observational study.[19] **Cohort:** All cases of adult OHCA (>18years) of presumed medical aetiology resuscitated by SJ-WA paramedics with ROSC and who required mechanical ventilation on arrival to an ICU. **Outcomes:** There is one primary and two secondary outcomes in this study: 1. Survival to hospital discharge (primary outcome) 2. 12-month survival (secondary outcome) 3. Good neurological outcome at hospital discharge (secondary outcome)
Chapter Seven	**Manuscript:** Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study.[20] **Cohort:** All cases of adult OHCA (>18years) of presumed medical aetiology resuscitated by SJ-WA paramedics with ROSC and who required mechanical ventilation on arrival to an ICU. **Outcomes:** There is one primary and two secondary outcomes in this study: 1. Survival to hospital discharge (primary outcome) 2. 12-month survival (secondary outcome) 3. Good neurological outcome at hospital discharge (secondary outcome)

Chapter	Study information
Chapter Eight	**Manuscript:** Neurological outcome in adult out-of-hospital cardiac arrest - Not all doom and gloom![21] **Cohort:** All cases of adult OHCA (>18years) of any aetiology who had resuscitation attempted by SJ-WA paramedics and who survived to hospital discharge at one of eleven hospitals with an emergency department (ED) in Perth, WA. **Outcome:** There is one primary outcome in this study: 1. 12-month survival (primary outcome)

3.8 Statistical analysis

In each of the four retrospective cohort studies, continuous variables were reported as means and standard deviation or medians and interquartile range, and categorical variables as counts and percentages. Differences between groups were assessed using the t-test or Mann-Whitney-U or Kruskal-Wallis test for continuous variables, and Chi-square or Fisher's exact test for categorical variables as appropriate. All statistical tests were two tailed and a p value <0.05 was considered statistically significant for all analyses. I used SPSS for Windows (version 24.0, IBM, USA) for all analyses with the exception of the restricted cubic spline regression used in the $PaCO_2$[19] and PaO_2[20] studies which was performed using S-PLUS software (version 8.2, TIBCP Software Inc., USA).

In the first study, I compared survival outcomes of adults with OHCA of medical aetiology directly transported by EMS to a PCI-capable hospital (direct transport) with patients transferred to a PCI-capable hospital via another hospital without PCI capability.[17] I analysed the total cohort of patients admitted to a PCI-capable hospital as well as three subgroups of patients admitted to ICU. Subgroup analysis included (a) all patients admitted to ICU with mechanical ventilation, (b) all patients who received coronary angiography within 24 hours of EMS call and (c) all patients who proceeded to PCI. I used multivariable logistic regression analysis to examine the independent association of transport group (direct versus indirect) and survival to hospital discharge. The multivariable model was adjusted for 'Utstein' variables and

other potential explanatory factors that have a known association with OHCA outcome[1] including age (years; continuous), sex (male/female), location of arrest (home versus public location), witness status (paramedic/bystander/unwitnessed), bystander CPR (yes/no), initial arrest rhythm (shockable versus non-shockable), prehospital ROSC (yes/no) and EMS response time (minutes; categorical). I also adjusted for time of arrest (day; 0700-1859), day of arrest (weekday versus weekend), and diagnosis of ACS in ED (yes/no). EMS response time was categorised as the data was not normally distributed. The median EMS response time was used to identify categories to separate patients with shorter and longer response times from the majority of patients included in the cohort.

In a separate analysis, I conducted a Cox-proportional hazards model to examine the independent association between transport group and survival to 12-months. I also used Kaplan-Meier survival curves and log rank tests to compare the direct and indirect transport groups and to eliminate the effect of any potential non-proportionality in the 12-month survival analysis. To test the robustness of my results, I performed two sensitivity analyses. The first analysis excluded all patients in the total cohort whose initial arrest rhythm was unknown to estimate the effect of these missing data. In the second analyses, I excluded all patients in the total cohort with a pre-arrest CPC score of 3 (or less) to eliminate the effect of poor neurological status on survival outcomes after OHCA.

In the second study, I hypothesised that the mean $PaCO_2$ in the first 24 hours after ICU admission has a non-linear relationship with survival and neurological outcome after OHCA and aimed to identify optimal $PaCO_2$ cut points for survival.[19] This hypothesis was based on the findings of published studies that report a non-linear relationship between physiological variables and clinical outcomes in critically ill adults [115,116] including those reporting the association between $PaCO_2$ and survival[69] and neurological outcome[117] after OHCA. It also reflected the findings of my systematic review and meta-analysis of 23,434 cardiac arrest patients that found $PaCO_2$ during the post-resuscitation phase had a significant inverted 'U-shaped' association with survival and neurological outcome after cardiac arrest.[18]

In this study, I used multivariable logistic regression analyses to adjust for the effect of biologically plausible predictors of survival after OHCA, irrespective of their p value in univariable analyses. These variables were selected *a priori* based on the Utstein template because they have a known association with OHCA outcomes.[1] I 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 in the multivariable logistic model.

I then identified optimal $PaCO_2$ cut-points based on the shape of the spline curve derived from a four-knot restricted cubic spline function.[118] A restricted cubic spline function is a way of summarising a relationship between dependent and independent variables that are not linear.[118] The range of values of the independent variable is split with "knots" defining the segments with separate curves being fitted to each segment with the resulting fitted curve being smooth and continuous.[119] The number of knots was based on the sample size to ensure that there were sufficient observations between each knot to fit each polynomial function.[119] In this study, restricted cubic spline regression was used to describe the dose-response association between $PaCO_2$ and outcome, provide a visual tool to check the assumption of linearity of the association and to minimise residual confounding when adjusting for the continuous exposure.[119]

In the third study, I used a near identical patient cohort and statistical analysis plan to the second, to determine if PaO_2 has a non-linear relationship with survival after OHCA.[20] I hypothesised that maintaining an intermediate level of PaO_2 in the first 24 hours of ICU admission would be associated with improved hospital survival and neurological outcome at hospital discharge and survival to 12 months.[20] I included a description of the statistical analyses in the supplementary material of the manuscript. This reads as follows: "As stated, we assessed the importance of mean PaO_2 relative to plausible physiological predictors in explaining the variability in the observed hospital mortality by each predictor's Chi Square contribution in a multivariable logistic regression. This is similar to the incremental contribution of

each predictor to the area under the receiver operating characteristics curve, or c-index, of the final model. After confirming a non-linear inverted U-shaped relationship between the mean PaO_2 and survival, cut points were then identified visually, based on the shape of the spline curve, and used to generate corresponding odds ratios to facilitate clinical interpretation of this inverted U-shaped relationship. We then performed a stepwise forward logistic regression to confirm the robustness and consistency of the non-linear relationship between the mean PaO_2 and survival, after adjusting for plausible physiological predictors of survival after OHCA. In conducting the multivariable analyses, we also added two *a priori* defined predictors to other known predictors of survival after OHCA, whether the patients had a diagnosis of ST-segment elevation myocardial infarction on arrival to the emergency department and received within 24-hours of the emergency medical services call".[20]

In the fourth and final retrospective cohort study, I aimed to describe neurological and functional outcomes among OHCA patients who survived to hospital discharge and to determine the association between neurological outcome at hospital discharge and 12-month survival.[21] I used adjusted multivariable logistic regression analysis to identify the association between CPC score at hospital discharge and 12-month survival.[21] Covariates included in the model were: age (years; continuous), sex (male/female), witness status (paramedic/bystander/unwitnessed), location of arrest (home versus public location), early CPR (includes 'bystander CPR' and 'paramedic CPR' for paramedic-witnessed arrests), initial arrest rhythm (shockable versus non-shockable), aetiology of arrest (cardiac versus non cardiac) and calendar year categorised into 4 year epochs.[21]

3.9 Conclusion

This chapter summarised the methods used for the four multicentre cohort studies included in this thesis. Further information about the methods used for the individual studies are detailed in the relevant study chapters. In each study, I used high quality data sources, included robust patient-centred outcomes and employed a rigorous approach to data collection to minimise loss to follow up.

The next chapter presents the findings of the first study investigating the association with EMS transport destination and survival after OHCA. This study is titled 'Direct transport to a PCI-capable hospital is associated with improved survival after adult out-of-hospital cardiac arrest of medical aetiology'.[17]

Chapter 4 EMS Transport Destination

4.1 Overview

In this chapter, the findings from the first multicentre retrospective cohort study included in this thesis are presented. This study investigates the association between EMS transport destination and survival after OHCA. Early access to post-resuscitation care is the fifth link in the 'Chain of Survival' concept.[120,121] International guidelines recommend direct transport of adult patients with OHCA of medical aetiology to a specialist cardiac arrest centre that can provide evidence-based post resuscitation treatments.[12] This includes early coronary revascularisation, targeted management of body temperature and control of oxygenation and ventilation.[12] However, these guidelines are based on very low certainty evidence and there are no large RCTs that demonstrate a survival benefit associated with direct transport to a specialist cardiac arrest centre in the overall patient population.[12] Further, while evidence suggests that direct EMS transport of STEMI patients with OHCA to a specialist cardiac centre improves survival,[122] it is unclear if this decision strategy benefits patients with OHCA from other medical causes. Observational studies that compare patient characteristics and outcomes following OHCA of medical aetiology (including subgroups of patients) are required to inform clinical decision making and EMS transport protocols.

The research aim was:

To compare survival outcomes of adults with OHCA of presumed medical aetiology directly transported to a PCI-capable hospital (direct transport) with patients transferred to a PCI-capable hospital via another hospital without PCI services available (indirect transport) by EMS.

The specific objectives were:

1. To undertake a retrospective cohort study of adult patients with OHCA of medical aetiology, attended by SJ-WA paramedics and admitted to a study hospital

2. To describe the characteristics and patient outcomes for the total cohort
3. To compare patient outcomes by transport group (direct versus indirect) for the total cohort
4. To describe OHCA characteristics and patient outcomes for a subgroup of patients admitted to ICU
5. To compare patient outcomes by transport group (direct versus indirect) for the ICU cohort
6. To conduct sensitivity analyses to assess the robustness of the results by excluding (a) patients whose initial arrest rhythm was unknown and (b) patients who had a CPC score of 3 (or less) prior to the arrest from the total cohort; and
7. To compare patients remaining at a non-PCI capable hospital with those transferred to a PCI-capable hospital.

This Chapter comprises a manuscript that has been published in a peer-reviewed journal and is inserted as a portable document format (PDF) in the format published by the journal:

McKenzie N, Williams TA, Ho KM, Inoue M, Bailey P, Celenza A, Fatovich D, Jenkins I, Finn J. Direct transport to a PCI-capable hospital is associated with improved survival after adult out-of-hospital cardiac arrest of medical aetiology. *Resuscitation*. 2018 Jul; 128:76-82.[17]

Supplementary material supporting this article is presented prior to the Chapter summary.

A poster related to this publication was presented at the 11th International Spark of Life Conference, Adelaide, South Australia, May 2017, and is included in Thesis Appendix C:

McKenzie N, Williams TA, Tohira H, Ho KM, Inoue M, Bailey P, Finn J. Direct transport to a tertiary hospital improves survival from out-of-hospital cardiac arrest in adults with acute coronary syndrome.

4.2 Manuscript

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Clinical paper

Direct transport to a PCI-capable hospital is associated with improved survival after adult out-of-hospital cardiac arrest of medical aetiology☆

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ABSTRACT

Aim: To compare survival outcomes of adults with out-of-hospital cardiac arrest (OHCA) of medical aetiology directly transported to a percutaneous-coronary-intervention capable (PCI-capable) hospital (direct transport) with patients transferred to a PCI-capable hospital via another hospital without PCI services available (indirect transport) by emergency medical services (EMS).

Methods: This retrospective cohort study used the St John Ambulance Western Australia OHCA Database and medical chart review. We included OHCA patients (≥18 years) admitted to any one of five PCI-capable hospitals in Perth between January 2012 and December 2015. Survival to hospital discharge (STHD) and survival up to 12-months after OHCA were compared between the direct and indirect transport groups using multivariable logistic and Cox-proportional hazards regression, respectively, while adjusting for so-called "Utstein variables" and other potential confounders.

Results: Of the 509 included patients, 404 (79.4%) were directly transported to a PCI-capable hospital and 105 (20.6%) transferred via another hospital to a PCI-capable hospital; 274/509 (53.8%) patients STHD and 253/509 (49.7%) survived to 12-months after OHCA. Direct transport patients were twice as likely to STHD (adjusted odds ratio 1.97, 95% confidence interval [CI] 1.13–3.43) than those transferred via another hospital. Indirect transport was also associated with a possible increased risk of death, up to 12-months, compared to direct transport (adjusted hazard ratio 1.36, 95% CI 1.00–1.84).

Conclusion: Direct transport to a PCI-capable hospital for post-resuscitation care is associated with a survival advantage for adults with OHCA of medical aetiology. This has implications for EMS transport protocols for patients with OHCA.

Introduction

Australian Resuscitation Council (ARC) guidelines recommend direct transport of adults with out-of-hospital cardiac arrest (OHCA) of presumed medical aetiology to a specialist cardiac arrest centre [1]. This recommendation is based on growing consensus that early access to a standardised post-resuscitation care bundle including percutaneous-coronary-intervention (PCI) and targeted-temperature-management (TTM) improves survival after OHCA [2]. However, Perth emergency medical services (EMS) have historically transported OHCA patients to the nearest emergency department (ED) [3], irrespective of whether PCI or an intensive care unit (ICU) is available.

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at https://doi.org/https://doi.org/10.1016/j.resuscitation.2018.04.039

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International consensus is that direct EMS transport of STEMI patients with OHCA to a PCI-capable hospital for early coronary revascularization and post-resuscitation care improves survival [4]. Whether this referral strategy increases survival in OHCA from medical causes other than STEMI is unknown. Observational studies from the United States [5,6], Japan [7], and Europe [1–10] suggest direct EMS transport of adult OHCA patients to a hospital with a high-level critical care service improves survival after adjustment for other risk factors. An Australian study found that in-hospital factors, including 24-h PCI-capability were significantly associated with improved survival to hospital discharge (STHD) for adult OHCA patients [11]. The authors concluded further research was needed to establish the generalisability of their findings given the variation in population distribution and distance to PCI-capable hospitals in Australia [11].

We aimed to determine if direct EMS transport of adults with OHCA of presumed medical aetiology, including those with OHCA due to non-STEMI or acute coronary syndrome (ACS), to a PCI-capable hospital (direct transport) was associated with improved STHD and 12-month survival compared to those transferred via another hospital where PCI was not available (indirect transport).

Methods

Study design

We conducted a retrospective cohort study across five PCI-capable hospitals in Perth for OHCA patients attended by St John Ambulance Western Australia (SJA-WA) between 1st January 2012 and 31st December 2015.

Study setting

Perth is the capital of Western Australia (WA). Its population was 2.04 million in 2015 [12]. Perth is serviced by a single road-based EMS provider, SJA-WA [13]. Paramedics provide advanced life support (ALS) according to SJA-WA Clinical Practice Guidelines [3] based on ARC Guidelines [14]. ALS skills include advanced airway management (endotracheal intubation or laryngeal mask), cardiac arrest drug administration and manual defibrillation [3].

In accordance with SJA-WA clinical guidelines at the time, OHCA patients who had resuscitation attempted by paramedics and not ceased in the field were transported to the nearest ED [3]. Subsequent inter-hospital transfer occurred when the diagnostic facilities, clinical expertise or therapeutic needs of a patient were beyond the capacity of the initial receiving hospital.

During the study, 11 hospitals had an ED that provided 24-h emergency services to adult OHCA patients; four tertiary, three general, three private public partnership (PPP) and one private hospital. Of these, six hospitals (four tertiary, one PPP and one private hospital) were PCI-capable as they had an onsite cardiac catheterisation laboratory (CCL) and the ability to perform PCI [15]. We excluded the few patients admitted to the private hospital as we did not seek Human Research Ethics Committee (HREC) approval at that hospital.

Of the five PCI-capable hospitals included in the study, two tertiary hospitals had restricted operating periods. Site A operated from January 2012 to February 2015 and site B operated from February 2015 to December 2015. The PPP hospital with PCI capability (site C) operated from November 2012. Patients transferred via another hospital where PCI was not available to a PCI-capable hospital within 24 h of the EMS call were defined as 'indirect transport' patients.

Study cohort

We included patients (≥18 years) with OHCA from presumed medical aetiologies (presumed cardiac or unknown, other medical causes) [16], resuscitated by paramedics and admitted with return of spontaneous circulation (ROSC). We excluded patients with missing medical charts, OHCA within 7 days of hospital discharge and 'Hospital in the Home' patients as they were already receiving acute hospital level care [17].

Data sources

Patients were identified from the prospectively collected SJA-WA OHCA Database. We abstracted demographic and clinical data including transport group (direct versus indirect), age, sex, arrest location, witness status (bystander, paramedic, unwitnessed), bystander cardiopulmonary resuscitation (CPR) (yes/no), initial arrest rhythm (unknown classified as non-shockable), asystole or ventricular fibrillation (VF) ever reported, day and time of arrest, and any prehospital ROSC.

Data abstracted from medical chart review included a medical diagnosis of ACS in ED, coronary angiography, PCI within the first 24 h of EMS call and therapeutic interventions in ICU, including mechanical ventilation (MV) and TTM. We defined TTM as any attempt to control core body temperature within the first 24-h of ICU admission [18,19].

Survival outcomes were collected from medical chart review and deaths were confirmed by the WA Death Registry [20]. All data were collected by trained research nurses and Cohen's Kappa inter-rater reliability was high ($\kappa = 0.96$, 95% CI 0.88–1.0, $p < 0.001$) [21].

Study outcomes

The primary outcome was STHD. Secondary outcomes were: 30-day survival, 12-month survival (both from the date of the OHCA) and good neurological outcome at hospital discharge using the Cerebral Performance Categories (CPC) Scale [22]. CPC scores of 1 (good cerebral performance) or 2 (moderate cerebral disability) were considered to be 'good' neurological outcomes [22].

Statistical analysis

To examine the association between transport group and survival, we analysed the total cohort of patients admitted to a PCI-capable hospital, as well as three subgroups of patients admitted to ICU. The first subgroup included all patients admitted to ICU and the second included patients who also received coronary angiography within 24 h of the EMS call. The third subgroup included patients who proceeded to PCI. Patients not receiving MV on arrival to ICU were excluded from subgroup analyses to reduce clinical heterogeneity.

Descriptive statistics describe and compare demographic and clinical characteristics and patient outcomes between the direct and indirect transport groups and also between these groups combined and those patients who remained at a non-PCI-capable hospital. Continuous variables were reported as medians with interquartile range (IQR) and categorical variables as percentages. Differences between transport groups were assessed using the student's t-test and Mann-Whitney U test for continuous variables, and Pearson chi-square analysis, Chi Square and Fisher's Exact Test for categorical variables as appropriate. A p value < 0.05 was considered statistically significant for all analyses. We used the Statistical Package for Social Sciences (SPSS) Version 24.0 (IBM, Armonk, NY, USA).

Multivariable logistic regression models examined the independent association of transport group with STHD and Cox proportional hazards models for 12-month survival. Multivariable models were adjusted for Utstein variables and other potential explanatory factors (Table 2). To eliminate the effect of any potential non-proportionality in hazards in the 12-month survival analysis, we used Kaplan-Meier survival curves and log rank test to compare transport groups.

We conducted two sensitivity analyses to assess the robustness of our results. Firstly, we excluded all patients in the total cohort whose initial arrest rhythm was 'unknown' to estimate the effect of these

missing data. Secondly, we excluded all patients in the total cohort who had a CPC score of 3 (or less) before the arrest, to eliminate the effect of poor prior neurological status on survival outcomes after OHCA.

Ethics approval

The study was approved by SJA-WA Research Advisory Group, Curtin University HREC (HR 199/2014) and each study hospital's HREC.

Results

OHCA characteristics and patient outcomes for total cohort

During the study 5079 OHCA patients with presumed medical aetiology were attended by paramedics. Of these 2,583/5079 (50.9%) had resuscitation attempted and 543/2,583 (21.0%) were admitted to hospital, of which 513/543 (94.5%) patients were admitted to a PCI-capable hospital. A total of 408/513 (79.5%) patients were directly transported to a PCI-capable hospital (direct transport) and 105/513 (20.5%) were transferred from another hospital (indirect transport). Only 4/513 (0.8%) patients were excluded from the study (Fig. 1).

The transport groups were similar in age and gender distribution (Table 1). In unadjusted analysis, direct transport patients (404/509, 79.4%) were more likely to have an OHCA at a public location and a paramedic-witnessed arrest; but a diagnosis of ACS in ED and ICU admission were less frequent compared to the indirect transport patients (105/509, 20.6%). Eleven patients (2.7%) in the direct transport group had a pre-arrest CPC score of 3. Direct transport patients had a significantly shorter transport time (time interval from EMS call to arrival at PCI-capable hospital) than indirect transport patients (median 47 min [IQR 38–56] versus 208 [IQR 149-255]).

Of the 509/513 (99.2%) patients included in the outcome analyses, 274 (53.8%) STHD, 268 (52.7%) survived to 30-days, and 253 (49.7%) survived to 12-months after OHCA. Of the 274/509 hospital survivors, 252/274 (92%) had a good neurological outcome at hospital discharge (CPC scores ≤ 2) (Table 1).

Comparison of patient outcomes by transport group for total cohort

Direct transport patients were significantly more likely to STHD (56.2% versus 44.8%, absolute risk difference = 11.4%, 95% CI 0.7–21.8). The 30-day and 12-month survival for patients transported directly to a PCI-capable hospital were not statistically different. (Table 1). The unadjusted odds of STHD were higher in the direct transport group (odds ratio [OR] 1.58, 95% confidence interval [CI] 1.03–2.44) than the indirect transport group (Table 2). After adjustment for confounders, direct transport patients were twice as likely to STHD (OR 1.97, 95% CI 1.13–3.43) than those transferred via another hospital (Table 2). Of the OHCA patients who survived to hospital admission, the number needed to treat for one additional survivor was six. Although more survived to 12-months with a lower hazard of death compared to the indirect group (adjusted HR 1.36 for the indirect group, 95% CI 1.00–1.84; $p = 0.05$), this did not reach conventional statistical significance (Table 3). However, Kaplan-Meier survival curves suggested the proportional hazards of death between the two groups was not constant; most of the difference in hazards occurred within the first 30 days (log rank test $p = 0.07$) (Supplemental Fig. S1).

OHCA characteristics and patient outcomes of the ICU cohort

A total of 382/509 (75%) OHCA patients, were admitted to the ICU of a PCI-capable hospital; 291/404 (72.0%) in the direct and 91/105 (86.7%) in the indirect transport group, and 377/382 (98.7%) required MV (Table 1). TTM was administered to 298/377 (79%) patients, 203/377 (53.8%) underwent coronary angiography, and 103/377 (27.3%) proceeded to PCI within 24 h of EMS call. Indirect transport patients were significantly more likely to have a medical diagnosis of ACS in the first ED (37.4% versus 24.4%), receive PCI overall (36.7% versus 24.4%) and receive PCI for STEMI (33% versus 16.2%) (Table 1). STHD, 30-days and 12-months were 172/382 (45%), 170/382 (44.5%) and 166/382 (43.5%) respectively (Supplemental Fig. S2). Most hospital survivors (154/172, 89.5%) had a good neurological outcome at hospital discharge. The outcomes of patients admitted to other wards are displayed in Supplemental Fig. S2.

Comparison of patient outcomes by transport group for ICU cohort

The results of this study remained consistent across all three subgroup analyses of patients admitted to ICU. The adjusted odds of STHD after direct transport to a PCI-capable hospital for (a) all patients requiring MV (OR 2.33, 95% CI 1.26–4.28), (b) those who had coronary angiography (OR 2.54, 95% CI 1.20–5.40), and (c) those who had PCI (OR 4.37 95% CI 1.49–12.79) were all better than those transferred via another hospital (Table 2 and Supplemental Tables S1–S3). Similarly, the direction and magnitude of the hazard for death within 12-months after OHCA remained higher for those transferred indirectly, although some of the differences did not reach statistical significance in some of these subgroups (Table 2) and Supplemental Figs. S3–S5.

Sensitivity analysis for total cohort

Excluding patients (n = 12/509, 2.4%) whose initial arrest rhythm was unknown did not change the association between direct transport and STHD (OR 1.97, 95% CI 1.12–3.46) or 12-month survival (HR 1.36, 95% CI 1.00–1.84) (Appendix 1). Excluding patients (n = 11, all in the direct transport group, 2.7%) who had a pre-arrest CPC score of 3 also did not change improved STHD (OR 2.28, 95% CI 1.34–3.90) or 12-month survival (HR 1.39, 95% CI1.02–1.88) associated with patients directly admitted to a PCI-capable hospital (Appendix 2).

Comparison of patients remaining at a non-PCI capable hospital compared to patients taken to a PCI-capable hospital

The 26/543 (4.8%) patients remaining at a non-PCI capable hospital (Fig. 1) had a significantly lower STHD: 7/26 (26.9%) versus 274/509 (53.8%); $p = 0.01$ and were less likely to be male: 13/26 (50%) versus 365/509 (71.7%); $p = 0.02$ or have an initial shockable rhythm: 8/26 (30.7%) versus 317 (62.3%); $p = 0.01$. There were no significant differences in age, arrest location, witness status, bystander CPR, day and time of arrest, and any prehospital ROSC.

Discussion

This multicentre retrospective study of adults with OHCA of presumed medical aetiology found direct EMS transport to a PCI-capable hospital was associated with improved STHD when compared to transfer via another hospital without PCI availability. This association remained significant across all subgroups of patients admitted to ICU. These results have potentially important implications for EMS transport protocols.

Our overall unadjusted survival rates for patients admitted to a PCI-capable hospital were 54% STHD, 53% 30-days and 50% at 12-months with most hospital survivors (92%) having a good neurological outcome. This compares to 34% STHD reported in a similar Australian study, however the study differed in excluding patients with EMS witnessed OHCA [11]. Our results suggest direct transport of OHCA patients to a PCI-capable hospital improves STHD compared to indirect transfer (56.2% versus 44.8%). There are at least two possible explanations. First, multiple studies show optimal post-resuscitation care is a pivotal component of the chain-of-survival after OHCA, and standardised treatment protocols for post-resuscitation care could improve

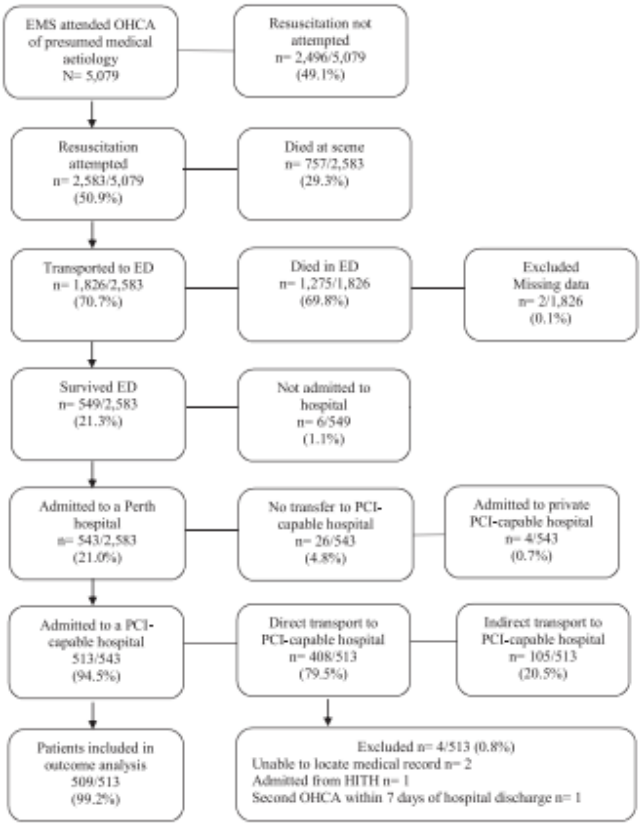

Fig. 1. Flow chart of included and excluded adult OHCA patients (≥ 18 years) with presumed medical aetiology attended by EMS paramedics and transported to a PCI-capable hospital in Perth, WA between the 1st of January 2012 and 31st of December 2015.

patient outcomes [5,23,24]. Indeed, ARC guidelines recommend consideration of transport to a specialist cardiac arrest centre with urgent access to PCI and TTM [1]. Second, both quality post-resuscitation care and timely initiation of optimal post-resuscitation care is vital. Patients directly transported to specialist cardiac arrest centers, including STEMI patients with OHCA, have improved outcomes [5,25] and the importance of early reperfusion of critical ACS is well established. We found patients transported directly to a PCI-capable hospital had shorter times to admission compared to those transported via another hospital (median 47 versus 208 min). Delays in initiating optimal post-resuscitation care after OHCA may partly explain why patients indirectly transported to a PCI-capable hospital had worse outcomes than those treated promptly. Survival in our patients who had PCI after direct transport to a PCI-capable hospital was greater than those who finally received PCI after transport from another hospital (STHD: adjusted OR 4.37, 95% CI 1.49–12.79). The importance of early coronary reperfusion and TTM after OHCA was also shown in a secondary analysis of a clinical trial of an impedance threshold device for CPR [26].

The role of specialised post-resuscitation care and PCI-capability for patients with OHCA is increasingly recognised. A Japanese study found direct transport to a hospital with a high level of critical care was associated with improved survival in patients with OHCA of cardiac aetiology [7]. However, the authors did not report in-hospital factors that may have improved survival. Similarly, an Australian study found admission to a hospital with 24-h PCI-capability was associated with increased STHD [27]. Whether this benefit was related to PCI itself or the whole bundle of specialised post-resuscitation was not fully addressed by the investigators, nor did they document neurological outcomes of patients at hospital discharge or 12-month survival [11]. A French study found the characteristics of receiving hospitals were not associated with STHD, but the authors commented that this might be partially explained by the pre-hospital triage organization [28]. The authors did not consider post resuscitation care in multivariate analysis and the French EMS system differs to that in Australia.

Studies considering in-hospital care factors include a German study reporting direct transport to a PCI-capable hospital after OHCA was an independent predictor of STHD even after considering the effect of PCI and TTM [8]. Another study from North America [29] found improved

Table 1
Demographic and OHCA characteristics of all patients admitted to a PCI-capable hospital stratified by transport group.

No. (%) of patients	All Patients 509	Direct transport 404 (79.4)	Indirect transport 105 (20.6)	*p*-value
Patient demographics of total cohort				
Median age, years	62 (50–73)	62 (51–73)	59 (47–69)	*0.07*
Male sex	365 (71.7)	288 (71.3)	77 (73.3)	*0.68*
Pre-arrest CPC score				
CPC-1	447 (87.8)	347 (85.9)	100 (95.2)	***0.02***
CPC-2	51 (10.0)	46 (11.4)	5 (4.8)	
CPC-3	11 (2.2)	11 (2.7)	0	
Prehospital OHCA characteristics of total cohort				
Location of arrest				
Home	312 (61.3)	232 (57.4)	80 (76.2)	***0.001***
Public place	168 (33.0)	149 (36.9)	19 (18.1)	
Other	29 (5.7)	23 (5.7)	6 (5.7)	
Witnessed arrest				
Paramedic	86 (16.9)	77 (19.1)	9 (8.6)	***0.04***
Bystander	230 (45.2)	179 (44.3)	51 (48.6)	
Unwitnessed	193 (37.9)	148 (36.6)	45 (42.9)	
Bystander CPR[a]	307 (60.3)	239 (59.2)	68 (64.8)	*0.19*
Initial arrest rhythm, shockable[b]	317 (62.3)	248 (61.4)	69 (65.7)	*0.42*
Asystole ever reported[c,d]	109 (21.4)	88 (21.8)	21 (20.0)	*0.72*
VF ever reported[c,e]	325 (63.9)	253 (62.6)	72 (68.6)	*0.22*
Time of arrest[f]				*0.08*
Day (07:00–18:59)	346 (68.0)	282 (69.8)	64 (61.0)	
Night (19:00–06:59)	163 (32.0)	122 (30.2)	41 (39.0)	
Day of arrest				*0.25*
Weekday	360 (70.7)	281 (69.6)	79 (75.2)	
Weekend	149 (29.3)	123 (30.4)	26 (24.8)	
Any prehospital ROSC	439 (86.2)	353 (87.4)	86 (81.9)	*0.15*
Median EMS response time, minutes[g]	8 (6–10)	8 (6–10)	7 (5–10)	*0.27*
Median time to first ED[h]	47 (39–56)	47 (38–56)	47 (39–54)	*0.24*
Median time to PCI-capable hospital, minutes[i]	52 (41–76)	47 (38–56)	208 (149–255)	***< 0.001***
In-hospital OHCA characteristics of total cohort				
Diagnosis of ACS in first ED	164 (32.2)	121 (30.0)	43 (41.0)	***0.03***
Coronary angiography (≤ 24 h)[j]	274 (53.8)	215 (53.2)	59 (56.2)	*0.59*
PCI (≤ 24 h)[j]	151 (29.7)	114 (28.2)	37 (35.2)	*0.19*
Admitting ward				
CCU	83 (16.3)	71 (17.6)	12 (11.4)	***0.004***
Other ward	43 (8.4)	41 (10.1)	2 (1.9)	
ICU	382 (75.0)	291 (72.0)	91 (86.7)	
Survival and neurological outcomes of total cohort				
STHD	274 (53.8)	227 (56.2)	47 (44.8)	***0.04***
30-day survival	268 (52.7)	222 (55.0)	47 (44.8)	***0.05***
12-month survival	253 (49.7)	210 (52.0)	43 (41.0)	***0.05***
Post arrest CPC score for hospital survivors				
CPC-1 or 2	252 (92.0)	206 (90.7)	46 (97.9)	*0.14*
CPC-3 or 4	22 (8.0)	21 (9.3)	1(2.1)	
In-hospital OHCA characteristics of ICU cohort (n = 382)				
Admitted to ICU	382 (75.0)	291 (76.2)	91 (23.8)	
Diagnosis of ACS in first ED	105 (27.5)	71 (24.4)	34 (37.4)	
MV in ICU	377 (98.7)	287 (98.6)	90 (98.9)	
TTM in ICU[k]	298 (79.0)	232 (80.8)	66 (73.3)	
Coronary angiography (≤ 24 h)[j,k]	203 (53.8)	151 (52.6)	52 (57.7)	
PCI (≤ 24 h)[j,k]	103 (27.3)	70 (24.4)	33 (36.7)	
STEMI with PCI (≤ 24 h)[j,k]	77 (20.2)	47 (16.2)	30 (33)	***< 0.001***

Data are presented as median (interquartile range) or count (percentage).
Abbreviations: ACS = Acute Coronary Syndrome, CCL = Cardiac Catheterisation Laboratory, CCU = Coronary Care Unit, CPC = Cerebral Performance Category, CPR = Cardiopulmonary Resuscitation, ED = Emergency Department, EMS = Emergency Medical Services, ICU = Intensive Care Unit, MV = Mechanical Ventilation, OHCA = Out-of-hospital cardiac arrest, PCI = Percutaneous coronary intervention, ROSC = Return of Spontaneous Circulation, STEMI = ST-elevation myocardial infarction, STHD = Survival to hospital discharge, TTM = Targeted Temperature Management, VF = Ventricular Fibrillation.
Bold/italic p-values indicates : Statistically significant result.
[a] Includes 1 patient where 'Bystander CPR' is unknown.
[b] Includes 12 patients where 'Initial arrest rhythm' is unknown.
[c] Covariate does not include 'Initial arrest rhythm'.
[d] Includes 2 patients where 'Asystole ever reported' is unknown.
[e] Includes 2 patients where 'VF ever reported' is unknown.
[f] Using time of arrest (if unavailable using time of EMS call).
[g] Using time interval from EMS call to arrival on scene.
[h] Using time interval from EMS call to arrival a first ED.
[i] Using time interval from EMS call to arrival at PCI-capable hospital.
[j] Using time interval from EMS call to arrival in CCL.
[k] Using the number of patients with MV as the denominator.

STHD in patients admitted to a PCI-capable hospital in univariate analysis.

Our findings have the following potential limitations. This was a retrospective observational study and the association of improved outcome with direct transport to a PCI-capable hospital does not indicate causation. Unknown confounders may have influenced the associations observed in the multivariable analyses. Paramedics can be biased in the choice of the initial destination hospital [30]. This is suggested by direct transport patients differing in some characteristics from indirect patients (Table 1). Similar considerations are also likely to have influenced decisions to transfer patients on from a non-PCI capable hospital. While significantly more indirect transport patients had an ED diagnosis of ACS, after adjustment this was not associated with improved survival in either the total cohort or in the subgroup analysis of ICU patients. Also, the patients who remained at non-PCI capable hospitals had a significantly lower STHD and were less likely to have an initial shockable rhythm.

The strengths of our study include the reporting of in-hospital post-resuscitation care factors known to affect patient outcome, adequate sample size to demonstrate clinically important differences between transport groups and follow up to 12-months. We also compared the outcomes of patients who remained at a non-PCI-capable hospital to address the potential for selection bias.

Conclusion

This multicentre retrospective study showed that direct EMS transport to a PCI-capable hospital for adults with OHCA of medical aetiology was associated with significant survival benefits compared to indirect transport via another hospital without PCI-capability. The improved survival is most likely due to early optimal, specialised, post-resuscitation care including early PCI and TTM. This has potential implications for EMS transport protocols including direct transport of patients with OHCA of presumed medical aetiology to a PCI-capable hospital.

Table 2
Univariate and multivariate factors associated with STHD for patients directly transported versus patients indirectly transported to a PCI-capable hospital.

All patients (N = 509)	Unadjusted OR (95%CI)	*p-value*	Adjusted OR (95%CI)	*p-value*
Transport group, direct	1.58 (1.03–2.44)	***0.04***	1.97 (1.13–3.43)	***0.02***
Patient demographics				
Age, years	0.98 (0.97–0.99)	***0.001***	0.96 (0.95–0.98)	***< 0.001***
Male sex	1.76 (1.03–2.44)	***0.04***	1.01 (0.60–1.70)	*0.97*
Prehospital OHCA characteristics				
Location of arrest, public	2.69 (1.81–3.98)	***< 0.001***	1.70 (1.01–2.87)	***0.05***
Witnessed arrest				
Paramedic	3.15 (1.82–5.46)	***< 0.001***	5.76 (2.54–13.07)	***< 0.001***
Bystander	1.46 (0.99–2.13)	*0.06*	0.97 (0.59–1.61)	*0.91*
Unwitnessed	1.0		1.0	
Bystander CPR[a]	1.20 (0.84–1.71)	*0.33*	0.97 (0.55–1.72)	*0.92*
Initial arrest rhythm, shockable[b]	5.57 (3.76–8.25)	***< 0.001***	2.33 (0.93–5.85)	*0.07*
Asystole ever reported[c]	0.10 (.06–0.18)	***< 0.001***	0.15 (0.08–0.29)	***< 0.001***
VF ever reported[d]	4.35 (2.95–6.44)	***< 0.001***	1.29 (0.52–3.15)	*0.58*
Time of arrest, day (07:00–18:59)	1.07 (0.73–1.55)	*0.74*	1.0 (0.61–1.63)	*0.99*
Day of arrest, weekday	0.69 (0.47–1.01)	*0.06*	0.81 (0.50-1.33)	*0.41*
Any prehospital ROSC	3.43 (1.98–5.96)	***< 0.001***	6.38 (3.10-13.13)	***< 0.001***
EMS response time, minutes[e]				
0– < 4	2.16 (1.05–4.42)	***0.04***	1.64 (0.65–4.12)	*0.29*
4– < 8	1.50 (0.88–2.55)	*0.14*	1.48 (0.73–3.03)	*0.28*
8– < 12	1.25 (0.73–2.13)	*0.42*	1.04 (0.51–2.11)	*0.09*
> 12	1.0		1.0	
In hospital OHCA characteristics				
Diagnosis of ACS in ED	2.75 (1.85–4.08)	***< 0.001***	1.59 (0.93–2.70)	*0.09*

Abbreviations: ACS = Acute Coronary Syndrome, CPR = Cardiopulmonary Resuscitation, ED = Emergency Department, EMS = Emergency Medical Service, OHCA = Out of Hospital cardiac arrest, ROSC = Return of Spontaneous Circulation, VF = Ventricular Fibrillation.
Bold/italic p-values indicates : Statistically significant result.
[a] Includes 1 patient where 'Bystander CPR' is unknown.
[b] Includes 12 patients where 'Initial arrest rhythm' is unknown.
[c] Includes 2 patients where 'Asystole ever reported' is unknown.
[d] Includes 2 patients where 'VF ever reported' is unknown.
[e] Using time interval from EMS call to arrival on scene.

Table 3
Results of logistic regression analysis and Cox proportional hazards regression analysis for STHD and survival to 12-months respectively for patients directly transported to a PCI-capable hospital.

	N (%)	STHD Adjusted odds ratio (95% CI)	12-month survival Adjusted hazard ratio (95% CI)
Patients admitted to a PCI-capable hospital (N = 509)			
Direct	404 (79.4)	1.97 (1.13–3.43)	1.36 (1.00–1.84)
Indirect	105 (20.6)	1.0	1.0
Patients admitted to ICU with MV (n = 377)			
Direct	287 (76.1)	2.33 (1.26–4.28)	1.38 (1.004–1.91)
Indirect	90 (23.9)	1.0	1.0
Patients admitted to ICU with MV and coronary angiography ≤ 24 h of EMS call (n = 203)			
Direct	151 (74.4)	2.54 (1.20–5.40)	1.50 (0.95–2.37)
Indirect	52 (25.6)	1.0	1.0
Patients admitted to ICU with MV and PCI ≤ 24 h of EMS call (n = 103)			
Direct	70 (68.0)	4.37 (1.49–12.79)	1.74 (0.89–3.38)
Indirect	33 (32.0)	1.0	1.0

Abbreviations: EMS = Emergency Medical Services, ICU = Intensive Care Unit, MV = Mechanical Ventilation, PCI = Percutaneous coronary intervention.

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Authors' contributions

MI is SJA-WA OHCA Database Manager. NM and TAW collected in-hospital data. TAW and KMH assisted with statistical analysis. All authors contributed to the interpretation of results and manuscript review.

Conflict of interest statement

JF is the Director of the Australian Resuscitation Outcomes Consortium (Aus-ROC). NM is a PhD candidate who receives funding from Aus-ROC. There are no other conflicts of interest to declare. All authors read and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2018.04.039.

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4.3 Supplemental Tables (Mckenzie et al. Resuscitation. 2018 Jul; 128:76-82)[17]

Table 4.1 *(Supplemental Table 1)* Univariate and multivariate factors associated with STHD for patients admitted to the ICU with MV.

All patients (n= 377)	**Unadjusted OR (95%CI)**	***p-value***	**Adjusted OR (95%CI)**	***p-value***
Transport group, direct	1.63 (1.00-2.66)	***0.05***	2.33 (1.26-4.28)	***0.01***
Patient demographics				
Age, years	0.98 (0.96-0.99)	***0.001***	0.96 (0.94-0.98)	***<0.001***
Male sex	1.63 (1.02-2.60)	***0.04***	0.87 (0.46-1.62)	*0.65*
Prehospital OHCA characteristics				
Location of arrest, public	2.46 (1.58-3.85)	***<0.001***	1.28 (0.70-2.31)	*0.42*
Witnessed arrest	1.20 (0.80-1.82)	*0.37*	1.02 (0.60-1.71)	*0.95*
Bystander CPR[(a)]	2.07 (1.33-3.24)	***0.001***	1.06 (0.59-1.92)	*0.84*
Initial arrest rhythm, shockable[(b)]	6.77 (4.13-11.10)	***<0.001***	2.43 (0.90-6.54)	*0.08*
Asystole ever reported[(c)]	0.13 (0.07-0.25)	***<0.001***	0.21 (0.10-0.45)	***<0.001***
VF ever reported[(d)]	6.57 (3.92-11.01)	***<0.001***	1.48 (0.56-3.93)	*0.43*
Time of arrest, day (07:00 - 18:59)	1.15 (0.74-1.77)	*0.53*	1.09 (0.62-1.91)	*0.78*
Day of arrest, weekday	0.58 (0.37-0.90)	***0.02***	0.59 (0.34-1.02)	*0.06*
Any prehospital ROSC	2.96 (1.59-5.51)	***0.001***	3.32 (1.54-7.17)	***<0.001***
EMS response time, minutes[(e)]				
0 to < 4	2.32 (0.99-5.40)	***0.05***	1.07 (0.37-3.03)	*0.90*
4 to < 8	1.63 (0.85-3.11)	*0.14*	0.87 (0.38-1.98)	*0.74*
8 to < 12	1.27 (0.66-2.44)	*0.48*	0.71 (0.31-1.62)	*0.41*
> 12	1.0		1.0	
OHCA characteristics in-hospital				
Diagnosis of ACS in ED	2.03 (1.28-3.20)	***0.002***	1.42 (0.79-2.55)	*0.24*
TTM in ICU	2.69 (1.55-4.65)	***<0.001***	1.42 (0.72-2.80)	*0.32*

(a) Includes 1 patient where 'Bystander CPR' is unknown
(b) Includes 3 patients where 'Initial arrest rhythm' is unknown
(c) Includes 1 patient where 'Asystole ever reported' is unknown
(d) Includes 1 patient where 'VF ever reported' is unknown

(e) Using time interval from EMS call to arrival on scene

Abbreviations indicate as follows: ACS; Acute coronary syndrome, CPR; Cardiopulmonary resuscitation, ED; Emergency department, EMS; Emergency medical services, ICU; Intensive care unit, OHCA; Out of hospital cardiac arrest, ROSC; Return of spontaneous circulation, STHD; Survival to hospital discharge, TTM; Targeted temperature management, VF; Ventricular fibrillation.

Table 4.2 *(Supplemental Table 2)* Univariate and multivariate factors associated with STHD for patients admitted to ICU with MV and who received coronary angiography within 24 hours of EMS call.

All patients (n= 203)	Unadjusted OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
Transport group, direct	2.43 (1.27-4.63)	***0.01***	2.54 (1.20-5.40)	***0.02***
Patient demographics				
Age, years	0.96 (0.94-0.98)	***0.001***	0.95 (0.93-0.98)	***<0.001***
Male sex	1.45 (0.68-3.09)	*0.34*	1.52 (0.62-3.71)	*0.36*
Prehospital OHCA characteristics				
Location of arrest, public	1.52 (0.85-2.70)	*0.16*	0.83 (0.30-2.36)	*0.73*
Witnessed arrest	0.80 (0.45-1.41)	*0.44*	0.74 (0.38-1.43)	*0.37*
Bystander CPR[(a)]	1.70 (0.90-3.22)	*0.10*	1.04 (0.48-2.29)	*0.91*
Initial arrest rhythm, shockable[(b)]	3.03 (1.39-6.62)	***0.01***	2.81 (1.16-6.81)	***0.02***
Time of arrest, day (07:00 to 18:59)	0.87 (0.48-1.58)	*0.64*	1.11 (0.53-2.31)	*0.78*
Day of arrest, weekday	0.79 (0.42-1.47)	*0.45*	0.96 (0.48-1.95)	*0.92*
Any prehospital ROSC	4.00 (1.75-9.13)	***0.001***	3.45 (1.31-9.12)	***0.01***
Median EMS response time, minutes[(c)]				
0 to < 5	2.17 (0.90-5.25)	0.09	1.45 (0.53-3.95)	*0.47*
5 to < 10	1.56 (0.80-3.04)	0.20	1.14 (0.52-2.47)	*0.74*
> 10	1.0		1.0	
OHCA characteristics in-hospital				
TTM in ICU	1.67 (0.70-3.99)	0.26	1.29 (0.49-3.43)	*0.60*

(a) Includes 1 patient where 'Bystander CPR' is unknown
(b) Includes 1 patient where 'Initial arrest rhythm' is unknown
(c) Using time interval from EMS call to arrival on scene

Abbreviations indicate as follows: CPR; Cardiopulmonary resuscitation, EMS; Emergency medical services, MV; Mechanical ventilation, OHCA; Out-of-hospital cardiac arrest, ROSC; Return of spontaneous circulation, TTM; Targeted temperature management.

