Improving Prognosis in Out-Of-Hospital Cardiac Arrest Through Cardiac Support and Optimization of Post-Resuscitative Care

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Contents

General Declaration

Monash University

Monash Research Graduate School

Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

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 and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 7 original papers published in peer reviewed journals. The core theme of the thesis is optimisation of post resuscitative care. The ideas, development and writing of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Alfred Hospital and Baker IDI Heart and Diabetes Institute under the supervision of Professor David Kaye, A.Professor Stephen Bernard and Dr Stephen Duffy.

[The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.]

In the case of all work presented in this thesis my contribution to the work involved the following: With the support of my supervisors, Prof David Kaye, A.Prof Stephen Bernard and Dr Stephen Duffy, I developed the key aims and hypotheses of this thesis. I undertook a comprehensive literature review and combined with my clinical experience managing cardiac arrest patients and that of my supervisors, published two review articles forming the main introduction to my thesis.

I then undertook a series of observational studies including single and multi-centre studies and a population based cohort study into aspects of post resuscitative care. With the help of senior Baker IDI Scientists, I also performed a sheep study examining prolonged cardiac arrest. Together with my supervisors and other colleagues at the Alfred hospital, we developed a pilot study into refractory out-of-hospital cardiac arrest as well as a post arrest team clinical guideline designed to streamline and optimize post cardiac arrest care. I performed all the experiments with much appreciated guidance from David Kaye, Melissa Byrne and the Heart Failure Research Group. I was responsible for analysis of data and manuscript production in all studies, and I am first author on all papers except chapter 4 in which I am co-first author.

Thesis chapter	Publication title	Publication status*	Nature of candidate's contribution
1	Post Cardiac Arrest Syndrome: A Review of Therapeutic Strategies.	Published *Circulation* 2011;123:1428-1435.	80%
2	Therapeutic Hypothermia in the cardiac catheterization laboratory.	Published International Journal of Clinical Reviews. 2012;01:10-14.	70%
3	Usefulness of Cooling and Coronary Catheterization to Improve Survival in Out-of-Hospital Cardiac Arrest.	Published *Am J Cardiol* 2011;107:522-527.	70%
4	Survival in patients with myocardial infarction complicated by out-of-hospital cardiac arrest undergoing emergency percutaneous coronary intervention.	Published *Int J Cardiol* 2011 epub ahead of print	50%
5	Hospital characteristics are associated with patient outcomes following out-of-hospital cardiac arrest.	Published *Heart* 2011;97:1489-1494.	70%
6	Do We Need Cardiac Arrest Centres in Australia?	Published *Intern Med J* 2012;42:1173-117	70%
7	Extracorporeal Membrane Oxygenation to Support Cardiopulmonary Resuscitation in a Sheep Model of Refractory Ischemic Cardiac Arrest	Published Heart Lung & Circulation Feb 1, 2013 epub ahead of print	70%

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed: [redacted]

Date: **4th January 2013**

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During my early resident training, I was fortunate to hear a lecture given by Stephen Bernard regarding the benefits of therapeutic hypothermia. I was awed at a how an Australian critical care physician had made such an impact on international resuscitation management, with a trial performed at an unassuming low profile hospital. I have been hooked on resuscitation medicine since and have been privileged to observe Steve's ever calm manner, whether it be in the midst of a cardiac arrest, during a research bureaucratic crisis, or even in a Formula 1 racing car.

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I am sincerely grateful for the relationships developed and continued collaboration with Ambulance Victoria. A. Professor Karen Smith leads a world class pre-hospital research team. I owe a huge thank you to Karen, together with Janet Bray who is now at Monash University AUS-ROC, Ziad Nehme, Michael Stephenson and all Ambulance Victoria paramedics. I think

they do a remarkable job of treating patients whilst attempting to answer important clinical problems through robust research methods. I look forward to many more collaborative efforts in the future.

Embarking on a PhD is a fulfilling, but at times a frustrating journey. To my colleagues in our research fellow's office, I extend a sincere note of appreciation for creating a warm and enjoyable atmosphere to work in each day. The office is a hive of rich ideas, collaborative efforts and many laughs. I wish you all the best in your research endeavors.

I have been fortunate to receive grant support during my PhD, which has been enormously appreciated. I wish to thank The National Heart Foundation, Cardiac Society of Australia and New Zealand and the Baker IDI Bright Sparks Program, with particular mention of Snowy Nominees and Rosetta and Alan Bloom.

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Publication and Awards

Peer Reviewed Publications during time as Doctorate Student

1. Stub D, Byrne M, Pellegrino V, Kaye D. Extracorporeal Membrane Oxygenation to Support Cardiopulmonary Resuscitation in a Sheep Model of Refractory Ischemic Cardiac Arrest. *Heart Lung Circ*. 2013 Epub ahead of print.
2. Stub D, Bernard S, Smith K, Bray JE, Cameron P, Duffy SJ, Kaye DM. Do We Need Cardiac Arrest Centres in Australia? *Intern Med J* 2012;42:1173-1179
3. Lee G, Stub D, Ling H. Atrial Fibrillation in the elderly – Not a benign condition. *Int Emerg Nurs* 2012;20:221-227.
4. Stub, D, Nichol G. Hospital Care After Resuscitation from Out-of-Hospital Cardiac Arrest: The Emperor's New Clothes? *Resuscitation*. 2012;83:793-794.
5. Stub D, Smith K, Bernard S, Bray J, Cameron P, Meredith I, Kaye D. A Randomised Controlled Trial of Oxygen Therapy in Acute Myocardial Infarction (AVOID) Study. *Am Heart J* 2012;163:339-345.
6. Stub D, Smith K, Bray J, Bernard S, Duffy S, Kaye D. Hospital characteristics are associated with patient outcomes following out-of-hospital cardiac arrest. *Heart* 2011;97:1489-1494.
7. Chan W, Stub D, Clark D, et al. Transient and Persistent No Reflow Predict Adverse Clinical Outcomes Following Percutaneous Coronary Intervention: Insights from a Multicentre PCI Registry; *Am J Cardiol* 2012;109:478-485.
8. Chan W, Ajani A, Clark D, Stub D, et al. Impact of peri-procedural Atrial Fibrillation on short term clinical outcomes following percutaneous coronary intervention. *Am J Cardiol* 2012;109:471-477.
9. Stub D, Bernard S, Duffy S, Kaye D. The Post Cardiac Arrest Syndrome: A review of therapies. *Circulation;* 2011.123: 1428-1435
10. Stub D, Hengel C, Chan W, Jackson D, Sanders K, Dart AM, Hilton A, Pellegrino V, Shaw JA, Duffy SJ, Bernard S, Kaye DM. Usefulness of Cooling and Coronary Catheterization to Improve Survival in Out-of-Hospital Cardiac Arrest. *American Journal Cardiology*; 2011;107(4):p522-527.
11. Stub D, Bernard S, Duffy S, Shaw J, Kaye D. Therapeutic Hypothermia in the cardiac catheterization laboratory. *International Journal of Clinical Reviews. IJCR* 2012;01:10-14.
12. Lim H, Stub D, Ajani A et al. Survival in Patients with Myocardial Infarction Complicated by Out-of-Hospital Cardiac Arrest Undergoing Emergency Percutaneous Coronary Intervention. *International Journal Cardiology.* In press 2011.
13. Jabour R, Stub D, Walton T. Aortic valvuloplasty - is a revival merited? *British Journal Cardiology*. 2011; 18(1). p34-36.

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3.	Rod Andrew Research Prize	2011
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Abbreviations

ACLS	Advanced cardiac life support
ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
AV	Ambulance Victoria
BLS	Basic life Support
CAD	Coronary artery disease
CPR	Cardiopulmonary resuscitation
CPC	Cerebral performance category
CPP	Coronary perfusion pressure
CS	Cardiogenic shock
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ECPR	Extracorporeal membrane oxygenation facilitated cardiopulmonary resuscitation
ED	Emergency department
EMS	Emergency medical services
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
LAD	left anterior descending artery
LCx	Left circumflex artery
MAP	Mean arterial pressure
MICA	Mobile intensive care ambulance
MIG	Melbourne interventional group registry
OHCA	Out-of-hospital cardiac arrest
PCI	Percutaneous coronary intervention
RCA	Right coronary artery
ROSC	Return of spontaneous circulation
STEMI	ST elevation myocardial infarction
TH	Therapeutic hypothermia
VACAR	Victorian ambulance cardiac arrest registry
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Abstract

Out-of-hospital cardiac arrest (OHCA) is a common lethal health problem. Despite significant advances in the diagnosis and treatment of cardiovascular disease, OHCA continues to be a major challenge with unacceptably high mortality and morbidity.

Although most research into OHCA has focused on improving rates of return of circulation, many patients die in the post resuscitative period from a unique set of physiological insults, collectively termed the post cardiac arrest syndrome. Over the last decade several clinical trials have highlighted the importance of post-resuscitative care in optimizing survival and neurological recovery. Recently, there have been significant advances in management including recommendations related to regional systems of care, application of therapeutic hypothermia and the utilization of investigative procedures including emergent coronary angiography, cardiac support devices and other tools which provide prognostic information. Despite these advances there has been poor uptake of post-resuscitative care guidelines with significant differences in clinical outcomes between regions and institutions. This thesis focuses on post-resuscitative management in Australia, whilst also exploring new systems and models for OHCA patients in an effort to improve clinical outcomes.

Synopsis

Heart disease is the leading cause of death both in Australia and around the world. Sudden out-of-hospital cardiac arrest (OHCA) accounts for over one half of fatal cardiac events[1, 2]. Cardiac arrest represents the loss of effective cardiac mechanical activity and despite advances in resuscitation techniques, the outcomes of patients with OHCA remain poor. A recent large systematic review reported an average survival of only 7.6%[3] . In many patients OHCA represents the end state of chronic conditions including congestive heart failure, ischemic heart disease and pulmonary disease. Unfortunately however, in a significant number of patients, their first cardiac symptom is their 'last' symptom with development of sudden cardiac arrest. Comparing outcomes in this heterogonous group of patients is difficult, but despite over 50 years of resuscitation guidelines most patients do not survive this sudden cardiac emergency.

The chain of survival for many years comprised four key elements important to the management of all cardiac arrests[4]. Firstly recognition and calling for help, followed by early cardiopulmonary resuscitation (CPR), prompt defibrillation if appropriate and advanced resuscitative care. There has been increasing awareness however, regarding the physiological consequences of prolonged whole body ischemia during cardiac arrest and the subsequent reperfusion injury following return of spontaneous circulation (ROSC) culminating in a complex array of pathophysiology, termed the post cardiac arrest syndrome[5, 6]. Recently a 'fifth link' in the chain of survival has been proposed, which specifically targets this syndrome collectively described as post-resuscitative care[7].

In this thesis I aim to explore the post cardiac arrest syndrome, with a specific focus on epidemiology, treatment pathways and their influence on outcomes, whilst also exploring the use of more novel resuscitation techniques. As an interventional cardiologist, the theme of the thesis steers towards an in-depth analysis of the role of cardiac intervention and support in patients with OHCA. This is fitting considering the high prevalence of coronary disease in patients with OHCA. Despite the fundamental role interventional cardiology plays in the management of these patients, there is at times reluctance by interventional cardiologists to participate in the acute care of survivors of OHCA. The lack of large randomized trials in this difficult cohort of patients is often used as a shield against early involvement in their care. It is incumbent upon the interventional cardiology community to be active contributors in the

optimization of these complex patients. This thesis will highlight the potential role for interventional cardiologists in managing patients with OHCA. I will examine aspects relating to systems of care, explore the use of coronary angiography and cardiac support, and raise the difficult to characterize early 'tone' of management, encompassing avoiding early prognostication, stringent application of therapeutic hypothermia and goal directed therapies.

In Chapter 1, I provide a clinical overview of OHCA, with a focus on the post cardiac arrest syndrome; exploring both pathophysiology and treatment strategies. In line with international guidelines, I discuss the development of specialist cardiac arrest centres that offer goal directed therapies including therapeutic hypothermia, early coronary angiography and optimization of other critical care measures such as oxygenation, blood pressure and glucose.

Chapter 2 is a further introductory chapter, focusing on therapeutic hypothermia (TH). A review of therapeutic hypothermia geared towards the interventional cardiology community is provided. An analysis of the use of TH in the management of anoxic brain injury is performed, exploring the history, early pre-clinical studies and later seminal clinical trials that have guided current guidelines. I also explore the more novel use of TH in the reduction of myocardial reperfusion injury for both cardiac arrest patients as well as those with coronary occlusion in the absence of cardiac arrest. The review highlights how cardiologists should be familiar with the principles and practice of therapeutic hypothermia and be comfortable with its application in the catheterization laboratory.

In chapter 3, I explore the effects of developing a standardized post-resuscitative care treatment protocol on patient survival and neurological recovery. This single centre study compares outcomes in a historical control group to contemporary post-resuscitation practice. The study's focus is on the two major post-resuscitative measures of therapeutic hypothermia and early coronary intervention, whilst indicating the potential benefits to a more aggressive, systematic approach to patient management.

A multicentre-study of percutaneous coronary intervention (PCI) in survivors of OHCA is performed in chapter 4, utilizing The Melbourne Interventional Group (MIG) Registry. The MIG registry is collaboration between 7 Australian tertiary referral hospitals, designed to record data pertaining to all PCI procedures, including follow up at 30 days and 12 months[8]. The registry is coordinated by the Centre of Cardiovascular Research and Education in Therapeutics, a

research body within the Department of Epidemiology and Preventive Medicine (Monash University, Melbourne, Australia). In this chapter short and medium term outcomes of patients with acute myocardial infarction (AMI) and OHCA are explored, highlighting excellent one year outcomes amongst survivors to discharge of OHCA, whilst also indicating the extremely high risk group of OHCA with concurrent cardiogenic shock.

There is increasing international evidence towards the benefit of a regional system of care for managing patients with OHCA. At present in Australia patients with OHCA and subsequent ROSC are transported to the nearest hospital. Chapter 5 explores whether or not hospital characteristics are associated with outcomes in these patients. The analysis is performed using the Victorian Ambulance Cardiac Arrest Registry (VACAR). The VACAR is managed by Ambulance Victoria and captures all OHCA attended by the emergency medical services (EMS) in the state. The VACAR collects Utstein elements[9] including demographics, arrest features, resuscitation care and hospital outcome data. The study of over 2,706 patients who were transported to hospital with return of a spontaneous circulation finds that survival to hospital discharge is significantly increased in patients transported to hospitals with 24 hour interventional cardiology facilities, with the best survival occurring in major trauma-level hospitals.

Chapter 6 is an opinion/review article highlighting international and local evidence towards the potential benefits of adopting a system of care approach towards management of patients with OHCA. It highlights the benefits that other local systems of care have had in critical illnesses, such as the improvements in clinical outcomes seen following the adoption of a system of care for the management of complex trauma and patients with AMI. The paper summarizes much of chapters 1-5, in calling for urgent further research into the implications of an Australian based cardiac arrest system of care.

In chapter 7, the focus changes from care of patients with OHCA following ROSC, to examining the significant proportion of patients with refractory cardiac arrest. In over 50% of patients with an initial rhythm of ventricular fibrillation (VF), resuscitation efforts fail to restore a heart beat despite defibrillation and advanced cardiac life support treatments such as intubation and intravenous adrenaline. In Victoria these patients are declared deceased by paramedics in the field and not transported to hospital. There is growing interest, however, in treatment strategies

in the setting of refractory cardiac arrest. One particular promising model of care is the use of extracorporeal membrane oxygenation facilitated CPR (ECPR).

In Chapter 7, I examine the efficacy of ECPR in restoring circulation compared to conventional resuscitation, in a sheep model of coronary occlusion and subsequent VF arrest. The pre-clinical study explores the hemodynamic differences between the two resuscitation techniques, whilst also providing a platform for the development of clinical skills in the use of ECPR. The second part of the chapter discusses the establishment and early findings of Australia's first pilot study into ECPR; The Refractory Out-Of-Hospital Cardiac Arrest Treated With Mechanical CPR, Hypothermia, ECMO And Early Reperfusion (CHEER) study.

In chapter 8 an integrative discussion and summary of the data is performed. My conclusions also highlight the urgent need for further local research on aspects of post-resuscitative care, including transport of the patient with persistent cardiac arrest. Many of these future projects have commenced already, as the beginnings of my post doctorate research and hopefully continuing career in cardiology and resuscitative medicine.

Chapter 1: The Post Cardiac Arrest Syndrome: A Review

Monash University

Declaration for Thesis Chapter 1

Stub D, Bernard S, Duffy SJ, Kaye DM. **Post Cardiac Arrest Syndrome: A Review of Therapeutic Strategies**. *Circulation* 2011;123:1428-1435.

Declaration by candidate

In the case of Chapter 1 the nature and extent of my contribution to the work was the following:

Name	**Nature of contribution**	**Extent of contribution (%)**
Stub D	Principle author, responsible for overall study concept, literature review, analysis, interpretation of results and development and writing of manuscript. Responsible author who effects overall responsibility of publication.	80%

Candidate's Signature	[redacted]	**Date** 1/11/2012

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**
Bernard S	Analysis of results and manuscript development and editing
Duffy S	Analysis of results and manuscript development and editing
Kaye D	Analysis of results and manuscript development and editing

Declaration by co-authors

The undersigned hereby certify that:

- the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
- they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
- there are no other authors of the publication according to these criteria;
- potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
- the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Alfred Hospital Heart Centre, Intensive Care Unit, Baker IDI Heart and Diabetes Institute, Monash University Faculty of Medicine Nursing and Health Sciences

		Date
Signature 1		1/11/2012
Signature 2		1/11/2012
Signature 3		1/11/2012

Introduction to the Post Cardiac Arrest Syndrome

Out of hospital cardiac arrest (OHCA) is a common initial presentation of cardiovascular disease. Whilst there is significant variation in the rates of survival after OHCA, it remains a devastating condition with significant morbidity and mortality. In a recent meta-analysis of over 140,000 patients, the pooled rate of survival to hospital admission after resuscitation from OHCA was 23.8% and survival to hospital discharge was 7.6%[3]. Despite advances in other areas of cardiovascular medicine, there has been little significant change in the rates of survival over the last 30 years. Much of the research into OHCA has focused on improving rates of return of circulation (ROSC) and there are international recommendations on the provision of optimal basic and advanced life support techniques prior to hospital arrival[6, 10].

The importance of early defibrillation and cardiopulmonary resuscitation, is in part explained by the well described three phase model of physiological effects following ventricular fibrillation cardiac arrest[11]. The first phase lasting from collapse through 4 minutes of resuscitation efforts is the electrical phase; considered the time when defibrillation will be most successful. Observational series have highlighted significant benefits in patients defibrillated between 2-3 minutes following VF arrest, compared to patients receiving defibrillation later in resuscitation[12, 13].

Following the electrical phase is the circulatory phase, in which the importance of high quality CPR is evident[14]. Pre-clinical models have highlighted that VF frequency and amplitude are important predictors of successful cardioversion[15, 16]. In both animal[17] and patients[18] receiving CPR prior to defibrillation, VF waveform parameters have been improved.

Prolonged whole body ischemia is responsible for the metabolic stage, commencing approximately 10 minutes after onset of cardiac arrest. This metabolic phase is the least understood of the three phases and is likely related to multifactorial insults including, an array of inflammatory mediators, cytokines and reperfusion injury[19].

Patients who initially achieve ROSC after this metabolic phase have significant rates of morbidity and mortality, which is largely due to cerebral and cardiac dysfunction that accompanies prolonged whole body ischemia. This syndrome has been called the post cardiac arrest syndrome and comprises anoxic brain injury, post cardiac arrest myocardial dysfunction,

systemic ischemia/reperfusion response, and persistent precipitating pathology[5]. The contribution of each of these components in an individual patient depends on various factors including pre-arrest co-morbidities, duration of the ischemic insult and the aetiology of the cardiac arrest. An understanding of each of these components of the post cardiac arrest syndrome is important in optimizing treatment strategies and clinical outcomes.

Post cardiac arrest anoxic brain injury is a major cause of morbidity and mortality in the post cardiac arrest period and is responsible for approximately two thirds of the deaths in patients who initially survive to admission to the intensive care unit[20]. The brain is highly sensitive to ischemic insult and reperfusion injury. Cardiac arrest causes injury to neurons via multiple mechanisms, including disrupted calcium homeostasis, free radical formation, and activation of cell-death signaling pathways. After ROSC and cerebral reperfusion the microcirculation may also be disrupted by an ongoing no-reflow phenomenon[21]. In addition to these insults, secondary neurological injury may be caused by pyrexia, hyperglycemia, hyperoxygenation and seizure activity[22].

Even in the absence of acute coronary occlusion or underlying cardiomyopathy, prolonged cardiac arrest causes on-going myocardial dysfunction that contributes significantly to post resuscitation syndrome and is associated with a third of in-hospital mortality[20]. Laboratory and clinical studies indicate that myocardial dysfunction begins within minutes of ROSC and is clinically seen as early instability in heart rate and blood pressure. This myocardial dysfunction is maximal at approximately 8 hours post ROSC and may show significant improvement by 24-48 hours[23]. Post cardiac arrest myocardial dysfunction appears to be a stunning phenomenon reflected by elevated left ventricular end diastolic pressure, reduced cardiac index and preserved coronary blood flow[24]. The use of catecholamines to maintain blood pressure and cerebral perfusion may potentiate post cardiac arrest myocardial dysfunction, although responsiveness of the myocardium to inotropic drugs is maintained[25].

Circulatory arrest leads to tissue hypoperfusion even with effective cardiopulmonary resuscitation (CPR). Following ROSC, a global reperfusion injury occurs leading to endothelial activation, systemic inflammation and activation of coagulation cascades[26]. Clinical features of this vasodilatory type state include hypotension, intravascular volume depletion, impaired vasoregulation, reduced oxygen utilization, and increased susceptibility to infection.

The final component of the post arrest syndrome is the initial pathological event that caused the cardiac arrest. A common cause of OHCA is coronary artery disease which may be either acute coronary occlusion due to plaque rupture and thrombus formation or ventricular arrhythmia due to previous scar formation. Together, these account for 40%-80% of cases[27, 28]. Rarer causes of cardiac related arrhythmias are dilated and hypertrophic cardiomyopathies, genetic ion-channel abnormalities and pulmonary embolism (PE). In one study, the latter was shown to account for 11% of cardiac arrests[29].

There are three major aspects in the management of the post-cardiac arrest patient. First, consideration must be given to triage to appropriate treatment centres[30]. Second, in-hospital treatment focuses on each component of the post-arrest syndrome. Finally, there are issues relating to prognostication and, in patients with good prognosis, consideration of placement of an automatic internal cardiac defibrillator (AICD). The following review article focuses on therapeutic strategies in the management of the post cardiac arrest syndrome patient and serves as a major introduction to my thesis.

Contemporary Reviews in Cardiovascular Medicine

Post Cardiac Arrest Syndrome

A Review of Therapeutic Strategies

Dion Stub, MBBS; Stephen Bernard, MBBS, MD; Stephen J. Duffy, MBBS, PhD; David M. Kaye, MBBS, PhD

Out-of-hospital cardiac arrest (OHCA) is a common initial presentation of cardiovascular disease, affecting up to 325 000 people in the United States each year.[1] In a recent meta-analysis of >140 000 patients with OHCA, survival to hospital admission was 23.8%, and survival to hospital discharge was only 7.6%.[2] In patients who initially achieve return of spontaneous circulation (ROSC) after OHCA, the significant subsequent morbidity and mortality are due largely to the cerebral and cardiac dysfunction that accompanies prolonged whole-body ischemia. This syndrome, called the post cardiac arrest syndrome, comprises anoxic brain injury, post cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology[3,4] (Table 1). The contribution of each of these components in an individual patient depends on various factors, including prearrest comorbidities, duration of the ischemic insult, and cause of the cardiac arrest. This review focuses on therapeutic strategies and recent developments in managing patients who are initially resuscitated from cardiac arrest.

There are 3 major aspects that require consideration in the management of the post cardiac arrest patient. After resuscitation, a decision must be made in relation to the appropriate triage of the OHCA patient. The next phase of management concerns the in-hospital treatment, which must address each component of the postarrest syndrome as appropriate for the individual patient. Finally, there are issues relating to prognostication and the deployment of various secondary prevention measures. Our recommended treatment algorithm is summarized in the Figure. This ideally follows from the implementation of basic and advanced life support measures, including effective cardiopulmonary resuscitation and defibrillation when appropriate, which are major determinants of outcome.[2] Such an approach to care may be further modified according to the presence of other comorbidities and precipitating factors, which should be assessed in as much detail as possible.

Regional Systems of Care

The treatment of the patient with ROSC after OHCA requires a multidisciplinary team with significant experience and expertise in the management of these patients. Regional systems of care are well established by other time-critical interventions in patients after trauma,[5] stroke,[6] and ST-elevation myocardial infarction (STEMI).[7]

In a similar manner, data are emerging to suggest that the development of cardiac arrest treatment centers may provide improved outcomes for the OHCA patient. A Japanese cardiac arrest register showed that OHCA patients transported to critical cardiac care hospitals had improved survival compared with patients transported to hospitals without specialized cardiac facilities (odds ratio, 3.39; $P<0.001$).[8] In a Swedish study of almost 4000 OHCA patients, there was marked variability in hospital outcomes after adjustment for prehospital factors, with survival varying from 14% to 42% in different centers.[9] A US cross-sectional study of 109 739 patients indicated that hospital factors, including teaching status, size, and urban location, were associated with outcome in patients resuscitated from cardiac arrest[10]; a separate study designed to optimize all facets of cardiac arrest care showed that transport to dedicated cardiac arrest centers was also associated with an improvement in outcomes.[11] Conversely, the recent study by the Resuscitation Outcomes Consortium Investigators of 4087 patients with OHCA found increased rates of survival in patients after OHCA who were treated at larger hospitals capable of invasive cardiac procedures, but this was not an independent association when adjusted for prehospital factors.[12]

One concern regarding the establishment of regional systems of care for post cardiac arrest management is the potential for longer transport times to hospital. However, recent data indicate that increasing transport time is not associated with adverse patient outcomes.[13] Further research into the safety of bypassing the nearest hospital to facilitate transfer to a cardiac center is needed.

The data supporting implementation of systems of care approach for OHCA are preliminary and limited. The American Heart Association, however, has recommended that patients with OHCA in whom the initial cardiac rhythm is ventricular fibrillation (VF) or OHCA with ST-segment elevation be transported directly to centers with expertise and facilities in the management of acute coronary syndromes.[14,15]

Initial Management

It is important that a comprehensive management algorithm is applied to the post cardiac arrest patient. This model is

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Table 1. Post Cardiac Arrest Syndrome: Pathophysiology and Potential Treatment Strategies

Post Cardiac Arrest Syndrome	Anoxic Brain Injury	Arrest-Related Myocardial Dysfunction	Systemic Ischemic/ Reperfusion Response	Persistent Precipitating Pathology
Pathophysiology	Disrupted calcium homeostasis Free radical formation Cell death signaling pathways Reperfusion injury No reflow Additional insults: pyrexia, hyperglycemia, hyperoxygenation	Stunning phenomenon Global hypokinesis Elevated LVEDP Preserved coronary blood flow (excluding patients with ACS)	Intra-arrest global tissue hypotension Reperfusion injury Endothelial activation Systemic inflammation Activation of clotting cascades Intravascular volume depletion Disturbed vasoregulation Risk of infection	ACS plaque rupture/thrombus formation Chronic ischemic myocardial scar Pulmonary embolism Cardiomyopathies: dilated, restrictive, hypertrophic, genetic, channelopathy, congenital
Potential therapeutic approaches	Therapeutic hypothermia Early hemodynamic optimization Ventilation and airway protection Seizure control Controlled oxygenation	Systems of care Revascularization Intravenous fluid Inotropes IABP ECMO LVAD	Goal-directed therapy Intravenous fluids Vasopressors Glucose control Hemofiltration Antimicrobials	Address disease specific origin

ACS indicates acute coronary syndrome; LVEDP, left ventricular end diastolic pressure; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; and LVAD, left ventricular assist device.

consistent with care in other emergent situations, such as early goal-directed therapy in patients with severe sepsis.[16] In patients with OHCA, goal-directed therapy protocols have been introduced as part of a package of postresuscitative care to improve survival.[17,18] Interventions include focusing on ensuring adequate oxygenation and ventilation, support of the circulation, timely institution of therapeutic hypothermia (TH), consideration of coronary angiography, and general critical care measures, such as blood glucose control.

Oxygenation and Ventilation

Although 100% oxygen is commonly used during initial resuscitation, both animal models and observational studies highlight the potential harm of oxygen toxicity.[19,20] In a multicenter cohort study of 6326 patients admitted to intensive care after OHCA, arterial hyperoxia (Pao_2 >300 mm Hg) was independently associated with increased in-hospital mortality compared with patients with normoxia or hypoxia.[20] Accordingly, until there are further data from prospective, controlled clinical trials, it seems reasonable to recommend that both hyperoxia and hypoxia after ROSC be avoided. In conjunction, careful control of Pco_2 is also critical because hypocarbia causes cerebral vasoconstriction and hyperventilation decreases cardiac output.

Circulatory Support

Hemodynamic instability is common after cardiac arrest, and may be associated with poorer prognosis. Stabilization of the circulation involves fluid therapy, vasoactive drug therapy, and consideration of mechanical support. Early echocardiography provides information on the extent of myocardial dysfunction and may assist in guiding treatment.[21]

The optimal hemodynamic targets in the postresuscitative period remain unclear. In a single-center study using a postresuscitative care treatment algorithm, there was a non-statistically significant 28% improvement in mortality in 20 patients compared with historical controls.[18] In that study, key aspects of therapy were the early initiation of TH, maintenance of a relatively elevated mean arterial pressure (80 to 100 mm Hg), use of a pulmonary artery catheter in cases of worsening cardiogenic shock, and early determination of left ventricular ejection fraction with echocardiography used to guide inotropic drug therapy. Another study used TH, urgent coronary reperfusion, and goal-directed therapy in 61 patients, and compared this strategy with historical controls.[17] There was a 30% improvement in favorable neurological outcome. Interestingly, this study had a target mean arterial pressure of 65 to 70 mm Hg. On the basis of the available evidence, it is reasonable to target a mean arterial pressure of 65 to 100 mm Hg, taking into consideration the patient's normal blood pressure and severity of myocardial dysfunction.

