ANGLIA RUSKIN UNIVERSITY

FACULTY OF MEDICAL SCIENCE

THERAPEUTIC HYPOTHERMIA IN CARDIOVASCULAR DISEASE

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A thesis in partial fulfilment of the requirements of Anglia Ruskin University for the degree of MD (Res)

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ABSTRACT

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Abstract

Introduction: Historical trials demonstrated clinical benefit of therapeutic hypothermia (TH) in unconscious cardiac arrest survivors. However, recent research raised important unanswered questions about this concept. Cardiac arrest associated mortality and morbidity including psychological trauma for survivors and caregivers remain alarmingly high, warranting further research in this field. TH has also been shown to offer additional protection against reperfusion injury in experimental models of myocardial ischaemia. However, co-administration of TH in conscious patients undergoing treatment for acute myocardial infarction (AMI) is potentially challenging.

Methodology: (i) Rhinochill®, a novel intranasal cooling device is compared to Blanketrol for TH induction in unconscious cardiac arrest survivors, investigating efficacy and clinical outcome at hospital discharge. (ii) The emotional burden of cardiac arrest in patients and their caregivers is documented and the impact of simple interventions on quality of life is assessed. (iii) The feasibility of co-administration of TH in conscious patients undergoing emergency treatment of AMI is investigated.

Results: (i) Rhinochill® is found to be more efficient in TH induction when measured from the tympanic membrane. However, Rhinochill® did not offer any superior clinical benefit. (ii) Simple psychological interventions are shown to improve quality of life in cardiac arrest survivors. (iii) Co-administration of endovascular cooling is shown to be feasible in conscious patients undergoing AMI treatment with minimum disruption to patient care.

Discussion: Delays in TH administration may offset any potential benefit that it can offer in neuroprotection and therefore, earlier targeted brain cooling with more efficient portable devices is worth investigating. Improving quality of life of cardiac arrest survivors has been shown to be cost effective and therefore, investing in resources to better identify and help those at risk is justified. Delivery of TH in conscious heart attack patients is feasible and safe but more efficient endovascular cooling devices are required and these will need to be assessed in larger trials to assess the effect on clinical outcomes.

Key Words: Therapeutic hypothermia, Cardiac arrest, Neuroprotection, Quality of life, Acute myocardial infarction, Reperfusion injury

Publications

Islam S, Hampton-Till J, Watson N, Mannakkara NN, Hamarneh A, Webber T, Magee N, Abbey L, Jagathesan R, Kabir A, Sayer J, Robinson N, Aggarwal R, Clesham G, Kelly P, Gamma R, Tang K, **Davies** JR, **Keeble** TR. Early targeted brain COOLing in the cardiac CATHeterisation laboratory following cardiac arrest (COOLCATH). Resuscitation. 2015 Dec;97:61-7. doi: 10.1016/j.resuscitation.2015.09.386.

Islam S, Hampton-Till J, MohdNazri S, Watson N, Gudde E, Gudde T, Kelly PA, Tang KH, **Davies** JR, **Keeble** TR. Setting Up an Efficient Therapeutic Hypothermia Team in Conscious ST Elevation Myocardial Infarction Patients: A UK Heart Attack Center Experience. Ther Hypothermia Temp Manag. 2015 Dec;5(4):217-22. doi: 10.1089/ther.2015.0012.

Poster Presentations

Islam S, Keeble TR, Davies JR, Magee N, Balasubramanian R, Watson N. Care after Resuscitation. CARE AFTER RESUSCITATION: An Innovative Early Psychological Support Service Proven To Improve The Quality Of Life, Cognitive Function, And Ability To Return To Work; An Early Intervention For Cardiac Arrest Survivors And Their Caregivers. Innovations in treating acute coronary syndromes, BCS Annual Conference 2015, Heart and Genes June 8-10, Manchester UK, 2015

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NHS Innovation Challenge Prize, NHS England, December 2014

HSJ Awards in the category of Compassionate Patient Care: Care after Resuscitation , November 2016

Commonly used Abbreviations

AED: Automated External Defibrillators

AHA: American Heart Association

AAN: American Academy of Neurology

ATP: Adenosine Triphosphate

BBB: Blood Brain Barrier

CPC: Cerebral Performance Category

CPR: Cardiopulmonary Resuscitation

CTC: Cardiothoracic Centre

CVD: Cardiovascular Disease

EMS: Emergency Medical Services

ESC: European Society of Cardiology

HAC: Heart Attack Centre

ICF: International Classification of Function

ICU: Intensive Care Unit

IHCA: In-hospital Cardiac Arrest

LAS: London Ambulance Service

MACE: Major Adverse Cardiac Events

mPTP: mitochondrial Permeability Transition Pore

NICE: National Institute of Clinical Excellence

NMDA: N-Methyl-D-Aspartate

OHCA: Out of Hospital Cardiac Arrest

PPCI: Primary Percutaneous Coronary Intervention

PTSD: Post-traumatic Stress Disorder

QoL: Quality of Life

RCT: Randomised Controlled Trial

ROS: Reactive Oxygen Species

ROSC: Return of Spontaneous Circulation

SPECT: Single Photon Emission Tomography

STEMI: ST Elevation Myocardial Infarction

TH: Therapeutic Hypothermia

TTM: Targeted Temperature management

WHO: World Health Organisation

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Overview

Hypothermia has been used as a therapeutic agent for many centuries in different forms of illness with variable success rates. Better understanding of the different stages of neuronal cell damage following cardiac arrest generated potential therapeutic targets aimed at minimising hypoxic brain injury. TH is one such intervention which demonstrated neuro-protective properties by influencing several of these downstream processes in a beneficial manner in vitro and in vivo. Landmark trials in early 2000s showed that mild to moderate TH was associated favourable clinical outcomes in human survivors of cardiac arrest. More recently, this theory was challenged suggesting that there are no significant differences in clinical outcomes in cardiac arrest survivors with temperature managed at 33°C over those maintained at 36°C. Unlike previous trials, fever was prevented in both groups by active temperature management. Post-hoc analysis of this latest trial revealed that a considerable amount of time elapsed before TH was applied and target temperature was achieved. The time lost in achieving target temperature could potentially offset any neuro-protective properties of TH.

Cardiac arrest is a leading cause of morbidity and mortality, irrespective of whether methods are applied to reduce core body temperature or prevent pyrexia and therefore, research to investigate more efficient methods of neuroprotection is warranted in this setting. Rhinochill® is a portable intranasal cooling device which is capable of delivering uninterrupted targeted brain cooling in intubated patients. In this thesis, the efficiency of Rhinochill® is investigated over conventional Blanketrol for TH induction in cardiac arrest survivors admitted to a tertiary heart attack centre.

Follow up of these patients highlighted that cardiac arrest survivors and their caregivers suffer from substantial psychological trauma and cognitive impairment leading to poor quality of life (QoL) perceptions and reduced participation in society. Recent data suggested that simple supportive measures provided by healthcare professionals can help to improve QoL, which was also associated with socio-economic benefits. A similar model of supportive network was set up in this single centre and its feasibility and subsequent impact was investigated.

And finally, there is emerging evidence to suggest that TH offers additional myocardial protection against reperfusion injury in the setting of AMI on restoration of circulation by minimising infarct size. In keeping with this theme, the feasibility of simultaneous administration of Thermoguard (Zoll, USA), a modern endovascular cooling device in patients undergoing emergency primary percutaneous intervention for AMI was tested.

1. Chapter 1: Introduction

1.1. Cardiac Arrest and Therapeutic Hypothermia (TH)

1.1.1. Definition of cardiac arrest

It is defined as 'the abrupt cessation of cardiac pump function which may be reversible, but will lead to death in the absence of prompt intervention' (Myerburg RJ, Castellanos A 2001). Many important organs in the body including the brain, liver, kidneys and the heart itself are heavily dependent on a healthy functioning heart for blood and nutritional supply including oxygen. Therefore, any period of pump failure/cessation results in hypoxic damage to these organs, that can result in debilitating morbidity and mortality.

1.1.2. Incidence of cardiac arrest

The annual worldwide incidence of cardiac arrest in the general population is estimated to be around 1-2/1000 persons but this has regional and countrywide variations (Myerburg RJ, Castellanos A 2001). In 2013, the emergency medical services (EMS) attempted to resuscitate approximately 28,000 out-of-hospital cardiac arrest (OHCA) patients in England and reported an overall survival to hospital discharge rate of 8.6% (NHS England 2013), which is similar to the United States of America (USA) (SCAFoundation 2014), but considerably lower than some of our European counterparts, where survival to hospital discharge rate approached 25% (Lindner, Soreide et al. 2011, Grasner, Herlitz et al. 2011). About 80% of OHCA were at home and 20% in public areas at the time of the incident. Only 20% of OHCA patients were found to be in shockable rhythm (ventricular fibrillation or ventricular tachycardia) (Nicholas P, Virdi G, Fothergill R September 2013). The survival rates are known to be better if patients are found to be in shockable rhythm as opposed to non-shockable rhythm (asystole or pulseless electrical activity) (Lindner, Soreide et al. 2011, Grunau, Reynolds et al. 2016). In contrast, the reported incidence of in-hospital cardiac arrest (IHCA) in the UK is 1.6 per 1000 hospital admissions and overall unadjusted survival rate to hospital discharge has been reported at 18.4% (Nolan, Soar et al. 2014). The better IHCA survival rate to hospital discharge can be partly explained by easier and quicker access to the chain of survival (Nolan, Soar et al. 2006).

The Essex Cardiothoracic Centre (CTC) is a busy tertiary unit that serves a population of 1.7million in the eastern county. Every year the centre carries out approximately 750 primary percutaneous interventions (PPCIs) for acute myocardial infarctions (AMIs).

Cardiac arrest account for about 100 emergency cardiac catheter laboratory admissions.

1.1.3. Causes of cardiac arrest

Cardiovascular disease (CVD) remains the leading cause of death worldwide (WHO factsheet 2016 September 2016) and mortality from cardiac arrest is most often related to ischaemic heart disease (Reichenbach, Moss et al. 1977, Davies 1992). Consequently, a large proportion of cardiac arrest patients, who can be successfully resuscitated, are taken to a tertiary heart attack centre with emergency cardiac catheter laboratory facilities to perform PPCI in order to treat the potential culprit coronary artery lesion. Other cardiovascular diseases such as cardiomyopathies, primary arrhythmias and non-cardiac causes such as intoxication, trauma and suffocation make up the remainder of the aetiology of cardiac arrests (Myerburg RJ, Castellanos A 2001). Whilst prompt resuscitation and early identification and correction of the underlying cause remain the clinical priority in a cardiac arrest situation, one can speculate that any delay in restoring circulation can result in significant damage to vital end organs including the heart itself, brain, kidney and liver.

1.1.4. Implication of cardiac arrest – Hypoxic brain injury

One of the major complications of cardiac arrest is irreversible brain injury or hypoxic-ischaemic brain injury caused by deprivation of oxygenated blood supply (Busl, Greer 2010). The length of delay in restoring circulation is directly proportional to the degree of irreversible brain damage sustained (Ames, Wright et al. 1968), which can present clinically as transient retrograde amnesia at the very least, to the worst outcome being coma or even death. Therefore, the focus of effective treatment in cardiac arrest is rapid restoration of circulation followed by attempts at minimising irreversible brain injury. The molecular mechanism of hypoxic brain injury will therefore provide better insight about therapeutic targets in minimising hypoxic insult to the brain tissue.

1.1.5. Molecular mechanism of Hypoxic brain injury

1.1.5.1. Pathophysiology

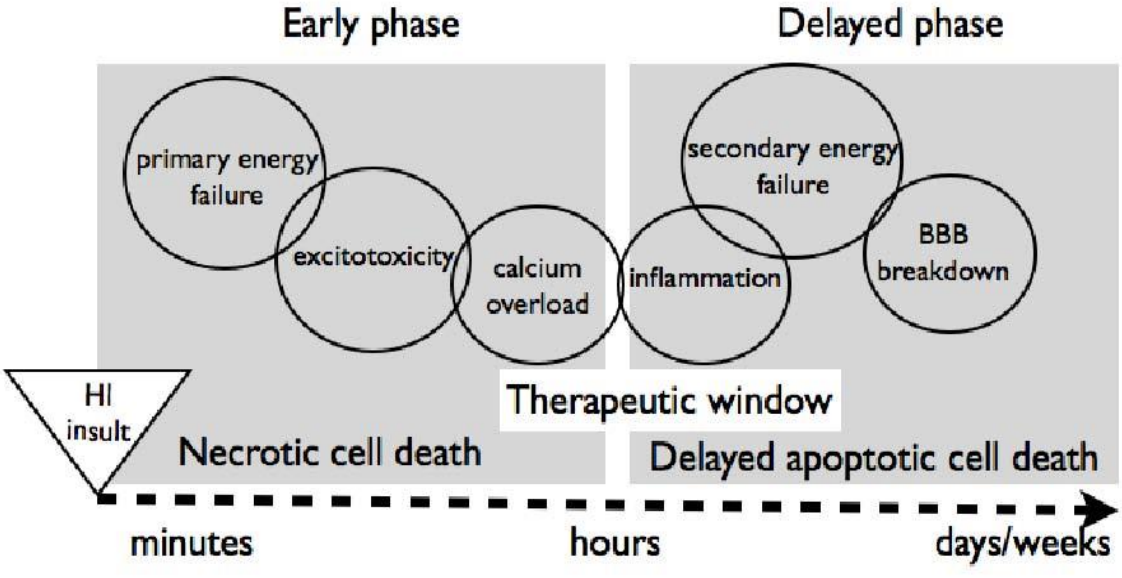
In the early phase, within 10-12 minutes after the onset of ischaemia, the concentration of brain nutrients including glucose, glycogen and adenosine triphosphate (ATP) have been shown to deplete completely resulting in primary energy failure (Wagner, Lanier 1994). This is followed by electrolyte imbalance within the intracellular and extracellular space (discussed in section 1.1.5.2), which create an environment for necrotic cell death. In animal models, neuronal damage and irreversible brain damage have been demonstrated within several minutes of cerebral hypoxia depending on the animal model and conditions (Miller, Myers 1972), although some animal models showed

considerable resilience to the degree of damage and reversibility (Hossmann, Zimmermann 1974). In humans, earlier research demonstrated that 95% of the brain tissue is damaged within 15 minutes of global ischaemia in the context of cardiac arrest (Ames, Wright et al. 1968), although in practice, the extent of tissue damage, the severity of neurological deficit and the potential for recovery are directly linked to the duration of the circulatory arrest.

The clinical manifestation of the brain cell damage can appear within few hours but can also be delayed for days after the initial insult, depending on the duration of the initial ischaemia (Lipton 1999). In the delayed phase (hours to days), the cerebrovascular auto regulation centre of the brain dictates the brain vasculature to go into a state of vasodilation to allow maximum perfusion in this compromised situation and the viscosity of blood decreases with prolonged ischaemia, so blood accumulates in areas of low resistance such as the capillaries and interstitial spaces, resulting in brain oedema (Fischer, Ames 1972).

Figure 1-1 Cascade of biochemical reactions following hypoxic-ischemic brain injury

This schematic diagram demonstrates biphasic pattern of brain injury over time. In the initial early phase, there is a failure in aerobic energy metabolism resulting in necrotic cell death. This is followed by a delayed phase lasting for hours to days during reperfusion and reoxygenation, where inflammatory changes and breakdown of the blood brain barrier can result in apoptotic cell death. Scientists have been trying to develop optimal neuro-protective strategies that can be implemented between these 2 phases, the 'therapeutic window', to rescue injured cells which are still alive (Lara-Celador, Goni-de-Cerio et al. 2013). HI: hypoxic ischaemic, BBB: blood brain barrier

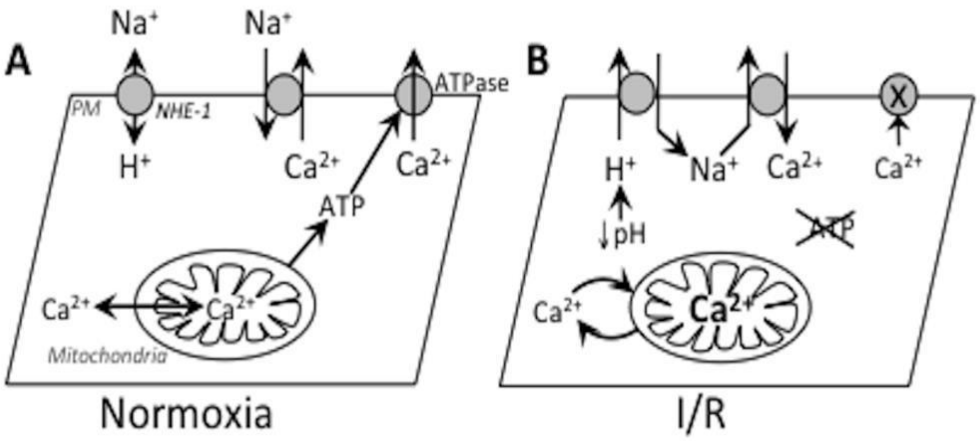


1.1.5.2. Biochemical changes

The biochemical changes during hypoxic ischaemic brain injury are driven by anoxic depolarisation of the cell membrane resulting in changes in intracellular and extracellular electrolyte composition and ATP depletion (Xie, Zacharias et al. 1995). There is an intracellular influx of sodium and calcium ions and efflux of potassium and hydrogen ions into extracellular space. The increased calcium concentration within the intracellular space triggers the initiation of many calcium dependent pathways including the calpain system that is involved in altering signal transduction, remodelling of membrane structures and apoptosis (Goll, Thompson et al. 2003). High energy ATP is used up within a couple of minutes of ischaemia (Katsura, Rodriguez de Turco et al. 1993) and lactic acid is released as an alternate source of energy along with hydrogen ions resulting in acidosis. The neurons can survive academia (pH 6.1-6.5) for 10-12 minutes (Hoxworth, Xu et al. 1999), after which the cell function deteriorates and cell oedema ensues.

Figure 1-2 Schematic diagram of biochemical changes during hypoxic brain injury

Panel A displays the normal pathways controlling cellular [Ca^{2+}]. Panel B displays the events leading up to [Ca^{2+}] overload during ischaemia and reperfusion. A drop in pH triggers Na+/H+ exchanger mediated Na+ influx, resulting in Na+ overload. Reverse-mode Na+/Ca+ exchange across the plasma membrane then results in Ca2+ overload and subsequent mitochondrial [Ca^{2+}] overload. Taken from (Brookes, Yoon et al. 2004)



In addition to the electrolyte imbalances, a number of destructive enzymes, including lipases, proteases and nucleases are activated, which along with glutamate, an excitotoxic neurotransmitter contribute to progressive neuronal damage (Busl, Greer 2010). There is also an increase in free radical formation (Piantadosi, Zhang 1996) and nitric oxide production (Endoh, Maiese et al. 1994) in anoxic conditions, which culminates in further neuronal cell loss.

1.1.5.3. Functional changes

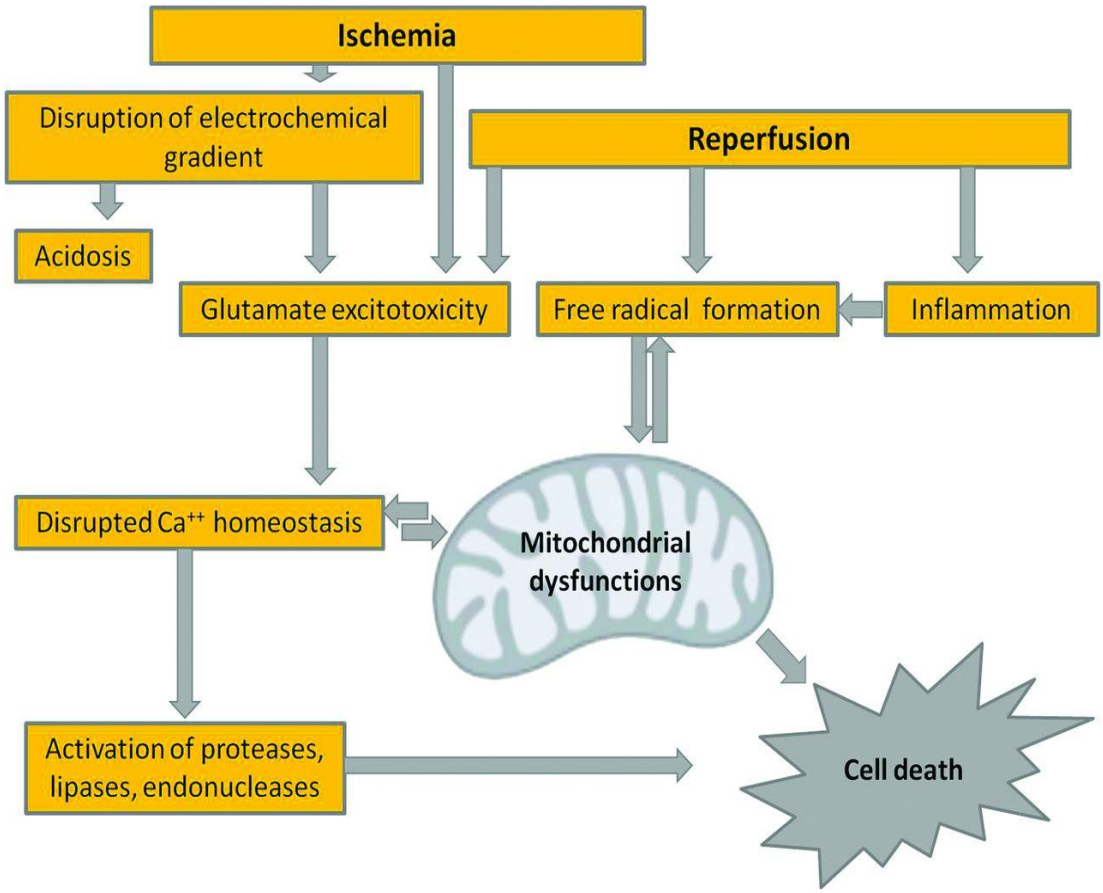
In the early stages of hypoxic-ischaemic insult, the mitochondrial structure and function undergoes destructive changes with calcium accumulation, resulting in further release of free radicals, lack of ATP repletion and inability to maintain cell structure, resulting in cell death (Busl, Greer 2010). Neuronal protein synthesis is also diminished as a consequence of increased cytosolic calcium and N-Methyl-D-Aspartate (NMDA) receptor activation (Raley-Susman, Lipton 1990). Up-regulation of glutamate receptors induces heat shock proteins and immediate early genes such as the BCL-2 group of proteins which can offer some protection against free radicals (Kane, Ord et al. 1995).

1.1.5.4. Reperfusion pathophysiology and reperfusion injury

Return of spontaneous circulation (ROSC) following a cardiac arrest marks the re-establishment of nutrient and oxygen supply to the brain. However, despite a functioning systemic circulation, cerebral circulation may remain impaired for hours (Ames, Wright et al. 1968). After ROSC, a brief period of hyperaemia that lasts for about 15 minutes is followed by a more protracted period of multifocal cerebral hypoperfusion that can last for up to 24 hours (Crumrine, LaManna 1991). This is most prominent in the microvasculature of the brain, which forms about 50% of the brain volume (Ginsberg, Myers 1972). Blood viscosity remains high in cerebral circulation due to inorganic nutrients and water being shifted into brain parenchyma from plasma. The resulting oedema from surrounding brain tissue further attenuates blood flow in the compromised capillary lumen along with greater adhesion of leukocytes to vascular endothelium and red blood cell sludging. Consequently, the mismatch from increased oxygen demand and pathophysiological hypoperfusion results in secondary hypoxia (Hossmann 1997).