Table 4.3 *(Supplemental Table 3)* Univariate and multivariate factors associated with STHD for patients admitted to ICU with MV and who received PCI within 24 hours of EMS call.

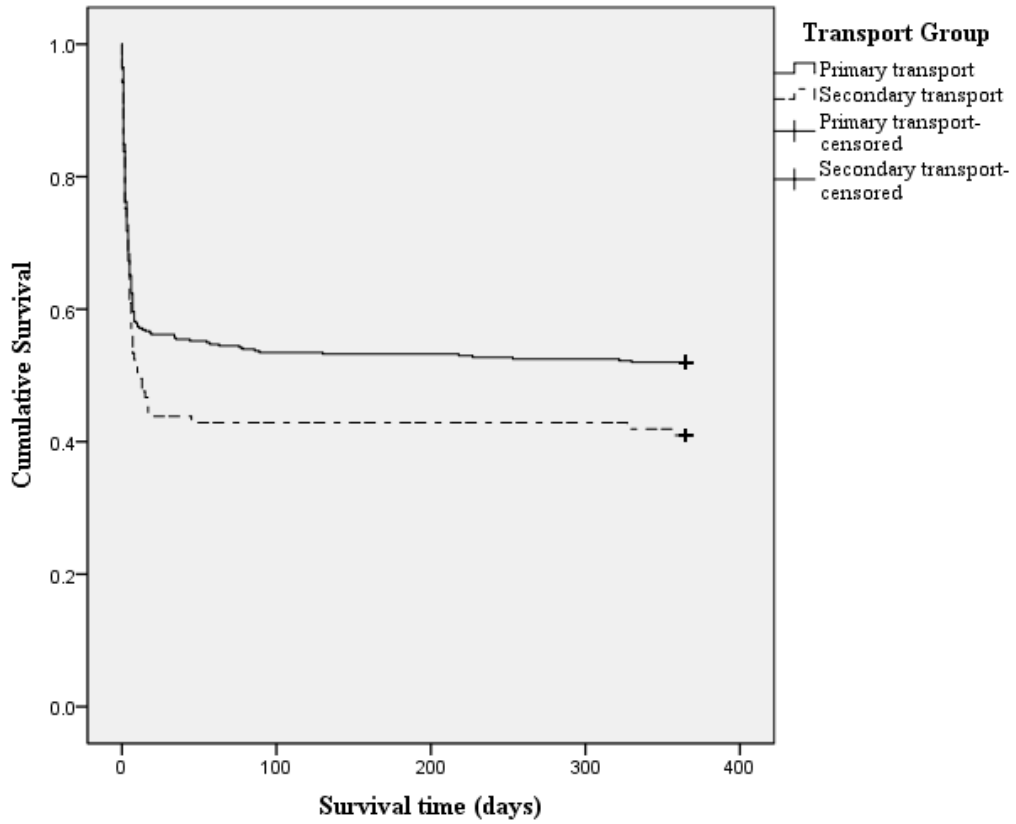
All patients (n= 103)	Unadjusted OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
Transport group, direct	3.58 (1.50-8.51)	***0.004***	4.37 (1.49-12.79)	***0.01***
Patient demographics				
Age, years	0.99 (0.96-1.02)	*0.36*	0.97 (0.93-1.003)	*0.07*
Male sex	3.54 (1.01-12.36)	***0.05***	3.01 (0.64-14.23)	*0.16*
Prehospital OHCA characteristics				
Location of arrest, public	1.64 (0.71-3.75)	*0.25*	1.07 (0.37-3.06)	*0.90*
Witnessed arrest	1.33 (0.59-2.98)	*0.50*	1.94 (0.69-5.44)	*0.21*
Bystander CPR[(a)]	2.10 (0.88-5.02)	*0.10*	1.41 (0.47-4.26)	*0.54*
Initial arrest rhythm, shockable[(b)]	1.67 (0.52-5.38)	*0.39*	1.60 (0.37-6.94)	*0.53*
Any prehospital ROSC	6.42 (1.94-21.24)	***0.002***	4.42 (0.96-20.24)	*0.06*
Median EMS response time, minutes[(c)]				
0 to < 5	1.62 (0.62-4.27)	0.33	1.55 (0.50-4.77)	*0.58*
5 to < 10	1.18 (0.38-3.67)	0.77	1.35 (0.36-5.09)	*0.66*
> 10	1.0		1.0	
OHCA characteristics in-hospital				
TTM in ICU	1.14 (0.37-3.48)	0.82	1.59 ((0.39-6.60)	*0.52*

(a) Includes 1 patient where 'Bystander CPR' is unknown
(b) Includes 1 patient where 'Initial arrest rhythm' is unknown
(c) Using time interval from EMS call to arrival on scene

Abbreviations indicate as follows: CPR; Cardiopulmonary resuscitation, EMS; Emergency medical services, ICU; Intensive care unit, ROSC; Return of spontaneous circulation, TTM; Targeted temperature management.

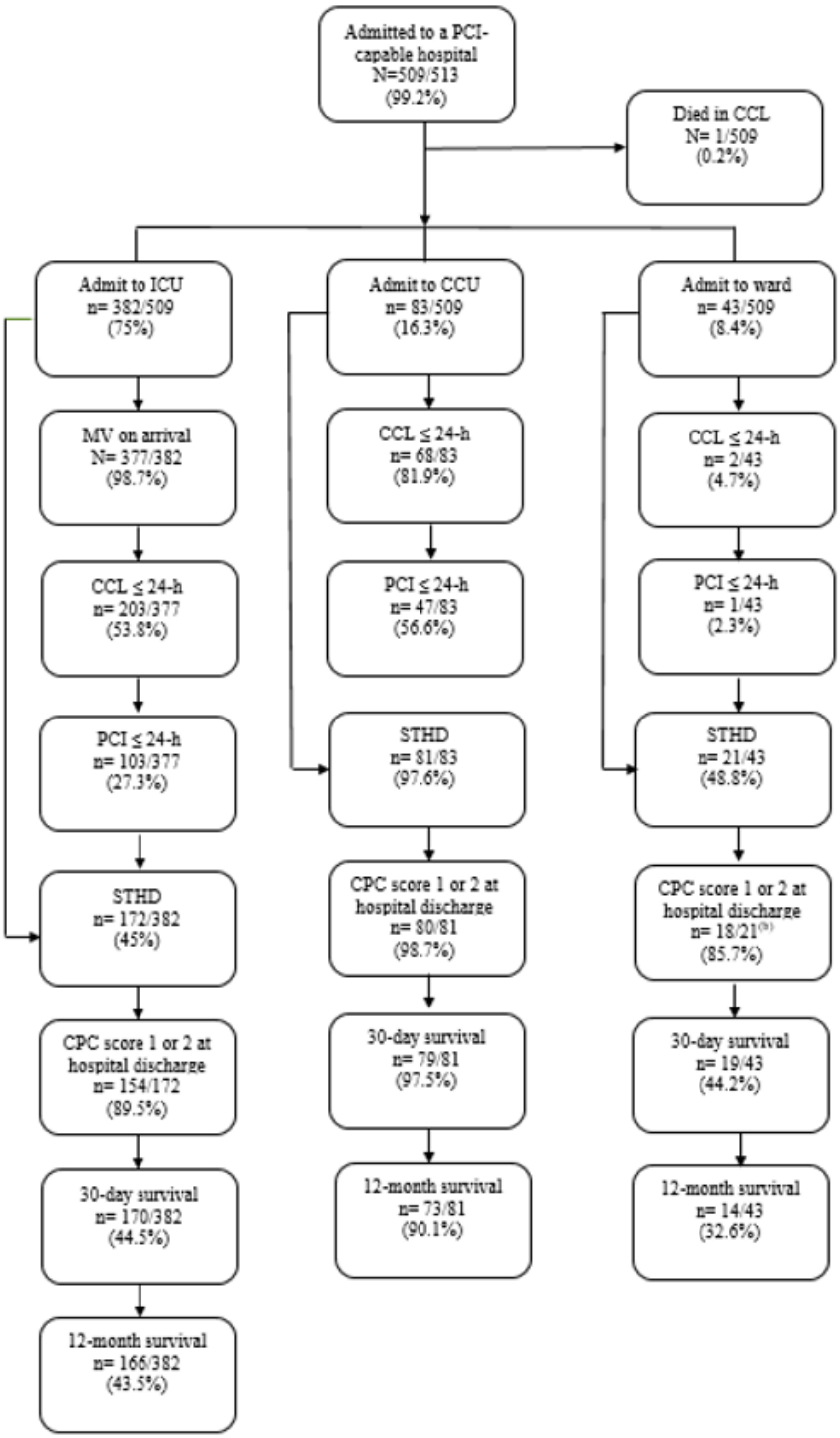
4.4 Supplemental Figures (Mckenzie et al. Resuscitation. 2018 Jul; 128:76-82)[17]

Figure 4.1 *(Supplemental Figure 1)* Kaplan-Meier survival plots stratified by transport group (direct versus indirect) for all patients admitted to a PCI-capable hospital (N=509) (Log Rank test *p=0.07*).



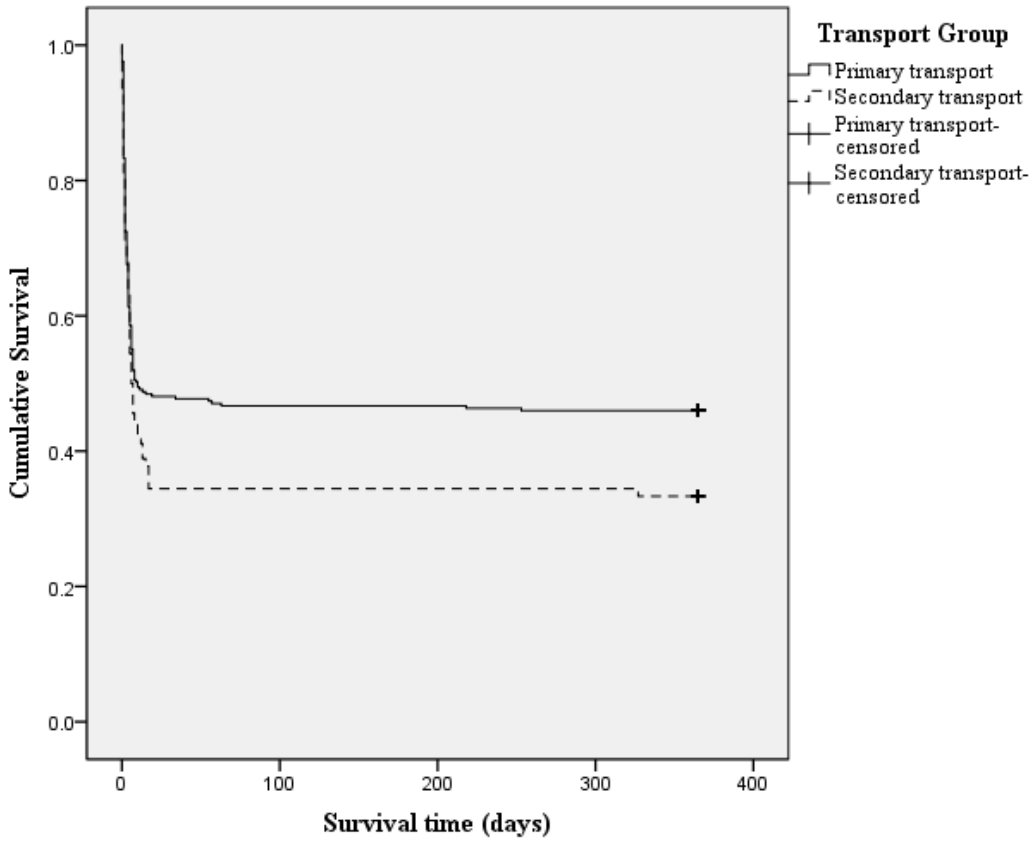
Abbreviations indicate as follows: PCI; Percutaneous coronary intervention.

Figure 4.2 *(Supplemental Figure 2)* Flow chart of included patients by admitting ward.



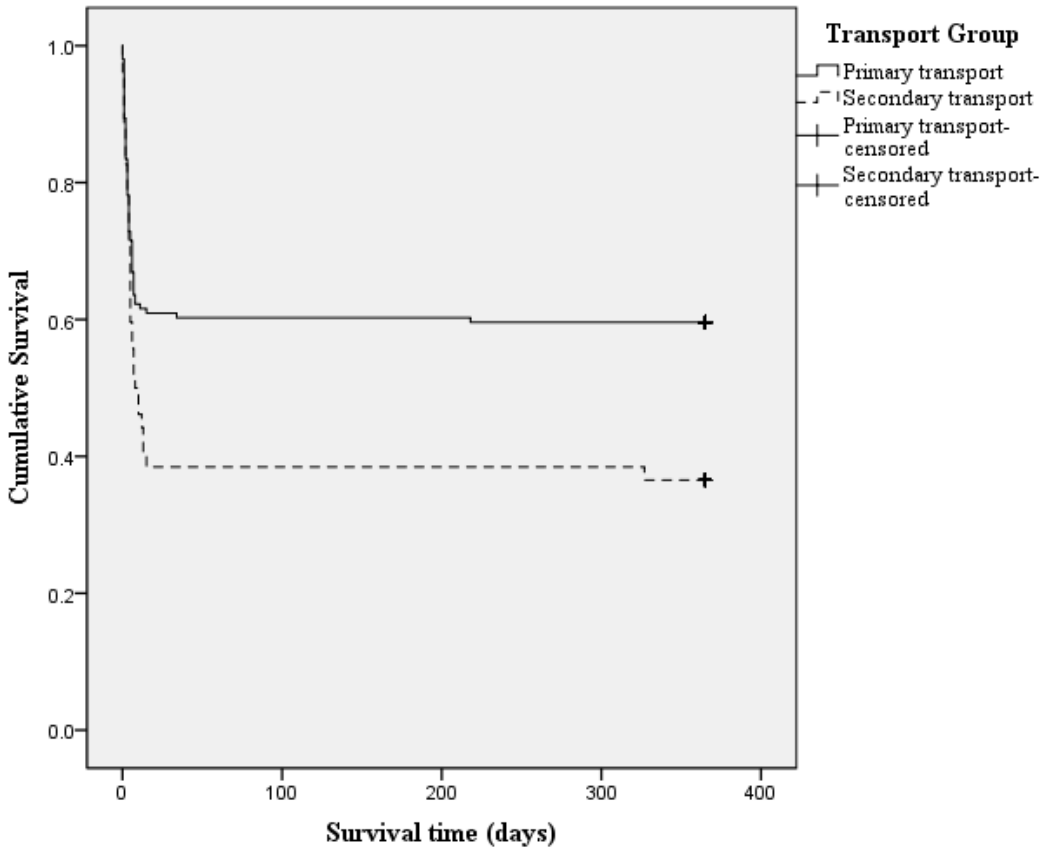
Abbreviations indicate as follows: CCL; Cardiac catheterisation laboratory, CCU; Coronary care unit, CPC; Cerebral Performance Category, ICU; Intensive care unit, MV; Mechanical Ventilation, PCI; Percutaneous coronary intervention, STHD; Survival to hospital discharge.

Figure 4.3 *(Supplemental Figure 3)* Kaplan-Meier survival plots stratified by transport group (direct versus indirect) for all patients receiving MV on admission to ICU of a PCI-capable hospital (n=377) (Log Rank test *p=0.07*).



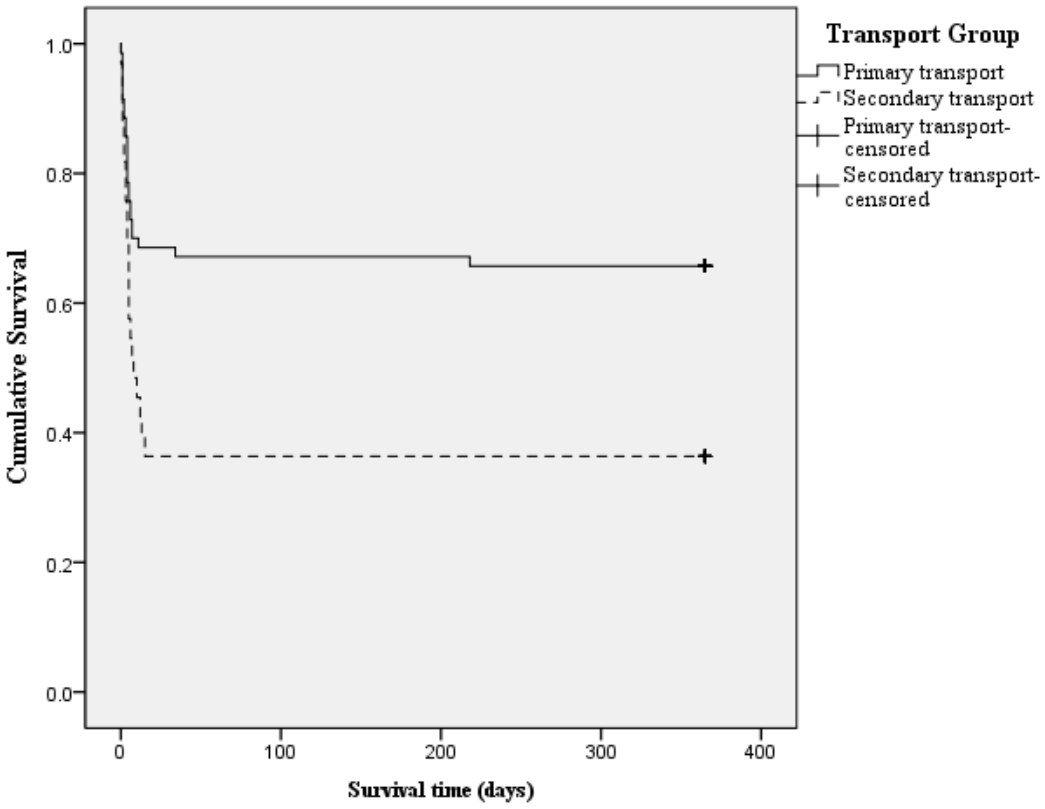
Abbreviations indicate as follows: ICU; Intensive care unit, MV; Mechanical ventilation, PCI; Percutaneous coronary intervention.

Figure 4.4 *(Supplemental Figure 4)* Kaplan-Meier survival plots stratified by transport group (direct versus indirect) for all patients receiving MV on admission to ICU of a PCI-capable hospital and who received coronary angiography within 24 hours of EMS call (n=203) (Log Rank test *p=0.01*).



Abbreviations indicate as follows: ICU; Intensive care unit, MV; Mechanical ventilation, PCI; Percutaneous coronary intervention.

Figure 4.5 *(Supplemental Figure 5)* Kaplan-Meier survival plots stratified by transport group (direct versus indirect) for all patients receiving MV on admission to ICU of a PCI-capable hospital and who received PCI within 24 hours of EMS call (n=103) (Log Rank test *p=0.01*).



Abbreviations indicate as follows: ICU; Intensive care unit, MV; Mechanical ventilation, PCI; Percutaneous coronary intervention.

4.5 Appendices (Mckenzie et al. Resuscitation. 2018 Jul; 128: 76-82)[17]

Table 4.4 *(Appendix 1)* Results of adjusted sensitivity analysis excluding 12 patients where 'initial arrest rhythm' is unknown.

		STHD	12-month survival
All patients (N= 509)	N (%)	Adjusted odds ratio (95% CI)	Adjusted hazard ratio (95% CI)
Direct transport	404 (79.4)	1.97 [1.12-3.46]	1.36 [1.003-1.84]
Secondary transport	105 (20.6)	1.0	1.0

Table 4.5 *(Appendix 2)* Results of adjusted sensitivity analysis excluding patients with a CPC score of 3 prior to OHCA.

		STHD	12-month survival
All patients (N= 498)	n (%)	Adjusted odds ratio (95% CI)	Adjusted hazard ratio (95% CI)
Direct transport	393 (78.9)	2.28 (1.34-3.90)	1.39 (1.02-1.88)
Secondary transport	105 (21.1)	1.0	1.0

4.6 Summary

This multicentre retrospective cohort study showed that for adults with OHCA of presumed medical aetiology, direct transport to a PCI-capable hospital for post-resuscitation care was associated with significant survival benefits compared to indirect transport via another hospital without PCI capability.[17] Specifically, direct transport patients were twice as likely to survive to hospital discharge, than those transferred via another hospital.[17] My findings suggest that while prehospital factors such as bystander CPR and early defibrillation are important, early access to a standardised post-resuscitation care bundle may also improve survival and neurological outcome in adult OHCA patients.[17] My findings are consistent with current international guidelines[12] and support the implementation of specialist cardiac arrest centres in Australia.[123]

This study forms part of a growing number of publications investigating whether care at specialist cardiac arrest centres improves patient outcomes. A subsequent publication comparing patient characteristics and outcomes following OHCA patients transported to hospitals with or without PCI-capability within New Zealand found improved 30-day survival for the direct transport group.[48] A 2019 systematic review and meta-analysis of 17 observational studies found that care at a cardiac arrest centre is associated with improved survival to hospital discharge with favourable neurological outcome.[51] However, the authors concluded that while their findings were generally supportive of transporting OHCA patients to cardiac arrest centres they should be interpreted with caution because of the nature of observational studies.[51] This systematic review and meta-analysis included the PhD study[17] that is subject of Chapter 4 in this thesis.

Improved patient outcomes with direct EMS Transport to specialist centres has been described for trauma,[52,124,125] stroke[126-128] and STEMI[122] leading to the acceptance of specialised treatment centres for these conditions. The weight of evidence, although this is not yet conclusive, supports the introduction of cardiac arrest centres. While it would be ideal to confirm these findings with a large multicentre RCT, the number

and consistency of observational studies supporting cardiac arrest centres suggests that equipoise no longer exists to conduct such studies.

In the next chapter, I consider another strategy that may help to improve patient outcomes after cardiac arrest. The targeted management of $PaCO_2$ in mechanically ventilated patients admitted to ICU. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest follows in Chapter Five.

Chapter 5 Systematic Review and Meta-analysis

5.1 Overview of Chapter 5

Chapter Two provided a contextual overview of OHCA and described post-resuscitation care strategies that have been shown to reduce the severity of post-cardiac arrest syndrome. One important strategy is the targeting of normal $PaCO_2$ levels in mechanically ventilated adult OHCA patients, but the evidence to inform international guidelines is weak.[12] While there have been multiple observation cohort studies investigating the relationship between $PaCO_2$ and survival in cardiac arrest patients these are inherently limited by lack of randomisation of exposure and subject to bias and confounding.[64,68,73,117] Further, there have been few RCTs investigating $PaCO_2$ as a potential therapeutic target in this population of critically ill patients[66,72] and results from an ongoing multinational study have yet to be published.[129,130]

Given the limited evidence, I aimed to assess the effect of a low or high $PaCO_2$ on patient outcomes after cardiac arrest by systematically reviewing the literature and by combining results from similar studies in meta-analysis.[18] The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) protocol directed this study.[131] Details of the protocol were registered in the international database of prospectively registered systematic reviews (PROSPERO; CRD42015024907).[132] The PRISMA protocol checklist and the PROSPERO registration are included in Thesis Appendix D and E respectively. This systematic review and meta-analysis provides the foundation for the second retrospective cohort study included in this thesis: Arterial carbon dioxide tension has a non-linear association with survival after OHCA: A multicentre observational study.[19]

This Chapter comprises a manuscript that has been published in a peer-reviewed journal and is inserted as a PDF in the format published by the journal:

McKenzie N, Williams TA, Tohira H, Ho KM, Finn J. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest. *Resuscitation*. 2017 Feb; 111: 116-126.[18]

Supplemental material supporting this article is presented prior to the Chapter summary.

A poster related to this publication was presented at the American Heart Association (AHA) Scientific Sessions, New Orleans, United States of America, 2016 and is included in Thesis Appendix F:

McKenzie N, Williams TA, Tohira H, Ho KM, Finn J. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest.

5.2 Manuscript

Resuscitation 111 (2017) 116–126

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Review article

A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest☆

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ABSTRACT

Introduction: Arterial carbon dioxide tension ($PaCO_2$) abnormalities are common after cardiac arrest (CA). Maintaining a normal $PaCO_2$ makes physiological sense and is recommended as a therapeutic target after CA, but few studies have examined the association between $PaCO_2$ and patient outcomes. This systematic review and meta-analysis aimed to assess the effect of a low or high $PaCO_2$ on patient outcomes after CA.
Methods: We searched MEDLINE, EMBASE, CINAHL and Cochrane CENTRAL, for studies that evaluated the association between $PaCO_2$ and outcomes after CA. The primary outcome was hospital survival. Secondary outcomes included neurological status at the end of each study's follow up period, hospital discharge destination and 30-day survival. Meta-analysis was conducted if statistical heterogeneity was low.
Results: The systematic review included nine studies; eight provided sufficient quantitative data for meta-analysis. Using $PaCO_2$ cut-points of <35 mmHg and >45 mmHg to define hypo- and hypercarbia, normocarbia was associated with increased hospital survival (odds ratio [OR] 1.30, 95% confidence interval [CI] 1.23, 1.38). Normocarbia was also associated with a good neurological outcome (cerebral performance category score 1 or 2) compared to hypercarbia (OR 1.69, 95% CI 1.13, 2.51) when the analysis also included an additional study with a slightly different definition for normocarbia ($PaCO_2$ 30–50 mmHg).
Conclusions: From the limited data it appears $PaCO_2$ has an important U-shape association with survival and outcomes after CA, consistent with international resuscitation guidelines' recommendation that normocarbia be targeted during post-resuscitation care.

Introduction

Elimination of arterial carbon dioxide is substantially impaired during cardiac arrest (CA) due to inadequate perfusion of the lungs. Both high and low arterial carbon dioxide tension (or partial pressure $PaCO_2$) after return of spontaneous circulation (ROSC) from CA are common, due to accumulation of carbon dioxide during CA and excessive mechanical ventilation, respectively.[1–3] Unintentional hypocarbia is particularly common during therapeutic hypothermia after CA because cooling reduces patient's metabolic rate and CO_2 production.[1,4,5]

Physiologically, $PaCO_2$ has an important regulatory role on cerebral blood flow[6]; hypercarbia dilates cerebral blood vessels resulting in an increase in cerebral perfusion and intracranial pressure, and hypocarbia induces cerebral vasoconstriction resulting in a reduction in cerebral blood flow.[7,8] Hypothetically, abnormal $PaCO_2$ may have the potential to increase the likelihood of further CA[9] and exacerbate ischaemic brain injury.[10] Conversely, maintaining a relatively normal $PaCO_2$ with mechanical ventilation and regular arterial blood gas (ABG) analysis may improve survival and neurological outcomes after CA.[9]

Observational data from CA registries suggest that derangements in $PaCO_2$ are associated with poorer neurological outcomes.[2,11] While some studies have suggested that mild hypercarbia may be better in optimising neurological outcomes after

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2016.09.019.

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0300-9572/

CA,[3,12] others have suggested either hypocarbia or hypercarbia can be harmful in both adults[1,2] and children.[13]

For patients who survive after a CA, neurological recovery is paramount and hence, good post-resuscitation care is essential in the chain of survival.[14] Because maintaining normocarbia after CA may avoid both cerebral ischaemia and hyperperfusion and there is no evidence to suggest this may cause harms after CA, international guidelines have recommended targeting normocarbia as part of the post-resuscitation care.[9,15] Whether this recommendation is fully supported by existing evidence remains uncertain, and will be assessed in this systematic review and meta-analysis.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was adhered to in this this systematic review and meta-analysis.[16]

Eligibility criteria

We included comparative studies if they investigated the association of $PaCO_2$ and survival to hospital discharge (hospital survival) or in-hospital mortality (hospital mortality) after CA. Studies were included if patients had suffered an in-hospital cardiac arrest (IHCA) or out-of-hospital (OHCA) of any aetiology and who had their exposure to $PaCO_2$ measured by ABG analysis. The search was limited to full manuscripts published in peer-reviewed journals and no language restriction was applied. We excluded studies that included paediatric patients (as defined by the authors), animal studies, case reports, reviews, editorials, letters and commentary. The authors' cut-points were used for the definitions of low, normal and high $PaCO_2$ and time of assessment of $PaCO_2$. When authors did not report outcomes by $PaCO_2$ group but provided their patient data we a priori defined cut-points according to published threshold values as hypocarbia <35 mmHg, normocarbia 35–45 mmHg and hypercarbia >45 mmHg.[3,4,17] The primary outcome was hospital survival after CA. Secondary outcomes included neurological status at the end of each study's follow-up period, hospital discharge destination and 30-day survival. Neurological status after CA is often described using the Cerebral Performance Category (CPC),[18] which is a five category scale ranging from unimpaired survival to severe dependence and death.[19] CPC scores of 1 or 2 are considered as good neurological recovery.[19] Hospital discharge destination has been reported as a surrogate marker for neurological outcome after CA, but few such markers have been adequately validated[3] and are subject to factors that affect discharge decision making e.g. availability of a care-giver.

Data sources

Databases were searched for eligible studies published between inception and August 2015: Ovid MEDLINE(R), Ovid MEDLINE (R) in process and other non-indexed citations, Ovid EMBASE, CINAHL Plus with Full Text (EBSCO) and Cochrane Central Register of Controlled Trials (CENTRAL). Reference lists from review articles, editorials and citation lists in Scopus were hand-searched to identify possible additional studies. The end date for the literature search was 31st August, 2015. Authors of the papers that met the inclusion criteria but did not report patient outcome by $PaCO_2$ group were contacted with a request for the original data.

Data search

We grouped search terms under three main subject headings: Heart Arrest, Carbon Dioxide and Outcomes Assessment. The three groups were combined using Boolean operators. The search strategy used for MEDLINE is provided in Supplementary Table S1 in the online version at DOI: 10.1016/j.resuscitation.2016.09.019. A similar search strategy was applied to the other databases.

Study selection

Titles and abstracts were reviewed by two investigators (NM and TAW) to identify relevant studies. Full text of the screened studies were reviewed when eligibility was unclear. Any differences in study selection were resolved by consensus between the authors. For studies reporting data on overlapping patient cohorts, we selected the reports that; (1) most closely examined our primary outcome of interest; (2) contained the largest sample size; or (3) contained data for our meta-analysis.

Data collection

Descriptive, methodological and outcome data were abstracted from the included studies using a pre-determined electronic spreadsheet developed by NM. Data extracted included location of CA (IHCA/OHCA), year of publication, study location, sample size, study year(s), study design, $PaCO_2$ cut-points used to define hypo-, normo- and hypercarbia, $PaCO_2$ sampling time, use of therapeutic hypothermia, whether the ABG was adjusted for body temperature or not (alpha-stat versus pH-stat),[20] and primary and secondary outcomes. We preferentially selected ABG results measured by alpha-stat to provide a more consistent interpretation of $PaCO_2$.[20] For studies that reported hospital mortality we have used this data to report hospital survival. For studies that reported CPC scores of 3–5 for poor neurological outcome, we have reported CPC scores of 1–2 for good neurological outcome. For studies that reported hospital discharge destination we selected and reported discharge home among survivors. A second author (HT) independently verified all the extracted data.

Risk of bias assessment

The Newcastle-Ottawa Scale (NOS)[21] was used to assess the methodological quality of studies included in this systematic review. Results were collated and accuracy independently checked by two authors (NM and HT). The authors' proposed to rate the methodological quality of each study as low, intermediate or high if they scored <4, between 4 and 6 or >6, respectively. In this systematic review, only intermediate and high quality studies were included for detailed analysis.

Data analysis

We performed meta-analyses of the association between $PaCO_2$ and patient outcomes, including hospital survival, CPC score of 1 or 2 at the end of each study's follow-up period and discharge home among survivors. The results were summarised by forest plots using weighted Peto odds ratio (OR) fixed effect model with 95% confidence interval (CI) (RevMan Version 5.3, Cochrane Collaboration).[22] Where patient data by $PaCO_2$ group was received from the authors,[4,12,23,24] we categorised $PaCO_2$: as hypocarbia (<35 mmHg), normocarbia (35–45 mmHg) and hypercarbia (>45 mmHg). If patient data were not explicitly stated in the table or text, we extracted the outcome data (rounded to the nearest whole number) reported in the studies' figures.[2] Where four $PaCO_2$ threshold groups were reported[12] we considered patients in the middle and intermediate $PaCO_2$ quartiles as being exposed to normocarbia. Where individual patient data by $PaCO_2$ group was available we calculated odds ratio (OR) for each outcome with 95% confidence intervals (CIs) and the associated 'p' value using IBM

Statistical Package for Social Sciences (SPSS) for Windows (Version 22.0).[25]

Heterogeneity

Studies were tested for heterogeneity using the I^2 statistic.[26] I^2 values of <25%, 25–50%, and >50% were considered to have a low, moderate, and high level of inconsistency between studies, respectively.[26] We proposed to report a pooled estimate only when the I^2 statistic was less than 50%. If the I^2 statistic was greater than 50%, forest plots would be used to display individual study results only. We considered IHCA/OHCA and OHCA as separate sub-groups in this meta-analysis so as to make comparisons between them. We also considered differences in the author's follow up time and variations in $PaCO_2$ cut-points used to define normocarbia as potential sources of clinical heterogeneity. We planned to conduct sensitivity analysis to determine the effect of these variations on the overall conclusion of the meta-analyses. The potential for publication bias was interpreted through visual inspection of funnel plot asymmetry.

Protocol and registration

The study protocol has been registered with the international Prospective Register of Systematic Reviews PROSPERO 2015:CRD42015024907.[27]

Results

Study selection

Our search strategy found no randomised control trials (RCT's) comparing $PaCO_2$ targets after CA. Of the 93 studies identified, 77 studies were excluded based upon review of the title and abstract against the inclusion/exclusion criteria. Sixteen studies with full text were further examined in detail and nine studies were considered eligible for this systematic review.[2–4,11,12,20,23,24,28] The inclusion and exclusion of the studies are described in Fig. 1. Two studies by Roberts et al.[2,29] appear to include patients from two overlapping periods: 2009–2011 and July 2010–July 2011. As such, only information contained in the larger patient cohort[2] was included in this review.

Study characteristics

All nine studies included were published in English between 1985 and 2015 from Australia and New Zealand (combined),[3] United States of America,[2,28] Korea,[4,24] Finland,[12] Australia,[20] Taiwan,[23] and Holland[11] and included 23,434 patients (range 44[24]–16,542[3]). Two studies[11,12] included OHCA patients, (n = 5667 in total), one study included IHCA patients,[23] (n = 550) and six studies included both IHCA/OHCA patients (n = 17,217 in total).[2–4,20,24,28] Three studies[3,11,12] used national multicentre databases, two of these included only OHCA patients (the Finnish Intensive Care Consortium database[12] and the Dutch National Intensive Care Evaluation registry[11]) and the third one included both IHCA and OHCA (Australian New Zealand Intensive Care Society–Adult Patient Database). The other six studies were single-centre studies.[2,4,20,28] Cohort design was used in all studies with four prospective studies[2,12,24,28] and five retrospective studies.[3,4,11,20,23]

The cut-points used to define hypocarbia and hypercarbia varied between 30 and 35 mmHg and between 45 and 50 mmHg, respectively, in the included studies. Two studies[24,28] reported $PaCO_2$ as a continuous variable and did not define threshold values to define hypo or hypercarbia. Additional patient data according to $PaCO_2$ group was received from the authors of one of these studies[24] and as such, the results on hospital survival from this study were included in this meta-analysis.

The timing and duration of ABG results in relation to CA in the included studies also differed. Three studies reported serial ABGs sampled across a number of time points, from ROSC to the end of therapeutic hypothermia,[4] first 24 h after ROSC[2] and first 24 h after ICU admission[12] ; three studies only reported a single ABG result within the first 24 h after CA corresponding to the worst oxygenation according to Acute Physiology and Chronic Health Evaluation (APACHE) III[3,20] and IV[11] scores and three studies reported the first $PaCO_2$ value recorded twenty minutes after sustained ROSC,[23] one hour after ROSC[28] or one hour after sustained ROSC.[24] Study characteristics of the included papers are reported in Table 1.

Patient centred outcomes

The unadjusted and adjusted outcome data from the included studies are summarised in Table 2.

Survival

Two retrospective multi-centre[3,11] and four single-centre[4,20,23,24] studies reported survival outcomes. Of the multi-centre studies, one study[3] reported hospital mortality for IHCA/OHCA patients and one study for only OHCA patients.[11] For the single-centre studies, one study[23] reported hospital survival for only IHCA patients and three studies[4,20,24] for IHCA/OHCA patients.

Neurological outcomes

One prospective multi-centre[12] and three single-centre studies[2,4,20] used CPC scores to evaluate the relationship between neurological outcome and $PaCO_2$ after CA. Vaahersalo et al.[12] reported CPC scores at 12 months for only OHCA patients. Wang et al.[23] reported a CPC score of 1 or 2 at hospital discharge for only IHCA patients. Roberts et al.[2] and Lee et al.[4] reported a CPC score of 3–5 at hospital discharge for both OHCA and IHCA patients.

Discharge home among survivors was used as surrogate marker of neurological outcome in two studies.[3,20] Discharge home was presumed to be a better neurological outcome compared to patients that could not be discharged home by the authors of both studies.

Methodological quality

Two studies were considered to be of intermediate quality[24,28] and seven studies were considered to be of high quality,[2–4,11,12,20,23] as shown in Supplementary Table S2 in the online version at DOI: 10.1016/j.resuscitation.2016.09.019. No study was excluded because of low methodological quality.

Results of meta-analysis

Eight studies[2–4,11,12,20,23,24] reported quantitative data suitable for meta-analysis (Fig. 1). Forest plots were constructed by combining additional patient data provided by the authors in four studies[4,12,23,24] with published results from another four studies.[2,3,11,20] In addition, data were extracted from the figure in the study by Roberts et al.[2] for the meta-analysis.

Association between $PaCO_2$ levels and survival

Six studies reported hospital survival data.[3,4,11,20,23,24] Of the six studies comparing hypocarbia with normocarbia, three studies[3,4,11] found a significant association between normocarbia and increased chance of hospital survival but there was significant heterogeneity between the six included studies (I^2 = 53%) so a meta-analysis was not performed (Fig. 2a). There were

Table 1
Characteristics of included studies.

Study ID/country	Total N=	Study years	Study design	$PaCO_2$ sampling time	$PaCO_2$ cut-points (mmHg)			$PaCO_2$ comparison groups	Primary outcome	Secondary outcome(s)
					Low	High	Normal			
OHCA										
Vaahersalo 2014[12] Finland	409	2010–2011	Prospective cohort, multicentre	All ABG's during first 24 h in ICU	<30	>45	Middle 30–37.5 Intermediate 37.5–45	Mean $PaCO_2$ tertiles and time weighted $PaCO_2$ quartiles	CPC at 12 months	N/R
Helmerhorst 2015[11] Holland	5258	2007–2012	Retrospective cohort, multicentre	ABG with worst oxygenation during first 24 h in ICU	<35	>45	35–45	Low vs. normal High vs. normal High vs. low	Hospital mortality	ICU mortality
IHCA										
Wang 2015[23] Taiwan	550	2006–2012	Retrospective cohort, single centre	First ABG after sustained ROSC	<30	>50	30–50	Mean $PaCO_2$ for patients with and without favourable outcome	CPC 1 or 2 at hospital discharge	Hospital survival
IHCA/OHCA										
Weil 1985[28] USA	105	N/R	Case series	First ABG one hour after ROSC	N/R	N/R	N/R	Mean $PaCO_2$ for survivors and non-survivors	Hospital survival	N/R
Moon 2007[24] Korea	44	2004–2006	Prospective cohort, single centre	First ABG one hour after ROSC	N/R	N/R	N/R	Mean $PaCO_2$ for survivors and non-survivors	Hospital mortality	N/R
Schneider 2013[3] Australia & New Zealand	16,542	2000–2011	Retrospective cohort, multicentre	ABG with worst oxygenation during first 24 h in ICU	<35	>45	35–45	Low vs. normal High vs. normal High vs. low	Hospital mortality	Hospital discharge destination among survivors Death or failure to be discharged home
Roberts 2013[2] USA	193	2009–2011	Prospective cohort, single centre	All ABG's in the first 24h after ROSC	≤30	≥50	≤30 or ≥50	Low vs. normal High vs. normal Both vs. normal	CPC 3 to 5 at hospital discharge	N/R
Lee 2014[4] Korea	213	2008 2012	Retrospective cohort, single centre	All ABG's between ROSC and end of TH	<35	>45	35–45	Low vs. normal High vs. normal	Hospital mortality	CPC 3 to 5 at hospital discharge
Eastwood 2015[20] Australia	120	2007– 2011	Retrospective cohort, single centre	ABG with worst oxygenation during first 24 h in ICU	<35	>45	35–45	Low vs. normal High vs. normal	Classification of patients into PaO_2 and $PaCO_2$ categories	Hospital mortality Discharge home among survivors

ABG = arterial blood gas analysis, CPC = Cerebral Performance Category, ICU = intensive care unit, N/R = Not reported, $PaCO_2$ = partial pressure of arterial carbon dioxide, ROSC = Return of spontaneous circulation.

Table 2
Unadjusted and adjusted outcome data extracted from the included studies by low, high and normal $PaCO_2$ (mmHg) exposure groups.

Study ID	Outcome(s) linked to survival and good neurological status at end of study follow up time[a]	Unadjusted outcome data by low, high and normal $PaCO_2$ (mmHg) exposure groups			Adjusted outcome data (OR, 95% CI) by low, high and normal $PaCO_2$ (mmHg) exposure groups		
		Low	High	Normal	Low	High	Normal
OHCA							
Helmerhorst 2015[11]	Hospital survival	473/1136[c]	793/1834[c]	1159/2288[c]	0.72 (0.61–0.85)[d] 1.00	0.91 (0.79, 1.05)[d] 1.27 (1.06, 1.49)[d]	1.00
Vaahersalo 2014[12]	CPC 1 or 2 at 12 months	76/170[b]	10/31[b]	82/208[b]	Association between proportion of time spent in $PaCO_2$ group and outcome 1.00 (0.99, 1.01)	1.02 (1.00, 1.03)	Middle 0.99 (0.99, 1.00) Intermediate 1.00 (0.99, 1.00)
IHCA							
Wang 2015[23]	CPC 1 or 2 at hospital discharge	41/261[b]	12/146[b]	21/143[b]	Overall OR (95% CI) for favourable outcome– 0.98 (0.95, 0.99)		
	Hospital survival	83/261[b]	26/146[b]	45/143[b]	Overall OR (95% CI) for favourable outcome– 0.98 (0.97, 0.99)		
IHCA/OHCA							
Weil 1985[28]	Hospital survival	N/R	N/R	N/R	N/R	N/R	N/R
Moon 2007[24]	Hospital survival	6/14[b]	5/15[b]	2/15[b]	N/R	N/R	N/R
Schneider 2013[3]	Hospital survival	1220/3010[c]	2882/6827[c]	3241/6705[c]	0.89 (0.81, 1.00)[d] 1.00	0.94 (0.87, 1.03)[d] 1.05 (0.94, 1.18)[d]	1.00
	Discharge home among survivors	730/1220[c]	1915/2882[c]	2105/3241[c]	0.81 (0.70, 0.94) 1.00	1.16 (1.03, 1.32) 1.43 (1.22, 1.69)	1.00
Roberts 2013[2]	CPC 1 to 2 at hospital discharge	9/52[e]	14/63[e]	26/60[e]	0.41 (0.18, 0.96)[d]	0.45 (0.21 0.97)[d]	1.00
Lee 2014[4]	Hospital survival	24/44[b]	11/17[b]	115/152[b]	0.40 (0.19, 0.84)[b]	0.50 (0.16, 1.55)[c]	1.00
	CPC 1 to 2 at hospital discharge	9/44[b]	7/17[b]	58/152[b]	0.45 (0.13, 1.55)[c]	0.84 (0.15–4.81)[c]	1.00
Eastwood 2015[20]	Hospital survival	Alpha-stat			Adjusted OR (95% CI) for favourable outcome after reclassification with pH-stat for high and normal $PaCO_2$ groups with alpha-stat		
		7/18[b]	25/53[b]	23/49[b]	High versus normal and low $PaCO_2$– 0.43 (0.11, 1.64)[d]	Normal versus low $PaCO_2$– 2.33 (0.36, 16.67)[d]	
	Discharge home among survivors	5/18	14/53	16/49	High versus normal and low $PaCO_2$– 5.76 (0.95, 35.1)	Normal versus low $PaCO_2$– 0.39 (0.07, 2.25)	

Abbreviations: CPC = cerebral performance category, OR (95% CI) = odds ratio (95% Confidence interval), N/R = not reported, $PaCO_2$ = partial pressure of arterial carbon dioxide.

[a] Where authors have reported hospital mortality and CPC scores of 3–5 at hospital discharge we have reported hospital survival and CPC scores of 1–2 respectively.
[b] Data based exclusively on additional information provided by authors to define threshold values as $PaCO_2$ low (<35 mmHg), $PaCO_2$ high (>45 mmHg) and $PaCO_2$ normal (35–45 mmHg).
[c] Data recalculated from results provided in original paper using authors threshold values of $PaCO_2$ low (<35 mmHg), $PaCO_2$ high (>45 mmHg) and $PaCO_2$ normal (35–45 mmHg) to report results for good outcome.
[d] Reciprocal ORs (95% CIs) for outcome(s) linked to survival and good neurological status at study follow up time recalculated from original study data.
[e] Data recalculated from figure provided in original paper using authors threshold values of $PaCO_2$ low (<30 mmHg), $PaCO_2$ high (>50 mmHg) and $PaCO_2$ normal (30–50 mmHg) to report results for good outcome.