If adequate circulatory stability is not achievable with the use of fluid therapy and modest inotropic drug therapy, the use of mechanical support should be considered. There is some clinical evidence of benefit with the use of the intra-aortic balloon pump in acute coronary syndrome complicated by cardiogenic shock[22]; however, a recent review indicated no overall benefit in patients with STEMI and cardiogenic shock.[23] Intra-aortic balloon pumps have been used to various degrees in observational series in cardiac arrest, with insertion rates of 22% to 46% of patients.[24–26]

Given that the level of circulatory support provided by the intra-aortic balloon pump may be inadequate in the setting of severe ventricular dysfunction, alternative devices that provide greater degrees of cardiac support may be considered. Percutaneous cardiopulmonary bypass with extracorporeal membrane oxygenation is one such option, with the additional benefits of possibly aiding resuscitation in prolonged arrest.[27–29] In a recent systematic review of extracorporeal

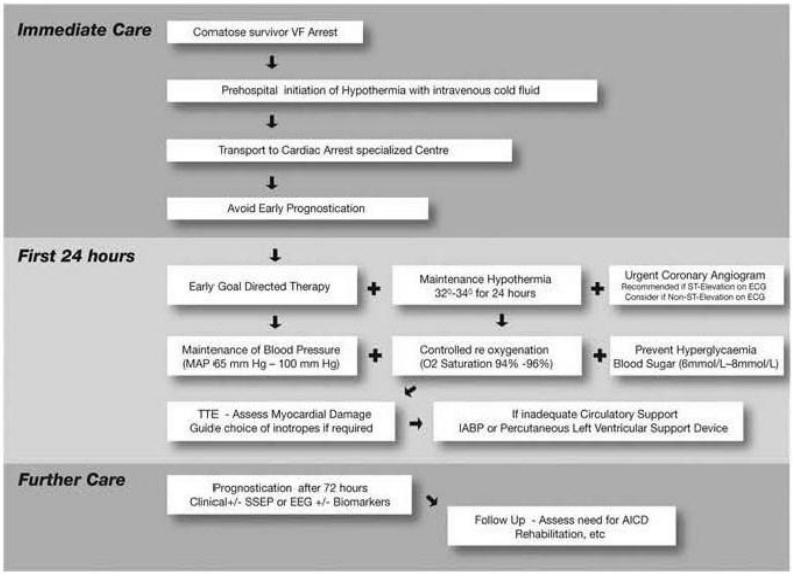

Figure. Post cardiac arrest treatment algorithm. MAP indicates mean arterial blood pressure; TTE, transthoracic echocardiogram; IABP, intra-aortic balloon pump; SSEP, somatosensory evoked potentials; EEG, electroencephalography; and AICD, automated internal cardioverter-defibrillator.

membrane oxygenation initiated during cardiac arrest, an overall in-hospital survival rate of 45% was found.[30] There is also interest in other percutaneous left ventricular assist devices that have hemodynamic profiles superior to the intra-aortic balloon pump that, if available, should be considered.[31,32]

Neuroprotection: Therapeutic Hypothermia

Post cardiac arrest anoxic brain injury is a major cause of morbidity and mortality, and is responsible for approximately two thirds of the deaths in the post cardiac arrest period.[33] One important advance in post-ROSC management is the use of TH to treat comatose survivors of OHCA. Two randomized, controlled trials have clearly confirmed the benefit of TH after cardiac arrest.[34,35] Both studies investigated mild TH in comatose adult patients after OHCA secondary to VF.

The first trial, the European Multicenter Trial, conducted by the Hypothermia After Cardiac Arrest Study group, enrolled 275 patients.[34] At 6 months, 55% of the cooled patients had a good outcome compared with 39% of normothermic control subjects. The second study, from Australia, enrolled 77 patients who were resuscitated from OHCA with an initial cardiac rhythm of VF.[35] At hospital discharge, 49% of patients who were cooled to 33°C for 12 hours had good neurological outcomes compared with 26% of the control group. A subsequent individual patient data meta-analysis indicated that the number needed to treat to provide a favorable neurological outcome is 6.[36] As a result of these trials, TH is now recommended in the management of anoxic neurological injury after cardiac arrest[3,4] (Table 2).

There is uncertainty regarding the applicability of TH to patients in cardiac arrest in whom the initial cardiac rhythm is asystole or pulseless electric activity.[40] These patients have significantly poorer outcomes compared with patients with an initial cardiac rhythm of VF/ventricular tachycardia.[2,4] There is some evidence, however, that TH will benefit patients with an initial rhythm of asystole or pulseless electric activity.[36,41] The most recent International Liaison Committee on Resuscitation guidelines recommend using hypothermia after cardiac arrest if the initial rhythm is ventricular tachycardia or VF and consideration of its use for other rhythm disturbances.[3,4]

The physiological benefits of TH are thought to be multifactorial, including decreases in cerebral oxygen demand and direct cellular effects and a reduction in reactive oxygen species generation.[42] Despite the recommendation that hypothermia should be initiated as soon as possible after cardiac arrest, the method, timing, and duration of hypothermia treatment have yet to be comprehensively studied. Hypothermia can be induced by a variety of different methods,

Table 2. Select Randomized Controlled Studies of Therapeutic Hypothermia in Out-of-Hospital Cardiac Arrest

Reference	n	Target Temperature, °C	Cooling Duration, h	Initial Rhythm	Target MAP, mm Hg	Survival, %	Good Neurological Recovery, %
Hachimi-Idrissi et al,[37] 2001	30	34	4	Asystole/PEA	>60	19 vs 7	13 vs 0
HACA Group,[34] 2002	275	32–34	24	VF/VT	>60	59 vs 45	55 vs 39
Bernard et al,[35] 2002	77	33	12	VF/VT	90–100	49 vs 32	49 vs 26
Bernard et al,[38] 2010	234	33	24	VF/VT	100	50*	49
Castren et al,[39] 2010	200	34	24	All rhythms	. . .	36*	27

MAP indicates mean arterial blood pressure; PEA, pulseless electric activity; HACA, Hypothermia After Cardiac Arrest Study; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Randomized study of prehospital vs in-hospital initiation of hypothermia (all patients cooled).

including surface cooling, ice-cold infusions, evaporative transnasal cooling, and endovascular cooling catheters.[37,39,43] Although studies have examined cooling efficacy and time to target temperature, no available studies have compared different cooling devices with respect to the key clinical end points of mortality and morbidity.

Given that animal models of early initiation of hypothermia lead to improved neurological outcomes, the prehospital induction of TH has been proposed.[44] Two randomized, controlled trials of paramedic administration of ice-cold fluids to induce TH have indicated that this is a safe and effective means of induction of cooling. These trials, however, have not shown clinical benefit compared with cooling patients on arrival to hospital.[38,45]

The rewarming phase can be regulated with external or internal devices used for cooling or by other heating systems. The optimal rate of rewarming is not known, but a current recommendation is to rewarm at ≈0.25°C/h to 0.5°C/h.[46] Care should be taken during the induction and rewarming phases to monitor electrolyte and hemodynamic changes carefully.

Therapeutic hypothermia decreases heart rate and increases systemic vascular resistance.[47] There is also evidence that TH may be beneficial to the heart in the postarrest period. Animal studies have shown improvement in myocardial function, myocardial salvage, and reduced infarct size in the setting of cardiac arrest or acute myocardial infarction with the use of TH.[48] Early studies of the use of TH, before cardiac magnetic resonance imaging, revealed a trend toward a reduction in infarct size.[43,49] In the setting of acute myocardial infarction and cardiac arrest, observational trials have also shown a nonsignificant reduction in infarct size with hypothermia.[50] A recent study of 20 patients with STEMI revealed a significant increase in myocardial salvage on cardiac magnetic resonance imaging in those patients who received TH before reperfusion.[51]

Possible adverse effects of hypothermia include electrolyte and intravascular volume changes, cardiac arrhythmias, immunological impairment, and altered coagulation profile. These complications, however, usually can be easily managed in an intensive care environment. Clinical trials have not found any significant increase in severe complications of TH compared with patients treated with normothermia.[34,35,38,46]

Overall, TH is an important intervention after cardiac arrest and resuscitation. Issues relating to the method and timing of cooling, use in non–VF/ventricular tachycardia, and use in patients with in-hospital cardiac arrest require further clinical trials.

Other Neuroprotective Strategies

Seizures increase the cerebral metabolic rate, and may accentuate neurological injury after OHCA. Phenytoin is used for seizure treatment, and, in a rat model of cardiac arrest, reduced brain edema by attenuating intracellular salt and water.[52] Although thiopentone is neuroprotective in animal models,[53] a large clinical trial showed no benefit.[54] Other neuroprotective agents, such as magnesium and calcium channel inhibition, have undergone prospective clinical trials with no improvement in outcomes.[55,56]

Management of Acute Coronary Syndrome in the OHCA Patient

Coronary artery disease is a major cause of OHCA, commonly related to the development of acute coronary syndrome or ventricular arrhythmia resulting from previous scar formation. Together, these account for 40% to 90% of cases.[57] Rarer causes of cardiac-related arrhythmias are dilated and hypertrophic cardiomyopathies, channelopathies, and pulmonary embolism.

Patients with OHCA have been excluded from most large, randomized trials that focus on the management of acute coronary syndrome, which makes decision making regarding the role of primary percutaneous coronary intervention (PCI) in this group of patients difficult. Observational data are strongest in the setting of OHCA and STEMI. The initial ECG shows ST elevation in 30% to 60% of patients with ROSC after OHCA.[25,58–60] In a multicenter French study of 186 patients with OHCA and STEMI, primary PCI was performed routinely, with stents inserted in 90% of patients. Survival at 6 months was 54%, with 46% of patients free of neurological impairment.[25] A number of other observational series have indicated high procedural success rates and in-hospital survival rates between 60% and 78%, with early coronary angiography for patients with STEMI after OHCA.[24,26,61,62]

Although an urgent interventional approach for OHCA with STEMI is recommended, the role of urgent coronary angiography in patients with OHCA and non-STEMI is uncertain. Many clinicians may advocate waiting to assess neurological recovery before proceeding to angiography.[63] Proponents of an early interventional approach suggest that 40% of cardiac arrests caused by unstable coronary plaques may be missed if decision making is based on ECG criteria alone[58,60] (Table 3). A recent study of cardiac arrest patients undergoing coronary angiography found that significant coronary lesions occur in up to 66% of patients without ST elevation.[59] The largest series in coronary intervention and OHCA has found that primary PCI was an independent predictor of survival regardless of initial ECG findings (odds ratio, 2.06; $P=0.013$).[60]

Given the available data, combined with the difficulties of early prognostication with TH, current guidelines suggest that it is reasonable to consider all survivors of OHCA of suspected cardiac origin for primary PCI.[14] When emergent coronary intervention is unavailable, treatment with thrombolytic drugs may be considered. The use of prehospital thrombolysis for cardiac arrest has been studied, but has not shown significant benefit compared with placebo.[64,65] If no facilities are available for immediate PCI, thrombolysis should be considered for patients with STEMI after OHCA.[66,67] The potential interaction between thrombolysis and TH has not been well studied, with possible issues of efficacy of thrombolysis and increased risk of hemorrhage.

Combining Hypothermia and Coronary Intervention

Combining TH with primary PCI is emerging as a new approach to further improve outcomes. Table 4 highlights recent observational studies in which, collectively, TH was used in 86% of patients and PCI in just under half, with a

Table 3. Select Studies of Coronary Angiogram After Resuscitation From Cardiac Arrest

Reference	Trial Details	n	STEMI, %	PCI, %	IABP, %	Survival, %	Good Neurological Recovery, %
Spaulding et al,[58] 1997	Prospective observational study; VF and non-VF arrest	84	42	44	11	38	36
Garot et al,[25] 2007	Retrospective observational study; STEMI after VF/VT	186	100	87	43	54	46
Gorjup et al,[61] 2007	Retrospective observational study; VF and non-VF arrest	135	100	80	16	69	55
Hosmane et al,[62] 2009	Retrospective observational study; STEMI after VF/VT	98	100	79	NA	64	59
Anyfantakis et al,[63] 2009	Retrospective observational study; VF and non-VF arrest	72	32	33	22	49	46
Lettieri et al,[26] 2009	Retrospective observational study; VF and non-VF arrest	99	100	90	22	78	68

STEMI indicates ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; IABP, intra-aortic balloon pump; VF, ventricular fibrillation; and VT, ventricular tachycardia.

cumulative survival of 47%.[24,50,60,68,69] These nonrandomized trials have revealed the combination of TH and PCI to be safe, feasible, and possibly more efficacious in comatose survivors of OHCA than either therapy alone.

Prognostication

Despite the advances in postresuscitative care, a significant proportion of patients will have a poor neurological outcome. The need for prolonged intensive care in patients with severe neurological impairment and little hope for recovery is devastating for families. This also consumes considerable resources. There is a need, therefore, for accurate and timely neurological prognosticating in comatose survivors of cardiac arrest. It is also important to avoid withdrawal of active management in patients who may make a meaningful recovery.

A number of prearrest factors, such as patient comorbidities, are associated with poorer survival.[70] Intra-arrest details, such as initial cardiac rhythm, time to ROSC, absence of bystander cardiopulmonary resuscitation, and maximal end-tidal CO_2, are also associated with patient outcome.[2] However, no factors are sufficiently reliable to conclude that continued care is futile.

An evidence-based approach to prognostication based on postarrest factors has been proposed by the American Academy of Neurology, including key clinical, biochemical, and neurophysiological parameters.[71] The role of neurological imaging at present is largely limited to the exclusion of intracranial pathologies, such as hemorrhage or stroke. These guidelines, however, are based on evidence that predates the widespread introduction of TH, which raises concern regarding the ongoing validity of this approach. Hypothermia may delay the clearance of sedation and mask return of neurological function.[72]

Clinical Examination

The most reliable predictor of neurological outcome in the prehypothermia era was the neurological examination.[71] A recent study examined the validity of clinical findings in patients who had received hypothermia. In a retrospective review of 36 patients, the authors found that the absence of motor responses better than extensor posturing on day 3 may not be reliable, whereas absent papillary and corneal reflexes at day 3 remained accurate at predicting hopeless prognosis in the hypothermia setting.[73]

Table 4. Select Studies of Combination Therapies for Out-of-Hospital Cardiac Arrest

Reference	Trial Details	n	Cooling, %	PCI, %	BSL, mmol/L	MAP, mm Hg	Survival, %	Good Neurological Recovery, %
Hovdenes et al,[24] 2007	Retrospective observational study after VF arrest	50	100	72	4–7	NA	82	68
Knafelj et al,[68] 2007	Retrospective observational study; STEMI after VF/VT arrest	40	100	90	NA	NA	75	55
Sunde et al,[17] 2007	Prospective observational study; VF and non-VF arrest	61	77	49	5–8	>65–70	56	56
Gaieski et al,[18] 2009	Prospective observational study; VF and non-VF arrest	18	100	39	<8.5	80–100	50	44
Dumas et al,[60] 2010	Prospective observational study; VF and non-VF arrest	435	86	41	NA	NA	40	37
Stub et al,[69] 2011	Retrospective observational study after VF arrest	81	75	38	NA	NA	64	57

PCI indicates percutaneous coronary intervention; BSL, blood sugar level; MAP, mean arterial blood pressure; VF, ventricular fibrillation; STEMI, ST-elevation myocardial infarction; and VT, ventricular tachycardia.

Neurophysiological Tests

The assessment of somatosensory evoked potentials is a commonly performed neurophysiological test of the integrity of central pathways. The absence of early cortical somatosensory evoked potentials has been shown to be a reliable predictor of poor outcome[74]; conversely, the presence of somatosensory evoked potentials does not necessarily guarantee good neurological outcomes.[75,76]

Electroencephalography has been used to evaluate the depth of coma and extent of damage after cardiac arrest. However, the predictive value of individual patterns is poor. A meta-analysis before the use of TH concluded that electroencephalography was strongly associated with poor outcome, but not invariably linked with futility, with a small false-positive rate of 3%.[71] A recent prospective study of prognostication in 111 patients receiving TH indicated that electroencephalography in this setting may be better than previously reported, but also suggested that clinical findings in patients who receive TH may be unreliable.[77]

Biochemical Markers

Biochemical markers in peripheral blood, such as neuron-specific enolase and S100β, have been used to prognosticate functional outcome after cardiac arrest.[78] Although a recommendation has been made on the use of biochemical markers as predictors of poor outcome,[71] care must be taken because of the lack of standardization of measurement techniques.[4] As with neurophysiological tests, there are conflicting data on whether there is decreased accuracy in the use of biochemical markers after the use of TH.[76,79]

The current evidence suggests that there is uncertainty in the prognostication of patients with coma after OHCA who have been treated with TH. The recovery period after hypothermia therapy has not been defined clearly, and early withdrawal of life-sustaining treatment may not be justified. Until more is known about the impact of TH, prognostication should probably be delayed until day 3 after rewarming from TH[3,4] and should use multiple modalities.

Further Care

The recovery of patients after cardiac arrest requires input from a multidisciplinary team with expertise in assessment for rehabilitation, neuropsychological assessment, if appropriate, and discharge planning. The decision regarding further therapy such as the need and timing of an automated implantable cardioverter-defibrillator is also important.[80]

Conclusions

In patients who achieve ROSC after OHCA, morbidity and mortality remain significant in part because of the development of a specific post cardiac arrest syndrome. To achieve improved survival and improved neurological outcomes, it will be necessary to develop and adopt a systematic approach to all elements of the pathophysiological process. Treatment strategies focusing on both prehospital and postresuscitative care are vital to improving patient outcomes, and may be further optimized with the development of regional systems of care. Specifically, emphasis should be placed on the development of specialist centers that offer goal-directed therapies, including TH, early coronary angiography, and temporary circulatory support when appropriate, together with comprehensive neurological assessment and therapy.

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None.

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Chapter 2: Therapeutic Hypothermia in the Cardiac Catheterization Laboratory

Monash University

Declaration for Thesis Chapter 2

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Declaration by candidate

In the case of Chapter 2 the nature and extent of my contribution to the work was the following:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Stub D	Principle Author, responsible for overall study concept, literature review, analysis, interpretation of results and development and writing of manuscript. Responsible author who effects overall responsibility of publication	70%

Candidate's Signature		**Date** 1/11/2012

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**
Bernard S	Analysis of results and manuscript development and editing
Duffy S	Analysis of results and manuscript development and editing
Shaw J	Analysis of results and manuscript development and editing
Kaye D	Analysis of results and manuscript development and editing

Declaration by co-authors

The undersigned hereby certify that:

- the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
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Signature 3		**Date** 13/11/2012
Signature 4		**Date** 1/11/2012

Therapeutic Hypothermia in the Cardiac Catheterization Laboratory

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Introduction

Out-of-hospital cardiac arrest (OHCA) is a common presentation of cardiovascular disease. Owing to the high incidence of acute coronary ischemia in this clinical scenario, consideration of emergent coronary angiography is currently recommended for all patients whose initial rhythm after OHCA is ventricular fibrillation (VF). Therapeutic hypothermia (TH) has been shown in randomized clinical trials to improve outcomes for comatose survivors of OHCA and, as such, interventional cardiologists and cardiac catheterization laboratory staff need to be familiar with the important role that TH has in managing these patients. In addition to the beneficial effects of TH on neurological reperfusion injury, there is accumulating evidence that TH may reduce myocardial reperfusion injury following percutaneous coronary intervention (PCI). Thus, there may also be a role for TH in alert patients with ST-segment elevation myocardial infarction (STEMI) without cardiac arrest. In this review, the current indications, physiological effects, and techniques for the induction and maintenance of TH in the catheterization laboratory are summarized.

TH in comatose survivors of cardiac arrest

Anoxic brain injury is a major cause of morbidity and mortality after initial resuscitation from OHCA, and is responsible for approximately two-thirds of the subsequent deaths seen in hospital[20]. One recent advance in the care of patients who are initially comatose after the return of spontaneous circulation following OHCA is the use of TH for the treatment of neurological injury. There has been interest in TH for this indication for many years. Although there were supportive anecdotal reports of the use of TH for neurological injury after in-hospital cardiac arrest in the 1950s[31], TH was largely abandoned until laboratory models of anoxic brain injury in the 1990s demonstrated improved outcomes with TH that was induced shortly after resuscitation[32]. Further laboratory studies in a range of animal models confirmed the potential efficacy of TH in the treatment of anoxic neurological injury after prolonged cardiac arrest[33, 34]. Preliminary clinical trials demonstrated the safety and feasibility of TH in patients with OHCA[35-38]. Subsequently, two randomized controlled trials confirmed the benefit of TH after cardiac arrest (Table 1) [39, 40]. Both trials investigated TH in comatose adult patients after OHCA when the initial cardiac rhythm was VF or ventricular tachycardia (VT).

A total of 275 patients were enrolled in the European, multicenter trial conducted by the Hypothermia After Cardiac Arrest (HACA) study group[39]. At 6 months, 55% of the cooled

patients had a good outcome compared with 39% of normothermic controls. In the second study, 77 patients who were resuscitated from OHCA with an initial cardiac rhythm of VF or VT were enrolled[40]. At hospital discharge, 49% of patients who were cooled to 33°C for 12 h had a favorable neurological outcome compared with 26% of the control group. A subsequent meta-analysis of individual patient data indicated that the number of patients needed to treat to provide a good neurological recovery was six[41]. As a result of these trials, the most recent American Heart Association (AHA) guidelines recommend that TH should be induced as soon as possible and maintained for 12–24 h in the management of anoxic neurological injury after cardiac arrest when the initial cardiac rhythm is VF or VT[5, 42].

Table 1. Studies of TH in out-of-hospital cardiac arrest.

Study (Year) [Reference]	n	Target temperature (°C)	Duration of cooling (h)	Initial rhythm	Survival rate [TH vs. normothermia] (%)	Neurorecovery rate [TH vs. normothermia] (%)
Hachimi-Idrissi et al. (2001) [67]	30	34	4	Asystole/pulseless electrical activity	19 vs. 7	13 vs. 0
Hypothermia after Cardiac Arrest (2002) [10]	275	32–34	24	VF/VT	59 vs. 45	55 vs. 39
Bernard et al. (2002) [11]	77	33	12	VF/VT	49 vs. 32	49 vs. 26
Kim et al. (2007) [74]	125	*	*	All rhythms	33 vs. 29	30 vs. 26
Bernard et al. (2010) [73]	234	33	24	VF/VT	50†	49
Castren et al. (2010) [68]	200	34	24	All rhythms	36†	27

*Patients were cooled systematically only in the prehospital field. †Randomized study of prehospital vs. in-hospital initiation of TH (all patients cooled).
TH: therapeutic hypothermia; VF: ventricular fibrillation; VT: ventricular tachycardia.

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However, there is uncertainty with regard to the applicability of TH to patients with OHCA in whom the initial cardiac rhythm is asystole or pulseless electrical activity[43, 44]. These patients have significantly poorer outcomes compared with patients with an initial cardiac rhythm of VF or VT[3]. To date, there has been no large randomized trial to compare the outcomes of TH with those of normothermia in these patients. Small trials and anecdotal reports have yielded conflicting results[41, 45]. Therefore, the most recent AHA guidelines suggest consideration of the use of TH after resuscitation from OHCA in patients whose initial cardiac rhythm is asystole or pulseless electrical activity[5, 42].

Urgent coronary angiography in survivors of OHCA

In addition to the induction of TH, early coronary angiography should be considered in patients who are successfully resuscitated from OHCA and in whom it appears that there was a cardiac cause for the arrest. However, the role of early PCI in this group of patients is uncertain. As a result of the inability to obtain informed consent, unconscious patients were not included in the large randomized trials of early PCI that demonstrated its efficacy in patients with STEMI.

There has been no prospective randomized trial in comatose patients after OHCA that has compared the outcomes of early transfer to the catheterization laboratory with either later or no cardiac catheterization. However, there is considerable observational evidence that supports early transfer of unconscious post-OHCA patients with STEMI to the catheterization laboratory. These data indicate high procedural success rates and in-hospital survival rates of 60–78% following early coronary angiography (and PCI where appropriate) for patients with STEMI following OHCA[46-49].

The role of primary PCI in patients who have been resuscitated from OHCA and who do not have evidence of STEMI on 12-lead electrocardiography (ECG) is more uncertain. On one hand, PCI is expensive and would not be justified if the neurological prognosis was poor[50]. On the other hand, unstable coronary plaques that are suitable for treatment with PCI may go untreated if the decision is based on 12-lead ECG criteria alone[51, 52]. In a recent study of OHCA patients who underwent coronary angiography, significant coronary lesions were found to occur in up to 66% of patients who did not have ST-segment elevation[53]. In the largest series of coronary interventions in the setting of OHCA, the authors found that PCI was an independent predictor of survival irrespective of the initial ECG findings (odds ratio 2.06; p=0.013)[52].

Given the relatively good prognosis of patients who receive TH following OHCA and who have an initial cardiac rhythm of VF or VT, the difficulties of accurate early prognostication, and the lack of sensitivity and specificity of the initial 12-lead ECG, it seems reasonable that all patients with coma following OHCA and an initial cardiac rhythm of VF or VT should undergo both immediate TH and early coronary angiography[54]. Table 2 highlights recent observational studies in which TH and coronary angiography were used as part of a routine care protocol for patients following OHCA[52, 55-60]. The results of these non-randomized trials have demonstrated the combination of TH and PCI to be safe, feasible, and possibly more efficacious in comatose survivors of OHCA than either of the two therapies alone[61].

Table 2. Cooling and cardiac catheterization for out-of-hospital cardiac arrest.

Study (Year) [Reference]	Initial rhythm	n	Patients who underwent cooling (%)	Patients who underwent PCI (%)	Survival rate (%)	Neurorecovery rate (%)
Hovdenes et al. (2007) [29]	Post-VF arrest	50	100	72	82	68
Knafelj et al. (2007) [30]	STEMI post-VF arrest	40	100	90	75	55
Sunde et al. (2007) [33]	VF and non-VF arrest	61	77	49	56	56
Wolfram et al. (2008) [31]	STEMI post-VF arrest	16	100	100	75	69
Gaieski et al. (2009) [28]	VF and non-VF arrest	18	100	39	50	44
Dumas et al. (2010) [25]	VF and non-VF arrest	435	86	41	40	37
Stub et al. (2011) [32]	Post-VF arrest	81	75	38	64	57

PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; VF: ventricular fibrillation.

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TH in Myocardial Infarction

Laboratory studies of TH in myocardial infarction

There is evidence from laboratory studies that TH reduces myocardial reperfusion injury and thus limits the size of myocardial infarction (MI). For example, Abendschien et al. examined whether TH affected infarct size in anesthetized dogs that underwent a 5-h left anterior descending (LAD) coronary artery occlusion without subsequent reperfusion[62]. They observed that the average infarct size in the dogs that received TH (core temperature 26°C for 3 h) was reduced by 35% compared with normothermic controls ($p=0.03$). In another early study, Haendchen et al. measured the effect of TH on experimental infarct size and survival rate in a canine model that included both ischemia and reperfusion[63]. The LAD coronary arteries of the dogs were occluded and, 30 min after occlusion, cooled arterial blood (20°C) was retroperfused into the coronary sinus. After 3 h, forward reperfusion was commenced for a duration of 7 days, after which the outcomes were measured. Both mortality rate (17% vs. 31%; $p<0.02$) and infarct size (2% vs. 4.2%; $p<0.02$) were significantly improved in the dogs that were treated with TH compared with normothermic controls.

Further animal studies indicate that TH initiated before coronary artery occlusion has a powerful myocardial protective effect, substantially reducing infarct size[64]. However, for TH to be used in the clinical setting, its protective effects need to persist when the procedure is initiated after the onset of ischemia or after reperfusion. When TH is started after ischemia but before reperfusion,

there is a time-dependent benefit. In rabbit and pig models, cooling initiated 10–20 min after coronary artery occlusion resulted in a reduction in infarct size, with the tissue-sparing effects of TH decreasing over time[65-68].

Conversely, preclinical models have revealed little to no reduction in infarct size when TH is initiated after reperfusion. For example, Maeng et al. inflated an angioplasty balloon in the LAD coronary arteries of pigs for 45 min, followed by 3 h of reperfusion[69]. The investigators found that systemic TH that was induced immediately before reperfusion did not significantly reduce infarct size.

The potential benefits of TH on the myocardium may extend beyond a reduction in infarct size. In a pig model, Gotberg and colleagues found that post-reperfusion TH reduced the degree of microvascular obstruction, even though the overall infarct size was similar to that in normothermia-treated hearts[70]. Other experimental studies have also indicated that TH is effective at reducing the “no reflow” phenomenon of microvasculature obstruction, an important clinical outcome measure[71], while also potentiating the effects of ischemic preconditioning in reducing reperfusion injury [72, 73].

TH may also have a positive effect on the myocardium by reducing heart rate without reducing left ventricular function[74]. TH has been shown to increase cardiac output and left ventricular wall motion in both healthy hearts and ischemic experimental models[75, 76], and also has potential benefits in ventricular remodeling following MI [77].

Clinical trials of therapeutic hypothermia in myocardial infarction

Primary PCI to facilitate reperfusion is the cornerstone of treatment for patients with STEMI. Despite the presence of strong experimental evidence of the benefit of TH in reducing reperfusion injury, the procedure has rarely been adopted in the clinical setting. Several small pilot trials have demonstrated that TH is feasible and safe to use in the catheterization laboratory to treat patients with STEMI (Table 3). Dixon et al. performed the first randomized trial of TH in patients with STEMI[78]. In this multicenter study of 42 patients, endovascular cooling was used to lower core temperature to 32–33°C in patients with STEMI of <6 h duration. The mean core temperature at the first balloon inflation was 34.7°C, and the mean duration of TH was 241 min. The primary endpoint of the study was the incidence of major adverse cardiac events at 30 days follow-up. No significant difference in this endpoint was found between

treated and non-treated patients (0% vs. 10%; p=non-significant). The secondary endpoint of infarct size (determined by single-photon emission computed tomography [SPECT]) at 30 days follow-up was also only marginally smaller in the cooled patients compared with normothermic controls (2% vs. 8%, p=non-significant). The results of other small trials of TH in alert patients with STEMI have indicated that both intravascular and surface cooling are feasible and are not associated with a higher rate of cardiovascular adverse events or a reduction in reperfusion times [79, 80].

Table 3. Cooling in acute ST-segment elevation myocardial infarction.

Study (Year) [Reference]	n	Cooling method	Target core temperature (°C)	Mean core temperature at reperfusion (°C)	Total cooling time (h)	Infarct size [therapeutic hypothermia vs. normothermia] (%)
Pilot studies						
Kandzari et al. (2004) [53]	18	Endovascular	32–34	34.2	5	8.5*
Ly et al. (2005) [52]	9	Surface	34.5	N/A	3	23.0*
Clinical trials						
Dixon et al. (2002) [51]	42	Endovascular	33	34.7	3	2.0 vs. 8.0
O'Neill et al. (2003) [54]	395	Endovascular	33	35.0	3	14.1 vs. 13.8
Grines et al. (2004) [55]	228	Endovascular	33	N/A	6	10.0 vs. 13.0
Gotberg et al. (2010) [56]	20	Cold fluid and endovascular	33	34.7	3	13.7 vs. 20.5

*Non-randomized, pilot trials without control groups.