Figure 1-3 Schema of ischaemia/reperfusion processes leading neuronal cell death

Taken from (Pundik, Xu et al. 2012)



Prior to ROSC, there is a toxic build-up of free radicals, nitric oxide and glutamate in the blood. The reinstatement of circulation allows these toxic components to reach cerebral circulation along with polymorphonuclear leukocytes, which induce perioxidative changes resulting in reperfusion injury (Bottiger, Schmitz et al. 1998). Additionally, the sheer nature of blood flow can cause further damage by causing microhaemorrhages to the damaged capillaries and inducing cerebral oedema (Busl, Greer 2010, Erecinska, Thoresen et al. 2003). These pathophysiological changes at the molecular level after ROSC constitute reperfusion injury and suggest that the brain sustains prolonged injury even hours after ROSC, some of which may not be reversible. However, it can be postulated that if the natural progression of these detrimental biochemical changes could be slowed down or better still, brought to a halt, any injured cells, which are not irreversibly damaged, will have the best chance of recovery. TH is believed to be an intervention which could play a key role in preventing reperfusion injury. The possible mechanism of this benefit will be discussed below.

1.1.6. The role of TH in minimising Hypoxic brain injury

1.1.6.1. Definitions of normothermia and TH

The thermoregulatory system in the brain hypothalamus allows maintenance of core temperature in the region of 36.5°C to 37.5°C in the human body despite fluctuations in environmental temperatures, often defined as normothermia (NICE, National Institute for Clinical Excellence 2016). In extremely hot environment, the hypothalamus sends downstream signals promoting heat loss through sweating and vasodilation. In very cold temperatures, the body preserves heat by vasoconstriction, increased metabolism and shivering.

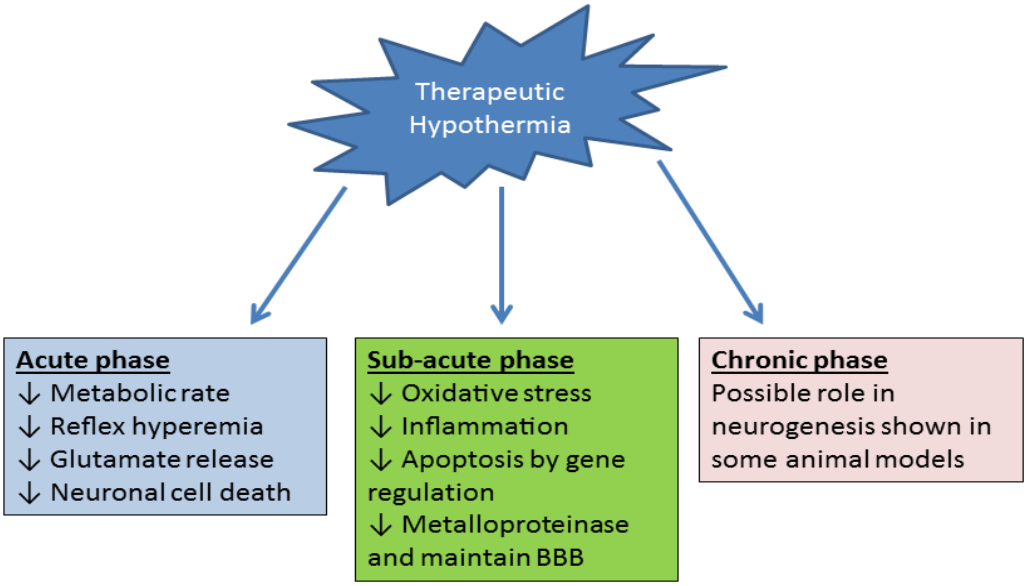
The intentional reduction of core body temperature to less than 36°C is defined as induced hypothermia (Polderman, Herold 2009). And, the iatrogenic application of induced hypothermia in a controlled environment to suppress or prevent deleterious effects such as shivering is defined as TH (Polderman, Herold 2009). TH can be further categorised into mild (34.0-35.9°C), moderate (32.0-33.9°C), moderately deep (30.0-31.9°C) or deep (<30°C) hypothermia. Deep hypothermia in the range of 20-28°C was used to perform open heart operations in 1950s, which allowed longer procedures to be performed in compromised conditions, but it was associated with terminal arrhythmia, coagulopathy and increased mortality (Walpoth, Locher et al. 1990, Walpoth, Walpoth-Aslan et al. 1997). Following a period of dormancy, several groups investigated the feasibility of mild to moderate TH in animal models in the 1980s (Leonov, Sterz et al. 1990, Busto, Dietrich et al. 1987) and human subjects (Bernard, Gray et al. 2002, Hypothermia after Cardiac 2002). They found that TH in the mild to moderate range (as defined above) was feasible and its application was associated with improved clinical outcomes.

1.1.6.2. The role of TH in minimising Hypoxic brain injury

TH has been trialled for many centuries in different forms of illness, including brain injury. Although several theories have been proposed and experimented, the exact mechanism of the therapeutic benefit of hypothermia in minimising brain injury is quite complex as it can influence several aspect of the damage cascade that follow a period of ischaemia. What is evident from experience of looking after patients suffering cardiac arrest is that, brain injury can continue for many days after the initial insult. The understanding from the molecular level of brain injury allowed researchers to investigate the possible beneficial role of TH at various time points from the original insult.

In the acute phase (minutes to hours), TH has been shown to reduce the metabolic rate by 6-7% for every 1°C drop in body temperature (Polderman 2009), which results in reducing brain oxygen demand, preserving ATP and reducing lactic acid formation (Zhao, Zhang et al. 2011). In 1954, a group of scientists demonstrated that there was reduced oxygen consumption and reduced blood flow with temperature reductions in a small experiment with dogs, resulting in beneficial effect on intracranial pressure (Rosomoff, Holaday 1954). One of the most significant benefits of TH in the acute phase seems to be the reduction in reflex hyperaemia following ROSC, as this sudden rush of blood carries toxic materials and can cause further damage to the microcirculation through haemorrhages (Erecinska, Thoresen et al. 2003, Busl, Greer 2010). In addition, TH has been shown to delay the release of glutamate, an excitotoxic amino acid (Nakashima, Todd 1996), downregulate glutamate induced increase in nitric oxide production (Polderman 2009) and inhibits phosphorylation of NMDA receptors (Mueller-Burke, Koehler et al. 2008). These changes translate into prevention of a detrimental acidic environment, which otherwise exacerbates neuronal cell death (Kuffler 2012).

Figure 1-4 Schema showing beneficial effects of TH on minimising hypoxic brain injury



In the subacute phase (hours to days) after the initial insult, the brain parenchyma can sustain further damage through reactive oxygen species (ROS) and nitrogen species, programmed cell death and generalised inflammation, leading to disruption of the BBB

and cerebral oedema (Yenari, Han 2012). TH has been shown to decrease hydrogen peroxide concentrations by 50 fold, which is an important ingredient for damage caused by oxidative stress (Zitta, Meybohm et al. 2010). Hypothermia also suppresses inflammation of the brain by downregulating astrocytes, microglial cells and pro-inflammatory cytokines (Polderman 2009). Additionally, TH has shown some promise in deferring apoptosis and promoting cell repair by attenuating the expression of p53 genes and augmenting bcl-2 expression (Zhang, Xu et al. 2010). More importantly, TH was found to play a vital role in maintaining the integrity of the BBB by deactivating metalloproteinases (Yenari, Han 2012), that degrade extracellular matrix and suppressing membrane permeability by reducing endothelial nitric oxide availability (Polderman 2009).

In the chronic phase (weeks to months), the role of TH is less well understood. There have been isolated reports of some evidence of neurogenesis in animal models with longer duration of hypothermia treatment (4-24hrs) (Silasi, Colbourne 2011). However, this effect has not been reproducible. Overall, the current evidence of the therapeutic benefit of hypothermia in the context of hypoxic brain injury is led by its role in reducing cerebral metabolic rate, oxygen demand, minimising reperfusion injury, attenuating apoptosis and maintaining the integrity of the blood brain barrier (Polderman 2009).

1.1.6.3. TH – historic use in medicine

Historic evidence of hypothermia being used as a therapeutic agent goes back about 5000 years as documented in an ancient Egyptian treatise on medicine and surgery (Wang, Olivero et al. 2006). In the late 1700s, Dr James Currie, a Scottish physician, was credited for using cold water (hydrotherapy) as a treatment in several clinical disorders and documenting changes in human body temperature in health and illness (Wang, Olivero et al. 2006). The Russians also used TH in the form of snow to resuscitate patients back in 1803 (Varon, Acosta 2008).

In the 1940s, Dr Temple Fay, a neurosurgeon from Seattle, USA, pioneered the role of hypothermia as a therapeutic agent for pain control and preventing disease progression in cancer patients (Fay 1959). Although he did not see much benefit of hypothermia in preventing cancer progression, the patients tolerated the treatment without much adverse events and reported significant reductions in pain perceptions (Fay 1959). He then went on to develop the first cooling blanket and successfully implanted a metal capsule intra-cranially to deliver localised cooling to the brain (Wang, Olivero et al. 2006). His research was however prematurely stopped by the Nazis during World War II due to negative associations with Nazi experiments. Following a

period of dormancy, hypothermia was successfully applied in animal models, including dogs, monkeys and groundhogs for neuro-protection during cardiac surgery (Bigelow, Mcbirinie 1953). In human cardiac surgery, moderate hypothermia (28-32°C) was investigated in closed environments by surgeons to provide neuro-protection, but deeper hypothermia (20-28°C) was required to perform longer open heart surgery under compromised conditions (Baffes 1958). However, deeper hypothermia came at a cost of inducing terminal fibrillation and coagulopathy (Tveita, Mortensen et al. 1994), which led to the development of cardiopulmonary bypass machine, to allow more complex open heart surgery without deep hypothermia. At this stage, whilst some argued that hypothermia would become an unnecessary intervention in cardiac surgery, many continued to use it as they believed that the benefit of neuro-protection with controlled hypothermia outweigh any risks associated with this treatment (Baffes 1958).

1.1.6.4. Early evidence of TH in cardiac arrest

In 1958, the first clinical trial of hypothermia in humans following cardiac arrest was published (Williams, Spencer 1958). In this early study, the authors reported on 4 cases of cardiac arrest outside the operating room, suffering severe neurological injury. They were cooled to 30-34°C and maintained for up to 72hrs. All patients survived, 3 patients in this study made complete recovery whilst the 4th patient exhibited moderate residual neurological deficit. The authors concluded that the observation in this study was due to hypothermia induced reduction in brain swelling. In 1959, a small controlled study involving 19 patients resuscitated from cardiac arrest was published (Benson, Williams et al. 1959). In this study, 12 patients were cooled to 30-32°C for variable duration depending on clinical condition, whereas 7 patients did not receive hypothermia (control). In this study, 50% of the patients in the hypothermia group survived compared to 14% in the control group. Although it is difficult to draw conclusions from these small non-randomised studies, Dr Peter Safar felt that there was enough reasoning to incorporate hypothermia in the heart-lung resuscitation algorithm in patients with ROSC after cardiac arrest within 30 minutes (Safar 1964).

After a further period of dormancy in the 1960s and 1970s due to concerns regarding deeper hypothermia induced ventricular fibrillation, infection and bleeding complications, there was resurgence in hypothermia research activity in the 1980s and 1990s, mostly involving animals. Safar et al (Leonov, Sterz et al. 1990) demonstrated that mild hypothermia (34-36°C) administered during cardiac arrest was associated with good neurological recovery in a group of dogs without inducing any adverse events that were observed with deeper or moderate hypothermia (<30°C). Another group of researchers (Dietrich, Busto et al. 1993) demonstrated that post-ischaemic

hypothermia offered greater neuro-protection in rat forebrain in the short term (3 day follow up) compared to normothermia (maintained at 37°C throughout ischaemia and recirculation). This observed advantage was lost at 2 months follow up. More importantly, intra-ischaemic hypothermia demonstrated even greater neuro-protection compared to post-ischaemic hypothermia at longer term (2 month) follow up. Subsequent animal studies focused on reduced ischaemia time, minimising delay in initiating hypothermia and longer duration of hypothermia treatment to show greatest neuro-protection after cardiac arrest (Kuboyama, Safar et al. 1993, Noguchi, Matsumoto et al. 2011).

1.1.6.5. Landmark clinical trials in humans in 2002

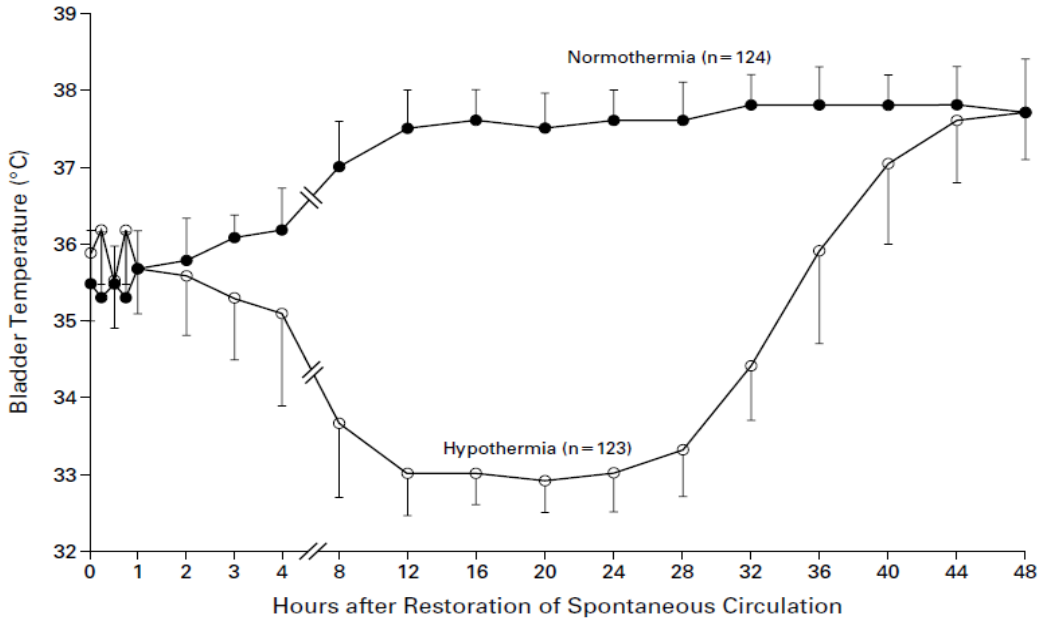
The promising results from animal studies prompted researchers to re-investigate the role of hypothermia in human survivors of cardiac arrest in the late 1990s. Earlier challenges faced by previous researchers warranted assessment of the feasibility of instituting hypothermia in the setting of cardiac arrest and several researchers concluded that this intervention was safe whilst also reporting some clinical advantage of using this therapy over historical controls (Felberg, Krieger et al. 2001, Zeiner, Holzer et al. 2000). On the basis of these safety reports, 2 significant randomised controlled trials (RCTs) were conducted in Europe (Hypothermia after Cardiac 2002) and Australia (Bernard, Gray et al. 2002), the experiences of which are discussed below:

1.1.6.5.1. Hypothermia after cardiac arrest study 2002

Hypothermia after cardiac arrest (HACA) was set up as a prospective multi-centre RCT involving 275 adult patients who suffered out of hospital cardiac arrest. Half the patients (n=137) were randomly assigned to mild TH after ROSC and the other half (n=138) received standard care without temperature management. Patients in the hypothermia group were cooled to 32-34°C within 4hrs using surface cooling blankets and maintained for 24hrs before passive rewarming was allowed.

Figure 1-5 Bladder temperature in normothermia and hypothermia groups

Please note that patients in the normothermia group did not have any temperature management and therefore, mean temperature in this group reached above 37°C during the study period. Adapted from (Hypothermia after Cardiac 2002)



The follow up of these patients at 6 months showed that, 55% of the patients in the hypothermia group made a statistically significant favourable neurological recovery compared to 39% in the standard care group (risk ratio 1.40: 95% confidence interval of 1.08 to 1.81). The mortality rates were also significantly lower in the hypothermia group compared with standard care group (41% v 55% respectively; risk ratio 0.74, 95% confidence interval 0.58-0.95). Whilst infection was more prevalent in the hypothermia group, the numbers did not reach statistical significance and the authors concluded that the benefit of the treatment outweighed any adverse events due to hypothermia institution. One of the limitations of this study was the inability to blind attending physicians from the mode of intervention. However, the authors claimed that the research team was unaware of the treatment modality at the time of 6 month assessment. Also, the restrictions on the selection criteria of the study meant that only 8% of screened patients were enrolled into the study. Therefore, the authors concluded that wider application of TH in cardiac arrest warranted further research in this area.

1.1.6.5.2. The Australian study 2002

This study was conducted across 4 hospitals in Australia as a prospective RCT involving 77 cardiac arrest survivors, out of whom 43 patients were randomly assigned to treatment with TH and 34 patients were allocated to standard post resuscitation treatment with temperature maintained at 37°C (control group). Patients in the hypothermia group were cooled to 33°C using surface ice packs and maintained for 12hours following hospital admission after which, they were actively rewarmed using warm blankets. The authors in this study concluded that 49% patients in the intervention group had a statistically significant improvement in neurological status and survival rate at hospital discharge in comparison to 26% in the control group (p=0.046). After adjustment of baseline characteristics, the odd ratio of a good outcome with hypothermia was 5.25 compared to the control group (95% confidence interval 1.47-18.76). The authors observed that hypothermia was associated with lower cardiac index and greater systemic vascular resistance, although these measures did not reach statistical significance. Similar to the HACA trial, it was difficult to establish blinding during treatment due to the nature of the intervention. However, the authors pointed out that due to strict adherence to the study protocol and the final assessment being carried out by an independent rehabilitation physician, any potential bias would have been minimised.

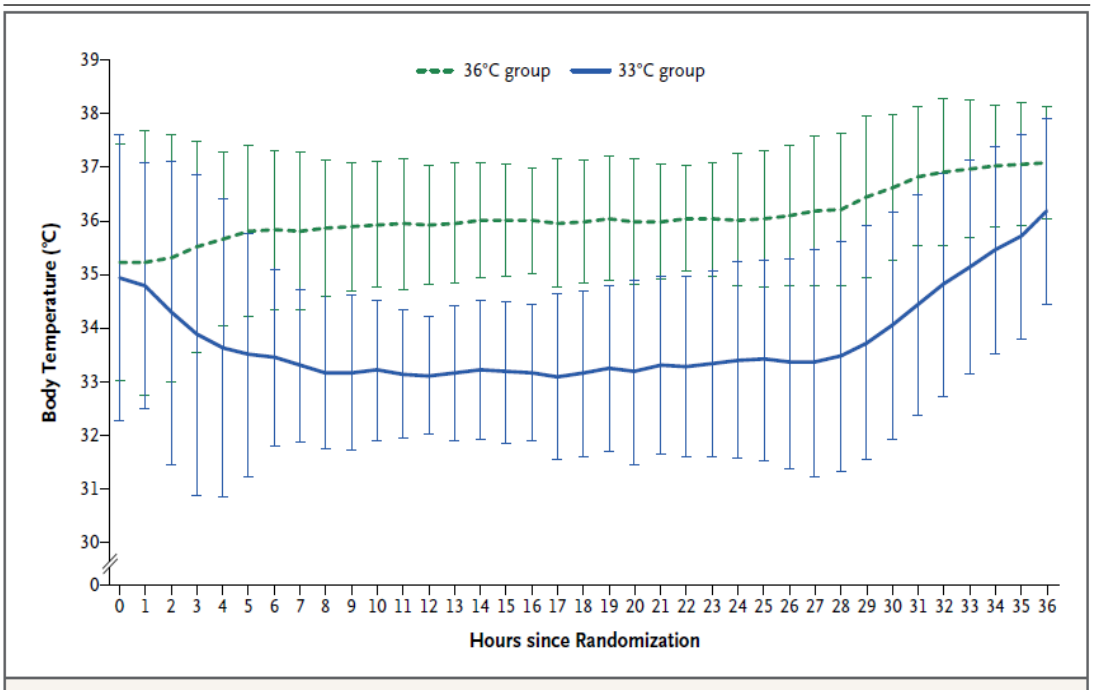
Despite the promising role TH shown in the context of cardiac arrest in these landmark trials in 2002, some researchers questioned whether any observed beneficial effect of TH was attributable to targeted temperature management (TTM) or fever prevention. In 2013, a group of researchers published a study that was aimed at answering some of these very important questions (Nielsen, Wetterslev et al. 2013).

1.1.6.6. TTM study 2013

This was by far the largest RCT in this field involving 36 intensive care units (ICUs) in Europe and Australia. Adult unconscious patients (>18yrs age) with at least 20 minutes of circulation after successful resuscitation from cardiac arrest were screened for enrolment. A total of 1431 patients were screened for eligibility, out of which 950 patients (66%) were enrolled into the study. Patients were then randomly assigned in a 1:1 manner into TTM at 33°C or 36°C for 28hrs from the time of randomisation and maintained below 37.5°C for 72hrs in total.

Figure 1-6 Bladder temperature during intervention period, shown as mean ± 2SD

Please note that patient in both groups had active temperature management during intervention and therefore, mean temperature never rose above 36°C in either group of patients. Adapted from (Nielsen, Wetterslev et al. 2013)



TH at different hospital sites were induced and maintained with application of ice packs, ice cold fluids and intravascular or surface temperature management devices. Although blinding was not possible during active temperature management, physicians carrying out neurological prognostication and research team carrying out follow up were unaware of trial intervention. Patients were followed up for 6 months or death, whichever happened first. At the end of the trial period, it was found that, 50% patients died in the 33°C group compared with 48% in the 36°C group (hazard ratio in 33°C group 1.06; 95% confidence interval 0.89-1.28). Also, at 6-month follow up, 54% patients in 33°C group had died or had poor neurological outcome compared to 52% in the 36°C group. (risk ratio 1.02; 95% confidence interval 0.88-1.16). The authors concluded that there was no significant difference in clinical outcome of patients with TTM at 33°C vs. 36°C in this group of patients.

Subsequently, the design of TTM trial has been critically appraised and it highlighted potential pitfalls in trial design that may have contributed to the equivocal outcome of the 2 study arms (Polderman, Varon 2015). There was a long delay of up to 4 hours (mean time to initiation 130 minutes) before cooling was initiated and a further 8 hours

before target temperature was reached, which translates into approximately 10 hours before target temperature of 33°C was reached from the time of ROSC. Any potential benefit offered to patients maintained at 33°C would be lost due to this prolonged delay in reaching target temperature, as a lot of irreversible damage may have already taken place. In addition, the TTM trial does not comment on temperature fluctuations during patient movement between various hospital departments. Portable cooling equipment was not readily available at all centres, which could result in rebound hyperthermia during patient movement and this may itself contribute to poor outcomes (Polderman 2008).

1.1.6.7. Meta-analysis and consensus guidelines

Several meta-analyses have been carried out at various time points with evolving research in this field of TH in cardiac arrest. The earliest was conducted in 2005 (Holzer, Bernard et al. 2005) which demonstrated that adult survivors of cardiac arrest who received TH within 6 hours of hospital admission were more likely to leave hospital with good neurological recovery than patients who were offered standard care (risk ratio 1.68; 95% confidence interval 1.29-2.07). The number needed to treat to allow one additional patient to leave hospital with good neurological recovery was 6 (95% confidence interval of 4-13). The 6-month survival data available from 1 study (Hypothermia after Cardiac 2002) also translated to better survival rate with favourable neurological recovery in patients treated with hypothermia (risk ratio 1.44; 95% confidence interval 1.11-1.76). The publication of this meta-analysis and historic evidence of the beneficial role of TH in cardiac arrest inspired many governing bodies to advocate the use of TH in patients surviving cardiac arrest (Peberdy, Callaway et al. 2010, Nolan, Neumar et al. 2008). In more recent times, 2 further meta-analyses also support the use of TH in cardiac arrest (Wang, Lin et al. 2013, Schenone, Cohen et al. 2016).