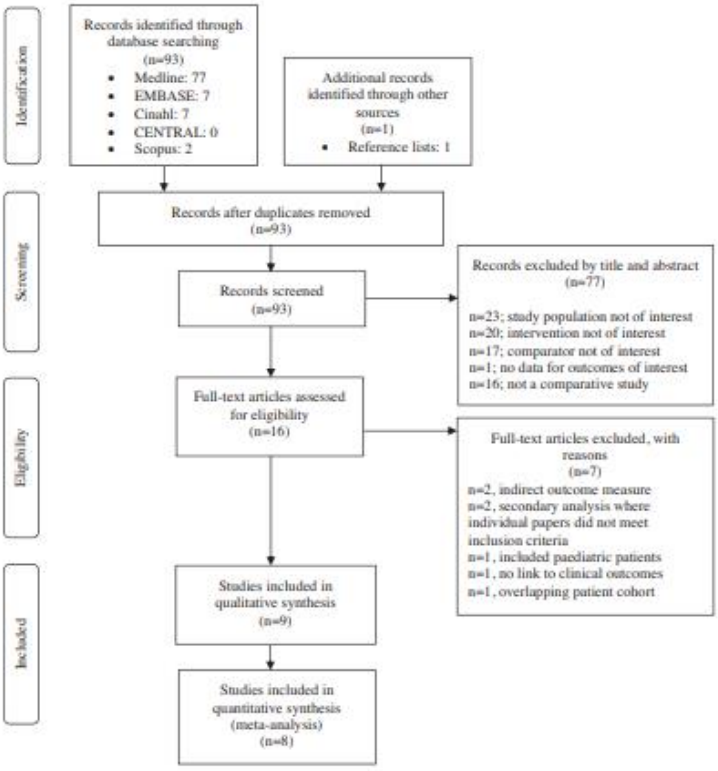

Fig. 1. PRISMA 2009 flow diagram.

six studies[3,4,11,20,23,24] comparing normocarbia with hypercarbia, and the meta-analysis found that normocarbia was associated with increased hospital survival (OR 1.30, 95% CI 1.23, 1.38; $p \leq 0.001$) with moderate heterogeneity ($I^2 = 26\%$) (Fig. 2b). Of the six studies[3,4,11,20,23,24] reporting comparative data between hypercarbia and hypocarbia, only one study[23] found a significantly improved hospital survival associated with hypocarbia (Fig. 2c). The significant heterogeneity ($I^2 = 58\%$) precluded a meta-analysis.

Association between $PaCO_2$ and neurological outcomes

Of the four studies included in this comparison, three studies[2,4,23] reported CPC score at hospital discharge and one reported CPC score at 12 months.[12] Two studies[2,4] showed that normocarbia was more likely than hypocarbia to be associated with a better neurological recovery (CPC scores 1 or 2) at hospital discharge. The statistical heterogeneity was too high ($I^2 = 78\%$) to perform a meta-analysis (Fig. 3a). However, a meta-analysis of four studies[2,4,12,23] did show that normocarbia was significantly associated with an increased chance of good neurological outcome (CPC scores 1 or 2) than patients with hypercarbia (OR 1.69, 95% CI 1.13, 2.51; $p = 0.01$) and the heterogeneity was low ($I^2 = 7\%$) (Fig. 3b). Data on the comparison between hypercarbia and hypocarbia was more limited, with only one study[23] out of four[2,4,12,23] showing a significant association between hypocarbia and good neurological recovery (CPC scores 1 or 2) at hospital discharge, and the heterogeneity was too high ($I^2 = 61\%$) to perform a meta-analysis (Fig. 3c).

Discharge home among survivors was reported in a large study[3] and in another small study.[20] A meta-analysis found the normocarbia was associated with a significantly higher chance of discharge home among survivors compared to hypocarbia (OR 1.25, 95% CI 1.09, 1.43; $p = 0.001$) (Fig. 4a), but not for hypercarbia (OR 1.06, 95% CI 0.96, 1.18; $p = 0.26$) (Fig. 4b). When hypercarbia was directly compared to hypocarbia, the pooled OR was in favour of hypercarbia (OR 1.33, 95% CI 1.16, 1.53; $p \leq 0.001$) with a higher chance for patients to be discharged home. The statistical heterogeneity for this outcome was low ($I^2 = 0\%$) (Fig. 4c).

Sensitivity analysis

After excluding the study by Vaahersalo et al.[12] which only reported CPC at 12 months, normocarbia was still significantly associated with an increased chance of good neurological outcome (CPC scores 1 or 2) at hospital discharge than patients with hypercarbia (Fig. 5b). A second sensitivity analysis was conducted to assess whether excluding the different $PaCO_2$ cut-points reported

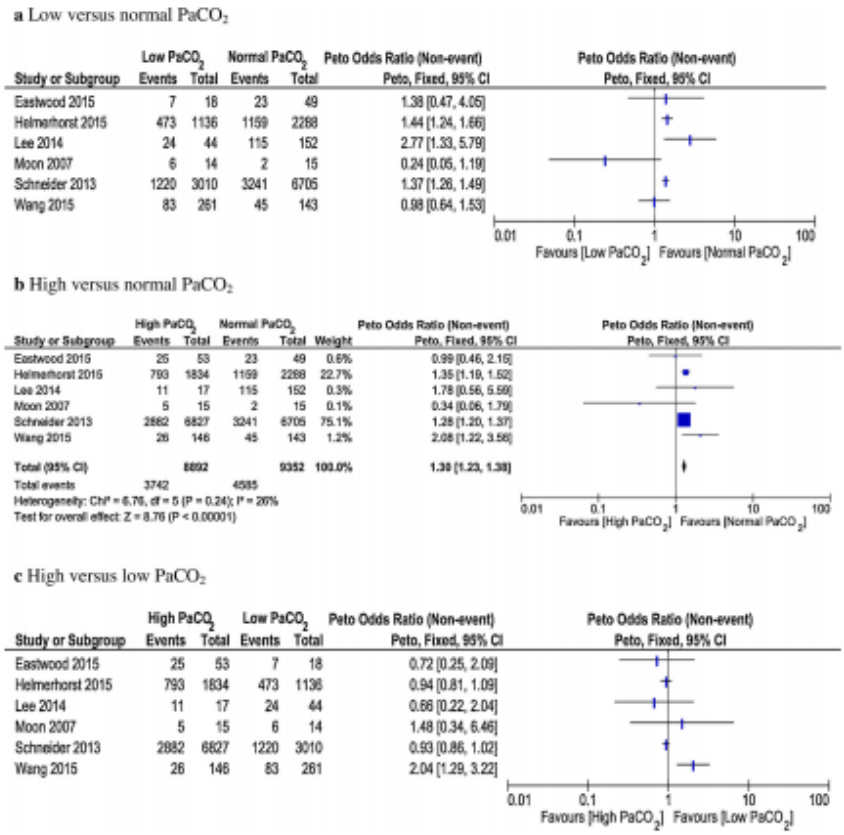

Fig. 2. Forest plot showing the association of $PaCO_2$ groups on hospital survival for patients suffering IHCA,[23] or OHCA[11] or IHCA/OHCA.[3,4,20,24] Pooled OR not provided for 2a and 2c due to heterogeneity >50%.

by Roberts et al.[2] changed the overall conclusions of meta-analysis for the same outcome. When we used a $PaCO_2$ between 35 and 45 mmHg as cut-points to define normocarbia, normocarbia was no longer statistically significantly associated with an increased chance of survival (OR 1.42, for hospital survival, 95% CI 0.89, 2.28; $p = 0.14$) without significant heterogeneity($I^2 = 0\%$) (Fig. 6b). A planned additional analysis to compare IHCA with OHCA was not possible because the OHCA studies[11,12] reported different outcomes and there was only one IHCA study.[23]

Publication bias

Visual inspection of the funnel plots suggests that there was no clear publication bias (Supplementary Figs. S1 and S2 in the online version at DOI: 10.1016/j.resuscitation.2016.09.019).

Discussion

Our systematic review and meta-analysis included 23,434 patients with CA and found that $PaCO_2$ during the post-resuscitation phase had a significant association with patient survival and neurological outcomes. The U-shaped relationship between outcomes from CA and $PaCO_2$ was in line with the most recent resuscitation guidelines that recommend normocarbia as the target of post-arrest mechanical ventilation, as determined by regular ABG analysis.[9] Our results are clinically relevant and require further discussion.

Not all studies included in this review showed that normocarbia was better than hypocarbia or hypercarbia. In the study by Eastwood et al.[20] no relationship between $PaCO_2$ and patient outcome was observed. However, the association between $PaCO_2$ and patient centered outcome was not the primary aim of the study nor was the study powered to detect such relationship.

Post-resuscitation care is an important link in the chain of survival after CA.[9] The idea that $PaCO_2$ levels are important for patient neurological outcomes is a significant consideration, particularly in an era of targeted temperature management in which hypocarbia (or hypercarbia) can occur during the period of post-resuscitation care if mechanical ventilation is not adjusted regularly to maintain normocarbia.[1,4] It is plausible that hypocarbia by inducing cerebral vasoconstriction might cause relative cerebral ischaemia and worsen neurological outcome.[7,8] Conversely, hyperaemia associated with hypercarbia might increase vasogenic oedema and intracranial pressure, which can worsen neurological outcome

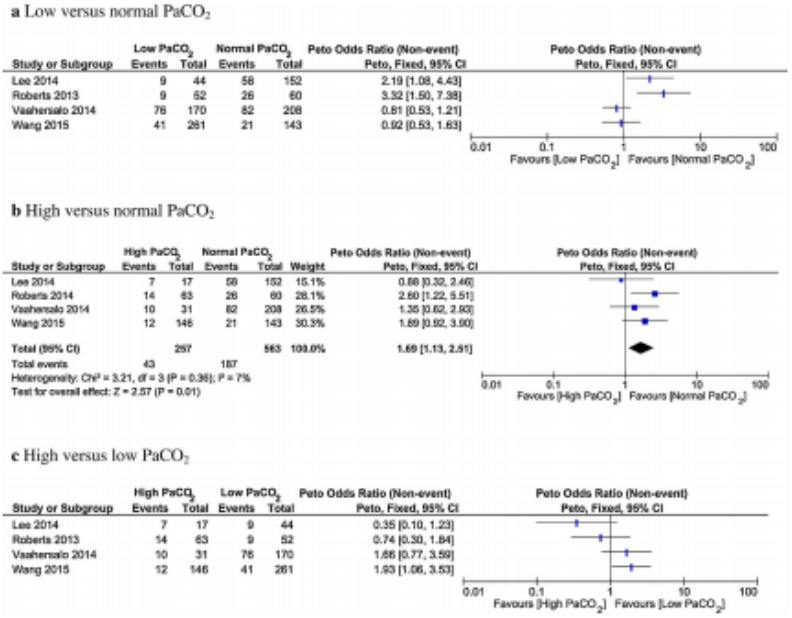

Fig. 3. Forest plot showing the association of $PaCO_2$ groups on neurological outcomes using CPC score 1 or 2 at hospital discharge[2,4,23] and 12 months[12] for patients suffering IHCA,[23] OHCA[12] or IHCA/OHCA.[2,4] Pooled OR not provided for 3a and 3c due to heterogeneity >50%.

directly.[1,2,30] It is also possible that excessive tidal volumes during mechanical ventilation after ROSC affects patient outcomes. In patients with adult respiratory distress syndrome, a RCT showed that excessive tidal volume (>6 mg/kg ideal body weight) is associated with an increase in mortality.[31]

This review has several limitations. Firstly, while, the patient $PaCO_2$ and outcome data received from four authors[4,12,23,24] enabled us to classify patients with different $PaCO_2$ values across seven out of eight studies in a much more consistent fashion, the definition of hypo-, normo- and hypercarbia differed slightly in the Roberts et al.[2] study so that the $PaCO_2$ groups between studies are not completely comparable in the meta-analysis of the association of $PaCO_2$ and neurological outcome. Exclusion of this study in the sensitivity analysis for the same outcome resulted in loss of statistical significance. The results of our meta-analyses were also influenced by the Schneider et al.[3] study which accounted for a high proportion of the pooled results for the outcomes 'hospital survival' and 'discharge home among survivors'.

Secondly, significant differences in patient characteristics between the included studies existed, including countries of the origin of the study, the location of CA (IHCA,[23] versus OHCA[11,12] versus IHCA/OHCA),[2–4,20,24] the use of therapeutic hypothermia (ranging from 0.5%[23] to 100%[4]) and the timing as well as frequency of the $PaCO_2$ measurement (single[4,23,24] versus multiple[2,12] versus selected ABG analysis).[3,11,20] Thus, it was not surprising that there was significant heterogeneity in some outcomes in this review, limiting our ability to draw a definitive conclusion on the optimal $PaCO_2$ level that clinicians should target for patients after CA.

Thirdly, the temporal heterogeneity in ABG sampling times within and between the included studies is relevant to the interpretation of the study results. In one study,[23] ABG measurements were conducted as early as twenty minutes after sustained ROSC and these values may partly represent the physiologic effects of CA and the prearrest state. Where $PaCO_2$ values were obtained later in the post-arrest period,[2–4,11,12,20,23,24] mechanical ventilation parameters,[3,29,32] metabolic rate[33] and lung abnormalities[32] are likely to be the major determinants of $PaCO_2$ and therefore reflect a target for ongoing patient management.

Finally, all included studies were observational studies. Pulmonary aspiration,[34–36] cardiogenic and non-cardiogenic pulmonary oedema[35–37] are known complications of patients with CA, especially for those with prolonged CA or with poor underlying myocardial function. In patients with these respiratory complications, it is possible for hypercarbia to occur and hypercarbia may represent as a confounder for poor outcome instead of a causative step in inducing poor outcome. Similarly, in patients with severe lactic acidosis due to prolonged CA[38] or repeated doses of adrenaline during cardiopulmonary resuscitation,[39] compensatory respiratory alkalosis with hypocarbia may occur and, again, this may represent as a confounder for poor outcome after CA. These and other potential confounders of $PaCO_2$ may have influenced the associations observed in the meta-analyses.

RCTs assessing different types of interventions for patients with CA have been conducted.[40–42] Currently there is at least one pilot study assessing therapeutic hypercapnia after CA (ACTRN 1261200069),[17] but more adequately-powered RCTs comparing different $PaCO_2$targets during the post-resuscitation care period are needed to confirm the possible therapeutic role of normocarbia after CA.

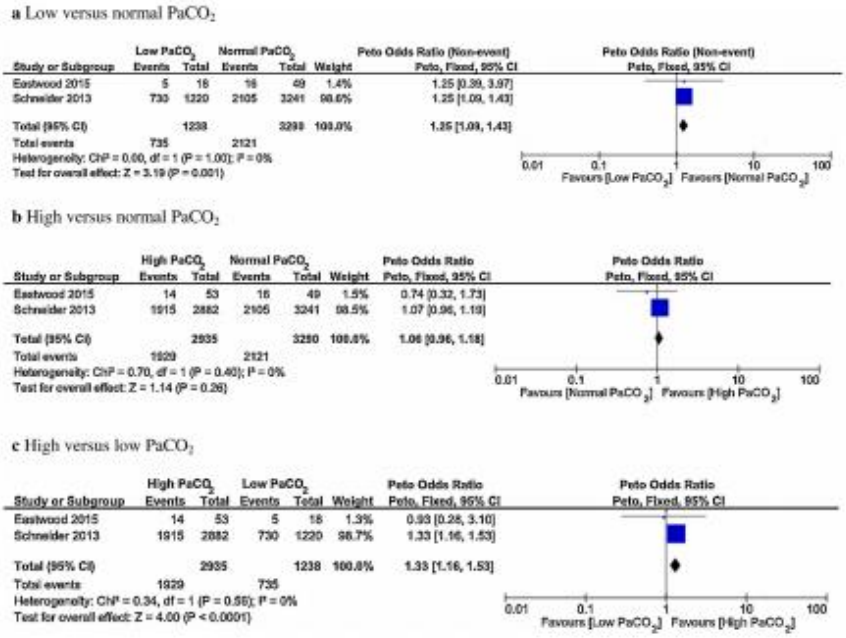

Fig. 4. Forest plot showing the association of $PaCO_2$ groups on neurological outcomes using discharge home among survivors for patients suffering IHCA/OHCA.[3,20]

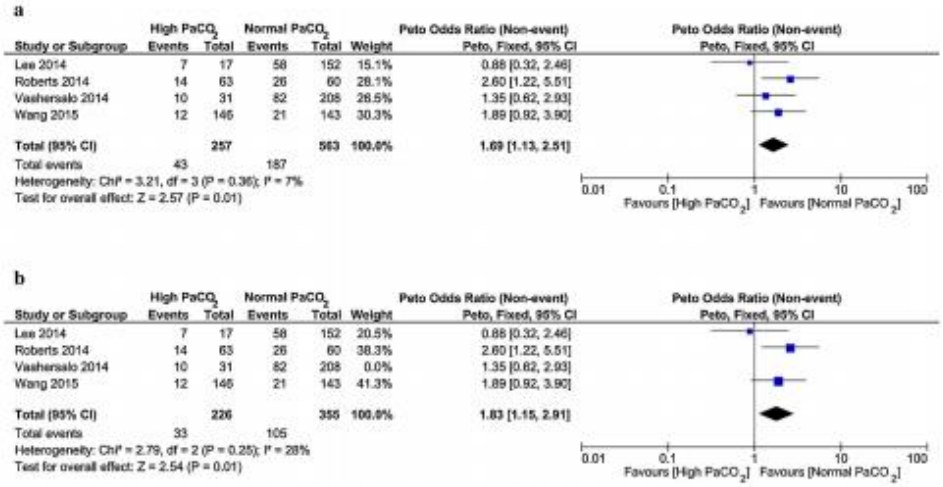

Fig. 5. Forest plots of sensitivity analysis showing the association of high versus normal $PaCO_2$ on neurological outcomes using (a) CPC score of 1 or 2 at hospital discharge[3,4,21] and 12 months[12] and (b) CPC score of 1 or 2 at hospital discharge only.[3,4,21]

Conclusion

In conclusion, with the limited data available, maintaining normocarbia after CA was associated with better patient-centred outcomes compared to either hypo- or hypercarbia, consistent with the current post-resuscitation guidelines' recommendations. Adequately powered RCTs are, however, needed to confirm our findings.

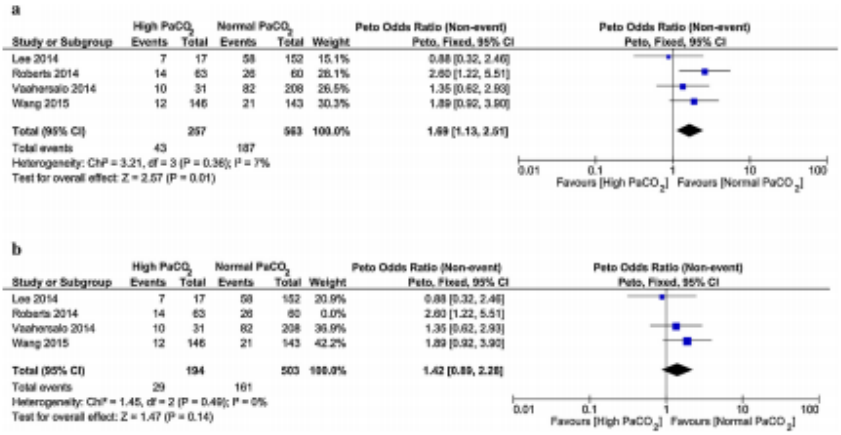

Fig. 6. Forest plots of sensitivity analysis showing the association of high versus normal $PaCO_2$ on neurological outcomes using CPC score of 1 or 2 at hospital discharge[2,4,21] and 12 months[12] by (a) hypo- hypercarbic cut-points of 30–35 and 45–50 mmHg and (b) hypo- hypercarbic cut-points of 35–45 mmHg.

Key messages

1. Meta-analysis of observational studies suggests that normocarbia is associated with improved patient outcomes compare to hypo- or hypercarbia after CA.
2. Different studies used different $PaCO_2$ cut-points to define normocarbia, with PaCO2 between 35 and 45 mmHg being the commonest definition for normocarbia.
3. Greater uniformity in reporting patient centred outcomes after CA would assist in valid interpretation of the available evidence.
4. Randomised controlled trials are needed to define the best $PaCO_2$ target during the post-resuscitation period after cardiac arrest.

Conflict of interest statement

JF is the Director of the Australian Resuscitation Outcomes Consortium (Aus-ROC). NM is a PhD candidate who receives funding from Aus-ROC. There are no other conflicts of interest to declare. All authors read and approved the final version of the manuscript.

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Authors' contributions

NM performed the literature search. NM and TAW identified eligible papers. NM performed the data extraction, synthesis and risk of bias assessment and TAW and HT confirmed the results. KMH provided assistance with the meta-analysis. NM drafted the paper and is accountable for the final manuscript as a whole. All authors contributed to the study conception and design, interpretation of results and review of draft and final manuscripts.

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5.3 Supplemental Tables (Mckenzie et al. Resuscitation 2017 Feb; 111:116-126)[18]

Table 5.1 *(Table S1)* Search strategy (Ovid MEDLINE(R) 1946 to Present with Daily Update).

Line Number	Searches	Subject Headings
1	exp heart arrest/	**Heart Arrest**
2	cardiac arrest.mp.	
3	in-hospital cardiac arrest.mp.	
4	out-of-hospital cardiac arrest.mp.	
5	cardiorespiratory arrest.mp	
6	cardiopulmonary resuscitation.mp.	
7	1 or 2 or 3 or 4 or 5 or 6	**Carbon Dioxide**
8	exp carbon dioxide/	
9	hypercarbia.mp.	
10	hypocarbia.mp.	
11	normocarbia.mp.	
12	dyscarbia.mp.	
13	hypercapnia.mp.	
14	hypocapnia.mp.	
15	normocapnia.mp.	
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	**Outcomes assessment**
17	exp outcomes assessment/	
18	survival.mp.	
19	neurological outcome.mp.	
20	prognosis.mp.	
21	cerebral performance category.mp.	
22	17 or 18 or 19 or 20 or 21	
23	7 and 16 and 22	
24	limit 23 to animals	
25	23 not 24	
26	limit 25 to review articles	
27	25 not 26	
28	limit 27 to case reports	
29	27 not 28	

30	limit 29 to letter	
31	29 not 30	
32	limit 31 to comment	
33	31 not 32	

Table 5.2 *(Table S2)* Newcastle-Ottawa Scale (NOS) risk of bias assessment.

Quality assessment criteria	**Acceptable[(*)]**	**Weil[28] 1985**	**Moon[24] 2007**	**Schneider[3] 2013**	**Roberts[2] 2013**	**Lee[4] 2014**	**Vaahersalo[12] 2014**	**Eastwood[20] 2015**	**Wang[23] 2015**	**Helmerhorst[11] 2015**
Selection										
Truly representative of the study cohort	CA with ROSC and ABG analysis demonstrating exposure to hypo- or hypercarbia	★	★							
Somewhat representative of the study cohort	CA with ROSC and ABG analysis demonstrating exposure to hypo- or hypercarbia and any clinical intervention that may select toward better overall outcome			★	★	★	★	★	★	★
Selection of the non-exposed cohort	CA with ROSC and ABG analysis demonstrating exposure to normocarbia		★	★	★	★	★	★	★	★

Quality assessment criteria	Acceptable[(*)]	Weil[28] 1985	Moon[24] 2007	Schneider[3] 2013	Roberts[2] 2013	Lee[4] 2014	Vaahersalo[12] 2014	Eastwood[20] 2015	Wang[23] 2015	Helmerhorst[11] 2015
Ascertainment of exposure	Secure medical record	★	★	★	★	★	★	★	★	★
Demonstration that outcome of interest was not present at start of study	Post-ROSC ABG analysis	★	★	★	★	★	★	★	★	★
Comparability										
Comparability of cohorts on the basis of a validated illness severity score	Yes			★		★	★	★		★
Comparability of the cohorts on the basis of a validated neurological assessment tool	Yes				★	★	★		★	
Outcome										

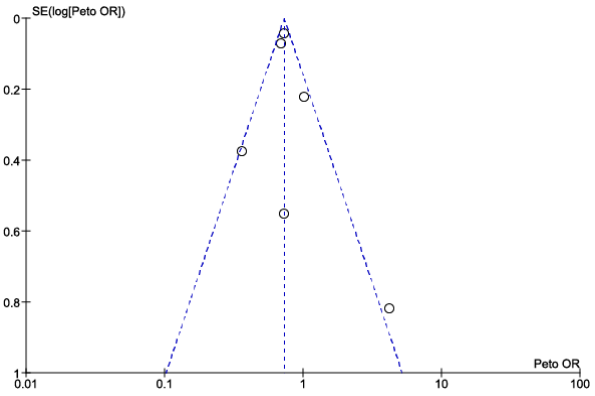
Quality assessment criteria	Acceptable(*)	Weil[28] 1985	Moon[24] 2007	Schneider[3] 2013	Roberts[2] 2013	Lee[4] 2014	Vaahersalo[12] 2014	Eastwood[20] 2015	Wang[23] 2015	Helmerhorst[11] 2015
Assessment of outcome	Independent blind assessment						★			
Was follow up long enough for outcomes to occur?	Assessment of outcome made at or after the time of hospital discharge	★	★	★	★	★	★	★	★	★
Adequacy of follow up of cohorts?	Greater than 90% follow up to the point of outcome	★	★	★	★	★	★	★	★	★
Overall quality score		**5**	**6**	**7**	**7**	**8**	**9**	**7**	**7**	**7**
Overall quality rating		**Inter-mediate**	**Inter-mediate**	**High**	**High**	**High**	**High**	**High**	**High**	**High**

Abbreviations indicate as follows: ABG; Arterial blood gas, CA; Cardiac arrest, ROSC; Return of spontaneous circulation

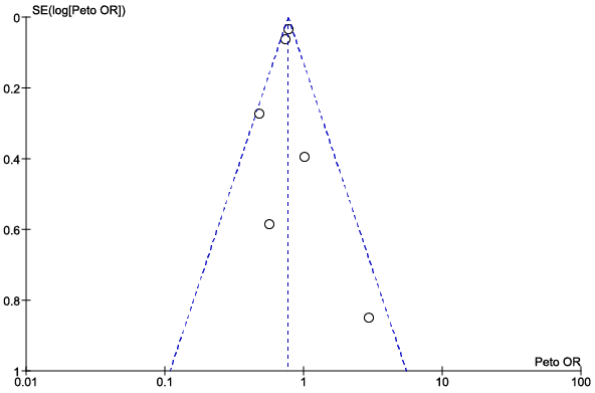
5.4 Supplemental Figures (Mckenzie et al. Resuscitation 2017 Feb; 111:116-126)[18]

Figure 5.1 *(Figure S1)* Funnel plot of comparison for $PaCO_2$ groups on hospital survival for patients suffering IHCA[23] or OHCA[11] or IHCA/OHCA.[3,4,20,24]

(a) Low versus normal $PaCO_2$



(b) High versus normal $PaCO_2$



(c) High versus low $PaCO_2$

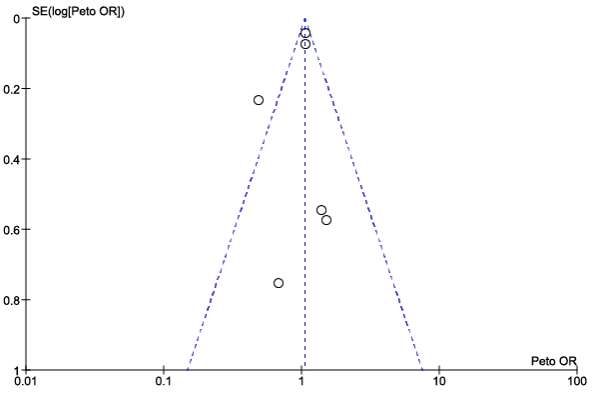
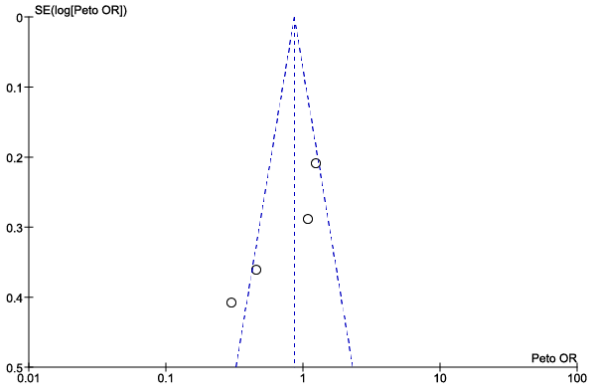
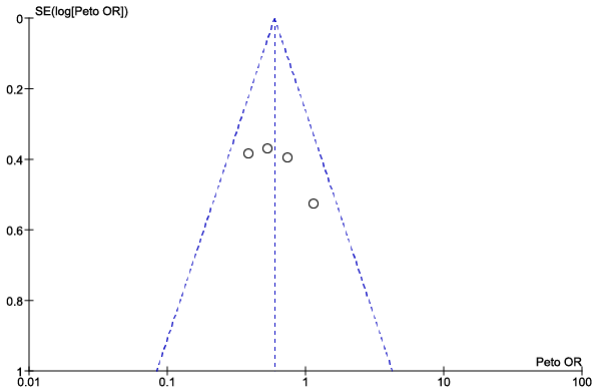


Figure 5.2 *(Figure S2)* Funnel plot of comparison for $PaCO_2$ groups on neurological outcomes using CPC score of 1 or 2 at hospital discharge[2,4,23] and 12 months[12] for patients suffering IHCA[23] or OHCA[12] or IHCA/OHCA.[2,4]

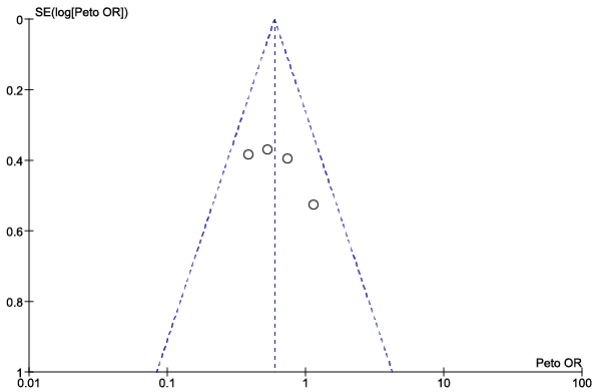
(a) Low versus normal $PaCO_2$



(b) High versus normal $PaCO_2$



(c) High versus low $PaCO_2$



5.5 Summary

This systematic review and meta-analysis[18] of eight observational cohort studies[64,68,69,73-76,117] included 23,434 patients with cardiac arrest. I found that targeting normocarbia in the post resuscitation phase was associated with improved hospital survival and improved neurologic outcomes compared to hypercarbia and improved rates of discharge home with normocarbia as compared to hypocarbia.[18] The inverted U-shape relationship between $PaCO_2$ and survival suggests that there may be a physiological “sweet spot" that corresponds to best patient-centred outcomes.[133] In the absence of conclusive clinical data and recognising the potential harm caused by hypo-and hypercarbia, international guidelines recommend that normocarbia be targeted during post-resuscitation care.[12] The results are clinically relevant and require further investigation by adequately-powered RCTs.[18]

The importance of this inverted U-shape relationship was highlighted by an accompanying editorial in Resuscitation titled ‘Optimal arterial carbon dioxide tension following cardiac arrest: Let Goldilocks decide?’ (Thesis Appendix G).[134] This editorial raised the question as to whether abnormalities in $PaCO_2$ are merely reflective of post-arrest pathophysiology or whether $PaCO_2$ is an independent promotor of secondary injury, with the authors concluding both propositions are likely true. The editorial also reiterated the limitations identified in the systematic review including the use of arbitrarily selected cut-points to define $PaCO_2$ thresholds and heterogeneity in the timing and duration of ABG analyses.[134] The authors concluded further studies are required to support the targeted management of $PaCO_2$ during the critical post resuscitation period where the patient is susceptible to the development of post cardiac arrest syndrome.

In the absence of results from large clinical trials targeting low or high-normal $PaCO_2$ levels after OHCA, I conducted a multicentre retrospective observational cohort study that aimed to determine the optimal $PaCO_2$ cut-points for survival after OHCA. The strengths and limitations of the studies included in this systematic review, findings from the meta-analysis and results from other published studies

investigating the association between physiological parameters and outcomes in critically ill patients informed the methods of this study. Firstly, I used a four-knot restricted cubic spline function to allow for the possibility of a non-linear relationship between $PaCO_2$ and outcome. Secondly, I 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 in the multivariable logistic model. This is consistent with the editorial comment that $PaCO_2$ could be an independent promotor of secondary injury. Thirdly, I avoided the use of arbitrarily selected $PaCO_2$ cut-points by identifying optimal cut-points based on the shape of the spline curve. Finally, I overcame limitations related to single or selected ABG analysis by using all ABG results obtained within the first 72 hours of ICU admission. This study is titled 'Arterial carbon dioxide tension has a non-linear association with survival after out-of-hospital cardiac arrest: A multicentre observational study' and the manuscript is presented in Chapter 6.

Chapter 6 Arterial Carbon Dioxide Tension

6.1 Overview

In this chapter the findings of the second multicentre retrospective cohort study included in this thesis are presented. In this study, I hypothesised that normocapnia within the first 24 hours after OHCA is associated with better patient-centred outcomes when compared to hypo-or hypercapnia.[19] This hypothesis was based on the findings of my systematic review and meta-analysis that identified an inverted U-shaped association between $PaCO_2$ and survival following adult cardiac arrest.[18] It found improved hospital survival and improved neurologic outcomes with normocapnia as compared to hypercapnia; and improved rates of discharge home with normocapnia as compared to hypocapnia.[18] The study was also based on the results of other published studies which have shown a non-linear relationship between $PaCO_2$ and patient survival[69] and neurological outcomes[117] in cardiac arrest populations.

Titration of mechanical ventilation to achieve a target range of $PaCO_2$ has become an integral component of post resuscitation care.[12] Evidence suggests that hypocapnia causes cerebral vasoconstriction and ischaemic injury while hypercapnia may lead to cerebral vasodilatation, increased cerebral blood flow and intracranial hypertension.[135,136] However, the optimal $PaCO_2$ targets during the post-resuscitation phase have yet to be identified and there may even be a subgroup of patients who derive benefit from mild hypercapnia.[66,137] The effect of targeted therapeutic mild hypercapnia after cardiac arrest is currently under investigation in clinical trials.[129,130] However, it is difficult to imagine that there is clinical equipoise to randomise adult OHCA patients to other $PaCO_2$ levels that are outside the normal range.

With consideration to the available evidence I conducted a multicentre retrospective cohort study to determine if $PaCO_2$ has a non-linear association with survival after OHCA.

The research aim was:

To assess the associations between different levels of $PaCO_2$ over the first 24 hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of non-traumatic aetiology.

The specific objectives were:

1. To undertake a retrospective cohort study of all adult patients with OHCA of medical aetiology, attended by SJ-WA paramedics and who achieved ROSC and received mechanical ventilation on arrival to a study hospital
2. To describe the characteristics and patient outcomes for the total cohort stratified by hospital survival status
3. To use a four-knot restricted cubic spline function to evaluate the potential for non-linearity in the relationship between $PaCO_2$ and survival
4. To identify optimal $PaCO_2$ cut-points for survival based on the shape of the spline curve
5. To employ multivariable logistic regression analyses to assess the association between mean $PaCO_2$ in the first 24-hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge or 12-months after stepwise forward adjustment for potential confounders and;
6. To conduct four sensitivity analyses examining whether the mean $PaCO_2$ during the first 48 and 72 hours in ICU after OHCA was associated with survival, if there was any clustering of mortality with either hypercapnia or hypocapnia within certain ICUs using Generalised Estimating Equations and if using different $PaCO_2$ cut-points would substantially affect the mortality risk estimates associated with hypo- or hypercapnia compared to normocapnia.

This Chapter comprises a manuscript that has been published in a peer-reviewed journal and is inserted as a PDF in the format published by the journal:

Mckenzie N, Finn J, Dobb G, Bailey P, Arendts G, Celenza A, Fatovich D, Jenkins I, Ball S, Bray J, Ho KM. Arterial carbon dioxide tension has a non-linear association with survival after out-of-hospital cardiac arrest: A multicentre observational study. *Resuscitation*. 2021 May; 162:82-90.[19]

Supplemental material supporting this article is presented prior to the Chapter summary.

6.2 Manuscript

RESUSCITATION 162 (2021) 82–90

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Clinical paper

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

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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-h 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 h 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-h 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: Normocapnia within the first 24-h of intensive care admission after OHCA was associated with an improved survival compared to patients with hypocapnia or hypercapnia.

Keywords: Arterial carbon dioxide tension, Out-of-hospital cardiac arrest, Post-resuscitation care, Survival, Neurological outcome

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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 normocapnia within the first 24 h 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-h 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-h 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 assessed 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 four sensitivity analyses examining whether the mean $PaCO_2$ during the first 48 and 72-h in ICU after OHCA remained associated with survival, any clustering of mortality with either hypercapnia or hypocapnia within certain ICUs

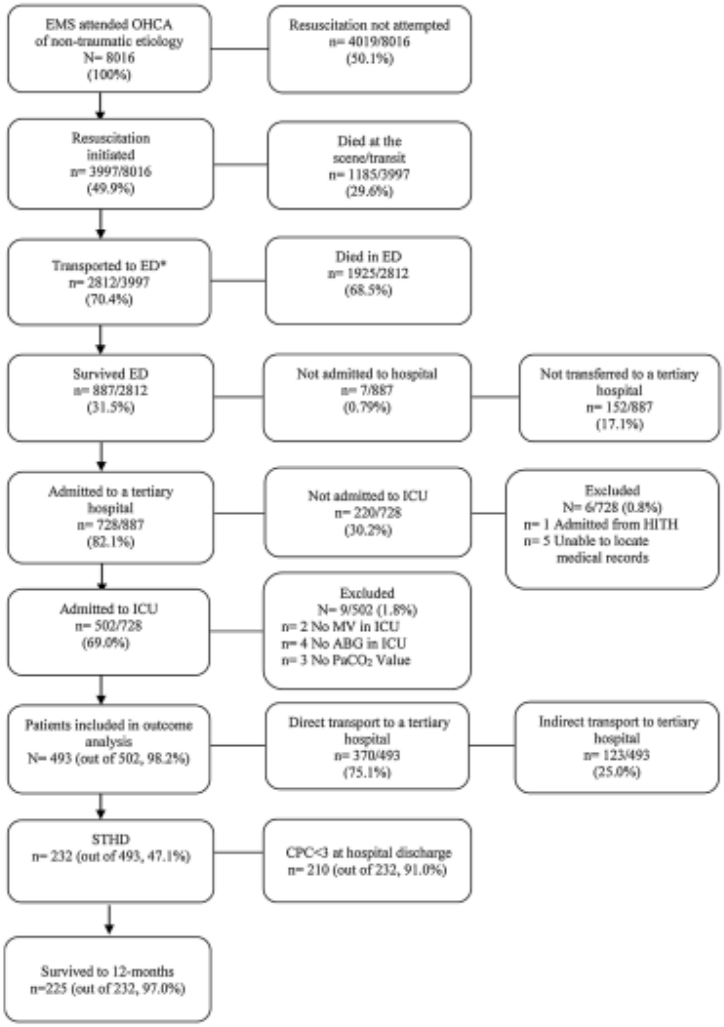

Fig. 1 – Flow chart showing the inclusion and exclusion of adult OHCA patients (≥18 years) of non-traumatic aetiology attended by paramedics and transported to a tertiary hospital.
***954 patients out of 2812 (33.9%) had ROSC on arrival to the first ED.**
ABG, arterial blood gases; CPC, cerebral performance category; ED, emergency department; EMS, emergency medical services; HITH, hospital in the home; ICU, intensive care unit; MV, mechanical ventilation; OHCA, out-of-hospital cardiac arrest; $PaCO_2$, arterial carbon dioxide tension; PCI, percutaneous-coronary-intervention; STHD, survival to hospital discharge.

(using Generalised Estimating Equations), and whether using different cut-points of $PaCO_2$ would substantially affect the mortality risk estimates associated with hypocapnia or hypercapnia compared to normocapnia.

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 h of ICU admission and 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

Table 1 – Characteristics of out-of-hospital cardiac arrest (OHCA) patients of non-traumatic aetiology stratified by hospital survival status.

	All patients (N = 493)	Survivors (n = 232, 47.1%)	Non-survivors (n = 261, 52.9%)	p-Values
$PaCO_2$ within the first 24-h of ICU admission, mean (± SD) in mmHg	40.0 ± 9.6	39.9 ± 7.6	40.1 ± 10.9	0.66
Age, median (IQR) in years	59 (48–70)	57 (46–67)	63 (50–72)	0.001
Sex, no. (%):-				
Male	352 (71.4)	182 (78.4)	170 (65.1)	0.001
Female	141 (28.6)	50 (21.6)	91 (34.9)	
Pre-arrest CPC score, no. (%):-				
CPC 1 or 2	487 (98.8)	231 (99.6)	256 (98.1)	0.22
CPC 3	6 (1.2)	1 (0.4)	5 (1.9)	
Witnessed arrest, no. (%):-				
Paramedic	43 (8.7)	21 (9.1)	22 (8.4)	0.60
Bystander	234 (47.5)	115 (49.6)	119 (45.6)	
Unwitnessed	216 (43.8)	96 (41.4)	120 (46.0)	
Bystander CPR, no (%)	345 (70.0)	180 (77.6)	165 (63.2)	0.001
Initial arrest rhythm, no. (%):-				
VF/VT	309 (62.7)	194 (83.6)	115 (44.1)	<0.001
PEA/Asystole[a]	176 (35.7)	32 (13.8)	144 (55.2)	
ROSC on arrival to first ED, no. (%)	416 (84.4)	216 (93.1)	200 (76.6)	<0.001
EMS response time, median (IQR) in minutes[b]	8 (6–10)	7 (6–10)	8 (7–10)	0.01
Time to arrive the first ED, median (IQR) in minutes[c]	46 (38–54)	43 (36–51)	48 (41–57)	<0.001
Time to tertiary ICU, median (IQR) in minutes[d]	228 (178–284)	217 (167–275)	236 (191–292)	0.07
Direct transport patients (n = 370)	211 (165–263)	202 (160–261)	217 (173–267)	0.055
Indirect transport patients (n = 123)	291 (243–343)	282 (242–351)	292 (248–339)	0.45
Diagnosis of ACS at ED, no. (%)	155 (31.4)	92 (39.7)	63 (24.1)	<0.001
Diagnosis of STEMI at ED, no. (%)	107 (21.7)	63 (27.1)	44 (16.9)	<0.001
PCI (≤24 h), no. (%)[e]	142 (28.8)	83 (35.8)	59 (22.6)	0.001
Duration of ICU stay, median (IQR) in days	2 (1–5)	3 (2–5)	2 (1–5)	0.07
TTM in ICU, no. (%)	401 (81.3)	205 (88.4)	196 (75.1)	<0.001
Inotropes in ICU, no. (%)	428 (86.8)	195 (84.1)	233 (89.3)	0.06

Data are presented as mean (standard deviation — SD), median (interquartile range — IQR) or count (percentage).
ACS, acute coronary syndrome; CCL, cardiac catheterization laboratory; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ED, emergency department; EMS, emergency medical services; ICU, intensive care unit; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; STEMI, ST-elevation myocardial infarction; STHD, survival to hospital discharge; TTM, targeted temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a] Includes 8 patients where 'initial arrest rhythm' is unknown.
[b] Time interval from EMS call to arrival on scene.
[c] Time interval from EMS call to arrival at first ED.
[d] Time interval from EMS call to arrival at a tertiary hospital ICU.
[e] Time interval from EMS call to arrival in CCL.

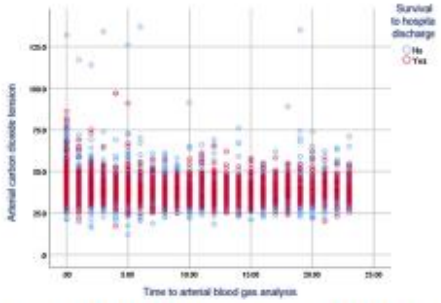

Fig. 2 – All individual arterial carbon dioxide tension ($PaCO_2$) values within the first 24-h of intensive care admission after out-of-hospital cardiac arrest, stratified by hospital survival status.

(27.1% vs 16.9%), received percutaneous coronary intervention within 24-h 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 h and survival

A total of 3769 ABG samples were collected within the first 24-h 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-h of ICU admission stratified by patients' hospital survival status. Modelling the mean $PaCO_2$ as a linear predictor 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

Table 2 – Final multivariable logistic regression assessing the associations between the *mean* arterial carbon dioxide tension ($PaCO_2$) within the *first 24-h* of admission to the intensive care unit (ICU) after out of hospital cardiac arrest and survival to hospital discharge or 12-months after stepwise forward adjustments for potential confounders (N = 493).

Predictors[a]	OR (95% CI) for survival to hospital discharge (n = 232, 47.0%)	OR (95% CI) for survival to 12 months (n = 225, 45.6%)
Mean $PaCO_2$ tension within the *first* 24 h after cardiac arrest in relation to survival[b]		
(i) normocapnia (35–45 mmHg)	1	1
(ii) hypocapnia (<35 mmHg)	0.45 (0.24–0.83)	0.37 (0.19–0.69)
(iii) hypercapnia (>45 mmHg)	0.45 (0.24–0.84)	0.42 (0.22–0.79)
- age	0.98 (0.96–0.99)	0.98 (0.96–0.99)
- sex (female)	0.63 (0.38–1.05)	0.60 (0.36–1.00)
- witness arrest:		
paramedic witnessed vs unwitnessed	6.05 (2.36–15.48)	6.32 (2.40–16.61)
bystander witnessed vs unwitnessed	0.86 (0.54–1.36)	0.90 (0.56–1.44)
- bystander CPR	1.94 (1.10–3.40)	2.24 (1.25–4.02)
- shockable first rhythm	7.21 (4.25–12.24)	7.94 (4.60–13.72)
- EMS response time (per min increment)	0.93 (0.87–0.99)	0.92 (0.86–0.98)
- time between EMS attendance and tertiary ICU admission	0.99 (0.99–1.000)	0.99 (0.99–1.000)
- good pre-cardiac arrest CPC score	5.92 (0.51–68.45)	6.04 (0.50–73.52)
- STEMI	1.14 (0.61–2.15)	1.33 (0.70–2.51)
- PCI	0.80 (0.45–1.43)	0.70 (0.39–1.27)
- Mean PaO_2 within the first 24 h:		
(i) mild to moderate hyperoxemic (100–180 mmHg) as the reference	1	1
(ii) hypo or normoxemic (<100 mmHg)	0.54 (0.32–0.92)	0.49 (0.28–0.84)
(iii) severe hyperoxemic (>180 mmHg)	0.75 (0.42–1.35)	0.75 (0.41–1.36)

CI, confidence interval; CPC, Cerebral Performance Category; CPR, Cardiopulmonary Resuscitation; EMS, Emergency Medical Services; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; OR, odds ratio; $PaCO_2$, arterial carbon dioxide oxygen tension; PaO_2, arterial oxygen tension. Normocapnia (35–45 mmHg) was used as the reference group.

[a] The Hosmer–Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to hospital discharge were 11.57 ($p = 0.17$) and 0.36, respectively. The Hosmer–Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to 12 months were 5.09 ($p = 0.75$) and 0.40, respectively.

[b] Patients were grouped as (a) normocapnia (35–45 mmHg, n = 332), (b) hypocapnia (<35 mmHg, n = 78) and (c) hypercapnia (>45 mmHg, n = 83).

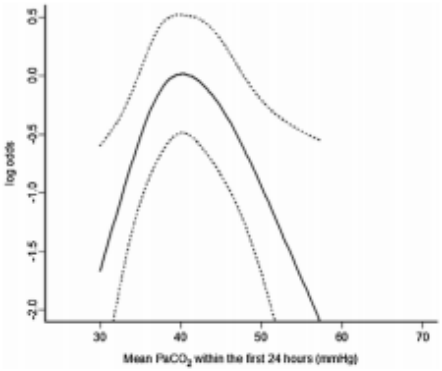

Fig. 3 – Mean arterial carbon dioxide tension ($PaCO_2$) within the first 24-h of intensive unit admission with log odds of survival to hospital discharge using restricted cubic spline function and centered with the median value. Dotted lines indicate 95%CI.
CI, confidence interval.

observed probabilities of STHD closely matched with 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 <35 mmHg (n = 78), 35–45 mmHg (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 initial 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.