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Based on the results of these smaller trials, a number of larger clinical trials were initiated to investigate the effect of TH with endovascular cooling on infarct size in patients with STEMI. In the COOL-MI (Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients with Acute MI) trial, O'Neill et al. reported the outcomes of cooling as an adjunct to PCI in patients with acute MI[81]. A total of 395 patients with MI of <6 h duration were randomized to either normothermia or TH with an endovascular cooling device (the Reprieve Temperature Therapy System; Radiant Medical, Redwood City, CA, USA). The mean core temperature reduction at the time of reperfusion was only 1°C, with the target temperature of 33°C being reached 75 min after initiation of TH and continuing for 3 h. There was no difference in the primary endpoint of infarct size at 30 days follow-up (as measured by SPECT) between the TH and normothermic treatment groups (14.1% vs. 13.8%; p=non-significant). A prespecified secondary analysis

revealed that patients with anterior infarcts who received effective TH (i.e. core temperature <35°C at reperfusion) had smaller infarcts than patients with core temperatures >35°C at reperfusion (5.0% vs. 16.5%; p=0.07) or normothermic controls (5.0% vs. 15.0%; p=0.03). The occurrence of major adverse cardiac events did not significantly differ between the two groups. However, there was a longer average door-to-balloon time in the TH group compared with controls (110 min vs. 92 min; p<0.01), which may have adversely affected infarct size.

In the ICE-IT (Cooling Adjunctive to Primary Coronary Intervention) trial, 228 patients were randomized to either normothermia or TH using an endovascular cooling device (Celsius Control System; Innercool, San Diego, CA, USA)[82]. Detailed results on temperature management were not made available, but the target core temperature was 33°C for 6 h. As in the COOL-MI trial, there was no difference in the primary endpoint of infarct size between the two groups (10% in the TH group vs. 13% in controls; p=non-significant), and there was a similar trend towards significance in the subgroup analysis comparing infarct sizes between patients with anterior infarction who were <35°C at time of reperfusion and those who had a higher temperature (13% vs. 23%; p=0.09).

The results of these clinical trials indicate that TH may be most effective in patients with larger infarcts who are able to be adequately cooled prior to reperfusion. With this in mind, in their recent small trial, Gotberg et al. examined the feasibility of combining 1–2 L of 4°C saline with intravascular cooling (Celsius Control System; Innercool), initiated prior to reperfusion and continuing for 3 h, in patients with anterior or inferior infarcts of <6 h duration[83]. The clinical endpoints differed from those of previous studies, in that infarct size was normalized to area at risk (myocardial salvage) utilizing cardiac magnetic resonance imaging, and traditional biomarkers were also investigated. In the patients who were treated with TH, a mean core body temperature of 34.7°C prior to reperfusion was achieved without causing significant increases in door-to-balloon or procedure times compared with controls. Despite similar durations of ischemia in the two groups, infarct size normalized to area at risk was significantly improved in the TH group (29.8% vs. 48.0%; p=0.04). This was accompanied by a significant reduction in both peak and cumulative troponin T concentrations. The authors assert that no complications were observed with the combination of cold fluid and endovascular cooling, but that larger trials, such as the currently recruiting CHILL-MI (Efficacy of Endovascular Catheter Cooling Combined with Cold Saline for the Treatment of Acute MI) study (clinicaltrials.gov identifier NCT01379261)

and the ongoing CAMARO (Hypothermia with Automated Peritoneal Lavage Following Cardiac Arrest of Acute STEMI) trial, are needed to confirm its efficacy.

Physiological effects of TH

The main goal of TH is to reduce the reperfusion injury, particularly to the injured brain, after resuscitation from OHCA, while also reducing the myocardial reperfusion injury that may occur when flow is restored to an occluded coronary artery during PCI. The mechanism by which TH reduces reperfusion injury is multifactorial. TH reduces metabolism by 8% per 1°C reduction in temperature, and therefore reduces tissue oxygen demand [84, 85]. In addition, TH attenuates tissue edema and intracellular acidosis[86]. Laboratory models of ischemia reperfusion reveal that hypothermia reduces the production of reactive oxygen species, as well as directly inhibiting cell apoptosis[87, 88]. TH may also improve tissue reperfusion by altering coagulation pathways and inflammatory responses[89]. Finally, TH alters gene expression, with a complex interplay between upregulation of anti-apoptotic proteins such as brain-derived neurotrophic factor, and down regulation of pro-apoptotic proteins such as matrix metalloproteinase-9[90].

Specific cardiac physiological effects of TH include a reduction in heart rate, with common ECG changes of QT interval prolongation and the appearance of Osbourne (J) waves[91]. Interestingly, there is evidence from the laboratory that TH increases the success rate of defibrillation in patients with a VF or VT rhythm[92]. It also has effects on coagulation, such as a mild increase in clotting times and a reduction in platelet function. TH may lead to a reduction in potassium levels owing to an intracellular shift. The effects of TH on the immune system usually occur over days, and are probably not relevant to short-term use of TH in the catheterization laboratory[93].

Techniques for inducing TH

TH can be induced by a variety of different methods, including surface cooling, ice-cold infusions, transnasal evaporative cooling, and endovascular cooling catheters[78, 94, 95]. Although there have been studies to examine cooling efficacy and time to target temperature for these methods, none is available in which the different cooling devices were compared with each other in terms of the key clinical endpoints of mortality and morbidity. One challenge for physicians is to make sure that the technique of TH induction does not delay the patient's surgery.

Surface cooling

In the original clinical trials of TH in OHCA survivors, simple ice packs and general anesthesia were used to reduce core temperature. Since that time, specialized technology has become available that incorporates electronic temperature feedback in order to control core temperature more accurately. Current surface cooling techniques use pads, jackets, and helmets that are applied closely to the skin. These contain circulating water which cool or warm the patient depending on the temperature setting. These machines improve temperature control compared with simple cooling blankets[96].

The use of this specialized surface cooling is applicable to anesthetized patients in the catheterization laboratory. The jackets are radio-opaque and allow coronary angiography to proceed without removal of the jacket. However, cooling using these devices is relatively slow. Furthermore, conscious patients do not tolerate surface cooling, and alternative core-cooling techniques are required in this patient group.

Intravascular cooling

Intravascular cooling involves the insertion of a large catheter into the inferior vena cava via the femoral vein that allows heat exchange by circulating saline through a balloon. This technology has been used for fever control in the intensive care unit (ICU)[97], for the induction of TH after OHCA[98], and to treat MI[78, 81]. Interestingly, core cooling appears not to generate shivering in conscious patients to the extent that surface cooling does. Therefore, this technology has been used in clinical trials of TH in conscious patients in the catheterization laboratory and patients with stroke[99]. Although intravascular cooling allows accurate temperature control and shorter times to target temperatures than surface cooling, intravascular cooling is still relatively slow, with mean times to target temperature of 3–4 h. In addition, the catheter is relatively expensive.

Large-volume, ice-cold infusion

There have now been a number of reports on the use of a rapid infusion of large-volume, ice-cold, crystalloid fluid to induce TH in prehospital settings [100, 101], emergency departments[102, 103], and ICUs[104] [77]. To date, there have been two randomized, controlled trials of the administration by paramedics of large-volume (30 mL/kg), ice-cold, intravenous fluids (LVICF) in order to induce TH [100, 101]. The results of these have indicated that this is a safe and effective means of TH induction. The combination of ice-cold saline and intravascular cooling in conscious patients, in order to facilitate cooling prior to reperfusion, has also been reported [83].

One concern with the use of a rapid infusion of LVICF is the risk of developing pulmonary edema, particularly in patients with poor left ventricular function. However, in ventilated patients, the development of pulmonary edema is very rare, and LVICF has been shown not to reduce lung function any further in ventilated patients[105]. The use of LVICF in non-intubated patients to induce TH requires further research; nonetheless, in preliminary reports it has been found to be safe and cause no ill effects[83].

Peritoneal Lavage

One novel approach to the rapid induction of TH is the insertion of a catheter into the abdominal cavity under local anesthesia and the instillation of 3–4 L of ice-cold saline. This approach has been shown to rapidly reduce core temperature to 33°C in approximately 10 min[106]. However, there is a risk of perforation of the bowel, and the widespread use of this technique will require clear indication that early TH is associated with significant improvement in neurological and myocardial outcomes.

Intranasal cooling

Another potentially rapid, but minimally invasive, means of inducing TH in intubated patients is nasopharyngeal cooling using evaporation of a perfluorocarbon via high-flow nasal prongs. In a recent pilot trial, intra-arrest nasal cooling in the prehospital setting was compared with hospital-initiated surface cooling in 200 patients[95]. The primary endpoint of time to the target tympanic temperature of 34°C was significantly shorter in the transnasal cooling group than the surface cooling group (102 min vs. 282 min; p=0.03). Intranasal cooling is not applicable in conscious patients, and requires subsequent surface or intravascular temperature control for the maintenance and reversal of TH.

Suppression of shivering

In conscious patients, the induction of TH may lead to shivering, particularly when core temperatures reach 34–35°C, and this may markedly increase metabolic rate and myocardial oxygen demand. However, suppression of shivering in conscious patients undergoing TH is problematic. There are several strategies that have been found to be effective. Firstly, core cooling techniques appear to be better tolerated than surface cooling techniques. Secondly, warming of the hands with heated gloves or warm blankets covering the chest and legs ("counter-warming") during core cooling has been found to be effective. Finally, pharmacological approaches such as the use of meperidine and buspirinone have some effect. Comatose

patients who have been resuscitated from OHCA are generally intubated, and general anesthesia including the use of muscle relaxants will effectively suppress shivering.

Duration of TH

The optimal duration of TH for the treatment of neurological injury after OHCA is unknown. In patients resuscitated from OHCA, Bernard et al. used TH for 12 h[40], and the HACA study group used it for 24 h [39]. Currently, it is unknown whether shorter or longer durations of treatment are indicated. Ongoing clinical trials investigating different durations of TH and different target temperatures will provide much needed information on this issue (clinicaltrials.gov identifiers NCT00878644 and NCT01155622).

In conscious patients who underwent TH for myocardial reperfusion, the duration of TH in previous trials was 3–6 h[78,83, 107]. However, recent animal data indicate that combination TH (1 L 4°C saline plus endovascular cooling) for only 30 min may be as effective as longer periods of TH at reducing myocardial reperfusion injury[108]. Based on these data, the CHILL-MI investigators will be maintaining TH for only 1 h, allowing for completion of TH in the catheterization laboratory, and possibly improving patient comfort and reducing the incidence of complications.

Rewarming from TH

The rewarming phase of TH can be regulated with the external or internal devices that were initially used for cooling, or with other heating systems. The current recommendation is to rewarm relatively slowly (0.25–0.5°C per h)[109]. Care should be taken during the induction and rewarming phases to carefully monitor the patient for the development of shivering as well as hemodynamic and electrolyte changes.

Conclusions

TH is an important intervention following resuscitation from OHCA when the patient's initial cardiac rhythm is VF or pulseless VT. Increasingly, such patients are being transferred to the cardiac catheterization laboratory to undergo coronary angiography. There is also growing interest in the role of TH in conscious patients undergoing PCI in order to limit myocardial reperfusion injury. Interventional cardiologists should be familiar with the physiology of TH and the current techniques for induction and maintenance of this treatment that are applicable in the cardiac catheterization laboratory.

Chapter 3: Usefulness of Cooling and Coronary Catheterization to Improve Survival in Out-Of-Hospital Cardiac Arrest

Monash University

Declaration for Thesis Chapter 3

Stub D, Hengel C, Chan W, Jackson D, Sanders K, Dart AM, Hilton A, Pellegrino V, Shaw JA, Duffy SJ, Bernard S, Kaye DM. **Usefulness of Cooling and Coronary Catheterization to Improve Survival in Out-of-Hospital Cardiac Arrest.** *Am J Cardiol* 2011;107:522-527.

Declaration by candidate

In the case of Chapter 3 the nature and extent of my contribution to the work was the following:

Name	**Nature of contribution**	**Extent of contribution (%)**
Stub D	Principle Author, responsible for overall study concept, literature review, analysis, interpretation of results and development and writing of manuscript. Responsible author who effects overall responsibility of publication	70%

Candidate's Signature	[redacted]	**Date** 1/11/2012

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Hengel C	Data collection for historical controls, manuscript development and editing
Chan W	Analysis of results and manuscript development and editing
Jackson D	Data collection for contemporary treatment paradigm
Sanders K	Analysis of results and manuscript development and editing
Dart A	Analysis of results and manuscript development and editing
Hilton A	Analysis of results and manuscript development and editing
Pellegrino V	Analysis of results and manuscript development and editing
Shaw J	Analysis of results and manuscript development and editing
Duffy S	Analysis of results and manuscript development and editing
Bernard S	Analysis of results and manuscript development and editing
Kaye D	Analysis of results and manuscript development and editing

Declaration by co-authors

The undersigned hereby certify that:

- the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
- they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
- there are no other authors of the publication according to these criteria;
- potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
- the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Alfred Hospital Heart Centre, Intensive Care Unit, Baker IDI Heart and Diabetes Institute, Monash University Faculty of Medicine Nursing and Health Sciences, Austin Hospital, Ballarat Hospital

Signature 1	[redacted]	**Date** 5/12/2012
Signature 2	[redacted]	**Date** 9/11/2012
Signature 3	[redacted]	**Date** 10/12/2012
Signature 4	[redacted]	**Date** 14/11/2012
Signature 5	[redacted]	**Date** 11/11/2012
Signature 6	[redacted]	**Date** 7/12/2012
Signature 7	[redacted]	**Date** 5/12/2012
Signature 8	[redacted]	**Date** 13/11/2012
Signature 9	[redacted]	**Date** 9/11/2012
Signature 10	[redacted]	**Date** 9/11/2012
Signature 11	[redacted]	**Date** 9/11/2012

Introduction to Cooling and Coronary Angiography in OHCA

This year marks the 10th anniversary of the two seminal trials into therapeutic hypothermia in the management of comatose survivors from OHCA. Since then there has been a significant increase in our understanding of the post cardiac arrest syndrome and more importantly how the early systematic management of these patients can significantly improve outcomes[42]. Hospital treatments that are thought to improve survival after OHCA resuscitation include therapeutic hypothermia[39, 40], early reperfusion of blocked coronary arteries[51, 52] and possibly optimization of hemodynamic parameters such as blood pressure and glucose[55, 60].

These interventions require a multi-disciplinary team with experience and expertise in the management of these patients. Despite the evidence supporting the use of hypothermia and other post resuscitative measures, the uptake of these interventions has been poor[110, 111]. In a recent small Australian single centre study examining rates of therapeutic hypothermia use in a tertiary trauma level 1 ICU, less than half of comatose survivors of OHCA received appropriate TH and only 12% of patients were at target temperature within 2 hours[112].

Major changes to cardiopulmonary resuscitation and post cardiac arrest care guidelines occurred in 2005[113]. In a recent study utilizing Ambulance Victoria registry data, comparing outcomes in patients with OHCA before and after these guideline changes, an increase in rates of spontaneous circulation and survival to hospital admission was observed, with no improvement in survival to hospital discharge[114].

As with all cardiac arrest data, there are a number of possible explanations to these findings, whilst also recognizing the limitations of an observational registry based conclusion. One worrying possibility, however, is that whilst pre-hospital acute care may be improving in line with guideline changes, post resuscitation care remains inadequate, and despite improving EMS treatments, a lack of coordinated use of measures such as TH and PCI are adversely impacting on patient outcomes.

There is very little Australian data on the adoption of updated post resuscitation care guidelines and more importantly how these may impact on neurological recovery. In Chapter 3, I examine one quaternary referral institution with significant expertise in managing critically ill patients, including those with OHCA, major trauma and advanced cardiac failure and transplant therapy. This single centre study comparing outcomes in a historical control group to contemporary post-resuscitation practice indicates what can be achieved, with a systematic approach to patient management in the post resuscitative period[59].

Usefulness of Cooling and Coronary Catheterization to Improve Survival in Out-of-Hospital Cardiac Arrest

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Survival rates after out-of-hospital cardiac arrest (OHCA) continue to be poor. Recent evidence suggests that a more aggressive approach to postresuscitation care, in particular combining therapeutic hypothermia with early coronary intervention, can improve prognosis. We performed a single-center review of 125 patients who were resuscitated from OHCA in 2 distinct treatment periods, from 2002 to 2003 (control group) and from 2007 to 2009 (contemporary group). Patients in the contemporary group had a higher prevalence of cardiovascular risk factors but similar cardiac arrest duration and prehospital treatment (adrenaline administration and direct cardioversion). Rates of cardiogenic shock (48% vs 41%, $p = 0.2$) and decreased conscious state on arrival (77% vs 86%, $p = 0.2$) were similar in the 2 cohorts, as was the incidence of ST-elevation myocardial infarction (33% vs 43%, $p = 0.1$). The contemporary cohort was more likely to receive therapeutic hypothermia (75% vs 0%, $p < 0.01$), coronary angiography (77% vs 45%, $p < 0.01$), and percutaneous coronary intervention (38% vs 23%, $p = 0.03$). This contemporary therapeutic strategy was associated with better survival to discharge (64% vs 39%, $p < 0.01$) and improved neurologic recovery (57% vs 29%, $p < 0.01$) and was the only independent predictor of survival (odds ratio 5.5, 95% confidence interval 1.2 to 26.2, $p = 0.03$). Longer resuscitation time, presence of cardiogenic shock, and decreased conscious state were independent predictors of poor outcomes. In conclusion, modern management of OHCA, including therapeutic hypothermia and early coronary angiography is associated with significant improvement in survival to hospital discharge and neurologic recovery. (Am J Cardiol 2011;107:522–527)

In a previous study conducted in Australia before the widespread adoption of postresuscitation strategies such as cooling, survival after admission to hospital for out-of-hospital cardiac arrest (OHCA) was 25%, comparable to most registry data.[1] Given the rapid uptake of such approaches since that time, we hypothesized that advances in basic life support and postresuscitation hospital care have improved outcomes. Accordingly, we performed a single-center retrospective review of all patients with OHCA admitted to our hospital from 2002 to 2003 and from 2007 to 2009.

Methods

Melbourne has approximately 3.9 million inhabitants, which is served by a comprehensive centrally co-ordinated ambulance system, which is described elsewhere.[1] The Alfred Hospital (Melbourne, Victoria, Australia) is a large tertiary-/quaternary-care referral center that provides 24-hour emergency coronary and cardiac surgical interventions for patients with acute coronary syndromes.

In this retrospective analysis we evaluated clinical characteristics and outcomes of all patients who had an out-of-hospital ventricular fibrillation arrest with sustained return of spontaneous circulation (ROSC), defined as >20 minutes, and who were subsequently hospitalized at the Alfred Hospital. Analysis was performed for 2 treatment periods: a modern treatment paradigm, 2007 to 2009 (contemporary group), and a historical control group, 2002 to 2003. Data were obtained from Ambulance Victoria and hospital records. The study was performed in accordance with the Alfred Hospital ethics committee guidelines. Interrogation of the hospital database identified 326 patients with presumed OHCA. Seventy-seven patients were excluded secondary to noncardiac causes such as trauma, stroke, and drug overdose. Excluded were 4 patients who did not have ROSC on arrival, 11 patients transferred from other institutions, and 109 patients because of asystole or pulseless electrical activity as their initial rhythm. Our study population, therefore, consisted of 125 patients with OHCA secondary to ventricular arrhythmia.

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Table 1
Baseline characteristics

Characteristic	Control (n = 44)	Contemporary (n = 81)	*p* Value
Age (years)	64 ± 17	61 ± 16	NS
Men	34 (77%)	68 (84%)	NS
Current/ex-smoker	10 (23%)	45 (56%)	<0.01
Diabetes mellitus	3 (7%)	9 (11%)	NS
Hypertension	13 (30%)	47 (58%)	<0.01
Hyperlipidemia	5 (11%)	37 (46%)	<0.01
History of coronary disease	14 (32%)	28 (35%)	NS
Initial rhythm			
Ventricular fibrillation	40 (91%)	77 (95%)	NS
Ventricular tachycardia	4 (9%)	4 (5%)	NS
Basic life support			
Witnessed arrest	41 (93%)	75 (93%)	NS
Bystander resuscitation	33 (75%)	57 (70%)	NS
Ambulance response			
Call to arrival (minutes)	6 (5–9)	7 (6–10)	NS
Total time until return of circulation (minutes)	26 (15–35)	23 (14–30)	NS
Number of shocks	3.9 ± 3.5	3.8 ± 4.3	NS
Adrenaline administration	35 (80%)	58 (72%)	NS
Cause			
Acute coronary syndrome	30 (68%)	50 (62%)	NS
ST-segment elevation myocardial infarct	19 (43%)	27 (33%)	NS
Condition on arrival to hospital			
Unconscious	38 (86%)	62 (77%)	NS
Cardiogenic shock	18 (41%)	39 (48%)	NS
Interventions			
Therapeutic hypothermia	0 (0%)	61 (75%)	<0.01
Coronary angiography	20 (45%)	62 (77%)	<0.01
Emergent angiography	11 (25%)	49 (61%)	<0.01
Percutaneous coronary intervention	10 (23%)	31 (38%)	0.03
Coronary bypass graft surgery	0 (0%)	4 (5%)	NS

Values are presented as mean ± SD, number of patients (percentage), or median (interquartile range).

Table 2
Outcome of coronary angiography in study population

Coronary Angiographic Variable	Control (n = 20)	Contemporary (n = 62)	p Value
Normal	6 (32%)	13 (21%)	0.36
Single-vessel disease	12 (63%)	17 (27%)	0.02
Multivessel disease	2 (11%)	31 (50%)	0.01
Coronary arteries >50% stenosis, mean ± SD	1.5 ± 0.8	1.9 ± 0.8	NS
Infarct-related artery			
Left anterior descending coronary artery	10 (53%)	17 (27%)	0.02
Left circumflex coronary artery	0 (0%)	6 (12%)	NS
Right coronary artery	1 (5%)	14 (23%)	NS
Grafts	0 (0%)	1 (2%)	NS
Left main coronary artery	1 (5%)	3 (2%)	NS
Multivessel with no clear culprit	2 (10%)	8 (16%)	NS
Preintervention Thrombolysis In Myocardial Infarction grade 0–2 flow	8 (42%)	23 (47%)	NS
Thrombus-containing lesion	4 (21%)	11 (22%)	NS

Ambulance Victoria uses a 2-tier system of ambulance paramedics, most of whom have advanced life support skills, and intensive care paramedics who are authorized to perform endotracheal intubation and administer a range of cardiac drugs. Melbourne also uses a medical emergency response program in which ambulance and fire brigade services respond to cardiac arrests.[2] Cardiac arrest protocols follow the recommendations of the Australian Resuscitation Council.[3] After hemodynamic stabilization, patients are transported urgently to the nearest hospital.

In the 2 treatment periods, hospital care for patients with OHCA was modeled on relevant International Liaison Committee on Resuscitation guidelines at the time.[4,5] Decision regarding need for cardiac catheterization was made by the treating cardiologist. Intensive care treatment including target hemodynamic and metabolic parameters and choice of inotropic agents were decided by the treating physician according to general critical care guidelines. Therapeutic hypothermia was induced and maintained through a combination of ice-cold intravenous fluids, simple ice packs, and surface cooling blankets. The 2 significant changes to postresuscitative care in patients with OHCA during the study period were use of mild therapeutic hypothermia for unconscious patients (to preserve neurologic function) and increasing use of emergency coronary angiography to assess and treat underlying coronary artery disease as the cause for OHCA.

The primary outcome was survival to hospital discharge. Secondary outcome was "good" neurologic recovery, defined as cerebral performance categories (CPCs) 1 and 2. The CPC is a simple-to-use widely used cerebral performance measurement.[6]

Statistical analyses were performed with SPSS 16 (SPSS, Inc., Chicago, Illinois). Numerical normally distributed data were analyzed using Student's *t* test (presented as mean ± SD) and non-normal data were compared by Mann-Whitney test (presented as median with interquartile range). Proportions were analyzed with Fisher's exact test. A p value <0.05 was regarded as statistically significant. Prognostic factors that were found to be significant (p <0.10) in preliminary univariate analyses were entered into a multivariate logistic regression analysis. All variables were entered into the equation simultaneously to control for effects of confounding (a subsequent stepwise analysis provided similar results).

Results

Baseline characteristics of the study population are presented in Table 1. Important prehospital factors including rates of witnessed cardiac arrest, bystander cardiopulmonary resuscitation, time until ROSC, and adrenaline administration by paramedics were similar in the control and contemporary cohorts. On arrival to the emergency department the incidence of cardiogenic shock, defined as systolic blood pressure <90 mm Hg or requiring inotropic support, did not differ significantly between treatment periods (41% vs 48%, p = NS) and rates of decreased conscious state requiring intubation did not differ significantly (86% vs 77%, p = NS).

Table 3
Outcome of percutaneous coronary intervention in study population

Variable	Historical Control PCI (n = 10)	Modern PCI (n = 31)	p Value
Procedural success	9 (90%)	29 (94%)	NS
Final Thrombolysis In Myocardial Infarction grade 3 flow	8 (80%)	28 (90%)	NS
Door-to-balloon time (minutes)	145 (112 to 345)	120 (105 to 167)	NS
Stents per patient	1.2 ± 0.4	1.3 ± 1.1	0.03
Mean stent length (mm)	17.9 ± 5	19.8 ± 10	NS
Mean stent diameter (mm)	3.1 ± 0.8	3.7 ± 3	NS
Drug-eluting stents	0 (0%)	7 (23%)	NS
Multivessel intervention	0 (0%)	6 (19%)	NS
Peak troponin mean (range)	92 (0–186)	53 (0–179)	NS
Intra-aortic balloon pump	4 (40%)	8 (30%)	NS
Glycoprotein IIb/IIIa inhibitor	4 (40%)	23 (56%)	NS
Aspiration catheter	0	5 (16%)	NS

Values are presented as mean ± SD, number of patients (percentage), or median (interquartile range).

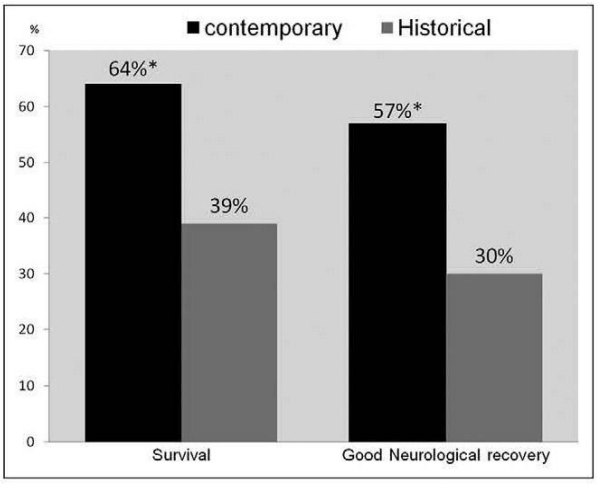

Figure 1. Outcomes based on contemporary *(black bars)* and historical control *(gray bars)* treatment periods (*p <0.01).

In the contemporary treatment group 75% of all patients received therapeutic hypothermia, representing 98% of comatose patients after ventricular fibrillation (Table 1). No patients in the control group received therapeutic hypothermia. Rates of coronary angiography and percutaneous coronary intervention (PCI) were significantly increased in the contemporary treatment group (77% vs 45%, p <0.01; 38% vs 23%, p = 0.03, respectively; Table 1). Of patients undergoing coronary angiography, 50% of patients did not go on to PCI for various clinical reasons (Table 2). PCI was successful in >90% of patients in the 2 treatment groups (see Table 3). Incidence of the left anterior descending coronary artery (LAD) as the culprit infarct-related artery was higher in the control group (53% vs 27%, p = 0.02). Multivessel disease (defined as multiple coronary lesions with >50% stenosis) was more prevalent in the contemporary treatment group (50% vs 11%, p <0.01).

Table 4
Significant univariate predictors of survival

Characteristic	Odds Ratio	95% Confidence Interval	p Value
Age	0.24	0.11–0.5	0.01
Basic life support			
Bystander resuscitation	3.3	1.5–7.5	0.01
Ambulance response			
Return of circulation >20 minutes	0.08	0.03–0.21	0.01
Number of shocks	0.83	0.73–0.94	0.01
Condition on arrival			
Unconscious	0.29	0.10–0.84	0.02
Cardiogenic shock	0.11	0.05–0.26	0.01
Interventions			
Cooling*	2.7	1.1–6.4	0.02
Coronary angiography	7.6	3.2–17.5	0.01
Successful coronary intervention	2.1	0.95–4.4	0.07
Contemporary management	2.9	1.3–6.1	0.01

* For unconscious patients only.

Survival to hospital discharge in the contemporary treatment group was 64% compared to 39% in the historical control (p <0.01). Discharge with favorable neurologic outcome (CPC 1 or 2) was also significantly improved (57% vs 30%, p = 0.01; Figure 1). Of survivors in the contemporary treatment group, 89% made a good neurologic recovery. Cause of death was similar in the 2 periods with 70% of patients dying due to poor neurologic outcome, 25% due to persistent cardiac dysfunction, and 5% due to multiorgan failure. Unadjusted predictors associated with survival are presented in Table 4. Survivors were significantly more likely to be managed by the contemporary treatment paradigm and undergo coronary angiography and successful PCI. In unconscious patients, there was a significant increase in survival (61% vs 37%, p = 0.03) and good neurologic outcome (54% vs 27%, p = 0.01) in those patients receiving therapeutic hypothermia. When adjusting for key prehospital and postresuscitative factors (Figure 2, Table 5), negative predictors of survival included cardiogenic shock, resuscitation times >20 minutes, and decreased conscious state. The contemporary treatment regimen was a significant independent predictor of survival (odds ratio 5.5, 95% confidence interval 1.2 to 26.2, p = 0.03).