The latest American Heart Association (AHA) guideline on TH in cardiac arrest has been updated in 2015 to reflect latest research findings and it says ‘all comatose adult patients with ROSC after cardiac arrest should have TTM, with a target temperature between 32°C and 36°C selected and achieved and then maintained constantly for at least 24 hours’ (Donnino, Andersen et al. 2015). The national institute of clinical excellence (NICE) also support the use of TH following cardiac arrest, however the guideline has not been updated since the publication of the TTM trial (NICE, National Institute for Clinical Excellence March 2011).

1.1.6.8. TH induction methods

Earlier trials used ice packs and/or cooling blankets for TH induction and maintenance (Benson, Williams et al. 1959, Bernard, Gray et al. 2002, Hypothermia after Cardiac 2002). These techniques come with innate problems in active temperature management as patients may need to be moved from site of cardiac arrest, often outside of hospital to different sites within the hospital, when these cooling devices may need to be switched off. This can result in unwanted temperature gain, potentially defeating any benefit implied by the original induction. More recently, ice cold saline infusion has been investigated to induce TH (Kim, Nichol et al. 2014) in patients surviving cardiac arrest. In this RCT, 688 patients were randomised to receiving pre-hospital TH induction with 2 litres of 4°C intravenous saline and a further 671 patients received standard care. Although the intervention with cold saline resulted in lower core body temperature on hospital arrival and quicker time to reach target temperature, there was no statistical difference in survival to hospital discharge and neurological recovery regardless of initial presenting rhythm. Moreover, patients treated with ice-cold saline were more likely to experience recurrence of cardiac arrest, develop pulmonary oedema and increased diuretic usage. A further multicentre RCT, the RINSE trial (Bernard, Smith et al. 2016) was conducted in 2016 with an aim to investigate if rapid infusion of 2 litres of intravenous cold saline resulted in better clinical outcomes in patients resuscitated from surviving a cardiac arrest. The RINSE trial did not demonstrate statistical superiority in survival to hospital discharge in patients treated with intravenous cold saline (10.2% in hypothermia group vs 11.4% in standard care). Moreover, there was a statistically significant reduction in ROSC rates (41.2% compared with 50.6%, $p = 0.03$) in patients treated with intravenous cold saline. Although the study closed early at 48% recruitment stage due to implementation of different temperature management strategies in different hospitals, the authors felt there was enough evidence to conclude that rapid infusion of cold saline may cause more harm in cardiac arrest patients with an initial shockable rhythm. In their latest update, the AHA recommends against using cold saline for TH induction in the pre-hospital setting (Donnino, Andersen et al. 2015).

Endovascular cooling has also been tested in some centres for TH induction and management. In one RCT (Deye, Cariou et al. 2015), 203 patients who survived OHCA were randomised to endovascular cooling induction and maintenance in the ICU and a further 197 patients received standard care. The authors found that, despite a more efficient arrival to target temperature and maintenance of target temperature during treatment, endovascular cooling did not provide statistically superior survival rate at hospital discharge with good neurological recovery at 28 days or 90 days, irrespective

of initial presenting heart rhythm after ROSC. The size and design of the endovascular cooling machine also limits it portability outside hospital. An effective cooling device is expected to have the following characteristics:

- easy to deploy without interfering other ongoing treatment such as CPR, ventilation, coronary angiography
- achieves target temperature rapidly and can maintain it
- portable from site of cardiac arrest to hospital and in between departments
- prevents rebound hyperthermia during patient movement

Rhinochill® is a novel portable cooling system, which was approved by European Resuscitation Council for commercial use. It can induce TH by selectively cooling the brain through spraying an evaporative coolant via intranasal catheters with minimal temperature fluctuations during patient transfer. A multicentre RCT (Castren, Nordberg et al. 2010) involving 200 patients surviving cardiac arrest, investigated the feasibility of Rhinochill® application in pre-hospital setting. The authors found that, Rhinochill® was more efficient in reaching target temperature without compromising on patient safety. They observed a trend towards improved survival rate to hospital discharge and better neurological recovery at discharge in patients treated with Rhinochill®, but these observations were not statistically significant. A larger RCT is currently being conducted where, intra-arrest TH is being investigated to assess impact on survival and neurological recovery at hospital discharge (Nordberg, Taccone et al. 2013).

1.1.6.9. Rationale for further research with TH in cardiac arrest

The latest RCT (Nielsen, Wetterslev et al. 2013) and previous studies (Bernard, Gray et al. 2002, Hypothermia after Cardiac 2002) raised important questions that remain unanswered about the role of TH in cardiac arrest survivors. While earlier studies suggested lower temperatures offered better neuroprotection and survival benefit, the latest TTM trial showed there was no difference in clinical outcome between patients maintained at 2 different temperatures, although neither group were allowed to have febrile episodes during active temperature management, It appears that the timing of initiation of TH, time to reach target temperature and optimal duration of maintenance therapy have yielded some considerable variations in clinical outcome (Polderman, Varon 2015). One retrospective registry based study demonstrated that every 5 minute delay in TH induction increased the odd of a poor neurological outcome in hospital, at discharge and post discharge follow-up (Sendelbach, Hearst et al. 2012). Additionally, the odd of a poor neurological outcome was also increased for every 30 minute delay in reaching target temperature at post discharge follow up (Sendelbach, Hearst et al. 2012). Irrespective of whether methods are employed to reduce core body temperature

or to prevent systemic pyrexia, the mortality rate and risk of permanent and disabling brain injury remains high in this patient group (Wachelder, Moulaert et al. 2009). In the TTM trial (Nielsen, Wetterslev et al. 2013), more than 50% patients in both treatment groups died or had poor neurological function at 180 day follow up. The alarming rates of morbidity and mortality associated with cardiac arrest provide a large incentive for research into novel methods of treating this important group of patients, and are the major driver behind the research described in Chapter 2 of this thesis.

1.2. Psychological wellbeing of cardiac arrest survivors

1.2.1. Better survival rates

Advances in technique and technology, as well as better access to the chain of survival (Nolan, Soar et al. 2006), have seen the number of successful resuscitations after cardiac arrest improve in recent times. The London Ambulance Service (LAS) reported a remarkable survival rate of 32% in bystander witnessed cardiac arrests with initial rhythm of ventricular fibrillation or ventricular tachycardia in 2011/2012 compared to just 5% over 10 years ago (Watson L: Virdi G, Fothergill R 2012).

Although the overall unadjusted survival rate after cardiac arrest is still relatively low (Berdowski, Berg et al. 2010), an increasing number of people in public areas are being trained to perform cardiopulmonary resuscitation (CPR) and operate automated external defibrillators (AEDs). In a benchmark trial (Weaver, Hill et al. 1988), provision of AEDs to firefighters resulted in improved survival as compared with CPR alone (30% versus 19%, $P<0.01$). Projects like the 'Shockingly easy campaign' sponsored by the LAS facilitated more AEDs being available in public areas and consequently, more victims of cardiac arrest can be resuscitated sooner, even before arrival of the emergency medical services (EMS). In their recent report (2014/15), the LAS reported 63.1% OHCA patients received bystander CPR compared to 55.8% in the previous year and 76.7% of those who had AED treatment, had ROSC at hospital arrival, with a remarkable survival to hospital discharge rates of 58.6% in this group of patients (Virdi G, Picton S, Fothergill R September 2015). The time to ROSC is an independent predictor of mortality (Myerburg RJ, Castellanos A 2001) and therefore, earlier ROSC is expected to translate to better chances of survival. Some of the more recent trials investigating mortality associated with cardiac arrest reported improved short term and medium term survival rates (Islam, Hampton-Till et al. 2015, Castren, Nordberg et al. 2010, Nielsen, Wetterslev et al. 2013). Historic data suggests that survivors of cardiac arrest have high incidence of neurological deficit, cognitive impairment and worsened emotional wellbeing if they survive (Moulaert, Verbunt et al. 2009), therefore posing a huge challenge in managing these patients. The success of resuscitation need to consider not only the survival rate, but also the subsequent quality of life (QoL) of the survivor (Beesems, Wittebrood et al. 2014).

1.2.2. Implications of cardiac arrest

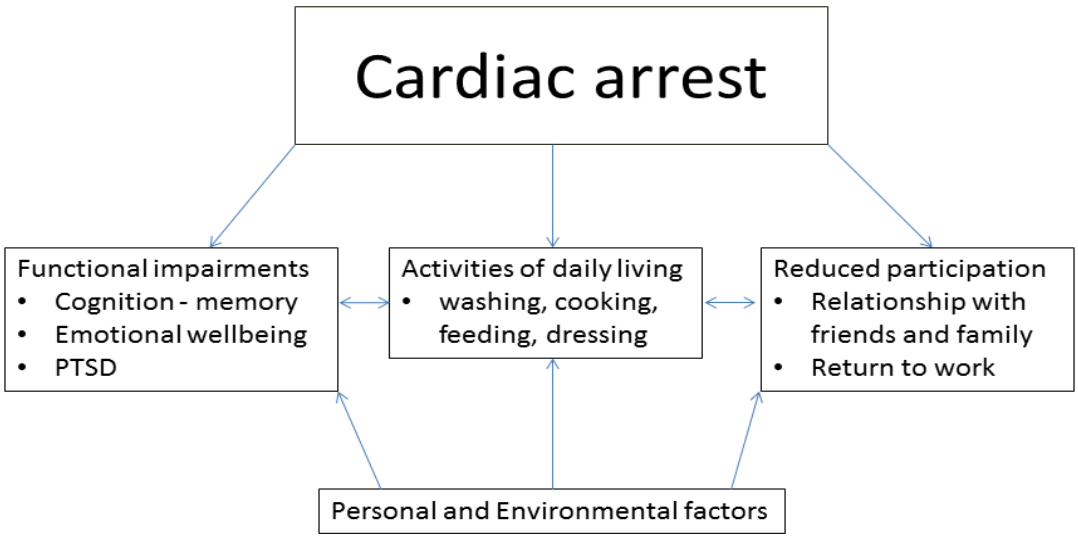
The brain is heavily dependent on the pumping action of the heart to receive blood and oxygen supply that are required for its metabolism and function. During a cardiac arrest, the brain is completely deprived of blood supply and therefore susceptible to brain injury. If cardiac arrest persists for several minutes, the brain may sustain

irreversible damage, called hypoxic-ischaemic brain injury (Busl, Greer 2010). The complex molecular mechanism of brain injury was discussed in an earlier section (1.1.5). The hypoxic-ischaemic brain injury has the potential to affect any part of the brain parenchyma. Therefore the resulting neurological deficit can be quite diverse and can range from variable levels of consciousness, movement disorders and impairment of cognitive function (Khot, Tirschwell 2006). Hence, the consequence of a cardiac arrest is not limited to the direct pathophysiological changes in the heart and the brain but has significant implications on other indirect functions of the brain, which include emotional wellbeing and cognitive function in patients who survive this life changing event. In this part of the introduction, the focus will be on these indirect consequences of hypoxic-ischaemic brain injury and the socio-economic impact.

1.2.3. A framework to understand the unseen consequences of cardiac arrest

The World Health Organisation (WHO) model of the International Classification of Function (ICF), Disability and Health provides a holistic and effective framework to understand the indirect and unseen consequences of cardiac arrest (WHO 2001). Through this framework, one can anticipate impairments in function, reduced performance in activities of daily living and withdrawal from participation in social activities as consequences of cardiac arrest.

Figure 1-7 Illustration of the ICF model



At a functional level, there can be impairments in cognition such as short term memory, executive function and emotional wellbeing such as anxiety and depression. Examples of activities of daily living include washing, cooking, cleaning and getting dressed, whilst social participation include return to work, visiting friends and family. These domains can also be seen to interact and influence each other through environmental factors, such as the presence or absence of supporting caregivers, financial situation, adaptation in accommodation and personal factors such as age, sex and personality.

QoL is not incorporated in the ICF framework as it is considered to be an umbrella term that reflects the feelings of an individual in a given situation under the influence of the circumstances. The WHO defined QoL as the ‘‘individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goal expectations, standards and concerns’’ (Saxena, Orley et al. 1997). Therefore QoL can be influenced by all the domains of the ICF model of cardiac arrest as described above. Indeed Moulaert et al (Moulaert, Wachelder et al. 2010) demonstrated via regression analysis in a retrospective cohort study that, physical QoL was significantly related to cognitive function, instrumental activities of daily living, post-traumatic stress disorder (PTSD) and fatigue ($p<0.001$) and mental QoL was significantly related to cognitive function, anxiety and depression ($p<0.001$).

1.2.3.1. Evidence of impaired cognitive function

Cognitive impairment has been reported in patients surviving cardiac arrest with variable frequencies. Moulaert et al (Moulaert, Verbunt et al. 2009) conducted a systematic review on studies published between 1980 and 2006 for adult survivors of cardiac arrest who were followed up for a minimum of 3 months after the index event. Using their selection criteria, only 10% of the originally screened studies were included in the final evaluation (n=28). The reported frequency of cognitive function ranged between 6% and 100% with memory problems being reported as the most common form of cognitive impairment followed by impairment in attention and executive functioning. The hippocampus, located on the elongated ridges on the floor of each lateral ventricle in the brain, is the centre of emotion and memory. It is very sensitive to changes in cerebral perfusion (Back, Hemmen et al. 2004, Harukuni, Bhardwaj 2006) and could explain why memory deficit is the commonest cognitive impairment, along with generalised cerebral atrophy associated with hypoxic brain injury (Grubb, Fox et al. 2000). Three of the 28 studies included in the final analysis (Moulaert, Verbunt et al. 2009) in the systematic review were considered to be high quality with relatively large number of participants (n=45, 57 and 58) and used a variety of neuropsychological tests (Sauve, Doolittle et al. 1996, van Alem, de Vos et al. 2004, Roine, Kajaste et al. 1993), that were considered to be reproducible. These studies reported cognitive

impairments in the range of 42-50%. The variation in the reported frequencies of cognitive impairment could be explained by selection of the patient population, timing of assessment and the assessment tool itself. In addition, the impact of confounding factors such as age, duration of hypoxia, co-morbidities were not consistently taken into consideration, which makes the interpretation of reported frequencies more challenging. Nevertheless, the recognition of cognitive impairment as an outcome of cardiac arrest survival is vital as it has been shown to affect both physical and mental QoL (Moulaert, Wachelder et al. 2010) and therefore, should remain an important focus in post resuscitation care.

1.2.3.2. Evidence of anxiety and depression

Patients have also been known to suffer variable degrees of emotional problems as a consequence of suffering cardiac arrest in the form of anxiety and depression. Anxiety can be defined as a state of apprehension, worry or uneasiness about one's current situation or an uncertain future (Torgersen, Strand et al. 2010). Depression is defined as a state of low mood, that results in feelings of hopelessness, disinterest and apathetic in any matters of life lasting for more than 2 weeks (Wilder Schaaf, Artman et al. 2013). Anxiety and depression often co-exist in cardiac arrest survivors and has been reported in frequencies of between 10-11% (Larsson, Wallin et al. 2014, Wachelder, Moulaert et al. 2009) to 51-52% (Bunch, White et al. 2004, Granja, Cabral et al. 2002, O'Reilly, Grubb et al. 2004). Larsson et al (Larsson, Wallin et al. 2014) found in a 6 month prospective follow up study, anxiety and depression were at their highest level whilst the patients were still in hospital and commented that this could improve over time. However, Wachelder et al (Wachelder, Moulaert et al. 2009) conducted a retrospective analysis and found that 38% patients still suffered anxiety and depression even at 3 years after cardiac arrest. In isolation, the reported frequency of depression has been found in the range of 16%-45% (de Vos, de Haes et al. 1999, Roine, Kajaste et al. 1993) and anxiety has been reported in 30%-41% patients in cardiac arrest survivors (Roine, Kajaste et al. 1993, O'Reilly, Grubb et al. 2004).

Some studies claim that there is no difference in the prevalence of anxiety and depression between cardiac arrest survivors and the general population (Lim, Verfaellie et al. 2014, Saner, Borner Rodriguez et al. 2002) and one study goes further to report that cardiac arrest survivors do not suffer any particular anxiety or depression (Nichol, Guffey et al. 2015). This sort of observation has to be considered in light of factors that may influence the actual reported statistics. With the exception of a few studies (Wilson, Staniforth et al. 2014, Larsson, Wallin et al. 2014), most of the data collection about anxiety and depression were carried out in neurologically intact survivors of cardiac arrest. Inevitably, neurological recovery is a very important confounder that

needs to be considered when reporting frequencies as patients with compromised neurological status are more likely to report symptoms of anxiety and depression. The timing of assessment is also hugely influential, as a later assessment can show improvement in reported frequencies of symptoms (Saner, Borner Rodriguez et al. 2002) because patients may have already sought and received treatment from specialists. In addition, the analysis tool needs to be validated and reproducible to provide meaningful comparison. Irrespective of the reported frequencies, anxiety and depression associated with cardiac arrest can significantly influence one's QoL (Larsson, Wallin et al. 2014, Wilson, Staniforth et al. 2014, Wachelder, Moulaert et al. 2009, Saner, Borner Rodriguez et al. 2002, O'Reilly, Grubb et al. 2004, Gamper, Willeit et al. 2004, Moulaert, Wachelder et al. 2010) and should therefore remain an important focus in post resuscitation care for best overall outcome.

1.2.3.3. Post-traumatic stress disorder (PTSD)

PTSD is described as a disorder that people may develop in response to a traumatic event resulting in intrusive memories, nightmares and avoidance of situations that remind of the offending incident (WHO 1993). Gamper et al (Gamper, Willeit et al. 2004) carried out a prospective cohort study spanning over an 8yr period and assessed neurologically intact cardiac arrest survivors at a mean 45 months after the index event. They found that 27% patients fulfilled the criteria for experiencing PTSD at follow up and younger age was an independent risk factor for developing PTSD. The authors also found that the presence of PTSD had a significant impact on QoL perceptions amongst these patients. In a separate case control study, there was almost a 3 fold increase in incidence of PTSD (19%) in cardiac arrest survivors compared to patients suffering myocardial infarction (7%) (O'Reilly, Grubb et al. 2004), supporting the greater traumatic impact of cardiac arrest on the victim. Identification and timely management of PTSD in cardiac arrest survivors is likely to have significant impact on QoL assessment (Moulaert, Wachelder et al. 2010) and improve patient outcome.

1.2.3.4. Evidence of reduced participation and return to work

There is evidence to suggest that the vast majority of neurologically intact cardiac arrest survivors resume basic activities of daily living at hospital discharge (de Vos, de Haes et al. 1999, Hofgren, Lundgren-Nilsson et al. 2008, Wachelder, Moulaert et al. 2009). Patients who require assistance with performing daily activities are more likely to be re-housed with better nursing facilities like sheltered accommodation (Hofgren, Lundgren-Nilsson et al. 2008). In a 1 year follow up study, it was found that about 55% patients still required assistance with performing more complex daily activities like

operating machines (Lundgren-Nilsson, Rosen et al. 2005). Interestingly, the authors discovered that all those who were dependent for performing activities of daily living, also had reduced cognitive function, supporting our ICF model of understanding the implications of cardiac arrest and the interconnection between the domains.

More recently, in a retrospective follow up study it was reported that, 86% patients functioned independently at 1-year follow up, however, half the patients complained of severe fatigue (Wachelder, Moulaert et al. 2009). It was also shown in this study that a significant proportion of patients (74%) had lower level of participation in society compared to general population. The authors concluded that age and gender influenced patient's QoL, participation in society and daily functioning, which has been reported in earlier studies (Saner, Borner Rodriguez et al. 2002, de Vos, de Haes et al. 1999).

The return to work rate has been found to be variable depending on the study population and the timing of the assessment and has been found to be in the range of 12% to 50% (Lundgren-Nilsson, Rosen et al. 2005, Saner, Borner Rodriguez et al. 2002, Wachelder, Moulaert et al. 2009). Other aspects of participation in society such as relationship with family and friends, performing in recreational activities have not been well documented in the context of cardiac arrest, which require further research to understand the true impact of the condition on wider participation. The return to work rate has important socioeconomic implication, which will be discussed in later section in discussion.

1.2.4. Burden on caregivers

The presence of a caregiver, when available, plays a huge supporting role for the recovery of the cardiac arrest survivor. However, studies have shown that adopting the role of a caregiver is associated with decline in physical and mental health, family relationships, employment and finances (Pearlin, Mullan et al. 1990). In practice, the role of the caregiver is often eclipsed by the more pressing recovery of the cardiac arrest survivor, until such time when caregiver may volunteer to voice their difficulty in coping with the situation (Kasuya, Polgar-Bailey et al. 2000). The caregiver is often a close family member such as a spouse or a very close friend, in whom patient can confidently trust with their wellbeing and assistance with performing activities of daily living, when necessary. It is important to recognise the role of the caregiver as it has been shown that patients' psychological recovery is linked to family function (Miller, Wikoff 1989), compliance to risk factor modification is linked to spousal anxiety and

marital function (Miller, Wikoff et al. 1990) and increased mortality in older caregivers associated with increased strain and marital quality (Schulz, Beach 1999).

The caregivers often make several adjustments to cope with the different physical and psychological needs of the cardiac arrest survivor in the immediate aftermath of the index event when the patient returns to usual place of residence. The recovery time is often prolonged and even when the physical health has made reasonable improvements in getting patient back to baseline function, the psychological trauma and participation in society can lag for years (Wachelder, Moulaert et al. 2009, Gamper, Willeit et al. 2004). Studies have shown that a multitude of factors, including the uncertainty about the prognosis of the cardiac arrest survivor, the fear of recurrence, the function of the implantable cardiac defibrillator (if inserted for medical reasons) and associated limitations in lifestyle, the unpredictable change in patients' personality and the increased reliance on performing activities of daily living increased the strain on the caregiver (Doolittle, Sauve 1995, Pycha, Calabrese et al. 1990). Doolittle et al carried out a longitudinal phenomenological study over 24 weeks interviewing 40 cardiac arrest survivors and 30 spouses (caregivers) (Doolittle, Sauve 1995). They found that, the reference point for the spouses for future decision making was the actual arrest itself, whereas the reference point for cardiac arrest survivor was pre-arrest lifestyle. This also explained why the spouses who witnessed the cardiac arrest were more protective about the patient, leading to entrapment of the patient in most severe situations, resulting in reduced participation in society, anger, frustration and turbulence in family relationship. In addition, the need to fulfil financial commitments like paying mortgage, adapting employment, disruption in sexual relationship also increases the strain on the caregiver (Steinke 2003).

Data on prevalence of caregiver strain related to cardiac arrest is less well documented. In a small cross sectional follow up study, 60% spouses complained of psychosomatic problems and 50% felt isolated at a mean 25 month after cardiac rehabilitation from the index event (Pusswald, Fertl et al. 2000). In a more robust retrospective follow-up study at a mean 36 months after cardiac arrest, the authors found that 17% caregivers reported high caregiver strain, which is lower than previously reported (Wachelder, Moulaert et al. 2009). This could be explained by the longer duration of follow-up in this study. They also found that 38% of caregivers reported higher anxiety and depression on the Hospital Anxiety and Depression scale and about a quarter of the caregivers reported reductions in both physical and mental components of the QoL.

Irrespective of the prevalence of anxiety, depression and caregiver strain, it is important to recognise caregivers as integral participants when post resuscitation care is planned. Inevitably, their QoL is affected by the unexpected life changing event and addressing their concerns individually alongside the patients is likely to yield the best possible outcome for both parties in the short and long term. An effective and transparent communication is sometimes all that is needed to address the concern of the caregiver to reduce their anxiety about coping with the situation and the uncertainties.

1.2.5. Landmark trial 2015

Having identified the huge burden of psychological trauma and limitations in social participation associated with cardiac arrest for the patient and the caregiver, the challenge for health care providers was to devise an intervention by which both participants will benefit in the short term and long term. In 2015, a landmark trial was published in the International Journal of Cardiology, where Moulaert et al discussed a novel intervention which was aimed at encouraging better participation in the society and an improvement in QoL for cardiac arrest survivors and their caregivers (Moulaert, van Heugten et al. 2015).