Normocapnia ($PaCO_2$ 35–45 mmHg) was significantly associated with a higher odd 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-h 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-h (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-h 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-h were assessed (Supplementary Table 4). Using slightly different cut-points for $PaCO_2$ did not significantly change the odd of STHD for those with hypocapnia (<33mmHg: aOR 0.42; 95% CI 0.19–0.96) or hypercapnia (>48 mmHg: aOR 0.29; 95% CI 0.18–0.72) compared to normocapnia (33–48 mmHg). Similarly, adjusting for centre-effect did not change the odd of STHD for those with hypocapnia (aOR 0.45; 95% CI 0.24–0.82) or hypercapnia (aOR 0.45; 95% CI 0.25–0.82) compared to normocapnia.

Discussion

This multicentre cohort study found that normocapnia during the first 24-h 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-shape 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-h 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-h 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[5,7]), 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-h 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,

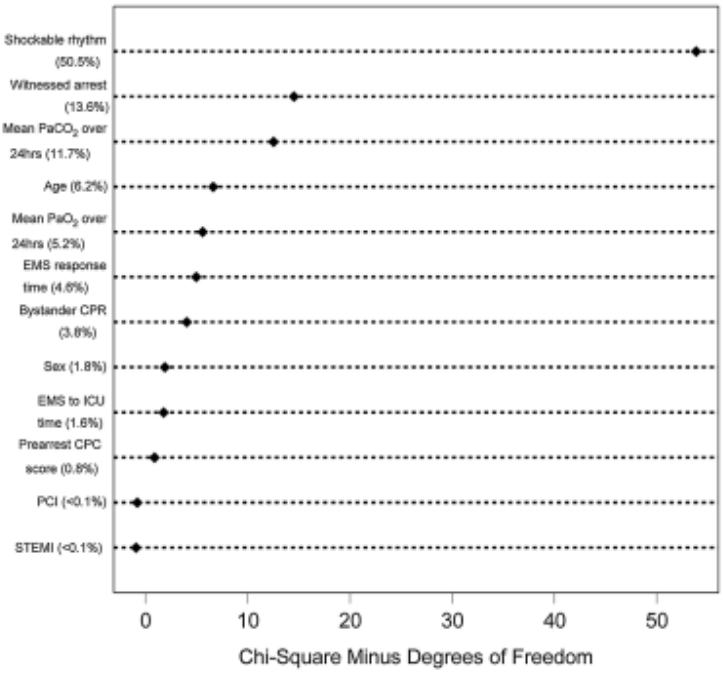

Fig. 4 – Relative contribution of each predictor included in the multivariable logistic regression model to predict survival to hospital discharge, including the use of restricted cubic spline function for $PaCO_2$ and PaO_2 within the first 24-h of ICU admission.
CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ICU, intensive care unit; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; PCI, percutaneous coronary intervention within the first 24-h; STEMI, ST-elevation myocardial infarction.

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 h) and allowing $PaCO_2$ to be modelled as a non-linear continuous predictor (Fig. 2), our results suggest that maintaining $PaCO_2$ within the 35–45 mmHg 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 (35–45 mmHg) 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-h 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. It is possible that patients with hypo or hypercapnia had a greater severity of illness leading to the association with increased mortality.[33] 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[34] is a

phase III clinical trial aiming to determine whether targeted therapeutic mild hypercapnia ($PaCO_2$ 50–55 mmHg) for 24 h 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), normocapnia (35–45 mmHg) within the first 24-h 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 implications on how OHCA patients should be managed within the first 24 h after ICU admission.

Conflict of interest

None.

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Janet Bray received a Heart Foundation Fellowship.

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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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2021.01.035.

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6.3 Supplemental Tables (Mckenzie et al. Resuscitation. 2021, May; 162:82-90)[19]

Table 6.1 *(Supplemental Table 1)* Characteristics of out-of-hospital cardiac arrest patients of non-traumatic etiology stratified by the mean $PaCO_2$ within the first 24-hours of ICU admission.

	Hypocapnia (<35 mmHg) n=78 (15.8%)	**Normocapnia (35-45 mmHg) n=332 (67.3%)**	**Hypercapnia (>45 mmHg) n=83 (16.8%)**	**p-values**
Mean $PaCO_2$, mmHg	32.3	39.7	51.1	<0.001
Age, median (IQR) in years	65 (53-73)	58 (47-70)	60 (49-69)	0.2700.
Sex, no. (%):-				
Male	44 (56.4)	246 (74.1)	62 (74.7)	0.01
Female	34 (43.6)	86 (25.9)	21 (25.3)	
Pre-arrest CPC score, no. (%):-				
CPC 1 or 2	78 (100%)	327 (98.5)	82 (98.8)	0.83
CPC 3	0 (0%)	5 (1.5)	1 (1.2)	
Witnessed arrest, no. (%):-				
Paramedic	8 (10.3)	20 (6.0)	15 (18.1)	0.01
Bystander	35 (44.9)	165 (49.7)	34 (41)	
Unwitnessed	35 (44.9)	147 (44.3)	34 (41)	
Bystander CPR, no. (%)	50 (64.1)	246 (74.1)	49 (59.0)	0.01
Initial arrest rhythm, no. (%):-				
VF/VT	44 (56.4)	225 (67.8)	40 (48.2)	0.001
PEA/Asystole[(a)]	32 (41.0)	101 (30.4)	43 (51.8)	
EMS response time, median (IQR) in minutes[(b)]	8 (6-10)	8 (6-10)	9 (7-12)	0.01
Time to arrive the first ED, median (IQR) in minutes[(c)]	47 (37-56)	46 (38-52)	48 (40-59)	0.02

	Hypocapnia (<35 mmHg) n=78 (15.8%)	Normocapnia (35-45 mmHg) n=332 (67.3%)	Hypercapnia (>45 mmHg) n=83 (16.8%)	p-values
Time to arrive the tertiary ICU, median (IQR) in minutes[(d)]	236 (182-278)	224 (176-285)	237 (172-292)	0.99
Direct transport patients (n=367)	214 (171-267)	213 (165-260)	205 (157-270)	0.79
Indirect transport patients (n=124)	268 (243-331)	288 (244-350)	296 (242-343)	0.55
ROSC on arrival to the first ED, no. (%)	60 (76.9)	292 (88.0)	64 (77.1)	0.01
Diagnosis of ACS at ED, no. (%)	18 (23.1)	117 (35.2)	20 (24.1)	0.02
Diagnosis of STEMI at ED, no. (%)	12 (15.4)	82 (24.7)	13 (15.7)	0.40
PCI (≤24-hours), no. (%)[(e)]	16 (20.5)	110 (33.1)	16 (19.3)	0.58
Duration of ICU stay, median (IQR) in days	2 (1-4)	3 (1-5)	1 (1-5)	
TTM in ICU, no. (%)	60 (76.9)	284 (85.5)	57 (68.7)	0.001
Inotropes in ICU, no. (%)	67 (85.9)	285 (85.8)	76 (91.6)	0.38

Data are presented as mean (standard deviation - SD), median (interquartile range - IQR) or count (percentage)

(a) Includes 8 patients where 'Initial arrest rhythm' is unknown
(b) Time interval from EMS call to arrival on scene
(c) Time interval from EMS call to arrival at first ED
(d) Time interval from EMS call to arrival at a tertiary hospital ICU
(e) Time interval from EMS call to arrival in CCL

Abbreviations indicate as follows: ACS; Acute coronary syndrome, CCL; Cardiac catheterization laboratory, CPC, Cerebral Performance Category, CPR; Cardiopulmonary resuscitation, ED; Emergency department, EMS; Emergency medical services; ICU, Intensive care unit, PCI; Percutaneous Coronary Intervention, PEA; Pulseless electrical activity, ROSC; Return of spontaneous circulation, STEMI; ST-elevation myocardial infarction, STHD; Survival to hospital discharge, TTM; Targeted temperature management, VF; Ventricular fibrillation; VT; Ventricular tachycardia.

Table 6.2 *(Supplemental Table 2)* Forward stepwise logistic regression assessing the associations between the mean arterial carbon dioxide tension ($PaCO_2$) within the first 24 hours of admission to the intensive care unit (ICU) – grouped as (a) normocapnia (35-45mmHg, n=332), (b) hypocapnia (<35mmHg, n=78) and (c) hypercapnia (>45mmHg, n=83) – after out of hospital cardiac arrest and survival to hospital discharge or 12 months (N=493).

Confounders used for adjustment	**Mean $PaCO_2$ tension within the *first 24 hours* after cardiac arrest in relation to survival**	**OR (95%CI) for survival to hospital discharge (n=232, 47.0%)**	**OR (95%CI) for survival to 12 months (n=225, 45.6%)**
None	(a) normocapnia	1 (reference)	1 (reference)
	(b) hypocapnia	0.42 (0.25-0.71)	0.36 (0.21-0.62)
	(c) hypercapnia	0.39 (0.23-0.64)	0.35 (0.21-0.59)
Age	(a) normocapnia	1	1
	(b) hypocapnia	0.44 (0.26-0.74)	0.38 (0.22-0.64)
	(c) hypercapnia	0.38 (0.23-0.64)	0.35 (0.21-0.59)
Age & sex	(a) normocapnia	1	1
	(b) hypocapnia	0.49 (0.29-0.83)	0.42 (0.24-0.72)
	(c) hypercapnia	0.37 (0.22-0.62)	0.34 (0.20-0.57)
Age, sex, & witnessed arrest	(a) normocapnia	1	1
	(b) hypocapnia	0.48 (0.28-0.82)	0.41 (0.24-0.72)
	(c) hypercapnia	0.35 (0.20-0.59)	0.32 (0.19-0.56)
Age, sex, witnessed arrest, & bystander CPR	(a) normocapnia	1	1
	(b) hypocapnia	0.49 (0.28-0.84)	0.42 (0.24-0.61)
	(c) hypercapnia	0.36 (0.21-0.61)	0.33 (0.19-0.57)
Age, sex, witnessed arrest, bystander CPR & shockable first rhythm	(a) normocapnia	1	1
	(b) hypocapnia	0.48 (0.27-0.86)	0.40 (0.22-0.73)
	(c) hypercapnia	0.41 (0.23-0.75)	0.38 (0.20-0.69)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, & EMS response time	(a) normocapnia	1	1
	(b) hypocapnia	0.49 (0.27-0.88)	0.41 (0.22-0.75)
	(c) hypercapnia	0.426 (0.23-0.78)	0.39 (0.21-0.72)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, & time between EMS	(a) normocapnia	1	1
	(b) hypocapnia	0.48 (0.26-0.86)	0.40 (0.22-0.72)
	(c) hypercapnia	0.42 (0.23-0.77)	0.38 (0.21-0.71)

Confounders used for adjustment	Mean $PaCO_2$ tension within the *first 24 hours* after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=232, 47.0%)	OR (95%CI) for survival to 12 months (n=225, 45.6%)
attendance and tertiary ICU admission			
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission & pre-cardiac arrest CPC score	(a) normocapnia (b) hypocapnia (c) hypercapnia	1 0.46 (0.25-0.83) 0.41 (0.23-0.75)	1 0.38 (0.21-0.70) 0.37 (0.20-0.69)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score & STEMI	(a) normocapnia (b) hypocapnia (c) hypercapnia	1 0.46 (0.25-0.83) 0.41 (0.23-0.76)	1 0.38 (0.21-0.71) 0.38 (0.20-0.70)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score, STEMI & PCI	(a) normocapnia (b) hypocapnia (c) hypercapnia	1 0.46 (0.25-0.83) 0.41 (0.22-0.75)	1 0.38 (0.20-0.70) 0.37 (0.20-0.69)
*Final fully adjusted multivariable model: Age, sex, witnessed arrest, bystander CPR,	(a) normocapnia (b) hypocapnia (c) hypercapnia	1 0.45 (0.24-0.83) 0.45 (0.24-0.84)	1 0.37 (0.19-0.69) 0.42 (0.22-0.79)

Confounders used for adjustment	Mean $PaCO_2$ tension within the *first 24 hours* after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=232, 47.0%)	OR (95%CI) for survival to 12 months (n=225, 45.6%)
shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score, STEMI, PCI & mean PaO_2 within the first 24 hours in ICU			
	- age	0.98 (0.96-0.99)	0.98 (0.96-0.99)
	- sex (female)	0.63 (0.38-1.05)	0.60 (0.36-1.00)
	- witness arrest:		
	paramedic witnessed vs unwitnessed	6.05 (2.36-15.48)	6.32 (2.40-16.61)
	bystander witnessed vs unwitnessed	0.86 (0.54-1.36)	0.90 (0.56-1.44)
	- bystander CPR	1.94 (1.10-3.40)	
	- shockable first rhythm	7.21(4.25-12.24)	2.24 (1.25-4.02)
	- EMS response time (per min increment)	0.93 (0.87-0.99)	7.94 (4.60-13.72)
	- time between EMS attendance and tertiary ICU admission	0.99 (0.99-1.00)	0.92 (0.86-0.98)
	- good pre-cardiac arrest CPC score	5.92 (0.51-68.45)	0.99 (0.99-1.00)
	- STEMI	1.14 (0.61-2.15)	6.04 (0.50-73.52)
	- PCI	0.80 (0.45-1.43)	
	- Mean PaO_2 within the first 24 hours:-		1.33 (0.70-2.51)
	(i) mild to moderate hyperoxemic (100-180mmHg) as the reference	1	0.70 (0.39-1.27)
		0.54 (0.32-0.92)	1

Confounders used for adjustment	Mean $PaCO_2$ tension within the *first 24 hours* after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=232, 47.0%)	OR (95%CI) for survival to 12 months (n=225, 45.6%)
	(ii) hypo or normoxemic (<100mmHg)	0.75 (0.42-1.34)	0.49 (0.28-0.84)
	(iii) severe hyperoxemic (>180mmHg)		0.75 (0.41-1.36)

*The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to hospital discharge were 11.57 (p=0.17) and 0.36, respectively. The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to 12 months were 5.09 (p=0.75) and 0.40,

Abbreviations indicate as follows: CI; Confidence interval, CPC; Cerebral Performance Category, CPR; Cardiopulmonary resuscitation, EMS; Emergency medical services, PCI; Percutaneous coronary intervention, STEMI; ST-segment elevation myocardial infarction, OR; Odds ratio, $PaCO_2$; Arterial carbon dioxide oxygen tension, PaO_2; Arterial oxygen tension.

Normocapnia (35-45mmHg) was used as the reference group.

Table 6.3 *(Supplemental Table 3)* Final multivariable logistic regression assessing the associations between the mean arterial carbon dioxide tension ($PaCO_2$) within the first 48 hours of admission to the intensive care unit (ICU) – grouped as (a) normocapnia (35-45mmHg, n=348), (b) hypocapnia (<35mmHg, n=81) and (c) hypercapnia (>45mmHg, n=63) – after out of hospital cardiac arrest and survival to hospital discharge or 12 months (N=492).

Predictors*	**OR (95%CI) for survival to hospital discharge (n=231, 47.0%)**	**OR (95%CI) for survival to 12 months (n=224, 45.5%)**
Mean $PaCO_2$ tension within the *first 48 hours* after cardiac arrest in relation to survival		
(i) normocapnia	1	1
(ii) hypocapnia	0.44 (0.24-0.79)	0.40 (0.22-0.74)
(iii) hypercapnia	0.31 (0.14-0.67)	0.26 (0.11-0.58)
- age	0.98 (0.96-0.99)	0.98 (0.96-0.99)
- sex (female)	0.62 (0.37-1.03)	0.58 (0.34-0.98)
- witness arrest:		
paramedic witnessed vs unwitnessed	5.73 (2.23-14.73)	5.91 (2.24-15.60)
bystander witnessed vs unwitnessed	0.80 (0.50-1.27)	0.84 (0.52-1.35)
- bystander CPR	1.76 (1-3.12)	2.02 (1.13-3.64)
- shockable first rhythm	7.12 (4.17-12.17)	7.82 (4.50-13.58)
- EMS response time (per min increment)	0.93 (0.88-1)	0.93 (0.87-0.99)
- time between EMS attendance and tertiary ICU admission	0.99 (0.99-1.00)	0.99 (0.99-1.00)
- good pre-cardiac arrest CPC score	6.15 (0.49-77.48)	6.25 (0.47-83.46)
- STEMI	1.10 (0.59-2.07)	1.28 (0.67-2.42)
- PCI	0.92 (0.51-1.65)	0.82 (0.45-1.49)
- mean PaO_2 groups within the *first 48hrs*:		
(i) mild to moderate hyperoxemic (100-	1	1

Predictors*	OR (95%CI) for survival to hospital discharge (n=231, 47.0%)	OR (95%CI) for survival to 12 months (n=224, 45.5%)
180mmHg) as the reference	0.64 (0.35-1.03)	0.63 (0.39-1.04)
(ii) hypo or normoxemic (<100mmHg)	0.32 (0.11-0.93)	0.36 (0.12-1.07)
(iii) severe hyperoxemic (>180mmHg)		

*The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to hospital discharge were 12.22 (p=0.14) and 0.38, respectively. The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to 12 months were 17.61 (p=0.02) and 0.41, respectively.

Abbreviations indicate as follows: CI; Confidence interval, CPC; Cerebral Performance Category, CPR; Cardiopulmonary resuscitation, EMS, Emergency medical services, PCI; Percutaneous coronary intervention, STEMI; ST-segment elevation myocardial infarction, OR; Odds ratio, $PaCO_2$; Arterial carbon dioxide tension, PaO_2; Arterial oxygen tension.

Normocapnia (35-45mmHg) was used as the reference group.

Table 6.4 *(Supplemental Table 4)* Final multivariable logistic regression assessing the associations between the mean arterial carbon dioxide tension ($PaCO_2$) within the first 72 hours of admission to the intensive care unit (ICU) – grouped as (a) normocapnia (35-45mmHg, n=348), (b) hypocapnia (<35mmHg, n=156) and (c) hypercapnia (>45mmHg, n=28) – after out of hospital cardiac arrest and survival to hospital discharge or 12 months (N=492).

Predictors*	**OR (95%CI) for survival to hospital discharge (n=231, 47.0%)**	**OR (95%CI) for survival to 12 months (n=224, 45.5%)**
Mean $PaCO_2$ tension within the *first 72 hours* after cardiac arrest in relation to survival		
(a) normocapnia	1	1
(b) hypocapnia	0.44 (0.24-0.80)	0.41 (0.22-0.75)
(c) hypercapnia	0.28 (0.13-0.62)	0.24 (0.11-0.54)
- age	0.98 (0.96-0.99)	0.98 (0.96-0.99)
- sex (female)	0.61 (0.37-1.02)	0.58 (0.34-0.97)
- witness arrest:		
paramedic witnessed vs unwitnessed	6.04 (2.33-15.71)	6.12 (2.31-16.50)
bystander witnessed vs unwitnessed	0.80 (0.50-1.27)	0.84 (0.52-1.35
- bystander CPR	1.77 (1-3.12)	2.02 (1.13-3.64)
- shockable first rhythm	7.08 (4.15-12.11)	7.81 (4.49-13.57)
- EMS response time (per min increment)	0.93 (0.87-0.99)	0.92 (0.87-0.99)
- time between EMS attendance and tertiary ICU admission	0.99 (0.99-1.00)	0.99 (0.99-1.00)
- good pre-cardiac arrest CPC score	6.15 (0.49-77.48)	6.6 (0.48-89.61)
- STEMI	1.08 (0.57-2.04)	1.25 (0.66-2.37)
- PCI	0.90 (0.50-1.62)	0.81 (0.45-1.46)
- mean PaO_2 within the *first 72 hours*:-		
(i) mild to moderate hyperoxemic (100-	1	1

Predictors*		OR (95%CI) for survival to hospital discharge (n=231, 47.0%)	OR (95%CI) for survival to 12 months (n=224, 45.5%)
	180mmHg) as the reference	0.74 (0.46-1.19)	0.75 (0.46-1.22)
(ii)	hypo or normoxemic (<100mmHg)	0.21 (0.06-0.71)	0.24 (0.07-0.81)
(iii)	severe hyperoxemic (>180mmHg)		

*The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to hospital discharge were 16.64 (p=0.03) and 0.38, respectively. The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to 12 months were 15.21 (p=0.06) and 0.41, respectively.

Abbreviations indicate as follows: CI; Confidence interval, CPC; Cerebral Performance Category, CPR; Cardiopulmonary resuscitation, EMS, Emergency medical services, PCI; Percutaneous coronary intervention, STEMI; ST-segment elevation myocardial infarction, OR; Odds ratio, $PaCO_2$; Arterial carbon dioxide tension; PaO_2; Arterial oxygen tension.

Normocapnia (35-45mmHg) was used as the reference group.

6.4 Supplemental Figures (Mckenzie et al. Resuscitation. 2021. May; 162:82-90)[19]

Figure 6.1 *(Supplemental Figure 1)* A lack of significant relationship between mean arterial carbon dioxide tension ($PaCO_2$) within the first 24-hours of intensive care admission and the odds of survival to hospital discharge when non-linearity of the effect of $PaCO_2$ on survival was not considered, while adjusting for all covariates described in Table 2. Dotted lines indicate 95% confidence interval.

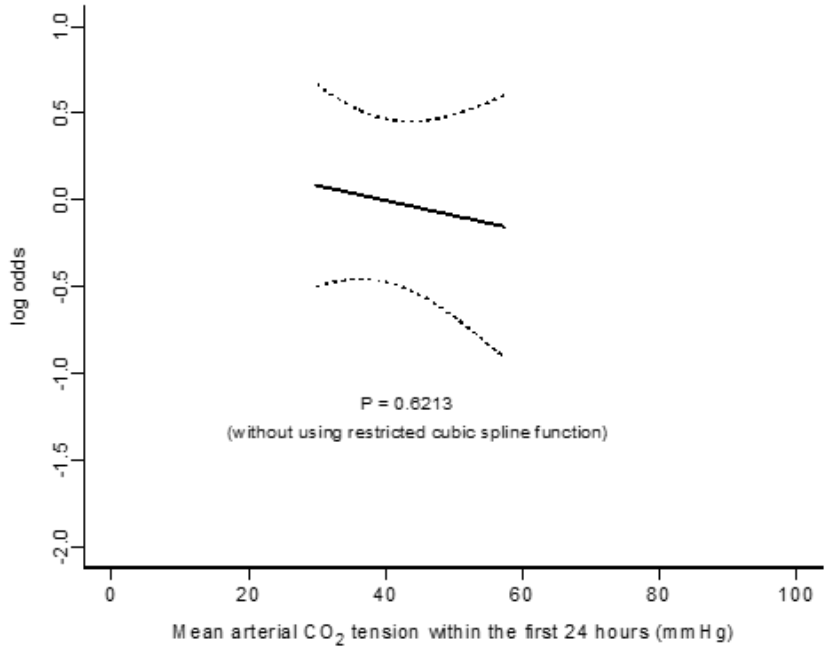
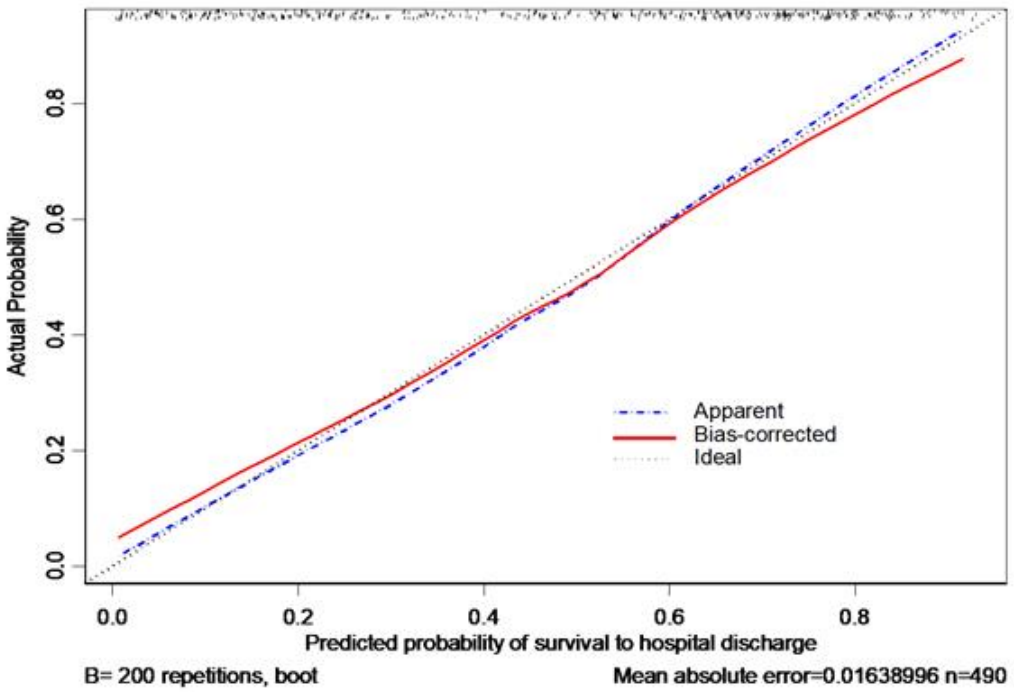


Figure 6.2 *(Supplemental Figure 2)* Calibration of the multivariable model (by comparing predicted and observed probability of survival to hospital discharge).



A 4-knot restricted cubic spline function was used for the mean arterial carbon dioxide (PaCO2) and oxygen tension (PaO2) within the first 24-hours of intensive care admission after out of hospital cardiac arrest, adjusting for all covariates listed in Table 2. The bias-corrected (continuous) line was derived from 200 bootstrapping repetitions to adjust for bias from overfitting. The distribution of the predicted probability of survival to hospital discharge of all patient is defined by the density of data points on the top of the graph.

Listed below are:
(1) Indexes of this multivariable model, including both original, training and testing sets.
(2) P value associated with each predictor in the multivariable model including the non-linear components of PaO_2 and $PaCO_2$.

(1) Indexes of this multivariable model, including both original, training and testing sets.

Index	Original set	Training set	Test set	Optimism	Index-corrected
Dxy	0.647591973	0.675893650	0.61817324	0.05772041	0.58987157
R^2	0.392066543	0.427037029	0.34201783	0.08501920	0.30704734
Intercept	0.000000000	0.000000000	0.00453844	-0.00453844	0.00453844
Slope	1.000000000	1.000000000	0.80369288	0.19630712	0.80369288
Emax	0.000000000	0.000000000	0.04949272	0.04949272	0.04949272
D	0.345648304	0.384317192	0.29422423	0.09009297	0.25555534
U	-0.004081633	-0.004081633	0.01390715	-0.01798878	0.01390715
Q	0.349729936	0.388398825	0.28031708	0.10808175	0.24164819
B	0.169787912	0.162398679	0.17794756	-0.01554888	0.18533679

NB: Dxy is the difference between concordance and discordance probabilities; R^2 is the Nagelkerke R^2; intercept reflects the systematic bias of the model; slope reflects whether the predicted risks of the model match the observed risks across the full spectrum of the observed risks; Emax is the maximum absolute error in predicted probability; indexes of unreliability (U), discrimination (D) and overall quality (Q=D-U) are derived from likelihood ratio tests. B is the Brier's index.

(2) P value associated with each predictor in the multivariable model including the non-linear components of PaO_2 and $PaCO_2$.

Predictors	Chi-Square	Degree of Freedom	P value
1. Shockable rhythm	55.87	2	<0.0001
2. Witnessed	16.53	2	0.0003
3. Mean $PaCO_2$ over the first 24 hours:-	15.53 (total)	3	0.0014
	15.53 (nonlinear component)	*2*	*0.0004*
4. Age	7.63	1	0.0057
5. Mean PaO_2 over the first 24hrs:-	8.60 (total)	3	0.0350
	8.58 (nonlinear component)	*2*	*0.0137*
6. Emergency medical services response time	5.97	1	0.0146
7. Bystander CPR	5.05	1	0.0247
8. Sex	2.89	1	0.0891
9. Emergency medical services arrival to ICU time	2.79	1	0.0948
10. Pre-arrest Cerebral Performance Category	2.90	2	0.2346
11. Percutaneous coronary intervention within the first 24 hours	0.20	1	0.6537
12. ST-segment elevation myocardial infarction	0.09	1	0.7632
TOTAL NON-LINEAR COMPONENT	***24.41***	***4***	***0.0001***
TOTAL	**106.70**	**19**	**<0.0001**

Figure 6.3 *(Supplemental Figure 3)* An inverted-U shape relationship between mean arterial carbon dioxide tension ($PaCO_2$) within the first 24-hours of intensive care admission and the odds of survival to 12 months when the non-linear effect of $PaCO_2$ on survival was considered using a 4-knot restricted cubic spline function, while adjusting for all covariates described in Table 2. Dotted lines indicate 95% confidence interval.

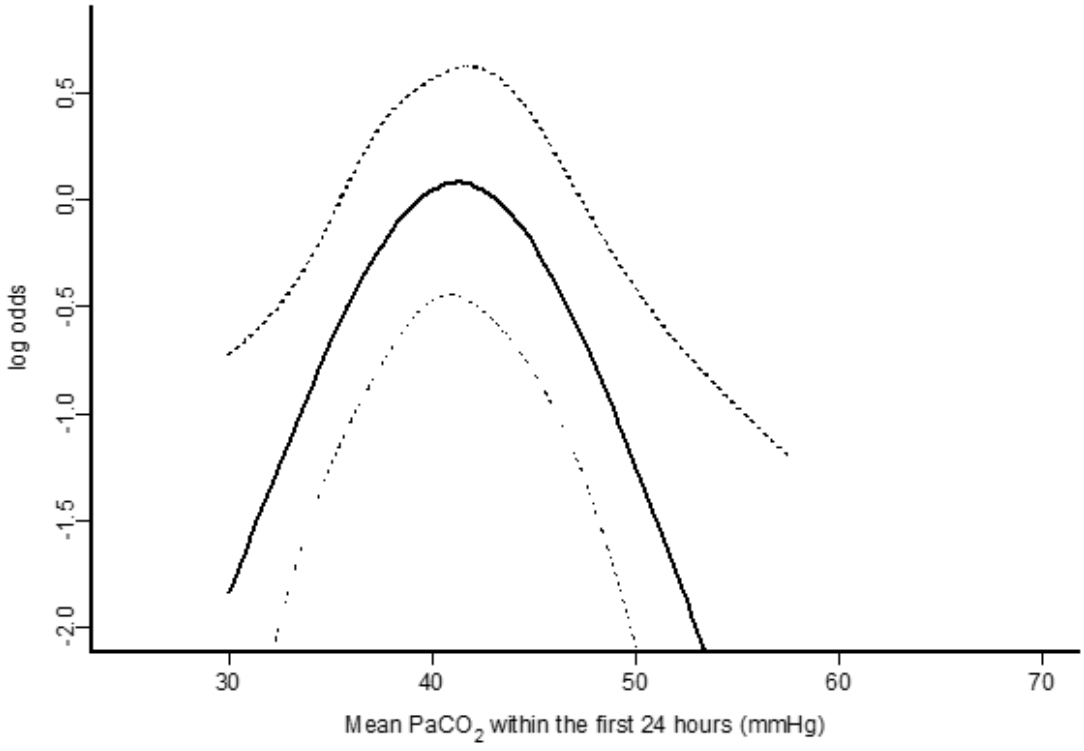
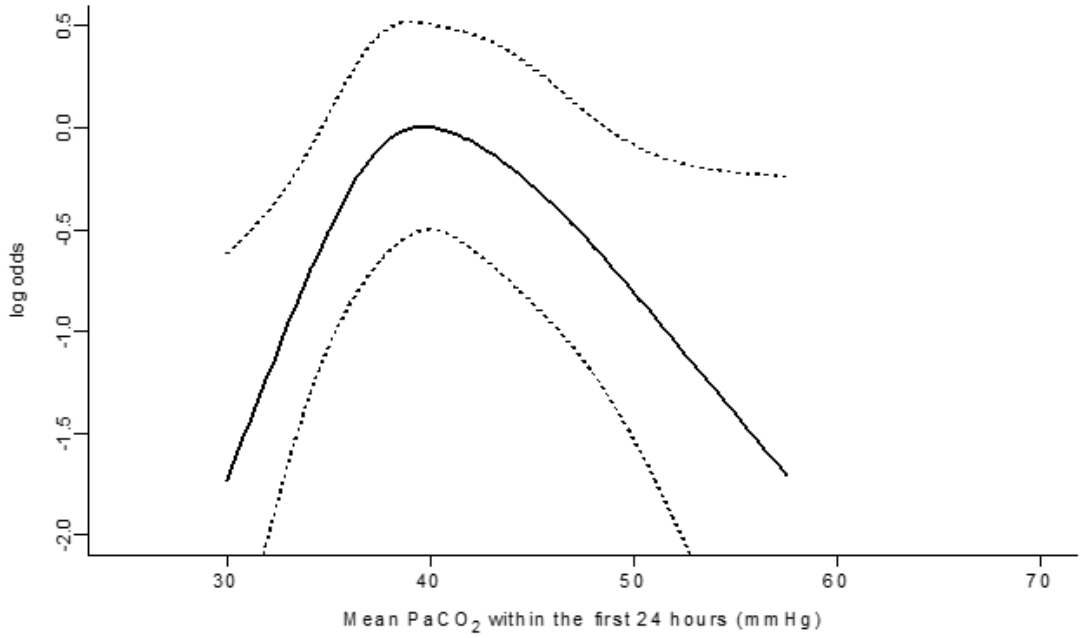


Figure 6.4 *(Supplemental Figure 4)* An inverted-U shape relationship between mean arterial carbon dioxide tension ($PaCO_2$) within the first 24-hours of intensive care admission and the odds of survival with a good Cerebral Performance Category (CPC) at hospital discharge when non-linear effect of $PaCO_2$ was considered using a 4-knot restricted cubic spline function, while adjusting for all covariates described in Table 6.2. Dotted line indicates 95% confidence interval.



6.5 Summary

In this study, I investigated whether $PaCO_2$ has a non-linear association with survival after adult OHCA of non-traumatic aetiology.[19] I found that the relationship between $PaCO_2$ and survival is indeed non-linear (inverted U-shape) and normocapnia within the first 24-hours of ICU admission is associated with improved survival when compared to patients with hypocapnia (<35 mmHg) or hypercapnia (>45 mmHg).[19] Further, mean $PaCO_2$ in the first 24 hours of ICU admission was the third most important predictor of survival, explaining 11.7% in the variability in survival to hospital discharge after OHCA.[18] My findings of improved patient outcomes are consistent with the results of other published studies reporting a non-linear relationship between $PaCO_2$ and patient outcomes[69,117] and in line with international guideline recommendations that ABG samples are monitored and normocapnia be targeted during post-resuscitation care.[12] As abnormalities in $PaCO_2$ are common after OHCA[64,71,138] and manipulation of $PaCO_2$ is relatively easy to achieve with mechanical ventilation,[64,139] these results have important clinical implications and require further consideration in RCTs.

The monitoring of physiological parameters and titration of medical therapies to achieve physiological target thresholds for treatment is standard practice in the ICU.[133] PaO_2 can be manipulated through the titration of inspired oxygen concentration (FiO_2) and positive end expiratory pressure. $PaCO_2$ can be manipulated through the titration of tidal volume, applied inspiratory pressure or respiratory rate.[133] RCTs investigating whether titration of PaO_2 or $PaCO_2$ to achieve a target level is associated with significant benefits with respect to outcome in critically ill patients remain the gold standard, but results are lacking. In the absence of results from RCTs and with consideration to the findings presented in systematic review and meta-analyses it is reasonable to hypothesise that a U-shaped curve describes the association between PaO_2[80] and $PaCO_2$[18] and patient centred outcomes after OHCA. Although wide reaching conclusions cannot be drawn from these analyses, until results from large RCTs are made available the current recommendation to target normocapnia makes physiological sense.

In the next chapter, I present the findings of the third multicentre retrospective cohort study included in this thesis. This is titled ‘Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study’.

Chapter 7 Arterial Oxygen Tension

7.1 Overview

In this chapter, I present the findings of the third multicentre retrospective cohort study included in this thesis. The aim of this study was to determine if a non-linear relationship exists between PaO_2 and survival and neurological outcome in adult patients with OHCA of medical aetiology. I hypothesised that abnormalities in mean PaO_2 (both high and low) in the first 24 hours of ICU admission would be associated with worse patient outcomes when compared to an intermediate level of PaO_2. This hypothesis was based on international guidelines that recommend avoiding hypoxaemia and hyperoxaemia in adult OHCA patients with ROSC.[140] It was also based on the results of observational studies that report a non-linear relationship between physiological parameters and outcome in other populations of critically ill patients.[115,116]

The explanations for the nonlinear association between PaO_2 and survival after adult OHCA have not been well established, with only one prior observational study reporting a curvilinear U-shaped relationship between supraphysiological PaO_2 levels and hospital mortality.[69] Further, while observational data consistently shows harm from hypoxaemia,[70,78,79,138,141] research is conflicting as to the harms of hyperoxaemia. A recent meta-analysis of ten observational studies investigating oxygen targets after cardiac arrest,[112] found no association between hyperoxaemia and patient outcomes in six studies[68,142-146] and lower survival to hospital discharge and/or lower survival with favourable neurological outcome in the remaining four studies.[86,138,147,148] Of the four studies, only one reported worse patient outcomes.[138] Despite these findings optimal PaO_2 targets to mitigate these harms remain unknown.[78,147]

With consideration to the available evidence, I conducted a multicentre observational study to determine whether PaO_2 has a non-linear relationship with survival and neurological outcome after OHCA. I also aimed to assess the associations

between different levels of PaO_2 over the first 24-hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of medical aetiology

The specific objectives were:

1. To undertake a retrospective cohort study of all adult patients with OHCA of medical aetiology, attended by SJ-WA paramedics and who achieved ROSC and received mechanical ventilation on arrival to a study hospital
2. To describe the characteristics and patient outcomes for the total cohort stratified by hospital survival status
3. To use a four-knot restricted cubic spline function to evaluate the potential for non-linearity in the relationship between PaO_2 and survival
4. To identify optimal PaO_2 cut-points for survival based on the shape of the spline curve
5. To assess the importance of mean PaO_2 relative to plausible physiological predictors in explaining the variability in observed hospital mortality by each predictors' chi square contribution in a multivariable logistic regression analysis and;
6. To conduct two sensitivity analyses examining whether the mean PaO_2 during the first 48 and 72 hours in ICU after OHCA was associated with hospital survival and survival to 12-months.

This Chapter comprises a manuscript that has been published in a peer-reviewed journal and is inserted as a PDF in the format published by the journal:

Mckenzie N, Finn J, Dobb G, Bailey P, Arendts G, Celenza A, Fatovich D, Jenkins I, Ball S, Bray J, Ho KM. Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study. *Resuscitation*. 2021 Jan; 158:130-138.[20]

Supplemental material supporting this article is presented prior to the Chapter summary.

7.2 Manuscript

RESUSCITATION 158 (2021) 130 –138

Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study

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Abstract

Background: Studies to identify safe oxygenation targets after out-of-hospital cardiac arrest (OHCA) have often assumed a linear relationship between arterial oxygen tension (PaO_2) and survival, or have dichotomised PaO_2 at a supra-physiological level. We hypothesised that abnormalities in mean PaO_2 (both high and low) would be associated with decreased survival after OHCA.

Methods: We conducted a retrospective multicentre cohort study of adult OHCA patients who received mechanical ventilation on admission to the intensive care unit (ICU). The potential non-linear relationship between the mean PaO_2 within the first 24 -hs of ICU admission and survival to hospital discharge (STHD) was assessed by a four-knot restricted cubic spline function with adjustment for potential confounders.

Results: 3764 arterial blood gas results were available for 491 patients in the first 24-hs of ICU admission. The relationship between mean PaO_2 over the first 24-hs and STHD was an inverted U-shape, with highest survival for those with a mean PaO_2 between 100 and 180 mmHg (reference category) compared to a mean PaO_2 of <100 mmHg (adjusted odds ratio [aOR] 0.50 95% confidence interval [CI] 0.30, 0.84), or >180 mmHg (aOR 0.41, 95% CI 0.18, 0.92). Mean PaO_2 within 24 -hs was the third most important predictor and explained 9.1% of the variability in STHD.

Conclusion: The mean PaO_2 within the first 24-hs after admission for OHCA has a non-linear association with the highest STHD seen between 100 and 180 mmHg. Randomised controlled trials are now needed to validate the optimal oxygenation targets in mechanically ventilated OHCA patients.

Keywords: Arterial blood gas analysis, Arterial oxygen tension, Cerebral performance category, Emergency medical services, Out-of-hospital cardiac arrest, Post-resuscitation care, Survival, Neurological outcome

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Introduction

Hypoxic-ischaemic encephalopathy after return of spontaneous circulation (ROSC) in out-of-hospital cardiac arrest (OHCA) is a major determinant of in-hospital mortality and neurological dysfunction.[1,2] The pathophysiology of hypoxic-ischaemic encephalopathy is complex,[2–4] with the nature and extent of the brain injury, at least in part, influenced by post-resuscitation management.[5,6]

Because both hypoxaemia and hyperoxaemia worsen outcomes in critically ill patients without OHCA,[7] such a relationship may also exist after OHCA. Research suggests that survival after OHCA depends on minimising secondary brain injury,[1,6] primarily by optimising the balance between adequate cerebral oxygen delivery and use,[8] and possibly also potential harm from generation of reactive oxygen free radicals through the presence of an excessive amount of oxygen.[8] Clinicians can theoretically optimise oxygen delivery and consumption through targeted temperature management (TTM) and maintaining arterial oxygen tension (PaO_2) at a certain target range in patients requiring mechanical ventilation after OHCA.[1] The scientific basis for avoiding excessive amount of oxygen after OHCA is strong, especially during the first 24-hs after cardiac arrest when reperfusion injury (including neuronal death) due to oxidative stress and mitochondrial production of reactive oxygen species is expected.[8] However, there are only limited number of randomised-controlled-trials (RCT's)[9,10] comparing different PaO_2 targets during the early post-resuscitation period, and results from observational studies are conflicting.[11–14]

Studies investigating the association between PaO_2 and outcome after OHCA have either assumed PaO_2 has a linear effect on survival or used arbitrarily cut points to model the effects of PaO_2.[11–13] The linearity assumption is problematic because excessive and inadequate amount of oxygen delivery to the brain can both theoretically be harmful.

We hypothesised that PaO_2 has a non-linear relationship with survival and neurological outcome after OHCA, with best outcomes when PaO_2 is maintained at an intermediate level. In this study, we assessed the associations between different levels of PaO_2 over the first 24-hs of intensive care unit (ICU) admission and survival to hospital discharge (STHD), neurological outcome at hospital discharge, and 12-month survival in adult patients with OHCA of medical aetiology.

Methods

Study design and setting

This retrospective cohort study recruited OHCA patients attended by the St John Western Australia emergency medical services, and admitted to the four adult tertiary hospitals[15] (see Supplementary Text 1) in metropolitan Perth, Western Australia between 1st January 2012 and 31st December 2017. Metropolitan Perth had a population of 2.05 million in 2017,[16] and emergency medical services advanced life support provided using the Australian and New Zealand Committee on Resuscitation guidelines.[17,18] During the study period, OHCA patients who were not declared dead at the scene were transported to the nearest emergency department for stabilisation.[17] In this study, patients admitted to a tertiary hospital via an emergency department of a non-tertiary hospital were defined as 'indirect' transport patients, as distinct to those directly transferred to a tertiary hospital ('direct transport') from the scene of OHCA.

Participants

We included adult patients (≥18 years) with OHCA of presumed medical aetiology.[19] Patients who did not receive mechanical ventilation on admission to ICU and those who did not have any arterial blood gases (ABG) recorded within the first six hours of ICU admission were excluded.

Post-Resuscitation care

Routine post-resuscitation care included (1) TTM and treatment of hyperpyrexia; (2) protective ventilation to maintain normoxia and normocapnia; (3) haemodynamic management; (4) percutaneous coronary intervention following ROSC for those with ST-elevation myocardial infarction; and (5) multimodal neurological prognostication at 72 h or later after OHCA.[20]

Data sources

The following data were extracted from the OHCA registry:[21] age, sex, arrest location (home/public location), witness status (paramedic witnessed/bystander witnessed/unwitnessed), bystander cardiopulmonary resuscitation (CPR), shockable first cardiac arrest rhythm, emergency medical services response time (from emergency call to arrival at the scene), time between emergency medical services attendance and tertiary ICU admission, and whether the patients were directly or indirectly transported to a tertiary hospital.

Neurological function prior to cardiac arrest, primary diagnosis of ST-segment elevation myocardial infarction, in-hospital clinical interventions including percutaneous coronary intervention, and TTM in ICU (within the first 24-hs of ICU admission),[1] all ABG results within the first 72-hs of ICU admission, and neurological outcomes were obtained using a structured approach to review the medical charts by a single data extractor (NM).

Outcome measures

The primary outcome was STHD; secondary outcomes were good Cerebral Performance Category (CPC) score[22] at hospital discharge and 12-month survival. Good CPC at hospital discharge was defined by either ability to work and might have mild neurologic or psychologic deficit (CPC grade 1) or independent daily living and able to work in a sheltered environment (CPC grade 2).[23] Twelve month survival was determined by the death records in the state's death registry.

Statistical analyses

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

As many physiological variables are related to clinical outcomes in a non-linear and non-monotonic fashion,[24,25] the relationship between

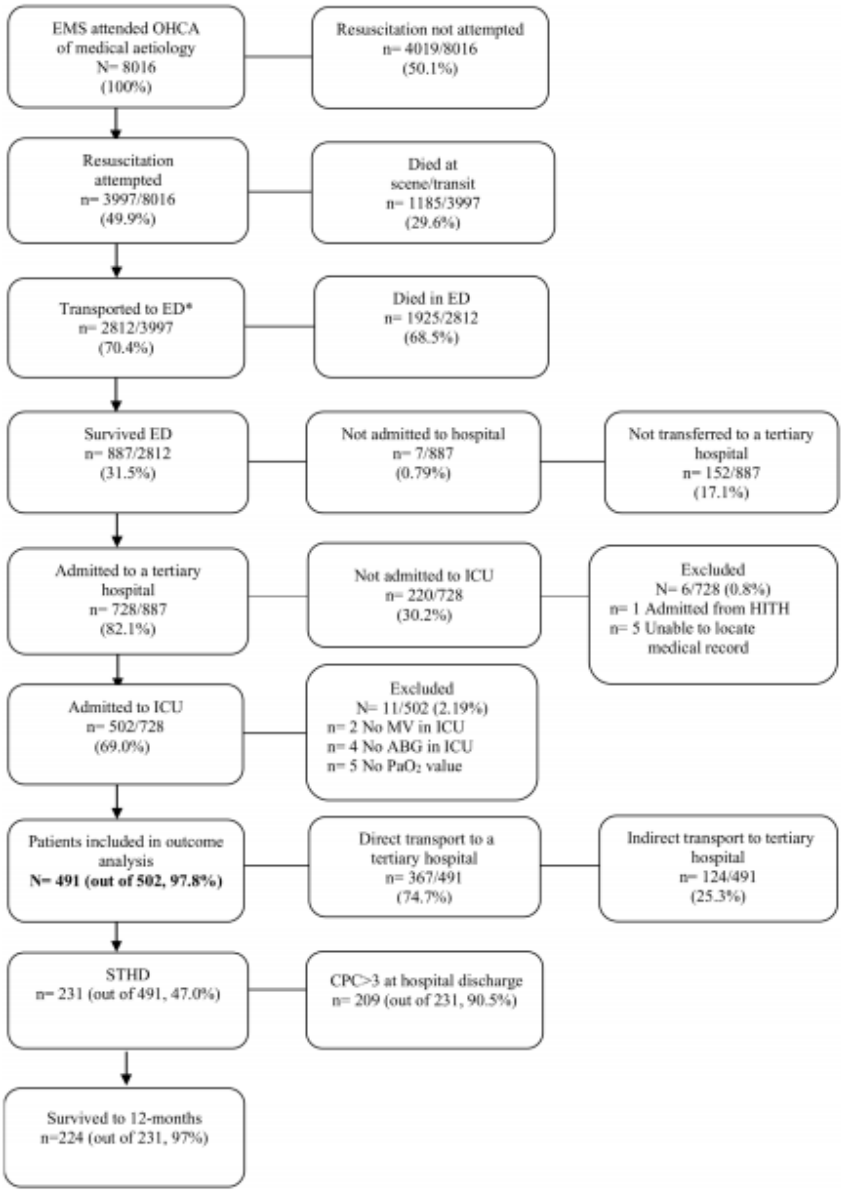

Fig. 1 – Flow chart of included and excluded adult OHCA patients (≥18 years) with OHCA of medical aetiology attended by emergency medical services (EMS) paramedics and transported to a tertiary hospital.
***954 patients out of 2812 (33.9%) had ROSC on arrival to the first ED.**
Abbreviations indicate as follows: ABG, arterial blood gas; CPC, cerebral performance category; ED, emergency department; EMS, emergency medical services; HITH, hospital in the home; ICU, intensive care unit; MV, mechanical ventilation; OHCA, out-of-hospital cardiac arrest; PaO_2, arterial oxygen tension; ROSC, return of spontaneous circulation; STHD, survival to hospital discharge.