Discussion

This study has demonstrated that a contemporary treatment paradigm with focused co-ordinated postresuscitative care combining therapeutic hypothermia with coronary angiography is associated with significant improvements in short-term clinical outcomes. The 64% survival to discharge rate is significantly better than other registry data of patients with OHCA and favorably compares to other institutions with similar treatment protocols.[7,8]

In the contemporary treatment group, 98% of comatose patients received therapeutic hypothermia. Of these patients, 60% survived, and of the survivors, 89% made a

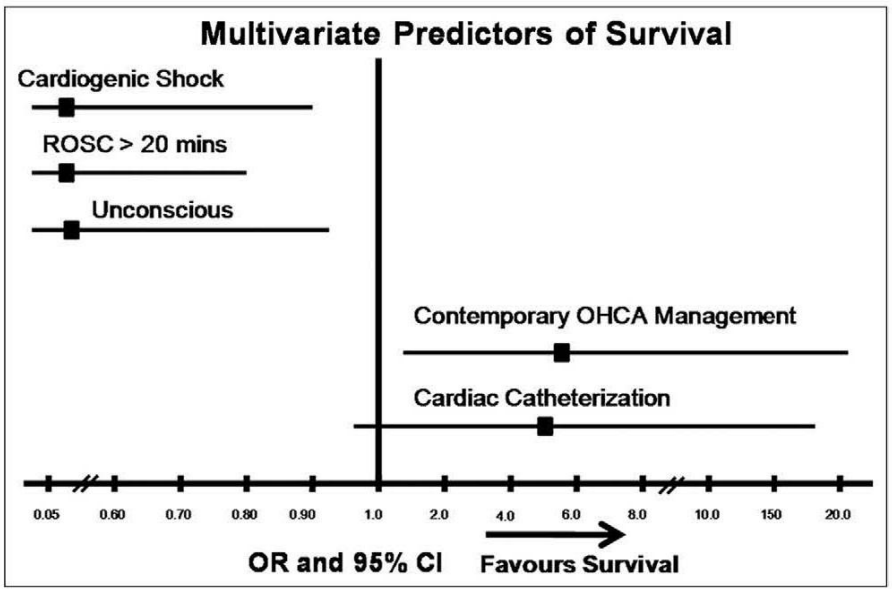

Figure 2. Independent predictors of survival. CI = confidence interval; OR = odds ratio.

Table 5
Multivariate predictors of survival

Characteristic	Odd Ratio	95% Confidence Interval	p Value
Contemporary management	5.5	1.2–26.2	0.03
Coronary angiography	4.3	0.97–19	0.06
Cardiogenic shock	0.12	0.02–0.54	0.01
Return of circulation >20 minutes	0.12	0.03–0.55	0.01
Unconscious on arrival	0.13	0.01–0.9	0.05

favorable neurologic recovery. This observation is important because uncertainty about neurologic recovery of patients with OHCA has previously cast doubt about the merits (and futility) of early invasive strategies such as coronary intervention. With the introduction of therapeutic hypothermia and the recognized difficulty in predicting neurologic outcomes when patients first arrive, there is a small role for early neurologic prognostication as a basis for further treatment decisions.[9,10] Therapeutic hypothermia was a significant unadjusted predictor of survival despite a large proportion of patients with cardiogenic shock who have previously been excluded from randomized studies. Use of mild therapeutic hypothermia is supported by 2 large randomized controlled trials[11,12] and is a recommended part of a standardized treatment strategy for comatose survivors of cardiac arrest.[13]

ST-segment elevation on initial electrocardiogram was similar in the 2 groups in approximately 1/3 of patients. There have been several observational studies and systematic reviews highlighting the importance of emergency PCI in patients with ST-segment elevation myocardial infarction and OHCA.[14–16] Recent reports have illustrated the further benefits of combining therapeutic hypothermia with early coronary intervention.[17–19] This has led to the recommendation by the American Heart Association that all patients with ST-segment elevation myocardial infarction and OHCA be managed at centers capable of 24-hour coronary intervention.[20]

Absence of ST-segment elevation in the setting of cardiac arrest has been shown to occur in up to 40% of OHCAs caused by unstable coronary plaques and coronary thrombosis.[21,22] Likewise, in our study 42% of patients undergoing emergency PCI did not have ST-segment elevation on electrocardiogram. This has led to the increasing adoption of emergency coronary angiography for all patients with OHCA of suspected cardiac origin and to developing appropriate systems of care to cater to such treatment protocols.[23–26]

The caveat to this approach is the significant number of patients with OHCA who undergo coronary angiography and do not go on to emergency revascularization. In our study 50% of patients undergoing angiography did not go on to PCI and 23% had angiographically normal coronary arteries. As part of an early cardiac catheterization protocol they received antiplatelet and antithrombotic agents, which have been hypothesized to have their own positive effects in the setting of cardiac arrest associated with coagulation disruption.[27,28] It was interesting to note that significantly more patients from the control group had the LAD as the infarct-related artery compared to the contemporary cohort (53% vs 27%, p = 0.02). This is possibly explained by the relatively small numbers of patients in the control group undergoing coronary angiography (n = 20). Most LAD infarcts are generally larger and associated with greater hemodynamic disturbance than non-LAD infarcts and more than likely influenced the decision to proceed to coronary angiography in the control group.

There was a trend to shorter resuscitation times in the contemporary treatment group, which may have contributed

to improved outcomes. However, this did not reach statistical significance ($p = 0.09$). During the study period several key changes to prehospital care included adopting a chest compression-to-ventilation ratio of 30:2, in line with International Liaison Committee on Resuscitation guidelines, and focusing on uninterrupted chest compressions.[4] As in other recent studies on optimizing prehospital care, it is reasonable to assume that these measures also contributed to improved patient survival.[29,30]

There are several limitations to our study. This is a single-center retrospective review and thus subject to potential confounders and selection bias contributing to results. The patients comprise a selected group who achieved ROSC before transport to hospital. Hospital and intensive care paramedics have extensive experience in managing patients with OHCA, and therefore the result's applicability to other health care networks is uncertain. In the assessment of neurologic recovery, the CPC score was chosen because of its ease of use and wide reporting in the literature. Although simple to use, this scoring system has not been well validated and was retrospectively assigned based on patient follow-up and clinical notes. With regard to therapeutic hypothermia, time spent at target temperature range was not recorded, making the quality of hypothermia difficult to ascertain. The study, however, does indicate that in a contemporary treatment era, an aggressive approach to patients with OHCA of suspected cardiac origin is associated with significantly improved survival to hospital discharge and neurologic recovery. Further study and randomized trials with particular focus on establishing systems of prehospital care and role of early coronary intervention are required.

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CHAPTER 4: Survival in Patients with Myocardial Infarction Complicated by Out-Of-Hospital Cardiac Arrest Undergoing Emergency Percutaneous Coronary Intervention

Monash University

Declaration for Thesis Chapter 4

Lim HS, Stub D, Ajani AE, Andrianopoulos N, Reid CM, Charter K, Black A, Smith K, New G, Chan W, Lim CC, Farouque O, Shaw J, Brennan A, Duffy SJ, Clark DJ**. Survival in patients with myocardial infarction complicated by out-of-hospital cardiac arrest undergoing emergency percutaneous coronary intervention.** *Int J Cardiol* 2011 epub ahead of print.

Declaration by candidate

In the case of Chapter 4 the nature and extent of my contribution to the work was the following:

Name	**Nature of contribution**	**Extent of contribution (%)**
Stub D	Co-principle Author, responsible for literature review, interpretation of results and development and writing of manuscript.	50%

Candidate's Signature	[redacted]	**Date** 1/11/2012

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**
Lim H	Co-principle Author, responsible for literature review, interpretation of results and development and writing of manuscript.
Ajani A	Analysis of results and manuscript development and editing
Andrianopoulos N	Statistical analysis, manuscript development and editing
Reid C	Analysis of results and manuscript development and editing
Charter K	Analysis of results and manuscript development and editing
Black A	Analysis of results and manuscript development and editing
Smith K	Analysis of results and manuscript development and editing
New G	Analysis of results and manuscript development and editing

Chan W	Analysis of results and manuscript development and editing
Lim C	Analysis of results and manuscript development and editing
Farouque O	Analysis of results and manuscript development and editing
Shaw	Analysis of results and manuscript development and editing
Brennan A	Analysis of results and manuscript development and editing
Duffy S	Analysis of results and manuscript development and editing
Clark D	Analysis of results and manuscript development and editing

Declaration by co-authors

The undersigned hereby certify that:

- the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
- they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
- there are no other authors of the publication according to these criteria;
- potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
- the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Alfred Hospital Heart Centre, Intensive Care Unit, Baker IDI Heart and Diabetes Institute, Monash University Faculty of Medicine Nursing and Health Sciences, Monash University Department of Epidemiology and Preventative Medicine, Ambulance Victoria, Austin Hospital, Royal Melbourne Hospital, Box Hill Hospital, Geelong Hospital

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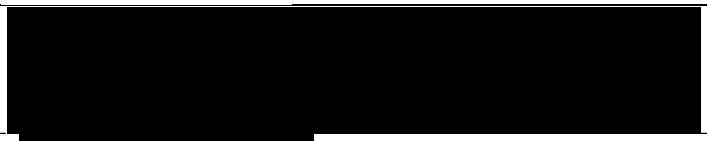
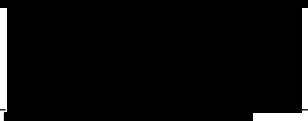
Signature 2		**Date** 11/11/12
Signature 3		**Date** 11/12/2012
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Exploring Outcomes Following Percutaneous Coronary Intervention in Patients with Out-Of-Hospital Cardiac Arrest

In adult patients, coronary artery disease (CAD) is the major cause of OHCA, responsible for 50-80% of all sudden cardiac deaths[27, 28]. Unfortunately in up to 10% of patients OHCA may be the first manifestation of CAD and is a major contributor to overall mortality from cardiovascular disease in the United States and other developed countries[2].

Coronary artery disease causes OHCA via two major mechanisms; acute plaque rupture with thrombus formation causing myocardial infarction and subsequent cardiac arrest, and secondly in patients with a history of CAD, chronic scar formation may establish a substrate for ventricular arrhythmias leading to OHCA. In autopsy derived studies of patients succumbing to OHCA, acute plaque rupture and thrombus formation is the cause of death in more than 60%-75% of cases[115]. Other studies highlight chronic scar formation as a significant cause of mortality in approximately 35% of cases[27]. Interestingly, even in patients whose death was attributed to chronic ischemic scar leading to a fatal arrhythmia, some post mortem studies have identified active coronary lesions in 46% of these patients[2].

These anatomical studies have been supported by observational series of routine coronary angiography in patients with OHCA surviving to hospital admission. Two large French series have identified culprit CAD in the majority of patients[51, 52]. Despite the evidence for CAD being the major cause of OHCA, there are no randomised trials exploring the role of coronary angiography and PCI in the treatment of survivors of OHCA[116].

As discussed in previous chapters, the lack of randomised data combined with historically poor outcomes in comatose survivors of OHCA prior to the adoption of therapeutic hypothermia, has led to some interventional cardiologists being reluctant to adopt a routine early invasive strategy in comatose survivors of OHCA. There is however, considerable observational evidence that supports early transfer of unconscious post-OHCA patients with STEMI to the catheterization laboratory[46-49].

The role of primary PCI in patients who have been resuscitated from OHCA and who do not have evidence of STEMI on 12-lead ECG is less certain. On one hand, PCI is expensive and would not be justified if the neurological prognosis was poor[50]. On the other hand, unstable

coronary plaques that are suitable for treatment with PCI may go untreated if the decision is based on 12-lead ECG criteria alone[51, 52]. There is also a significant body of observational evidence, including evidence from chapter 3, to suggest that routine angiography combined with other post resuscitative measures such as TH, even in the absence of STEMI, will improve outcomes in comatose survivors of OHCA[52, 55-60, 117]. As with all observational trials, the data is limited by the limitations of study design. There are fewer observational trials questioning the efficacy of a routine early invasive approach[118]. Until quality randomized trials are performed in this population, much like cardiologists have done in other high risk cohorts such as cardiogenic shock[119], there will remain lingering doubt to the efficacy of a routine invasive approach for all survivors of OHCA.

On the balance of evidence, however, combined with overwhelming pathophysiologic data highlighting the high incidence of CAD in patients with OHCA, the current guidelines suggest that it is reasonable to consider all survivors of OHCA of suspected cardiac aetiology for primary coronary angiography and PCI where appropriate[54].

The Melbourne Interventional Group Registry

This chapter builds on the international observational data in patients with AMI and OHCA undergoing PCI. This is a multicentre-study of PCI in survivors of OHCA utilizing The Melbourne Interventional Group (MIG) Registry. The MIG registry is a collaborative venture of interventional cardiologists practicing at 7 Australian tertiary referral hospitals, designed to record data pertaining to all PCI procedures and to perform follow up at 30 days and periodically thereafter. Demographic, clinical and procedural characteristics of consecutive patients undergoing PCI are prospectively recorded on case report forms using standardized definitions for all fields[120]. The registry is coordinated by the Centre of Cardiovascular Research and Education in Therapeutics, a research body within the Department of Epidemiology and Preventive Medicine (Monash University, Melbourne, Australia). An audit of 15 verifiable fields from 5% of randomly selected procedures at each institution is performed periodically by an investigator not affiliated with the institution; data accuracy is consistently about 97%, which compares favorably with other large registries[121].

The MIG registry has been approved by the ethics committee in each participating hospital. “Opt-out” informed consent was obtained in all patients, as previously described[8, 120, 122]. Among other clinical variables, the indication for the PCI was recorded, and included stable angina, unstable angina (with no rise in blood biomarkers), NSTEMI and STEMI. The interventional strategy, stent selection, and antithrombotic therapy are left to the discretion of the operator in all procedures.

In this chapter short and medium term outcomes of patients with AMI and OHCA are explored, highlighting excellent one year outcomes amongst survivors to discharge of OHCA, whilst also indicating the extremely high risk group of OHCA with concurrent cardiogenic shock.

Survival in Patients with Myocardial Infarction Complicated by Out-Of-Hospital Cardiac Arrest Undergoing Emergency Percutaneous Coronary Intervention

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Survival in patients with myocardial infarction complicated by out-of-hospital cardiac arrest undergoing emergency percutaneous coronary intervention

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ABSTRACT

Objectives: We sought to evaluate the clinical outcomes of patients with myocardial infarction (MI) complicated by out-of-hospital cardiac arrest (OHCA) undergoing percutaneous coronary intervention (PCI).
Background: Controversy remains regarding the benefit of early PCI in patients with MI complicated by OHCA.
Methods: We analyzed the outcomes of 88 consecutive patients presenting with MI complicated by OHCA compared to 5101 patients with MI without OHCA who underwent PCI from the Melbourne Interventional Group registry between 2004 and 2009.
Results: Patients with OHCA had a higher proportion of ST-elevation MI presentations (90.9% vs. 50%, $p<0.01$) and were more likely to be to be in cardiogenic shock (38.6% vs. 4.6%, $p<0.01$). Procedural success was similar in the two groups (95.5% OHCA vs. 96.5% non-OHCA MI cohort, $p=0.65$). In-hospital, 30-day, and 1-year survival in the OHCA cohort versus the non-OHCA MI cohort were 62.5% vs. 97.2% ($p<0.01$), 61.4% vs. 96.5% ($p<0.01$), and 60.2% vs. 94.2% ($p<0.01$), respectively. Within the OHCA cohort, presentation with cardiogenic shock (OR 7.2, 95% CI: 2.7–18.8; $p<0.01$) was strongly associated with in-hospital mortality. Importantly, 1-year survival of patients discharged alive from hospital was similar between the two groups (96% vs. 97% $p=0.8$).
Conclusion: Patients with MI complicated by OHCA remain a high-risk group associated with high mortality. However, high procedural success rates similar to non-OHCA patients can be attained. Survival rates better than previously reported were observed with an emergent PCI approach, with 1-year survival comparable to a non-OHCA cohort if patients survive to hospital discharge.

1. Introduction

Sudden cardiac death claims more than 300,000 lives in the United States annually, and accounts for approximately 50% of cardiovascular deaths in developed nations [1,2]. Out-of-hospital cardiac arrest (OHCA) remains a serious clinical problem associated with high mortality [3]. These patients are often excluded from clinical trials, are difficult to enroll, with studies yielding varying results [4–9]. An emergent percutaneous coronary intervention (PCI) approach has been found to benefit other high-risk groups such as those with cardiogenic shock [10,11]. There is increasing evidence that emergent PCI will also benefit those patients with OHCA [4–7,12–14], though some cardiologists still prefer to defer coronary angiography until the neurological outcome is unequivocal.

The aim of this study was to evaluate the clinical characteristics, procedural details and clinical outcomes of patients with myocardial infarction (MI) complicated by OHCA undergoing PCI compared to patients with MI without OHCA utilizing a large, prospective, contemporary multicenter PCI registry. Within the OHCA cohort, patients

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were further dichotomized into in-hospital survivors and non-survivors and factors associated with hospital mortality were determined.

2. Methods

2.1. Study population

There were 5753 patients with MI, including both ST-elevation MI (STEMI) and non-STEMI (NSTEMI) in the Melbourne Interventional Group (MIG) registry that underwent PCI from 1st April 2004 to April 1st 2009. Complete 12-month follow-up data were available on 5189 patients (90.2%). Of these 5189 patients, 88 (1.7%) were complicated by an OHCA, compared with 5101 patients without an OHCA ("non-OHCA MI cohort").

Melbourne has approximately 4 million inhabitants, and is served by a comprehensive, centrally coordinated ambulance system which has been described in detail elsewhere [15]. The treating hospitals are large tertiary care referral centres that provide 24-hour emergency coronary and cardiac surgical intervention for patients with acute coronary syndromes.

2.2. Data collection and registry design

The MIG registry is a collaborative PCI registry comprising 7 Australian public referral hospitals, and has been previously been described in detail [16–18]. Baseline demographics, clinical, angiographic and procedural characteristics of consecutive patients undergoing PCI are prospectively recorded on case report forms using standardized definitions for all fields [18]. The study protocol has been approved by the ethics committee in each participating hospital, and "opt-out" informed consent from the patient or next of kin was obtained in all patients [16,18].

In-hospital outcomes and complications were recorded at the time of discharge or death. Thirty-day and 12-month follow-up was conducted by telephone, using a standardized questionnaire [16,18]. All adverse events were confirmed by reviewing the patient medical records at the relevant hospitals. The registry is coordinated by the Centre for Cardiovascular Research & Education in Therapeutics, a research body within the Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia. An independent audit was conducted at all enrolling sites by an investigator not affiliated with that institution, in which 15 verifiable fields from 5% of all patients enrolled from each site were randomly selected and audited. Data accuracy was 97%, comparable to other large registries [19].

Cardiac arrest data were sourced via the Victorian Cardiac Arrest Registry (VACAR). All OHCA patient care data are recorded electronically by the treating paramedics at the completion of the case and downloaded to a central server on return to the ambulance station. Cases of OHCA are identified, reviewed for completeness and recorded in the VACAR according to Utstein definitions [20]. This information was linked to patients in the MIG registry using patient initials, date of birth, gender, date of cardiac arrest, and treating hospital.

2.3. Definitions and outcomes

OHCA of suspected cardiac origin was defined according to the Utstein template [21]. MI was defined as STEMI or non-STEMI. STEMI was defined by the presence of at least 0.1 mV ST-segment elevation or new pathological Q-waves in ≥2 contiguous ECG leads or new left bundle branch block (LBBB) with elevation of cardiac enzyme levels above the reference range. Non-STEMI was defined by the presence of ST-segment depression or T-wave abnormalities or ischemic symptoms with elevation of cardiac enzyme levels above the reference range.

In-hospital outcomes included all-cause mortality, peri-procedural MI (defined as new MI, distinct from the original event, during or after the catheterization laboratory visit with at least one of: elevation of creatine kinase/creatine kinase-myocardial band (CK/CK-MB) more than three times upper limit of normal and/or evolutionary ST-segment elevation, development of new Q-waves in 2 or more contiguous ECG leads, or new LBBB pattern on the ECG), bleeding (defined as requiring a transfusion and/or prolonged hospital stay and/or causing a drop in hemoglobin >3.0 g/dL), heart failure, renal failure (defined as an increase of creatinine to >0.20 mmol/L and two times the baseline creatinine level or a new requirement for dialysis), stroke, emergency PCI and emergency coronary artery bypass graft (CABG) surgery. Procedural success was defined as <50% residual stenosis after angioplasty and <20% after stenting in the treated lesions. Thirty-day and 1-year outcomes included all-cause mortality, cardiac and non-cardiac deaths, MI, target-lesion revascularization (TLR; defined as repeat revascularization within 5 mm of the treated segment) and target-vessel revascularization (TVR; defined as repeat revascularization of the treated vessel). Major adverse cardiac events (MACE) were a composite of death, MI and TVR.

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical data expressed as numbers/percentages, except where indicated. Continuous variables were compared using Student's *t*-tests or ANOVA as appropriate. Categorical variables were compared using Fisher's exact or Pearson's chi-square tests as appropriate. All calculated p-values were two-sided and p-values <0.05 were considered statistically significant. Cumulative incidence of mortality was also estimated according to the Kaplan–Meier method and the log-rank test was used to evaluate differences between groups.

Within the whole cohort, univariate and multivariate logistic regression analyses were used to determine independent predictors of 1-year mortality. Variables used were OHCA, age, gender, diabetes mellitus, hypertension, dyslipidemia, renal failure, cardiogenic shock, family history of coronary artery disease, previous MI or PCI, stroke, history of heart failure, smoking status, chronic lung disease, STEMI, left main procedure, proximal lesions, bypass graft lesions, American College of Cardiology and American Heart Association (ACC/AHA) type B2 and C lesions, ostial lesions, bifurcation lesions, use of glycoprotein IIb/IIIa inhibitors, drug-eluting stent use, stent length ≥20 mm, and stent diameter ≤2.5 mm. All univariate predictors with p<0.10, and age group were then added to a multivariate model.

Given the sample size (n=88), within the OHCA cohort, a comparison of in-hospital survivors and non-survivors was performed to determine predictors of in-hospital mortality using only univariate logistic regression analysis., All statistical analyses were performed using Stata Version 10.1 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Baseline OHCA details

Data from the Victorian Cardiac Arrest Registry indicates that in the study period, there were 558 patients with OHCA brought to registry-participating hospitals with return of spontaneous circulation (ROSC) in the field or emergency department. 373 (67%) had an initial rhythm of ventricular fibrillation/ventricular tachycardia (VF/VT) and 185 (33%) had an initial rhythm of asystole or pulseless electrical activity. Survival was significantly better in patients with an initial rhythm of VF/VT, 48% vs. 17% (p<0.001). Of the total cohort of OHCA patients transported to MIG registry hospitals, 88 patients (16%) went on to percutaneous coronary intervention. One-year survival rate in this group was 60.2%. Cardiac arrest details were obtainable in 80 of the 88 patients (91%). All patients had ROSC prior to catheterization. Three patients had ongoing cardiopulmonary resuscitation (CPR) to hospital with ROSC in the emergency department, whilst all other patients had ROSC prior to transport to hospital. Eighty three percent of patients with OHCA undergoing PCI had VF or VT as their initial rhythm.

3.2. Baseline clinical characteristics

There were no significant differences in age or gender between the OHCA cohort and non-OHCA MI cohort (Table 1). Patients in the non-OHCA MI cohort had a higher proportion of hypertension and hypercholesterolemia. The majority of OHCA cohort was STEMI presentations (90.9% vs. 50%, p<0.001). Median STEMI symptom to balloon inflation time for OHCA patients was 190 min (IQR 150–270 min) compared to 217 min (IQR 159–331 min) for non-OHCA MI patients (p<0.01), whilst door-to-balloon time was marginally longer in the OHCA group; 104 min vs. 92 min, p<0.01. Eighty percent of OHCA patients underwent PCI within 6 h from symptom onset. Patients with OHCA were more likely to be in cardiogenic shock (38.6% vs. 4.6%, p<0.001).

3.3. Lesion characteristics and procedural details

Patients with OHCA had a higher proportion of complex ACC/AHA B2 and C lesions and culprit lesions in the left anterior descending (LAD) artery (Table 2) compared to the non-OHCA MI cohort. Mean stent length was longer in the OHCA cohort, and although overall stent use was similar, drug-eluting stent use was less in OHCA patients. There was higher usage of glycoprotein IIb/IIIa inhibitors and intra-aortic balloon pumps (IABPs) in the OHCA cohort. Sixty-five percent of OHCA patients had Thrombolysis in Myocardial Infarction (TIMI) 0 flow prior to PCI, compared to 31% in the non-OHCA MI cohort, p<0.001. Procedural success was similar in the 2 groups, 95.5% OHCA vs. 96.5% non-OHCA MI cohort, p=0.65.

3.4. Clinical outcomes

In-hospital survival was 62.5% for OHCA patients, compared to 97.2% in the non-OHCA MI cohort (p<0.01), with significantly higher rates of in-hospital complications due to cardiac failure (27.6%) and

Table 1
Clinical characteristics of the OHCA vs. non-OHCA MI cohort.

	OHCA	Non-OHCA	p value
Number of patients	88 (1.7)	5101 (98.3)	
Age (years)	62.3 ± 12.3	63.6 ± 12.7	0.31
Males	70 (79.5)	3847 (75.4)	0.37
Diabetes mellitus	15 (17.1)	1058 (20.8)	0.39
Hypertension	36 (40.1)	2918 (57.3)	<0.01
Hypercholesterolemia	33(38.3)	3216 (63.4)	<0.01
Current smokers	21 (25.3)	1579 (31.3)	0.25
Current or ex-smoker	48 (57.8)	3430 (67.9)	0.05
Family history of CAD	26 (30.6)	1997 (39.9)	0.08
Previous myocardial infarction	11 (12.8)	1042 (20.5)	0.08
Peripheral vascular disease	4 (4.6)	315 (6.2)	0.53
Heart failure	1 (1.2)	168 (3.3)	0.26
Stroke	4 (4.6)	303 (5.6)	0.60
Previous PCI	7 (7.9)	729 (14.3)	0.09
Previous CABG	3 (3.4)	292 (5.7)	0.35
Renal failure[a]	6 (6.9)	223 (4.4)	0.26
Cardiogenic shock	34 (38.6)	233 (4.6)	<0.01
Clinical presentation			
Non-STEMI	8 (9.1)	2552 (50.0)	<0.01
STEMI	80 (90.9)	2549 (50.0)	<0.01
Median symptom-to-door time mins(IQR)[b]	75 (54–102)	105 (60–184)	<0.01
Median door-to-balloon time min (IQR)[b]	104 (86–153)	92 (64–126)	<0.01
Median symptom-to-balloon inflation time (min)[b]	190 (150–270)	217 (159–331)	0.02
Time period from symptom onset to PCI			
<6 h	71 (80.6)	1503 (29.8)	<0.01
6–24 h	4 (4.6)	947 (18.8)	<0.01
25 h–7 days	13 (14.8)	2501 (49.6)	<0.01

Data are *n* (%) or mean ± SD unless otherwise stated.
Abbreviations: CAD = coronary artery disease; PCI = percutaneous coronary interventions; CABG = coronary artery bypass graft; STEMI = ST-elevation myocardial infarction; IQR = Inter-quartile range (25th–75th percentile).
[a] Renal failure defined as baseline creatinine > 0.20 mmol/L.
[b] For STEMI patients only.

Table 2
Lesion characteristics, procedural details and interventional strategies of the OHCA vs. non-OHCA MI cohort.

	OHCA	Non-OHCA	p value
Mean number of lesions per procedure	1.1 ± 0.4	1.2 ± 0.4	0.51
Target vessel			
Left main	0 (0)	48 (0.8)	0.37
Left anterior descending	46 (45.5)	2113 (34.9)	0.03
Circumflex	12 (11.9)	787 (13.0)	0.74
Right coronary artery	30 (29.7)	2050 (33.8)	0.39
Multivessel disease	55 (62.5)	2775 (56.4)	0.26
ACC/AHA B2&C lesions	69 (68.3.)	3421 (56.4)	0.02
Stent use	78 (88.6)	4564 (89.5)	0.80
Drug-eluting stent use	10 (11.4)	1879 (36.8)	<0.01
Mean number of stents per patient	1.02 ± 0.48	1.03 ± 0.49	0.93
Mean stent length (mm)	18.6 ± 5.78	17.1 ± 5.3	0.02
Mean stent diameter (mm)	2.96 ± 0.48	2.99 ± 0.47	0.58
Glycoprotein IIb/IIIa inhibitor use	55 (62.5)	2403 (47.1)	<0.01
IABP use	30 (34.1)	209 (4.1)	<0.01
Thrombolysis	8 (9.1)	505 (9.9)	0.80
TIMI flow pre-procedure	N = 101 lesions	N = 6020 lesions	<0.01
TIMI 0	66 (65.4)	1870 (31.0)	
TIMI 1	5 (5.0)	275 (4.6)	
TIMI 2	14 (13.8)	623 (10.4)	
TIMI 3	16 (15.8)	3252 (54.0)	
TIMI flow post-procedure			0.09
TIMI 0	2 (2)	104 (1.7)	
TIMI 1	0 (0)	46 (0.8)	
TIMI 2	7 (6.9)	176 (2.9)	
TIMI 3	92 (91.1)	5722 (94.6)	
Procedural success	84 (95.5)	4915 (96.5)	0.65

Data are *n* (%) or mean ± SD unless otherwise stated.
Abbreviations: ACC/AHA = American College of Cardiology and American Heart Association; IABP = intra-aortic balloon pump; TIMI = Thrombolysis in Myocardial Infarction.

renal failure (10.3%), as shown in Table 3. No strokes were recorded during the peri-procedural period or hospital admission in our cohort of OHCA patients. Thirty-day survival for the OHCA cohort was (61.4%) with cardiac cause of death being the primary cause of death (87.9%). One-year survival was 60.2% in the OHCA cohort compared to 94.2% in the non-OHCA MI cohort, p<0.01 (Table 3 and Fig. 1). Non-cardiac deaths accounted for 14.7% and cardiac deaths for 85.3% in the OHCA cohort. MACE was higher at 48.9% vs. 15.2% in the non-OHCA MI cohort, p = 0.01. Of the patients who survived to hospital discharge, 12-month survival was similar between the OHCA and non-OHCA groups (96% vs. 97% p = 0.8) (Fig. 2). Furthermore, there was no difference in 12-month rates of MI (9% vs. 6%, p = 0.3), stroke (0% vs. 1% p = 0.5) and MACE (13% vs. 18% p = 0.3) in survivors of OHCA with MI compared to survivors of non-OHCA MI.

3.5. Independent Predictors of 1-Year Mortality

Cardiogenic shock (OR 9.4, 95% CI: 6.3–13.9; p<0.01) and OHCA (OR 6.4, 95% CI: 3.4–11.9; p<0.01) were the strongest independent predictors of 1-year mortality. Other independent predictors were age, renal failure, left main procedure, history of heart failure, peripheral vascular disease, chronic lung disease and diabetes mellitus (Table 4).

3.6. Hospital survivors and non-survivors amongst OHCA patients

Within the OHCA cohort, a comparison of clinical and procedural characteristics between the in-hospital survivors and non-survivors is shown in Table 5. Hospital non-survivors had longer times from cardiac arrest to arrival of paramedics (7.8 min vs. 6.9 min, p = 0.03), as well as significantly longer times until ROSC (24 min vs. 9 min, p = 0.001). Hospital non-survivors were also more likely to present in cardiogenic shock, receive an IABP, and have an unsuccessful PCI procedure, with

Table 3
Clinical outcomes: in-hospital, 30-days and 1-year of the OHCA vs. non-OHCA MI cohort.