This was designed as a multicentre single blinded RCT where patients and caregivers were recruited from 5 different hospitals in the Netherlands between 2007 and 2010. All hospitals offered standard management of cardiac arrest patients, in line with international guidelines to avoid bias in treatment modalities. Adult survivors (age >18yrs) of IHCA or OHCA with life expectancy of greater than 3 months were screened for recruitment. Caregivers, if available, were encouraged to participate but the absence of caregiver was not considered to be an exclusion criteria. Assessments were made at 2 weeks, 3 months and 12 months after index event. Participants were randomised in a 1:1 manner to intervention group or control group. If allocated to intervention, patients and caregivers were screening for cognitive and emotional problems, provided with verbal and written information and support, encouraged self-management strategies and referred to specialist care if warranted from initial assessment. Patients and caregivers in the control group received standard cardiac rehabilitation but no intervention was offered as part of the study.

A total of 185 patients were randomised of which 97 patients were allocated to intervention and 88 patients were randomised to control group. In addition, 155 caregivers participated in the study. At 12 months, 143 patients completed the trial.

At the analysis of the primary outcomes at 12 months, patients in the intervention group reported significantly better scores in role emotional, mental health and general health components of the SF-36 QoL questionnaire ($p<0.01$). In terms of secondary outcome measures, there was significant improvement in overall emotional state and anxiety levels ($p<0.01$) in the intervention group and the return to work rate was significantly higher at 3 months follow-up in the intervention arm, but this statistical superiority was lost at 12 month follow-up. There was no significant difference with regard to participation in society. Interestingly, the authors reported that there were no significant improvements in the caregivers' response to either primary or secondary outcome measures although higher levels of anxiety, depression and PTSD were reported in both groups. This re-affirms earlier observation that caregivers are also a vulnerable group of individuals whose care needs may be different in the context of cardiac arrest and warrants more research to understand and address their problems with coping.

One of the limitations discussed in the paper was that blinding was not always possible at home visits as participants could spontaneously disclose their group allocation to the research assistants, who attended follow-up and collected data. However, research assistants were not involved in data analysis and therefore negate any potential bias. The authors concluded that, the introduction of this comprehensive intervention resulted in significant improvements in QoL and emotional state after cardiac arrest and resulted in more rapid return to work and therefore, recommended regular implementation in routine clinical practice to improve outcome.

The above data clearly demonstrate an on-going medium to long-term physical and psychological burden affecting cardiac arrest patients and their care givers. The work presented in Chapter 3 attempts to address this problem in a sample of patients from our local population.

1.3. Acute Myocardial Infarction and therapeutic hypothermia

1.3.1. Definition

Acute myocardial infarction (AMI) or heart attack is defined as cardiomyocyte cell death as a direct result of severe and prolonged oxygen deprivation (often referred to as ischaemia). The commonest cause of AMI is the abrupt cessation of blood supply in one or more coronary arteries resulting in regional cardiomyocyte necrosis, delineated by the territory supplied by the culprit coronary artery. If left untreated or treatment is delayed, this may progress into life threatening arrhythmia, cardiac arrest and death in the acute setting (minutes to hours). Chronically (days to weeks), patient may suffer debilitating heart failure, secondary end organ damage, such as kidney disease and liver disease, the extent of which is partly determined by the size of the initial heart attack or myocardial area at risk (Reimer, Lowe et al. 1977) and the duration of ischaemia (Christian, Schwartz et al. 1992). At the molecular level, the damage happens in a more complex manner which will be discussed below.

1.3.2. Incidence

The leading cause of worldwide mortality is CVD with an estimated 17.5 million CVD related deaths reported in 2012, representing 31% of all deaths. Furthermore, almost 7.4 million of these deaths were due to coronary heart disease, which refers to disease of the blood supply to the heart (WHO factsheet 2016 September 2016). Likewise, CVD is also the principal cause of mortality in the UK, accounting for 180,000 deaths in 2010, almost half of which were attributed to coronary heart disease (Townsend, N., Wickramasinghe, K., Bhatnagar, P., Smolina, K., Nichols M, Leal J, R, L.-F. & Rayner, M. 2012). More alarmingly, 46,000 premature deaths in the UK are attributed to CVD and cost the UK economy an estimated £19 billion in 2009 in healthcare cost and loss of income (Townsend, N., Wickramasinghe, K., Bhatnagar, P., Smolina, K., Nichols M, Leal J, R, L.-F. & Rayner, M. 2012). In recent years however, death from coronary heart disease has been falling in younger age group and death rates from heart attack is reported to have halved since 2002 (Townsend, N., Wickramasinghe, K., Bhatnagar, P., Smolina, K., Nichols M, Leal J, R, L.-F. & Rayner, M. 2012).

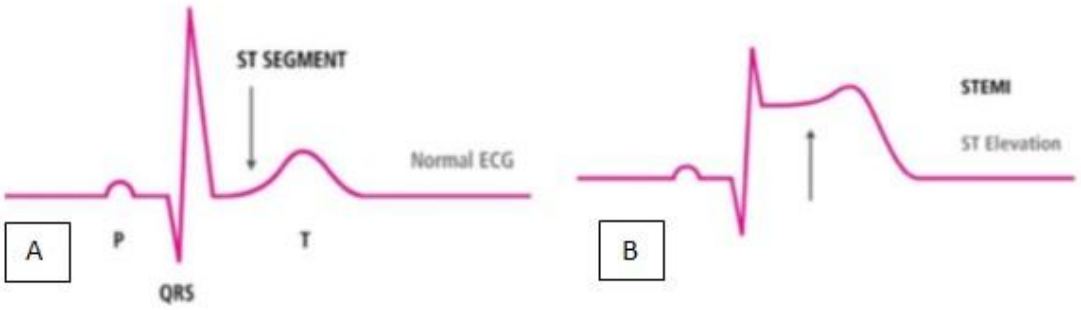
1.3.3. Pathophysiology of acute myocardial infarction (AMI)

The formation of atheromatous plaques, lipid rich complexes, within the epicardial coronary arteries result in coronary artery disease. With time, the arterial lumen becomes progressively smaller contributing commonly to symptoms of chest pain or angina that becomes worse on exertion or can come on at rest if the luminal obstruction is severe. A plaque may rupture resulting in intra-coronary thrombosis which, may subsequently occlude the artery at the site of plaque rupture or embolise

and block the vessel further downstream. If this results in severe and prolonged deprivation of oxygen to the heart muscle then AMI ensues (Thim, Hagensen et al. 2008). Patients will often experience severe crushing chest pain, with or without other symptoms such as breathlessness and clamminess and generally seek urgent medical help. A timely electrocardiogram (ECG) is vital in this situation, as it can often confirm the diagnosis of acute myocardial infarction, thus allowing emergency medical personnel to commence the initial management, including administering appropriate medications and deciding on the most appropriate destination hospital for the patient. If ST elevation myocardial infarction (STEMI) is present on the ECG, a complete occlusion of a major coronary artery is highly likely, and the priority will be to transfer the patient to a tertiary heart attack centre with facilities to perform emergency PPCI to mechanically restore coronary blood flow (Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg et al. 2012).

Figure 1-8 ECG representation of STEMI

Panel A shows normal electrocardiogram (ECG); Panel B shows STEMI on ECG



In the UK alone, approximately, 100,000 people suffer from STEMI every year (Townsend, N., Wickramasinghe, K., Bhatnagar, P., Smolina, K., Nichols M, Leal J, R, L.-F. & Rayner, M. 2012). The recognition of STEMI as an indicator for myocardial ischaemia dates back to around 1920, when Harold Pardee described it as *''T wave as being tall and starts from a point well up on the descent of the R wave"* (Pardee H. E. B. 1920). The amount of damage done by STEMI is time dependent (Reimer, Lowe et al. 1977) as has been shown in animal model of experimental ischaemia, that spreads

like a ‘wave-front’ from the inner layer of heart muscle (endocardium) to the outer layer of the heart muscle (epicardium), thereby completing a trans-mural infarct. Any delay in treating in the underlying occlusion can result in acute and chronic complications as described earlier.

1.3.4. Minimising injury

At present, on recognition of a patient suffering STEMI, an early transfer to a tertiary heart attack centre, with facilities to perform emergency PPCI to reperfuse the occluded artery is the most effective recommended treatment (Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg et al. 2012). The aim of this treatment, which involves a variable combination of thrombus removal, balloon dilatation of the occluded vessel followed by a stent insertion, is to minimise the myocardial infarct size and preserve left ventricular ejection fraction (Berger, Ellis et al. 1999, Lambert, Brown et al. 2010). In the absence of PPCI facilities, fibrinolysis can be delivered to break up and dissolve intra-coronary thrombus and thus re-establish blood flow (Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg et al. 2012). However, despite the introduction of the PPCI and national targets such as reducing symptom to balloon time (total ischaemia duration), the morbidity and mortality associated with STEMI is still high. In-hospital mortality rates are in the range of 3-7% with regional variation, whilst 30-day mortality is in the region of 3-6% (Lambert, Brown et al. 2010). At 1 year, the combined risk of a further cardiac event, congestive cardiac failure and mortality is reported at 9-15% (Lambert, Brown et al. 2010). One of the major determinants of prognosis from STEMI is the size of the myocardial injury or infarct size (Burns, Gibbons et al. 2002, Wu, Ortiz et al. 2008) and it has been shown that, infarct size has a strong associated with development of heart failure and arrhythmias (Timmer, Breet et al. 2010, Saia, Grigioni et al. 2010). Therefore, these findings warrant further research into finding ways of minimising infarct size and improving clinical outcome, hence the research presented in Chapter 4.

1.3.5. Ischemia/Reperfusion injury of the myocardium

Emergency PPCI or thrombolysis is the mainstay of treating STEMI caused by thrombotic occlusion of an epicardial coronary artery to restore coronary blood flow. However, much like the situation in the brain following cardiac arrest described earlier in this chapter, the sudden restoration of circulation in a previously ischaemic myocardium can result in further damage, a phenomenon called reperfusion injury (Yellon, Hausenloy 2007). This may explain why patients still have high risk (9-15%) of major adverse cardiac event at 1 year after the index event. Yellon et al. demonstrated

in animal models that 50% of infarct size is determined by ischaemia, and the remaining 50% is caused by reperfusion injury (Yellon, Hausenloy 2007). Whilst in recent times, there have been developments including emergency revascularisation and anti-thrombotic pharmacotherapy to reduce ischaemic injury; there have been no specific developments that substantially minimise reperfusion injury.

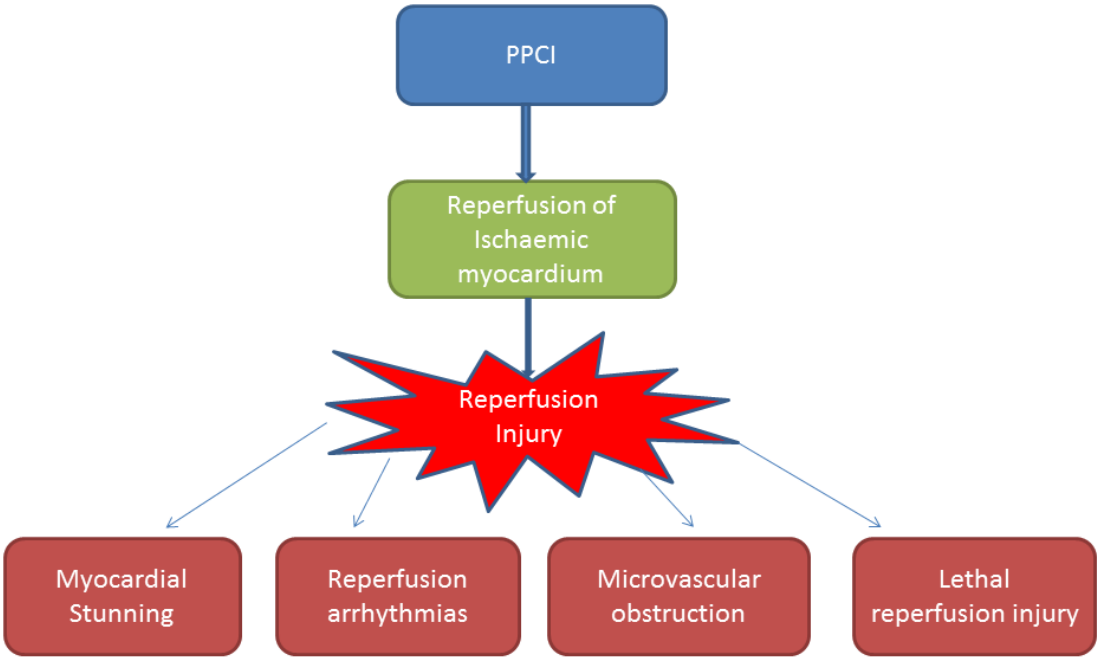
1.3.6. Mechanism of reperfusion injury – molecular level

In order to understand possible therapeutic targets to minimise reperfusion injury, it is important to understand the mechanism of injury at the molecular level. Scientists demonstrated histological changes that took place in an experimental dog model of coronary artery occlusion and subsequent reperfusion, where necrosis was evident within 30-60 minutes that was similar in presentation to degree of necrosis seen in permanent coronary occlusion without reperfusion for 24 hours (Jennings, Sommers et al. 1960). These histological changes of necrosis comprised of intra-mitochondrial calcium phosphate deposition, disruption of the sarcolemma and contracture of myofibrils, which are distinct changes that are not seen in injuries sustained from myocardial ischaemia alone. These observations further supported the definition of reperfusion injury as a separate pathophysiological phenomenon that occurs on restoration of coronary circulation.

Reperfusion injury can cause 4 types of cardiac dysfunction. Some of these are reversible, last for a short duration and can be easily managed such as myocardial stunning and reperfusion arrhythmia. However, other changes are irreversible including microvascular obstruction and lethal reperfusion injury and it is the degree of these irreversible damages that define infarct size and subsequent prognosis from the reperfusion injury.

Figure 1-9 Schema of reperfusion injury mechanisms

After PPCI restores circulation, reperfusion injury can exacerbate tissue damage by myocardial stunning, reperfusion arrhythmias, microvascular obstruction and lethal reperfusion injury.



1.3.6.1. Myocardial stunning

Originally described in 1975 (Heyndrickx, Millard et al. 1975), this is a period of transient mechanical dysfunction of the cardiac myocyte contractility that can persist for hours to days despite restoration of the coronary circulation. It is self-limiting process where the myocardium is essentially 'stunned' from the shock of sustaining coronary artery occlusion but will inevitably recover completely with time.

1.3.6.2. Reperfusion arrhythmias

On reperfusion, patients who presented with STEMI can develop transient reperfusion arrhythmia (Manning, Hearse 1984) which tends to be ventricular arrhythmia in anterior STEMI and brady-arrhythmia in inferior STEMI patients due to the nature of sympathetic and parasympathetic innervation. Again, these can be self-limiting sequelae from reperfusion injury and expected to revert to sinus rhythm spontaneously or with minimal medical intervention.

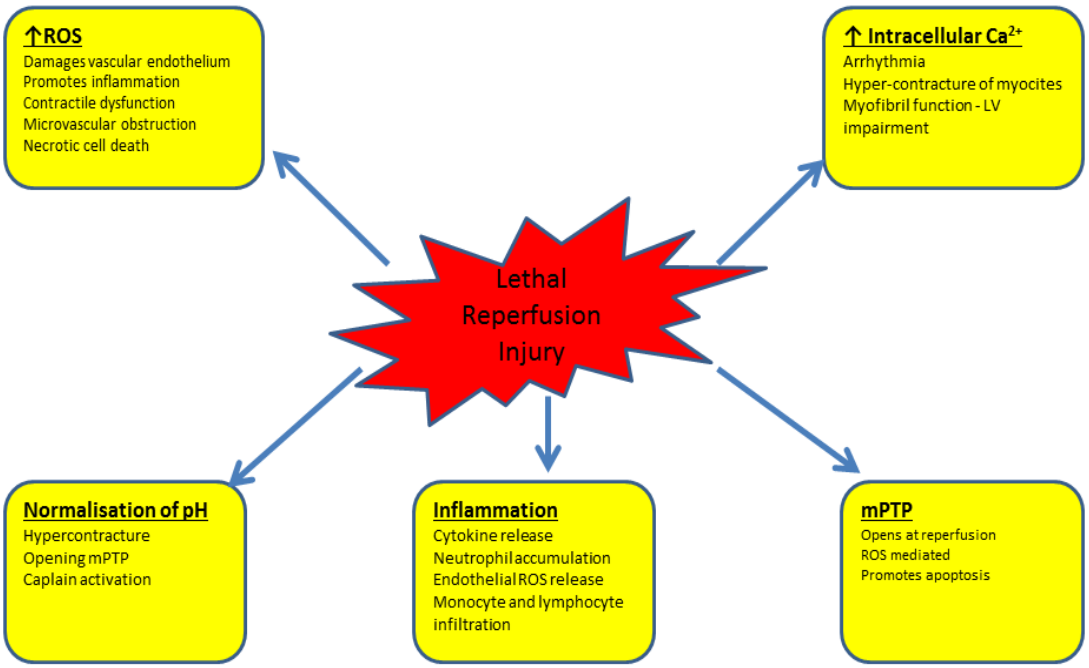
1.3.6.3. Microvascular obstruction

Originally described as 'inability to reperfuse a previously ischaemic region' in animal model (Krug, Du Mesnil de et al. 1966), the exact mechanism of this cardiac dysfunction induced by reperfusion injury is incompletely understood. It is assumed that a combination of intrinsic capillary damage with impaired vasodilation, extra-luminal compression from cardiac myocite swelling and distal embolization of the culprit atherosclerotic plaque, platelet and neutrophil deposition can all contribute to microvascular obstruction (Ito 2006). Angiographically, this may not be evident at the completion of PPCI but subsequent cardiac imaging with cardiac MRI can reveal microvascular obstruction in 30-40% patients (Bogaert, Kalantzi et al. 2007) who appear to have good coronary blood flow by TIMI criteria (The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. 1985). The presence of microvascular obstruction after STEMI indicates a larger infarct size, increased risk of impaired left ventricular ejection fraction, minimises potential for beneficial left ventricular remodelling and therefore, unfavourable clinical outcomes in the short and the long term (Bogaert, Kalantzi et al. 2007).

1.3.6.4. Lethal reperfusion injury

The immediate death of cardiac myocytes within minutes to hours after restoration of coronary circulation, which were considered viable or only reversibly injured during ischaemia, is termed lethal reperfusion injury (Piper, Garcia-Dorado et al. 1998). It has been difficult to demonstrate this process of injury directly as a distinct entity for cardiac dysfunction, but indirect evidence from animal studies has shown an additional 40-50% reduction in infarct size with therapeutic intervention at the onset of reperfusion suggesting that lethal reperfusion injury as an additional mechanism of further myocardial damage after treatment of ischaemia (Yellon, Hausenloy 2007)**.** Lethal reperfusion injury comprises several complex mechanisms that can cause contractile dysfunction, metabolic derangement and cardiac cell death by necrosis and apoptosis (programmed cell death) (Piper, Garcia-Dorado et al. 1998)**.** These mechanisms include generation of ROS, intracellular calcium accumulation, rapid normalisation of intracellular pH, a generalised inflammatory response and opening of the mitochondrial permeability transition pore (mPTP).

Figure 1-10 Schema of components of Lethal Reperfusion Injury



1.3.6.4.1. Reactive oxygen species (ROS)

Within a few minutes of restoration of coronary blood flow, when molecular oxygen is reintroduced into previously ischaemic myocardium, it undergoes sequential reduction leading to ROS formation such as superoxide anion (O_{2-}), hydroxyl radical (OH) and perioxynitrite (ONOO-) (Bolli, Jeroudi et al. 1989). These ROS damages the vascular endothelium, activates adhesion molecules attracting polymorphonucleotides (Serrano, Mikhail et al. 1996), disrupts phospholipid bilayer membrane resulting in calcium influx within the cells (Steinberg 2013), damages sarcoplasmic reticulum leading to contractile dysfunction (Rowe, Manson et al. 1983), induces derangement of several metabolic pathways including glycolysis and act as chemo attractants to neutrophils and other inflammatory cells, which contribute to microvascular obstruction (Zimmet, Hare 2006). Moreover, ROS stimulates the opening of mPTP (Zorov, Juhaszova et al. 2009), which promotes necrotic cell death. ROS has also been found to interfere with the bioavailability of cardio protective endogenous nitric oxide, the lack of which contributes to larger infarct size (Johnson, Tsao et al. 1991, Jones, Girod et al. 1999).

1.3.6.4.2. Intracellular calcium accumulation

In ischaemic state, the reduction in high energy ATP levels results in inhibition of energy dependent sarcolemmal Na^+/K^+ ATPase transporter, increased activity of

Na+/H+ exchanger and reverses the activity of the Na^{+}/Ca^{2+} exchanger (Inserte, Garcia-Dorado et al. 2005), which increases intra-cellular calcium levels. At reperfusion, there is further influx of calcium intro intracellular space as ROS degrades membrane integrity, as described above. Consequently, there is increased risk of arrhythmias due to electrolyte imbalance, hyper-contracture of the cardio-myocytes resulting in cell death. In addition, there is desensitisation of the cardiac contractile apparatus causing impairment of the myofibril function (Piper, Garcia-Dorado et al. 1998), which can then lead to impaired left ventricular function.

1.3.6.4.3. Normalisation of intracellular pH

During ischaemia, an acidic environment prevents lethal tissue injury by preventing hyper-contracture (Ladilov, Siegmund et al. 1995), calpain activation, Na+/H+ exchanger and opening of the mPTP (Piper, Abdallah et al. 2004, Kim, Jin et al. 2006). However, the sudden restoration of coronary blood flow results in rapid normalisation of intracellular pH by activating the Na+/H+ exchanger and washing out the lactic acid and is termed the pH paradox (Lemasters, Bond et al. 1996) and therefore, promotes all the processes described above that contribute to cardiac dysfunction.

1.3.6.4.4. Inflammatory response

An active inflammatory process already takes place during the ischaemic phase, which is part of the innate immune system response (Entman, Smith 1994). At reperfusion, the inflammatory response is more adaptive, which involves activation of the complement system; cytokine release and ROS secretion from endothelial cells attract neutrophils into the myocardium. Neutrophil accumulation contribute to further reperfusion injury by influencing further pro-inflammatory cascade, including: endothelial ROS release (Albertine, Weyrich et al. 1994); release of elastase and collagenase (Weiss 1989), distal embolization into microcirculation resulting in secondary ischaemia (Mehta, Nichols et al. 1988), further damage to coronary endothelium by recruiting more neutrophils through adhesion molecules (Jordan, Zhao et al. 1999), severe vasoconstriction through release of lipoxygenase products (Nichols, Mehta et al. 1988), platelet activation (Alloatti, Montrucchio et al. 1992) and further enhancing apoptosis towards the late reperfusion (Zhao, Velez et al. 2001). Neutrophil accumulation is followed by monocyte and lymphocyte infiltration which contribute to the reperfusion injury cascade (Wan, LeClerc et al. 1997, Yang, Day et al. 2006, Chen, Crispin et al. 2009).

1.3.6.4.5. Opening mitochondrial permeability transition pore (mPTP)

It has been increasingly recognised that opening of the mPTP, a latent non-specific pore within the inner mitochondrial membrane, plays a significant role in programmed cell death during early reperfusion (Crompton, Costi et al. 1987). Indeed, mPTP remain closed during ischaemia (Griffiths, Halestrap 1995) and under normal physiological conditions, but opens in response to rising ROS, increased intracellular calcium and rapid restoration of physiological pH at the onset of reperfusion (Griffiths, Halestrap 1993, Lapidus, Sokolove 1994). Consequently, it has been demonstrated that mPTP inhibitors, cyclosporine A, NIM811 or sanglifehrin A offer some degree of cardio protection during early reperfusion (Griffiths, Halestrap 1995, Griffiths, Halestrap 1993, Hausenloy, Duchen et al. 2003).