Table 1 – Differences in patient characteristics between hospital survivors and non-survivors after out-of-hospital cardiac arrest (OHCA) of medical aetiology.

No. (%) of patients	Total 491	Survivors (% survivors) 231 (47.0)	Non-survivors (% non-survivors) 260 (53.0)	p-Values
Median (IQR) Age, years	59 (48–70)	56 (46–67)	63 (50–72)	0.001
Sex				
Male	351 (71.5)	182 (78.8)	169 (65.0)	0.001
Female	140 (28.5)	49 (21.2)	91 (35.0)	
Pre-arrest CPC score				
CPC 1 or 2	485 (98.8)	230 (99.6)	255 (98.1)	0.22
CPC 3	6 (1.2)	1 (0.4)	5 (1.9)	
Witnessed arrest				
Paramedic	43 (8.8)	21 (9.1)	22 (8.5)	0.65
Bystander	233 (47.5)	114 (49.4)	119 (45.8)	
Unwitnessed	215 (43.8)	96 (41.6)	119 (45.8)	
Bystander CPR	344 (70.1)	180 (77.9)	164 (63.1)	<0.001
Initial arrest rhythm				
VF/VT	308 (62.7)	194 (84.0)	114 (43.8)	<0.001
PEA/Asystole[a]	183 (37.3)	37 (16.0)	146 (56.2)	
Median (IQR) EMS response time, minutes[b]	8 (6–10)	7 (6–10)	8 (6–10)	0.01
Median (IQR) time to first ED, minutes[c]	46 (38–54)	43 (36–51)	48 (41–57)	<0.001
Median (IQR) time to tertiary ICU, minutes[d]	228 (178–284)	216 (167–275)	236 (192–292)	0.06
Direct transport patients (n = 367)	211 (165–262)	201 (160–261)	217 (174–266)	0.05
Indirect transport patients (n = 124)	291 (243–342)	282 (242–351)	292 (248–337)	0.44
ROSC on arrival to first ED	414 (84.3)	215 (93.1)	199 (76.5)	<0.001
Place of intubation[f]				
Pre-hospital	202 (41.1)	53 (22.9)	149 (57.3)	<0.001
ED	285 (58.0)	176 (76.2)	109 (41.9)	
Diagnosis of ACS at ED discharge	155 (31.6)	92 (39.8)	63 (24.2)	<0.001
Diagnosis of STEMI at ED discharge	107 (21.8)	63 (27.3)	44 (16.9)	0.01
PCI (≤24-hs)[e]	142 (28.9)	83 (35.9)	59 (22.7)	0.001
Median (IQR) duration of ICU stay (days)	2 (1–5)	3 (2–5)	2 (1–5)	0.002
TTM in ICU	399 (81.3)	204 (88.3)	195 (75.0)	<0.001
Inotropes in ICU	427 (87.0)	194 (84.0)	233 (89.6)	0.06

Data are presented as count (percentage) unless indicated otherwise.

Abbreviations indicate as follows: ACS, acute coronary syndrome; CCL, cardiac catheterization laboratory; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ED, emergency department; EMS, emergency medical services; ICU, intensive care unit; OR, operating room; PCI, percutaneous coronary intervention within the first 24-hours; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; STEMI, ST-elevation myocardial infarction; STHD, survival to hospital discharge; TTM, targeted temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a] Includes 8 patients where 'initial arrest rhythm' is unknown.

[b] Time interval from EMS call to arrival on scene.

[c] Time interval from EMS call to arrival at first ED.

[d] Time interval from EMS call to arrival at a tertiary hospital ICU.

[e] Time interval from EMS call to arrival in CCL.

[f] Excludes 3 patients intubated in CCL and one patient intubated in OR.

mean PaO_2 during the first 24-hs in ICU after OHCA and survival was analysed using a four-knot restricted-cubic-spline function.[26] We assessed the importance of mean PaO_2 relative to plausible physiological predictors in explaining the variability in observed hospital mortality by each predictor's chi square contribution in a multivariable logistic regression[27] (Supplementary Text 2).

We conducted two sensitivity analyses examining whether the mean PaO_2 during the first 48 and 72-hs in ICU after OHCA remained important in determining survival. All statistical tests were two-tailed and analysed using SPSS for Windows (version 24.0, IBM, USA) and S-PLUS (version 8.2, 2010; TIBCP Software Inc., USA); an α-value <5% was taken as significant.

Ethics approval

The study was approved (with waiver of consent) by the human research ethics committees at the Curtin University, (HR 199/2014) Royal Perth Hospital (13-044), Sir Charles Gairdner Hospital (2012-184), Fremantle Hospital (AR-13-96) and Fiona Stanley Hospital (2015-091), and St John Western Australia.

Results

Patient characteristics

Of the 8016 OHCA recorded during the study period (Fig. 1), 491 patients met the inclusion criteria and were further analysed. Of these, 231 (47.0%) STHD with 90.5% (209/231) of them with a good neurological outcome and 97% (224/231) survived to 12-months.

Table 1 describes the differences in patient characteristics between those who survived and did not survive to hospital discharge. Male (51.9% vs 35%), younger patients (56 vs 63 years-old), shockable initial arrest rhythm (84.0% vs 43.8%), having bystander

CPR (77.9% vs 63.1%), ROSC on arrival to the first emergency department (93.1% vs 76.5%), a diagnosis of acute coronary syndrome (39.8% vs 24.2%), ST-segment elevation myocardial infarction (27.3% vs 16.9%), percutaneous coronary intervention within 24-hs (35.9% vs 22.7%) and TTM in ICU (88.3% vs 75.0%) were all associated with an increased chance of STHD.

The association between oxygen tension after OHCA and survival

A total of 3764 ABG samples were collected with the first 24 h of ICU admission from the study patients, with a median of seven ABG per patient (IQR 5–10). Supplementary Fig. 1 shows the individual PaO_2 data within the first 24-hs of ICU admission, stratified by STHD.

When PaO_2 was modelled without allowing non-linearity, the mean PaO_2 had no significant association with STHD after adjusting for known predictors of survival after OHCA (p = 0.97) (Supplementary Fig. S2). Conversely, PaO_2 was strongly associated with both STHD and 12-month survival (Figs. 2 and 3), with an inverted U-shaped relationship, once PaO_2 was allowed to change with STHD in a non-linear fashion using a 4-knot restricted-cubic-spline function. This non-linear multivariable model was well calibrated (Supplementary Fig. 3).

The non-linear relationship between PaO_2 and survival (Figs. 2 and 3) suggests that survival among those with low to normal PaO_2 (<100 mmHg; n = 115), mild to moderately elevated PaO_2 (100–180 mmHg; n = 336), and highly elevated PaO_2 (>180 mmHg; n = 40) were different; and we referred these three categories as normoxaemic, mildly to moderately hyperoxaemic, and severely hyperoxaemic, respectively. We found that an episode of hypoxaemia (PaO_2 <60 mmHg) was uncommon in our cohort and this was more common among those in the normoxaemic group than among those in the mild to moderate hyperoxaemia and severe hyperoxaemia groups (4.3% vs 0.6% vs 0.0%, respectively; p = 0.011) (Supplementary Fig. S4).

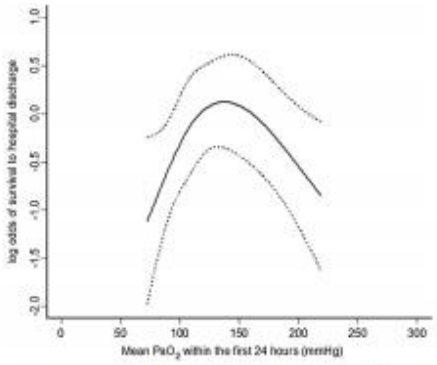

Fig. 2 – Mean PaO_2 within the first 24-hs of ICU admission with log odds of STHD using RCS function. Dotted lines indicate 95% CI.
Abbreviations indicate as follows: CI, confidence interval; ICU, intensive care unit; PaO_2, arterial oxygen tension; RCS, restricted cubic spline function; STHD, survival to hospital discharge.

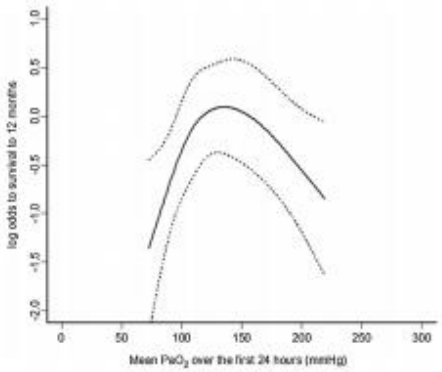

Fig. 3 – Mean PaO_2 within the first 24-hs of ICU admission with log odds of survival to 12-months using RCS function. Dotted lines indicate 95 % CI.
Abbreviations indicate as follows: CI, confidence interval; ICU, intensive care unit; PaO_2, arterial oxygen tension; RCS, restricted cubic spline function.

In univariate analyses, patients in the mildly to moderately hyperoxaemic group were more likely to have a shockable initial cardiac arrest rhythm (67.9% vs 53.9% vs 45.0%), ROSC on arrival to the first emergency department (87.8% vs 74.8% vs 82.5%), a diagnosis of ST-segment elevation myocardial infarction (25.6% vs 17.4% vs 2.5%), percutaneous coronary intervention within 24-hs (32.1% vs 24.3% vs 15.0%) and received TTM in ICU (86.0% vs 73.9% vs 62.5%) compared to those in the normoxemic and severe hyperoxaemic groups (Supplementary Table S1).

The association between mean PaO_2 within the first 24-hs of ICU admission (categorised using the cut points defined above) and STHD or 12-month survival remained unchanged throughout the stepwise forward logistic regression (Table 2 and Supplementary Table 2). Compared to the reference group of those with PaO_2 100–180 mmHg, normoxemia (adjusted odds ratio [aOR] 0.50; 95% confidence interval [CI] 0.30–0.84) and severe hyperoxaemia (aOR 0.41; 95% CI 0.18–0.92) were both associated with a reduced odd of STHD. Results for 12-month survival and good CPC at hospital discharge were also similar (Supplementary Fig. S5).

Relative importance of PaO_2 on survival compared to other known predictors

In the restricted-cubic-spline multivariable model, shockable initial rhythm was most important, and explained 55.2 % of the variability in STHD, followed by witnessed arrest (12.0%). Mean PaO_2 within 24 -hs was the third most important factor and explained 9.1% of the variability in STHD (Fig. 4).

Table 2 – Logistic regression assessing the associations between the mean arterial oxygen tension (PaO_2) within the *first 24-hs* of admission to the intensive care unit (ICU) – grouped as (a) normoxaemic (<100 mmHg), (b) mild to moderate hyperoxaemic (100–180 mmHg) and (c) severe hyperoxaemic (>180 mmHg) after out of hospital cardiac arrest and survival to hospital discharge or 12-months (N = 491). Mild to moderate hyperoxaemic (100–180 mmHg) was used as the reference group.

Confounders used for adjustment	Mean arterial oxygen tension within the first 24-hs after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n = 231, 47.0%)	OR (95%CI) for survival to 12-months (n = 224, 45.6%)
*Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score, STEMI & PCI	mild to moderate hyperoxaemic	1#	1##
	normoxaemic	0.50 (0.30–0.84)	0.46 (0.27–0.77)
	severe hyperoxaemic	0.41 (0.18–0.92)	0.43 (0.19–0.99)
	age	0.98 (0.96–0.99)	0.98 (0.96–0.99)
	sex (female)	0.62 (0.38–1.02)	0.59 (0.35–0.97)
	witness arrest (paramedic witnessed vs	5.19 (2.05–13.14)	5.19 (2.01–13.41)
	unwitnessed)	1.99 (1.14–3.48)	2.30 (1.30–4.09)
	bystander CPR	7.01 (4.15–11.83)	7.61 (4.44–13.04)
	shockable first rhythm	0.92 (0.86–0.98)	0.91 (0.85–0.97)
	EMS response time (per min increment)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
	time between EMS attendance and	4.47 (0.37–53.62)	4.36 (0.34–55.28)
	tertiary ICU admission	1.18 (0.63–2.20)	1.38 (0.73–2.59)
	category 1 pre-cardiac arrest CPC score	0.84 (0.47–1.49)	0.75 (0.42–1.34)
	(no disability vs with disability)		
	STEMI		
	PCI		

Sensitivity analyses

The associations between mean PaO_2 and STHD or 12-month survival remained similar when the period of oxygen exposure was extended to the first 48-hs or 72-hs after OHCA (Supplementary Tables S3 and S4).

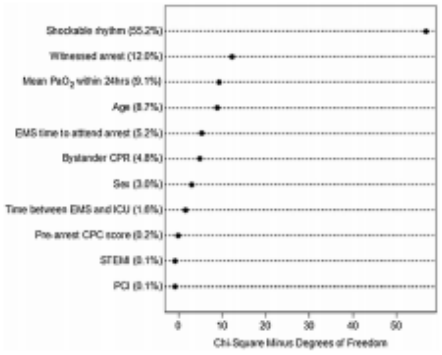

Fig. 4 – Predictors of in-hospital mortality using mean PaO_2 within the first 24-hs of ICU admission.
Abbreviations indicate as follows: CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ICU, intensive care unit; PaO_2, arterial oxygen tension; PCI, percutaneous coronary intervention within the first 24-hours; STEMI, ST-segment elevation myocardial infarction; STHD, survival to hospital discharge.

Discussion

In this multicentre retrospective cohort study, we found that maintaining mild to moderate hyperoxaemia within the first 24-hs after OHCA was associated with a significantly higher odd of STHD and 12-month survival compared to normoxaemia (<100 mmHg) or severe hyperoxaemia (>180 mmHg). Our results suggest that titrating PaO_2 for patients after OHCA may represent a potential simple intervention we can use to improve patient outcomes.

The American Heart Association guidelines recommend monitoring oxyhemoglobin saturation by titrating the inspired oxygen concentration to avoid use of excessive amount of inspiratory oxygen after ROSC.[28] These recommendations were based on observational studies suggesting that hyperoxaemia may increase mortality after cardiac arrest through inducing reactive-oxygen-species with an exposure to a high level of oxygen in the blood.

Existing studies assessing the effect of PaO_2 on survival after OHCA have substantial methodological limitations. First, using a single PaO_2 data point as a measure of oxygen exposure is unlikely to reflect a patient's overall oxygen exposure during the vulnerable period of reperfusion injury to the brain. The use of the first recorded PaO_2,[29,33] the highest PaO_2,[31,32] or worst PaO_2[13,30,34] within the first 24-hs of ICU admission in these studies was primarily driven by the fact that was the only data they had in their databases. Using a single highest or lowest value of PaO_2 recorded within the first 24 -hs after OHCA as a measure of oxygen exposure can induce misclassification of the true extent of oxygen exposure. Palmer et al. found that a high PaO_2 in the first ABG results was likely to trigger actions to decrease inspired oxygen concentration to normalise the arterial oxygen tension.[36] More recent studies have sought to overcome this problem by analysing PaO_2 beyond a single time point. For example, Roberts et al. measured PaO_2 at both one and six hours after ROSC.[35] Even

so, this study was limited by only studying oxygen exposure at two time points within the first six hours.

Second, arbitrarily categorising PaO_2 without considering its potential non-linear effect on patient outcome will not only reduce statistical power but it also has the potential to make incorrect inferences and conclusions, as we have demonstrated (in Supplementary Fig. S2 compared to Figs. 2 and 3). Our results suggest that the effect of PaO_2 on survival is "dose dependent" with potential harm occurring at a PaO_2 level that has been suggested to be safe (e.g. >180 mmHg but <300 mmHg[12,14] and <100 mmHg). The strong non-linear association between PaO_2 and survival after OHCA demonstrated in our study suggests that adequately-powered randomised-controlled-trials are now needed to validate the best PaO_2 target for OCHA patients.

Study strengths and limitations

By including only OHCA patients in this study, we could identify and adjust for a number of important pre-hospital and in-hospital predictors of survival after OHCA. Using the mean PaO_2 values derived from multiple ABG results over the first 24-hs is also a more representative of the real oxygen exposure during the crucial reperfusion injury period after OHCA than using data a single time point. More importantly, we have allowed the association between this more accurate measure of oxygen exposure and survival to be modelled non-linearly, instead of forcing the data to fit into a linear relationship which may be non-physiological.[31] Our hypothesis and study results are indeed consistent with the evidence indicating that both hypoxaemia and hyperoxaemia can worsen outcomes in critically ill patients without OHCA,[7] similar to the non-linear effects of some other physiological derangements on patient outcomes.[24,25]

This study has limitations. First, our results can only imply association and suggest a need to conduct an adequately-powered RCT to validate the optimal oxygenation targets in mechanically ventilated OHCA patients. Results from the EXACT study[37], a multicentre, single-blind, randomised, parallel-group, controlled trial to determine whether early oxygen titration improves STHD in adult OHCA patients will provide further evidence on the potential effect of hyperoxaemia on outcomes. Second, the majority of our patients (75.0%) were directly transported to a tertiary hospital after OHCA. Patients who had OHCA but were not transferred to a tertiary hospital might have different characteristics and our results may not be generalizable to OHCA patients who did not require tertiary care. Third, due to the observational nature of the study, there were variations in the timing and frequency of ABG analyses and other interventions between different study centres. An important therapy after OHCA is TTM which was used in most study patients, although the precise targets did vary (33–37 °C).[38] Fourth, it is unclear whether clinicians corrected the ABG values to the patient's actual body temperature (pH-stat) or not (alpha-stat), which may potentially induce a small degree of variability in the reported PaO_2 data.[39] Fifth, in highlighting a PaO_2 of 100–180 mmHg as an optimal target for patients who require mechanical ventilation after OHCA, we acknowledge that this is a target averaged over the first 24-hs, and that real-time (minute-by-minute) targets could potentially be broader without causing significant harm. Sixth, it is possible that cofounding by severity has influenced our results when patients with more severe illness might have received a higher inspired oxygen concentration, resulting in poorer outcomes because of their severity of illness instead of oxygen exposure.[40] Hypoxemia (PaO_2 <60 mmHg) was uncommon in our cohort but we acknowledge that cerebral hypoxia may still have occurred, for example, in patients with more severe illness as a result of cardiogenic shock, hypotension or underlying cerebral vascular disease regardless of PaO_2. Finally, we have no information on the PaO_2 levels before ICU admission where patients may have received a higher inspired oxygen concentration in the prehospital period because the standard St John Western Australia clinical management protocol for OHCA during the study period was to administer 100% inspired oxygen in the prehospital setting.

Conclusions

When compared to an arterial oxygen tension that is considered low or normal (<100 mmHg) or severely hyperoxaemic (>180 mmHg), an exposure to mild to moderate hyperoxaemia (100–180 mmHg) within the first 24-hs of ICU admission after OHCA was associated with a significantly higher chance of survival to hospital discharge and at 12-months. This result has important clinical implications requiring further confirmation by an adequately-powered RCT.

Authors' contributions

Study design: NM, JF.
Data retrieval: NM, GD.
Data interpretation: KM, JF, SB, GD, JB.
Statistical data analysis: KM, NM (non-cubic spline analysis).
Drafting of article: NM.
Critical revision: all authors.

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Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2020.11.021.

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7.3 Supplemental Tables (Mckenzie et al. Resuscitation. 2021 Jan; 158:130-138)[20]

Table 7.1 *(Supplemental Table 1)* Demographic and OHCA characteristics of patients with OHCA of medical aetiology admitted to a tertiary hospital stratified by mean PaO_2 in the first 24-hours of ICU admission.

	Normoxaemic group (<100 mmHg)	Mild to moderate hyperoxaemic group (100-180 mmHg)	Severe hyperoxaemic group (>180 mmHg)	p-values
No. (%) of patients	**115 (23.4)**	**336 (68.4)**	**40 (8.1)**	
Mean PaO_2, mmHg	81.2 (11.95)	125.2 (19.6)	280.2 (110.2)	**<0.001**
Median (IQR) Age, years	64 (52-73)	59 (47-69)	53 (44-68)	**0.01**
Sex				
Male	87 (75.7)	238 (70.8)	26 (65.0)	0.39
Female	28 (24.3)	98 (29.2)	14 (35.0)	
Pre-arrest CPC score				
CPC 1 or 2	113 (98.3)	333 (99.1)	39 (97.5)	0.38
CPC 3	2 (1.7)	3 (0.9)	1 (2.5)	
Witnessed arrest				
Paramedic	16 (13.9)	24 (7.1)	3 (7.5)	0.25
Bystander	53 (46.1)	164 (48.8)	17 (42.5)	
Unwitnessed	46 (40.0)	148 (44.0)	20 (50.0)	
Bystander CPR	77 (67.0)	237 (70.5)	29 (72.5)	0.72
Initial arrest rhythm				
VF/VT	62 (53.9)	228 (67.9)	18 (45.0)	**0.001**
PEA/Asystole*	53 (46.1)	108 (32.1)	22 (55.0)	
Median (IQR) EMS response time, minutes†	8 (6-11)	8 (6-10)	8 (5-11)	0.23
Median (IQR) time to first ED, minutes‡	48 (38-56)	46 (38-53)	47 (37-56)	0.42
Median (IQR) time to tertiary ICU, minutes§	250 (196-321)	224 (172-281)	196 (163-253)	**0.01**
Direct transport patients (n=367)	224 (186-267)	211 (160-265)	179 (155-222)	0.20
Indirect transport	327 (284-366)	274 (242-339)	251 (233-295)	0.21

	Normoxaemic group (<100 mmHg)	Mild to moderate hyperoxaemic group (100-180 mmHg)	Severe hyperoxaemic group (>180 mmHg)	p-values
patients (n=124)				
ROSC on arrival to first ED	86 (74.8)	295 (87.8)	33 (82.5)	**0.004**
Place of intubation[#]				
Pre-hospital	50 (43.5)	137 (40.8)	15 (37.5)	**0.76**
ED	64 (55.7)	196 (58.3)	25 (62.5)	
Diagnosis of ACS at ED discharge	30 (26.1)	115 (34.2)	10 (25.0)	0.18
Diagnosis of STEMI at ED discharge	20 (17.4)	86 (25.6)	1 (2.5)	**0.002**
PCI (≤24-hours)[‖]	28 (24.3)	108 (32.1)	6 (15.0)	**0.04**
Duration of ICU stay (days)	2 (1-5)	3 (1-5)	2 (0-5)	0.67
TTM in ICU	85 (73.9)	289 (86.0)	25 (62.5)	**<0.001**
Inotropes in ICU	102 (88.7)	291 (86.6)	34 (85.0)	0.78

Data are presented as mean (standard deviation), median (interquartile range) or count (percentage)

* Includes 8 patients where 'Initial arrest rhythm' is unknown

† Time interval from EMS call to arrival on scene

‡ Time interval from EMS call to arrival at first ED

§ Time interval from EMS call to arrival at a tertiary hospital ICU

‖ Time interval from EMS call to arrival in CCL

\# Excludes 3 patients intubated in CCL and one patient intubated in OR

Abbreviations indicate as follows: ACS; Acute coronary syndrome, CCL; Cardiac catheterisation laboratory, CPC; Cerebral Performance Category, CPR; Cardiopulmonary resuscitation, ED; Emergency department, EMS; Emergency medical services, ICU; Intensive care unit, PCI; Percutaneous coronary intervention, PEA; Pulseless electrical activity, ROSC; Return of spontaneous circulation, STEMI; ST-elevation myocardial infarction, STHD; Survival to hospital discharge, TTM; Targeted temperature management, VF; Ventricular fibrillation, VT; Ventricular tachycardia.

Table 7.2 *(Supplemental Table 2)* Logistic regression assessing the associations between the mean arterial oxygen tension (PaO_2) within the first 24-hours of admission to the intensive care unit (ICU) – grouped as (a) normoxaemic (<100 mmHg), (b) mild to moderate hyperoxaemic (100-180 mmHg) and (c) severe hyperoxaemic (>180 mmHg) after out of hospital cardiac arrest and survival to hospital discharge or 12-months with stepwise adjustments for potential confounders (N=491). Mild to moderate hyperoxaemic (100-180 mmHg) was used as the reference group.

Confounders used for adjustment	**Mean arterial oxygen tension within the first 24-hours after cardiac arrest in relation to survival**	**OR (95%CI) for survival to hospital discharge (n=231, 47.0%)**	**OR (95%CI) for survival to 12-months (n=224, 45.6%)**
None	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 (reference) 0.43 (0.28-0.68) 0.42 (0.21-0.84)	1 (reference) 0.40 (0.26-0.63) 0.44 (0.22-0.88)
Age	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.47 (0.30-0.73) 0.38 (0.19-0.77)	1 0.43 (0.27-0.68) 0.40 (0.20-0.81)
Age & sex	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.44 (0.28-0.70) 0.39 (0.19-0.79)	1 0.41 (0.25-0.64) 0.41 (0.20-0.84)
Age, sex, & witnessed arrest	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.43 (0.27-0.68) 0.39 (0.19-0.80)	1 0.40 (0.25-0.64) 0.41 (0.20-0.85)
Age, sex, witnessed arrest, & bystander CPR	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.42 (0.26-0.67) 0.37 (0.18-0.76)	1 0.39 (0.24-0.62) 0.39 (0.19-0.80)
Age, sex, witnessed arrest, bystander CPR & shockable first rhythm	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.47 (0.29-0.78) 0.44 (0.20-0.98)	1 0.43 (0.26-0.72) 0.47 (0.21-1.05)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, & EMS response time	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.48 (0.29-0.80) 0.43 (0.19-0.95)	1 0.44 (0.26-0.73) 0.45 (0.20-1.02)
Age, sex, witnessed arrest, bystander CPR, shockable first	(a) mild to moderate hyperoxaemic	1 0.50 (0.30-0.83)	1 0.46 (0.27-0.77)

Confounders used for adjustment	Mean arterial oxygen tension within the first 24-hours after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=231, 47.0%)	OR (95%CI) for survival to 12-months (n=224, 45.6%)
rhythm, EMS response time, & time between EMS attendance and tertiary ICU admission	(b) normoxaemic (c) severe hyperoxaemic	0.41 (0.18-0.91)	0.43 (0.19-0.98)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, & pre-cardiac arrest CPC score	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.50 (0.30-0.84) 0.41 (0.18-0.92)	1 0.46 (0.28-0.78) 0.43 (0.19-0.98)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score & STEMI	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.51 (0.30-0.84) 0.41 (0.18-0.93)	1 0.46 (0.28-0.78) 0.44 (0.19-1.00)
*Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score, STEMI & PCI	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1[#] 0.50 (0.30-0.84) 0.41 (0.18-0.92)	1[##] 0.46 (0.27-0.77) 0.43 (0.19-0.99)
	- age - sex (female) - witness arrest (paramedic witnessed vs unwitnessed) - bystander CPR - shockable first rhythm - EMS response time (per min increment) - time between EMS attendance and tertiary ICU admission - category 1 pre-cardiac arrest CPC score	0.98 (0.96-0.99) 0.62 (0.38-1.02) 5.19 (2.05-13.14) 1.99 (1.14-3.48) 7.01 (4.15-11.83) 0.92 (0.86-0.98) 1.00 (1.00-1.00) 4.47 (0.37-53.62) 1.18 (0.63-2.20) 0.84 (0.47-1.49)	0.98 (0.96-0.99) 0.59 (0.35-0.97) 5.19 (2.01-13.41) 2.30 (1.30-4.09) 7.61 (4.44-13.04) 0.91 (0.85-0.97) 1.00 (1.00-1.00) 4.36 (0.34-55.28) 1.38 (0.73-2.59)

Confounders used for adjustment	Mean arterial oxygen tension within the first 24-hours after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=231, 47.0%)	OR (95%CI) for survival to 12-months (n=224, 45.6%)
	(no disability vs with disability) - STEMI - PCI		0.75 (0.42-1.34)

Hosmer-Lemeshow Chi-Square and Nagelkerke R2 for the final fully adjusted model for survival to 12-months were 7.867 (p=0.45) and 0.370, respectively. #The p-value for PaO2 modelled as a continuous variable, allowing non-linearity with a 4-knot restricted cubic spline function to predict hospital survival, was 0.006; the p-value for shockable rhythm, witnessed arrest, age, sex, bystander CPR, EMS response time, EMS to ICU admission, pre-arrest CPC score, STEMI and PCI were <0.001, <0.001, 0.002, 0.04, 0.01, 0.01, 0.10, 0.10, 0.37, 0.58 and 0.61. ##The p-value for PaO2 modelled as a continuous variable, allowing non-linearity with a 4-knot restricted cubic spline function to predict survival to 12-months, was 0.004; the p-value for shockable rhythm, witnessed arrest, age, sex, bystander CPR, EMS response time, EMS to ICU admission, pre-arrest CPC score, STEMI and PCI were <0.001, 0.001, 0.003, 0.027, 0.004, 0.008, 0.06, 0.46, 0.30 and 0.38

Abbreviations indicate as follows: CI; Confidence interval, CPC; Cerebral Performance Category, CPR; Cardiopulmonary resuscitation, EMS; Emergency medical services, ICU; Intensive care unit, OR; Odds ratio, PCI; Percutaneous coronary intervention within the first 24-hours, STEMI; ST-segment elevation myocardial infarction.

Table 7.3 *(Supplemental Table 3)* Logistic regression assessing the associations between the mean PaO_2 within the first 48-hours of admission to the ICU – grouped as (a) normoxaemic (<100 mmHg), (b) mild to moderate hyperoxaemic (100-180 mmHg) and (c) severe hyperoxaemic (>180 mmHg) after out of hospital cardiac arrest and survival to hospital discharge or 12-months with stepwise adjustments for potential confounders (N=491). Mild to moderate hyperoxaemic (100-180 mmHg) was used as the reference group.

Confounders used for adjustment	**Mean arterial oxygen tension within the first 48-hours after cardiac arrest in relation to survival**	**OR (95%CI) for survival to hospital discharge (n=231, 47.0%)**	**OR (95%CI) for survival to 12-months (n=224, 45.6%)**
None	(a) mild to moderate hyperoxaemic	1 (reference)	1 (reference)
	(b) normoxaemic	0.52 (0.35-0.78)	0.50 (0.34-0.75)
	(c) severe hyperoxaemic	0.28 (0.11-0.66)	0.29 (0.12-0.70)
Age	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.56 (0.37-0.83)	0.53 (0.36-0.80)
	(c) severe hyperoxaemic	0.24 (0.10-0.60)	0.26 (0.11-0.63)
Age & sex	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.52 (0.35-0.60)	0.50 (0.33-0.76)
	(c) severe hyperoxaemic	0.24 (0.10-0.60)	0.26 (0.11-0.64)
Age, sex, & witnessed arrest	(d) mild to moderate hyperoxaemic	1	1
	(e) normoxaemic	0.51 (0.33-0.77)	0.49 (0.32-0.75)
	(f) severe hyperoxaemic	0.24 (0.10-0.59)	0.26 (0.10-0.64)
Age, sex, witnessed arrest, & bystander CPR	(d) mild to moderate hyperoxaemic	1	1
	(e) normoxaemic	0.50 (0.33-0.77)	0.49 (0.32-0.75)
	(f) severe hyperoxaemic	0.25 (0.10-0.61)	0.27 (0.11-0.67)

Confounders used for adjustment	Mean arterial oxygen tension within the first 48-hours after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=231, 47.0%)	OR (95%CI) for survival to 12-months (n=224, 45.6%)
Age, sex, witnessed arrest, bystander CPR & shockable first rhythm	(d) mild to moderate hyperoxaemic (e) normoxaemic (f) severe hyperoxaemic	1 0.52 (0.33-0.82) 0.27 (0.10-0.77)	1 0.50 (0.31-0.79) 0.30 (0.11-0.85)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, & EMS response time	(d) mild to moderate hyperoxaemic (e) normoxaemic (f) severe hyperoxaemic	1 0.55 (0.35-0.87) 0.29 (0.11-0.82)	1 0.53 (0.33-0.85) 0.33 (0.12-0.93)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, & time between EMS attendance and tertiary ICU admission	(c) mild to moderate hyperoxaemic (d) normoxaemic (e) severe hyperoxaemic	1 0.56 (0.35-0.88) 0.28 (0.10-0.77)	1 0.54 (0.34-0.87) 0.31 (0.11-0.87)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, & pre-cardiac arrest CPC score	(iv) mild to moderate hyperoxaemic (v) normoxaemic (vi) severe hyperoxaemic	1 0.56 (0.35-0.89) 0.28 (0.10-0.78)	1 0.55 (0.34-0.88) 0.31 (0.11-0.88)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score & STEMI	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.56 (0.35-0.89) 0.28 (0.10-0.79)	1 0.55 (0.34-0.87) 0.31 (0.11-0.88)
*Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS	(a) mild to moderate hyperoxaemic (b) normoxaemic	1 0.56 (0.35-0.89)	1 0.55 (0.34-0.88)

Confounders used for adjustment	Mean arterial oxygen tension within the first 48-hours after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=231, 47.0%)	OR (95%CI) for survival to 12-months (n=224, 45.6%)
attendance and tertiary ICU admission, pre-cardiac arrest CPC score, STEMI & PCI	(c) severe hyperoxaemic	0.28 (0.10-0.79)	0.31 (0.11-0.89)
	- age	0.98 (0.96-0.99)	0.98 (0.96-0.99)
	- sex (female)	0.62 (0.38-1.01)	0.59 (0.35-0.97)
	- witness arrest (paramedic witnessed vs unwitnessed)	5.27 (2.08-13.33)	5.22 (2.02-13.44)
	- bystander CPR	1.87 (1.07-3.27)	2.16 (1.22-3.83)
	- shockable first rhythm	7.05 (4.18-11.91)	7.67 (4.48-13.15)
	- EMS response time (per min increment)	0.93 (0.87-0.99)	0.92 (0.86-0.98)
	- time between EMS attendance and tertiary ICU admission	1.00 (0.99-1.00)	0.99 (0.99-1.00)
	- category 1 pre-cardiac arrest CPC score *(no disability vs with disability)*	4.67 (0.38-58.02)	4.61 (0.35-60.64)
	- STEMI	1.20 (0.63-2.24)	1.39 (0.74-2.62)
	- PCI	0.93 (0.52-1.65)	0.83 (0.46-1.49)

*The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to hospital discharge were 6.644 (p=0.58) and 0.348, respectively. The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to 12-months were 7.135 (p=0.52) and 0.369, respectively.

Abbreviations indicate as follows: CI; Confidence interval, CPC; Cerebral Performance Category, CPR; Cardiopulmonary resuscitation, EMS; Emergency medical services; OR; Odds ratio, PCI; Percutaneous coronary intervention within the first 24-hours, STEMI; ST-segment elevation myocardial infarction.

Table 7.4 *(Supplemental Table 4)* Logistic regression assessing the associations between the mean PaO_2 within the first 72- hours of admission to the ICU – grouped as (a) normoxaemic (<100 mmHg), (b) mild to moderate hyperoxaemic (100-180 mmHg) and (c) severe hyperoxaemic (>180 mmHg) after OHCA and STHD or 12-months with stepwise adjustments for potential confounders (N=491). Mild to moderate hyperoxaemic (100-180 mmHg) was used as the reference group.

Confounders used for adjustment	**Mean arterial oxygen tension within the first 72-hours after cardiac arrest in relation to survival**	**OR (95%CI) for survival to hospital discharge (n=231, 47.0%)**	**OR (95%CI) for survival to 12-months (n=224, 45.6%)**
None	(a) mild to moderate hyperoxaemic	1 (reference)	1 (reference)
	(b) normoxaemic	0.61 (0.41-0.90)	0.59 (0.40-0.88)
	(c) severe hyperoxaemic	0.19 (0.10-0.52)	0.20 (0.10-0.55)
Age	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.66 (0.44-0.98)	0.64 (0.43-0.95)
	(c) severe hyperoxaemic	0.17 (0.10-0.47)	0.18 (0.10-0.50)
Age & sex	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.62 (0.42-0.93)	0.60 (0.40-0.90)
	(c) severe hyperoxaemic	0.17 (0.10-0.48)	0.18 (0.10-0.51)
Age, sex, & witnessed arrest	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.58 (0.39-0.88)	0.58 (0.38-0.87)
	(c) severe hyperoxaemic	0.17 (0.10-0.46)	0.18 (0.10-0.50)
Age, sex, witnessed arrest, & bystander CPR	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.57 (0.38-0.87)	0.57 (0.37-0.86)
	(c) severe hyperoxaemic	0.17 (0.10-0.48)	0.19 (0.10-0.53)
Age, sex, witnessed arrest, bystander CPR & shockable first rhythm	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.61 (0.39-0.95)	0.60 (0.38-0.94)

Confounders used for adjustment	Mean arterial oxygen tension within the first 72-hours after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=231, 47.0%)	OR (95%CI) for survival to 12-months (n=224, 45.6%)
	(c) severe hyperoxaemic	0.20 (0.10-0.65)	0.22 (0.10-0.72)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, & EMS response time	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.63 (0.40-0.99) 0.21 (0.10-0.99)	1 0.63 (0.40-0.99) 0.24 (0.10-0.77)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, & time between EMS attendance and tertiary ICU admission	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.65 (0.41-1.03) 0.19 (0.10-0.63)	1 0.65 (0.41-1.03) 0.21 (0.10-0.70)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, & pre-cardiac arrest CPC score	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.65 (0.41-1.04) 0.19 (0.10-0.63)	1 0.65 (0.41-1.04) 0.21 (0.10-0.70)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score & STEMI	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.66 (0.41-1.04) 0.19 (0.10-0.63)	1 0.65 (0.41-1.04) 0.21 (0.10-0.71)
*Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score, STEMI & PCI	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1[#] 0.66 (0.42-1.04) 0.19 (0.10-0.64)	1[##] 0.66 (0.41-1.05) 0.22 (0.10-0.71)
	- age	0.98 (0.96-0.99)	0.98 (0.96-0.99)

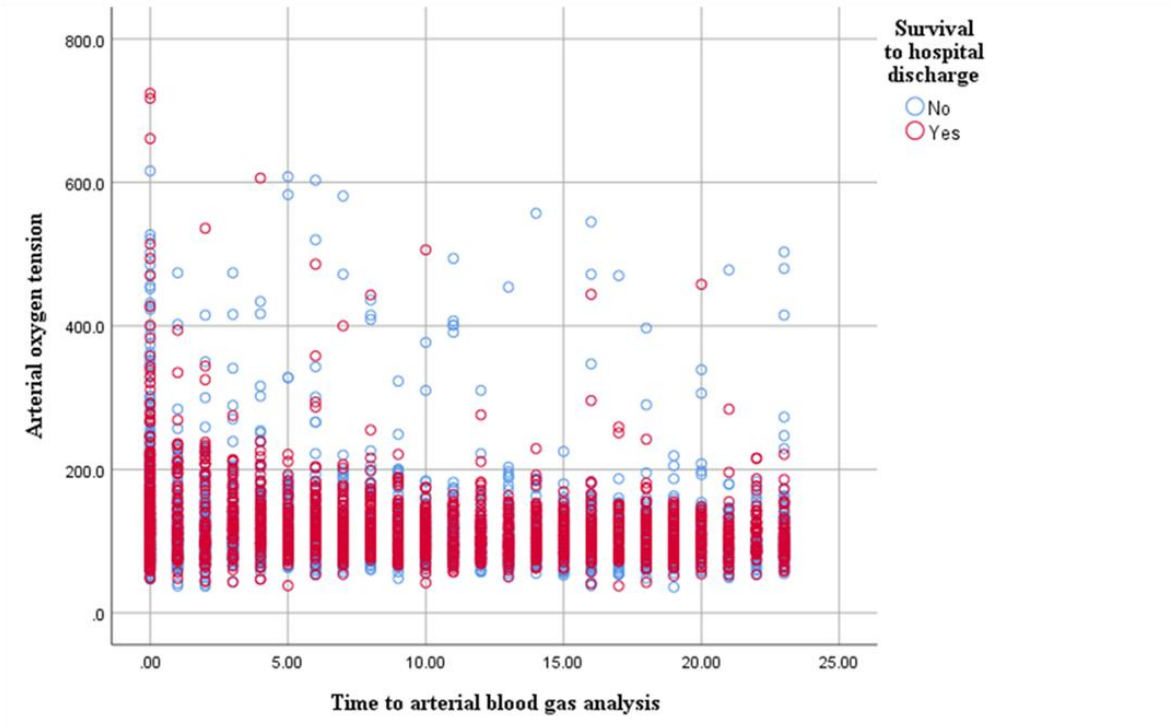
Confounders used for adjustment	Mean arterial oxygen tension within the first 72-hours after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=231, 47.0%)	OR (95%CI) for survival to 12-months (n=224, 45.6%)
	- sex (female)	0.63 (0.38-1.03)	0.60 (0.36-0.99)
	- witness arrest (paramedic witnessed vs unwitnessed)	5.79 (2.28-14.69)	5.74 (2.23-14.82)
	- bystander CPR	1.89 (1.01-3.32)	2.18 (1.23-3.88)
	- shockable first rhythm	7.04 (4.17-11.88)	7.69 (4.49-13.15)
	- EMS response time (per min increment)	0.92 (0.87-0.98)	0.91 (0.86-0.97)
	- time between EMS attendance and tertiary ICU admission	0.99 (0.99-1.00)	0.99 (0.99-1.00)
	- category 1 pre-cardiac arrest CPC score *(no disability vs with disability)*	5.02 (0.40-63.40)	4.93 (0.37-66.73)
	- STEMI	1.18 (0.63-2.21)	1.38 (0.73-2.60)
	- PCI	0.92 (0.52-1.64)	0.83 (0.46-1.48)

*The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to hospital discharge were 13.208 (p=0.11) and 0.349, respectively. The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to 12-months were 10.408 (p=0.24) and 0.369, respectively.

Abbreviations indicate as follows: CI; Confidence interval, CPC; Cerebral Performance Category, CPR; Cardiopulmonary resuscitation, EMS; Emergency medical services; OR; Odds ratio, PCI; Percutaneous coronary intervention within the first 24-hours, STEMI; ST-segment elevation myocardial infarction.

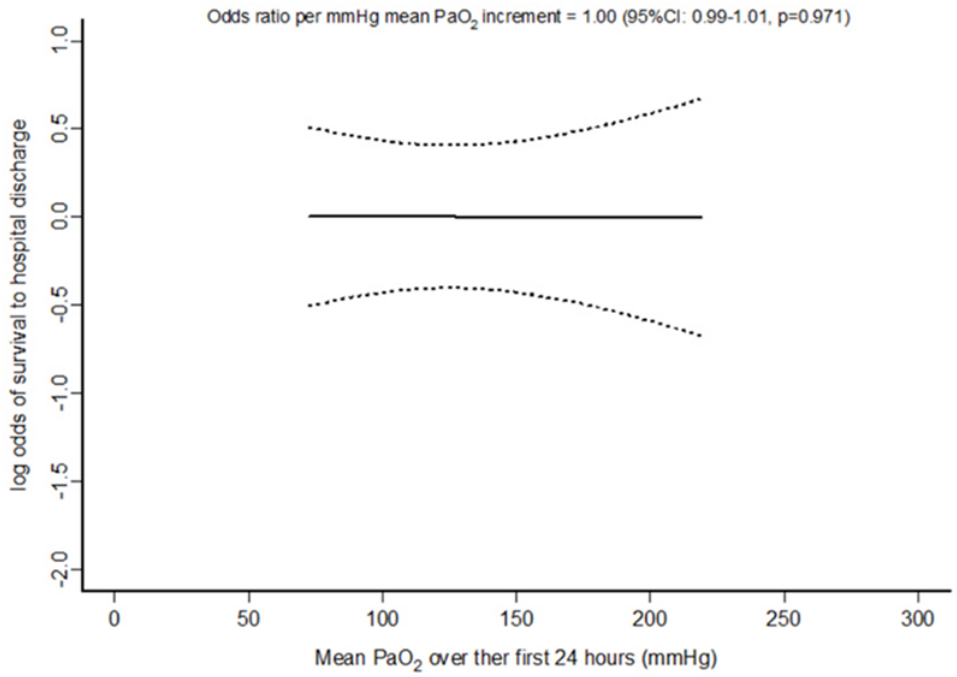
7.4 Supplemental Figures (Mckenzie et al. Resuscitation 2021 Jan; 158:130-138)[20]

Figure 7.1 *(Supplemental Figure 1)* All individual PaO_2 values (mmHg) over the first 24-hours of ICU admission. Data are shown according to STHD.