	OHCA	Non-OHCA	p Value
In-hospital			
Survival	55 (62.5)	4955 (97.2)	<0.01
In-hospital complications			
Peri-procedural MI	5 (6.0)	70 (1.4)	<0.01
Emergency PCI	4 (4.8)	59 (1.2)	<0.01
Unplanned CABG	0 (0)	44(0.9)	0.39
Bleeding	3 (3.5)	134 (2.6)	0.64
Heart failure	24 (27.6)	252 (4.9)	<0.01
Renal failure	9 (10.3)	84 (1.7)	<0.01
Stroke	0 (0)	18 (0.4)	0.58
30-days			
Survival	54 (61.4)	4922 (96.5)	<0.01
Mortality	34 (38.6)	179 (3.5)	<0.01
Cardiac death	29 (87.9)	143 (81.3)	0.36
Non-cardiac death	4 (12.1)	33 (18.7)	
MI	5 (5.7)	130 (2.6)	0.07
TVR	5 (5.7)	150 (2.9)	0.13
TLR	5 (5.7)	126 (2.5)	0.06
MACE	39 (44.3)	386 (7.6)	<0.01
1-year			
Survival	53 (60.2)	4803 (94.2)	<0.01
Mortality	35 (39.8)	298 (5.8)	<0.01
Cardiac death	29 (85.3)	193 (65.4)	0.02
Non-cardiac death	5 (14.7)	102 (34.6)	
MI	5 (5.7)	294 (5.7)	0.97
TVR	8 (9.1)	367 (7.2)	0.50
TLR	6 (6.8)	248 (4.9)	0.40
MACE	43 (48.9)	777 (15.2)	<0.01

Data are *n* (%) unless otherwise stated.
Abbreviations: MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TLR = target-lesion revascularisation; TVR = target-vessel revascularisation; MACE = major adverse cardiac events.

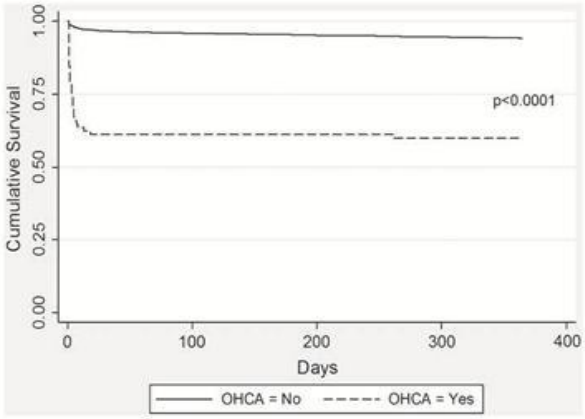

Fig. 1. Kaplan–Meier estimates of 1-year survival for OHCA vs. non-OHCA MI cohort.

a trend towards higher lesion complexity. Significant univariate predictors of in-hospital mortality within the OHCA cohort were paramedic response time (OR 1.36 95% CI: 1.04–1.77, p = 0.02), time until ROSC (OR 1.11 95% CI: 1.05–1.17, p<0.01), cardiogenic shock (OR 7.2, 95% CI: 2.7–18.8; p<0.01) and IABP use (OR 3.4, 95% CI: 1.4–8.6; p<0.01). The Kaplan–Meier survival curve of Fig. 3 demonstrates the high mortality rate amongst patients presenting with both OHCA and cardiogenic shock.

4. Discussion

This multicenter observational study underscores the fact that OHCA is associated with significant morbidity and mortality, with significantly worse outcomes compared to a non-OHCA MI cohort. In this study which included both STEMI and non-STEMI cases, OHCA patients were more likely to have associated cardiogenic shock and renal failure, have more complex lesions, lesions involving the LAD artery and a totally occluded vessel at presentation. Despite these features, OHCA patients who underwent PCI had a similarly high procedural success rate (95.5%) compared to non-OHCA MI patients, and a successful PCI procedure was associated with better in-hospital outcomes. Interestingly OHCA patients had significantly shorter symptom-to-balloon time compared to the non-OHCA cohort, likely reflecting proximity of time of arrest to time of infarct.

Patients surviving an OHCA fall into a high-risk group. Within one third of our OHCA cohort, cardiogenic shock was present and these patients had very high in-hospital mortality. This was also reflected

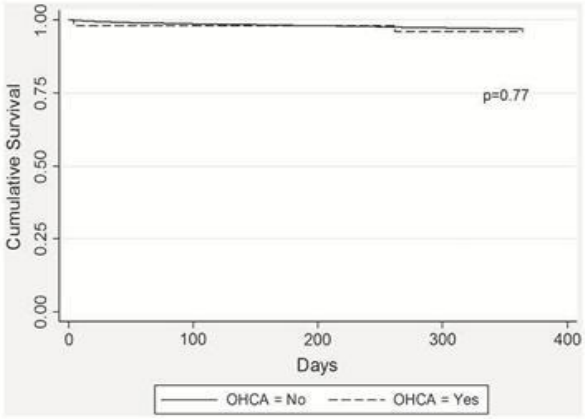

Fig. 2. Kaplan–Meier estimates of 1-year survival for patients who survived to hospital discharge; survivors of OHCA and non-OHCA MI had similar outcomes at 1 year.

Table 4
Multivariate predictors of 1-year mortality for the entire AMI cohort.

Variable	OR	95% CI	p Value
Age (per year)	1.04	1.02–1.06	<0.001
Out-of hospital cardiac arrest	6.37	3.42–11.90	<0.001
Cardiogenic shock	9.35	6.29 - 13.90	<0.001
Renal failure	5.57	3.67–8.45	<0.001
Left main procedure	2.72	1.21–6.13	<0.02
History of heart failure	2.25	1.53–3.31	<0.001
Peripheral vascular disease	1.83	1.18–2.84	<0.01
Chronic lung disease	1.63	1.10–2.41	<0.02
Diabetes mellitus	1.50	1.08–2.07	<0.02

with the use of IABP, which was higher in the OHCA cohort, and similar to previous reports, was significantly associated with in-hospital mortality [5,22,23]. Our study, however, is consistent with the concept that these high-risk patients, much like those described in studies of cardiogenic shock, are known to benefit from emergent revascularization [10,11,24]. With emergent PCI, in-hospital survival of 62.5% and 1-year survival of 60.2% were observed (Fig. 1). Whilst acknowledging the possibility of selection bias, with only 16% of the total OHCA cohort proceeding to PCI (although our registry does not record coronary angiography without PCI), these outcomes are

Table 5
In-hospital survivors vs. non-survivors in the OHCA cohort.

Out-of-hospital cardiac arrest	Survivors	Non-survivors	p value
N	55 (62.5)	33 (37.5)	
Arrest details			
Call to arrival, median (IQR), minutes	6.9 (5.2–9.1)	7.8 (7.1–12.1)	0.03
Arrival to ROSC, median (IQR), minutes	9 (4–20)	24 (14–38)	0.001
Transport time, median (IQR), minutes	15 (8–20)	17 (12–24)	0.11
Initial rhythm VF/VT	44/50 (88)	22/30 (73)	0.07
Baseline characteristics			
Age	61.4 ± 12.29	63.7 ± 12.4	0.40
Males	44 (80.0)	26 (78.8)	0.90
Diabetes	7 (12.7)	8 (24.213.0)	0.16
Hypertension	23 (41.8)	13 (39.4)	0.82
Family history of CAD	20 (36.41)	6(20.0)	0.12
Previous CABG	1 (1.8)	2 (6.1)	0.29
Cardiogenic shock	12 (21.8)	22 (66.7)	<0.01
STEMI presentation	48 (87.3)	32 (97.0)	0.13
Median symptom-to-door time (min)[a]	75 (54–111)	75 (54–97)	0.79
Median door-to-balloon time (min)[a]	100 (78–126)	117 (94–162)	0.10
Median symptom-to-balloon inflation time (min)[a]	187 (149–227)	209 (158–282)	0.10
Lesion characteristics and procedural details			
Left anterior descending	28 (45.2)	18 (46.2)	0.92
Circumflex	8 (12.9)	4 (10.3)	0.68
RCA	18 (29.0)	12 (30.8)	0.85
Bypass graft	0 (0)	1 (2.6)	0.21
ACC/AHA B2&C lesions	38 (61.3)	31 (79.5)	0.06
Stent use	50 (90.1)	28 (851)	0.62
Drug-eluting stent use	7 (11.3)	4 (10.3)	0.87
IABP use	13 (23.6)	17 (51.5)	0.01
Thrombolysis	7 (12.7)	1 (3.0)	0.13
Unsuccessful procedure	0 (0)	4 (12.1)	0.01

Data are *n* (%) or mean ± SD unless otherwise stated.
Abbreviations: CAD = coronary artery disease; PCI = percutaneous coronary interventions; CABG = coronary artery bypass graft; STEMI = ST-elevation myocardial infarction; IQR = Inter-quartile range (25th–75th percentile); ACC/AHA = American College of Cardiology and American Heart Association; IABP = intra-aortic balloon pump; ROSC = return of spontaneous circulation.
[a] For STEMI patients only.

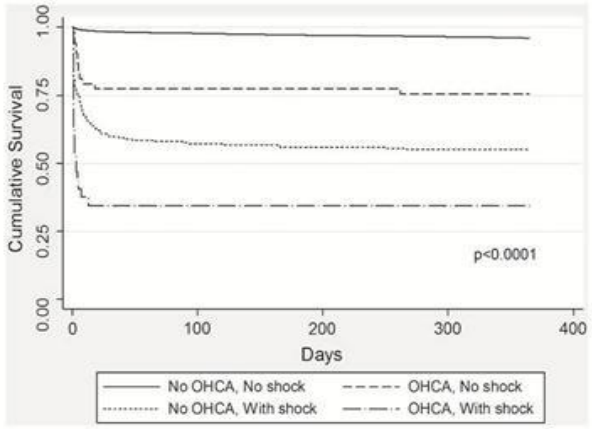

Fig. 3. Kaplan–Meier estimates of 1-year survival for the entire AMI cohort. Patients with both OHCA and cardiogenic shock had the lowest survival rate.

significantly better than registry data of patients with OHCA and comparable favorably to other series of PCI in OHCA [4,5,25–27].

Coronary artery disease is responsible for most OHCA, predominantly related to unstable plaque rupture and acute coronary syndromes (ACS) [28,29]. In our study 80 (90%) of patients had ST elevation on initial ECG, with associated TIMI 0/1 flow of 64%. This rate of ST elevation is higher than the previously reported rates of 30–60% [4,5,30], but understandable in the context of this study given our review of only patients undergoing PCI. Despite the lack of randomized trials, there is a growing body of observational evidence to suggest the benefit of early routine coronary angiography, and intervention where appropriate, in the setting of cardiac arrest and STEMI. In a multicenter French study, Garot et al. performed PCI (90% stent rate) in patients with OHCA complicated by STEMI and reported procedural success rates of 87%, in-hospital survival of 55% and 6-month survival of 54% [5]. Lettieri et al. reported PCI procedural success rates of 80% in OHCA with STEMI patients and in-hospital survival of 78% [31]. Six-month composite rate of death, MI and revascularization among survivors of the acute phase was comparable to non-OHCA patients [31]. In another study, Hosmane et al. reported successful restoration of flow from PCI in 62 out of 64 OHCA patients complicated by STEMI (96.8%), and in-hospital survival of 64% [32].

Our study is consistent with the findings from these recent studies that high PCI procedural success rates (95.5%) can be achieved in OHCA patients complicated by MI using contemporary strategies, with procedural success being associated with in-hospital survival. Furthermore, in-hospital survival nearing two-thirds of patients may be attained with post-discharge survival to 12 months equivalent to MI patients without OHCA. Our study supports the recent recommendation by the American Heart Association that all patients with STEMI and OHCA undergo emergent coronary angiography and be managed at centers capable of 24-hour coronary intervention [33].

Whilst an emergent PCI approach for OHCA with STEMI is now recommended, traditionally there has been some hesitation in patients with OHCA and non-STEMI. However, Spaulding et al. highlighted that up to 40% of OHCA caused by unstable coronary plaques would be missed if decision making was based on ECG alone [4]. A recent study of cardiac arrest patients undergoing coronary angiography, also found significant coronary lesions in up to 66% of patients without ECG changes of STEMI or new LBBB [30]. The largest published series in OHCA was recently reported and demonstrated that emergent PCI was an independent predictor of survival irrespective of initial ECG findings [24]. Although warranting further study, there is mounting evidence of benefit to a standardized post-resuscitation treatment approach, including routine coronary angiography for all survivors of OHCA of suspected cardiac etiology [34,35]. Routine PCI post cardiac arrest would have significant implications on potential reporting of outcomes for cardiac centres. With the current trend towards public based procedural reporting, risk adjusted quality estimates are necessary [36,37], to encourage optimal management of these high-risk patients.

Survivors in the OHCA cohort had significantly shorter paramedic response times and time until ROSC. Although our focus in this study has been on PCI in the post resuscitative setting, this ideally follows on from the implementation of basic and advanced life support measures, including effective CPR and defibrillation where appropriate, which are major determinants of outcome [38,39].

5. Limitations

This study was a non-randomized, observational registry. The number of OHCA patients who underwent PCI were limited, an issue common to all studies of OHCA. Nevertheless, OHCA was the presenting feature in nearly 1 in 50 cases of MI. The favorable outcomes after PCI in the OHCA patients may have been influenced by physician selection bias for patients deemed most likely to benefit from PCI, and exclusion of those patients in whom an invasive strategy was deemed clinically futile. This study was based on a multicenter PCI registry and outcomes therefore, did not include pre-hospital details or other in-hospital resuscitative measures such as controlled hypothermia, which are associated with clinical outcomes [40,41]. Although not captured by this registry, previous reports by the authors would estimate the use of hypothermia in these PCI capable hospitals, for comatose survivors of VF arrest, at 75% [14].

6. Conclusion

Patients with MI complicated by OHCA remain a high-risk group with high mortality, often complicated by cardiogenic shock. Those that survive to hospital admission and are selected for PCI have a relatively high procedural success rate, similar to non-OHCA patients. In-hospital and 1-year survival rates better than previously expected are observed with an emergent PCI approach utilizing contemporary interventional strategies, with 1-year survival comparable to a non-OHCA cohort if patients survive to hospital discharge.

Disclosures

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CHAPTER 5: Hospital Characteristics Are Associated With Patient Outcomes Following Out-Of-Hospital Cardiac Arrest

Monash University

Declaration for Thesis Chapter 5

Stub D, Smith K, Bray JE, Bernard S, Duffy SJ, Kaye DM. **Hospital characteristics are associated with patient outcomes following out-of-hospital cardiac arrest.** *Heart* 2011;97:1489-1494.

Declaration by candidate

In the case of Chapter 5 the nature and extent of my contribution to the work was the following:

Name	**Nature of contribution**	**Extent of contribution (%)**
Stub D	Principle Author, responsible for overall study concept, literature review, analysis, interpretation of results and development and writing of manuscript. Responsible author who effects overall responsibility of publication	70%

Candidate's Signature	[redacted]	**Date** 1/11/2012

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

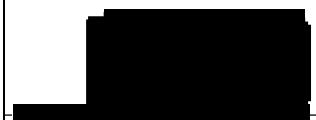
Name	Nature of contribution
Smith K	Analysis of results and manuscript development and editing
Bray J	Analysis of results and manuscript development and editing
Bernard S	Analysis of results and manuscript development and editing
Duffy S	Analysis of results and manuscript development and editing
Kaye D	Analysis of results and manuscript development and editing

Declaration by co-authors

The undersigned hereby certify that:

- the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
- they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
- there are no other authors of the publication according to these criteria;
- potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
- the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Alfred Hospital Heart Centre, Intensive Care Unit, Baker IDI Heart and Diabetes Institute, Monash University Faculty of Medicine Nursing and Health Sciences, Monash University Department of Epidemiology and Preventative Medicine, Ambulance Victoria

Signature 1		**Date** 15/11/2012
Signature 2		**Date** 12/11/2012
Signature 3		**Date** 9/11/2012
Signature 4		**Date** 9/11/2012
Signature 5		**Date** 9/11/2012

Introduction to Systems of Care in Out-Of-Hospital Cardiac Arrest

"Where we cannot invent, we may at least improve."

Charles Caleb Colton

It has long been recognized in both Australia[123] and overseas[124] that there is a significant regional variation in out-of-hospital cardiac arrest outcomes. For many years this variation in survival was thought to be largely driven by pre-hospital factors such as rates of bystander resuscitation, early defibrillation[125] and to a lesser extent advanced life support measures[126]. Accordingly significant efforts have been made to improve community awareness and training coupled with rigorous EMS protocols. Despite these efforts, survival to hospital discharge with good neurological recovery has remained poor[3].

Much of this thesis has highlighted the developments and recognition of the importance of post resuscitative hospital care in maximizing neurological recovery. Previous chapters have emphasized treatments that are thought to improve outcome after OHCA resuscitation including therapeutic hypothermia[39, 40], early reperfusion of blocked coronary arteries[51, 52] and possibly optimization of hemodynamic parameters such as blood pressure and glucose[55, 60].

These interventions require a multi-disciplinary team with experience and expertise in the management of these patients. Despite the evidence supporting the use of hypothermia and other post resuscitative measures, the uptake of these interventions has been poor[110, 111]. In a recent small Australia single centre study examining rates of therapeutic hypothermia use in a tertiary trauma level 1 ICU less than half of comatose survivors of OHCA received appropriate TH and only 12% of patients were at target temperature within 2 hours[112].

There is increasing evidence that differences in the delivery of post resuscitative measures may be partly responsible for the significant regional variations observed in cardiac arrest outcomes. Implicit assumptions of these reports are that care provided for patients with OHCA is better at some hospitals that receive such patients than others and that resuscitated patients should be preferentially transported to higher-performing hospitals. Recent international guidelines have called for the introduction of robust systems of care maximizing both pre-hospital and in-hospital management into the treatment of patients with OHCA[30]. In, Australia however, patients with OHCA are transported to the nearest hospital. We have the interesting situation where a patient

in a rural community who suffers a major trauma will be airlifted to a world class trauma facility in the city[127]. Whereas in the same community a patient suffering an OHCA will be transported to an often small local hospital, with significant variation in cardiac and intensive care services.

Previous data utilizing the Victorian Ambulance Cardiac arrest registry has indicated significantly worse outcomes in patients suffering OHCA in rural compared to metropolitan areas[123]. Chapter 5 aims to further characterize regional variation in OHCA outcomes in Australia, but at an institutional level; investigating hospital factors that may influence survival and neurologic recovery in OHCA.

Ambulance Victoria and the Victorian Ambulance Cardiac Arrest Registry

Ambulance Victoria

Ambulance Victoria (AV) was formed in 2008, combining the metropolitan ambulance service, rural ambulance service and Alexandra district ambulance service. AV is now the primary provider of the state's Emergency Medical Services, covering 227,000 square kilometres and providing a response to more than 5.5 million people.

Paramedics in Victoria have a base qualification of a three year bachelor degree in health sciences. Mobile Intensive Care Ambulance (MICA) paramedics are more experienced and undergo a post graduate diploma in Intensive Care paramedical practice. Ambulance paramedics have some advanced life support skills (laryngeal mask, intravenous adrenaline), and MICA paramedics are able to administer a wider range of cardiac drugs and perform endotracheal intubation.

Emergency call taking is performed using the Medical Priority Dispatch System (MPDS), with advanced life support and MICA paramedics dispatched to all suspected cardiac arrests. Basic life support trained fire-fighters, equipped with automatic defibrillators, co-respond to cardiac arrest calls across parts of Melbourne[128]. Paramedics operate under Ambulance Victoria Clinical Practice Guidelines, which for resuscitation follow the Australian Resuscitation Council Guidelines[129, 130]. Paramedics may withhold or cease resuscitation under specific circumstances, including clear evidence of prolonged arrest (e.g. rigor mortis, decomposition). Patients who achieve ROSC are transported to the nearest facility.

Victorian Ambulance Cardiac Arrest Registry

The Victorian Ambulance Cardiac Arrest Registry (VACAR) is a database of all cases of OHCA attended by AV, metropolitan fire brigade, the country fire authority and the community emergency response teams. The VACAR is funded by the Department of Health and commenced in 1999 as a quality initiative. The registry is maintained within the department of research and evaluation at AV, and is the largest and most comprehensive cardiac arrest data bank in Australia. The VACAR collects Utstein elements[9] including demographics, arrest features, resuscitation care and hospital outcome data. The etiology of cases is considered presumed cardiac when no other cause is apparent (e.g. excludes trauma, hanging, drowning, exsanguination and other obvious non-cardiac causes).

Hospital Characteristics Are Associated With Patient Outcomes Following Out-Of-Hospital Cardiac Arrest

Hospital characteristics are associated with patient outcomes following out-of-hospital cardiac arrest

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ABSTRACT

Objective Post-resuscitation care may influence outcome following transport to hospital after resuscitation from out-of-hospital cardiac arrest (OHCA). This study aimed to determine whether receiving hospital characteristics such as 24-h cardiac catheterisation services, total bed number or OHCA patient volume influence the rate of survival.

Setting Data were analysed from the Victorian Ambulance Cardiac Arrest Registry of patients from January 2003 to March 2010 who were transported to hospital with return of spontaneous circulation (ROSC) after OHCA.

Results Ambulance paramedics attended 9971 patients with OHCA of suspected cardiac cause during the study period. Of these, 2902 (29%) achieved ROSC and were transported to one of 70 hospitals. 1816 (63%) were treated at hospitals with 24-h cardiac interventional services. After adjusting for differences in baseline characteristics, hospital factors significantly associated with survival were treatment at hospitals with 24-h cardiac interventional services (OR 1.40; 95% CI 1.12 to 1.74, p=0.003) and patient reception between 08:00 and 17:00 hours (OR 1.34; 95% CI 1.10 to 1.64, p=0.004). OHCA patient volume and total hospital bed number were not independently associated with outcome.

Conclusion Hospital characteristics are associated with improved survival in patients with OHCA. This finding has implications for the establishment of regionalised systems of care for patients who have been resuscitated from OHCA.

Out-of-hospital cardiac arrest (OHCA) is a common manifestation of cardiovascular disease, with an incidence in Australia of 148 per 100 000 persons per year.[1] The mortality rate post admission to hospital after successful resuscitation from OHCA is high.[2] While prehospital factors such as age, bystander cardiopulmonary resuscitation and total cardiac arrest time are known to influence outcome,[3] several aspects of post-resuscitative care may also influence overall patient survival. In particular, hospital factors such as hospital size and interventional cardiac care capabilities have been found to influence patient outcome in Sweden,[4] Japan[5] and North America.[6 8] In North America, particularly, healthcare is largely provided in private institutions. Australia, like many countries, has universal healthcare, with a system of government funded hospitals predominating and statewide ambulance services who are directed to take patients with OHCA to the nearest hospital with an emergency department. These factors may influence outcomes. We therefore sought to determine the relationship between receiving hospital characteristics on outcomes at hospital discharge in the setting of a government-funded healthcare system.

METHODS

The study was conducted in Victoria, an Australian state that has an area of 227 000 km^2 and a population of approximately 5.5 million inhabitants, the majority of whom reside in the city of Melbourne (the state capital; population 4.1 million).[9] Emergency medical services (EMS) are provided solely by Ambulance Victoria. The EMS consist of a two-tier system consisting of 1200 advanced life support paramedics who are authorised to provide defibrillation, laryngeal mask airway insertion and intravenous administration of epinephrine, along with 300 intensive care paramedics, who are authorised to perform endotracheal intubation and administer a range of additional cardiac drugs such as amiodarone and sodium biacarbonate. A first responder programme for early defibrillation by fire fighters operates for suspected cardiac arrest patients in the inner area of Melbourne.[10] The cardiac arrest protocols follow the recommendations of the Australian Resuscitation Council[11] (see http://www.ambulance.vic.gov.au/clinicalpracticeguidelines). Patients with return of spontaneous circulation (ROSC) are transported to the nearest hospital with an emergency department.

In Melbourne, among public and private institutions there are 10 hospitals that provide 24-h interventional cardiac services, four hospitals that during the study period provided variable cardiac interventional services (no routine after hours interventional service) and a further nine hospitals that do not have an interventional service. In rural Victoria, there is one hospital with 24-h interventional cardiac services, two hospitals with variable cardiac interventional services and 44 hospitals that do not provide this service.

All OHCA patient care data are recorded electronically by the treating paramedics at the completion of the case and downloaded to a central server on return to the ambulance station. Cases of OHCA are identified, reviewed for completeness and recorded in the Victorian Ambulance Cardiac Arrest Registry (VACAR) according to Utstein definitions.[12] Hospital follow-up is obtained from the hospital medical record.

For this study, the VACAR records for all OHCA patients between January 2003 and March 2010

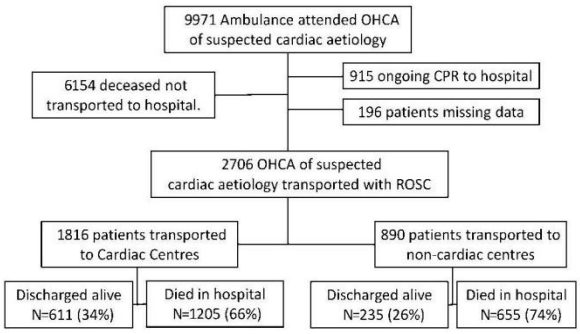

Figure 1 Out-of-hospital cardiac arrests of suspected cardiac aetiology transported to hospital from January 2003 to March 2010. CPR, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

were analysed. Patients were included if they met the following criteria: age 18 years or older, OHCA of suspected cardiac cause, resuscitation was attempted and the patient was transported to hospital with ROSC. Patients were excluded if the cardiac arrest was witnessed by the EMS, ROSC was not achieved, or the arrest was suspected to be due to a non-cardiac cause such as trauma, drowning, drug overdose, or asphyxia.

Hospital characteristics were defined by the Australian Institute of Health and Welfare (http://www.aihw.gov.au) and the Victorian Department of Health (http://www.health.vic.gov.au). For this study, a 'cardiac centre' was defined as a hospital providing 24-h, 7 days per week emergency cardiac catheterisation facilities for acute coronary syndrome patients (including patients resuscitated from OHCA). Hospitals were categorised as large (>400 beds), medium (250–400 beds) and small (<250 beds).[13] The volume of OHCA patients per annum for each hospital was available from the registry. Survival was also analysed based on the day and time of admission. Outcomes based on OHCA occurring on Monday to Friday were compared with those with events on weekends and patients admitted in working hours (08:00–17:00 hours) were analysed versus those admitted after hours.[14]

Ethics approval for non-consent data collection from the medical record was obtained from all hospitals. Approval for this specific data analysis was obtained from the Alfred Hospital Committee on Ethics in Research involving Humans and the Research Committee of Ambulance Victoria.

The primary outcome measure was survival to hospital discharge. Discharge direction to home, rehabilitation or nursing facility was a secondary outcome measure. Patient and arrest characteristics were tabulated with descriptive statistics and compared between metropolitan and rural hospitals and hospitals that were cardiac centres or not. Unadjusted analyses were performed using the χ^2 test, the Mann–Whitney U test and the Student's t test.

Univariate analysis was undertaken to identify OHCA baseline and hospital variables that influenced survival to hospital discharge. Two-way interactions in hospital characteristics were examined and a multivariate analysis was conducted using a stepwise selection procedure and validated using a backward elimination procedure. Conditional standardisation was used to estimate the probability of survival for a patient at various hospital types. All statistics were performed using SPSS version 16. Predictors included in the model were considered statistically significant at a p value of less than 0.05, and are reported as OR with 95% CI and associated p values.

RESULTS

Between January 2003 and March 2010 Ambulance Victoria attempted resuscitation in 9971 adults with OHCA of suspected cardiac aetiology. Figure 1 summarises the numbers of patients who were eligible for analysis and subsequent survival. There were 2902 patients (29.1%) who were transported to hospital

Table 1 Baseline characteristics comparing metropolitan and rural patients transported to cardiac and non-cardiac centres

	Metropolitan			Rural		
Characteristic	Cardiac centre (n=1728)	Non-cardiac centre (n=659)	p Value	Cardiac centre (n=88)	Non-cardiac centre (n=231)	p Value
Age, years (mean±SD)	67±15	67±14	0.71	66.6±13	68.5±15	0.26
Male sex	72%	65%	<0.001	57%	62%	0.37
Witnessed arrest	76%	75%	0.51	73%	77%	0.41
Initial cardiac rhythm						
Ventricular fibrillation	57%	55%	0.19	55%	53%	0.51
Ventricular tachycardia	1.5%	1.1%		0.0%	2.4%	
Asystole	19%	21%		17%	23%	
Pulseless electrical activity	21%	23%		28%	20%	
EMS time intervals, median (IQR) min						
Call to arrival	7 (6–9)	8 (6–10)	<0.001	9 (6–12)	8 (6–10)	0.08
Arrival to ROSC	15 (10–22)	16 (10–23)	0.23	17 (10–26)	16 (10–23)	0.65
ROSC to ED	37 (28–47)	36 (27–48)	0.66	28 (22–45)	23 (16–41)	0.002
Transport time	14 (10–19)	14 (10–19)	0.22	10 (7–19)	9 (5–18)	0.04
Cardiac arrest treatment						
Bystander CPR	55%	55%	0.94	54%	50%	0.58
Defibrillation	71%	68%	0.10	73%	64%	0.11
Epinephrine	82%	85%	0.07	73%	75%	0.80
Intubation	92%	94%	0.05	87%	73%	0.007
Patient vital signs post-ROSC, median (IQR)						
Systolic blood pressure	120 (100–140)	120 (100–140)	0.09	110 (85–127)	105 (65–140)	0.83
Heart rate	96 (80–116)	94 (78–115)	0.14	100 (80–120)	92 (74–115)	0.14
Glasgow coma score <8	97%	98%	0.04	99%	94%	0.05

CPR, cardiopulmonary resuscitation; ED, emergency department; EMS, emergency medical services; ROSC, return of spontaneous circulation.

Table 2 Outcomes at hospital discharge

Characteristic	Metropolitan			Rural		
	Cardiac centre (n=1728)	Non cardiac centre (n=659)	p Value	Cardiac centre (n=88)	Non cardiac centre (n=231)	p Value
Survival	587 (34%)	176 (26.7%)	<0.001	24 (27.3%)	59 (25.5%)	0.40
Discharge home	456 (26.4%)	131 (19.9%)	0.02	15 (17%)	47 (20.3%)	0.08
Discharge to rehabilitation	98 (5.7%)	40 (6.1%)		5 (5.6%)	6 (2.1%)	
Discharge to nursing home	23 (1.3%)	4 (0.6%)		3 (3.4%)	1 (0.5%)	
Died	1141 (66%)	483 (73.3%)	<0.001	64 (72.7%)	172 (74.5%)	0.40

with ROSC and 915 patients transported to hospital with on-going cardiopulmonary resuscitation. Survival data including discharge direction was available for 2706 patients (93.2%). Survival to hospital discharge was achieved in 31.3% of these patients. Of the survivors, 76% were discharged directly home, 18% were discharge to a rehabilitation facility and 4% were discharged to a nursing facility. There were 2% of surviving patients whose discharge destination was not documented in the medical record.