1.3.7. Hypothermia in STEMI

The knowledge of molecular level of ischaemia/reperfusion injury of the myocardium during AMI enabled a better understanding and appreciation of the potential therapeutic targets in minimising infarct size. Hypothermia is one such intervention which has been investigated extensively in animal models and more recently, in humans with an attempt to reduce infarct size related morbidity and mortality. One of the very first animal studies conducted the early 1990s showed a linear relationship between hypothermia and infarct size, demonstrating an 8% reduction in infarcted region for every 1°C drop in temperature from 42°C to 35°C (Chien, Wolff et al. 1994). Importantly, it has been demonstrated in experimental models that, pre-ischaemic hypothermia reduces infarct size by 100%, while peri-ischaemic hypothermia can reduce infarct size by up to 80% and the therapeutic benefit of hypothermia is negligible if instituted after reperfusion (Maeng, Mortensen et al. 2006, Gotberg, Olivecrona et al. 2008b, Erlinge 2011). In practice, pre-ischaemic cooling is however not applicable to humans as patients only present to hospital after the onset of STEMI. Hence, most of the research has been centred on the feasibility of hypothermia prior to reperfusion and its translation into clinical outcomes.

1.3.8. Role of Hypothermia in reperfusion injury from STEMI

The precise mechanism of hypothermia related cardio-protection in STEMI is less well understood, although some potential therapeutic targets at the molecular level have been proposed and investigated. Hypothermia has been shown to protect against myocardial stunning in rabbit model, where segment length shortening, used as a surrogate for cardiac contractility, was significantly increased in rabbit heart (Tissier, Couvreur et al. 2009), suggesting a reduction in myocardial stunning in those treated with hypothermia.

In another experimental model of coronary artery occlusion, hypothermia (32°C) initiated late during ischaemia but continued for 2 hours afters reperfusion was associated with significant reductions in necrotic zone and no-reflow zones (Hale, Dae et al. 2003) compared to control group maintained at 37°C, suggesting a therapeutic benefit in the microvascular circulation. This observation was reinforced by a separate observational animal study (Gotberg, Olivecrona et al. 2008a), where hypothermia before reperfusion was associated with significant reduction in infarct size and complete disappearance of microvascular obstruction.

Hypothermia has been shown to play a beneficial role in several pathways that form the hallmark of lethal reperfusion injury. At lower temperatures, ATP consumption was lower in experimental animal models of coronary artery occlusion (Simkhovich, Hale et al. 2004) resulting in reduced lactic acid production. This is expected to have protective effect on ATP dependent membrane ion channels, involved in maintaining intracellular calcium levels and pH homeostasis, which was confirmed on a further observational study (Inoue, Ando et al. 2003). More importantly, hypothermia has also been shown to maintain the integrity of myocardial cell membranes and myocardial mitochondrial function, which is integral in preserving cell function, ATP synthesis and reducing apoptosis (Ning, Xu et al. 1998, Ning, Chi et al. 2007, Huang, Chen et al. 2009). Additionally, hypothermia significantly reduced ROS, one of the key mediators of lethal reperfusion injury and showed preservation of mitochondrial function in animal models of ischaemia (Tissier, Chenoune et al. 2013). At macrovascular level, hypothermia has been shown to decrease post-ischaemic reactive hyperaemia at the onset of reperfusion (Olivecrona, Gotberg et al. 2007), which can be hugely beneficial in minimising reperfusion injury and preserving contractile function of the heart (Bopassa, Vandroux et al. 2006).

1.3.9. Methods of hypothermia induction in experimental STEMI

Whilst earlier animal studies used methods such as ice-pack surface cooling (Hale, Kloner 1997), infusing cold fluid directly into the pericardium (Dave, Hale et al. 1998) and cold fluid infusions into the epicardial coronary arteries (Otake, Shite et al. 2007), these techniques are innately complex and carry a high risk of complication, in addition to potentially interfering with PPCI. The introduction of endovascular cooling has been a revelation in this field, having been experimented in human size porcine models of coronary artery occlusion (Dae, Gao et al. 2002) and found to be feasible. The authors also demonstrated that hypothermia at 34°C induced by endovascular cooling in the inferior vena cava, resulted a significant reduction in infarct size in relation to area at risk (9% vs. 45%; $p<0.001$).

1.3.10. Early Hypothermia trials in the setting of STEMI in humans

The first prospective RCT was carried out with STEMI patients where 21 patients were randomised to endovascular cooling and 21 patients received standard PPCI with no temperature management (Dixon, Whitbourn et al. 2002). The authors reported that 95% patients in the hypothermia group reached the target temperature of 33°C and the mean temperature at reperfusion was 34.7°C. There were no major cardiovascular events (MACE) reported in the hypothermia group and a non-significant trend towards reduction in infarct size (2% vs. 8%; $p=0.80$) was observed on single-photon emission computed tomography (SPECT) scan. The authors concluded that hypothermia intervention was feasible in the setting of STEMI and that larger studies were required to verify the potential reduction in infarct size that was noted here. There were 2 further small sized cohort studies carried out to assess feasibility of hypothermia induction in the setting of STEMI. The LOWTEMP study (Kandzari, Chu et al. 2004) and the NICAMI study (Ly, Denault et al. 2005) reported that institution of hypothermia is feasible in patients undergoing PPCI for STEMI, although the surface cooling employed in the NICAMI study required a mean of 79 minutes to reach target temperature, which for the purposes of hypothermia induction is very slow prior to reperfusion with PPCI.

Two further relatively larger prospective RCTs were conducted with endovascular cooling and presented at the Transcatheter Cardiovascular Therapeutics conferences in Washington DC. The COOL-MI trial (O'Neill 2004) included 357 patients who were randomised to PPCI alone (n=180) or endovascular cooling for 3hrs + PPCI (n=177). There were no significant differences in infarct size measured by SPECT scan at 30days ($p=0.45$). A post hoc analysis of the study showed that patient presenting with anterior STEMI who reached 35°C or less prior to reperfusion, showed a 49% trend towards reduction in infarct size. The study group reported that the mean door to balloon time was extended by 18 minutes, but there was no significant difference in

MACE or death rates between the 2 groups. The ICE-IT trial (Grines CL 2004) recruited 228 STEMI patients and randomised them to PPCI (n=114) or endovascular cooling for 6 hours + PPCI (n=114). Again, there was no significant reduction in infarct size reported on SPECT scan at 30 days (p=0.14), although a post hoc analysis of patients presenting with anterior STEMI who reached a target temperature of <35°C prior to reperfusion, a more promising trend of 43% reduction in infarct size was observed (p=0.09). The mean door to balloon time was increased by about 10 minutes in patients receiving hypothermia, but there was no significant difference between MACE and death rates between the groups.

1.3.11. Timing, speed and duration of hypothermia

The findings of the COOL-MI and ICE-IT trials attenuated interest in hypothermia treatment in the setting of STEMI. The discovery of a potential beneficial impact of hypothermia in patients who reached target temperature of <35°C before reperfusion in reducing infarct size raised important questions about devising a more efficient system of inducing hypothermia. Indeed, only a small proportion of patients (about 30%) in the COOL-MI and ICE-IT trials reached a temperature of <35°C before reperfusion and earlier studies had already confirmed that hypothermia after reperfusion generates little or no impact on infarct size (Maeng, Mortensen et al. 2006, Gotberg, Olivecrona et al. 2008a, Erlinge 2011). Gotberg et al (Gotberg, Olivecrona et al. 2008a) showed that the combination of induction with 1 litre of cold saline followed by endovascular cooling was able to achieve target temperature of <35°C within 5 minutes and more importantly, it was associated with 43% reduction in infarct size compared to post-reperfusion hypothermia. In a further experiment, it was shown that 5 minutes of hypothermia prior to reperfusion, at the end of 40 minutes of normothermic ischaemia, delivered with a combination of intravenous cold fluid and endovascular cooling was associated with 18% reduction in infarct size in relation to area at risk (Gotberg, van der Pals et al. 2011). Furthermore, extending post-reperfusion hypothermia duration by an extra 45 minutes was not associated with additional reduction in infarct size, suggesting that hypothermia treatment can be withdrawn soon after reperfusion. This observation has important implications in clinical practice as it may potentially avoid extra resources that may otherwise need to be employed to look after patients undergoing hypothermia treatment. This study suggests that the hypothermic intervention could potentially be completed within the cardiac catheter laboratory with the patient transferred directly to coronary care unit without any additional invasive hypothermia management.

1.3.12. Contemporary TH clinical research in STEMI

The RAPID MI-ICE trial (Gotberg, Olivecrona et al. 2010) was designed as a pilot study to investigate the feasibility and effect of combination cooling (cold saline and endovascular cooling) on infarct size. Twenty STEMI patients were randomised to hypothermia + PPCI or standard PPCI alone. All patients in the hypothermia group achieved a temperature of <35°C with a mean 3 minute delay in door to balloon time (p=0.12). Despite similar ischaemia duration, the authors found that hypothermia was associated with significant 38% reduction in infarct size in relation to area at risk measured by cardiac MRI scan (p=0.041). Interestingly, the authors observed that there was also a trend towards less heart failure in the hypothermia group.

On the back of this strong performance, the CHILL MI study (Erlinge, Götberg et al. 2014) was designed as a multi-centre prospective RCT where 120 STEMI patients were randomised to hypothermia with cold fluid and endovascular cooling or standard PPCI. Unlike previous trials, the cooling duration after reperfusion was reduced to 1hr. The authors reported that the trial was feasible with a mean 9 minute increase in door to balloon time due to hypothermia intervention and 76% patients reached temperature <35°C prior to reperfusion. In the overall group, the primary end point of median infarct size relative to myocardium at risk was not significantly reduced. However, sub-group analysis showed that there was a significant 33% reduction in infarct size when patients presenting with anterior STEMI within 4 hours were cooled. The incidence of heart failure was significantly reduced in the hypothermia group at a mean 45 day follow-up (3% vs. 14%; p <0.05).

The pooled analysis of the ICE-IT and RAPID MI-ICE (Erlinge, Gotberg et al. 2013) showed a 24% reduction in infarct size as a percentage of the left ventricular myocardium (p<0.049) and for patients achieving <35°C prior to reperfusion, there was a significant similar reduction in infarct size for both anterior (33%, p = 0.03) and inferior STEMI (42%, p = 0.04). The combined analysis of the RAPID MI-ICE and CHILL MI study (Erlinge, Gotberg et al. 2015) showed that hypothermia resulted in 15% relative reduction in infarct size normalised to myocardium at risk (p=0.046). Patients with larger area of myocardium at risk (>30% of left ventricular volume) showed the most reductions in infarct size when treated with hypothermia (p=0.03).

In recent times, a different way of hypothermia induction using peritoneal lavage has been investigated (Nichol, Strickland et al. 2015). Despite demonstrating feasibility and the median temperature reached at perfusion being 34.7°C, there was no significant reduction in infarct size reported. Moreover, this study showed a higher incidence of

MACE in the hypothermia group primarily driven by a higher rate of stent thrombosis (11% vs. 0%).

1.3.13. Shivering and side-effects of hypothermia

One of the most challenging aspects of hypothermia induction and maintenance in the setting of STEMI is shivering in the conscious patients. The thermoregulatory centre in the brain has an involuntary reflex to systemic cooling and responds by reducing skin circulation and inducing shivering to raise core temperature. Shivering seems to most prominent between 35°C and 36°C, below which shivering becomes less prominent. The most important patient factors that determine shiver response to treatment are age and weight. Elderly and lean patients are easier to cool, whereas the shiver response seems to be more vigorous in young and overweight patients. One effective way of managing shivering is by applying surface counter-warming on the skin with warm blankets and hot air blankets such as Bair Hugger, as it has been shown that a 1°C drop in core temperature can be compensated for by a 4°C rise in skin temperature (Cheng, Matsukawa et al. 1995). In addition, pharmacological agents such as oral buspirone in combination with intravenous meperidine have been shown to act synergistically to suppress shivering without causing respiratory depression (Mokhtarani, Mahgoub et al. 2001). The combination of pharmacological agents and skin counter-rewarming has been used successfully in the vast majority of reported hypothermia STEMI trials involving conscious patients, with no studies reporting early termination due to cold intolerance or shivering (Dixon, Whitbourn et al. 2002, O'Neill 2004, Gotberg, Olivecrona et al. 2010, Nichol, Strickland et al. 2015).

Deeper hypothermia (<30°C) has been associated with QT interval prolongation, widening QRS complexes, ventricular fibrillation and reduced cardiac function (Polderman 2009, Tveita, Mortensen et al. 1994). However, mild hypothermia (up to 32°C) is not associated with electrical disturbance of heart rhythm (Grines CL 2004, Kandzari, Chu et al. 2004, Ly, Denault et al. 2005, Gotberg, Olivecrona et al. 2010, Testori, Sterz et al. 2013, Erlinge, Götberg et al. 2014, Blatt, Elbaz-Greener et al. 2015, Nichol, Strickland et al. 2015). Cardiac output has also been shown to drop by 30-40% during mild hypothermia, but this is compensated by a greater drop in metabolic rate by 50-65%, resulting in net improvement in demand and supply (Polderman 2009). In addition, hypothermia has been associated with reduced immune response, resulting in slightly higher risk of pneumonia (Polderman 2009) and therefore, shorter duration of hypothermia treatment is preferable.

The original research that is presented in this thesis concentrates on the three main areas that have been covered in the above introduction. The introduction summarises the following key areas which form the core of this thesis:

- The historical role and the current consensus on the use of TH in cardiac arrest in minimising hypoxic brain injury are discussed.
- The enormous psychological burden experienced by cardiac arrest survivors and their caregivers is highlighted and recent research suggesting that simple interventions could improve the QoL and its cost effectiveness is underlined.
- The role of TH in AMI as an adjunct to PPCI in minimising reperfusion injury of the myocardium and its potential role in future clinical practice is discussed.

1.4. Hypothesis of the study

The research within this thesis was conducted with to investigate the following hypotheses:

1. Rhinochill®, a trans-nasal cooling device is more efficient in inducing TH in patients successfully resuscitated from cardiac arrest than conventional Blanketrol.

2. Simple psychological interventions improve QoL and cognitive function in cardiac arrest survivors and their caregivers and can be delivered in a Tertiary Heart Attack Centre (HAC).

3. Simultaneous induction and maintenance of TH in conscious patients presenting with STEMI using an endovascular cooling device is feasible and safe and can be delivered with minimal delay in the delivery of PPCI.

2. Chapter 2: COOLCATH

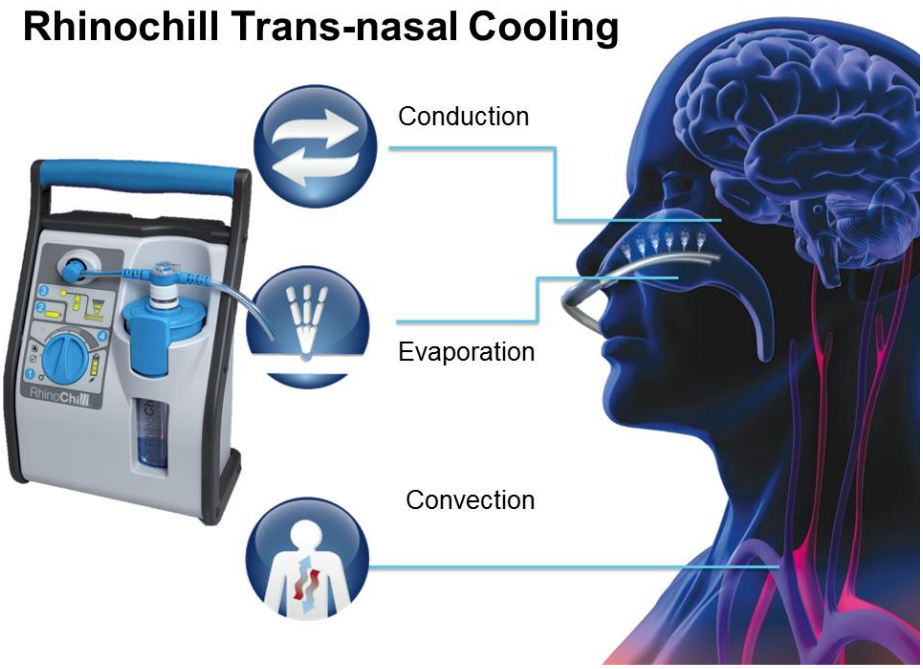
Early targeted brain COOLing in the cardiac CATHeterisation laboratory following cardiac arrest (COOLCATH)

2.1. Introduction

Temperature management has been shown to improve clinical outcomes in patients suffering OHCA (Bernard, Gray et al. 2002, Hypothermia after Cardiac 2002). Retrospective registry data demonstrated that delays in TH induction increases mortality (Mooney, Unger et al. 2011, Sendelbach, Hearst et al. 2012). More recent data from a large randomized trial has shown no difference in outcomes when comparing targeted temperature management (TTM) at 36°C or 33°C, suggesting the possibility that, prevention of fever following cardiac arrest could be an important mechanism by which neurological injury can be prevented (Nielsen, Wetterslev et al. 2013). However, in this latest study, delays in initiation of cooling (mean 130 minutes) and time to reach 34°C (mean 5 hours) could have offset any potential benefit that TTM at 33°C could offer in comparison to 36°C (Nielsen, Wetterslev et al. 2013, Polderman, Varon 2015).

Irrespective of whether methods are employed to reduce core body temperature or to prevent systemic pyrexia, the mortality rate and risk of permanent and disabling brain injury remains high in this patient group. In the TTM trial (Nielsen, Wetterslev et al. 2013), more than 50% patients in both treatment groups died or had poor neurological function at 180 day follow-up. The alarming rates of morbidity and mortality associated with cardiac arrest provide a large incentive for research into novel methods of treating this important group of patients.

Figure 2-1 An Illustration of the Rhinochill® device and its components



In practice, several modalities of hypothermia induction exist including cold saline infusion (Kim, Nichol et al. 2014), surface blankets (Don, Longstreth et al. 2009) and endovascular cooling (Gillies, Pratt et al. 2010). Earlier studies indicated that targeted brain cooling is more important in cerebral protection than whole body cooling (Busto, Dietrich et al. 1989) and associated with lesser side effects (Harris, Muh et al. 2009). Rhinochill® is a portable, intranasal cooling system that is capable of rapid targeted brain cooling (Figure 2.1), as demonstrated in jugular venous temperature recordings in animal models (Yu, Barbut et al. 2010). Thus, it may be able to reduce the risk of neurological injury associated with cardiac arrest (Castren, Nordberg et al. 2010, Sendelbach, Hearst et al. 2012, Busto, Dietrich et al. 1989). In addition to its innovative mode of action, its portability allows it to be applied to patients in confined spaces and to be used whilst transferring patients either from the field to the hospital, or between different departments within the hospital.

Coronary artery disease is the most common cause of cardiac arrest (Reichenbach, Moss et al. 1977, Davies 1992) and it is becoming increasingly common for these patients to be brought directly to HAC with cardiac catheter laboratory facilities for emergency PPCI. Although, ECG remains a key diagnostic tool by the bedside and provide invaluable information in any patient suspected of suffering a myocardial infarction as well as cardiac arrest setting, the clinical translation of a normal or non-ischaemic ECG does not always equate to unobstructed coronary artery in the setting

of a cardiac arrest and even myocardial infarction (Spaulding, Joly et al. 1997). Therefore if the clinical suspicion is high for a coronary event and transfer of patient to a HAC is not considered futile by the attending EMS for reasons such as poor prognosis, prolonged hypoxia, severe academia, then resuscitated patients should be considered for emergency revascularization. In a relatively small observational study, Sunde et al demonstrated that an aggressive post resuscitation protocol aimed at supporting vital organs by a combination of TH, PPCI, control of haemodynamics, blood glucose, ventilation and seizures resulted in 56% survival to hospital discharge with favourable neurological recovery compared to 26% in historical control group, who received standard care (Sunde, Pytte et al. 2007). Similar findings with improved survival to hospital discharge (64% v 39%, $p<0.05$) and favourable neurological outcomes (57% v 29%, $p<0.05$) have also been reported by combining TH and early coronary angiography by Stub et al (Stub, Hengel et al. 2011). The Parisian Region Out of Hospital Cardiac Arrest (PROCAT) registry demonstrated that 96% patients with STEMI and 58% patients without STEMI had at least one significant coronary artery lesion and early PCI was associated with significantly improved survival to hospital discharge (Cronier, Vignon et al. 2011, Dumas, Cariou et al. 2010). Hence, the European Society of Cardiology revised their guideline to recommend early PPCI for survivors of cardiac arrest, irrespective of their initial post-arrest ECG if no obvious non-coronary cause of arrhythmia is present (Noc, Fajadet et al. 2014, Authors/Task Force members, Windecker et al. 2014).

Whilst there is evidence to suggest temperature management in combination with PPCI result in better clinical outcomes for survivors of cardiac arrest, the primary survey to ensure adequate airway protection, ongoing monitoring of ventilation by expert anesthetist, correction of any simple reversible causes, such as electrolyte imbalance should also be done simultaneously to ensure a safety for the patient at all times. Therefore, it goes without saying that the treatment of the cardiac arrest survivor is in the hands of a multi-disciplinary team with different specialist skillset who work together as a team and communicate effectively.

In this randomized study, we test the hypothesis that Rhinochill® device is more efficient in TH induction than surface cooling Blanketrol® for cardiac arrest patients presenting to a HAC, in whom an underlying coronary etiology is suspected. The safety of Rhinochill® application is also closely monitored as it is an additional procedure that is implemented in a busy cardiac catheter laboratory environment.

2.2. Methods

2.2.1. Study design

Early targeted brain cooling in the cardiac catheterisation laboratory following cardiac arrest (COOLCATH) was designed as a single centre, prospective, open labelled, randomised controlled clinical trial to compare the efficiency of Rhinochill® intranasal cooling device (BeneChill International AG) in TH induction to our standard surface-cooling protocol with the Blanketrol® III device (Cincinnati Sub-Zero Products). The study received ethical approval from the National Research Ethics Service (Ref: 12/EE/0472). An independent data and safety monitoring committee reviewed the data and performed a comprehensive interim analysis. An independent data monitor performed regular data checks to ensure accuracy and completeness of data collection and strict adherence to the study protocol.

2.2.2. Patients

74 adult patients suffering cardiac arrest, irrespective of any specific initial presenting heart rhythm with ROSC after resuscitation were enrolled between January 2013 and November 2014. The main exclusion criteria were cardiac arrest caused by trauma, head injury, massive haemorrhage, patients without a definitive airway and patients who were already hypothermic on arrival (< 34°C). The full list of inclusion and exclusion criteria can be found in Appendix 1.1. As eligible patients were unconscious on admission, initial written informed consent was obtained from a legal surrogate in accordance with the Helsinki declaration (The Helsinki Declaration of the World Medical Association (WMA). Ethical principles of medical research involving human subjects. 2014). However, if the patient made sufficient neurological recovery and demonstrated mental capacity, a further informed consent was obtained from the patient.

2.2.3. Randomisation

Patients were admitted directly to the HAC by the ambulance crew, bypassing the local emergency department for emergency catheter laboratory based diagnostics and therapies. Patients fulfilling the selection criteria were enrolled and randomised (by allocation of a random sealed envelope) in the cardiac catheter laboratory to receive TH induction by either Rhinochill® or Blanketrol® III cooling blanket in a 1:1 manner. Randomisation was pre-performed by the local research and development office using a computer generated assignment sequence dictating envelope allocation.

2.2.4. Trial intervention

Baseline tympanic temperatures were recorded immediately after randomisation as a surrogate for brain temperature and an oesophageal temperature probe inserted

simultaneously to measure core body temperature in both treatment arms. The oesophageal temperature recordings were taken as a surrogate for core body temperature. Both tympanic and oesophageal temperatures were measured during TH induction every 10 minutes up to 5 hours. It was not in our study protocol to administer any additional TH inducing agent and therefore, no cold intravenous saline was given to patients in either group.