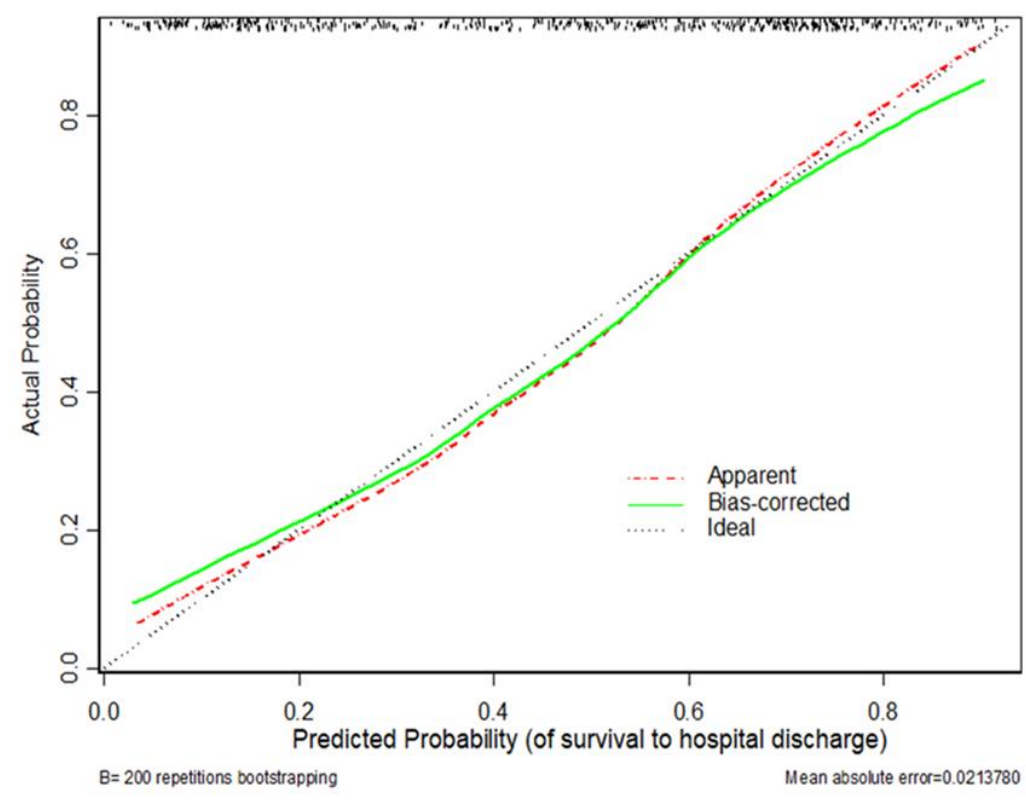
Abbreviations indicate as follows: ICU; Intensive care unit, PaO_2; Arterial oxygen tension, STHD; Survival to hospital discharge.

Figure 7.2 *(Supplemental Figure 2)* Mean PaO2 within the first 24-hours of ICU admission with log odds of STHD adjusting for plausible physiological predictors of survival (listed in Table 2) without allowing non-linearity with a restricted cubic spline function for the mean PaO2. Dotted lines indicate 95 % confidence intervals.



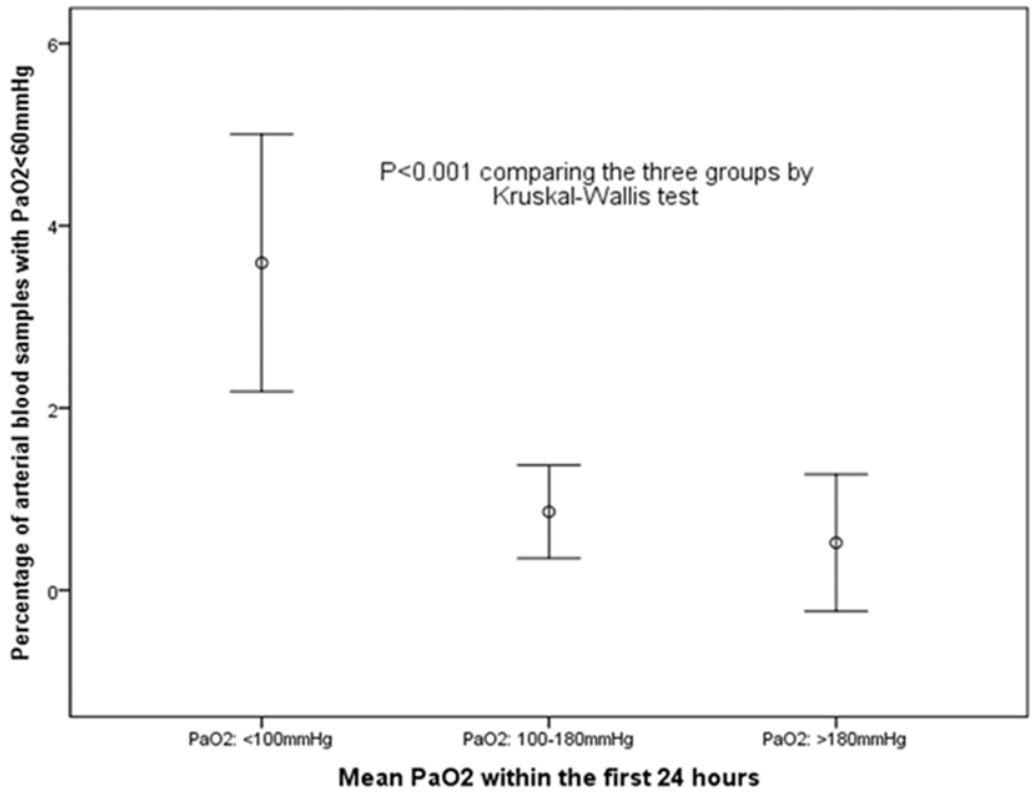
Abbreviations indicate as follows: PaO_2; Arterial oxygen tension, STHD; Survival to hospital discharge.

Figure 7.3 *(Supplemental Figure 3)* Calibration of the final multivariable model allowing non-linearity for the mean PaO_2 within the first 24-hours of admission after OHCA after adjusting for the plausible predictors of survival (listed in Table 2). The ideal calibration line is defined by the black dotted line, the apparent calibration line of the model is defined by the red dotted line and the bias-corrected (using bootstrapping sampling with 200 repetitions) is defined by the green continuous line. The distribution of the predicted chance of survival to hospital discharge of all patients is defined by the density of data points on the top of the graph.



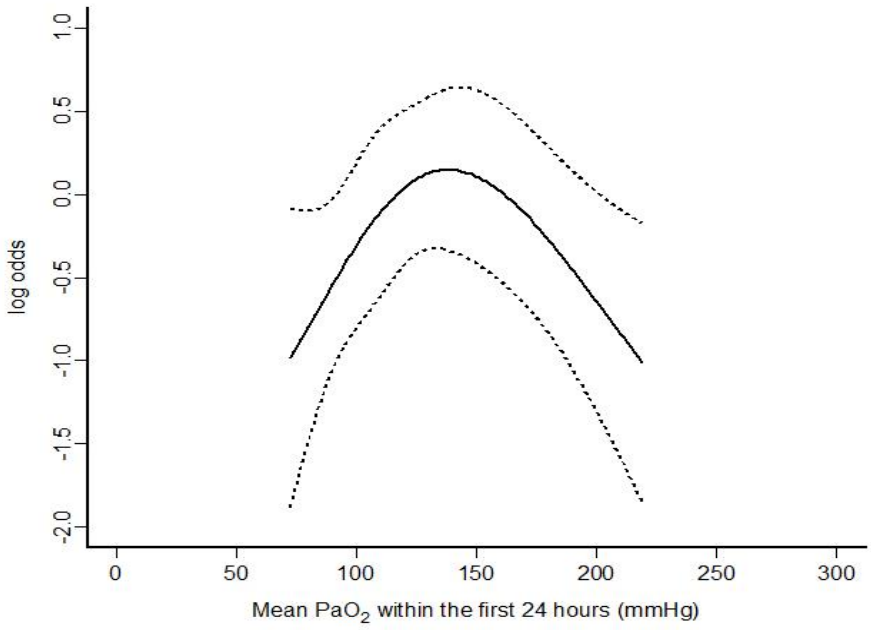
Abbreviations indicate as follows: OHCA; Out-of-hospital cardiac arrest, PaO_2; Arterial oxygen tension.

Figure 7.4 *(Supplemental Figure 4)* Percentage of ABG samples and 95% CI with PaO_2 <60mmHg in the first 24-hours of ICU admission.



Abbreviations indicate as follows: ABG; Arterial blood gas, CI; Confidence interval, ICU; Intensive care unit, PaO_2; Arterial oxygen tension.

Figure 7.5 *(Supplemental Figure 5)* The association between the mean PaO_2 within the first 24-hours after OHCA and odd of having a good CPC score - independent in activities of daily living - at hospital discharge. Contribution of each predictor including the non-linear component of the PaO_2 in the multivariable model is listed below the graph.



	Wald Statistics		
Factors	Chi-Square	d.f.	P value
Mean PaO_2 within 24hrs	12.03	3	0.007
Nonlinear	11.99	2	0.003
Age	6.07	1	0.014
Sex	0.88	1	0.35
Bystander CPR	6.71	1	0.01
Witnessed arrest	13.68	2	0.001
CPC score pre-arrest	1.95	2	0.38
Shockable	55.56	2	<0.001
EMS time	5.02	1	0.03
EMS to ICU time	4.01	1	0.05
STEMI	0.01	1	0.94
PCI	0.36	1	0.55
TOTAL	**97.78**	**16**	**<0.001**

Abbreviations indicate as follows: CPC; Cerebral Performance Category, CPR; Cardiopulmonary resuscitation, EMS; Emergency medical services, ICU; Intensive care unit, STEMI; ST-segment elevation myocardial infarction, PaO_2; Arterial oxygen tension, PCI; Percutaneous coronary intervention within the first 24-hours.

7.5 Summary

In this study, I investigated whether PaO_2 has a non-linear relationship with survival and neurological outcome in adult OHCA patients admitted to ICU. I assessed the potential for a non-linear relationship with a 4-knot restricted cubic spline function and determined that an inverted U-shape relationship exists between PaO_2 and favourable patient outcomes. Using the shape of the spline curve to identify optimal PaO_2 cut-points, I defined normoxaemia as <100 mmHg, mild to moderate hyperoxaemia as 100 to 180 mmHg and severe hyperoxaemia as >180 mmHg. I then used stepwise forward logistic regression analysis to generate corresponding odds ratios. I found that when compared to normoxaemia or severe hyperoxaemia, exposure to mild to moderate hyperoxaemia within the first 24 hours of ICU admission was associated with a significantly higher chance of survival to hospital discharge, good neurological outcome at hospital discharge and survival to 12-months. I also found that mean PaO_2 within 24 hours of ICU admission was the third most important predictor of in-hospital mortality, explaining 9.1% of the variability in survival to hospital discharge.

These results are consistent with other retrospective studies[86,138,147,148] and meta-analysis[112] that suggest abnormalities in PaO_2 are associated with worse patient outcomes after cardiac arrest. They also highlight an important variability in the definition of hyperoxaemia and normoxaemia used in other published studies. Many studies reporting PaO_2 cut-points after adult cardiac arrest define hyperoxaemia [69,78,79,138,141,143,145-147,149] as PaO_2 of approximately 300 mmHg and normoxaemia as a PaO_2 between 60 and 299 mmHg.[69,78,79,138,141,145,146,148] However, evidence to support the use of these cut-points in humans is lacking.[150] By allowing PaO_2 to be associated with patient outcomes in a non-linear and non-monotonic fashion, I demonstrated that harm from hyperoxaemia may occur at levels lower than 300mmHg.

A second source of heterogeneity in observational studies investigating the association between PaO_2 and patient outcomes is the time point used to measure oxygen exposure. Studies that have used the first,[78] worst,[79,141] or highest[85,86,149] PaO_2 during ICU admission are at risk of exposure misclassification as PaO_2 values may vary according to clinical interventions and over time, thereby increasing the risk of under or overestimating abnormalities in PaO_2.[150] By using the mean PaO_2 in the first 24 hours of ICU admission my results are more representative of real oxygen exposure in the critical post-ROSC period.

There are few RCTs investigating different levels of PaO_2 in adult cardiac arrest patients admitted to ICU and results are inconclusive.[72,151,152] Of these, only one study found increased survival at 90 days in a sub-group of cardiac arrest patients in whom hyperoxaemia was aggressively avoided.[152] It is hoped that results from the EXACT study, an Australian multicentre, single-blind, randomised, parallel-group, control trial, will determine whether early oxygen titration improves survival to hospital discharge in adult OHCA patients.[153] In the interim period, my study demonstrates a potential opportunity for improvement in clinical care and suggests that clinicians should remain judicious in the use of supplemental oxygen therapy in adult OHCA patients.

The next chapter presents the findings of the fourth and final multicentre retrospective cohort study included in this thesis. It aims to describe survival and neurological outcomes after OHCA and to determine the association between neurological outcome at hospital discharge and 12-month survival. It is titled 'Neurological outcome in adult out-of-hospital cardiac arrest - Not all doom and gloom!'

Chapter 8 Survival and Neurological Outcome after OHCA

8.1 Overview

In this chapter, I present the findings of the fourth and final multicentre study included in this thesis. In this short paper, I aimed to describe neurological and functional outcomes among OHCA patients who survived to hospital discharge and to determine the association between neurological outcome at hospital discharge and 12-month survival.[21] This research was based on the observation that although the main treatment goal for OHCA survivors is a favourable neurological outcome, relatively little is known about the association between neurological outcome at hospital discharge and longer-term survival after OHCA.[154-157]

Studies assessing the neurological and functional status of OHCA survivors are important for evaluating the outcomes of resuscitation interventions and post-resuscitation care.[90] As prognostication has become an integral part of post-resuscitation care,[158] such studies are equally important for informing discussions with patients and family members and guiding clinical decision making. This includes decisions around the appropriateness of admission to the ICU,[159] the validity of providing ongoing active treatment[95,159] and the withdrawal of life-sustaining treatment in patients who may otherwise have a chance of achieving a good neurological recovery.[160]

The specific objectives of this study were:

1. To undertake a retrospective cohort study of all adult patients with OHCA of any aetiology, having resuscitation attempted by SJ-WA paramedics and surviving to hospital discharge at one of eleven hospitals with an ED in Perth, WA, between 1st January 2004 and 31st December 2019 attended by SJ-WA

2. To describe demographic characteristics of OHCA patients stratified by CPC score and;
3. To use a multivariable logistic regression analysis adjusted for prognostic variables to identify the association between CPC score and 12-month survival.

This Chapter comprises a manuscript that has been published in a peer-reviewed journal and is inserted as a PDF in the format published by the journal:

Mckenzie N, Ball S, Bailey P, Finn L, Arendts G, Celenza A, Fatovich D, Jenkins I, Mukherjee A, Smedley B, Ghedina N, Bray J, Ho KM, Dobb G, Finn J. Neurological outcome in adult out-of-hospital cardiac arrest - Not all doom and gloom! Resuscitation. 2021 Oct; 167:227-232.[21]

Supplementary material supporting this article is presented prior to the Chapter summary.

There are three posters related to the data used in this study.

1. **McKenzie N,** Cheetham S, Williams TA, Inoue M, Fatovich D, Celenza A, Sprivulis P, Jenkins I, Tohira H, Ho KM, Bailey P, Finn J. Neurological outcome in adult out-of-hospital cardiac arrest (OHCA) patients – Not all doom and gloom!

Poster presentation at the 11th International Spark of Life Conference, Adelaide, South Australia, May 2017 (Thesis Appendix H).

Poster presentation at the Innovation and Research Week Recycle Conference Poster Display, Faculty of Health Sciences, Curtin University, Perth, Western Australia October 2017 (Thesis Appendix H)

2. The Effect of Sex and Age on Survival and Neurological Outcome of Out-Of-Hospital Cardiac Arrest Patients Admitted to Tertiary Intensive Care Units.

Mckenzie N, Ho KM, Bray J, Bailey P, Celenza A, Fatovich D, Jenkins I, Arendts G, Dobb G, Ball S, Finn J. The Effect of Sex and Age on Survival and Neurological Outcome of Out-Of-Hospital Cardiac Arrest Patients Admitted to Tertiary Intensive Care Units.

Poster presentation at the Australia and New Zealand Intensive Care Society (ANZICS) 14th World Congress of Intensive Care, Melbourne, Victoria, October 2019 (Thesis Appendix I)

Poster presentation at the 7th Emergency Medicine Society of South Africa, Cape Town, South Africa, November 2019 (presented by Prof. Finn, J) (Thesis Appendix J).

8.2 Manuscript

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Short paper

Neurological outcome in adult out-of-hospital cardiac arrest – Not all doom and gloom!

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Abstract

Aims: To describe neurological and functional outcomes among out-of-hospital cardiac arrest (OHCA) patients who survived to hospital discharge; to determine the association between neurological outcome at hospital discharge and 12-month survival.

Methods: Our cohort comprised adult OHCA patients (≥18 years) attended by St John WA (SJWA) paramedics in Perth, Western Australia (WA), who survived to hospital discharge, between 1st January 2004 and 31st December 2019. Neurological and functional status at hospital discharge (and before the arrest) was determined by medical record review using the five-point 'Cerebral Performance Category (CPC)' and 'Overall Performance Category (OPC)' scores. Adjusted multivariable logistic regression analysis was used to estimate the association of CPC score at hospital discharge with 12-month survival, adjusted for prognostic variables.

Results: Over the study period, SJWA attended 23,712 OHCAs. Resuscitation was attempted in 43.4% of cases (n = 10,299) with 2171 subsequent admissions, 99.4% (n = 2158) of these were admitted to a study hospital. Of the 1062 hospital survivors, 71.3% (n = 757) were CPC1 (highest category of neurological performance), 21.4% (n = 227) CPC2, 6.3% (n = 67) CPC3 and 1.0% (n = 11) CPC4. OPC scores followed a similar distribution. Of the 1,011 WA residents who survived to hospital discharge, 92.3% (n = 933) survived to 12-months. A CPC1-2 at hospital discharge was significantly associated with 12-month survival (adjusted odds ratio 3.28, 95% confidence interval 1.69–6.39).

Conclusion: Whilst overall survival is low, most survivors of OHCA have a good neurological outcome at hospital discharge and are alive at 12-months.

Keywords: Out-of-hospital cardiac arrest, Survival, Neurological outcome, Cerebral performance category, Overall performance category

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Introduction

Survival rates and neurological outcomes after out-of-hospital cardiac arrest (OHCA) vary between overly optimistic perceptions portrayed by media[1,2] and overly pessimistic predictions by some clinicians.[3] Determination of poor prognosis may become self-fulfilling if the decision to withdraw life sustaining treatment is made.[4,5] Studies examining the association between survival and neurological outcome after OHCA are required to support clinical judgment and minimise prognostic errors in decision making.[4]

From a patient-centred perspective the best outcome after OHCA is survival with a good neurological outcome.[6,7] While global OHCA registry data reports variation in survival between 3.1% and 20.4% in different healthcare settings; most survivors to hospital discharge have good neurological outcomes.[8]

To inform clinical decision-making, we aimed to describe neurological and functional outcomes in OHCA patients who survived to hospital discharge and determine the association between neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of any aetiology admitted to hospitals in Perth, Western Australia (WA).

Methods

Study design and setting

This multicentre population-based retrospective cohort study included patients with OHCA of any aetiology, having resuscitation attempted by St John Western Australia (SJWA) paramedics and surviving to hospital discharge at one of eleven hospitals with an emergency department (ED) in Perth, WA, between 1st January 2004 and 31st December 2019. SJWA operates a single tier service of advanced life support paramedics and receives all WA emergency calls requiring ambulance attendance.[9] Between 2004 and 2019, the Perth metropolitan area population increased from 1.48 to 2.09 million.[10] Patients (≥18 years) were identified from the SJWA OHCA Database (described elsewhere).[11]

Exposure and outcome measures

Neurological and functional status at hospital discharge, and before the arrest, was determined by retrospective medical record review at each hospital using five-point Cerebral Performance Category (CPC) and Overall Performance Category (OPC) scores.[12,13] CPC and OPC scores were independently collected for hospital survivors by research nurses (NM & LF) who were blinded to the study hypothesis. Cohen's Kappa inter-rater reliability, calculated from a random sample of 50/1062 (4.7%) medical records was high (= 0.82, 95% CI 0.66–0.98, $p < 0.001$).

CPC scores at hospital discharge estimated neurological outcomes as follows: CPC1: full recovery; CPC2: moderate disability; CPC3: severe disability; CPC4: coma or vegetative state; and CPC5: died. OPC scores at hospital discharge, ranged from OPC1 (capable of normal life) to OPC5 (death). Good neurological outcome was defined as a CPC score of 1 or 2.

The primary outcome was survival to 12-months from the date of OHCA, ascertained from the WA Death Registry;[14] and was restricted to WA residents only to minimise loss to follow up (Fig. 1).

Statistical analyses

Continuous variables are reported as means and standard deviation (SD) or medians and interquartile range (IQR), and categorical variables as counts and percentages. Differences between groups were assessed using the t-test or Mann-Whitney-U for continuous variables, and Chi-square or Fisher's exact test for categorical variables. Adjusted multivariable logistic regression analysis was used to identify the association between CPC score and 12-month survival, adjusted for prognostic variables. Covariates included in the model were: age, sex, arrest aetiology, witness status, arrest location, early cardiopulmonary resuscitation (CPR), initial arrest rhythm and calendar year categorised into 4 year epochs.

All analyses were two-sided tests using SPSS for Windows (version 24.0, IBM, USA). 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 the relevant hospital HRECs.

Results

Study population

Over the study period, SJWA attended 23,712 OHCAs. Resuscitation was attempted in 10,299/23,712 (43.4%) and 7076/10,299 (68.7%) patients were transported to ED. 2197/7076 (31.0 %) survived ED and 2171/2197 (98.9%) were admitted to a study hospital. 1062/2171 (49.2%) patients survived to hospital discharge and formed the study cohort (Fig. 1).

OHCA characteristics and patient outcomes

Of the 1062 hospital survivors, 757 were CPC1 (71.3%; 95% confidence interval [CI] (69.6–73.0), 227 CPC2 (21.4%; 95% CI 16.7–26.1), 67 CPC3 (6.3%; 95% CI 0.7–11.9) and 11 CPC4 (1.0%; 95% CI 4.9 to 6.9). OPC scores followed a similar distribution (Supplementary Table 1). 984 patients had a CPC1-2 at hospital discharge and 938 (93.7%) were alive at 12-months. Of the hospital survivors with CPC1-2, 35 (3.6%) patients had OPC3-4 (Supplementary Table 1).

Of the 78/1062 (7.3%) hospital survivors with poor neurological outcome (CPC3-4), 14 patients (17.9%) also had poor neurological status before the OHCA. Supplementary Figs. 1 and 2 show the proportion and number of hospital survivors with CPC and OPC scores of 1 or 2 at hospital discharge by calendar year, respectively. Table 1 summarises study cohort characteristics stratified by CPC score at hospital discharge.

Of the hospital survivors, n = 51/1062 (4.8%) non-WA residents were excluded leaving n = 933/1011 (92.3%) patients surviving to 12-months for inclusion in the multivariable logistic regression analysis (Fig. 1). Multivariable logistic regression analysis showed that patients with a CPC1-2 had an increased likelihood of 12-month survival compared to those with a CPC3-4 (fully adjusted odds ratio [aOR] 3.28, 95% CI 1.69–6.39). Other factors associated with an increase in 12-month survival were initial shockable arrest rhythm and younger age (Table 2).

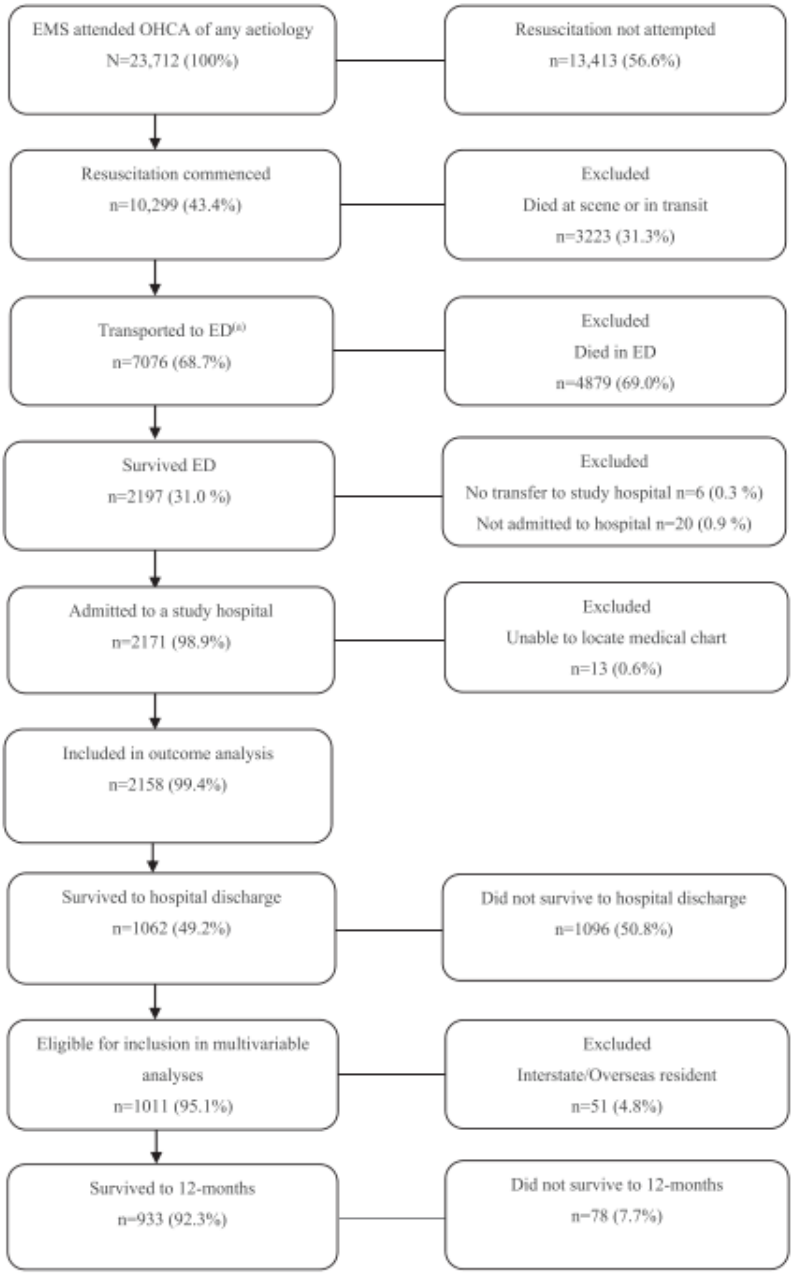

Fig. 1 – Flow chart showing the inclusion and exclusion of adult OHCA patients (≥18 years) of any aetiology attended by paramedics and transported to a study hospital. [a] 2141 patients out of 7076 (30.3%) had return of spontaneous circulation on arrival to the first ED. [b] 1048 hospital survivors out of 1062 (98.7%) had a CPC1-2 prior to OHCA. CPC, cerebral performance category; ED, emergency department; EMS, emergency medical services; OHCA, out-of-hospital cardiac arrest.

Table 1 – Demographic characteristics of patients with OHCA of any aetiology who survived to hospital discharge in Perth WA between 2004 and 2019, stratified by Cerebral Performance Category (CPC) score.

	Total	CPC 1–2	CPC 3–4	Test for difference (p)
No. (%) of patients	1062 (100)	984 (92.7)	78 (7.3)	
Aetiology of arrest, presumed cardiac	965 (90.9)	899 (93.2)	66 (84.6)	0.05
Median (IQR) age, years	60 (49–71)	60 (49–71)	60 (45–78)	0.88
Sex				
Male	803 (75.6)	747 (75.9)	56 (71.8)	0.42
Female	259 (24.4)	237 (24.1)	22 (28.2)	
Location of arrest, public	395 (37.2)	379 (38.5)	16 (20.5)	0.002
Witnessed arrest				
Paramedic	305 (28.7)	292 (29.7)	13 (16.7)	0.01
Bystander	556 (52.4)	514 (52.2)	42 (53.8)	
Unwitnessed	201 (18.9)	178 (18.1)	23 (29.5)	
Early CPR[a]	910 (85.7)	855 (86.9)	55 (70.5)	<0.001
Initial arrest rhythm				
VF/VT	809 (76.2)	768 (78.0)	41 (52.6)	<0.001
PEA/Asystole[b]	253 (23.8)	216 (22.0)	37 (47.4)	
ROSC on arrival to first ED	978 (92.1)	910 (92.5)	68 (87.2)	0.10
Median (IQR) EMS response time, minutes[c]	8 (6–10)	8 (6–11)	7 (5–9)	<0.001
Survived to 12 months[d]	933 (92.3)	879 (89.3)	54 (69.2)	<0.001

CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IQR, interquartile range; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a] Includes 'bystander CPR' and 'paramedic CPR' for paramedic-witnessed arrests.
[b] Includes 18 patients where 'initial arrest rhythm' is unknown.
[c] Using time interval from EMS call to arrival on scene.
[d] Denominator is 1,011 WA residents who survived to hospital discharge.

Table 2 – Factors associated with 12-month survival in univariable and multivariable analyses.

All patients (N = 1011)	12-month survival Unadjusted OR (95 %CI)	12-month survival Adjusted OR (95% CI) (age and sex)	12-month survival Fully adjusted OR (95% CI)
CPC1-2 at hospital discharge	5.24 (2.91–9.41)	4.87 (2.63–9.04)	3.28 (1.69–6.39)
Age, years	0.96 (0.94–0.97)	0.96 (0.95–0.98)	0.96 (0.95–0.98)
Sex, Male	1.48 (0.9–0·2.4)	1.23 (0.73–2.10)	0.86 (0.48–1.52)
Aetiology of arrest, presumed cardiac	1.02 (0.46–2.30)		0.72 (0.29–1.82)
Location of arrest, public	2.2 (1.26–3.91)		1.47 (0.77–2.79)
Witnessed arrest			
Paramedic	1.47 (0.78–2.80)		1.68 (0.74–3.84)
Bystander	1.49 (0.84–2.6)		1.02 (0.52–2.01)
Unwitnessed	(1.0)		(1.0)
Early CPR[a]	2.68 (1.59–4.51)		1.29 (0.65–2.56)
Initial arrest rhythm, shockable	4.56 (2.84–7.31)		3.96 (2.23–7.03)
Year of OHCA			
2004–2007	(1.0)		(1.0)
2008–2011	0.90 (0.39–2.10)		0.72 (0.29–1.80)
2012–2015	0.90 (0.41–2.00)		0.76 (0.32–1.84)
2015–2019	1.27 (0.58–2.80)		1.14 (0.47–2.77)

OHCA, out of hospital cardiac arrest. CPC, cerebral performance category. CPR, cardiopulmonary resuscitation. OR, odds ratio. CI, confidence interval.
[a] Includes 'bystander CPR' and 'paramedic CPR' for paramedic-witnessed arrests.

Discussion

We found that while overall survival after admission for OHCA was low, most of those surviving (994/1062, 92.7%) had a good neurological and functional outcome at hospital discharge. Also, most (93.7%) patients surviving to hospital discharge with a CPC1-2 were alive at 12 months. Patients with a CPC1-2 were 3.3 times more likely to survive to 12-months than those with a CPC3-4, after adjustment in multivariable analysis. This has important implications for the future medical management and prognostic discussions with these patients and their families.

A recent survey of 16 national and regional OHCA registries reported between 53.2 and 97.0% of patients surviving to hospital discharge had a good neurological outcome, with six regions cluster-

ing between 80 and 97%.[8] This is similar to our finding that 92.7% of survivors had a good neurological outcome at hospital discharge. The survival to 12-months of patients with a CPC1-2 at hospital discharge is also similar to previous reports.[15,16]

During the study, the proportion of survivors with a good neurological outcome showed little improvement despite changes in post-resuscitation care. This finding was unexpected but we note that the actual number of patients surviving with a CPC1-2 has increased over time, perhaps reflecting the increased population, advancements in post resuscitation care[17–19], or greater prognostic certainty on behalf of clinicians.[3,17] Many patients who survive to hospital admission die as a result of withdrawal of life sustaining treatment due to suspected hypoxic ischemic brain injury.[3,20]

Study strengths and limitations

This study included all of the adult OHCA patients admitted to any of 11 hospitals in Perth over sixteen years. Loss to 12-month survival follow up (due to exclusion of inter-state and overseas residents) was low (51/1062, 4.8%). We report both neurological and functional performance pre-arrest and at hospital discharge. Also, the pre-hospital variables included in the multivariable analysis were collected prospectively (prior to knowing neurological and survival outcomes). This study is one of few that have assessed the relationship between CPC and long-term survival in a large multicentre cohort.

The limitations include potential for misclassification of pre-arrest CPC/OPC scores as the data was collected retrospectively. However, only 14/1062 (1.3%) of hospital survivors had a poor pre-arrest neurological status so that even a substantial misclassification, for example 50% would have minimal impact upon the study outcome. We were unable to account for changes in post-resuscitation care during the study period that may have impacted on patient outcome. Therefore, we divided the cohort into four-year epochs and included this as a covariate. There are also limitations of using CPC/OPC scores at hospital discharge as measures of neurological outcome as the patient's condition may continue to improve or deteriorate and hence a 12-month neurological follow up provides a better indication of neurological and functional recovery.[15]

Conclusions

In our population-based study cohort, most patients who survived to hospital discharge after OHCA had good neurological and functional outcomes. For these patients, the prognosis for 12-month survival was encouraging. OHCA outcomes are not all doom and gloom for the small proportion of patients who survive to hospital discharge after OHCA.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.08.042.

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8.3 Supplemental Tables (Mckenzie et al. Resuscitation. 2021 Sept; 167:227-32)[21]

Table 8.1 *(Supplemental Table 1)* The number, proportion and 95% Confidence Interval for the proportion shown as a percentage for pre-and post-arrest CPC and OPC scores.

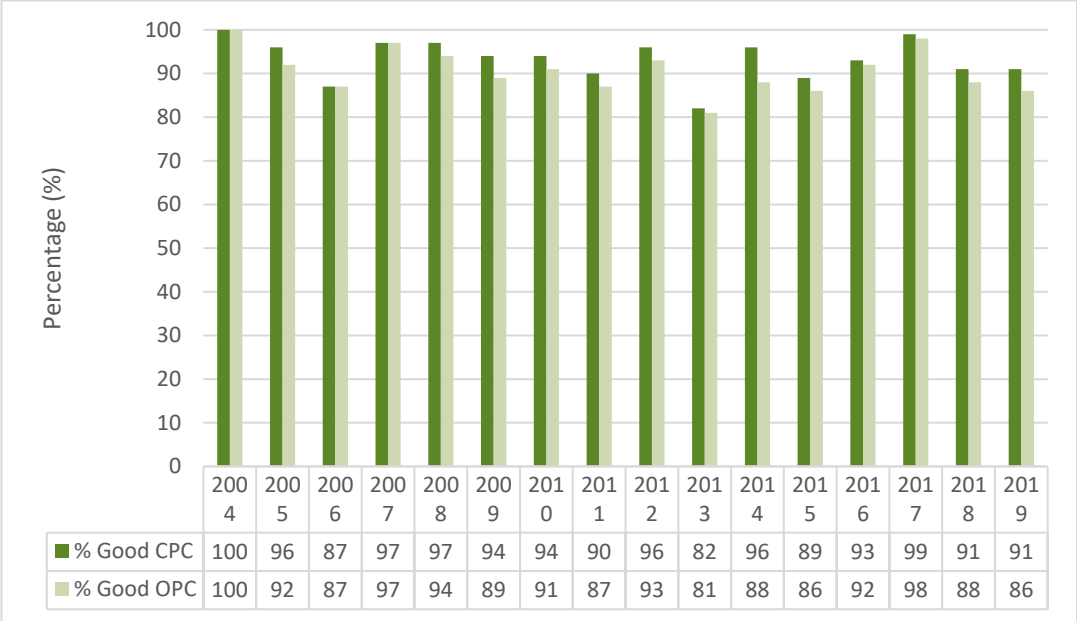
Pre-arrest CPC Score	**No. (%)**	**95% CI**	**Post-arrest CPC Score**	**No. (%)**	**95% CI**	**Pre-arrest OPC Score**	**No. (%)**	**95% CI**	**Post-arrest OPC Score**	**No. (%)**	**95% CI**
CPC 1	983 (92.6)	90.8-94.1	**CPC 1**	757 (71.3)	68.5-74.0	**OPC 1**	861 (81.1)	78.6-83.4	**OPC 1**	620 (58.4)	55.4-61.4
CPC 2	65 (6.1)	4.8-7.7	**CPC 2**	227 (21.4)	18.9-24.0	**OPC 2**	159 (15.0)	12.9-17.3	**OPC 2**	329 (31.0)	28.2-33.9
CPC 3	14 (1.3)	0.72-2.2	**CPC 3**	67 (6.3)	4.9-7.9	**OPC 3**	42 (4.0)	2.9-5.3	**OPC 3**	102 (9.6)	7.9-11.5
CPC 4	0	0	**CPC 4**	11 (1.0)	0.52-1.85	**OPC 4**	0	0	**OPC 4**	11 (1.0%)	0.52-1.85

Total N=1062

Abbreviations indicate as follows: CPC; Cerebral Performance Category, OPC; Overall Performance Category, CI; Confidence interval.

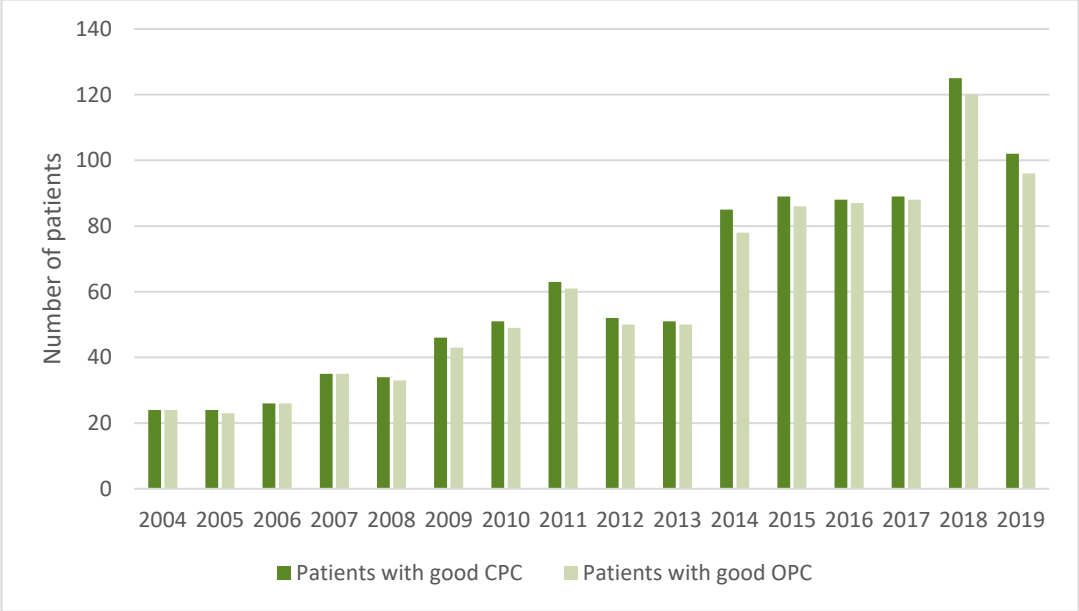
8.4 Supplemental Figures (Mckenzie et al. Resuscitation. 2021 Sept; 167:227-32)[21]

Figure 8.1 *(Supplemental Figure 1)* Proportion of hospital survivors with cerebral performance category (CPC) and overall performance category (OPC) scores of 1 or 2 at hospital discharge by calendar year.



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
% Good CPC	100	96	87	97	97	94	94	90	96	82	96	89	93	99	91	91
% Good OPC	100	92	87	97	94	89	91	87	93	81	88	86	92	98	88	86

Figure 8.2 *(Supplemental Figure 2)*: Number of hospital survivors with cerebral performance category (CPC) and overall performance category (OPC) scores of 1 or 2 at hospital discharge by calendar year.



8.5 Summary

In this cohort of OHCA survivors, I found that whilst overall survival was low, most survivors had a good neurological and functional outcome at hospital discharge. Further, patients with a CPC of 1 or 2 at hospital discharge were significantly more likely to survive to 12-months than those with a CPC of 3 or 4, after adjustment in multivariable analysis. These results support the implementation of multimodal prognostication strategies to inform clinical decision making[95] and reduce the risk of premature withdrawal of life sustaining treatment in patients who may have a chance of a good neurological recovery.[160] Future research should investigate the utility of the CPC score and other neurological and functional scoring systems in different subgroups of OHCA patients across different time points. In the final chapter of this thesis, I summarise the key findings of my doctoral research, discuss the methodological strengths and limitations and provide recommendations to inform future research and clinical care.

Chapter 9 Discussion and Conclusions

9.1 Overview

In this chapter, I summarise the key findings of my doctoral research, in relation to each research objective and in the context of recent literature and international guideline recommendations. I then discuss the strengths and limitations of my research, and outline a set of recommendations to inform policy, practice and research, as it applies to the local EMS and hospital system. The chapter concludes with an overarching statement of how my research could strengthen the post-resuscitation link in the Chain of Survival and improve survival and neurological outcomes in adult OHCA patients.

9.2 Discussion

This thesis includes five peer reviewed manuscripts published in Resuscitation, the highest ranked journal in emergency medicine.[161] The primary purpose of my research was to identify strategies to optimise care in the post-resuscitation link in the chain of survival by examining the effect of in-hospital factors on survival and neurological outcome after OHCA. The following section provides a summary of my research in relation to each of the five research objectives included in this thesis. These findings are presented in the context of other comparable studies published in peer-reviewed journals.

9.2.1 Summary of Key Findings

The key findings of each study are summarised in Table 9.1, before they are discussed further below.

Table 9.1 Summary of Key Findings

Research Objective/ Chapter	Key Finding
One Chapter Four	Direct EMS transport to a PCI-capable hospital for post resuscitation care is associated with a survival advantage for adults with OHCA of medical aetiology.[17]
Two Chapter Five	$PaCO_2$ has an important inverted U-shape (non-linear) association with survival and patient outcomes after cardiac arrest, consistent with international guideline recommendations that normocarbia be targeted during post-resuscitation care.[19]
Three Chapter Six	Maintaining normocapnia ($PaCO_2$ 35-45 mmHg) within the first 24-hours of ICU admission is associated with improved survival when compared to patients with hypocapnia (<35 mmHg) or hypercapnia (>45 mmHg). The relationship between $PaCO_2$ and survival is non-linear (inverted U-shape).[19]
Four Chapter Seven	Maintaining mild to moderate hyperoxaemia (PaO_2 100-180 mmHg) within the first 24-hours of ICU admission is associated with improved survival when compared to patients with normoxaemia (<100 mmHg) or hyperoxaemia (>180 mmHg). The relationship between PaO_2 and survival is non-linear (inverted U-shape).[20]
Five Chapter Eight	Whilst overall survival is low, most survivors of OHCA have a good neurological outcome at hospital discharge and are alive at 12-months.[21]

Research Objective One: The Association between EMS Transport Destination and Survival after OHCA

My first research objective was to compare survival outcomes of adults with OHCA of medical aetiology directly transported by EMS to a PCI-capable hospital (direct transport) with patients transferred to a PCI-capable hospital via another hospital without PCI services available (indirect transport). I used PCI-capability as a surrogate measure for a higher level of post-resuscitation care as that delivered in a cardiac arrest centre. To achieve this objective, I conducted a retrospective cohort study of 509 adults (≥18 years) with OHCA of medical aetiology, attended by SJ-WA paramedics between 2012 and 2015 (4 years), who were transported to one of five PCI-capable hospitals in Perth, WA.[17] The majority of these patients (n=404, 79.4%)

were directly transported to a PCI-capable hospital, and after adjusting for known confounders, these patients were twice as likely to survive to hospital discharge (aOR 1.97, 95% CI 1.13-3.43) when compared to those transferred to a PCI-capable hospital from another hospital.[17] Transport to a PCI-capable hospital also showed a survival benefit in three predefined patient subgroups for: (a) all patients requiring mechanical ventilation (aOR 2.33, 95% CI 1.26-4.28), (b) all patients who had coronary angiography (aOR 2.54, 95% CI 1.20 – 5.40) and (c) all patients who had PCI (aOR 4.37, 95% CI 1.49-12.79).[17] Further, the adjusted hazard ratio for possible increased risk of death up to 12-months was 1.36 (95% CI 1.00 – 1.84), for indirect transport patients.[17]

My study showed significant variability between direct and indirect transport to a PCI capable hospital in the rate of survival to hospital discharge after OHCA.[17] One possible contributing factor is the standard of post resuscitation care available at each site. Addressing clinical variation through the use of standardised evidence-based guidelines and protocols is critical to the delivery of high quality patient care.[162] This is likely to be best achieved through a multi-disciplinary approach in a tertiary hospital. While there is no universal definition of what constitutes the minimum requirements for post resuscitation care in a tertiary hospital,[51] a recent expert consensus paper recommended that a cardiac arrest centre should provide access to an ED, ICU, 24/7 coronary angiography and medical imaging.[163] Despite growing evidence to suggest that post-resuscitation care at a cardiac arrest centre is associated with improved patient outcomes at hospital discharge,[51] post-ROSC patients in Australia are not routinely admitted to a hospital capable of providing the highest level of post- resuscitation care.[123]

Post-resuscitation care is time critical, complex, and requires rapid and decisive decision making to maximise survival and neurological recovery. There are precedents for direct transport to a tertiary hospital for other critically ill patient groups including those with STEMI.[122] SJ-WA Clinical Practice Guidelines require patients with ST elevation on initial field ECG be directly transported to a PCI-capable hospital with transmission of the ECG to the treating medical team prior to patient

arrival.[105] Studies have also shown improved outcomes for patients with major trauma transported directly to level 1 trauma centres,[164,165] supporting the regionalisation of care into trauma centres and EMS hospital bypass protocols that ensure trauma patients are directly transported to an appropriate trauma facility rather than to the closest hospital.[166]

The central distribution of tertiary hospitals in the Perth metropolitan area means that paramedics may need to bypass secondary hospitals so that OHCA patients can be directly admitted to a hospital capable of providing a full range of post-resuscitation care interventions. This will mean an increase in transport time for some patients. However, a systematic review and meta-analysis investigating the prognostic impact of transport time in adult OHCA patients found that transport time was not associated with hospital survival or neurological outcome at hospital discharge.[167] This would support a policy of direct transport of OHCA patients to cardiac arrest centres even if the initial transport time is increased.

Previous literature has also shown a survival benefit for adult OHCA patients admitted to hospitals with PCI-capabilities. A 2017 United Kingdom pilot trial randomising 40 OHCA patients without ST-elevation to an intervention arm to receive expedited transfer to a cardiac arrest centre or a control arm with delivery to the geographically closest hospital, found that transport of OHCA patients to a cardiac arrest centre led to significantly higher one-month survival rates with favourable neurological outcome.[168] The authors recommended the conduct of a large RCT comparing the delivery of OHCA patients without ST-elevation to a dedicated cardiac arrest centre for post-resuscitation care, compared with standard care based on the safety and feasibility of their pilot study.[168] Whether this treatment effect would remain in other EMS settings is unknown.

Observational studies have also reported increased survival rates with direct transport to a cardiac arrest centre. Two Australian studies found that care at a cardiac arrest centre is associated with survival to hospital discharge[50] and long term survival post hospital discharge[169] in multivariable analyses. These findings are

consistent with six American studies that report care at cardiac arrest centres after OHCA was also associated with increased hospital survival,[49,170-172] good neurological outcome at hospital discharge[49,170,172,173] and long term survival in adjusted analysis.[174] A more recent study comparing patient characteristics and outcomes between adults with OHCA of presumed cardiac aetiology transported to hospitals with or without PCI-capability in New Zealand, found that survival to 30-days was significantly increased in patients conveyed directly to a hospital with PCI-capability.[48] However, not all studies report a survival benefit associated with direct transport to a cardiac arrest centre[175,176] and the reasons for these conflicting findings warrants further investigation.