Table 1 shows the baseline characteristics and EMS treatment of these patients divided into metropolitan and rural patients. The EMS response time differed between patients treated in metropolitan and rural areas, and in patients transported to cardiac centres and non-cardiac centres. EMS rates of intubation were higher in patients transported to metropolitan hospitals, corresponding with increased rates of patients with a reduced conscious state post-ROSC. The EMS transport time was similar between metropolitan cardiac centres and non-cardiac centres, but was increased in patients taken to the rural cardiac centre compared with rural non-cardiac centres.

Table 2 shows the numbers and outcomes for patients taken to each of the types of hospital. The majority of patients (63%) were treated at metropolitan cardiac centres. Twenty-five per cent of patients were treated at metropolitan non-cardiac centres, 10% were treated at rural non-cardiac centres and 3% were treated at the rural cardiac centre. Survival was increased in patients transported to cardiac centres compared with non-cardiac centres (33.6% vs 27.8%, p<0.001). This survival difference was largely due to the increased rates of survival of patients with ventricular fibrillation/ventricular tachycardia (48.4% vs 37.0%, p<0.001). For survivors, there was also an increase in the rate of discharge directly to home from a cardiac centre compared with a non-cardiac centre (24.5% vs 18.2%, p<0.001). There was no difference in rates of survival in patients with asystole or pulseless electrical activity in cardiac centres compared with non-cardiac centres (12.9% vs 13.5%, p=0.44).

Outcomes of patients according to the number of OHCA treated per annum are shown in table 3. These data highlight the fact that most hospitals (55/70) received fewer than 10 patients with OHCA per year. However, when adjusting for important prehospital factors there were no differences in outcomes between hospitals with a high volume of OHCA patients compared with those with a lower volume. Survival was also independent of the size of the treating hospital (table 4). Survival was also analysed based on the day and time of admission. There were no significant differences in outcomes based on admission day, but those patients admitted in working hours (08:00–17:00 hours) had improved survival at both cardiac centres (36.1% vs 31.3%, p=0.03) and non-cardiac centres (30% vs 23%, p=0.01).

Patient and arrest characteristics associated with survival in a multivariable logistic model are shown in table 5. These included younger age, male gender, an initial rhythm of ventricular fibrillation/ventricular tachycardia, witnessed collapse with bystander cardiopulmonary resuscitation, no EMS intubation and a shorter EMS response time and total time until ROSC (all p<0.05). Transport time was not associated with outcome. After adjusting for relevant covariates, treatment at a cardiac centre was independently associated with improved survival to hospital discharge (OR 1.40; 95% CI 1.12 to 1.74, p=0.003) as was admission in working hours (OR 1.34; 95% CI 1.10 to 1.64, p=0.004; table 5). Including the four hospitals with variable (<24 h) cardiac intervention services in the analysis still yielded a significant result (OR 1.3; 95% CI 1.03 to 1.6, p=0.03). The highest survival was seen at the two hospitals that are also major trauma centres, with a conditional probability of survival of 42.1% compared with 29% at non-cardiac centres (figure 2).

Table 3 Outcomes by hospital volume of OHCA cases

Annual case no	No of hospitals (no of events)	Survival to discharge	Adjusted odds of survival (95%)	p Value
1–9	55 (252)	31.0%	Baseline	NA
10–19	4 (140)	25.0%	0.73 (0.42–1.3)	0.28
20–29	3 (357)	30.5%	0.93 (0.61–1.4)	0.93
30–39	3 (573)	27.9%	0.86 (0.59–1.3)	0.45
≥40	5 (1384)	33.5%	1.02 (0.71–1.5)	0.93

Adjusted for age, witnessed collapse, ventricular fibrillation/ventricular tachycardia, time to return of spontaneous circulation.
OHCA, out-of-hospital cardiac arrest.

DISCUSSION

This study of the effect of hospital characteristics after resuscitation from OHCA on outcome has found improved survival in patients treated at hospitals that provide 24-h interventional cardiac services and who are admitted in working hours (08:00–17:00 hours). Perhaps surprisingly, however, this study also found that hospital size (numbers of beds) and OHCA patient throughput did not influence outcome.

It is well established that the outcomes of patients with OHCA are affected by EMS interventions such as early defibrillation[15] but not advanced life support.[16] Treatments that are thought to improve outcome after OHCA resuscitation include therapeutic hypothermia,[17 18] early reperfusion of blocked coronary arteries[19 20] and possibly optimisation of critical care parameters such as blood pressure and glucose.[21 22] These

Table 4 Outcomes by hospital bed size

Hospital bed no	No of hospitals (no of events)	Survival to discharge	Adjusted odds of survival (95%)	p Value
<250	55 (363)	28.4%	Baseline	NA
250–400	7 (816)	26.1%	0.86 (0.66–1.20)	0.37
>400	8 (1527)	34.7%	1.20 (0.89–1.63)	0.23

Adjusted for age, witnessed collapse, ventricular fibrillation/ventricular tachycardia, time to return of spontaneous circulation.

Table 5 Multivariate analysis of predictors of survival

Characteristic	OR (95% CI)	p Value
Age	0.957 (0.950 to 0.964)	<0.001
EMS arrival to ROSC time	0.998 (0.896 to 0.920)	<0.001
EMS response time	0.968 (0.940 to 0.997)	0.03
EMS intubation	0.523 (0.328 to 0.630)	<0.001
Initial rhythm VF/VT	4.31 (3.41 to 5.45)	<0.001
Witnessed arrest	1.50 (1.16 to 1.93)	0.002
Bystander CPR	1.31 (1.06 to 1.61)	0.011
Transport to cardiac centre	1.40 (1.12 to 1.74)	0.003
Admission in hours (08:00–17:00)	1.34 (1.10 to 1.64)	0.004
Male gender	1.30 (1.03 to 1.64)	0.025

CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation; VF/VT, ventricular fibrillation/ventricular tachycardia.

interventions require a multidisciplinary team with experience and expertise in the management of these patients.

Systems of care are well established for other time-critical interventions such as in patients with severe trauma,[23] major stroke[24] and ST-elevation myocardial infarction in patients without cardiac arrest.[25–27] The benefit of hospitals with 24-h cardiac interventional services is therefore likely to be multifaceted, related to the availability of specialised procedures such as coronary intervention combined with the less defined attributes of comprehensive emergency units, coronary care and intensive care services, as well as skilled multidisciplinary teams experienced in dealing with critically ill patients. This concept is supported by our finding that the two quaternary trauma referral centres had the best outcomes in the present study. The recent policy statement from the American Heart Association recommended that patients with OHCA with ST-elevation or a high suspicion of acute coronary syndrome be transported directly to cardiac arrest centres.[28 29] Our findings support this recommendation.

Previous studies have also found an increase in survival in patients transported following resuscitation from OHCA to centres with cardiac services.[4 5] For example, in Japan, transfer of patients with OHCA to hospitals certified to provide critical care for cardiac arrest and acute coronary syndromes was associated with improved survival (OR 3.39, p<0.001).[5] A Swedish study of almost 4000 patients with OHCA showed marked variability in outcomes between hospital outcomes after adjusting for prehospital factors.[4] In a USA study of 109 739 patients, hospital factors including teaching status, size and urban location were associated with improved outcomes in patients resuscitated from cardiac arrest.[30] Another study of a community-based programme focusing on optimising all facets of cardiac arrest care including transport to dedicated cardiac arrest centres demonstrated improvement in outcomes.[31]

Conversely, the Resuscitation Outcomes Consortium (ROC) investigators examined the outcomes of 4087 patients with OHCA. In that study, patients post-OHCA who were treated at hospitals capable of invasive cardiac procedures did not have increased rates of survival after adjusting for prehospital factors.[6] One explanation for this finding may be that the ROC registry included data from over 250 EMS sites across North American and Canada, resulting in the possibility of significant heterogeneity between regions. Also, the definition of 'cardiac centre' in the ROC study included all centres performing coronary intervention, rather than those with 24-h, 7 days a week services.

An important result of our study was that increased transport time to hospital did not adversely affect outcome. This is supported by other studies indicating that increased transport time to facilitate transfer to a cardiac centre did not adversely impact on patient survival.[32 33] Therefore, bypass of the closest hospital for transport to a cardiac centre may be appropriate in a regionalised system of care.

Issues of transport distance may also be more significant in rural areas. However, trauma systems of care for rural patients in the state of Victoria have been highly successful.[23] Unlike metropolitan cardiac centres, the one rural cardiac centre did not show a statistically significant survival advantage compared with rural non-cardiac centres (27.3 vs 25.5, p=0.40; table 2). This subgroup analysis is potentially limited by only 88 patients being transported to the rural cardiac centre during our study period. Other factors, including the availability of interventional cardiologists and door-to-balloon time in rural areas, could also influence outcome.

An interesting finding of our study was the poorer outcomes in patients admitted after hours regardless of hospital type. Similar findings have previously been reported for both inhospital[34] and OHCA patients.[14] After hours admission but not weekend admission was an independent predictor of outcome (OR 1.34, 95% CI 1.09 to 1.64, p=0.004). These results are preliminary and require further analysis regarding the effects of

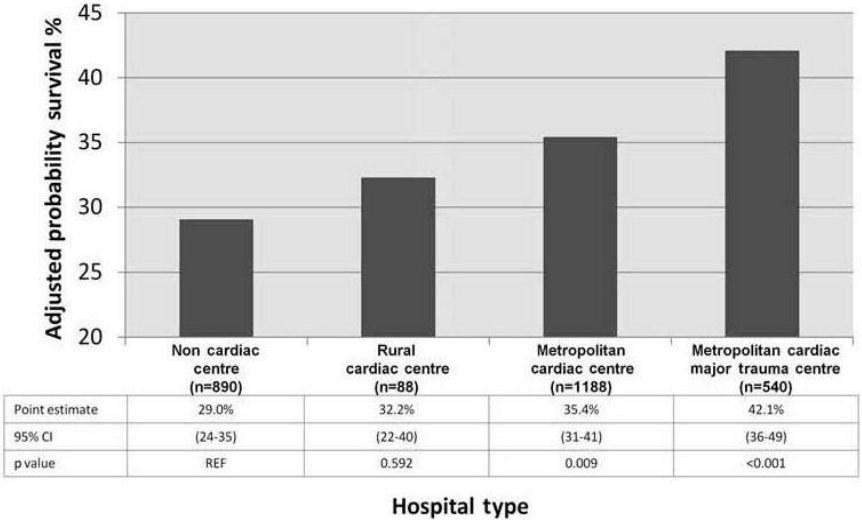

Figure 2 Survival to discharge based on hospital characteristics. Adjusted for age, initial rhythm, witnessed cardiac arrest, time until return of circulation.

diurnal variation[35] on the incidence of cardiac arrest, and issues such as hospital staffing, but lend further weight to the highlighted importance of dedicated systems of care for patients with OHCA.

When compared with patients who were intubated by EMS, both conscious and unconscious patients who did not receive an EMS advanced airway had superior outcomes. The role of advanced airways in the management of OHCA is controversial. There are data both supporting timely intubation for patients with OHCA[1 36] and studies questioning the efficacy of prehospital intubation by highlighting poorer patient outcomes.[37] Clinical trials examining the role, timing and nature of advanced airways are needed.

In our study women post-OHCA had poorer adjusted survival than men (OR of male survival 1.30, p=0.025). This differs from previous literature revealing improved outcomes in women with OHCA.[38 39] One report does describe, however, women being more likely to survive to hospital admission following OHCA, but less likely to survive their hospital stay.[40] Further studies into gender differences and the mechanisms of differences in cardiac arrest are warranted.

The development of a system of care for high-risk cardiac patients such as those with OHCA would have significant implications on the potential reporting of outcomes for cardiac centres. With the current trend towards public-based procedural reporting, risk adjusted quality estimates are necessary[41] to encourage the optimal management of these high-risk patients.

Our study has several limitations. The study is observational, lacks survival data in approximately 7% of patients, and there may be bias in the transport of selected patients to different hospitals. Also, the VACAR does not document actual inhospital treatment such as rates of therapeutic hypothermia or procedures such as coronary intervention. We are therefore unable to confirm whether patients in fact received such interventions. The authors, however, recently reported on the OHCA experience at one of the large cardiac centres in Victoria indicating the significant use of coronary angiography (77%), coronary revascularisation (43%) and therapeutic hypothermia (77%) as part of a post-resuscitation bundle of care treatment algorithm.[42] Despite these limitations our study provides new insights into major factors that may influence outcome in patients after OHCA.

CONCLUSION

Our study of 2706 patients who were transported to hospital with ROSC found that survival to hospital discharge was significantly increased in patients transported to hospitals with 24-h interventional cardiology facilities during working hours. The best survival was in major trauma-level hospitals. Further research into the individual components of post-resuscitative care is required to determine those factors within hospitals that improve outcomes.

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CHAPTER 6: Do We Need Cardiac Arrest Centres in Australia?

Monash University

Declaration for Thesis Chapter 6

Stub D, Bernard S, Smith K, Bray JE, Cameron P, Duffy SJ, Kaye DM. **Do We Need Cardiac Arrest Centres in Australia?** *Intern Med J* 2012;42:1173-117

Declaration by candidate

In the case of Chapter 6 the nature and extent of my contribution to the work was the following:

Name	**Nature of contribution**	**Extent of contribution (%)**
Stub D	Principle Author, responsible for overall study concept, literature review, analysis, interpretation of results and development and writing of manuscript. Responsible author who effects overall responsibility of publication	70%

Candidate's Signature	[redacted]	**Date** 1/11/2012

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Bernard S	Analysis of results and manuscript development and editing
Smith K	Analysis of results and manuscript development and editing
Bray J	Analysis of results and manuscript development and editing
Cameron P	Analysis of results and manuscript development and editing
Duffy S	Analysis of results and manuscript development and editing
Kaye D	Analysis of results and manuscript development and editing

Declaration by co-authors

The undersigned hereby certify that:

- the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
- they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
- there are no other authors of the publication according to these criteria;
- potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
- the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Alfred Hospital Heart Centre, Intensive Care Unit, Baker IDI Heart and Diabetes Institute, Monash University Faculty of Medicine Nursing and Health Sciences, Monash University Department of Epidemiology and Preventative Medicine, Ambulance Victoria

Signature 1		**Date** 9/11/2012
Signature 2		**Date** 15/11/2012
Signature 3		**Date** 14/11/2012
Signature 4		**Date** 15/11/2012
Signature 5		**Date** 9/11/2012
Signature 6		**Date** 9/11/2012

INTERNAL MEDICINE JOURNAL

CURRENT CONTROVERSIES

Do we need cardiac arrest centres in Australia?

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Key words
cardiac arrest, systems of care, resuscitation, myocardial infarction, hypothermia

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Abstract

The mortality rate post admission to hospital after successful resuscitation from out-of-hospital cardiac arrest is high, with significant variation between regions and individual institutions. While prehospital factors such as age, bystander cardiopulmonary resuscitation and total cardiac arrest time are known to influence outcome, several aspects of post-resuscitative care including therapeutic hypothermia, coronary intervention and goal-directed therapy may also influence patient survival. Regional systems of care have improved provider experience and patient outcomes for those with ST elevation myocardial infarction and life-threatening traumatic injury. In particular, hospital factors such as hospital size and interventional cardiac care capabilities have been found to influence patient mortality. This paper reviews the evidence supporting the possible development and implementation of Australian cardiac arrest centres.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a common cause of cardiac death with an incidence in Australia of 148 per 100 000 persons per year.[1] In a recent meta-analysis of over 140 000 patients with OHCA, survival to hospital admission was 23.8%, and survival to hospital discharge was only 7.6%.[2] In patients who initially achieve return of spontaneous circulation (ROSC) after OHCA, the

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Conflict of interest: None.

significant subsequent morbidity and mortality are largely due to cerebral and cardiac dysfunction that accompanies prolonged whole body ischaemia. This syndrome has been called the 'post-cardiac arrest syndrome' and comprises anoxic brain injury, post-cardiac arrest myocardial dysfunction, systemic ischaemia/reperfusion response and persistent precipitating pathology.[3] Implementation of a comprehensive care plan for these patients has been shown to lead to improved outcomes[4] and was recently promoted by the American Heart Association guidelines.[5] However, delivery of systematic care for this patient population can be problematic because of administrative, resource and logistical barriers, leading to an underutilisation of important post-resuscitative interventions.[6,7] Additionally, hospital factors such as hospital size and 24 hours a day interventional cardiac care capabilities have been found to influence patient outcome in Sweden,[8] Japan,[9] North America[10–12] and Australia.[13]

Despite these facts, patients resuscitated from cardiac arrest in Australia are not routinely hospitalised at specific cardiac centres,[13] are cared for in many different intensive care units (ICU) and often receive care from teams with little experience in the management of these patients. Regional systems of care are well established for other time critical interventions in patients following trauma,[14,15] stroke[16] and ST elevation myocardial infarction (STEMI).[17] Dedicated cardiac arrest centres have been established in North America[18,19] and Europe,[20] and in order to maintain optimal international treatment standards, urgent local research is needed into the implications of a regional system of care for patients resuscitated from OHCA in Australia.

Trauma systems of care

In the state of Victoria, a dedicated state-wide system of care for patients suffering traumatic injury was established in the year 2000.[21] Key components of the system are highly trained emergency medical service (EMS), with triage guidelines that direct all patients with suspected major trauma to one of three major trauma services (MTS) if accessible within 30 minutes of the scene, and non-major trauma hospitals are advised to transfer patients to a MTS if patients meet criteria for major trauma. Another crucial aspect of the system was the development of the Victorian State Trauma Registry, a population-based registry collecting information on prehospital, in-hospital and post-discharge phases. Such data are important for guiding improvements in trauma management processes, and the registry has already highlighted a significant reduction in mortality and disability for patients treated in the Victorian trauma system[14,15]

Systems of care for patients with myocardial infarction

In a similar manner, there has been considerable progress in the development of models of care for patients with acute STEMI. These have evolved over a considerable period of time, including the creation of coronary care units and the development of mobile intensive care paramedic services. More recently, most states in Australia have adopted prehospital, EMS 12-lead electrocardiography (ECG) programmes in which patients with ST elevation on initial field ECG are transported directly to hospitals capable of emergency coronary intervention with field transmission of ECG and notification to cardiac team prior to patient arrival. Such programmes have been shown to reduce significantly door-to-balloon time, which is associated with improved patient outcomes.[22,23] The system of care for STEMI patients requires further development with regard to integration of non-metropolitan patients, data collection and monitoring systems but may provide a framework for the integration of patients with OHCA.

Current state of cardiac arrest management in Australia

Many states in Australia have highly developed EMS systems but with a wide variety of quality outcome reporting. For instance, in Victoria, the EMS consists of a two-tier system of advanced life support paramedics who are authorised to provide defibrillation, laryngeal mask airway insertion and intravenous administration of adrenaline. This is in addition to intensive care paramedics, who also perform endotracheal intubation and administer a range of additional cardiac drugs. A first responder programme by fire fighters operates for suspected cardiac arrest patients in the inner area of Melbourne,[24] with a similar programme being currently piloted in outer regions. The cardiac arrest protocols follow the recommendations of the Australian Resuscitation Council.[25]

Victoria has a well-established Victorian Ambulance Cardiac Arrest registry (VACAR) (>59 000 patient episodes) providing key data on prehospital care and patient outcomes.[26] Since 2008, all OHCA patient care data are recorded electronically by the treating paramedics at the completion of the case and downloaded to a central server on return to the ambulance station. Cases of OHCA are identified, reviewed for completeness and recorded in the VACAR according to Utstein definitions.[27]

Evidence for the regional systems of care for cardiac arrest

At present in Australia, patients with return of a spontaneous circulation (ROSC) after OHCA are transported to the nearest hospital with an emergency department, despite increasing data to suggest that the development of cardiac arrest treatment centres, may provide improved outcomes for the OHCA patient. A Japanese cardiac arrest register of over 10 000 patients showed that OHCA patients transported to critical cardiac care hospitals had improved 1-month survival compared with patients transported to hospitals without specialised cardiac facilities (6.7% vs 2.8%, $P < 0.001$, adjusted odds ratio 3.39, $P < 0.001$).[9] In a Swedish study of almost 4000 OHCA patients, there was marked variability in hospital outcomes after adjusting for prehospital factors, with survival varying from 14% to 42% in different centres.[8] A US cross-sectional study of 109 739 patients indicated that hospital factors including teaching status, size and urban location were associated with outcome in patients resuscitated from cardiac arrest.[28] Recent studies designed to optimise all facets of cardiac arrest care, including transport to dedicated cardiac arrest centres, have also been associated with improvement in outcomes.[19,29]

The Take Heart America Program, a community-based initiative aimed at increasing OHCA survival, recently reported their results after the development of a regional system of cardiac arrest care for Minnesota. The programme involved optimisation of prehospital care including EMS and community training while also establishing protocols for transport to and treatment by three dedicated cardiac arrest centres providing therapeutic hypothermia (TH), coronary artery evaluation and treatment, and electrophysiological evaluation. When compared with historical controls, survival to hospital discharge improved from 8.5% to 19%, $P = 0.01$ (odds ratio 2.60, 95% confidence interval (CI) 1.19–6.26). Importantly, this outcome was driven by a dramatic improvement in survival after admission to intensive care (24% vs 51%, $P = 0.011$), with no significant improvement in rates of admission to ICU (35% vs 38%, $P = 0.51$). A financial analysis revealed that the cardiac arrest centres concept was financially feasible despite the costs associated with the development of high-quality post-resuscitation care.[29]

Another US-based programme, The Cool It Protocol, has also reported on the successful implementation of dedicated cardiac arrest centres being established from a pre-existing system of care for patients with STEMI. The Cool It protocol is a multidisciplinary system of care that affords regional and timely access to a standardised post-resuscitative care protocol through the rapid and coordinated transfer of patients to cardiac arrest centres.[19] In their preliminary results of the first 140 patients who remained unresponsive post-ROSC, 56% of patients survived to hospital discharge with 92% of survivors discharged with a positive neurological outcome.[19]

Conversely, the Resuscitation Outcomes Consortium investigators examined the outcomes of 4087 patients with OHCA. In that study, patients post-OHCA who were treated at hospitals capable of invasive cardiac procedures centres did not have increased rates of survival after adjusting for prehospital factors.[10] Similarly, a recent retrospective analysis that combined quality improvement data from the Cardiac Arrest Registry to Enhance Survival registry evaluated the influence of hospital characteristics on survival in patients with OHCA of suspected cardiac aetiology.[30] A significant relationship was observed between trauma centre designation but not presence of a coronary catheterisation laboratory or the volume of patients received, and survival or neurological outcome.

With regard to Australian data, we recently published results from Victoria using the VACAR registry highlighting that hospital characteristics were associated with patient survival.[13] Our study examined 2902 patients who achieved ROSC and were transported to one of 70 Victorian hospitals. Two thirds (63%) of patients were treated at hospitals with 24-hour cardiac interventional services. After adjusting for differences in baseline characteristics, hospital factors significantly associated with survival were: treatment at hospitals with 24-hour cardiac interventional services (odds ratio 1.40; 95% CI 1.12–1.74, $P = 0.003$), and patient admission between 0800 and 1700 hours (odds ratio 1.34; 95%CI 1.10–1.64, $P = 0.004$). OHCA patient volume and total hospital bed numbers were not independently associated with outcome.

An important observation in our study was that increased transport time to hospital did not adversely affect outcome. This is supported by other studies indicating that increased transport time to facilitate transfer to a cardiac centre did not adversely impact on patient survival.[31] Therefore, bypass of the closest hospital for transport to a cardiac centre may be appropriate in a regionalised system of care. Long transport times may be more significant in a rural Australian setting and consideration of developing dedicated rural cardiac arrest centres, akin with the recent development of rural percutaneous coronary intervention (PCI) services needs to be considered. However, the trauma system of care for rural patients in the state of Victoria has been highly successful.[14]

Standardising post-resuscitative care

Aiming for improvements in post-resuscitative care at all treatment centres who care for patients post-OHCA is vital and represents a possible alternative to dedicated cardiac arrest centres. Treatments that are thought to improve outcome after OHCA resuscitation include therapeutic hypothermia (TH),[32,33] early reperfusion of blocked coronary arteries[34,35] and possibly optimisation of critical care parameters, such as blood pressure, glucose, and optimisation of oxygenation and haemodynamics.[4] Cardiogenic shock in this patient population is common and associated with significant morbidity and mortality.[36] In many instances, cardiac support with an intra-aortic balloon pump is inadequate to maintain adequate organ perfusion. As such, advanced cardiac support with percutaneous cardiopulmonary bypass with extracorporeal membrane oxygenation is an alternative option, with the additional benefits of possibly aiding resuscitation in prolonged arrest.[37] These interventions require a multidisciplinary team with experience and expertise in the management of these patients.

Post-cardiac arrest anoxic brain injury is a major cause of morbidity and mortality, and is responsible for approximately two thirds of the deaths in the post-cardiac arrest period.[38] One important advance in post-ROSC management is the use of TH for the treatment of comatose survivors of OHCA. Two randomised, controlled trials have clearly confirmed the benefit of TH after cardiac arrest.[32,33] Both studies investigated mild TH in comatose adult patients after OHCA secondary to ventricular fibrillation (VF). A subsequent individual patient data meta-analysis indicated the number of patients needed-to-treat to provide a good neurological recovery is six.[39] As a result of these trials, the most recent American Heart Association guidelines recommend TH be induced as soon as possible and maintained for 12–24 hours in the management of anoxic neurological injury post-cardiac arrest when the initial cardiac rhythm is VF/ventricular tachycardia (VT) and suggests consideration of its use after resuscitation from OHCA when the initial cardiac rhythm is asystole or pulseless electrical activity.[40]

In addition to the induction of TH, early coronary angiography should be considered in patients with OHCA and successful resuscitation where it appears that there was a cardiac cause for the arrest. However, the role of early PCI in this group of patients is uncertain. There have been no prospective randomised trials in comatose patients post-OHCA examining the role of coronary angiography. However, there is considerable observational data that support the role of early angiography and PCI if needed in patients post-OHCA with STEMI.[3,41,42]

The role of primary PCI in patients who have been resuscitated from OHCA and who do not have STEMI on 12-lead ECG is uncertain. On the one hand, this procedure is expensive and would not be justified if the neurological prognosis was very poor.[43] On the other hand, unstable coronary plaques suitable for treatment with PCI may be missed if decision-making is based on 12-lead ECG criteria alone.[34,44] A recent study of cardiac arrest patients undergoing coronary angiography found significant coronary lesions occur in up to 66% of patients without ST elevation.[45] The largest series of coronary intervention in the setting of OHCA has found that PCI was an independent predictor of survival irrespective of initial ECG findings (odds ratio 2.06, $P = 0.013$).[34] Given the relatively good prognosis of patients who receive TH following OHCA and who have an initial cardiac rhythm of VF or VT, the difficulties of accurate early prognostication and the lack of sensitivity and specificity of the initial 12-lead ECG, it seems reasonable that all patients with coma following OHCA, and an initial cardiac rhythm of VF or VT, should undergo both immediate TH and early coronary angiography.[46]

Despite the evidence supporting the use of TH and PCI in the post-cardiac arrest patient, the uptake of these important post-resuscitative measures has been poor.[6,7] Therefore, developing dedicated centres with standardised post-resuscitative treatment guidelines has the potential for significant improvement in patient outcomes. One of the early cardiac arrest centres in Europe developed a post-resuscitative care treatment protocol including TH, early PCI for ST segment-elevation myocardial infarction and early haemodynamic optimisation. In their initial intervention period, 26% of OHCA survivors admitted to the hospital with a pulse survived to discharge prior to implementation of the protocol, and this increased to 56% following implementation of the post-resuscitation care protocol ($P = 0.001$).[4] A recent report indicated maintenance of this relatively good survival rate 5-year post-protocol implementation.[20] Locally, we have shown at a large hospital with expertise in acute cardiac care that a contemporary post-resuscitation treatment strategy including TH and coronary intervention in patients admitted post-OHCA was independently associated with survival when compared with historical controls (odds ratio 5.5 95% CI 1.2–26.2, $P = 0.03$).[35]

Organisation of clinical care services

As with trauma and STEMI systems, many regions overseas are developing systems of care for patients with OHCA, incorporating dedicated cardiac arrest centres. In these regions specific criteria have been developed to enable categorisation, verification and designation of

Table 1 Potential clinical services needed at Australian Cardiac Centres

Clinical Service
Therapeutic hypothermia
24-h percutaneous coronary intervention service
Mechanical cardiac support services
Cardiac arrest consultation service
Ventilator management strategies
Electrophysiology cardiac service
Neurology/neurosurgical consultation
Multimodal neuroprognostication diagnostic service
Physiotherapy/social work/occupational therapy
Neuropsychology service

centres for the treatment of patients with ROSC post-OHCA (Table 1). These centres have commonly been founded on multidisciplinary collaboration including staff from emergency medicine, critical care, cardiology, respiratory and neurology. Much like trauma teams, many centres coordinate care through dedicated cardiac arrest referral teams.[18] Together, these teams are responsible for initially stabilising the patients, making decisions on continuation or implementation of TH after hospital arrival, and helping to direct additional post-arrest care.

The development of a system of care for high-risk cardiac patients such as those with OHCA could potentially carry significant adverse implications for the cardiac arrest centre in terms of healthcare expenditure and non-adjusted patient outcome figures. Accordingly, given the importance of transparent clinical outcome reporting, the use of appropriate risk-adjusted quality estimates are necessary.[47] With regards to healthcare costs, resuscitation interventions that increase survival have been associated with good quality of life[48] and acceptable costs to society.[49]

The data supporting implementation of cardiac arrest centres are predominantly observational and derived from international studies. Further research into the impact of developing a system of care for cardiac arrest patients in Australia is urgently needed. Studies with a focus on defining the relative contribution of prehospital and in-hospital factors, how cardiac arrest centres may be incorporated into pre-existing trauma and STEMI systems of care, and the implications on EMS services, hospital capacity, cost and longer term patient outcomes accompanied by quality of life measures are required. Based on the available evidence, however, the American Heart Association has recently recommended that regional systems of care be developed for patients with OHCA, and more specifically that within the context of a regional approach to acute interventional cardiology, patients with OHCA where the initial cardiac rhythm is VF or OHCA with ST segment elevation be transported directly to cardiac arrest centres.[5,50]

Conclusion

In patients who achieve return of circulation after OHCA, morbidity and mortality remain significant. Treatment strategies focusing on both prehospital and post-resuscitative care are vital in improving patient outcomes and may be further optimised with the development of regional systems of care. Specifically, emphasis should be placed on the development of specialist cardiac arrest centres that offer goal-directed therapies including TH, early coronary angiography and temporary circulatory support where appropriate, together with comprehensive neurological assessment and therapy. We would call for urgent research into the efficacy and implications of establishing a regional system of care for patients post-OHCA in Australia.