Rhinochill® (BeneChill International AG)

The RhinoChill® is the only CE marked intranasal evaporative cooling system (National Institute of Clinical Excellence February 2014) that is capable of inducing TH in cardiac arrest patients. In patients randomised to the Rhinochill® group, TH was initiated in the cardiac catheter laboratory by advancing the intranasal cannulae into each nostril, and switching on the Rhinochill® device to deliver cold vapour into the nasal cavity. The cooling continued throughout the initial induction period, during PCI if performed, and patient transfer to the intensive care unit (ICU), where maintenance cooling by conventional Blanketrol® III could be commenced and Rhinochill® discontinued when the core temperature reached ≤ 34°C. As mentioned earlier, the portability of the Rhinochill® allowed for continuous delivery of TH during transfer between hospital departments and minimised temperature fluctuations.

Blanketrol® cooling system (Cincinnati Sub-Zero Products)

Patients allocated to Blanketrol® arm received TH induction in the catheter laboratory by application of surface cooling blankets covering the whole body but sparing a small area in the femoral region to allow arterial access if needed for coronary intervention. Unlike the Rhinochill® device, the Blanketrol® cooling machine needed to be switched off during patient transfer from the catheter laboratory to the ICU.

2.2.5. General patient management

Patients in both intervention arms were maintained at <34°C for 24 hours with active sedation and protected airway management. The trust protocol for active sedation (Propofol infusion at 0.3 to 4.0 mg/kg/hr, Morphine Sulphate infusion at 1-2mg/hr) and shiver prevention (Atracurium at 5mg/hr) was followed for all enrolled patients. After the maintenance phase (24hrs), patients were gradually rewarmed to 36°C in hourly increments of 0.25–0.5°C and sedation weaned to allow the patients to regain consciousness. If patients were in cardiogenic shock, intra-aortic balloon pumps were inserted at the discretion of the treating physician in the cardiac catheter laboratory and inotropes infusion was administered in the ICU (Table 2.1). The patient's next of kin was kept informed about the progress at all times and members of the research team

explained the treatment received by the patient, including participation in the research, at a time that was convenient for the family or close friend. This was also an opportunity to address any concerns and answer questions about any uncertainties raised by the next of kin.

2.2.6. Outcome measures

Primary outcomes

Primary outcome measures were time to reach tympanic ≤34°C from randomisation as a surrogate for brain temperature and oesophageal ≤34°C from randomisation as a measurement of core body temperature.

Secondary outcomes

Secondary outcomes included rate of cooling in the first hour, length of stay in ICU, hospital stay, neurological recovery and all-cause mortality at hospital discharge. The neurological assessment was made using the cerebral performance category (CPC) scale (Jennett, Bond 1975). The CPC scale ranges from 1 to 5, with 1 indicating an excellent recovery and 5 signifying brain death (Appendix 1.2).

Adverse events were reported and documented as either related to the study intervention or related to the presenting medical condition by the safety monitoring committee. All significant events were reported to the trial sponsor and a written report sent to the responsible ethics committee for acknowledgement. Decisions relating to patient care, other than the method of TH induction, such as withdrawal of active treatment, were taken at the discretion of the treating physician, who was blinded to the trial intervention. Initial temperature data collection and progress of patients' health were monitored daily by the research team, who were not blinded due to the nature of the study intervention. If patients were discharged from hospital within 30 days, then a telephone call was made to ascertain the patient's physical health status.

2.2.7. Statistics

Statistical analysis was conducted in a modified intention to treat population, defined as all randomly assigned patients excluding those withdrawn from the study due to a delayed diagnosis or meeting one of the exclusion criteria. Descriptive statistics are presented for continuous, as well as categorical variables as mean (standard deviation) and tabulated by treatment. Analyses were performed using the computer program R (Gentleman Robert 2013). The time taken to reach target temperature (≤34°C),

duration of ventilation hours, ICU stay and hospital stay were expected to have a non-normal distribution and so the means for the two groups were compared using a two-sample permutation t-test with bootstrap 95% confidence limits for the difference between the means. The CPC between the 2 groups were described in a contingency table and compared using Fisher's exact test. For statistical significance, a p-value of 0.05 was adopted. The analysis was performed by an independent statistician.

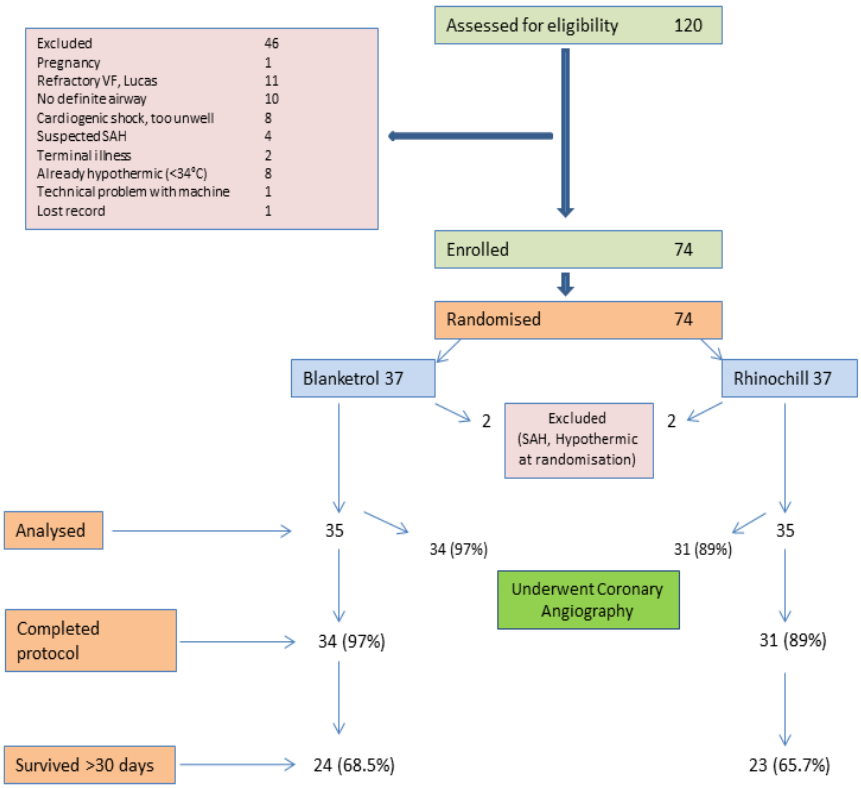
2.3. Results

2.3.1. Patients

A total of 120 cardiac arrest patients were screened for enrolment, out of which 46 patients were excluded for not meeting selection criteria. All 74 eligible patients were enrolled, of which 37 were allocated to Blanketrol® and 37 were allocated to Rhinochill® therapy.

Exclusions after enrolment: There were 4 exclusions from patients enrolled: 2 patients in the Blanketrol® arm and 1 patient in the Rhinochill® arm were found to have sub-arachnoid haemorrhage on subsequent CT scan following randomisation and 1 patient in the Rhinochill® arm was already hypothermic (≤34°C) at randomisation (Figure 2.2).

Figure 2-2 Flow of participants from recruitment to analysis



Coronary angiography: Although, all patients were received and enrolled in the cardiac catheter laboratory, 4 patients allocated to Rhinochill® did not undergo coronary angiography at the physician's discretion (2 patients had pre-existing 3 vessel coronary artery disease, not amenable for PCI and 2 patients were haemodynamically very unstable for catheter laboratory admission). One patient randomised to Blanketrol therapy did not undergo coronary angiography as the admitting physician reported that there was no clear ST elevation on ECG. This is in contrast to latest recommendation by the ESC as discussed in the introduction (Authors/Task Force members, Windecker et al. 2014). However, the revision on the ESC guideline was published after our trial initiation.

2.3.2. Adverse Events

There were no trial related adverse events or serious adverse events in patients randomised to Blanketrol®. One patient allocated to Blanketrol® TH induction was withdrawn prematurely due to development of retroperitoneal bleed, unrelated to trial intervention and required surgical intervention equating to 97% success rate of TH device application in this group.

There were 4 trial related adverse events in patients treated with Rhinochill® – 2 patients (5.7%) experienced epistaxis and 2 patients (5.7%) experienced white nose tip. These adverse events recovered without any further intervention upon termination of Rhinochill® induction phase. Four patients randomised to Rhinochill® therapy required early termination of trial intervention and crossed over to Blanketrol® for TH induction and maintenance equating to a success rate of 89% for device employment within the catheter laboratory in this group. Only 1 of these incidents was trial related: epistaxis (n=1) and the others were unrelated events: acute respiratory distress (pulmonary oedema and peri-arrest gastric aspiration; n=2) and technical difficulties with the device as it ran out of coolant (n=1).

There were no exclusions due to withdrawal of consent. All enrolled patients were followed up according to trial protocol. The two groups had similar baseline characteristics prior to randomisation including the mean first temperature recordings (Table 2.1).

Table 2-1 Baseline Characteristics of patients in Blanketrol and Rhinochill® group.

Values are presented as mean (standard deviation) and n (%); p>0.05 for all comparisons

	Blanketrol	**Rhinochill®**
Age - mean (SD)	62.1 (12.5)	63.5 (12.3)
Male sex – n (%)	26 (74.3)	30 (85.7)
Body Surface Area - mean (SD) in m^2	1.93 (0.29)	2.03 (0.22)
Cardiac History - n (%)	9 (25.7)	16 (45.7)
Bystander CPR - n (%)	22 (62.9)	24 (68.6)
Ventricular fibrillation - n (%)	33 (94.3)	32 (91.4)
Time of untreated cardiac arrest - mean (SD) in mins	5.06 (11.7)	2.83 (4.7)
Recurrence of cardiac arrest - n (%)	13 (37.1)	16 (45.7)
Shocks - mean (SD)	2.89 (2.23)	3.88 (4.56)
Median Time to ROSC from cardiac arrest in mins (IQR)	21 (15-35)	20 (10-36)
Percutaneous intervention - n (%)	24 (68.6)	19 (54.3)
Inotropes - n (%)	12 (34.3)	10 (28.6)
Intra-Aortic Balloon Pump - n (%)	12 (34.3)	12 (34.3)
Mean 1st Tympanic temperature (^{0}C)	**35.3 (0.80)**	**35.3 (1.0)**
Mean 1st Oesophageal temperature (^{0}C)	**35.3 (0.70)**	**35.1 (1.0)**

2.3.3. Primary Outcomes: TH induction

From randomisation, the mean time-to-target tympanic temperature (≤34°C) as a surrogate for brain temperature was 75 minutes (median 45; range: 0-240) in the Rhinochill® arm in comparison to 107 minutes in the Blanketrol® arm (median 70; range: 0-366) (*p=0.101*).

The mean time to oesophageal temperature (≤34°C) was 85 minutes (median 50; range 0-270) in the Rhinochill® arm compared to 115 minutes (median 80; range 10-366) in the Blanketrol® arm from randomisation (*p=0.151*).

The results are summarised in Table 2.2 and shown in graphical form in figure 2.3.

Table 2-2 Temperature data of the two groups:

Comparison of group means using two-sample permutation t-tests and bootstrap 95% confidence limits

	Blanketrol	**Rhinochill®**	**Residual standard deviation**	**P value**
	Mean	mean		
Outcome measure				
Time to tympanic temp ≤34^{0}C from randomisation	107.2	75.2	78.4	0.101
	(n = 32)	(n = 33)		
Time to oesophageal ≤34^{0}C from randomisation	114.9	84.7	83.4	0.151
	(n = 33)	(n = 32)		
Tympanic temperature drop (^{0}C in first hr)	0.935	1.75	0.897	**< 0.001**
	(n = 31)	(n = 30)		
Oesophageal temperature drop (^{0}C in first hr)	0.904	1.148	0.573	0.152
	(n = 24)	(n = 23)		
Tympanic temperature slope (^{0}C in first hr)	-0.808	-1.615	0.867	**< 0.001**
	(n = 35)	(n = 35)		
Oesophageal temperature slope (^{0}C in first hr)	-0.823	-1.21	0.829	0.054
	(n = 35)	(n = 32)		

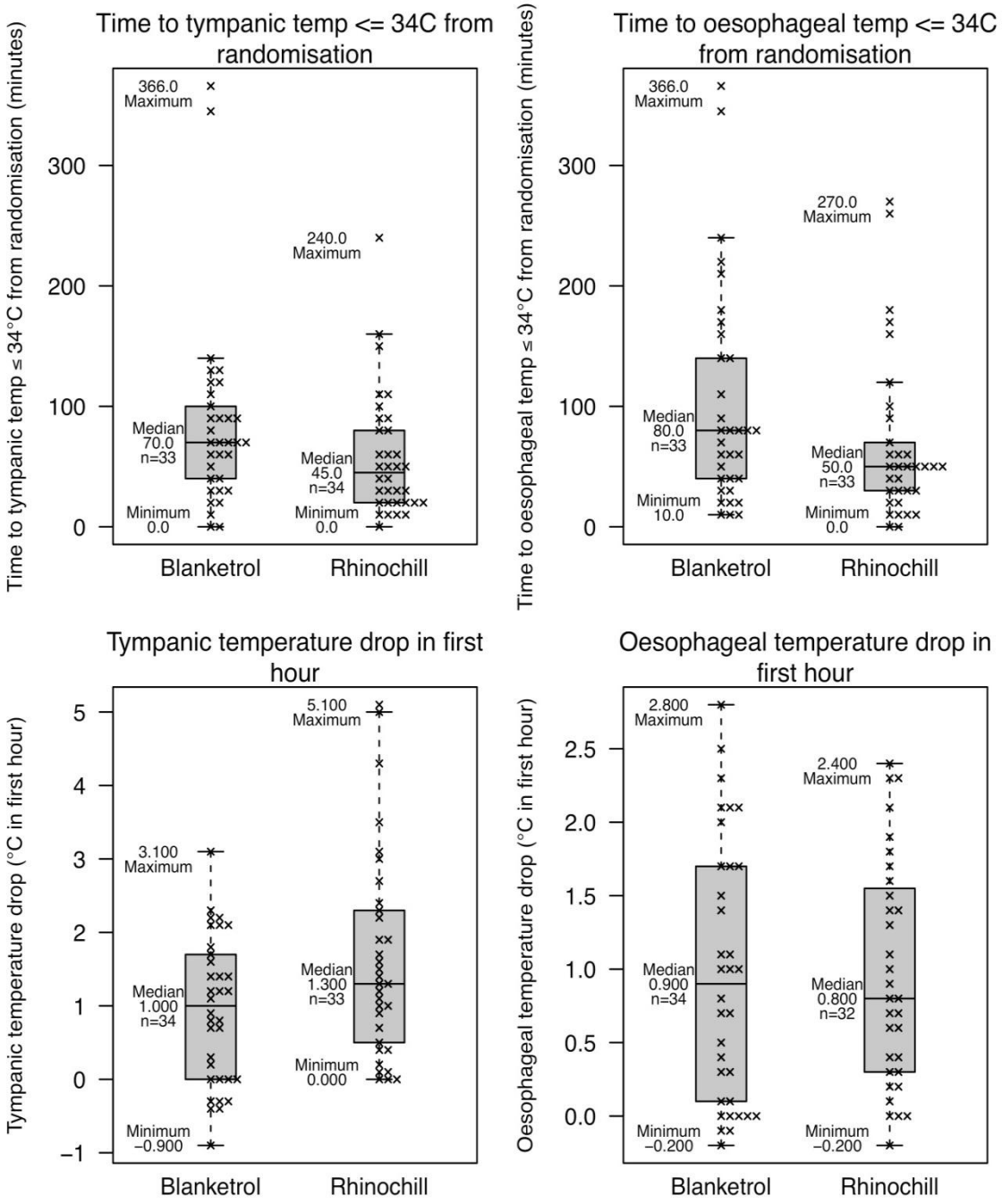
2.3.4. Secondary outcomes

In the first hour of cooling, the tympanic temperature dropped significantly more quickly in the Rhinochill® arm than the Blanketrol® arm (1.75°C vs. 0.94°C; p<0.001) (Table 2.2). There were no significant differences between length of ventilation hours, stay in ICU, duration of hospital stay, and CPC 1-2 outcomes between the 2 groups (Table 2.3 and Table 2.4).

There were no significant differences in survival to hospital discharge between patients treated with Rhinochill® and Blanketrol® therapy (65.7% vs 68.6% respectively, Table 2.5). This equates to a combined survival to hospital discharge of 67.1%.

Figure 2-3 Efficiency of Blanketrol and Rhinochill® in reaching target temperature

Medians and ranges of outcome measures for patients in Blanketrol and Rhinochill® arm



2.4. Discussion

Rhinochill® did not achieve statistical superiority in achieving target temperature (≤34°C) from randomisation, although there is trend towards faster cooling with Rhinochill® therapy in both tympanic and oesophageal temperature recordings as surrogate for brain temperature and core body temperature respectively. Rhinochill® induction achieved statistically significant tympanic temperature reductions compared to Blanketrol® during the first hour of cooling suggesting more rapid and focused brain cooling (Table 2.2).

Table 2-3 Length of ventilation hours, duration of stay in ICU and hospital: comparison of group means using permutation t-tests and bootstrap 95% confidence intervals

	Blanketrol	**Rhinochill®**	**Residual standard deviation**	**Difference:**	**P value**
	mean	**mean**		**Rhinochill® – Blanketrol**	
Outcome measure				**(95% confidence limits)**	
Length of ventilation (hours)	100.7	218	280.9	117.2	0.079
	(n = 35)	(n = 35)		(-12.3, 254.2)	
Length of ICU stay (hours)	145.6	210.5	169.3	64.9	0.122
	(n = 34)	(n = 34)		(-14.5, 142.1)	
Length of hospital stay (hours)	447.9	508.9	656.9	61	0.709
	(n = 35)	(n = 35)		(-239.9, 381.9)	

Table 2-4 Cerebral performance category (CPC): comparison of percentages using Fisher's Exact Test

	Blanketrol	**Rhinochill®**	**Difference:**	**P value**
Outcome category			**Rhinochill® – Blanketrol**	
			(95% confidence limits)	
CPC (1-2) at ICU discharge	51.40%	45.70%	-5.7	0.811
	(18/35)	(16/35)	(-27.5, 16.9)	
CPC (1-2) at hospital discharge	57.10%	54.30%	-2.9	1
	(20/35)	(19/35)	(-24.8, 19.5)	

Table 2-5 Comparison of survival to hospital discharge between 2 groups

	Blanketrol	**Rhinochill®**	**Overall**
Survival to hospital discharge	68.60%	65.70%	67.10%
	(24/35)	23/35	(47/70)

The cooling times in both groups in this trial are impressive when one compares to other trials carried out in this field (Hypothermia after Cardiac 2002, Kim, Nichol et al. 2014, Nielsen, Wetterslev et al. 2013). While we have shown that an aggressive cooling strategy in the catheter laboratory can result in a mean time-to-target tympanic temperature (≤34°C) of 75 minutes and 85 minutes with Rhinochill® and Blanketrol® respectively, there is still a 1-2 hour period in the field and during transfer to the HAC where no brain cooling is initiated. It may be that even earlier and even more aggressive targeted brain cooling is required to show a significant survival and neurological improvement as compared to TTM. The PRINCESS trial that is currently recruiting in Europe will help to answer this question, as to whether pre-ROSC targeted brain cooling can improve cardiac arrest outcomes (Nordberg, Taccone et al. 2013) and if successful, a future large scale randomised controlled study can be designed to compare intra-arrest cooling and TTM protocol at 36°C.

Irrespective of the study intervention, COOLCATH demonstrates a combined survival rate of over 67.1% at hospital discharge in both groups, which is better than previously reported trials with similar study designs (Table 2.5) (Castren, Nordberg et al. 2010, Mooney, Unger et al. 2011, Bernard, Gray et al. 2002). Sub-group analysis of patients presenting with initial shockable rhythm demonstrates a combined survival rate was 75.3% which is favourable to previously reported data (Kim, Nichol et al. 2014, Don, Longstreth et al. 2009). This could be partly explained by simultaneous coronary intervention and early TH induction in the catheter laboratory, providing maximal myocardial salvage and neuro-protection in these patients. TH has been shown to have beneficial effects on left ventricular myocardial salvage in animal models of coronary artery occlusion and reperfusion (Dae, Gao et al. 2002, Gotberg, Olivecrona et al. 2008a, Erlinge 2011). Studies of TH in humans presenting with STEMI have so far not established significant clinical benefit (Erlinge, Götberg et al. 2014, Erlinge, Gotberg et al. 2013, Dixon, Whitbourn et al. 2002). However, a recent multi-centre RCT (Erlinge, Götberg et al. 2014) demonstrated a 33% reduction in infarct size if TH was administered within 4 hours of symptom onset in patients with anterior STEMI, and also a reduction in incidence of heart failure was noted in this group. Although, some basic information was collected about initial myocardial damage, including measurement of troponin enzyme and an assessment of the left ventricular function is routinely measured by transthoracic echocardiogram; our study was not designed to answer questions regarding myocardial salvage with different TH induction methods.

Our trial has limitations. In retrospect, the sample size was not sufficient to detect a difference in the primary outcome measure. A post hoc calculation would suggest that a minimum of 192 patients would be required to have 80% power to detect a

statistically significant difference in the time to reach ≤34°C from randomisation. Secondly, TH was only initiated when the patients were admitted to hospital but ROSC was usually achieved at the site of cardiac arrest. Therefore, valuable time is lost during patient transfer, when no TH is offered to patients, and neurological damage is inflicted. Thirdly, tympanic temperature recordings were taken as a surrogate marker of brain temperature. Whilst earlier studies reported a close correlation between tympanic temperature recordings and brain temperature (Mariak, Lewko et al. 1994), other studies have challenged this concept (Kirk, Rainey et al. 2009). Magnetic resonance spectroscopy (Corbett, Laptook et al. 1997) and other novel methods of measuring brain temperature can be explored in future trials. Fourthly, the nature of the intervention used meant that the trial was unblinded to some of the treating medical team, which may introduce some bias. Finally, patients were followed up to hospital discharge, which may not give us adequate information regarding neurological recovery and mortality following a cardiac arrest.

2.5. Conclusions

Rhinochill® can be applied safely in the cardiac catheter laboratory for the vast majority of patients undergoing emergency PCI following cardiac arrest and during transfer to ICU. Its portability, ease of use and non-intrusive nature make it user friendly for cardiac catheter laboratory use. The combination of aggressive catheter laboratory cooling and urgent coronary revascularisation in a specialist cardiac unit resulted in a mean overall trial survival rate to hospital discharge of 67.1%. In this study population, Rhinochill® did not achieve better efficiency in TH induction compared to Blanketrol® surface cooling and there were no differences in clinical outcomes between the 2 groups. There is, however, a non-significant trend in favour of Rhinochill® that potentially warrants further investigation with a larger trial. If such a trial was to show a statistically significant advantage, then future research would be required to determine whether earlier and more rapid targeted brain hypothermia induction improves neurological outcome and mortality in patients presenting with cardiac arrest.

Declaration of interest

Rhinochill® equipment and monitoring support were provided by Benechill GmbH.

3. Chapter 3: CARE

CARE: Care after Resuscitation – An observational study to assess the impact of simple psychological intervention on the quality of life and cognitive function of cardiac arrest survivors and caregivers

3.1. Introduction

In the UK, the incidence of cardiac arrest is approximately 30,000 per year (Berdowski, Berg et al. 2010). Better access to early chain of survival and aggressive treatment of underlying cause has translated to better cardiac arrest survival rates (10-32%) (Watson L: Virdi G, Fothergill R 2012). Recent studies have shown that, survivors are living with the psychological consequences of cardiac arrest event even months after the index presentation (Saner, Borner Rodriguez et al. 2002, Moulaert, Verbunt et al. 2009). A large proportion of these survivors, between 25 to 50%, experience cognitive impairment, emotional problems, fatigue, difficulty in performing daily activities and perceive a poor quality of life (Moulaert, Verbunt et al. 2009, Wachelder, Moulaert et al. 2009). These experiences can have direct negative implications on their ability to reintegrate into society including relationship within family and return to work if appropriate. Caregivers of cardiac arrest survivors may experience both physical and psychological strain through witnessing the cardiac arrest itself and adapting to life with the cardiac arrest survivor (Pusswald, Fertl et al. 2000, Wachelder, Moulaert et al. 2009).