Research Objective Two: To Conduct a Systematic Review and Meta-Analysis

The second research objective of my thesis was to assess the effect of a low or high $PaCO_2$ on patient outcomes after cardiac arrest (both in-hospital cardiac arrest [IHCA] and OHCA) by systematically reviewing the literature and by combining results from similar studies in meta-analyses.[18] I searched across five electronic databases and article reference lists using predetermined inclusion criteria to retrieve comparative studies investigating the association of $PaCO_2$ and hospital survival or in-hospital mortality after cardiac arrest.[18] Of the 93 studies identified, nine studies[64,68,69,73-76,117,177] were considered eligible for the systematic review and eight studies provided sufficient quantitative data for meta-analysis.[18] In a meta-analysis of six studies[64,69,73-76,177] reporting hospital survival data, I found that normocarbia (35-45 mmHg) was associated with increased hospital survival (OR 1.30, 95% CI 1.23-1.28) when compared to hypo-or hypercarbia.[18] In a meta-analysis of four studies[68,73,76,117] reporting CPC scores, I found that normocarbia was also associated with a good neurological outcome (CPC 1 or 2) when compared to hypercarbia (OR 1.69, 95% CI 1.13-2.51).[18] My finding that $PaCO_2$ has an inverted U-shaped association with hospital survival is in line with the most recent international guidelines[12] that normocarbia be targeted during post resuscitation care.

This systematic review and meta-analysis highlighted a gap in the literature with respect to the optimal $PaCO_2$ targets after OHCA.[18] A literature search failed to

identify any previous similar English language systematic reviews. As such, this meta-analysis was an original piece of research that contributed to the evidence base for post-resuscitation care. I used the PRISMA Checklist[131] to ensure that all essential items for the systematic review were reported (Thesis Appendix D) and registered the protocol in PROSPERO[132] an international prospective register of systematic reviews (Thesis Appendix E). I undertook two sensitivity analyses to determine if the choice of studies included in the meta-analysis resulted in major alterations to the conclusions.[18] The results of these did not have a major impact on the overall conclusions of the study.[18]

The limitations of meta-analyses mean that their conclusions may be superseded by larger multicentre high quality RCTs that are considered the second highest level of evidence (after systematic reviews of RCTs) for evaluation of the effect of clinical interventions.[178] Furthermore, there are many examples of differences in the outcomes estimated in meta-analyses and subsequent large RCTs.[179] Such a RCT, TAME Cardiac Arrest (NCT03114033) is currently underway comparing normocapnia (35-45 mmHg) with mild hypercapnia (50-55 mmHg) during the first 24 hours of ICU admission after cardiac arrest with a recruitment target of 1700 patients.[130]

A recent systematic review and meta-analysis of oxygenation and ventilation targets after cardiac arrest was published in Resuscitation in 2020.[112] This study included seven trials and 36 observational studies comparing oxygenation or ventilation targets.[112] The authors followed the PRISMSA guidelines and registered the meta-analysis on PROSPERO but did not report any sensitivity analyses.[112] A total of 203 patients were included in the meta-analysis of clinical trials but the total number of patients in the meta-analysis of observational studies was not reported.[112] The included studies largely overlapped with those included in my meta-analysis,[18] with the exception of two studies published after the conduct of my systematic review and meta-analysis.[71,146] With respect to $PaCO_2$, the authors concluded point estimates of individual studies generally favoured normocapnia over hypo- or hypercapnia[112] which aligns with the findings of my meta-analysis.[18]

Research Objective Three: The Association of $PaCO_2$ and Survival after OHCA

The third research objective of my thesis was to assess the association between different levels of $PaCO_2$ over the first 24 hours of ICU admission and survival to hospital discharge, neurological outcome at hospital discharge and 12-month survival in adult patients with OHCA of non-traumatic aetiology. To achieve this objective, I conducted a retrospective cohort study[19] of adults (≥18 years) with OHCA of non-traumatic aetiology, attended by SJ-WA paramedics between 2012 and 2017 (6 years), who were transported to one of four tertiary ICUs in Perth, WA and who received mechanical ventilation on arrival. I used a four knot restricted cubic spline function to model the relationship between $PaCO_2$ and patient outcomes.[19] I then inspected the shape of the spline curve to identify optimal $PaCO_2$ cut-points, before performing multivariable logistic regression analysis to generate corresponding odds ratios.[19] After analysing a total of 3769 ABG samples collected during the first 24 hours of ICU admission from 493 patients, I found that the relationship between mean $PaCO_2$ over the first 24 hours and hospital survival was non-linear (inverted U-shape) and the best $PaCO_2$ cut-points to differentiate survival for the hypocapnic, normocapnic and hypercapnic groups was <35 mmHg, 35 to 45 mmHg and >45 mmHg respectively.[19] The highest survival occurred in the normocapnic group with a mean $PaCO_2$ between 35 to 45 mmHg (reference category), compared to those with a mean $PaCO_2$ of <35 mmHg (aOR 0.45, 95% CI 0.24-0.83) or >45 mmHg (aOR 0.45, 95% CI 0.24-0.84).[19] Mean $PaCO_2$ in the first 24 hours of ICU admission was the third most important predictor, explaining 11.7% of the variability in survival to hospital discharge.[19]

Most OHCA patients admitted to ICU for post-resuscitation care are comatose and require mechanical ventilation.[95] As mechanical ventilation affects $PaCO_2$ and cerebral blood flow is in part regulated by $PaCO_2$,[180] it is important to characterise the relationship between cerebral blood flow and changes in $PaCO_2$. In cardiac arrest, cerebral blood flow is partially restored with the onset of CPR.[180] However, it remains well below the approximately 50% of normal flow needed to avoid ischaemic injury and maintain neuronal integrity.[181] If ROSC occurs, cerebral blood flow is restored but this can trigger a reperfusion injury leading to secondary brain injury.[181]

The cellular components of reperfusion injury are complex as is the activation of immunological responses and subsequent tissue inflammation.[181] A low $PaCO_2$ decreases cerebral blood flow owing to cerebral vasoconstriction.[182] This potentially worsens hypoxic ischaemic brain injury.[182] Conversely, a high $PaCO_2$ increases cerebral blood flow by causing vasodilation, which in turn increases the volume of intracranial blood, increasing intracranial pressure and therefore reducing cerebral perfusion pressure (systemic mean arterial pressure minus intracranial pressure).[182]

$PaCO_2$ is determined by metabolic rate and is inversely proportional to minute alveolar ventilation, thus for example, halving alveolar ventilation will double the $PaCO_2$.[135] Manipulation of $PaCO_2$ is relatively easy in mechanically ventilated ICU patients by adjusting tidal volume and respiratory rate.[12] $PaCO_2$ is also affected by changes in metabolic rate and body temperature.[12] Lowering body temperature will reduce CO_2 production but shivering as a possible side effect of the cooling phase of TTM may significantly increase metabolic rate and therefore increase $PaCO_2$.[180] It follows, that careful monitoring of $PaCO_2$ in the post-resuscitation phase is of critical importance. My finding that mean $PaCO_2$ in the first 24 hours of ICU admission is the third most important predictor (after initial shockable rhythm and witnessed arrest) of the variation in survival,[19] highlights the importance of monitoring $PaCO_2$ and adjusting ventilation to maintain $PaCO_2$ in the normal range.

In addition to the TAME Cardiac Arrest trial which remains in the recruitment phase,[130] two smaller multicentre RCTs have evaluated the benefits of mild hypercapnia after OHCA.[66,72] The COMACARE trial (NCT02698917) was designed to assess the feasibility and effect on brain injury markers of targeting low-normal (34-35 mmHg) or high normal (44-45 mmHg) $PaCO_2$ during the first 36 hours after ROSC in comatose mechanically ventilated patients. The authors' primary endpoint was neuron-specific enolase (NSE) concentration which is a widely used biomarker (but not in WA ICUs) for prognostication of neurological outcome after cardiac arrest.[183] This small phase II trial found no significant difference in NSE concentration between the two groups.[72] In the Carbon Control and Cardiac Arrest (CCC; ACTRN12612000690853) trial, patients were randomised to target normocapnia

($PaCO_2$ 35-45 mmHg) or mild hypercapnia ($PaCO_2$ 50-55 mmHg) for the first 24 hours after randomisation into the trial.[66] The primary outcome was NSE and S100b protein concentrations during the first 72 hours in the first 50 patients surviving to day three.[66] Mild hypercapnia was associated with significantly less increase in NSE during the 72 hours of follow-up but S100b protein concentrations did not differ significantly between the groups.[66]

The systematic review and meta-analysis investigating oxygenation and ventilation targets after cardiac arrest[112] identified 15 observational studies comparing the impact of different $PaCO_2$ exposures on patient outcomes published since 2010,[64,68,69,71,76,77,117,138,142,144,146,184-187] but only six studies[68,71,77,117,138,146] were assessed as having less than a critical risk of bias; and only six studies were confined to patients with OHCA.[68,69,71,138,146,185] Other studies included patients with both IHCA and OHCA and one study did not report the location of the cardiac arrest.[64] Considerable heterogeneity also existed in the timing and duration of ABG analysis and study endpoints with the most common being the short term end point of in-hospital mortality.[64,69,76,138,187] Normocapnia was most commonly defined as a $PaCO_2$ of 35 to 45 mmHg, however slight variations to this range were reported. Roberts et al,[117,184] Wang et al.[138] and Von Auenmueller[146] and colleagues defined normocapnia as a $PaCO_2$ of 30 to 50 mmHg. Two other studies[71,144] report normocapnia as between 4.5 to 6 kPa equating to 34 to 45 mmHg. Irrespective of their definition for normocapnia, most researchers applied linear models to investigate the relationship between $PaCO_2$ and patient outcome after cardiac arrest.

Two studies used non-linear modelling to investigate the association between $PaCO_2$ in-hospital mortality[69] and neurological function at hospital discharge in cardiac arrest patients.[77] In the first of these, Helmerhorst et al.[69] used the $PaCO_2$ value associated with the ABG with the lowest PaO_2/FiO_2 ratio. That is, the ABG with the "worst" oxygenation during the first 24 hours of ICU admission collected for the purposes of illness severity scoring.[69] The authors found that $PaCO_2$ had an independent U-shaped relationship with hospital mortality. After adjustment for confounders, hypocapnia was a significant predictor of hospital mortality (OR 1.37,

95% CI 1.17–1.61).[69] In the second study, Hope Kilgannon et al.[77] did not define normocapnia but applied a quadratic function to model the association between mean $PaCO_2$ within six hours after ROSC and estimated the optimal $PaCO_2$ for a mRS ≤3 at hospital discharge as a mean $PaCO_2$ of 68 mmHg.[77] Their modelling showed an inverted U-shaped relationship between mean $PaCO_2$ and neurological outcome at hospital discharge.[77] The optimal $PaCO_2$ of 68 mmHg is notably higher than suggested by other observational studies but the authors do note an interaction with metabolic acidosis, such that the optimal $PaCO_2$ for a good neurological outcome decreased in patients with metabolic acidosis.[77]

My study, addressing the association of $PaCO_2$ and survival after OHCA, also used non-linear modelling, namely a four-knot restricted cubic spline function.[19] This did not force the data into a preconceived relationship between mean $PaCO_2$ and patient outcome and allowed the use of data driven $PaCO_2$ cut-points. A further point of differentiation from other studies is the inclusion of multiple $PaCO_2$ values up to 72 hours after ICU admission, thereby overcoming the limitations associated with single or selected ABG analysis. This is more representative of the $PaCO_2$ exposure during mechanical ventilation in ICU. The fact that this study only included patients with OHCA of non-traumatic aetiology provided a more homogeneous population than studies that include both IHCA and OHCA. The study provides robust evidence, albeit still observational, to support targeting $PaCO_2$ between 35 to 45 mmHg in mechanically ventilated OHCA patients. Until evidence from adequately-powered RCTs is available, high quality observational studies, such as the one included in this thesis[19], provide an underlying basis for guidelines on post resuscitation care ventilation strategies.

Research Objective Four: The Association of PaO_2 and Survival after OHCA

The fourth research objective of my thesis was to assess the association between different levels of PaO_2 over the first 24 hours of ICU admission with survival to hospital discharge in adult OHCA patients. I conducted a retrospective cohort study[20] of adult (≥18 years) patients with OHCA of presumed medical aetiology, attended by SJ-WA paramedics between 2012 and 2017 (6 years) and admitted to one of four ICUs

in Perth WA, with mechanical ventilation. The potential non-linear relationship between PaO_2 and survival was assessed by a four-knot restricted cubic spline function and PaO_2 cut points were chosen.[20] I then performed multivariate logistic regression analysis to assess the association between the mean PaO_2 within the first 24 hours of ICU admission after OHCA and survival to hospital discharge with adjustments for potential confounders.[20] After analysing a total of 3,764 ABG samples collected within the first 24 hours of ICU admission for 491 patients, I found that the relationship between mean PaO_2 and hospital survival was non-linear (inverted U-shape) and the best PaO_2 cut-points to differentiate survival for the normoxaemic, mild to moderate hyperoxaemic and the severe hyperoxaemic groups was <100 mmHg, 100 to 180 mmHg and >180 mmHg respectively.[20] When compared to mild to moderate hyperoxaemia, normoxaemia (aOR 0.50, 95% CI 0.30-0.84) and severe hyperoxaemia (aOR 0.41, 95% CI 0.18-0.92) were associated with a decreased odds of survival to hospital discharge.[20] Mean PaO_2 within 24 hours of ICU admission was the third most important predictor (after initial shockable rhythm and witnessed arrest) and explained 9.1% of the variability in survival to hospital discharge.[20] (Note: Both $PaCO_2$ and PaO_2 were the third most important predictors of survival to hospital discharge in the studies assessing the association between $PaCO_2$[19] and PaO_2[20] and survival after OHCA respectively. PaO_2 was the fifth most important predictor of survival explaining 5.2% of the variation in survival in the PaCO2 study.[19] $PaCO_2$ was not included as a confounder for adjustment in the PaO_2 study, because at the time the study was designed the outcomes from the $PaCO_2$ study were unknown).[20]

After ROSC, both cerebral oxygen consumption and the cerebral oxygen extraction fraction are decreased for 24 to 72 hours, implying that the physiological coupling between cerebral blood flow and cerebral requirement is maintained.[188,189] However, brain tissue hypoxia, defined as a brain tissue oxygen tension <20 mmHg, has been observed in about half of all comatose patients after ROSC during the period of 13 to 40 hours after cardiac arrest.[190,191] These studies used an intra-parenchymal micro catheter to measure parenchymal brain tissue oxygen tension.[190,191] Furthermore, the patients with brain tissue hypoxia had increased release of biomarkers of neuronal injury in jugular venous blood,[191] thus there is evidence that

hypoxaemia is detrimental after ROSC. Conversely, hyperoxaemia can cause harm through the increased production of free oxygen radicals which have been shown to worsen neurological injury in experimental studies.[192] In other experimental models, ventilation with 100% oxygen after cardiac arrest resulted in both worse neurological deficit scores and greater histological evidence of neurological damage.[192]

A recent systematic review and meta-analysis by Holmberg et al.[112] on behalf of ILCOR, identified seven trials and 30 observational studies related to oxygenation and ventilation targets after adult cardiac arrest. The seven trials [66,151,193-196] published between 2006 and 2019 involved between 17 and 166 subjects.[112] Six trials[72,151,193-196] compared oxygen targets only but only three of these were after admission to the ICU,[72,151,196] with three being in the pre-hospital setting;[193-195] one study spanned both settings.[151] The meta-analysis for the comparison of low oxygen to high oxygen targets in the prehospital setting, included two RCTs[193,194] and found a risk ratio of 0.97 (95% CI 0.68-1.37), which is a non-significant finding.

Each of the three RCTs[72,151,196] that included the ICU stay had less than 100 survivors in both arms.[112] Of the two trials[72,196] investigating oxygen strategies in the ICU only, one of the trials comparing normoxaemia to moderate hyperoxaemia found no difference in hospital survival (Relative Risk [RR] 1.07, 95% CI 0.84-1.36) or hospital survival with a favourable neurological outcome at six months (RR 1.13, 95% CI 0.87-1.47).[72] Another small trial with only 17 subjects also found no benefit from lower oxygen concentrations on survival (RR 1.13, 95% CI 0.41-3.08) or discharge home (RR 0.56, 95% CI 0.14-2.29), albeit with wide confidence limits.[151] A third investigation was a subgroup analysis of 164 patients from a larger cardiac arrest trial[196] that reported increased survival at 90 days in patients where hyperoxaemia was aggressively avoided (RR 1.39, 95% CI 1.01-1.92) but there was no benefit in terms of survival to 6 months with a favourable neurological outcome (RR 1.4, 95% CI 0.93-2.13).[196]

The observational studies included in the Homberg et al.[112] systematic review examining the association between PaO_2 and patient outcomes after cardiac arrest

are generally of poor quality; with only ten studies being assessed as having less than a critical risk of bias, and in all of these studies the risk was assessed as 'serious'. The results from ten observational studies[68,86,138,142-148] (rated as having less than a critical risk of bias) were inconsistent in terms of the relationship between hyperoxaemia and patient outcome after cardiac arrest. In four studies, hyperoxaemia was associated with lower survival to hospital discharge and/or less favourable neurological outcome.[86,138,147,148] In the other six studies there was no association between hyperoxaemia and patient outcomes.[68,142-146] One study also found an association between hypoxaemia and worse patient outcomes.[138]

Overall, eleven of the observational studies defined the upper limit of normoxaemia as approximately 300 mmHg,[69,78,79,138,141,143,145-147,149,197]; which is well above the 180 mmHg identified in my study as being the PaO_2 above which patient outcomes deteriorated.[20] Other studies used a wide variety of upper limits for PaO_2 or oxygen saturation to define hyperoxaemia.[112] Ten studies defined hypoxia as a PaO_2 of <60 mmHg, [69,79,85,138,141,143-146,148] which is well below the PaO_2 cut-point of 100 mmHg associated with worse patient outcomes in my study.[20]

Most observational studies included in the Holmberg et al.[112] systematic review report survival to hospital discharge, in-hospital mortality or mortality at 28 to 30 days, with the exceptions being Javaudin et al.[198] (CPC 3 to 5 at 30 days), Ebner et al.[143] (CPC 1 to 2 at six months), Vaahersalo et al.[68] (CPC 1 to 2 at one year), Von Auenmueller et al. (mortality at 5 days) and Humaloja et al.[144] (mortality at one year) demonstrating significant heterogeneity in reported outcome measures. I reported survival to hospital discharge, survival to hospital discharge with a good neurological outcome (CPC 1 or 2) and 12-month survival[20] providing a mix of short and longer term outcomes for comparison with other studies.

Other sources of heterogeneity in the observational studies included in this systematic review[112] include ABG sampling times which ranged from first[78,85] to worst[69,79,141] to selected[145] to all ABGs[86,138,149] within specified time points. My study included all PaO_2 measurements within the first 72 hours of ICU admission, providing

a longer time frame for the mean PaO_2 to which patients were exposed. Only Nelskyla and colleagues[149] used $PaCO_2$ values from the first 72 hours of ICU admission, finding there were no statistically significant difference in the number of patients discharged from the hospital and thirty day survival between patients exposed to hyperoxaemia (>300 mmHg) and those not exposed. This study used a linear model, as have all others with the exception of Helmerhorst and collegues,[69] to assess the relationship between PaO_2 and patient outcomes after cardiac arrest. While I also found no significant relationship between mean PaO_2 and patient outcomes using a linear model in my study, when the data was analysed using a 4 knot restricted cubic spline function, there was an inverted U-shaped relationship between PaO_2 and patient outcomes.[20] This is similar to the findings of Helmerhorst et al.[69] who reported a U-shaped relationship between PaO_2 and in-hospital mortality. In this study, after adjustment for confounders, hypoxia (PaO_2 <60 mmHg) was a significant predictor of hospital mortality after OHCA (OR 1.34, 95% CI 1.08–1.66).[69] However, this study used only a single PaO_2 measurement, namely that associated with the lowest PaO_2/FiO_2 ratio within the first 24 hours of ICU admission.[69]

My study, was confined to adults with OHCA of presumed medical aetiology, included all PaO_2 results over the first 72 hours of ICU admission, reported both short and long term patient outcomes and used non-linear modelling instead of forcing the data to fit into a linear relationship which may be non-physiological.[20] While other publications have featured one or two of these characteristics, this is the only OHCA publication to date to feature them all.

Research Objective Five: Neurological Outcome at Hospital Discharge and Survival to 12-months

My final research objective was to describe neurological and functional outcomes among OHCA patients who survived to hospital discharge and to determine the association between neurological outcome at hospital discharge and 12-month survival. To achieve this objective, I conducted a multicentre retrospective cohort study of adult OHCA patients (≥18 years) attended by SJ-WA paramedics in metropolitan Perth who survived to hospital discharge between 1st January 2004 and

31st December 2019 (16 years).[21] Neurological and functional status at hospital discharge (and before the arrest) was determined by CPC and OPC scores, through medical record review.[21] Using multivariable logistic regression analysis to estimate the adjusted association between CPC score at hospital discharge and 12-month survival, I found that while overall survival after OHCA remains low, most of those surviving had a good neurological outcome (CPC 1 or 2) at hospital discharge.[21] Of the hospital survivors, the scores were: CPC1 n=757/1062 (71.3%), CPC2 n=227/1062 (21.4%), CPC3 n=67/1062 (6.3%) and CPC4 n=11/1062 (1.0%).[21] OPC scores followed a similar distribution.[21] Of the patients with a CPC 1 or 2 at hospital discharge, 938 (93.7%) were alive at 12-months.[21] A good CPC score at hospital discharge (CPC1-2) was significantly associated with 12-month survival (aOR 3.28, 95% CI 1.69-6.39).[21]

Analysis of data from large OHCA registries and clinical trials show that approximately 80% of patients who survive to hospital discharge do so with a good neurological recovery as defined by a CPC score of 1 or 2.[26,155,199] This compares with 92.7% of survivors to hospital discharge with a CPC of 1 or 2 in my study described above.[21] The high proportion of survivors with good neurological outcome may reflect Australian medical practice in withdrawal of life sustaining treatment in ICU patients who do not show signs of neurological recovery after OHCA.[200] It has been stated that achieving an adequate quality of life is the ultimate goal of resuscitation.[180] However, clinician reported measures of neurological and functional outcome do not necessarily correlate with self-perceived quality of life.[180] Patients with CPC score of 1, generally have similar health related quality of life to comparable health populations,[201] but patients with a CPC score of 2 may be significantly impaired when assessed by health related quality of life measures.[202] The Health Utilities Index (version III), the Short-Form 36-Item Health Survey and the EuroQol EQ-5D_5L are recommended to assess quality of life after cardiac arrest.[94] Individual patient follow-up to complete one or more of these questionnaires is time consuming and prone to loss to follow-up[203] and did not form part of the methods for this thesis. The challenges of longer term follow-up of ICU patients has been reported elsewhere.[204] I therefore restricted this study to the ascertainment of CPC and OPC at hospital

discharge (through medical record review) and 12-month survival as determined by death registry data, with minimal loss to follow-up.

9.3 Research Findings in the Context of International Resuscitation Guidelines

The results of my research are consistent with international guideline recommendations,[12] with the exception of optimal oxygenation targets as discussed below. The European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) algorithm for post-resuscitation care has recently been updated to incorporate resuscitation science that has been published since 2015.[12] The ERC–ESICM guidelines on adult post-resuscitation care are based on ILCOR's Consensus on Science Treatment Recommendations (CoSTR).[12] Of the recommendations included in this document, those most relevant to my research relate to the transport of OHCA patients to a cardiac arrest centre, control of oxygenation and ventilation through measurement of PCO_2 and PaO_2, and the reporting of short and long-term outcomes. These are discussed further below.

Cardiac Arrest Centres

ERC–ESICM guidelines recommend transport of adult OHCA patients with presumed non-traumatic aetiology to a cardiac arrest centre in accordance with local transport protocols.[12] Cardiac arrest centres are hospitals capable of providing a high level of post resuscitation care including emergency interventional cardiology, protocolised cardiorespiratory support, targeted management of body temperature and prognostication.[12] This recommendation is based on very-low-certainty evidence from a meta-analysis of 17 observational studies that found patients cared for at cardiac arrest centres had improved survival to hospital discharge with a favourable neurological outcome (OR 2.22, 95% CI 1.74–2.84) and improved survival to hospital discharge (OR 1.85, 95% CI 1.46–2.34).[51] This recommendation is consistent with the results of my study investigating the association between EMS transport destination and survival after OHCA, which found higher adjusted hospital survival for patients directly transported to a PCI-capable hospital when compared to patients indirectly

transferred to a PCI-capable hospital via another hospital.[17] My study was included in the meta-analysis used to inform this guideline recommendation.[51]

Control of Ventilation

ERC–ESICM guidelines recommend that patients requiring mechanical ventilation after ROSC, receive lung protective ventilation with a tidal volume of 6-8 mL/kg of ideal body weight.[12] Ventilation should be adjusted to achieve a target $PaCO_2$ of 35 to 45 mmHg, monitored via end tidal CO_2 values and ABG analysis. Patients receiving TTM to achieve a lower body temperature should have $PaCO_2$ measured frequently due to the increased risk of hypocarbia.[12] This recommendation is based on an ILCOR systematic review and meta-analysis that found point estimates of individual studies favoured normocapnia compared to hypo or hypercapnia in the critical post-ROSC phase.[112] My findings that normocapnia within the first 24 hours of ICU admission after OHCA is associated with improved survival compared to patients with hypocapnia or hypercapnia is consistent with these guideline recommendations.[19]

Control of Oxygenation

ERC–ESICM guidelines recommend that post-ROSC, patients receive 100% inspired oxygen (or maximum available) until the arterial oxygen saturation or the PaO_2 can be measured.[12] When arterial oxygen saturation or ABG measurements are available, FiO_2 should be titrated to achieve a PaO_2 of 75 to 100 mmHg. Hypoxaemia (PaO_2 <60 mmHg) and hyperoxaemia (>100mmHg) should be avoided.[12] The upper boundary for PaO_2 recommended by the ERC-ESICM guidelines[12] and the lower boundary identified by the cut-point in my study assessing the association of PaO_2 and survival after OHCA coincide at 100 mmHg.[20] Complying with these guidelines would suggest that the range of 100 to 180 mmHg that I identified as cut-points for optimal patient outcomes should be avoided. Visual inspection of Figure 2 (Mean PaO_2 within the first 24 hours of ICU admission and log odds of survival to hospital discharge) in my study assessing the association of PaO_2 and survival after OHCA,[20] would suggest that a PaO_2 <100 mmHg is associated with a significant decrease in hospital survival as the mean PaO_2 approaches the 75 mmHg lower limit recommended by the ERC–ESICM

guidelines.[12] A number of reasons may explain the discrepancy between my finding and the international guideline recommendations. These are discussed below.

The ERC–ESICM guidelines oxygenation targets were informed by the Holmberg et al.[112] 2020 systematic review and meta-analysis of oxygenation and ventilation targets after cardiac arrest. Only four RCTs without a high risk of bias were included in the systematic review and two in the meta-analysis. The two RCTs included in the meta-analysis had a total of 89 patients and reported survival to hospital discharge.[193,194] The authors compared 100% oxygen to a lesser FiO_2 titrated using a pulse oximeter in the prehospital setting with there being no significant association between low oxygen therapy and survival to hospital discharge (RR 0.97, 95% CI 0.68–1.37).[112]

Of the two small RCTs included in the systematic review[151,195] but not the meta-analysis, the first targeted an oxygen saturation of 90-94% in the intervention group in both the prehospital setting and during the first 72 hours of ICU admission or extubation if this occurred first.[151] The authors concluded that targeting an oxygen saturation of 90 to 94% in the pre-hospital setting was not feasible and may potentially expose patients to inadvertent hypoxaemia.[151] The primary outcome of discharge to home did not significantly differ between the intervention and control groups (RR 0.56, 95% CI 0.14–2.29). The second study[195] was a cluster randomised feasibility study that enrolled only 35 patients. Control patients received 100% oxygen and in the intervention group an oxygen saturation of 94 to 98% was targeted for one hour after ROSC.[195] While the authors report a higher chance of survival in patients receiving low oxygen therapy (RR 3.15, 95% CI 1.04–9.52) with a very wide confidence interval, they also acknowledge the limitations of the study including that it was un-blinded and that the paramedics enrolled for the intervention arm were subject to selection bias.[195] Thus, the evidence from existing small RCTs to support the current ERC–ESICM guidelines is weak and does not exclude the possibility that optimal patient outcomes are associated with a PaO_2 of 100 to 180 mmHg during the first 24 to 72 hours of admission to an ICU after OHCA.

The second reason that may explain the discrepancy between my findings and the international guideline recommendations is that a low PaO_2 may have been a surrogate marker of illness severity.[20] This is an inevitable limitation of observational studies in which the finding of association should not imply causality. This is acknowledged as an important limitation in my study assessing the association between PaO_2 and Survival after OHCA.[20]

The third reason is that the oxygenation targets in the current ERC–ESICM guidelines were not updated in 2015[205] and have not been updated since 2010.[206] The ILCOR systematic review and meta-analysis concluded that a large number of studies related to oxygenation targets did not reach statistical significance and were limited by an excessive risk of bias.[112] While point estimates of individual studies generally favoured normoxemia as variously defined by the authors, the overall level of evidence is low.[112]

Outcome measures

ERC–ESICM guidelines recommend that assessments of physical and non-physical capability are performed before hospital discharge in order to identify any requirement for patient rehabilitation.[12] Other recommendations are to organise three month follow-up of hospital survivors to screen for cognitive and emotional problems and fatigue and to provide information and support to patients and family members.[12] These guidelines refer to suggested follow up at 3, 6 and 12 months and to limitations in usual activities at 12-months.[12] However, they do not refer specifically to OPC scores as a functional outcome measure at hospital discharge or longer.[12]

The most common summary measure of neurological and functional outcome after OHCA is the CPC score.[12,93] While ILCOR recommends the use of mRS rather than CPC scores, as the mRS is better at discriminating between mild and moderate disability[90,207] and has substantial interrater reliability,[208] it is acknowledged that most studies on neurological outcome after cardiac arrest use CPC scores.[12] I used CPC scores to define neurological outcome at hospital discharge in each of the four

observational studies included in this thesis.[17,19-21] I also used OPC scores at hospital discharge to differentiate between neurological and functional outcome in my fifth paper assessing the association between neurological outcome at hospital discharge and survival to 12-months.[21] I preferentially selected CPC and OPC scores as this information has been routinely collected for the SJ-WA OHCA Database since 2004. This database is one of four data sources used to inform the research included in this thesis.

The current ERC–ESICM guidelines note that in countries where the withdrawal of life sustaining treatment is uncommon, the longer term prognosis for patients who are still comatose one month after cardiac arrest is poor.[12] In high income countries such as Australia, where withdrawal of life sustaining treatment in ICU is relatively common[200] (after prognostication and discussion with family), the majority of survivors are defined as having a 'good' neurological outcome based on global outcome measures such as the mRS and CPC.[12] In my study assessing neurological outcome at hospital discharge and survival to 12-months, I found that 92.7% of hospital survivors had a CPC score of 1 or 2 at hospital discharge and this was significantly associated with longer term 12-month survival.[21] Revisions of the ERC–ESICM guidelines could usefully include additional preferred outcome measures in order to promote standardised reporting of neurological and functional outcomes and long term survival after cardiac arrest.

9.4 Strengths and Limitations

Strengths

There are seven main strengths to my research. First, I conducted four multicentre population-based retrospective cohort studies investigating in-hospital prognostic determinants after OHCA. These studies were informed by pre-hospital and in-hospital factors that have previously been found to affect patient outcomes in this subpopulation of critically ill adults. In Australia, there are few multicentre population-based studies that describe the prehospital and in-hospital management of OHCA patients; and that assess the association between post-resuscitation care factors, neurological outcome at hospital discharge and 12-month survival.

Second, each retrospective cohort study was conducted using high quality prospectively collected data from the SJ-WA OHCA Database as well as three other reliable data sources; the WA Registry of Births, Deaths and Marriages, PathWest Laboratory Medicine WA and medical chart review. The SJ-WA OHCA Database operates under rigorous data collection and reconciliation processes that are closely monitored and include manual checking of each case. Hospital survival and neurological outcomes at hospital discharge were determined by myself, through a detailed review of emergency department and inpatient medical records. Assessment of inter-rate reliability was conducted on a regular basis to determine the level of agreement between myself and another experienced research nurse data collector. A defined database was developed *a priori* to record pre-determined data points. Long term patient survival outcomes were ascertained by checking against death records from the WA State Registry of Births, Deaths and Marriages.

Third, important methodological limitations identified in previous studies were addressed through the use of rigorous analytical and statistical techniques. For example, I used a restricted cubic spline function in two studies[19,20] to test the hypothesis that the relationship between $PaCO_2$ and PaO_2 is non-linear, before modelling the data in a regression model. I did not force the data to fit a linear regression model when testing suggested the relationship between the exposure and patient outcome was non-linear (inverted U-shaped).[19,20]

Fourth, In the same two studies[19,20], my extensive dataset of consecutive ABG values (up to 72 hours of ICU admission), enabled me to overcome issues associated with ABG sampling times and increased the likelihood that my results were more representative of the true exposure to $PaCO_2$ and PaO_2 during the critical post-ROSC period.

Fifth, my study investigating the association between neurological outcome at hospital discharge and survival to 12-months,[21] is one of few that have assessed the relationship between CPC score at hospital discharge and survival in a large

multicentre cohort. This study was also informed by a large comprehensive data set with neurological and functional outcomes at hospital discharge measured over 16 years.

Sixth, the long-term patient outcomes (survival to 12-months) included in each study are arguably more patient-centred than survival to hospital discharge or 30-days after OHCA. It is probable that most patients will view a reasonable life expectancy as an appropriate trade-off for the burden of intensive care treatment.

Finally, I received patient $PaCO_2$ and outcome data from four authors[68,73,75,76] whose studies were included in my systematic review[18] and meta-analysis and who only reported aggregate data in their respective reviews. This meant that the results of my meta-analyses were informed by individual patient level data from seven out of eight included studies. This allowed me to better assess the non-linear relationship between $PaCO_2$ and patient outcomes and pool these results in meta-analyses.

Limitations

I acknowledge that my research has potential limitations. These are discussed below.

First, in addition to the fact that causality cannot be definitively established through a cohort study, the findings of each study may have been confounded by the severity of patient illness, resulting in a biased estimate of the effect of the exposure on patient outcome. In the study investigating the association between $PaCO_2$ and patient outcomes,[19] patients with abnormal $PaCO_2$ levels may have had a greater severity of illness leading to the association with increased in-hospital mortality. Similarly, in the study investigating the association between PaO_2 and patient outcomes,[20] patients with more severe illness may have received a higher FiO_2 resulting in worse outcomes because of their illness severity and not their exposure to oxygen. In both of these studies, outcomes were adjusted for use of inotropic medications as a surrogate marker for illness severity. It is possible that the use of a recognised measure of illness severity in intensive care patients such as the Acute Physiology and Chronic Health Evaluation (APACHE II) score[209] may have provided a more robust adjustment for

illness severity, but this was not assessed. However, in the absence of results from large RCTs, well controlled observational studies such as those included in this thesis, provide the best available indication of a possible causal relationship between an exposure and patient outcome.

Second, owing to the non-randomised study design of the included studies, I cannot exclude the possibility that my results might be confounded by other unmeasured factors. For example, in the study investigating the association between EMS transport destination and survival after OHCA,[17] paramedics may have been biased in their choice of initial destination hospital. It is also possible that clinicians at the initial destination hospital were biased in their decision to transfer a patient to a PCI-capable hospital. To examine clinical decision making as a possible source of bias in this study, I compared demographic and OHCA characteristics of all patients admitted to a PCI-capable hospital by transport group and identified significant differences. I then adjusted for these variables in multivariable logistic regression analysis.

Third, the extent to which the research findings and conclusions of each cohort study included in this thesis are applicable to other settings is unknown. As the inclusion criteria for each study was restricted to adult patients who had an OHCA in the Perth metropolitan area, these results may not be generalisable to non-metropolitan areas of WA. This is because the medical services available outside the metropolitan area (perhaps with the exception of Bunbury) are limited as a result of highly dispersed population over 2.5 million square kilometres. The findings may also not be generalisable to other Australian capital cities. However, the ICUs involved in the studies included in this thesis have been submitting their patient data to the ANZICS Centre for Outcome and Resource Evaluation (ANZICS CORE Registries)[210] regularly and the patient characteristics, outcomes and the standardised mortality ratios are found to be similar to ICUs in other parts of Australia as well as in New Zealand.[210] While my findings may not be generalisable to other countries due to differences in EMS systems and hospital and health services, most are consistent with international (ERC–ESICM) guideline recommendations.

Fourth, in my final study investigating the association between neurological outcome at hospital discharge and 12-month survival,[21] I included adult OHCA patients admitted to any of 11/11 (100%) Perth hospitals with an ED accepting adult OHCA patients in Perth over 16 years. Given the number of admitting hospitals and the extended data period, I was unable to fully account for changes in post-resuscitation care that may have impacted upon patient outcomes. I addressed this issue by dividing the cohort into four year epochs and including these as a covariate in multivariable logistic regression analysis.

Finally, with respect to my systematic review and meta-analysis,[18] I could not draw definitive conclusions on the optimal $PaCO_2$ level that clinicians should target after cardiac arrest. All studies included in the meta-analysis were observational in nature and subject to the fundamental limitations inherent in the study design resulting in an inability to attribute causation. The majority of the patients included in the review were from a single study[64] and this may have influenced my findings that patients with normocarbia are more likely to survive to hospital discharge as compared to patients with hypercarbia. Further, significant heterogeneity existed within and between the included studies, including country of origin, location of cardiac arrest (IHCA versus OHCA), the use of TTM and the timing, frequency and selection of ABG results.

Acknowledging the limitations of the studies included in my thesis, I have translated the main findings of my research into a set of final recommendations for policy, practice and research. These are outlined below.

9.5 Recommendations for Policy, Practice and Research

The following policy, practice and research recommendations are provided on the basis of my doctoral research.

Policy and Practice

- For adult patients with OHCA of presumed medical aetiology, local EMS should consider direct transport of the patient to a PCI-capable hospital, bypassing closer EDs, when safe to do so.
- WA Department of Health consider regionalisation of care into cardiac arrest centres with clinical services that include targeted management of body temperature (fever avoidance), oxygenation and ventilation management strategies, a 24/7 percutaneous coronary intervention service and a multimodal neuro-prognostication diagnostic service.
- For adult OHCA patients admitted to ICU with mechanical ventilation, $PaCO_2$ should be maintained at 35 to 45 mmHg for at least the first 72 hours of ICU admission.
- For adult OHCA patients admitted to ICU with mechanical ventilation, PaO_2 should be maintained at 100 to 180 mmHg for at least the first 72 hours of ICU admission.
- Clinicians should be aware that the neurological and functional outcomes of adult OHCA patients who survive to hospital discharge are good. Further, a good neurological outcome at hospital discharge is significantly associated with survival to 12-months. This information should help inform clinical decision making.
- Longer-term survival and neurological outcomes (such as 30 days and 12-months) should be incorporated into routine reporting by OHCA registries.

Research

- Investigate the implementation of a post-resuscitation bundle of care for OHCA patients who cannot access a PCI-capable hospital in a timely way (e.g. rural patients) and determine the effect on patient outcomes.
- A large prospective study with pre-determined ABG sampling times over the first 72 hours would provide additional and stronger evidence (by reducing heterogeneity in sampling times) to support the non-linear association between ABG tensions ($PaCO_2$ and PaO_2) and patient outcomes.

- In the absence of data from large RCTs, conduct a prospective observational study that assumes a non-linear relationship between ABG tensions ($PaCO_2$ and PaO_2) and survival and neurological outcome after OHCA.
- Undertake RCTs of different $PaCO_2$ and PaO_2 targets within the normal range with end-points that include patient-centred outcomes such as quality of life and functional outcomes 12-months after OHCA.
- Conduct a prospective observational study investigating the relationship between neurological function and quality of life measures at predetermined points after hospital discharge following OHCA, for example 3, 6 and 12-months.

9.6 Concluding Remarks

The evidence is clear, strengthening each link in the OHCA Chain of Survival improves patient outcomes and saves lives. The overall aim of this thesis was to strengthen the evidence for elements of the post-resuscitation care link in the chain of survival by exploring the effect of in-hospital factors on patient survival and neurological outcome after OHCA. I found that the initial destination hospital and oxygenation and ventilation targets are potentially modifiable post-resuscitation care factors that were associated with survival and neurological outcomes after OHCA. I also found that most hospital survivors have a good neurological outcome at hospital discharge and are alive at 12-months, supporting the need for careful prognostic decision making after OHCA. My findings support treatment recommendations in international guidelines and have important clinical implications. They will also help to inform future clinical trials. RCTs are now needed to provide higher level evidence of the effect of in-hospital factors on patient outcomes. These include RCTs investigating different PaO_2 and $PaCO_2$ targets within the normal range with end-points that include patient-centred outcomes. Population-based studies that describe neurological and functional outcomes after OHCA and that examine the association between survival and neurological outcome are required to minimise errors in prognostic decision-making. This program of research has highlighted the

importance of post-resuscitation care on patient outcomes and extends current understanding. Given the high rates of OHCA and low survival, small gains are large.

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Appendices

Appendix A Research Ethics Approval

Curtin University

Research Office at Curtin

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863
Facsimile +61 8 9266 3793
Web research.curtin.edu.au

17-Jun-2021

Name: Judith Finn
Department/School: Curtin School of Nursing
Email: Judith.Finn@curtin.edu.au

Dear Judith Finn

RE: Reciprocal ethics approval
Approval number: HRE2021-0347

Thank you for your application submitted to the Human Research Ethics Office for the project RECIPROCAL - (OHCA) Functional status of survivors of out-of-hospital cardiac arrest in Perth Western Australia.

Your application has been approved by the Curtin University Human Research Ethics Committee (HREC) through a reciprocal approval process with the lead HREC.

The lead HREC for this project has been identified as St John of God Health Care Human Research Ethics Committee.

Approval number from the lead HREC is noted as 1209.

The Curtin University Human Research Ethics Office approval number for this project is **HRE2021-0347**. Please use this number in all correspondence with the Curtin University Ethics Office regarding this project.

Approval is granted for the period **17-Jun-2021** to **10-Feb-2026**. Continuation of approval will be granted on an annual basis following submission of an annual report.

Personnel authorised to work on this project:

Name	Role
Finn, Judith	
Morgan, Alani	Co-Inv
McKenzie, Nicole	Co-Inv
Finn, Lyndall	Co-Inv

You must comply with the lead HREC's reporting requirements and conditions of approval. You must also:

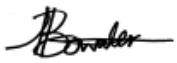
- Keep the Curtin University Ethics Office informed of submissions to the lead HREC, and of the review outcomes for those submissions
- Conduct your research according to the approved proposal
- Report to the lead HREC anything that might warrant review of the ethics approval for the project
- Submit an annual progress report to the Curtin University Ethics Office on or before the anniversary of approval, and a completion report on completion of the project. These can be the same reports submitted to the lead HREC.
- Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
- Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project
- Data and primary materials must be managed in accordance with the Western Australian University Sector Disposal Authority

(WAUSDA) and the Curtin University Research Data and Primary Materials policy
- Where practicable, results of the research should be made available to the research participants in a timely and clear manner
- The Curtin University Ethics Office may conduct audits on a portion of approved projects.

This letter constitutes ethical approval only. This project may not proceed until you have met all of the Curtin University research governance requirements.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely



Amy Bowater
Ethics, Team Lead

Curtin University

Research Office at Curtin

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863
Facsimile +61 8 9266 3793
Web research.curtin.edu.au

21-May-2019

Name: Judith Finn
Department/School: School of Nursing, Midwifery and Paramedicine
Email: Judith.Finn@curtin.edu.au

Dear Judith Finn

RE: Amendment approval
Approval number: HR199/2014

Thank you for submitting an amendment request to the Human Research Ethics Office for the project **Functional status of survivors of out-of-hospital cardiac arrest in Perth, Western Australia**.

Your amendment request has been reviewed and the review outcome is: **Approved**

The amendment approval number is HR199/2014-12 approved on 21-May-2019.

The following amendments were approved:

The Curtin PhD student (Nicole McKenzie) project 'Post-resuscitation care following out-of-hospital cardiac arrest: identification of in-hospital prognostic determinants' received approval to collect data on post-resuscitation management from hospital medical records, including blood gas data from Path West from 2012-2015 (Amendment numbers HR199/2014/AR1 16-Jun-2015 and HR199/2014/AR2, approval date 14-Jul-2015).

Approval has been granted to extend the data collection from hospital medical records and Path West to include data to 31-Dec-2017 for the PhD project.

Any special conditions noted in the original approval letter still apply.

Standard conditions of approval

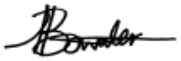
1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
   - proposed changes to the approved proposal or conduct of the study
   - unanticipated problems that might affect continued ethical acceptability of the project
   - major deviations from the approved proposal and/or regulatory guidelines
   - serious adverse events
3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)
4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project
7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority

(WAUSDA) and the Curtin University Research Data and Primary Materials policy

9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Ethics approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements
12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely



Amy Bowater
Ethics, Team Lead

Government of **Western Australia**
North Metropolitan Health Service
Sir Charles Gairdner Osborne Park Health Care Group

Sir Charles Gairdner Hospital

18 April 2019

Professor Judith Finn
Curtin University
Kent Street
Bentley Western Australia 6102

Dear Professor Finn,

PRN: RGS0000001631
Migrated ID: 2012-184
Project Title: Functional status of survivors of out-of-hospital cardiac arrest in Perth Western Australia.

Thank you for submitting the Amendment Form for the above project. This submission was reviewed and approved on behalf of the HREC on 18 April 2019.
The expiry of your HREC approval is 25 March 2024.

As the Delegate of the Chair I have been designated the authority to acknowledge amendments in accordance with the *Standard Operating Procedures 2016* and the *HREC Terms of Reference* both of which are available on the HREC's website. The submission will be tabled for information at the next HREC meeting on 23 May 2019.

This letter approves the following documentation or information:

Document	Version	Version Date
Change to Project Personnel: Ms Shelley Cheetham resigned from PRECRU at Curtin Uni in Feb 2019. Ms Alani Morgan is the new research officer employed in PRECRU at Curtin Uni and will be the CPI delegate for this project.		

As the CPI you are required to ensure that the project is conducted at all sites under the conditions of approval that accompanied the initial approval of this project.
The next progress report for this project is due 25 March 2020.

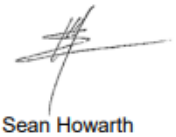
Post migration, please review the study title within RGS to ensure the title is accurate in description and has been documented in full.

This letter constitutes ethical approval only. Please ensure a copy of your submission is made to the SCGOPHCG Research Governance Office for their continuing Institutional Approval.
If this project is conducted at multiple sites utilising this HREC's approval, a copy of this letter must be made available to all site PIs to obtain Institutional authorisation from their site.

Should you require further information, please contact the HREC Office on 08 6457 2999 or SCGH.HREC@health.wa.gov.au. To find the original letter and any possible attachments, click here when logged into RGS.

Sir Charles Gairdner and Osborne Park Health Care Group Human Research Ethics Committee,
Level 2 A Block, Hospital Ave, Nedlands, WA 6009
Telephone (08) 6457 2999 Fax (08) 6457 3307 ABN: 61 282 636 952
Email HREC.SCGH@health.wa.gov.au Website www.scgh.health.wa.gov.au

Yours sincerely,



Sean Howarth
Delegate of the Chair
Sir Charles Gairdner and Osborne Park Health Care Group
Human Research Ethics Committee
18/04/2019 12:39

Curtin University

Office of Research and Development

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Perth Western Australia 6845

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Web research.curtin.edu.au

15-Oct-2018

Name: Judith Finn
Department/School: School of Nursing, Midwifery and Paramedicine
Email: Judith.Finn@curtin.edu.au

Dear Judith Finn

RE: Annual report acknowledgment
Approval number: HR199/2014

Thank you for submitting an annual report to the Human Research Ethics Office for the project **Functional status of survivors of out-of-hospital cardiac arrest in Perth, Western Australia.**.