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CHAPTER 7: Extracorporeal Membrane Oxygenation to Support Cardiopulmonary Resuscitation

Monash University

Declaration for Thesis Chapter 7

Stub D, Byrne M, Pellegrino V, Kaye DM. **Extracorporeal Membrane Oxygenation to Support Cardiopulmonary Resuscitation in a Sheep Model of Refractory Ischemic Cardiac Arrest.** *Heart Lung and Circulation.* In Press January 2013

Declaration by candidate

In the case of Chapter 7 the nature and extent of my contribution to the work was the following:

Name	Nature of contribution	Extent of contribution (%)
Stub D	Principle Author, responsible for overall study concept, literature review, analysis, performance of experiments interpretation of results and development and writing of manuscript. Responsible author who effects overall responsibility of publication	70%

Candidate's Signature	[redacted]	**Date** 27/11/2012

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution
Byrne M	Responsible for animal surgery. Analysis of results and manuscript development and editing
Pellegrino V	ECMO technical expertise. Analysis of results and manuscript development and editing
Kaye D	Supervision of experiment. Analysis of results and manuscript development and editing

Declaration by co-authors

The undersigned hereby certify that:

- the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
- they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
- there are no other authors of the publication according to these criteria;
- potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
- the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Alfred Hospital Heart Centre, Intensive Care Unit, Baker IDI Heart and Diabetes Institute, Monash University Faculty of Medicine Nursing and Health Sciences.

Signature 1	[redacted]	28/11/2012
Signature 2	[redacted]	30/11/2012
Signature 3	[redacted]	9/11/2012

Introduction to Extracorporeal Membrane Oxygenation to Support Cardiopulmonary Resuscitation

Cardiac Arrest with failure of ROSC

Thus far the focus of my thesis has been on highlighting aspects of post-resuscitative care in optimising outcomes of patients with OHCA who achieve ROSC and are admitted to hospital. As we have previously discussed however, data from the Victorian Ambulance Cardiac Arrest Register indicates that only 50% of OHCA patients with an initial cardiac rhythm of VF, respond to paramedic resuscitation and achieve ROSC in the field[131].

It is clear therefore, that despite our best efforts at improving all links in the chain of survival, a significant proportion of patients with OHCA will not achieve ROSC. Traditionally outcomes in patients with OHCA who do not achieve ROSC have been dismal[3]. Accordingly rules for when to terminate resuscitative efforts have been developed in the attempt to avoid transporting patients to hospital with no hope of survival[132-134]. Most of these rules include factors such as unwitnessed cardiac arrest, the patient having a non-shockable rhythm and inability to achieve ROSC. Similarly the clinical practice guidelines of Ambulance Victoria indicate that resuscitation efforts in the field may be ceased after 30 minutes if ROSC has not been achieved, the patient remains in a non-shockable rhythm, without signs of life such as gasping or pupil reactions[135].

Where however does this leave the significant number of patients with OHCA and an initial cardiac rhythm of VF? The above paradigm, however, does not provide clear guidance for the significant number of patients with OHCA and a persistent, albeit potentially 'shockable' cardiac rhythm of VF. At a pragmatic level more than 55% of these patients are greater than 65 years of age[136], who inevitably descend into a non-shockable rhythm during resuscitation efforts, which are ultimately ceased in the field. This still leaves a significant proportion of younger patients, with refractory VF who never achieve ROSC. Failure to respond to timely resuscitation may be due to the complete blockage of a coronary artery and inability to restore any myocardial oxygen delivery, or less commonly large pulmonary embolism, congenital cardiomyopathy or cardiac channelopathy. In Victoria, patients are transported to hospital with ongoing CPR in less than 1% of cases[137], with at present no established system of care for patients with otherwise positive pre-hospital prognostic markers such as younger age, bystander CPR, and an initial rhythm of VF but failure of ROSC.

Most patients with refractory cardiac arrest in Victoria are not transported to hospital for two reasons. Firstly, transport to hospital would require on-going external chest compressions in the back of a fast-moving ambulance and this would be unsafe for the crew. Secondly, given that advanced life support measures have been provided at the scene by paramedics, there have traditionally been no additional treatment options in the emergency department.

Resuscitation strategies in setting of prolonged OHCA

Recently, a number of new resuscitation strategies have become available that may be applicable to this group of patients who would otherwise die. Firstly portable automated CPR devices are now available that deliver quality mechanical chest compressions, whilst potentially facilitating safe transport of a patient with CPR in progress[138, 139]. Of these two devices, the Autopulse machine has been trialled by Ambulance Victoria in rural settings without any adverse events. It is a battery powered board that incorporates a wide chest strap that contracts and provides at least equal quality chest compressions compared with human chest compressions. Importantly, it allows CPR to be safely and effectively undertaken during transfer to hospital[140]. The machine is approved by the Therapeutic Goods Administration Australia.

Secondly, as I have extensively discussed in earlier chapters, protection of the brain following prolonged CPR is now possible using therapeutic hypothermia[39, 40]. More recently, the induction of therapeutic hypothermia in the pre-hospital setting using a rapid intravenous infusion of 2 litres of ice-cold saline has been tested in clinical trials and found to be an effective induction strategy[100, 101]. Preliminary studies of hypothermia during CPR in laboratory studies suggest a powerful neuroprotective effect[32, 141] and clinical trials testing this approach are currently underway[142].

With these relatively novel aggressive pre-hospital strategies it may be possible to preserve neurological function whilst continuing chest compressions for extended periods of time enabling transport to hospital of patients with refractory cardiac arrest and failure of ROSC. Given many of these patients have cardiac arrest due to coronary occlusion and myocardial infarction; there are reports of performing PCI with ongoing automated chest compressions enabling subsequent ROSC and patient recovery[143, 144]. This strategy of performing CPR during PCI is limited however, by a number of issues including; technical difficulties, the lack of subsequent cardiac support for possible hemodynamic instability, whilst not addressing treatment of other possible aetiologies. Ongoing CPR whilst in the catheterization laboratory,

facilitating PCI, is therefore not routinely recommended by most cardiologists who specialise in the management of OHCA[145].

ECMO facilitated CPR (ECPR)

Another treatment option for refractory cardiac arrest that is gaining international prominence is the use of extracorporeal membrane oxygenation to augment CPR (ECPR). The concept of establishing rapid total cardiopulmonary support in the form of ECMO for refractory cardiac arrest was described over 30 years ago[146]. In the paediatric population, ECPR in the management of prolonged in-hospital cardiac arrest is considered a standard of care at tertiary paediatric centres[147]. Its use in adult refractory cardiac arrest has been a little slower in becoming part of clinical practice. The use of ECPR in the management of adult cardiac arrest is gradually gaining prominence[148]. The Extracorporeal Life Support Organization (ELSO) registry has recently reported on 297 adult patients (11% of 2,633 adult ECMO uses) who underwent ECMO to support CPR. Median age was 52 years and 75% of patients had cardiac disease. Survival to hospital discharge in this registry was 27%[149]. Mirroring its use in paediatric patients, in tertiary centres with ECMO capabilities, the use of ECPR for inpatients with prolonged cardiac arrest has been shown to be safe and possibly more efficacious than standard resuscitation measures[150, 151]. It is only more recently however, in particular when combined with other therapeutic strategies such as hypothermia and automated CPR, which help overcome issues of prolonged CPR in transport, that the use of ECPR for adult patients with OHCA and failure of ROSC has been increasingly described.

The largest international experience in the development of a system of care involving ECPR to treat patients with refractory OHCA has been in Japan[152]. One of the first reports of ECPR, hypothermia and PCI in patients with OHCA was described by Nagao and colleagues, in a single centre experience from Tokyo[38]. In this prospective study of 50 patients with prolonged OHCA, 32 patients had failure of ROSC on arrival to hospital and were initiated on ECMO. Therapeutic hypothermia was induced and maintained for 48 hours in those patients with systolic blood pressures >90mmHg and coronary angiography was performed after being established on ECMO support. This pioneering ECPR protocol achieved ROSC in 46/50 (92%) of patients and survival to discharge with good neurological recovery in 12/50 (24%). Since the use of ECPR in Japan has expanded widely. A recent Japanese Systematic review of 1282 cases of OHCA managed with ECPR at over 30 centres, indicated a similar survival rate of 26%[152].

Increasing international experience with ECPR highlights the significant possibilities of combining ECPR with other resuscitative strategies in the management of refractory OHCA[153-158]. There are relatively few basic mechanistic studies into the effectiveness of ECPR, but these studies highlight improvements in tissue oxygenation, calcium handling and a possible attenuation of reperfusion injury[159], increases in coronary perfusion during resuscitation[160] and improvements in ventricular waveform parameters during ECPR[161]. At a clinical level ECPR may effectively be established on immediate arrival to hospital by a variety of health care providers[158], enable a much needed window of time for further appropriate investigations[155], whilst providing a more stable scenario than continued CPR for potentially critical interventions, such as PCI to facilitate ROSC[153].

Tempering these relatively positive international reports of ECPR in the management of patients with prolonged OHCA is the recent study from Paris by Le Guen[162]. This single centre study evaluated the outcomes of 51 patients with refractory OHCA treated with ECPR established on admission to hospital. Only 2 patients (4%) were alive at 28 days with good neurological recovery. 90% of patients had died within 48 hours of multi-organ failure (47%), brain death (20%) and hemorrhagic shock (14%). Crucially the median time from collapse to establishment of ECMO support was 120 minutes (IQR 102-149 minutes), significantly longer than other studies.

The observational series of adult patients undergoing ECPR in both in-hospital cardiac arrest and OHCA indicate that survival and neurological recovery dramatically deteriorates if ECMO support is not established within 60 minutes after patient collapse[155, 163]. Thus any system of care designed for patients with refractory OHCA must consider the time spent at the scene, factors regarding patient transport, and cannulation requirements, in ensuring suitable patients are established on support within one hour of initial cardiac arrest. Although there have been case reports of ECPR inserted in the field, this is unlikely at the present to be applicable to most EMS systems[164].

The use of ECMO has increased significantly in Australia over the last 10 years[165, 166]. Whilst its regular application in patients with severe cardiac or respiratory failure is predominantly occurring in large tertiary centres[166], an increasing number of regional centres are developing expertise in the initial cannulation and establishment of ECMO support, with later transfer of the

patient to a suitable centre with expertise in ongoing ECMO support. At present, however, there are no reports, of Australian centres offering ECPR in the management of patients with OHCA.

In Victoria the Alfred Hospital is the state referral centre for ECMO cases, managing more than 50 cases per year[167]. It is a quaternary level hospital with a large ICU catering to mixed medical/surgical/trauma cases whilst also serving as the state's heart and lung transplant centre. The hospital has significant expertise in managing critically ill patients and patients post OHCA[59].

Given the increasing international data and experience of ECPR as a possible strategy for certain patients with refractory OHCA, we aimed to develop the first Australian feasibility study into developing a treatment paradigm for refractory OHCA. As an adjunct to this endeavour, whilst also providing much needed mechanistic data into the benefits of ECPR during prolonged resuscitation, we performed a pre-clinical study exploring the hemodynamic effects of ECPR.

Original Article

Extracorporeal Membrane Oxygenation to Support Cardiopulmonary Resuscitation in a Sheep Model of Refractory Ischaemic Cardiac Arrest

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Background: **Survival after out-of-hospital cardiac arrest remains limited. It is therefore imperative to develop new resuscitation techniques. We aimed to determine the potential role of extracorporeal membrane oxygenation assisted CPR (ECPR) in an animal model of refractory ischaemic cardiac arrest.**

Methods: **Twelve sheep were assigned to either ECPR ($n = 6$) or 'conventional' ($n = 6$) resuscitation. All sheep had coronary occlusion, followed by induction of ventricular fibrillation (VF). CPR was than commenced for 10 min in both groups, followed by randomisation to ECPR or CPR for a further 10 min. At 23 min post induction of VF, advanced life support measures were commenced with direct cardioversion, adrenaline and amiodarone. Outcomes measures included rates of return of spontaneous circulation (ROSC), and analysis of VF wave form.**

Results: **Baseline haemodynamics were similar between the two groups. CPR consistently produced coronary perfusion pressures (CPP) greater than 15 mmHg in both groups, with significantly increased CPP post commencement of ECMO in the ECPR group (17.84 ± 2 mmHg vs 22.94 ± 3 mmHg, $p = 0.04$). Number of shocks, pH, lactate and oxygenation were also comparable. Significantly greater rates of ROSC were seen in the ECPR sheep, 3/6 (50%) vs 0/6 (0%) ($p = 0.032$), which was also associated with significantly increased VF amplitude measures (0.51 ± 0.08 mV vs 0.42 ± 0.06 mV, $p = 0.04$).**

Conclusions: **This study indicates that ECPR increases return of circulation and coronary perfusion pressure in a sheep model of ischaemic VF arrest. Our findings have supported the development of a pilot trial into the effectiveness and feasibility of ECPR in the clinical setting.**

(Heart, Lung and Circulation 2013;xxx:1–7)

Keywords. Cardiac arrest; Cardiopulmonary bypass; Extracorporeal membrane oxygenation; Resuscitation

Introduction

Out-of-hospital cardiac arrest (OHCA) is a common cause of cardiac death affecting up to 325,000 people in the United States each year [1]. Despite significant recent efforts to improve pre-hospital resuscitative care, a recent meta-analysis of over 140,000 patients with OHCA revealed survival to hospital discharge to be only 7.6% [2]. Commonly, resuscitation attempts fail as a result of the inability of CPR to generate sufficient recovery of myocardial function. Given the poor rates of return of spontaneous circulation (ROSC) and the incomplete support native post arrest cardiopulmonary function provides to injured organs, there is growing interest and experience in extracorporeal means of providing oxygen delivery during and after cardiac arrest. Extensive animal data [3–6] and non-randomised reports of clinical experience suggest that veno-arterial extracorporeal membrane oxygenation (VA-ECMO) assisted CPR (ECPR) might be a superior means of resuscitating some victims of cardiac arrest [7–13].

The majority of the pre-clinical models of ECPR have utilised healthy animals with cardiac arrest induced by means unrelated to myocardial ischaemia. Moreover, the majority of studies have been conducted with relatively short cardiac arrest times. By contrast, most adult non-traumatic cardiac arrests occur in the setting of coronary artery disease with unstable plaque rupture and thrombus formation, or ventricular arrhythmia due to previous scar formation accounting for 40–90% of cases [14]. We

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Abbreviations: OHCA, out of hospital cardiac arrest; VF, ventricular fibrillation; ROSC, return of spontaneous circulation; ECMO, extra corporeal membrane oxygenation; ECPR, extra corporeal membrane oxygenation assisted cardiopulmonary resuscitation.

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therefore aimed to examine the efficacy of ECPR in restoring circulation compared to conventional resuscitation, in a sheep model of coronary occlusion and subsequent VF arrest, whilst exploring haemodynamic differences between the two resuscitation techniques.

Methods

The study was approved by the Animal Ethics Research Committee, Victorian Institute of Animal Science, and animals were handled in accordance with NIH guidelines, 'Principles of Laboratory Animal Care by the National Society for Medical Research and Guide for the Care and Use of Laboratory Animals'.

Twelve adult merino sheep (59.2±3 kg) were premedicated with 5 mg/kg propofol intravenously and flunixin 2.2 mg/kg intramuscularly. Endotracheal intubation anaesthesia was maintained with inhaled isoflurane (2–2.5%) using a ventilator at 16–18 breaths per minute. Heart rate and rhythm were determined by electrocardiography. Aortic pressure was measured via 6F right carotid arterial catheter, whilst left ventricular continuous pressure monitoring was performed using a millar mikrotip catheter (SPR 320 ADInstruments, NSW, Australia) inserted through the right carotid artery sheath. Normal saline solution was infused at 3–5 mL/kg/h via cannulation of femoral vein which was also utilised for resuscitative drugs. Baseline transthoracic echocardiography was performed (Cypress, Acuson, Siemens Medical Solutions, Malvern, PA, USA). In ECPR sheep, additional arterial (15F) and venous (17–19F) cannula were inserted into the left carotid artery and left internal jugular vein prior to commencement of arrest protocol.

Cardiac Arrest and Resuscitation Protocol

After baseline measurements, systemic heparin (15,000 IU) was given. A left thoracotomy and pericardotomy were performed. The protocol sought to mimic the process of acute coronary ischaemic driven cardiac arrest and subsequent prolonged resuscitation. Myocardial infarction was induced via ligation of the mid left anterior descending artery (see Fig. 1). VF was induced with direct application of a 9 V battery to the myocardial surface, confirmed by ECG and aortic pressure trace, followed by 3 min of no-flow cardiac arrest without ventilation. Open chest cardiac-massage was performed due to the anatomy of the ovine thorax. Cardiac compressions were performed for 10 min followed by randomisation (performed prior to protocol commencing) to ECPR or Control groups. A further 10 min of chest massage were performed for both groups. Compressions were maintained at 80–100 beats per minute with an intensity aimed at achieving a coronary perfusion pressure of greater than 15 mmHg based on mean arterial and left ventricular filling pressures.

After 23 min of VF arrest, advanced resuscitation measures were commenced in both ECPR and control sheep, adapted from the American Heart association guidelines [15]. Defibrillation was performed using 40 J internal defibrillation paddles and repeated after every 2 min until

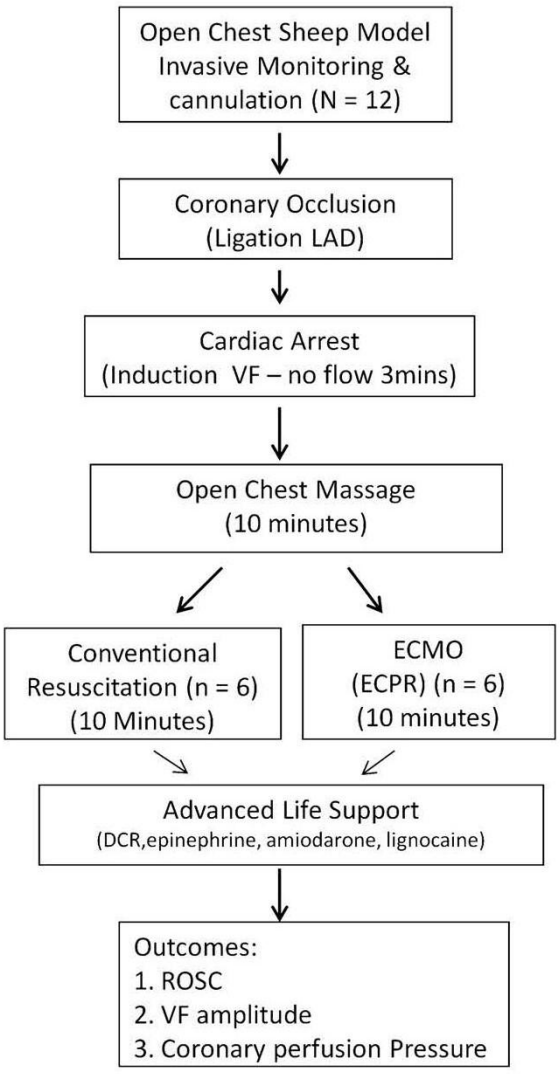

Figure 1. *Study protocol. DCR – direct cardio version, VF – ventricular fibrillation, LAD – left anterior descending artery, ROSC – return of spontaneous circulation.*

ROSC was restored. Intravenous epinephrine (0.02 mg/kg) was administered 1 min after initial defibrillation and repeated every 5 min as required. Amiodarone (150 mg) and lignocaine (1 mg/kg) were administered, with a further dose repeated after 10 min if a shockable rhythm persisted. ROSC was defined as an organised ECG with systolic blood pressure >80 mmHg for 10 min.

The extracorporeal circuit consisted of a membrane oxygenator (Quadrox D, Maquet, Germany), an arterial pump head (RotaFlow, Maquet, Germany) and a centrifugal pump (Biomedicus, Medtronic, Inc). The ECMO circuit was primed with approximately 800 mL of Haartmans solution, and the air mix delivered to the oxygenator was 50% oxygen. A water-circulating heat exchanger

provided temperature control of the circuit at 36.5 C. Pump speeds were adjusted to optimise flow and mean arterial blood pressure during ECPR.

Haemodynamic and Biochemic Measurements

Haemodynamic measurements were made at baseline, after myocardial infarction (before VF) and throughout resuscitation. The number of shocks during CPR, minutes of CPR, quantities of epinephrine and mortality were recorded. Arterial blood was sampled at baseline and at regular intervals throughout resuscitation. Cellular injury was determined with creatinine kinase (CK) troponin, lactate and creatinine.

VF Waveform Analysis

The VF signal at selective time points throughout cardiac arrest were taken and analysed in 10 s intervals, to determine amplitude of VF waveform. Peak-to-peak amplitude was measured via visual inspection of epoch of the electrocardiographic signal and was defined as the difference between the maximum and minimum recorded voltages [16].

Statistical Analysis

Continuous variables were expressed as mean ± standard error of the mean, or median (interquartile range) as appropriate, and categorical data expressed as numbers/percentages, except where indicated. Continuous variables were compared using Student's *t*-tests, ANOVA or Kruskal–Wallis equality-of-populations rank test as appropriate. Categorical variables were compared using Fisher's exact or Pearson's chi-square tests as appropriate. All calculated p values were two-sided and p values <0.05 were considered statistically significant.

Results

Baseline haemodynamic and biochemistry parameters were similar between conventional and ECPR groups (Table 1). Baseline echocardiography revealed no evidence of structural heart disease with normal biventricular function and no significant valvular pathology.

Haemodynamic Measurements

Following ligation of the left anterior descending artery, there was a significant fall in mean arterial blood pressure (MAP) (87–79 mmHg, $p = 0.03$) and associated increase in left ventricular end diastolic pressure (LVEDP) (5.4–11.6 mmHg, $p < 0.01$) in both groups.

Open chest direct cardiopulmonary resuscitation consistently produced coronary perfusion pressures greater than 15 mmHg in both groups. Prior to randomisation, during the first 10 min of open chest massage, the CPP was similar between control and ECPR groups (17.4 ± 3 mmHg vs 17.8 ± 3 mmHg, $p = 0.37$). After randomisation, however, CPP in the control group remained consistent whereas the CPP increased after commencement of ECMO in the ECPR cohort (17.4 ± 2 mmHg vs 22.94 ± 3 mmHg, $p = 0.04$) (Fig. 2). Number of defibrillation attempts were similar between the two groups (7.0 vs 8.5, $p = 0.2$), as was quantities of epinephrine, amiodarone and lignociane.

Table 1. *Baseline Haemodynamic and Cardiac Arrest Characteristics.*

Variable	Control ($n = 6$)	ECPR ($n = 6$)	p Value
Baseline			
Weight (kg)	61 ± 2.7	58 ± 3.3	0.10
HR (bps)	111 ± 9	101 ± 7	0.26
MAP (mmHg)	84 ± 7	89 ± 8	0.62
LVEDP (mmHg)	5 ± 1	6 ± 1	0.69
LV DP/DT	1365 ± 132	1281 ± 83	0.37
Post LAD occlusion–pre arrest			
HR (bps)	106 ± 5	91 ± 9	0.19
MAP (mmHg)	78 ± 10[a]	81 ± 6[a]	0.83
LVEDP (mmHg)	11 ± 2[a]	13 ± 2[a]	0.31
LV DP/DT	1051 ± 107[a]	1092 ± 107[a]	0.74
Cardiac arrest details			
CPR (min)	37 (34–41)	41 (36–44)	0.09
Shocks	7 (6–9)	8.5 (6–10)	0.21
Epinephrine (mg)	1.8 ± 0.3	1.9 ± 0.4	0.62
ECMO time (min)	–	33 (32–38)	–
ROSC	0/6 (0%)	3/6 (50%)	0.03

HR – heart rate, MAP – mean arterial pressure, LVEDP – left ventricular end diastolic pressure, LV DP/DT – left ventricular change pressure/change time, ECMO – extra corporeal membrane oxygenation, ROSC – return of spontaneous circulation.
[a] $p < 0.05$ compared with baseline values.

Biochemical and VF Waveform Measurements

Table 2 summarises biochemical markers, in which creatinine, lactate, troponin and creatinine kinase were all similarly increased between control and ECPR groups at study completion, indicating significant ischaemic tissue damage. There was also no significant difference in serum pH between the two groups, and oxygenation (mean $PaO_2 = 149$ mmHg) was maintained equally between ECPR and control groups.

As expected the VF amplitude significantly deteriorated post commencement of no-flow cardiac arrest (Table 3 and Fig. 3). There was significant increase in both groups in VF amplitude with commencement of CPR. The VF amplitude prior to randomisation indicated no significant difference between groups (0.38 ± 0.07 mV vs 0.37 ± 0.06 mV, $p = 0.85$). There was, however, significant increase in the VF amplitude of the ECPR cohort following commencement of ECMO support, whereas the VF amplitudes stayed relatively constant in the control group (Table 3 and Fig. 3). This resulted in significantly increased mean peak–peak–amplitude of ECPR compared to controls following randomisation (0.42 ± 0.06 mV vs 0.51 ± 0.08 mV, $p = 0.04$).

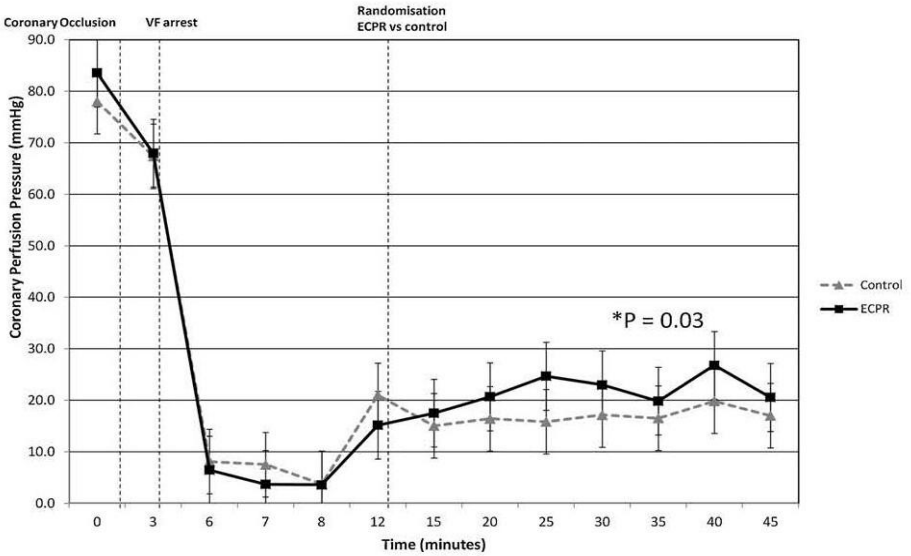

Figure 2. *Coronary perfusion pressure during study protocol. *Mean coronary perfusion pressure post randomisation in conventional vs ECPR (17 mmHg vs 21 mmHg, p = 0.03).*

Table 2. *Biochemistry Values.*

Variable	CK (U/L)	Troponin (μg/L)	Lactate (mmol/L)	Creatinine (U mol/L)	AST (U/L)
Baseline					
Control	564 ± 179	0.1 ± 0.06	3.3 ± 0.6*	112 ± 8	52.8 ± 1
ECPR	744 ± 210	0.2 ± 0.1	2.6 ± 0.5*	91 ± 8	61.2 ± 5
Final					
Control	1311 ± 443*	12 ± 4*	9.5 ± 0.8*	137 ± 7*	60.8 ± 2
ECPR	1393 ± 211*	18 ± 7*	10.3 ± 1.2*	120 ± 7*	78.8 ± 8

CK – creatinine kinase, AST – aspartate transaminase.
* $p < 0.05$ compared to baseline values.

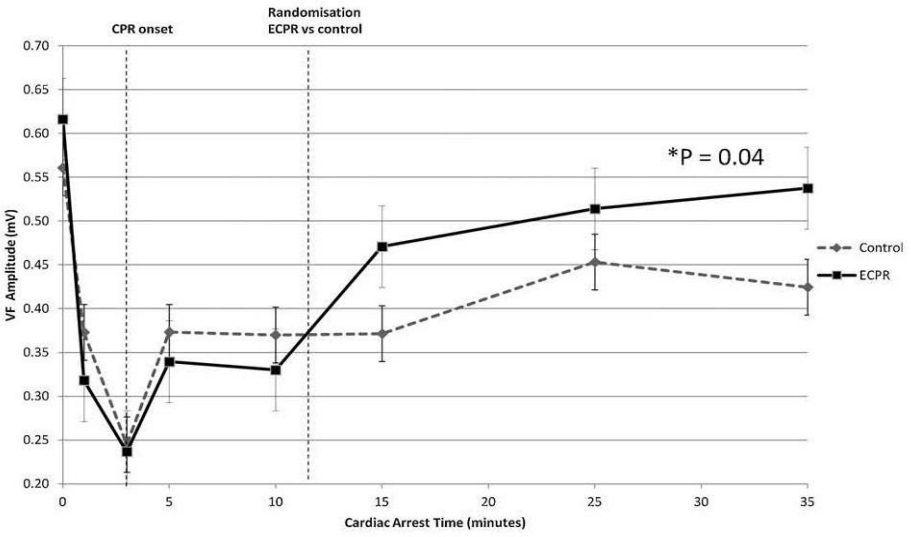

Figure 3. *Ventricular fibrillation amplitude. *Mean amplitude post randomisation in conventional vs ECPR (0.42 ± 0.06 mV vs 0.51 ± 0.08 mV p = 0.04).*

Table 3. *Ventricular Waveform Amplitudes.*

Time (min)	Control (mV)	ECPR (mV)	*p* Value
Onset VF	0.56 ± 0.10	0.62 ± 0.04	0.24
1	0.37 ± 0.09	0.32 ± 0.07	0.20
3	0.24 ± 0.06	0.24 ± 0.04	0.25
5	0.37 ± 0.05	0.34 ± 0.06	0.35
10	0.37 ± 0.04	0.33 ± 0.08	0.08
15	0.37 ± 0.08	0.47 ± 0.10	0.06
25	0.45 ± 0.06	0.51 ± 0.08	0.08
35	0.42 ± 0.09	0.54 ± 0.05	0.04

VF – ventricular fibrillation.

Survival

Return of spontaneous circulation was achieved in 3/6 (50%) of the ECPR group. None of the control sheep, 0/6 (0%) could successfully achieve ROSC. When comparing differences between survivors and non survivors in the ECPR group, there was a trend towards increased CPP (23.5 mmHg vs 21.9 mmHg, $p = 0.06$) and VF amplitude (0.53 mV vs 0.48 mV, $p = 0.07$) in those that achieved ROSC.