At Essex CTC, a retrospective overview of current practice demonstrated that the conventional psychological support arrangements for cardiac arrest survivors and their caregivers were inadequate. A recently conducted RCT at the CTC suggested overall survival to hospital discharge rates of 67.1% amongst patients presenting after cardiac arrest (Islam, Hampton-Till et al. 2015). Of the 750 PPCI performed annually at the CTC, approximately 100 admissions are accounted by OHCA patients. Therefore, a significant proportion of these patients are expected to survive and live with the unseen consequences of the cardiac arrest.

Recently, a large RCT conducted in the Netherlands, have shown significantly improved quality of life in cardiac arrest survivors receiving psychological support from health care professionals (Moulaert, van Heugten et al. 2015). It has also shown better

socio-economic benefit on patients receiving intervention compared to control groups (Moulaert, Goossens et al. 2016).

On the basis of this strong evidence, care after resuscitation (CARE) study was designed to document the burden of psychological problems in cardiac arrest survivors and caregivers and to investigate if simple psychological intervention can improve their QoL and cognitive function in the short term.

3.2. Study design and methods

CARE was set up as a single centre non-randomised placebo controlled trial, investigating early psychological support for cardiac arrest survivor and caregivers. The study was registered with the institution of clinical trials (NCT02275234) and ethics approval was obtained from National Research and Ethics Service (14/EE/1019). The study was carried out in 2 phases using 2 groups of participants. The focus of the first group was to establish the residual psychological burden at a mean of 6 months after cardiac arrest, who received standard care. In the second group, simple psychological interventions were introduced from the outset to see if they made an impact on psychological wellbeing and cognitive function of the participants.

3.2.1. Setup

The CTC is the regional tertiary cardiac centre, serving a large population in the east of Essex with approximately 100 emergency admissions with out-of-hospital cardiac arrest. A recent study has confirmed that, the short term survival rate of patients admitted with cardiac arrest are in the region of 67.1% in this centre (Islam, Hampton-Till et al. 2015) and therefore, any potential benefit of the CARE study would be available to a significant proportion of cardiac arrest survivors and their caregivers in this region.

3.2.2. Participants and study materials

Consecutive patients were recruited from hospital registry of cardiac arrest admissions. Inclusion criteria for the study were English speaking; cardiac arrest survivors aged 18 years or older, with good neurological recovery - CPC of 1-2 (Jennett, Bond 1975) and their caregivers. Exclusion criteria were cardiac arrest survivors with poor neurological recovery (CPC 3-5) with a poor prognosis (assessed by the clinical team) (Appendix 1.2). In this study, caregiver was defined as a family member or a close friend, who had the most connection with the patient during the initial presentation and recovery. There were no additional selection criteria for caregivers. It was not obligatory for a survivor to assign a caregiver to be included in the study.

The study assessment team consisted of a research fellow, a cardiologist, a clinical psychiatrist, a senior intensive care nurse with specialist interest in cardiac rehabilitation. Psychological wellbeing, including quality of life, was assessed by RAND SF36 questionnaire (RAND as part of the Medical Outcomes Study) and cognitive function was assessed by MOCA (Julayanont, Tangwongchai et al. 2015) and COGFAIL questionnaires (Broadbent, Cooper et al. 1982) (Appendix 1.3). The same assessment tools were used for both groups of patients and caregivers.

3.2.3. Group 1 (assessment of standard care)

20 cardiac arrest survivors and their caregivers were invited to attend a one-off cardiac arrest clinic at an average of 6 months after the index event. They received standard treatment and follow-up after cardiac arrest. The study objectives were explained and an informed consent obtained. An assessment of their psychological wellbeing and cognitive function were made. Patients and/or caregivers exhibiting signs or symptoms of severe depression or post-traumatic stress were referred to our team psychiatrist for further management. This additional follow-up was beyond the remit of the study protocol and the impact of this specialist service was not evaluated.

3.2.4. Group 2 (intervention group)

A further 20 cardiac arrest survivors and their caregivers were identified during index admission to the cardiac catheter laboratory at the CTC. If they met the selection

criteria, patients and their caregivers were approached to discuss the study objectives and informed consent obtained. Baseline assessments of quality of life and cognitive function made. They were then offered simple psychological interventions as follows:

1. Detailed information leaflet for patient and caregivers, explaining the mechanism and consequences of cardiac arrest, how to adapt with challenging circumstances and when to seek help (Appendix 1.4).
2. Immediate referral to a clinical psychiatrist on recognition of moderate to severe depression or signs of post-traumatic stress disorder
3. Dedicated telephone helpline on discharge for patients and caregivers to get direct access to a health care professional to discuss any clinical or psychological challenges during recovery.
4. Attendance at a focused cardiac arrest clinic with health care professionals, where a physical health check and psychological wellbeing was evaluated and managed appropriately

At 6 months after the index event, patients and caregivers were then re-invited to attend an outpatient clinic, where a re-assessment of quality of life and cognitive function was made using the same assessment tool to see the impact of the aforementioned interventions.

3.2.5. Outcomes

The primary outcome of this study was to establish if simple psychological interventions improved quality of life perceptions in patients and caregivers in the short term. The secondary outcome measures were to assess impact of simple psychological intervention on cognitive function of cardiac arrest survivors and caregivers. During consultations, the psychiatrist identified participants with moderate to severe depression, PTSD and offered them further appointments. These additional data about prevalence of depression, PTSD, psychiatry follow up and return to work were also documented but not measured as an outcome for this study.

3.2.6. Statistical analysis

Baseline characteristics between Group 1 and Group 2 (Table 3.1) are compared using descriptive statistics. The baseline and 6 month data in Group 2 (intervention group) were compared using the total scores from the three questionnaires (SF36, MOCA, and Cognitive Failures) using a paired sample t-test, at a 5% significance level and 95% confidence limits were obtained for the change in means of the scores using a

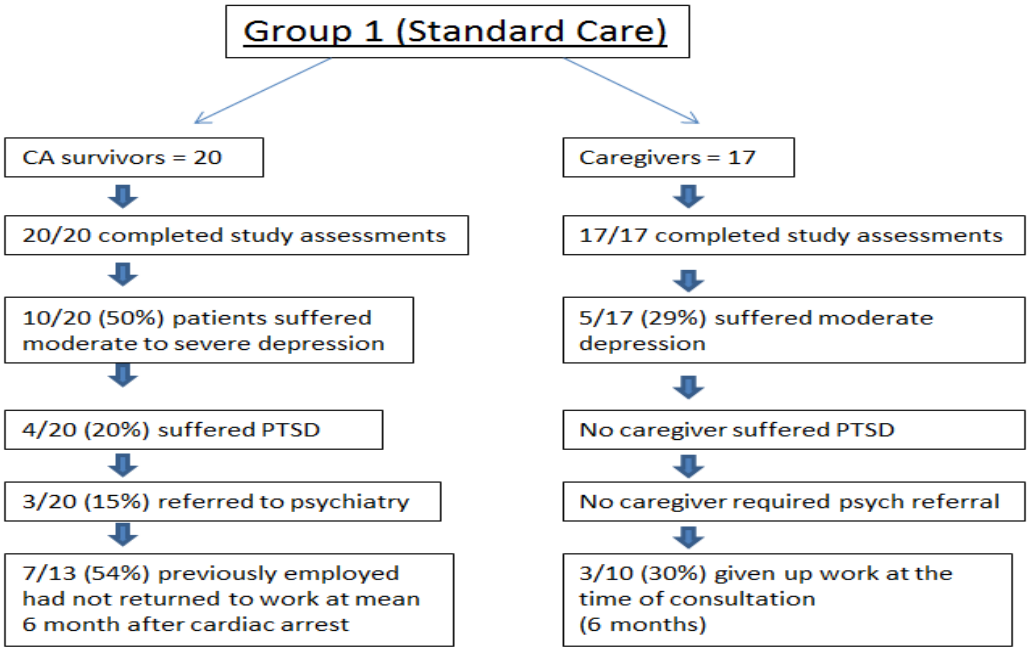
bootstrap approach. Group 2 (intervention) assessments at 6 months was then compared with assessments of Group 1 patients (standard care) using unpaired t-test at a 5% significance level and 95% confidence limits were obtained for the difference between the means of the scores using a bootstrap approach. The computer software SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) was used to analyse the data.

3.3. Results

3.3.1. Patient flow

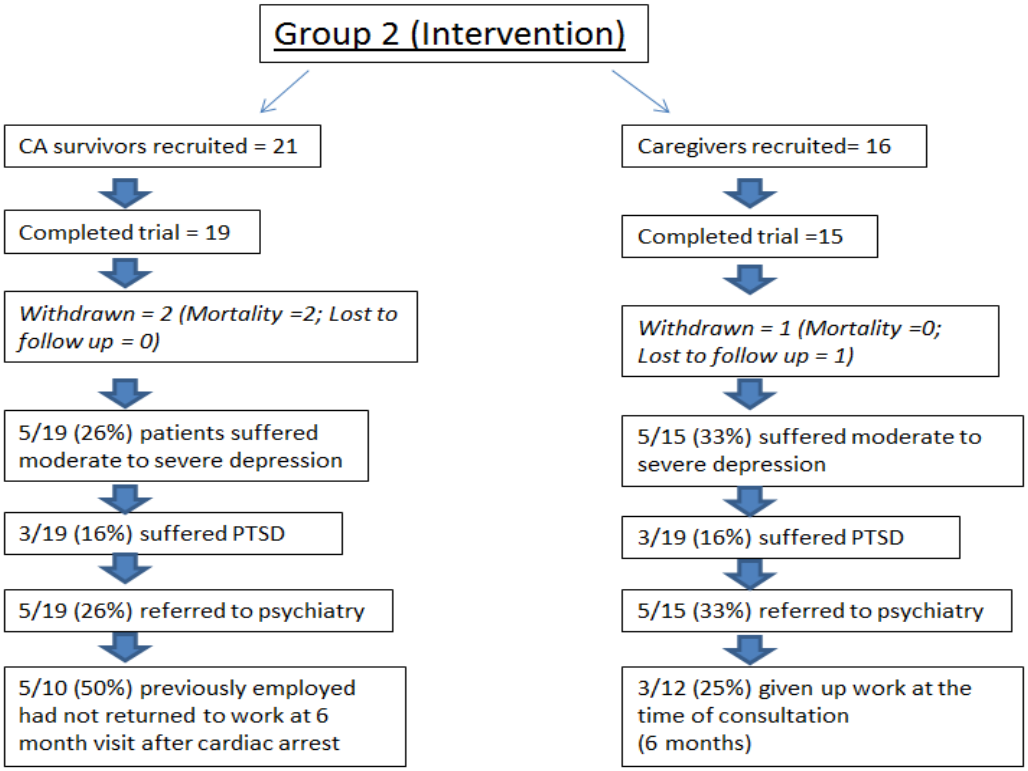
The flow of patients in Group 1 and Group 2 are shown in Figure 3.1 and Figure 3.2 respectively. As demonstrated, 50% patients in Group 1 were still suffering from moderate to severe depression and 20% suffered from PTSD, out of which 15% warranted referral to our team psychiatrist. Of the caregivers in Group 1, 29% suffered moderate depression but none required referral to psychiatry services.

Figure 3-1: Group 1 patient and caregiver flow chart



Two patients in Group 2 were withdrawn from the study due to mortality (unrelated to participation in the study) and 1 caregiver was lost to follow up at 6 months. In Group 2 patients, 26% suffered moderate to severe depression, 16% experienced PTSD and 26% required referral to psychiatry. Of the caregivers, 33% suffered moderate to severe depression, 16% experienced PTSD and 33% required psychiatry referral. The unemployment rates at 6 month follow-up were similar in both groups for patients and caregivers.

Figure 3-2: Group 2 patient and caregiver flow chart



3.3.2. Baseline demographic data

The baseline demographic data for patients in Group 1 and Group 2 are shown in Table 3.1. Despite being a non-randomised controlled trial, there was no notable difference between the 2 groups of patients from descriptive statistics.

Table 3-1: Baseline demographics of patients in Group 1 and Group 2;

CV = cardiovascular, PCI = percutaneous intervention, CABG: coronary artery bypass grafting

	Group 1 (n=20) n(%) or mean (SD)	**Group 2 (n=19)** n(%) or mean (SD)
Age	59.15 (9.85)	61.68 (13.98)
Male	16 (80%)	16 (84%)
Marital status		
Married/partner	13 (65%)	15 (79%)
Single/Divorced/Widowed	7 (35%)	4 (21%)
Education		
Basic	16 (80%)	14 (74%)
Higher	4 (20%)	5 (26%)
Employment		
Paid job	10 (50%)	9 (47%)
Unemployed/Retired	10 (50%)	10 (53%)
Medical history		
No CV history	15 (75%)	15 (79%)
CV risk factors	5 (25%)	4 (21%)
Medical outcome		
PCI	20 (100%)	16 (84%)
CABG	0 (0%)	3 (15%)
Heart failure	2 (10%)	1 (1%)
Location of discharge		
Home	20 (100%)	19 (100%)
Rehab/Nursing home	0 (0%)	0 (0%)

3.3.3. Primary outcome

Quality of life assessment: Patients

The analysis of the impact of simple psychological interventions showed that there was significant improvement in all domains of SF36 except general health when patients within Group 2 were reassessed at 6 months follow up (Table 3.2).

Table 3-2 Comparison of baseline and 6 month quality of life assessment for patients within Group 2 by RAND SF36

SF36 Domains	Baseline Mean (SD)	6 month Mean (SD)	Mean change	SEM	p value	Lower (95% CI)	Upper (95% CI)
Physical functioning	35.79 (30.15)	66.84 (24.70)	31.05	7.95	**0.001**	-47.76	-14.35
Social functioning	23.03 (23.67)	71.71 (33.03)	48.68	8.05	**<0.001**	-65.59	-31.77
Role Physical	10.53 (24.03)	55.26 (49.71)	44.73	11.72	**0.001**	-69.36	-20.11
Role Emotional	40.35 (46.59)	77.19 (36.95)	36.84	11.08	**0.004**	-60.11	-13.55
Vitality	31.84 (23.23)	58.16 (21.55)	26.32	6.40	**0.001**	-39.75	-12.88
Mental Health	64.00 (24.15)	78.11 (17.04)	14.11	4.15	**0.003**	-22.83	-5.38
Bodily Pain	40.66 (28.90)	77.89 (23.29)	37.23	8.19	**<0.001**	-54.45	-20.02
General Health	52.63 (19.10)	63.95 (25.69)	11.32	6.16	0.083	-24.26	1.63

When patients in Group 1 (standard care) were compared with patients in Group 2 (intervention) at 6-month follow-up, there was some improvement in perceptions of mental health, general health, bodily pain and role limitations due to physical health. However, these improvements did not reach statistical significance between the 2 groups (Table3.3).

Table 3-3: Comparison of quality of life assessment for patients between Group 1 and Group 2 by RAND SF36

SF36 Domains	Group 1 (6m) Mean (SD)	Group 2 (6m) Mean (SD)	Mean Difference	SEM	p value	Lower (95% CI)	Upper (95% CI)
Physical functioning	70.25 (23.98)	66.84 (27.4)	-3.41	8.23	0.681	-13.27	20.08
Social functioning	79.38 (21.94)	71.71 (33.03)	-7.67	8.94	0.397	-10.44	25.77
Role physical	45 (41.83)	55.26 (49.71)	10.26	14.68	0.489	-40.01	19.49
Role Emotional	78.33 (36.32)	77.19 (36.95)	-1.14	11.73	0.923	-22.63	24.91
Vitality	58.75 (19.59)	58.16 (21.55)	-0.59	6.59	0.929	-12.76	13.94
Mental Health	75.6 (20.88)	78.11 (17.04)	2.51	6.12	0.685	-14.91	9.9
Bodily Pain	72.13 (23.23)	77.89 (23.29)	5.76	7.45	0.444	-20.87	9.32
General Health	62.5 (21.3)	63.95 (25.69)	1.45	7.54	0.849	-16.72	13.83

Quality of life assessment: Caregivers

When caregivers within Group 2 were reassessed at 6 months, there was improvement in all domains of SF36, except physical functioning, bodily pain and general health perception. However, these changes were not statistically significant (Table 3.4).

Table 3-4: Comparison of baseline and 6 month quality of life assessment for caregivers within Group 2 by RAND SF36

SF36 Domains	Baseline Mean (SD)	6 month Mean (SD)	Mean change	SEM	p value	Lower (95% CI)	Upper (95% CI)
Physical functioning	84.67 (23.02)	83.00 (20.16)	-1.67	3.44	0.64	-5.71	9.04
Social functioning	42.19 (34.33)	57.50 (33.67)	15.31	13.25	0.36	-40.92	15.92
Role physical	54.69 (46.93)	71.66 (37.64)	16.97	10.02	0.21	-34.82	8.16
Role Emotional	43.74 (46.80)	71.11 (45.19)	27.37	14.72	0.12	-56.02	7.11
Vitality	37.81 (25.83)	45.33 (22.08)	7.52	8.00	0.38	-24.49	9.83
Mental Health	50.50 (23.15)	58.40 (22.87)	7.90	8.29	0.38	-25.24	10.31
Bodily Pain	70.49 (30.82)	70.33 (30.12)	-0.16	8.30	0.69	-14.48	21.15
General Health	63.44 (20.83)	55.67 (19.26)	-7.77	5.14	0.14	-3.02	19.02

When caregivers in Group 1 (standard care) were compared with caregivers in Group 2 (intervention) at 6-month follow-up, there was no statistically significant difference in any domain of the SF36 questionnaire (Table 3.5).

Table 3-5: Comparison of quality of life assessment for caregivers between Group 1 and Group 2 by RAND SF36

SF36 Domains	Group 1 (6m) Mean (SD)	Group 2 (6m) Mean (SD)	Mean difference	SEM	p value	Lower (95% CI)	Upper (95% CI)
Physical functioning	84.54 (26.44)	83.00 (20.16)	-1.54	8.40	0.86	-15.62	18.70
Social functioning	72.50 (29.39)	57.50 (33.67)	-15.00	11.15	0.19	-7.76	37.76
Role physical	75.00 (43.30)	71.66 (37.64)	-3.34	14.44	0.82	-26.15	32.82
Role emotional	76.47 (40.24)	71.11 (45.19)	-5.36	15.13	0.73	-25.55	36.26
Vitality	54.90 (20.08)	45.33 (22.07)	-9.57	7.45	0.21	-5.65	24.79
Mental Health	68.47 (19.89)	58.40 (22.87)	-10.07	7.56	0.19	-5.36	25.50
Bodily Pain	79.26 (26.06)	70.33 (30.12)	-8.93	9.93	0.38	-11.35	29.21
General Health	67.06 (23.85)	55.67 (19.26)	-11.39	7.73	0.15	-4.40	27.19

3.3.4. Secondary Outcome

Cognitive function: Patients

The analysis of the impact of simple psychological interventions showed that there was statistically significant improvement in cognitive function assessed by MOCA but not with Cogfail, when patients within Group 2 were reassessed at 6 months follow-up (Table 3.6).

Table 3-6: Comparison of cognitive function assessments by Cogfail and MOCA in patients within Group 2

	Baseline Mean (SD)	6 month Mean (SD)	Mean change	SEM	p value	Lower (95% CI)	Upper (95% CI)
Cogfail	27.95 (12.50)	26.95 (16.97)	-1.00	4.67	0.833	-8.81	10.81
MOCA	24.53 (2.91)	27.26 (2.18)	2.73	0.83	**0.004**	-4.47	-1.00

When patients in Group 1 (standard care) were compared with patients in Group 2 (intervention) at 6-month follow-up, there was no difference in cognitive function between the 2 groups (Table 3.7).

Table 3-7: Comparison of cognitive function between Group 1 and Group 2 by Cogfail and MOCA

	Group 1 (6m) Mean (SD)	Group 2 (6m) Mean (SD)	Mean difference	SEM	p value	Lower (95% CI)	Upper (95% CI)
Cogfail	30.15 (14.33)	26.95 (16.97)	-3.2	5.02	0.527	-6.97	13.37
MOCA	27.5 (1.76)	27.26 (2.18)	-0.24	0.63	0.711	-1.05	1.52

Cognitive function: Caregivers

When caregivers within Group 2 (intervention) were reassessed at 6 months, there was non-significant improvement in cognitive function assessed by both Cogfail and MOCA (Table 3.8).

Table 3-8: Comparison of cognitive function for caregivers within Group 2 by Cogfail and MOCA

	Baseline Mean (SD)	6 month Mean (SD)	Mean change	SEM	p value	Lower (95% CI)	Upper (95% CI)
Cogfail	31.13 (15.51)	36.67 (14.24)	5.54	5.83	0.36	-18.03	6.97
MOCA	27.00 (3.59)	27.67 (2.09)	0.67	0.66	0.21	-2.28	0.55

When caregivers in Group 1 (standard care) were compared with caregivers in Group 2 (intervention) at 6-month follow-up, there was non-significant improvement in cognitive function assessed by both Cogfail and MOCA (Table 3.9).

Table 3-9: Comparison of cognitive function for caregivers between Group 1 and Group 2 by Cogfail and MOCA

	Group 1 (6m) Mean (SD)	Group 2 (6m) Mean (SD)	Mean difference	SEM	p value	Lower (95% CI)	Upper (95% CI)
Cogfail	30.18 (18.98)	36.67 (14.24)	6.49	6.00	0.29	-18.74	5.76
MOCA	26.31 (2.68)	27.67 (2.09)	1.36	0.87	0.13	-3.12	0.42

3.4. Discussion

The CARE study demonstrates that patients and caregivers experience enormous emotional burden of surviving a cardiac arrest even months after the index event. The assessment of QoL perceptions in Group 1 and Group 2 is comparable to the Medical Outcomes study, where 2471 patients with chronic health conditions completed the SF36 survey (Tarlov, Ware et al. 1989). The recognition of this finding, along with evidence from the Dutch study (Moulaert, van Heugten et al. 2015) warrants further research and investment in this very important area of post resuscitation care.

Our study demonstrated that, there is statistically significant improvement in all domains of the SF36 except general health in patients who were offered simple

psychological intervention at 6-month follow-up, consistent with the finding of the Dutch study (Moulaert, van Heugten et al. 2015). Although there was a trend in improvement for QoL measures in caregivers at 6 months, these did not reach statistical significance. This finding was also consistent with the Dutch study, where caregivers in the intervention arm did not report a statistically significant improvement in QoL (Moulaert, van Heugten et al. 2015). This observation reaffirms the point that caregivers may sustain the effects of the cardiac arrest in a worse manner as a consequence of witnessing the event and adapting to enforced changes to their lifestyle (Zimmerli, Tisljar et al. 2014). Therefore, more needs to be done to identify the individual care needs of the caregivers and address them appropriately for better participation in the society.

In comparison to patients in group 1, patients and caregivers in group 2 did not score highly on any domain of QoL assessments at 6 months follow up, suggesting that there are more factors influencing QoL perceptions than the simple psychological interventions offered in this study. Indeed, some of the patients recruited in group 2 were physically quite unwell and had residual problems with heart failure and other chronic illnesses requiring multiple hospital admissions. These factors can indeed add further strain on patients and the caregivers and influence their perception of QoL. Other factors such as finances, redundancies, worries about uncertain futures also played an important role in determining QoL of the individuals.