The Human Research Ethics Office acknowledges the project is ongoing and approval will remain current until 21-Oct-2019.

Any special conditions noted in the original approval letter still apply.

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
   - proposed changes to the approved proposal or conduct of the study
   - unanticipated problems that might affect continued ethical acceptability of the project
   - major deviations from the HREC approved protocol procedures and/or regulatory guidelines
   - serious adverse events
3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)
4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project
7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy
9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Ethics approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures

and governance requirements

12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely

Catherine Gangell
Manager, Research Integrity

MEMORANDUM

Curtin University

To:	Professor Judith Finn Nursing & Midwifery
CC:	
From	Prof Peter O'Leary, Chair HREC
Subject	Amendment approval Approval number: HR199/2014
Date	14-Jul-15

Office of Research and Development
Human Research Ethics Office

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

Thank you for submitting an amendment to the Human Research Ethics Office for the project:

HR199/2014 Functional status of survivors of out-of-hospital cardiac arrest in Perth, Western Australia.

The Human Research Ethics Office approves the amendment to the project.

Amendment number: HR199/2014/AR2

Approval date: 14-Jul-15

The following amendments were approved:

The PhD student project 'Post-resuscitation care following out-of-hospital cardiac arrest: identification of in-hospital prognostic determinants' will examine post-resuscitation management of OHCA patients in Perth, Western Australia.
In addition to the data already collected for study HR199/2014, researchers will be collecting data on post-resuscitation management. This will include routinely collected laboratory data from Path West including blood gas data.

Please ensure that all data are stored in accordance with WAUSDA and Curtin University Policy.

Yours sincerely,

Professor Peter O'Leary
Chair, Human Research Ethics Committee

MEMORANDUM

Curtin University

To:	Professor Judith Finn Nursing & Midwifery
CC:	
From	Professor Peter O'Leary, Chair HREC
Subject	Amendment approval Approval number: HR199/2014
Date	16-Jun-15

Office of Research and Development
Human Research Ethics Office

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

Thank you for submitting an amendment to the Human Research Ethics Office for the project:

HR199/2014 Functional status of survivors of out-of-hospital cardiac arrest in Perth, Western Australia.

The Human Research Ethics Office approves the amendment to the project.

Amendment number: HR199/2014/AR1

Approval date: 16-Jun-15

The following amendments were approved:

1) In adult patients admitted to an intensive care unit (ICU) following an out-of-hospital cardiac arrest, does the arterial oxygen concentration in the first 24 hours following cardiac arrest (in the range 60mmHg to 200mmHg vs. outside this range) affect the length of ICU stay, ICU survival, survival to hospital discharge, neurological outcome on survival (CPC) and 30-day survival?
2) In adult patients admitted to an intensive care unit (ICU) following an out-of hospital cardiac arrest, does the arterial carbon dioxide concertation in the first 24 hours following cardiac arrest (in the range 25mmHg to 50mmHg vs outside this range) affect the length of ICU stay, ICU survival, survival to hospital discharge, neurological outcome on survival (CPC) and 30-day survival?
3) In adult patients admitted to an intensive care unit (ICU) following an out-of-hospital cardiac arrest, does targeted temperature management in the first 24 hours following cardiac arrest (in the range <36 degrees Celsius vs > 36 degrees Celsius) affect the length of ICU stay, ICU survival, survival, survival to hospital discharge, neurological outcome on survival (CPC) and 30-day survival?
4) In adult patients admitted to an intensive care unit (ICU) after an out-of-hospital cardiac arrest, does the serum lactate level up to 6 hours after cardiac arrest affect the length of ICU stay, ICU survival, survival to hospital discharge, neurological outcome on survival (CPC) and 30-day survival?
5). The data already collected for our study HR199/2014 we will be collected data on post-resuscitation management. This will include routinely collected laboratory data from Path West including blood gas data, i.e. pH, PO2, PC02, base excess, lactate and chloride.

Please ensure that all data are stored in accordance with WAUSDA and Curtin University Policy.

Yours sincerely,

Professor Peter O'Leary
Chair, Human Research Ethics Committee

Curtin University

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 4447
Email judith.finn@curtin.edu.au
Web http://precru.org.au
http://curtin.edu.au

07 Oct 2015

Mr Brett Cawley
PathWest
J Block, QEII Medical Centre
Hospital Avenue, Nedlands WA 6009

Dear Brett,

The Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU), based in the School of Nursing, Midwifery and Paramedicine in the Faculty of Health Sciences at Curtin University is conducting a study entitled the ***Functional status of survivors of out-of-hospital cardiac arrest in Perth Western Australia.*** This study aims to determine the functional/neurological outcome of out-of-hospital cardiac arrest (OHCA) survivors discharged from hospital in Perth, Western Australia and to estimate the prevalence of post-resuscitation practices in Perth hospitals. This study has been approved by the Human Research Ethics Committees (HREC) at Curtin University (HR 199/2014), Joondalup Health Campus (HREC 1225), Sir Charles Gairdner Hospital (HREC 2012-184), Royal Perth Hospital (EC Reg 13-044) Fremantle Hospital (AR/13/96) and Princess Margaret Hospital (2013 014EP).

This PhD candidate sub-study entitled ***Post resuscitation care following out-of-hospital cardiac arrest – identification of in-hospital prognostic determinants***, aims to test the hypothesis that there is no relationship between the in-hospital post-resuscitation care, and in-hospital mortality and neurological outcomes in OHCA patients admitted to an intensive care unit (ICU). In order to answer the specific research questions, the data pertaining to the in-hospital clinical management of these patients will be collected from the patients' medical record. We also require primary data from PathWest, specifically results from arterial blood gas (ABG) analysis. Curtin University granted HREC approval for this amendment on the 14th July 2015 (HR 199/2014 AR2).

Please find attached the ammendment for the ethics application, the PathWest Laboratory Medicine Data Extraction Request Form as well as a one page summary of the PhD candidate sub-study.

Please do not hesitate to contact me if you require further information / clarification.

Kind regards

Professor Judith Finn
PhD, MEdSt, GradDipPH, BSc, DipAppSc, RN, RM, ICCert, FACN, FAHA
Director: Prehospital, Resuscitation & Emergency Care Research Unit (PRECRU)
School of Nursing, Midwifery & Paramedicine
Faculty of Health Sciences
Adjunct Research Professor: St John Ambulance Western Australia

REQUEST FOR LABORATORY DATA EXTRACT

Requestor Information

Request Date: 10/09/2015

Name:	Professor Judith Finn	Signature:
Department:	Prehospital Resuscitation and Emergency Care Research Unit (PRECRU), School of Nursing, Midwifery & Paramedicine, Curtin University	
Contact Information:	Phone: 9266 4447 Mobile: 0417 189 841 email: judith.finn@curtin.edu.au	

Supervisor Name:	Professor Judith Finn	Signature:
Department:	Prehospital Resuscitation and Emergency Care Research Unit	
Contact Information:	Phone: 9266 4447 Mobile: 0417 189 841 email: judith.finn@curtin.edu.au	

Extract Information

Purpose of the Extract / Use of the information:

We are conducting a study *"Functional status of survivors of out-of-hospital cardiac arrest in Perth Western Australia"*. This study aims to (1) determine functional/neurological outcome of out-of-hospital cardiac arrest (OHCA) survivors discharged from hospital in Perth, Western Australia; and (2) estimate the prevalence of post-resuscitation practices in Perth hospitals such as targeted temperature management (TTM) and coronary reperfusion.

In a sub-study entitled "*Post resuscitation care following out-of-hospital cardiac arrest – identification of in-hospital prognostic determinants*" we aim to test the hypothesis that a relationship exists between in-hospital prognostic determinants, in-hospital mortality and neurological outcome at hospital discharge as measured by the Cerebral Performance Category (CPC) scale by (1) describing the in-hospital post resuscitaion management of OHCA; and (2) identifying the in-hospital prognostic determinants of OHCA.

The specific research questions will include:

In adult patients (aged > 18 years) admitted to an intensive care unit (ICU) following an OHCA does;

(1) arterial oxygen concentration in the first 24 hours of ICU admission (in the range 60mmHg to 200mmHg vs. outside this range);

(2) arterial carbon dioxide concentration in the first 24 hours of ICU admission (in the range 25mmHg to 50mmHg vs. outside this range);

(3) targeted temperature management (in the range < 36 degrees Celsius vs. ≥ 36 degrees Celsius); in the first 24 and 72 hours of ICU admission; and

(4) serum lactate level up to 6 hours of ICU admission;

affect the length of ICU stay, ICU survival, survival to hospital discharge, neurological outcome on survival (CPC) and 30-day survival?

To assist in answering these questions we request patients' arterial blood gas (ABG) results that contain the date, time and location the specimen was taken, body temperature if recorded at time of collection, FiO_2, pH, PO_2, PCO_2, bicarbonate, oxygen saturation, whole blood chloride, base excess and whole blood lactate.

	Yes	No	
Ethics Approval Obtained	√	❑	If approved please attach details
Patient identifiers required	√	❑	If so, coded ❑ or full √

Data Retention Period	25 years
Frequency of extract	Yearly
Delivery method/location	Hand delivery to PathWest, J Block, QEII Medical Centre, Hospital Avenue, Nedlands WA 6009
Describe your secure storage of the information.	Data security is of paramount importance to the Prehospital Resuscitation and Emergency Care Research Unit (PRECRU) and robust data security measures are put in place to minimise risk to the individual and organisation. PRECRU researchers are required to comply with the Australian Code for the Responsible Conduct of Research. Data is stored on PRECRU's secure 'J' drive at Curtin University. Data is encrypted using TrueCrypt v7.1.a and the Advanced Encryption Standard (AES-256) software for data privacy. The encrypted data is password protected and only accessible to authorised study team members. An automatic screen locking system is initiated with the screen saver after a 5 minute period of inactivity. Access to the network used by PRECRU is securely controlled and protected by measures including firewalls and anti-virus software. Potential patient identifiers (i.e. name, address, date of birth) are removed from the database after data cleaning is completed and before data analysis is commenced. Only de-identified data will be used in any report or publication. Data is stored in compliance with Curtin University's policy on data storage.
Presentation Format (eg CSV, Excel Spreadsheet, etc)	Microsoft Excel 2010 spreadsheet

Data Selection Criteria:

PRECRU will supply a list of patients who suffered an OHCA, transported to the Emergency Department at Royal Perth Hospital, Sir Charles Gairdner Hospital, Fremantle Hospital or Fiona Stanley Hospital by St John Ambulance-WA between 2012 and 2015 and who survived to hospital admission.

Data Items Required	**Data Manipulation** (Examples follow this table)
Surname	Truncated to the first six characters
Given Name	Truncated to the first six characters
Middle Name	Initial Only
UMRN	Alphanumeric, 8 characters
Date of birth	dd/mm/yyyy
Arterial blood gas results	
FiO_2	Numeric to 2 decimal places
Body temperature (° C)	Numeric to 1 decimal place
pH	Numeric to two decimal places
PO_2 (mm Hg)	3 numeric characters
PCO_2 (mm Hg)	3 numeric characters
Bicarbonate (mmol/L)	3 numeric characters
Oxygen Saturation	Percentage as 3 numeric characters
Base Excess	Numeric to 1 decimal place
Whole blood lactate (mmol/L)	Numeric to 2 decimal places
Whole blood chloride (mmol/L)	Numeric to 2 decimal places
Location	ED/ICU/CCU/other ward

Approvals

	Name/Signed	**Date**
Anatomical Pathology		
Biochemistry		
Haematology		
Immunology		
Microbiology		
Data Custodian	Brett Cawley	
IMU Completed		
IMU Data Delivered		

Appendix B SJ-WA Problem/Dispatch Codes

DISPATCH/PROBLEM CODES (reviewed June 2014)

01 TRAUMA	26 INFECTION	35 ENVIRONMENT	TRANSMISSION CODES
010 Other	261 Significant risk to AO	351 Hypothermia	62 Ambulance Not
011 Domestic	262 Septicaemia	352 Hyperthermia	73 On an Errand
012 MVA	263 Localised Infection	353 Barotrauma/DCS	79 Arrive at Scene
013 Sporting/Recreational	264 Pyrexia Unknown Origin	354 Near Drowning	80 Mobile
014 Industrial	27 GERIATRIC/ DEBILITY	355 Electric Shock	81 Arrived Destination
015 Assault	271 Generalised Debility	356 Burns	82 Cleared
016 Hanging	273 Vertigo/Dizziness	357 Bites & Stings	83 At Station
017 Sexual Assault	274 GP Hospital Referral	358 Dehydration	84 Police
018 Shooting	275 Mobility Assistance only	36 MALIGNANCY	85 Petrol
019 Stabbing	28 ILLNESS	361 Malignancy	86 Spare
20 ABDOMINAL	281 Unspecified (text explanation)	37 PSYCHO/SOCIAL	87 Workshops
201 Pain	282 Flulike Illness	371 Psychiatric Illness	88 Belmont HQ
202 Hematemesis	29 ENDOCRINE/ METABOLIC	372 On Forms	89 Return to Station
203 Melena	291 Ketoacidosis	373 Social Problem	90 Patient Deceased
204 Aneurysm	292 Hypoglycaemia	41 CARDIAC	99 Meal Break
205 GIT Bleed	293 Hyperglycaemia	410 APO (Cardiac)	AMBULANCE NOT REQUIRED
206 Vomiting +/- Diarrhoea	30 MUSCULO/SKELETAL	411 Chest Pain / ACS	The codes for non transport are as follows:
21 OBST/GYNY	301 Pain/Inflammatory	412 Angina Diagnosed	1 No Emergency care
211 Vaginal Bleed	302 Quad/Para	413 AMI diagnosed	2 Patient refused
212 Pre-Eclampsia	303 Amputee	414 CCF	3 Patient assessed – no Problem found
213 Ectopic Pregnancy	31 NEUROLOGICAL	415 Cardio Shock	4 Patient assessed – Seek further treatment
214 Miscarriage	310 Convulsions Other	416 Pacemaker Fail	5 Transported by another Ambulance
215 Normal Labour	311 Altered Conscious State	417 Cardiac Dysrhythmia	6 Transported by another Means
216 Comp. Labour	312 CVA/Stroke	418 Cardiac Arrest	7 Doctor in attendance
217 Baby Born	313 Headaches	419 Post Cardiac Arrest	8 Call Cancelled
218 Neonatal Resus	314 Convulsions - Febrile	44 NEO NATAL	9 Stood down
219 Other	315 Convulsions - Epileptic	440 Neo Natal	10 Patient not ready – to Rebooked
22 ALLERGY	316 Status Epilepticus	50 PR VISIT	11 Clinic appointment
221 Anaphylaxis	317 Syncope	500 PR Visit	12 Unable to locate scene
222 Localised	318 Unconscious Unknown	59 STANDBY	13 Patient absconded
223 Medication Reaction	319 TIA (Recovered)	591 Wait for other amb	14 Hoax
24 RESPIRATORY	32 POISONING	592 Major Incident	15 Care given. Transport Declined
240 Pulmonary Embolism	321 Ingested	593 Dangerous Incident	16 Patient Deceased
241 Asthma	322 Absorbed	594 Disaster Exercise	
242 APO (Non Cardiac)	323 Gaseous	60 SPORTING STAND BY	
243 CAL/COAD	33 DRUG/ALCOHOL INDUCED	602 Sporting Fixture	
244 Pneumothorax	331 Drug Induced Mental Illness	80 TRANSFERS	
245 Respiratory Tract Infection	332 O/dose intent harm	801 Trauma	
246 Aspiration/Regurgitation.	333 Alcohol Intoxication	802 Abdominal/Renal	
247 Obstruction Upper Airway	334 Overdose (Unintentional)	803 Obstetrics/Gynaecology	
248 Resp Arrest	335 Narcotic OD	804 Respiratory	
249 Other	34 UROLOGY	805 Endocrine/Environmental	
25 EAR/NOSE/THROAT	341 Haematuria	806 Drug/Alcohol	
250 ENT	342 Retention	807 Psychological	
251 Epistaxis	343 Renal Colic	808 Cardiac	
	344 Incontinence	809 Other	
	345 Renal Failure (Renal Dialysis)		
	346 Urinary Tract Infection		

Problem Urgency

Australasian Triage Scale	Treatment Acuity	Numeric Code	Example of Diagnosis
Resuscitation	Immediate	1	Shock, Cardiac Arrest, Unconscious
Emergency	Within 10 Minutes	2	Chest Pain, Severe Dyspnoea
Urgent	Within 30 Minutes	3	Moderate Trauma- Ankle Wrist Fracture
Semi Urgent	Within 60 Minutes	4	Acute Abdominal Pain, Sprained Ankle
Non Urgent	Within 120 Minutes	5	Chronic Disorder, Rash, Back Pain
Non-ATS case	Not Applicable	6	Transfer to NH, Transport Home, Clinic Run

Appendix C EMS Transport Destination Poster

Direct Transport To A Tertiary Hospital Improves Survival From Out-of-hospital Cardiac Arrest In Adults With Acute Coronary Syndrome

Nicole MCKENZIE,[1, 3] Teresa A WILLIAMS,[1, 2, 3, 5] Hideo TOHIRA,[1, 5] Kwok M. HO,[1, 3] Judith FINN[1, 2, 4, 5]

[1] Prehospital Resuscitation and Emergency Care Research Unit (PRECRU), School of Nursing, Midwifery and Paramedicine, Curtin University, Bentley, WA
[2] St John Ambulance Western Australia, Belmont, WA
[3] Royal Perth Hospital, Perth, WA
[4] School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC
[5] Division of Emergency Medicine, University of Western Australia, Crawley , WA

Introduction

International resuscitation guidelines recommend direct transport of out-of-hospital cardiac arrest (OHCA) patients to a specialist cardiac arrest centre.[1] Whether this recommendation is fully supported by existing evidence remains uncertain and additional studies are required.

Objective

To determine if adult OHCA patients with acute coronary syndrome (ACS) benefit from direct transport to a tertiary hospital.

Methods

This retrospective cohort study used the St John Ambulance Western Australia OHCA Database and medical record review. We included adults (≥18 years) admitted to the intensive care units (ICU) of five tertiary hospitals in Perth, with mechanical ventilation and a hospital discharge diagnosis of ACS between January 2012 and December 2015.

We compared survival to hospital discharge (STHD) and 12-month survival between patients directly transported to a tertiary hospital and patients transferred to a tertiary hospital and its ICU from another hospital using multivariate logistic regression and Cox proportional hazards regression model adjusted for Utstein variables and other known confounders.

Results

Of the 146 patients included in the analysis, 104 patients (71%) were directly transported to a tertiary hospital and 42 (29%) were transferred from another hospital. A total of 76 patients survived to hospital discharge.

Patients admitted directly to a tertiary hospital were 3.3 times (adjusted odds ratio 3.3, 95% confidence interval [CI] 1.5, 7.3) more likely to survive to hospital discharge and 1.9 times (hazard ratio 1.9, 95% CI 1.2, 3.1) more likely to survive for 12 months than those transferred from another hospital despite adjustment for important confounders

References

Finn, J. C., P. Bhanji, A. Lockey, E. Monsieurs, R. Frengley, T. Iwami, e. al. (2015). "Part 8: Education, implementation, and teams: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations." Resuscitation 95: e203-224.

Results

Table 1. Cohort characteristics stratified by transport type

Characteristics	Direct transport (n= 104)	Secondary transfer (n= 42)	*P-value*
Patient demographics			
Age, years	63 (54-71)	59 (51–75)	*0.47*
Sex, male	86 (83)	38 (90)	*0.23*
OHCA characteristics prehospital			
Place of arrest, public	41 (40)	9 (21)	***0.04***
Witnessed arrest	58 (56)	23 (55)	*0.91*
Bystander performed CPR	75 (72)	30 (71)	*0.93*
Initial rhythm, shockable	82 (79)	38 (90)	*0.10*
Time of arrest			
Day (07:00 to 18:59)	70 (67)	29 (69)	*0.84*
Night (19:00 to 06:59)	34 (33)	13 (31)	
Day of arrest			
Weekday	71 (68)	34 (81)	*0.12*
Weekend	33 (32)	8 (19)	
Response time*1 (min)	7 (5-9)	7 (4-10)	*0.88*
Total prehospital time *2 (min)	45 (36-56)	193 (138-232)	***<0.001***
OHCA characteristics in hospital			
TTM	89 (86)	37 (88)	*0.69*
Diagnosis of STEMI at hospital discharge	52 (50)	27 (64)	*0.12*
Urgent coronary angiography with PCI (< 24 hours)	63 (61)	28 (67)	*0.49*
Patient outcomes			
STHD	60 (58)	16 (38)	***0.03***
Survival to 12 months	58 (56)	16 (38)	***0.053***

Table 2. Results of logistic regression and Cox proportional hazards regression analysis for survival to hospital discharge and 12 month survival respectively

		Survive to hospital discharge	12 month survival
	N (%)	Adjusted OR (95% CI)	Hazard ratio (95% CI)
Secondary transfer	42 (29)	1	1
Direct transport	104 (71)	**3.3 (1.5, 7.3)**	**1.9 (1.2, 3.1)**

OR: odds ratio; CI: confidence interval

Conclusion

Direct transport to a tertiary hospital for intervention and intensive care may confer a significant survival advantage for adult OHCA patients with acute coronary syndrome. This has implications for the development of efficient and streamlined cardiac arrest centres in Western Australia.

Corresponding author
Nicole Mckenzie
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GPO Box U1987, Perth, WA 6845, Australia
Telephone: +61 8 9226 4182; Email: nicole.mckenzie@curtin.edu.au

Appendix D PRISMA 2009 Checklist*

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	116
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	116
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	116-117
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	116-117
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	118
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	117
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	117
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	117
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	117
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	117
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	117
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	117
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	117
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	117-118
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	117
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	117
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	118
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	118
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	118
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	118
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	118
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	119
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	120
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	122
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	123
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	124
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	125

*Page numbers refer to those included in the publication in Chapter Six of this thesis.

Appendix E PROSPERO Registration

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Citation

Nicole Mckenzie, Teresa Williams, Hideo Tohira, Kwok Ho, Judith Finn. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest. PROSPERO 2015 CRD42015024907 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42015024907

Review question

Is the partial pressure of carbon dioxide in arterial blood (PaCO2) following cardiac arrest associated with survival to hospital discharge and survival to hospital discharge with good neurological outcome?

Searches

Ovid MEDLINE(R) 1946 -
Ovid MEDLINE (R) in process and other non-indexed citations 1996 –
EMBASE (via Ovid) 1974 -
CINAHL Plus with Full Text (EBSCO)
Cochrane Central Register of Controlled Trials (CENTRAL)
No language restriction. Review articles, editorials and selected citation lists in Scopus will be used to find other relevant articles. Reference lists will be checked to identify additional papers not found with literature search strategy.
Search terms:
First group -
Heart arrest (MeSH heading),
Cardiac arrest,
In-hospital cardiac arrest,
Out-of-hospital cardiac arrest,
Cardiorespiratory arrest,
Cardiopulmonary resuscitation.
Second group -
Carbon dioxide (MeSH heading),
Hypercarbia,
Hypocarbia,
Normocarbia,
Dyscarbia,
Hypercapnia,
Normocapnia,
Hypocapnia.
Third group -
Outcomes assessment (MeSH heading),
Survival ,
Neurological outcome,
Prognosis,
Cerebral Performance Category.
These three groups will be combined using Boolean operators. The "OR" operator will be used to link terms within the groups. The "AND" operator will be used to link terms between the groups.

Types of study to be included

Randomised control trials Cohort StudyCross sectional studyCase Control studyAny other type of comparative study

Condition or domain being studied

Cardiac arrest (CA) is an often fatal event resulting from the sudden loss of heart function. Patients who respond to resuscitation with return of spontaneous circulation (ROSC) may develop post-CA abnormalities in the partial pressure of arterial carbon dioxide (PaCO2). High arterial carbon dioxide may result in vasodilation of cerebral blood vessels with a subsequent rise in intracranial pressure (ICP). Low arterial

carbon dioxide levels can potentiate cerebral vasoconstriction and exacerbate post-CA brain injury. Little has been published on the topic and there are no data to support ventilation to a specific PaCO2 goal after ROSC. The aim of this systematic review is to investigate the association between arterial carbon dioxide and survival to hospital discharge and neurological outcome following CA.

Participants/population

Inclusion criteria - Studies which evaluate the association between the partial pressure of arterial carbon dioxide and survival and neurological outcome at hospital discharge, in-hospital or out-of-hospital cardiac arrest, human studies of CA that include arterial blood gas (ABG) results, ROSC at time of ABG measurement.
Exclusion criteria - Children (as defined by the authors), animal studies case reports, reviews, editorials, letters and commentary.

Intervention(s), exposure(s)

Exposure to abnormal level of carbon dioxide (hypercapnia and hypocapnia) as measured by ABG analysis.

Comparator(s)/control

Exposure to different levels of carbon dioxide from exposure group as measured by ABG analysis.

Context

CA of any aetiology will be included
Both in-hospital and out-of-hospital cardiac arrest will be included
Patients may be sub-grouped by aetiology (depending on patient numbers)

Main outcome(s)

Survival to hospital discharge after CA

Additional outcome(s)

Neurological status at hospital discharge as defined by a validated scoring system
Survival to 30 days or later if reported
Any other reported study outcomes

Data extraction (selection and coding)

Titles and abstracts will be reviewed by NM and TW to identify potentially relevant studies.Full text articles will be reviewed by NM and TW to ensure the eligibility criteria is met using pre-determined forms (study design, population characteristics, exposure to carbon dioxide, outcome measures, results). Results will be discussed at team meeting with NM, TW, HT and JF. Differences will be resolved by consensus.

Risk of bias (quality) assessment

The Newcastle-Ottawa Scale (NOS) will be used to assess the quality of nonrandomised studies in meta-analyses.
The GRADE system will be used to assess bias in RCT's

Strategy for data synthesis

I-squared statistic will be used to assess heterogeneity between studies.
Group consensus will determine clinical heterogeneity (NM, TW, HT, JF).

Analysis of subgroups or subsets

Sub group analysis will be performed for the following groups
In-hospital cardiac arrest / out-of-hospital cardiac arrest
Adults / paediatrics
Initial rhythm
Aetiology
Targeted temperature management / no temperature management

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https://www.ausroc.org.au/, https://healthsciences.curtin.edu.au/research/precru/index.cfm

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Anticipated or actual start date
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None known

Language
English

Country
Australia

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McKenzie N, Williams TA, Tohira H, Ho KM, Finn J. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest. Resuscitation. 2017 Feb;111:116-126. doi: 10.1016/j.resuscitation.2016.09.019. Epub 2016 Sep 30. PMID: 27697606.
https://PubMed.ncbi.nlm.nih.gov/27697606/

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Carbon Dioxide; Cardiopulmonary Resuscitation; Heart Arrest; Humans; Partial Pressure

Date of registration in PROSPERO
14 September 2015

Date of first submission
25 February 2021

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

We have revised the title of the article for improved readability only. The revised title does not alter the methodology or result of the systematic review or meta analysis.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

14 September 2015
13 April 2016
25 February 2021

Appendix F Systematic Review and Meta-Analysis Poster

A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest

Nicole **MCKENZIE**,[1, 3] Teresa A **WILLIAMS**,[1, 2, 3, 5] Hideo **TOHIRA**,[1] Kwok M. **HO**,[1, 3] Judith **FINN**[1, 2, 4, 5]

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Introduction

Arterial carbon dioxide ($PaCO_2$) elimination is impaired during cardiac arrest (CA) due to inadequate perfusion of the lungs. Both high and low $PaCO_2$ after return of spontaneous circulation from CA are common due to accumulation of CO_2 during CA and excessive mechanical ventilation respectively. [1-3] Maintaining a normal $PaCO_2$ is recommended as a therapeutic target after CA. [4,5] Whether this recommendation is fully supported by existing evidence remains uncertain, and is assessed in this systematic review and meta-analysis.

Objective

To conduct a systematic review and meta-analysis to examine the association between arterial carbon dioxide tension and outcomes after CA.

Methods

Databases: MEDLINE(R), Ovid MEDLINE(R) in process and other non-indexed citations, Ovid EMBASE, CINAHL Plus with Full Text (EBSCO) and Cochrane Central Register of Controlled Trials (CENTRAL)

Key words: Heart Arrest, Carbon Dioxide, Outcomes Assessment

Inclusion criteria:
1. Comparative studies published between inception and August 2015
2. Investigating the association of $PaCO_2$ and survival
3. In adult patients who suffered either in-hospital CA (IHCA) or out-of-hospital CA (OHCA)
4. Of any aetiology
5. Who had their exposure to $PaCO_2$ measured by arterial blood gas (ABG) analysis

Outcome measures:
1. Survival to hospital discharge (hospital survival) after CA
2. Neurological status at the end of each study's follow-up period as defined by validated scoring system

Study selection: Two independent reviewers and a third reviewer if no consensus

Risk of bias (quality) assessment: The Newcastle-Ottawa Scale (NOS)

Comparator(s): Exposure to different levels of $PaCO_2$ from exposure group as measured by ABG analysis

Summary measure: Odds ratio (OR)

Strategy for data synthesis: Meta-analysis only if I^2 statistic < 50%

Synthesis of results: Peto OR fixed effect model (RevMan Version 5.3, Cochrane Collaboration)

Protocol and registration: PROSPERO 2015: CRD42015024907

Results

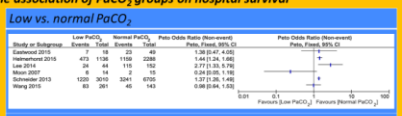
- Nine relevant studies out of 93 citations
- No study excluded due to methodological quality
- Eight studies provided sufficient quantitative data for meta-analysis
- No randomised control trials comparing $PaCO_2$ targets after CA found

Results

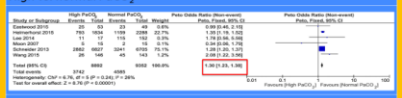
- A total of **23,434** patients with CA (range 44 to 16,542)
- A total of **16,542** patients from a single large Australian & New Zealand study
- Cut-points used to define low and high $PaCO_2$ varied between **35 and 45 mmHg** and between **45 and 50 mmHg** respectively, in the included studies
- Other major sources of heterogeneity included country of origin of the study, location of CA (IHCA vs. OHCA vs. IHCA/OHCA) and $PaCO_2$ sampling times

The association of $PaCO_2$ groups on hospital survival

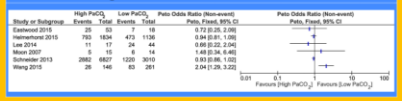
Low vs. normal $PaCO_2$



High vs. normal $PaCO_2$

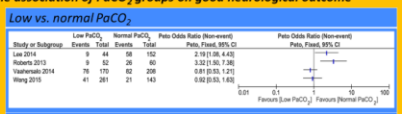


High vs. low $PaCO_2$

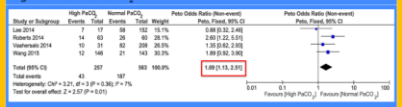


The association of $PaCO_2$ groups on good neurological outcome

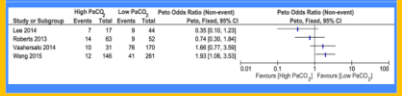
Low vs. normal $PaCO_2$



High vs. normal $PaCO_2$



High vs. low $PaCO_2$



Conclusion

- From the limited data, it appears $PaCO_2$ has an important U-shape association with survival and outcomes after CA, consistent with international resuscitation guidelines that normocarbia be targeted during post-resuscitation care.
- Significant clinical heterogeneity limited our ability to draw a definitive conclusion on the optimal $PaCO_2$ level that clinicians should target.
- RCT's are needed to define the best $PaCO_2$ target during the post resuscitation period after CA.

References
(1) Falkenbach P, et al. Resuscitation 2009; 80: 990-3. **(2)** Roberts BW, et al. Circulation 2013; 127:2107-13. **(3)** Schneider AG, et al. Resuscitation 2013; 84: 927-34. **(4)** Nolan JP, et al. Intensive Care Med 2015; 41: 2039-56. **(5)** Nolan JP, et al. Resuscitation 2008; 79:350-79.

Appendix G Systematic Review and Meta-Analysis Editorial

Resuscitation 111 (2017) A1–A2

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Resuscitation

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Editorial

Optimal arterial carbon dioxide tension following cardiac arrest: Let Goldilocks decide?

Despite initially successful cardiopulmonary resuscitation, a substantial proportion of patients who survive cardiac arrest die prior to hospital discharge and those that survive often have severe neurologic injury.[1] Following arrest, the initial hours and days are defined by the post-cardiac arrest syndrome,[2] with a significant inflammatory response, organ bioenergetic failure,[3] and high risk of morbidity and mortality. This period of time requires vigilant monitoring and intervention, and is the subject of intense investigation to identify markers of ongoing neurologic injury and therapeutic development.

In cardiac arrest patients who achieve return of spontaneous circulation, 45–60% have hypocarbia or hypercarbia in the subsequent hours.[4,5] Hypocarbia may be present soon after cardiac arrest due to inadvertent overventilation or due to a decreased metabolic rate precipitated by therapeutic hypothermia and other interventions.[5–7] Alternatively, hypercarbia immediately following cardiac arrest is often secondary to concomitant lung disease or asphyxia, or as a marker of limited pulmonary perfusion due to low cardiac output.[8,9]

Given the effects of $PaCO_2$ on the cerebral circulation and the burden of severe anoxic injury following cardiac arrest, recent interest has been placed on the prognostic capabilities of $PaCO_2$ in patients who are resuscitated from cardiac arrest.[4,6,10–12] In the present issue of *Resuscitation*, McKenzie et al. summarize the prognostic value of $PaCO_2$ in their systematic review and meta-analysis. The authors identify nine prospective and retrospective cohort studies of out-of-hospital or in-hospital cardiac arrest for inclusion. Eight studies, with over 23,000 patients, are included in the meta-analysis. Despite being limited in conducting some analyses by excessive statistical heterogeneity between studies, the authors report improved hospital survival and improved neurologic outcomes with normocarbia as compared to hypercarbia; and improved rates of discharge home with normocarbia as compared to hypocarbia.[13]

McKenzie et al. should be commended for this sophisticated meta-analysis. As the authors acknowledge, the analysis has some limitations. First, the authors reasonably define normocarbia as a $PaCO_2$ of 35–45 mmHg, with values below and above this range being defined as hypocarbia and hypercarbia, respectively.[13] However, these definitions were not consistent across all studies included in the meta-analysis. In fact, the authors excluded one study[10] that differed from the set definitions of hypocarbia and hypercarbia as defined above, and this resulted in the loss of statistical significance in one analysis.

Additionally, the timing of blood gas acquisition varies from study to study. Whereas immediate post-resuscitation $PaCO_2$ is indicative of the pre-arrest and intra-arrest state, $PaCO_2$ values measured later in the post-arrest period likely reflect post-arrest pathophysiology and interventions. Knowledge of the relationship of these values to outcome is undoubtedly valuable, but the variability in when these values are obtained and what they represent limit how clinicians can or should employ this information in practice.

Another concern is that the majority of patients included in this review are from the Schneider et al. study, which includes 16,542 patients, approximately 71% of the patients included in the meta-analysis.[4] This study is the primary factor influencing the conclusion that patients with normocarbia are more likely to survive to hospital discharge as compared to patients with hypercarbia.[13] Interestingly, in Schneider's original study, there was no difference between these groups in the adjusted analysis. Additionally, Schneider et al. found that hypercarbic patients were more likely to be discharged home than the normocarbic cohort.[4] This finding provided the rationale for a randomized controlled trial between controlled normocarbia and mild hypercarbia,[14] with a Phase II feasibility study demonstrating promising results for the potentially protective effects of therapeutic mild hypercarbia.[15]

Hypocarbia has the potential to decrease cerebral blood flow by altering cerebral vascular resistance following cardiac arrest. Thus, current guidelines for the care of patients following successful resuscitation endorse the avoidance of hypocarbia except as a temporizing measure to inhibit intracranial hypertension. These guidelines also acknowledge an unclear link between hypercarbia and clinical outcome, but suggest a normocarbic goal "unless patient factors prompt more individualized treatment."[16] Intuitively, having a goal of maintaining normocarbia seems reasonable. The question still remains, are derangements in arterial carbon dioxide tension merely reflective of post-arrest pathophysiology or are they actually independent promotors of secondary injury. Likely, both are true.

With a large proportion of patients who survive their initial resuscitation suffering neurologic injury that results in death or permanent disability, resuscitation centers should be focused on the development of mutli-modal neuromonitoring platforms to assess ongoing injury and initiate early intervention. Armed with

http://dx.doi.org/10.1016/j.resuscitation.2016.11.016
0300-9572/

real-time data related to cerebral blood flow, cerebral oxygenation, and cerebral metabolism[17–19] clinicians should be able to tailor therapies to the individual patient rather than to simply prognosticate across a population. Measurement and manipulation of arterial carbon dioxide is one piece of the complex management for post-cardiac arrest syndrome that deserves continued study.

Conflict of interest statement

The authors (Ryan Morgan and Todd Kilbaugh) report no relevant financial disclosures or conflicts of interest related to this editorial.

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20 November 2016

Appendix H Neurological Outcomes Poster

Neurological outcome in adult out-of-hospital cardiac arrest patients - not all doom and gloom!

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5 Sir Charles Gairdner Hospital, Perth
6 Fiona Stanley Hospital, Perth
7 Fremantle Hospital, Perth
8 St John of God Murdoch Hospital, Perth
9 School of Public Health and Preventative Medicine, Monash University, Melbourne

Source: Take Heart Australia. www.takeheartaustralia.com.au

Introduction

The aim of post resuscitation care in OHCA patients is to maximise survival and neurological outcomes. However, little is documented about the reality of neurological outcomes of adult out-of-hospital cardiac arrest (OHCA) in Australia.

Objective

To describe neurological outcomes in adult OHCA patients who survived to hospital discharge (STHD).

Methods

- Retrospective cohort study of all OHCA patients (≥16 years) attended by St John Ambulance WA in the Perth metropolitan area and admitted to hospital, between January 2004 and December 2015 (12 years).
- Neurological status at hospital discharge (and prior to the arrest) was determined by medical record review using the five point 'Cerebral Performance Category (CPC)' to assess neurological recovery.
- Adjusted multivariable logistic regression analysis was used to identify patient and/or prehospital factors associated with a good neurological outcome as defined by a CPC score of 1 or 2.
- Covariates included in the analysis included age, gender, aetiology of arrest, location of arrest, bystander cardiopulmonary resuscitation, initial arrest rhythm and witness status.

Results and discussion

- Over the study period SJA-WA attended 16,160 adult OHCA's.
- Resuscitation was attempted in 6,822/16,160 (42%) cases, with 1,341/6822 (20%) patients admitted to hospital and 680/6,822 (10%) STHD.
- Of those patients who STHD with CPC data available (n=649/680; 95%), the scores were: CPC 1 n=469 (72%); CPC 2 n=133 (21%); CPC 3 n=40 (6%); CPC 4 n=7 (1%) (Figure 1).
- There were 31/680 (5%) cases with missing CPC scores. The majority of these cases were transferred to one of five non-tertiary hospitals where ethics approval for medical record review had not previously been sought.
- Of those patients with poor neurological outcome (CPC= 3,4 or 5); n=5/47 (11%) also had poor neurological status prior to the arrest (Table 1).
- Patients who arrested at public locations were 2.6 times more likely to have a good neurological outcome at hospital discharge compared to those who arrested at other locations.
- Patients whose arrest was witnessed by paramedics were 7.8 times more likely to have a good neurological outcome at hospital discharge compared to those with arrest not witnessed by paramedics.
- There was a significant difference in location of arrest but no difference in age and witness status between those with (n=649) and without (n=31) CPC scores available.
- Limitations of the study included the potential for selection bias, as we cannot exclude the possibility that neurological outcomes might differ in patients with and without CPC scores.

Results and discussion

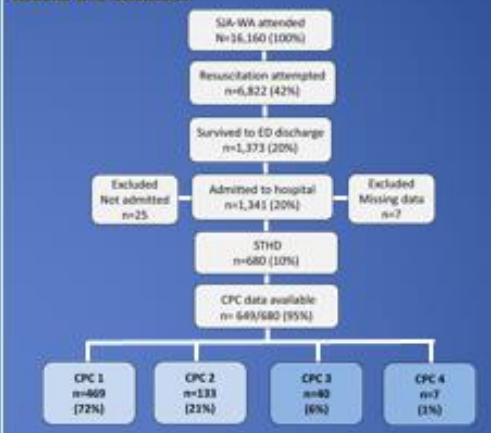

Figure 1. Flow chart of included and excluded patients

Table 1. Cohort characteristics stratified by neurological outcome

Characteristics	Good outcome (n=602)	Poor outcome (n=47)	p-value
Patient demographics			
Age, years	60 (48-70)	56 (33-73)	0.270
Sex, male	454 (75)	36 (77)	0.856
Pre-arrest CPC score			
Good (CPC=1)	563 (94)	34 (72)	
Moderate (CPC=2)	39 (6)	8 (17)	**<0.001**
Severe (CPC=3)	0	5 (11)	
OHCA characteristics prehospital			
Aetiology of arrest, cardiac	554 (92)	36 (77)	**<0.001**
Location of arrest, public	268 (45)	13 (28)	**0.025**
Witnessed arrest			
Bystander	284 (47)	20 (43)	
Paramedic	163 (27)	4 (8)	**<0.001**
Unwitnessed	155 (26)	23 (49)	
Bystander performed CPR	335 (56)	23 (49)	0.373
Initial rhythm, shockable	440 (73)	24 (51)	**<0.001**
OHCA characteristics in hospital			
Admitted to ward*			
ICU	338 (57)	41 (87)	
CCU	194 (33)	1 (2)	**< 0.001**
Other	60 (10)	5 (11)	

Values are median (interquartile range) or n (%). * 18 cases where admitting ward is unknown
CCU= Coronary Care Unit, CPC= Cerebral Performance Category, CPR= Cardiopulmonary resuscitation, ICU= Intensive Care Unit

Conclusions

It is important for clinicians to recognise that whilst overall survival is low, most hospital survivors of OHCA have a good neurological outcome. Nevertheless, the potential for clinician pessimism about prognosis in OHCA generates questions about the approach to assessment and treatment of OHCA in patients who survive long enough to be admitted to hospital.

Appendix I Effect of Sex and Age Poster One

The effect of sex and age on survival and neurological outcome In patients admitted to tertiary intensive care units after out-of-hospital cardiac arrest.

Nicole MCKENZIE[1, 2], Kwok M. HO[1, 2], Janet BRAY[3], Paul BAILEY [1,4,5], Antonio CELENZA[6,7], Daniel FATOVICH[1,6,8], Ian JENKINS[9], Geoffrey DOBB[2,10], Stephen BALL[1,4], Judith FINN[1, 3,4,6]

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Introduction

Studies report varying effects of sex and age on survival and neurological outcome in patients admitted to hospital following OHCA.

Methods

Retrospective medical chart review of **OHCA** patients with medical aetiology ≥18 years attended by St John WA in Perth and admitted to **four tertiary intensive care units**, 2012 to 2017 **(6 years).**

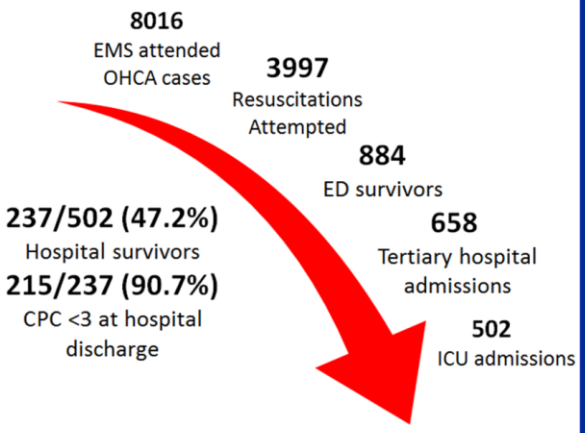
Adjusted multivariable logistic regression analysis identified patient and pre-hospital factors associated with **survival** or **good neurological outcome** (Cerebral Performance Category Scale [CPC]<3) **at hospital discharge.**

Covariates included age, sex, arrest location, bystander CPR, initial arrest rhythm, witness status and prehospital ROSC.

Results

Outcome differences between sexes were not statistically significant after multivariable adjustment (survival to hospital discharge p=0.46; CPC<3 p=0.06).

Compared with patients 18-44 years, only those >65 years had significantly lower survival (odds ratio 0.32; 95% confidence interval 0.17-0.57); however CPC<3 was not significantly different between age groups.



Conclusion

Age but not Sex is associated with hospital survival after out-of-hospital cardiac arrest. Neither impacted neurological outcome.

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Appendix J Effect of Sex and Age Poster Two

THE EFFECT OF SEX AND AGE ON SURVIVAL AND NEUROLOGICAL OUTCOME IN PATIENTS ADMITTED TO TERTIARY INTENSIVE CARE UNITS AFTER OUT-OF-HOSPITAL CARDIAC ARREST

Nicole MCKENZIE[1, 2], Kwok M. HO[1, 2], Janet BRAY[1,3], Paul BAILEY [1,4,5], Antonio CELENZA[6,7], Daniel FATOVICH[1,6,8], Ian JENKINS[9], Geoffrey DOBB[2,10], Stephen BALL[1,4], Judith FINN[1, 3,4,6]

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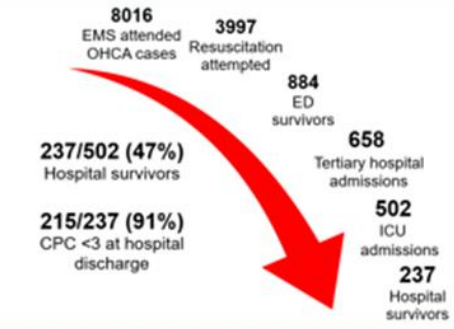
INTRODUCTION

Studies report varying effects of sex and age on survival and neurological outcome in patients admitted to hospital following OHCA.

METHODS

- **Retrospective medical chart review** of **OHCA** patients with medical aetiology ≥18 years attended by St John WA in Perth and admitted to **four tertiary intensive care units**, 2012 to 2017 (6 years).
- **Adjusted multivariable logistic regression** analysis identified patient and pre-hospital factors associated with **survival** or **good neurological outcome** (Cerebral Performance Category Scale [CPC]<3) at **hospital discharge.**
- Covariates included **age, sex, arrest location, bystander CPR, initial arrest rhythm, witness status** and **prehospital ROSC.**

RESULTS



- **Outcome differences between sexes were not statistically significant after multivariable adjustment** (survival to hospital discharge p=0.46; CPC<3 p=0.06).
- **Compared with patients 18-44 years, only those >65 years had significantly lower survival** (odds ratio 0.32; 95% confidence interval 0.17-0.57); however **CPC<3 was not significantly different between age groups.**

CONCLUSION

Age but not Sex is associated with hospital survival after out-of-hospital cardiac arrest. Neither impacted neurological outcome.

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