Discussion

Successful resuscitation was significantly improved by utilising ECPR in this sheep model of myocardial infarction and prolonged cardiac arrest. Considering no sheep could be salvaged without the use of cardiopulmonary support, ECPR provided an acute treatment option to animals with an otherwise lethal injury.

Despite major recent advances in the treatment of cardiovascular disease, there has been little improvement in survival following cardiac arrest [2]. Given ongoing poor outcomes following cardiac arrest, there is growing interest and experience in extracorporeal means of providing oxygen delivery during and after cardiac arrest. Preliminary clinical data indicates that ECPR might be a superior means of resuscitating some victims of cardiac arrest [10,17,18]. Studies to date have had variable success, with survival to hospital discharge ranging from 10% to 60%, depending on the clinical scenario [8–10,19–22].

In our model of refractory ischaemic arrest, ECPR was associated with significantly greater rates of ROSC than the non ECPR 'conventional' group. The cardiac sequelae of prolonged VF include increased myocardial oxygen consumption, depletion of high-energy phosphates, and calcium overload, resulting in myocardial stunning, and cardiac necrosis [23]. Additionally the effectiveness of repeated defibrillation significantly diminishes over time [24]. The high mortality in our model of intractable VF is consistent with other pre-clinical studies of prolonged VF arrest, documenting similar dismal outcomes without use of cardiopulmonary support [4,25,26].

The benefits of ECPR are likely to be multifactorial. In our model, coronary perfusion pressure gradually increased with institution of ECMO (17.4 ± 2 mmHg vs 22.94 ± 3 mmHg, $p = 0.04$), a similar finding in other studies of refractory arrest and cardiopulmonary support [4]. Despite no significant difference between surrogate markers of tissue injury in our report, ECPR may contribute to improved tissue oxygenation, calcium handling and a possible attenuation of reperfusion injury [27].

The nature of the ventricular waveform also serves as a marker of underlying cardiac substrate, with coarse VF occurring early and less organised, lower amplitude VF occurring later, associated with decreased likelihood of conversion to an organised rhythm post shock [16]. There has been longstanding interest in analysis of VF waveforms to predict success of resuscitation efforts and potentially guide timing of chest compressions and defibrillations [28,29]. Previous models of ECPR have demonstrated improved VF waveform characteristics with use of ECMO [30]. Our study demonstrated significantly greater VF amplitude in ECPR sheep compared to non-ECPR controls, which although is a relatively older method of waveform analysis, has been closely associated with rates of ROSC [31].

There are a number of limitations to our study, including use of jugular and carotid vessels for cannulation, due to difficulties with small peripheral vessels in Marino sheep, and pre-insertion of cannula prior to myocardial infarct and cardiac arrest. It is possible that bilateral carotid arterial cannulation may have induced cerebral ischaemia, however there was no evidence of haemodynamic instability during the placement of the cannulae prior to induction of cardiac arrest. The use of an open chest model is also less clinically applicable to non-post cardiotomy situations, but allowed highly effective CPR and direct defibrillation to provide maximal opportunity for successful resuscitation. Systemic heparinisation before study commencement might also have influenced outcomes. It has, however, been previously demonstrated that pre-arrest anticoagulation has little influence on haemodynamics or rates of ROSC after prolonged VF arrest [32]. The lack of native collateral circulation in sheep renders their myocardium highly sensitive to coronary occlusion [33]. We believe that the lack of collaterals is actually highly clinically relevant. Specifically, patients presenting with OHCA due to coronary occlusion frequently have fewer coronary collaterals compared to patients with unstable angina or myocardial infarction in the setting of previously known coronary disease [34].

Our acute model of refractory cardiac arrest did not assess neurological outcomes, a major determinant of survival in this group of patients. This study, however, focused on acute haemodynamic impacts of ECPR. The Extracorporeal Life Support Organization (ELSO) registry has reported on 297 cases of ECPR with a survival to hospital discharge of 27%, with 33% of all patients suffering central nervous system injury [18]. Our study was also performed under normothermic conditions. The use of therapeutic hypothermia is recommended for comatose survivors of VF arrest [35] but if administered in the intra-arrest setting, may also be associated with improved rates of ROSC and improved cardiac function [36]. The combination of ECPR and therapeutic hypothermia has demonstrated promising preliminary results in both the pre-clinical [3,37] and clinical settings [20]. A recent single centre, study however,

reported a survival of only 4% in patients with refractory OHCA undergoing ECPR. Median time until establishment of ECMO support was 120 min with the majority of patients succumbing to multi-organ failure and haemorrhagic complications [38]. Duration of cardiac arrest and time until establishment of ECMO support are clearly important variables determining outcomes, with further clinical experience in developing appropriate systems and selection criteria for who may or may not be suitable for ECPR urgently required.

Despite these limitations, our study provides further pre-clinical support for the ability of ECPR to provide an additional treatment option in the setting of refractory cardiac arrest. It has also served as a training tool for the authors currently enrolling patients in the single centre pilot study; Refractory Out-Of-Hospital Cardiac Arrest Treated With Mechanical CPR, Hypothermia, ECMO and Early Reperfusion (CHEER) trial (NCT number: 01186614). This small pilot trial together with larger clinical experiences such as the SAVE-J: Study of advanced life support for Ventricular Fibrillation with Extracorporeal Circulation in Japan [11], clinical registry will provide much needed evidence for the emerging role of ECPR in prolonged cardiac arrest.

Conclusion

This study found that the use of ECPR in this ovine model of refractory ischaemic VF arrest was associated with a 50% rate of resuscitation, with improvements in coronary perfusion pressures and VF waveform parameters. Further research into the effectiveness, feasibility and limitations of ECPR in the clinical setting is required.

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Contributorship

All authors were involved in study design, implementation and manuscript development.

Conflict of interest

None to declare.

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Refractory Out-Of-Hospital Cardiac Arrest Treated With Mechanical CPR, Hypothermia, ECMO and Early Reperfusion (CHEER) Study

Informed by the international experiences described above and our pre-clinical data we have developed a single centre pilot study of ECPR for the treatment of OHCA. With the aim of determining whether mechanical CPR, therapeutic hypothermia, emergency ECMO and transfer to the cardiac catheter laboratory for coronary reperfusion results in a return of a spontaneous circulation and neurological recovery in patients with refractory out-of-hospital cardiac arrest (Clinicaltrials.gov NCT01186614).

CHEER Study Methodology

The Refractory Out-Of-Hospital Cardiac Arrest Treated with Mechanical CPR, Hypothermia, ECMO and Early Reperfusion (CHEER) Study is a pilot, non-randomised clinical trial. Selected Ambulance Victoria paramedic units in The Alfred Hospital catchment area have been trained and equipped to use the Autopulse automated CPR device.

Inclusion Criteria:

- Adults 18-60 years
- Out of hospital cardiac arrest due to presumed cardiac cause
- Chest compressions are commenced within 10 minutes by bystanders or emergency medical services
- Initial cardiac arrest rhythm of ventricular fibrillation
- Remains in cardiac arrest at 30 minutes post collapse
- Autopulse machine is available
- Within 10 minutes ambulance transport time to the Alfred Hospital
- During normal working hours (9am-5pm, Monday to Friday)
- ECMO commences within 60 minutes of the initial collapse

Exclusions

- Presumed non-cardiac cause of cardiac arrest such as trauma, hanging, drowning, intracranial bleeding
- Any pre-existing significant neurological disability
- Significant non-cardiac co-morbidities that cause limitations in activities of daily living such as COPD, cirrhosis of the liver, renal failure on dialysis, terminal illness due to malignancy

Treatment Protocol:

Patients who meet the above inclusion criteria and who do not have exclusion criteria will be eligible for the study.

Step 1:

The patient remains in cardiac arrest at 30 minutes post collapse will be evaluated for inclusion/exclusion criteria

Step 2:

The patient will be placed on the Autopulse machine and chest compressions will be mechanically commenced. Mechanical ventilation and intravenous adrenaline (1mg every 5 minutes) will be continued.

Step 3:

The patient will be loaded into the ambulance and transported Code 1 to the Alfred Hospital. The Alfred Emergency Department will be notified of the expected time of arrival of the patient. A rapid infusion of 2L ice-cold saline will be commenced en-route to hospital (if not already administered during CPR).

Step 4:

The ED will page the ICU team.

Two Intensivists trained in cannulation will attend the ED and prepare to cannulate the patient.

The equipment to be brought from ICU to the ED will be

- ECMO 15F and 17F cannulae (x2 each)
- A primed ECMO circuit

Step 5:

The ED will receive the patient and transfer to the hospital stretcher with Autopulse compressions continuing. A further 2L of ice cold saline will be infused rapidly for a target temperature of 33°C.

Step 6:

The Intensivists will

- Cannulate the right femoral artery and vein (using ultrasound if needed)
- Administer 5000U heparin IV
- Connect to the ECMO circuit
- Commence blood flows at 3L/min with oxygen gas flow 3L/min

Other physiological targets will include maintenance of cerebral normoxia (pO2 90mmHg, pCO2 40mmHg) and perfusion pressure (MAP=90mmHg) with inotropic/vasoconstrictor agents. An adrenaline infusion as the vasoconstrictor of first choice will be commenced if needed.

Step 7:

Once placed on VA ECMO and cooled to 33°C, the patient will be transported to the cardiac catheterization laboratory for a coronary angiogram and stenting of any blocked coronary artery.

Step 8:

The patient will be transported from the cardiac catheterization laboratory to the ICU. The temperature will be maintained at 33°C for 24 hours. If an arterial pulse in the leg with the arterial cannula does not return within 4 hours and the distal leg is ischaemic, an arterial backflow cannula will be inserted. If the patient is taken off ECMO, continued therapeutic hypothermia will be undertaken using surface cooling as per current ICU guidelines. Sedation will be commenced if the patient starts shivering or has some early recovery of neurological function and appears to be awakening.

Subsequent management:

At 24 hours, the patient will be rewarmed slowly (0.25°C per hour). Sedation will be ceased at 36 hours. If there is adequate cardiac function, the ECMO will be weaned and discontinued, with vascular repair of the femoral artery if needed. In the event of neurological recovery but inadequate cardiac recovery, VA ECMO will be continued and consideration given to longer term cardiac support (i.e. a left ventricular assist device).

Patients who remain unconscious at 96 hours will be assessed by an Intensive Care Physician and a Neurologist. Based on the clinical indicators that are strongly associated with a poor prognosis; deep coma, presence of myoclonic jerks, fixed pupils and/or absent somatosensory responses, consideration will be given to the withdrawal of active treatment and palliative care instituted. These neurological assessments are part of current routine ICU practice.

Ethical considerations

Since all patients in the study are unconscious and the study must commence immediately during patient resuscitation, it is not possible to obtain informed consent prior to enrolment from the patient or next-of-kin.

Under Section 42A of the Medical Treatment Act, a registered practitioner may carry out, or supervise the carrying out of, a medical research procedure on a patient without consent or authorisation (under section 42T) if the practitioner believes on reasonable grounds that the treatment is necessary, as a matter of urgency—(a) to save the patient's life; or (b) to prevent serious damage to the patient's health.

This research meets the intent of this section of the Medical Treatment Act. A medical practitioner is supervising the carrying out of these possibly life saving procedures. The treatment is a matter of urgency and has the intention of saving life and preventing serious neurological injury

There is a possibility that some patients would make some neurological recovery but be left with severe disability. However, our previous study of paramedic cooling in patients with out-of-hospital cardiac arrest showed that only 2 patients of 396 enrolled were discharged with significant disability to a nursing home. The current approach in critical care medicine is that

palliative care is considered in the event that the patient remains comatose after 96 hours. This approach has meant that very few patients are left in a state of severe disability.

The restriction of age to <60 years is justified for several reasons. Firstly, younger patients better tolerate anoxic neurological injury compared with older patients. Secondly, this “proof of concept” study should not include patients with only a remote chance of return to complete recovery.

Finally, it is possible that there will be neurological recovery but inadequate cardiac recovery. The current approach in such patients at The Alfred is consideration of left ventricular assist device as a bridge to cardiac transplantation. Such a treatment is not generally available to patients aged >65 years due to the poorer clinical outcomes in that age group.

Sample Size Estimation

As this is a feasibility trial, a sample size of 24 patients will determine whether the treatment is a reasonable therapeutic option. Based on Ambulance Victoria results there was a 10% survival of patients with VF/VT who were transported with continuing CPR to hospital. Therefore utilising an estimated survival with the novel treatment plan of 30% the calculated sample size for one-sample comparison is as follows:

- Test Ho: p = 0.1000, where p is the proportion in the population

Assumptions:

- alpha = 0.0500 (two-sided)
- power = 0.8000
- alternative p = 0.3000

Estimated required sample size:

- n = 24

An interim analysis into safety and feasibility to study will be performed after 10 patients.

CHEER Study Progress and Results

The study received Ethics Approval in February 2011. Significant time was then spent in paramedic training and familiarisation with the study protocol and 'autopulse' device. Concurrent development of an ECPR protocol for the hospital was also established ensuring a primed ECMO circuit was ready for immediate use and a roster of suitable intensive care physicians, capable of emergent ECMO, cannulation was established.

An ECPR cart was created, with the necessary equipment for urgent ECPR including (See Figure 1):

- Primed ECMO Circuit and pump
- Arterial and venous Cannulae
- Autopulse CPR device
- Ice Cold intravenous saline

Figure 1: Alfred Hospital ECPR Cart

An ECPR clinical roster and response team was also created. This includes

- 2 ECMO Cannulators
- 1 Doctor/Technologist to manage vascular and cardiac ultrasound.
- Doctor to manage hypothermia therapy
- ECMO Nurse for circuit commencement
- Doctor or Nurse managing Autopulse
- ED team for conventional ACLS care

Baseline characteristics

As of 31st December 2012, 5 patients with refractory OHCA meeting inclusion criteria had been enrolled in the study protocol. The patients had a median age of 56 years (IQR 45-59 years). Four of the patients (80%) were male. In all 5 patients OHCA represented their first cardiac symptom, with no patients having a significant history of cardiovascular disease. All patients did however, have at least one major cardiovascular risk factor (Table 1).

Pre-Hospital Care

Given requirements of the inclusion criteria, as expected all patients had an initial rhythm of VF with witnessed collapse and very short periods to initiation of first CPR (range 0-2minues). Patient 4 had an EMS witnessed VF arrest during transport to hospital in the setting of an AMI and therefore, had a very short collapse to arrival to ED time of only 7 minutes. The other 4 patients had an average pre-hospital time of 68 +/- 21 minutes (Table 1).

Survival and Neurological Recovery

Return of spontaneous circulation was achieved in 4/5 (80%) of patients with survival to hospital discharge in 3/5 (60%) patients. All survivors made a complete neurological recovery with cerebral performance scores of 1 at hospital discharge. Both patients, who did not survive, died in the first 36 hours. One patient died due to persistent hemodynamic collapse in the setting of an initially unrecognised Type A Aortic Dissection as the cause of his OHCA. The other non-survivor was successfully established on ECMO achieving ROSC but died at 34 hours post admission due to multi-organ failure and severe coagulopathy.

Issues with ECPR

Two of the study patients achieved ROSC in the setting of prolonged automated CPR, without the need for ECMO support in the emergency department. Both of these patients made full neurological recoveries. Of the three patients established on ECPR, the first patient had both femoral arteries initially cannulated, which was then corrected. The use of real time vascular ultrasound during cannulation in the two subsequent patients ensured that both were promptly established on ECMO support without incident, after arrival to hospital. The time from collapse until establishment of ECMO support on these 3 patients were 100 minutes, 117 minutes and 50 minutes respectively. Only the patient receiving establishment of ECMO prior to 60 minutes survived to hospital discharge.

Aetiology of cardiac arrest

All 5 patients underwent early coronary angiography, following stabilisation in the emergency department. Significant coronary stenoses were present in 3/5 patients (60%). In the two remaining cases, coronary angiogram highlighted an unrecognised type A dissection in one patient, with no significant coronary disease in the other patient. Cardiac MRI performed on day 4 indicated arrhythmogenic right ventricular cardiomyopathy (ARVC).

Progress in Hospital

Survivors had a relatively short ICU stay with an average time of 105 +/- 17 hours (Table 2). There were no major issues with neurological prognostication and they were all awake by day 4. Hospital length of stay ranged between 9-17 days. Patient 3 had insertion of an automated internal cardiac defibrillator prior to discharge given her diagnosis of ARVC whilst the other two survivors underwent coronary revascularisation with good cardiac recovery and did therefore not receive defibrillators.

Patient 2 died of hemodynamic collapse in the setting of a type A aortic dissection and never achieved ROSC in hospital. Patient 3, however had a prolonged resuscitative effort in the field, and was ultimately established on ECMO support at 117 minutes post collapse (table 1). He remained in VF post ECMO deployment, with PCI to his LAD being performed in constant VF. Interestingly post establishing flow to his LAD, significant coarsening of his VF waveform occurred, with one further 150J DCR then required to achieve ROSC (table 2). He deteriorated rapidly in ICU post procedure with progressive multi-organ failure and haemorrhage.

Table 1: Baseline and Arrest Characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	56 years	60 years	62 years	39 years	38 years
Gender	Male	Male	Male	Male	Female
Location of OHCA	Public Place	Work	Home	Ambulance	Public place
Witnessed	Yes – but no Bystander CPR	Yes Bystander CPR	Yes Bystander CPR	Yes EMS witnessed	Yes Bystander CPR
Cardiac risk factors	Hypertension, Dyslipidaemia	Hypertension, Dyslipidaemia	Hypertension	Smoker, Dyslipidaemia	Family history
Collapse to CPR	2 mins	1 min	1 mins	0 mins	1 mins
Collapse to arrival hospital (minutes)	45 mins	73 mins	87 mins	7mins	62 mins
ED to ECMO time	NA	27 mins	30 mins	35mins	NA
Collapse to initiation ECMO	NA	100 mins	117 mins	42mins	NA
Collapse to ROSC	80 mins	Nil	135 mins	50 mins	66 mins

OHCA - out of hospital cardiac arrest, CPR – cardiopulmonary resuscitation, ED - emergency department, ECMO – extracorporeal membrane oxygenation, ROSC – return of spontaneous circulation, mins – minutes. NA - Not applicable, ROSC obtained without ECMO support.

Table 2: In hospital Care and Outcomes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Coronary angiography	Triple Vessel RCA culprit	Type A Aortic Dissection	Double vessel LAD Culprit	Single vessel LAD culprit	Normal
TIMI flow pre	TIMI 0	NA	TIMI 0	TIMI 2	TIMI 3
TIMI flow post	TIMI 3	NA	TIMI 3	TIMI 3	TIMI 3
PCI	PCI BMS	NA	PCI BMS	PCI BMS	No
Duration of ECMO	NA	NA	30 hours	48 hours	NA
RRT	No	No	Yes	No	No
Awake	Day 4	NA	NA	Day 3	Day 2
ICU length stay	122 hours	2 hours	30 hours	106 hrs	88hrs
Hospital length stay	15 Days	1 day	2 days	9 days	17 days
ROSC	Yes	No	Yes	Yes Post ECMO	Yes
Survival to hosp discharge	Yes	No	No	Yes	Yes
Neurological Outcome	CPC 1	-	-	CPC 1	CPC 1

TIMI – Thrombolysis in myocardial infarction score, RCA – right coronary artery, left anterior descending artery, RRT – renal replacement therapy, ROSC – return of spontaneous circulation, ECMO - extracorporeal membrane oxygenation, CPC – cerebral performance category. NA – not applicable

Discussion CHEER study

The results of these initial five cases offer a preliminary analysis of the feasibility of the CHEER study. Given current local OHCA protocols, in all probability without this study protocol these 5 patients would not have been transported to hospital and ultimately been declared deceased in the field. The fact that 4 (80%) patients obtained ROSC and 3 (60%) patients survived to hospital discharge with full neurological recovery is extremely encouraging.

Of concern however is the slow rate of recruitment into the trial, questioning its applicability to a wider population. The study has been recruiting for over 18 months, albeit with a significant lead in training time, and only recruited 5 patients. A number of study design features make recruitment challenging; firstly the study includes only one hospital, in which patients are recruited in daytime working hours with rigid inclusion criteria. Given recent favourable reports of ECPR[153, 158] and that that up to 15% of all Victorian VF arrests occur in patients aged 60-65 years[136], the CHEER trial has recently amended its maximum age cut off to 65 years. This change, together with further education and EMS encouragement, in light of recent successful patient outcomes should lead to increased enrolments moving forward.

The two patients obtaining ROSC with merely ongoing mechanical CPR and standard ACLS, without the requirement for ECMO, highlight the possibilities of good outcomes in patients with prolonged VF arrest. These patients raise the scenario that termination of resuscitative efforts in some patients with ventricular fibrillation may be occurring prematurely. At present we are undertaking an in-depth analysis of pre-hospital management of patients with OHCA and VF in Victoria in conjunction with the VACAR team, to explore the issue of patients with persistent VF and at what time termination of resuscitative efforts are being made. These cases also raise the question of whether more patients should be transported to hospital with ongoing CPR, as occurs in many other international EMS systems. Further research into persistent VF and an examination of the efficacy, clinical outcomes and resource implications of transport to hospital with ongoing CPR including more widespread use of automated CPR devices is clearly required.

Growing international experience and our own initial cases indicate that ECPR has a potential role to play in the management of refractory cardiac arrest. Patient selection is a major issue that remains challenging and requires further study and experience. In most cases, however, early prognostication at the time of cardiac arrest is inappropriate. Consideration should

therefore be given to aggressively treating all patients with basic positive clinical features such as younger age, witnessed cardiac arrest, and VF as initial rhythm without significant known co-morbidities, as used in the CHEER study and the SAVE-J Japanese experience[152].

A major factor in determining outcomes in patients with prolonged cardiac arrest utilising ECPR is establishing prompt ECMO support. Recent reports indicate that survival significantly deteriorates if ECMO is not established within 60 minutes after patient collapse[155, 163]. In our 3 cases of ECPR only one patient with an EMS witnessed OHCA whilst en-route to hospital achieved ECMO support in less than 60 minutes of low flow time. This target will clearly be very challenging in the CHEER study as paramedics are not considering transport until 30 minutes after patient collapse. Significant efforts are being made in educating local MICA paramedics to minimise delays in recruited patients. Patient 3 who despite 130 minutes of VF achieved ROSC post PCI to his LAD, but then succumbed to multi organ failure and coagulopathy associated with severe post cardiac arrest syndrome, is an example of what may be achieved if timing issues can be improved. The planned European study by Belohlavek and colleagues of a "Hyperinvasive approach to out-of hospital cardiac arrest using mechanical chest compression device, pre hospital intraarrest cooling, extracorporeal life support and early invasive assessment compared to standard of care[168]", will be very informative regarding developing systems of care that involve more rapid transfer or patients with OHCA to dedicated ECPR capable hospitals.

Conclusions CHEER study

This study represents a first step in developing a protocol to manage select patients with refractory out-of-hospital cardiac arrest. Whilst further research into the efficacy and resource implications of ECPR is needed, it is clear that establishing an ECPR program with cooperation from local ambulance crews is feasible. These initial results highlight the need for caution in terminating resuscitative efforts in patients with persistent VF in the field. When developing a system of care for patients with OHCA, consideration should be made to ensure that all 'cardiac arrest centres' have ECMO capabilities.

CHAPTER 8: Conclusions and Recommendations

Out-of-hospital cardiac arrest is a major cause of death and disability affecting over 35,000 Australians every year. The chain of survival, in which all aspects of cardiac arrest care are optimised, is critical in improving patient outcomes. Traditionally the primary focus has been on pre-hospital links in the chain, including early recognition, increasing rates of community cardiopulmonary resuscitation, prompt defibrillation and advanced life support. Recently the importance of post resuscitative care has been emphasised in mitigating the physiological consequences of prolonged whole body ischemia resulting in the post cardiac arrest syndrome.

My thesis encompasses a collection of papers exploring aspects of post resuscitative care, founded in the hope of contributing to the rapidly expanding body of literature influencing the care of patients with OHCA.

The main conclusions are:

- The post cardiac arrest syndrome is a complex physiological process causing neurologic, cardiac and systemic dysfunction and is responsible for significant morbidity and mortality. A systematic approach to all elements of the pathophysiologic process is required in the care of these patients. Treatment strategies focussing on both pre-hospital and post-resuscitative elements are vital to improving patient outcomes. Emphasis should be placed on implementation of therapeutic hypothermia, early coronary angiography, and temporary circulatory support where appropriate, combined with goal directed therapies together with comprehensive neurological assessment and care.

- Therapeutic hypothermia is a crucial aspect of post resuscitative care with proven efficacy in comatose survivors of out-of hospital VF arrest. In the past there have been concerns regarding its use in patients with cardiac instability and hemodynamic compromise. Emerging evidence suggests that TH actually aids post cardiac arrest myocardial dysfunction by reducing myocardial infarct size, improving cardiac output in the setting of cardiogenic shock and reducing cardiac metabolic demand.

- Cardiologists need to take a greater role in the post-resuscitative management of patients following OHCA. With advances such as pre-hospital induction of therapeutic hypothermia and an increased awareness of the dangers of early neurological prognostication, there is no longer a role for 'a wait and see' attitude in managing these complex patients. Despite the lack of large randomised trials, a coordinated approach to post resuscitative care has repeatedly been shown to improve clinical outcomes. The cardiologist is an integral part of this emerging post resuscitative team.

- Coronary artery disease is the commonest cause of out-of hospital VF arrest in adult patients. This thesis confirms international recommendations that routine coronary angiography should be performed in survivors of OHCA with STEMI. Whilst the benefits of early coronary angiography in OHCA patients without STEMI is less certain, our research also confirms large international reports highlighting the poor predictive value of an ECG in the post OHCA setting. Particularly when provided as part of a bundle of care with TH, routine early coronary angiogram, regardless of initial ECG, is associated with improved patient outcomes.

- The procedural success rate of patients with OHCA undergoing percutaneous coronary intervention are similar to lower risk patients with acute coronary syndromes without OHCA. Similarly hospital survivors of OHCA have comparable rates of major adverse cardiac events at 12 months as those patients with ACS without OHCA.

- Post cardiac arrest myocardial dysfunction is common and underappreciated in patients following OHCA. Based on our Victorian data, in patients with OHCA and AMI, cardiogenic shock occurs in 40% of cases. This combination of OHCA and cardiogenic shock portends a significantly worse prognosis than patients without cardiogenic shock. Further research regarding the role of TH, PCI and cardiac support devices are urgently needed in this particularly high risk cohort of patients.

- There are clear regional and institutional differences in outcomes following OHCA. In data exploring the Victorian Ambulance Cardiac arrest registry we have shown that hospital characteristics including cardiac intervention capabilities and admitting a patient in working hours are independently associated with survival and neurological outcome. Whilst auditing pre-hospital cardiac arrest care in the form of large registries is performed well in parts of

Australia, there is a distinct lack of systematic reporting of quality and compliance of post-resuscitative measures. This information will be crucially important in improving quality of care to patients moving forward.

- In line with international guidelines and based on local data we would recommend urgent consideration of developing a hospital system of care for patients with OHCA. Existing frameworks include our state wide trauma system of care and AMI management pathways that could serve as a model for a regional approach to patients with OHCA. This would ensure that patients are transported to facilities capable of dealing with the complexities of the patient with post cardiac arrest syndrome.

- Our pre-clinical model of prolonged cardiac arrest in sheep with associated myocardial infarction, confirms other mechanistic studies that ECPR improves coronary perfusion pressure and VF waveform parameters during resuscitation, whilst significantly improving rates of return of spontaneous circulation.

- Significant proportions of patients with out-of-hospital VF arrest do not achieve ROSC and in Victoria are declared deceased in the field without transport to hospital. Our preliminary results from the Refractory Out-Of-Hospital Cardiac Arrest Treated With Mechanical CPR, Hypothermia, ECMO and Early Reperfusion (CHEER) Study, would suggest that continued CPR to hospital may lead to successful outcome in some patients and that the ECPR may have a potential role to play in select patients with refractory OHCA.

There have been significant advances made in the area of post resuscitative care over the last decade, with an equal number of unanswered questions and issues to explore. The undertaking of my doctorate studies has provided me with a solid platform for a career incorporating clinical research, whilst igniting a passion for resuscitative medicine. At the time of thesis preparation my post doctorate endeavors have already begun taking shape and hope to address some of the unanswered questions highlighted in these chapters.

It is clear that whilst we have a growing body of observational series in many aspects of post-arrest care there is still a relative paucity of randomized clinical data in the post arrest setting. Moving beyond clinical trials of therapeutic hypothermia to exploring issues of bundles of care, oxygenation, PCI, optimum hemodynamic support and ECPR will be a crucial aspect of

convincing the medical community of the relative importance of optimized post-resuscitative care.

That said we have significant observational evidence to promote many aspects of post resuscitative care, which are not major additions to health care spending or resources, but are potential system improvements that may have dramatic impacts on clinical outcomes. All treating centres should strive for rigorous adherence to the established post resuscitative measures of TH, avoidance of early prognostication, recognition and management of post arrest myocardial dysfunction. Far too many patients, however, miss out on optimized post-resuscitative measures, and it is more than likely that patient outcomes are suffering as a result of these inequities in care delivery.

To that end addressing quality of current post resuscitative care is a major focus of my early post doctorate work, including a planned audit of every out-of-hospital-cardiac arrest case in 2012 in Victoria. Planned future comparisons of OHCA care delivery between Australia and North American will also be performed as part of post doctorate work at the University Washington, Seattle USA.

The other major focus of my early post doctorate work will be on the role of oxygenation in the critically ill cardiac patient. As has been alluded earlier in the thesis, there are growing concerns regarding hyperoxia in patients with OHCA. Hyperoxia mediated reperfusion injury has also been reported in AMI patients without cardiac arrest[169]. As such, I have been a key contributor to the currently enrolling Victorian clinical Air Versus Oxygen in, Myocardial infarction (AVOID) trial[170]. This study as well as planned pilot trials into oxygen delivery in the early post resuscitative period in patients with OHCA will be most informative regarding the use of supplemental oxygen in patients with myocardial infarction and cardiac arrest.

Much is changing in the field of resuscitative medicine. In the words of 12th century theologian John of Salisbury, "We are like dwarfs sitting on the shoulders of giants. We see more, and things that are more distant, than they did, not because our sight is superior or because we are taller than they, but because they raise us up, and by their great stature add to ours[171]." However the fundamentals of patient care are timeless and need to be perpetually reinforced through good clinical medicine and research.

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Addendum

Page 42 Line 9:

'radio-opaque' should be replaced with 'radio-lucent'

Page 43 4th paragraph replace with*:*

Firstly, core cooling techniques appear to be better tolerated than surface cooling techniques, since the skin can be kept relatively warm during induction of hypothermia, which may reduce thermoregulatory vasoconstriction[1, 2].

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