Patients within Group 2 demonstrated superior cognitive function by MOCA assessments at 6 months. However, caregivers within Group 2 did not show such improvement in cognition. Neither patients nor caregivers in Group 2 showed superior cognition in comparison to participants in Group 1, an observation that was also consistent with the Dutch study (Moulaert, van Heugten et al. 2015). This mirrors the QoL assessments between the 2 groups, suggesting that there is a close relationship between QoL and cognitive function, as previously documented (Andersson, Rosen et al. 2015). Cardiac arrest can lead to transient or more long lasting cognitive impairment through hypoxic brain injury, which may explain the time dependent recovery in cognitive function in group 2 patients at 6 month follow up. Although, it is difficult to draw conclusions from this relatively small study, the absence of hypoxic brain injury could explain the unchanged cognitive function in caregivers.

Our study had limitations and therefore, the findings have to be considered in light of these factors. Firstly, it was a small non-randomised placebo controlled trial aimed at reinforcing the findings of the Dutch study in a UK healthcare setting. However, the fact that there is so much resemblance in our findings with the benchmark RCT (Moulaert,

van Heugten et al. 2015) suggest that, this is a realistic reflection of the problems faced by cardiac arrest survivors and caregivers. Secondly, limitations in resources and research timeframe meant that we did not have access to a clinical psychologist, who could provide a more focussed therapy to those in need of treatment. And finally, the nature of the trial meant that, blinding could not be achieved during stages of recruitment, provision of psychological intervention and reassessment. However, as the assessment tools were scored independently by the research participants, the risk of bias was minimised.

NICE recommends follow up critically ill patients (discharged from ICU) with a face to face consultation within 2-3 months after hospital discharge with an emphasis to recognise the residual physical and emotional needs of the patients and referral to appropriate services as indicated (CG83). The CARE study has reaffirmed that cardiac arrest survivors and caregivers live with the invisible negative emotional consequences even months after the index event. Our attempt at offering the simple psychological interventions is just a small step towards addressing the much bigger problems faced by these very important group of individuals. It will require much more resource allocation, individualised care support for both patient and caregiver to enable them to reintegrate into society and there is an anticipated health economic benefit attached to this approach. Indeed, a post-hoc analysis of the data has shown significant economic benefit of psychological intervention in this important group of patients (Moulaert, Goossens et al. 2016).

4. Chapter 4: COOLAMI

Setting up an efficient TH (TH) team in conscious ST Elevation Myocardial Infarction (STEMI) patients

A UK Heart Attack Centre Experience

4.1. Introduction

The primary therapeutic aim of treating patients presenting with STEMI is to restore blood flow in any occluded coronary artery at the earliest opportunity to reduce infarct size and any associated complications. However, restoring blood flow can itself lead to further myocardial damage by complex molecular mechanisms leading to reperfusion injury (Kloner 1993). Therefore recent research has focused on ways of minimising reperfusion injury.

TH has been shown to have beneficial effects on left ventricular myocardial salvage in animal models of coronary artery occlusion and reperfusion (Dae, Gao et al. 2002, Gotberg, Olivecrona et al. 2008a, Erlinge 2011). The exact mechanism of this benefit remains unclear, although it has been suggested that at lower core body temperatures, there is significant reduction in reactive hyperaemia (Olivecrona, Gotberg et al. 2007) and also complex molecular regulation including suppression of destructive enzymes, free radicals, protection of the cellular phospholipid bilayer membrane and reduction of intracellular acidosis resulting in reduced reperfusion injury (Chopp, Knight et al. 1989, Dempsey, Combs et al. 1987). There seems to be a strong relationship between the timing of hypothermic temperature achievement and reduction in infarct size - with 100% reduction in infarct size demonstrated, if TH is achieved before onset of ischaemia although of course this is not realistically possible in practice (Gotberg, Olivecrona et al. 2008a, Erlinge, Gotberg et al. 2013, Dixon, Whitbourn et al. 2002). There is no reduction in infarct size if TH is initiated after reperfusion. However, some report up to 80% reduction in infarct size can be achieved if TH can be initiated at the earliest recognition of onset of ischaemia and TH achieved before reperfusion (Gotberg, Olivecrona et al. 2008a, Erlinge, Gotberg et al. 2013, Dixon, Whitbourn et al. 2002). Therefore, it can be postulated that, an efficient transfer of patient suffering STEMI and initiating TH simultaneously early in the catheter lab before reperfusion, is likely to offer most potential therapeutic benefit of this treatment.

Studies of TH in humans presenting with STEMI have so far not demonstrated significant clinical benefit (Erlinge, Götberg et al. 2014, Erlinge, Gotberg et al. 2013,

Dixon, Whitbourn et al. 2002). In the latest multi-centre RCT (Erlinge, Götberg et al. 2014), it was shown that TH administered simultaneously at the time of PPCI did not reduce the infarct size significantly. However, exploratory analysis demonstrated that there was a significant 33% reduction in infarct size if TH was administered within 4 hours of symptom onset in patients with anterior STEMI, and also a significant reduction in incidence of heart failure was noted in this group. Future studies on TH will focus on early presenting anterior STEMI, using more powerful TH devices enabling a more rapid cooling profile, and to achieve a lower temperature before reperfusion specifically in these larger infarcts. Some investigators are also looking at commencement of TH at an earlier stage including during ambulance transfer. (Testori 2014) It has been learnt that an important aspect of future potential success in this area is efficiency of the clinical team in administering TH simultaneously with PPCI. The time of coronary intervention following symptom onset is vital in dictating prognosis and therefore, any delay following hospital admission should be minimised. There is a nationally agreed consensus to target door to balloon time of < 60 mins in HAC offering PPCI service (Authors/Task Force members, Windecker et al. 2014). The introduction of TH intervention in the setting of STEMI can potentially prolong door to balloon time and therefore, it is vitally important to look at the framework that exist to ensure safety and efficacy of any intervention that might affect current practice. In this paper, we focus our discussion on our experience of running a TH interventional research trial in the setting of patients presenting with STEMI.

4.2. Methods

The Essex CTC is a tertiary HAC serving a population of 1.7 million in the county. Every year the centre carries out approximately 750 PPCIs. It is the first UK centre that received ethical approval to conduct a feasibility study of TH in patients presenting with STEMI, sponsored by ZOLL Circulation (USA).

The purpose of the study is to:

A. Investigate the feasibility of administering TH simultaneously with PPCI and before reperfusion.
B. Organise an efficient team to minimise time delays to TH without compromising patient care.
C. Controlling shivering in conscious patients who are actively cooled with an intravenous cooling device.

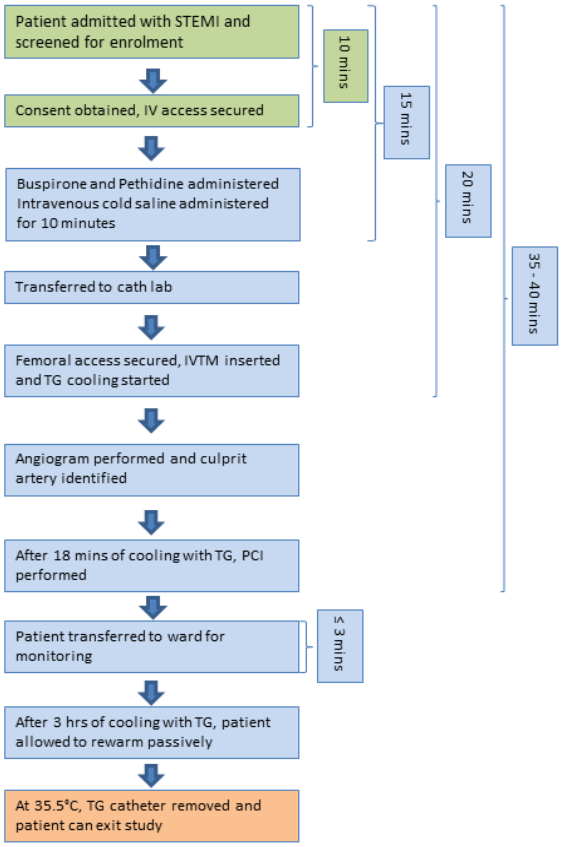
Recruitment model

Preparation

All 24/7 heart attack centres are well trained and efficient in the assessment and treatment of the STEMI patient. Teamwork in this potentially stressful clinical arena is vital, and currently the roles and responsibilities of all PPCI team members are well described and understood. Implementing a TH service in the setting of STEMI clinical trial adds further complexity. To ensure efficient enrolment and cooling, it is paramount that these extra tasks are defined and delegated.

The day is started by briefing all members of the cardiac catheter lab and research team that if a suitable patient with STEMI is admitted, he/she will be approached to participate in the study. Members of the team are given clear instructions about their roles during various stages of the recruitment. All medications, including Buspirone, Pethidine, and cold intra-venous saline are checked to ensure adequate supply. The Essex CTC is notified in advance by ambulance crew when a patient suffering STEMI is identified and boarded for transfer with an expected arrival time. The ZOLL Thermoguard (TG) cooling machine is pre-cooled to ensure immediate availability at the optimum temperature. A typical patient flow diagram is illustrated in figure 4.1.

Figure 4-1: Flow diagram of COOL AMI EU patient flow with time for completing each part of study protocol.



Stage 1: Holding Bay / Consent

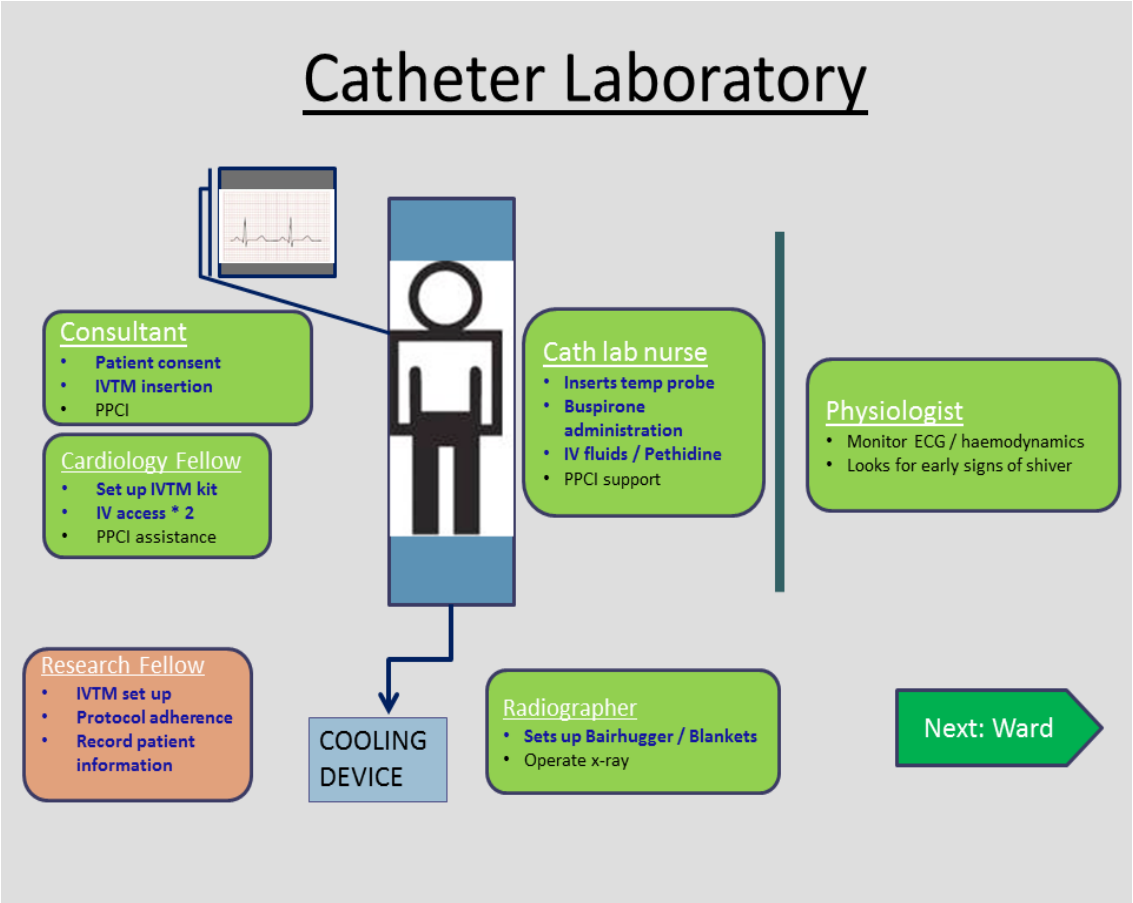
On arrival, the patient is taken to the holding bay outside the catheter lab for initial assessment by the study team. If haemodynamically stable, the patient is screened against the inclusion / exclusion criteria of the ZOLL COOL AMI EU Study. An informed consent is obtained if patient decides to take part in the study and baseline data is collected. Two intravenous access sites are secured, and the patient is then transferred to the catheter laboratory for urgent TH and coronary intervention. We aim for the consenting and IV access step to be completed within 10 minutes where possible.

Stage 2: Catheter Lab

Once included into the trial the focus is on delivering the maximum “dose” of cooling prior to early reperfusion therapy. A bair-hugger is already placed on the catheter lab table in anticipation for the patient’s arrival and it is set at 43°C. Using warming blankets on the skin, while cooling within the vena cava with a cooling catheter is a recognised strategy for preventing shivering. For successful and rapid reduction in patient core temperature shivering must be prevented. Once shivering occurs core

temperature will reduce no further and may in-fact increase until the shivering is suppressed. The anti-shiver regimen includes 60mg Buspirone orally; with the oesophageal temperature probe inserted simultaneously, as it is easier to pass the tube when the patient is swallowing which minimises the gag reflex. A bolus of pethidine is then administered at a dose of 1mg/kg, followed by intravenous cold saline to initiate TH. The patient is then wrapped up in blankets to provide surface warming. We aim to have the patient on the catheter lab table, consented, anti-shiver regimen delivered, intravenous iced saline commenced and patient ready for cooling catheter insertion within 15 minutes from arrival. The layout of the cardiac catheter laboratory during PPCI and simultaneous application endovascular TH is shown in figure 4.2.

Figure 4-2: An illustration of the catheter laboratory layout during PPCI and simultaneous administration of endovascular therapeutic hypothermia



The volume of cold saline administered is dependent on the suspected area of myocardial infarction. In inferior myocardial infarction, up to 2 litres of cold saline is administered compared to 1 litre in anterior myocardial infarction. The rationale for this is related to the territory of the myocardium supplied by the coronary arteries. The right coronary artery (inferior STEMI) supplies predominantly the right ventricle and consequently the left ventricle is more susceptible to volume depletion due to reduced right ventricular contractility (Cohen, Guyon et al. 1995), whereas the left anterior descending artery supplies the bulk of the left ventricle and it is more susceptible to volume overload following a myocardial infarction (Opie, Commerford et al. 2006).

Following routine sterilisation procedures, the consultant cardiologist secures right femoral vein access to pass the cooling catheter (ZOLL Quattro catheter). The optimal catheter position in the inferior vena cava is confirmed under x-ray guidance. The catheter is then connected to the TG cooling device to initiate cooling with a set point temperature of 32°C. The oesophageal temperature probe is connected to the TG cooling device which then displays core body temperature changes. Peripheral tympanic temperatures are also obtained at regular intervals according to the study protocol and this allows checking for any discrepancy in temperature measurement.

We aim for the cooling catheter to be inserted and cooling commenced within 20 minutes of hospital arrival.

Arterial access is then obtained preferably via the right radial artery as there is a lower bleeding risk for the procedure and it is easier to manage the radial sheath on the ward and monitor arterial blood gases if required. Baseline bloods are taken and sent off to the laboratory for analysis. Coronary angiogram images are obtained and the occluded artery is identified. Following 18 minutes of cooling via TG cooling device, the consultant cardiologist proceeds to appropriate coronary intervention. We aim for a door to balloon time in this trial of between 35-40 minutes, with 18 minutes of cooling prior to reperfusion.

According to the study shiver management protocol, a pethidine infusion is set up that can be titrated between 24mg/hr to 32mg/hr depending on the level of shivering and respiratory drive and administered 15 minutes after the initial loading dose. The patient is closely monitored during this active cooling phase to ensure haemodynamic stability, adequate shiver management, and end tidal CO_2 is monitored via a sensor within the oxygen mask to ensure the patient has adequate ventilation.

Stage 3: Transfer from catheter laboratory to ward

At the end of the coronary intervention, the patient is prepared for transfer to the ward. This phase of the cooling maintenance is vital. The TG cooling device currently needs to be turned off for transfer, and as a result patients can increase in temperature about 0.5^{o}C within 5 minutes. We have developed an iced cold saline protocol, where during transfer the patient is given a bolus 250ml of ice cold saline to cover the transfer time. We have learnt from our experience that this intervention minimises any rebound temperature gain during the transfer from the catheter lab to the ward. The Essex CTC is well designed for a quick and efficient transfer between lab and the coronary care unit and the average journey time is 3 minutes or less.

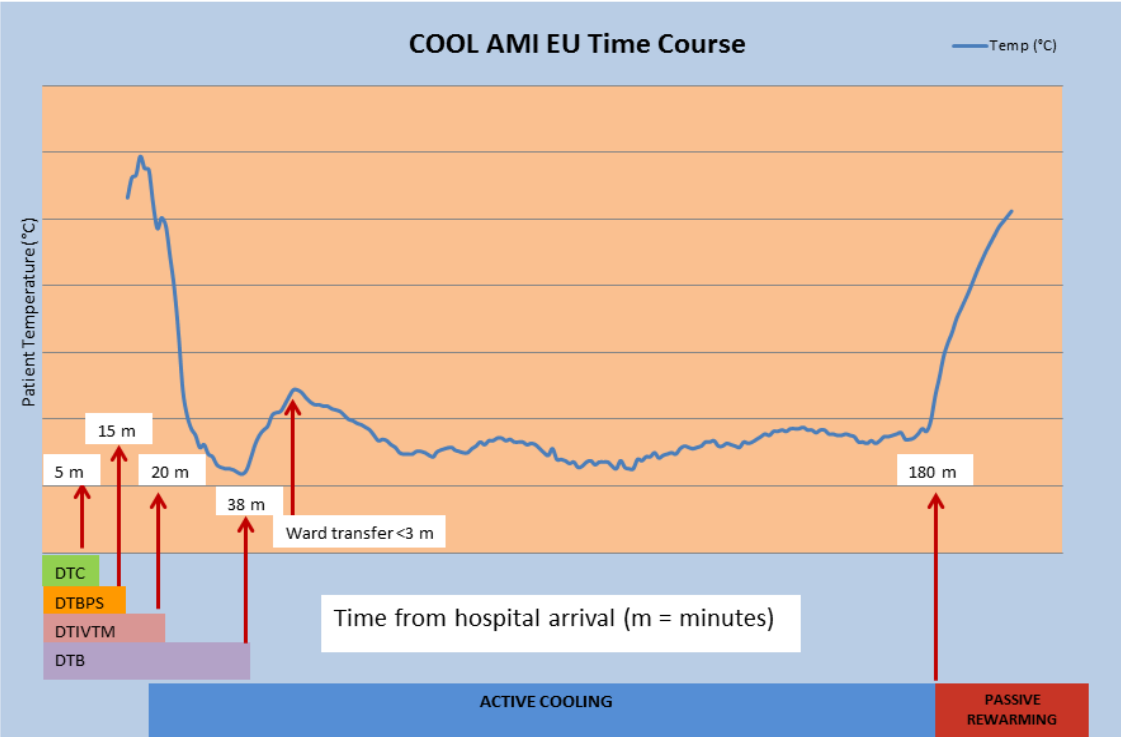
Stage 4: Ward

On arrival to the ward, the TG cooling device and the Bair Hugger machine are both switched on immediately to continue the active cooling therapy to a target temperature of 32±1°C. The pethidine infusion rate is tailored to patient's clinical condition. The radial sheath is kept in situ to monitor arterial blood pressures and blood gas on the ward. The right femoral vein site is inspected on regular intervals for any vascular complications. After 3 hrs of active cooling, the patient is re-warmed passively. The TG cooling is turned off, but the oesophageal temperature probe is still kept in situ until core temperature warms to above 35.5°C, defined as normothermia. A cooling curve of a typical patient is shown in figure 4.3. The femoral catheter is then removed in a sterile

fashion, and manual pressure is applied for 10-15 minutes. At this point, usual post PCI care is resumed by the ward team. All steps of research participation are documented in the medical notes and formally handed over to the clinical team for continuation of care.

Figure 4-3: Cooling curve of a typical patient recruited to COOL AMI trial

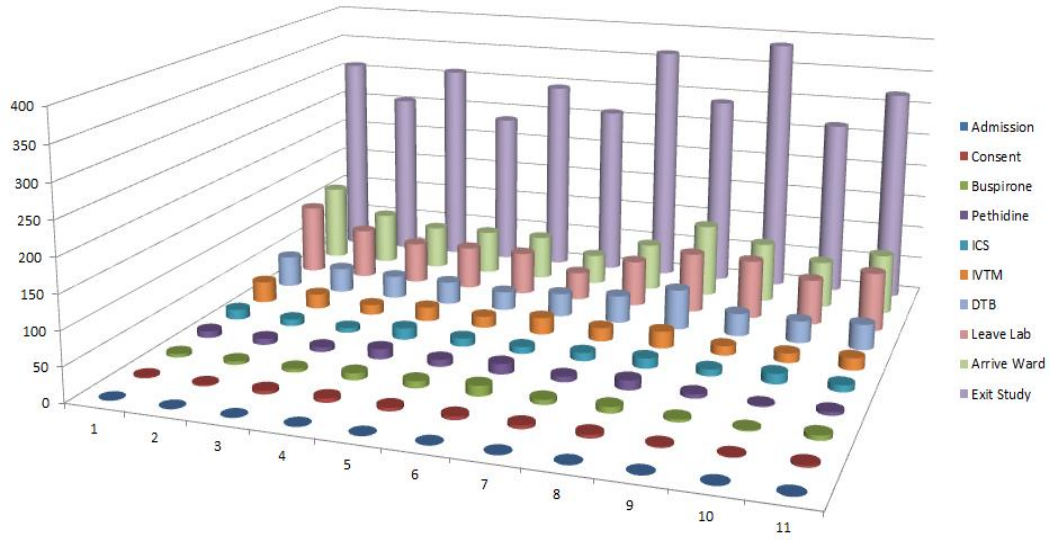
Please note mild temperature rise during ward transfer; DTC = Door to consent; DTBPS = Door to Buspirone, Pethidine, ice-cold Saline; DTIVTM = Door to IVTM; DTB = Door to Balloon



4.3. Results and Discussion

It is feasible to deliver efficient TH within the setting of a clinical trial to patients presenting with STEMI in a tertiary PPCI centre. The average door to balloon (DTB) time for the first 11 patients recruited into the trial was 38 minutes with an average of 16.5 minutes of intra-venous catheter cooling before reperfusion. This compares with a DTB mean of 37 minutes for all patients presenting with STEMI without administration of TH at the Essex CTC during 2014. This observed 1 minute delay is favourable to the mean 9 minute delay observed in the CHILL MI trial, although their sample size was much larger across multiple sites (Erlinge, Götberg et al. 2014, Canadian Cardiovascular Society, American Academy of Family Physicians et al. 2008). More importantly, this minor delay is well within the 60 minute door to balloon time target that PPCI centres are expected to meet (Authors/Task Force members, Windecker et al. 2014).

Figure 4-4: An illustration of the DTB achieved through our case series at CTC



Evidence from external monitors suggest that our performance improved significantly over time in terms of achieving minimal delay in door to balloon time and shiver management. This can be attributed to a combination of factors including strict adherence to protocol, co-ordination of team and clearly defined roles. Following the enrolment of each patient, we conduct a debrief session where we discuss different aspects of the patient treatment and areas for improvement. We, as a team got better in speed, efficiency by practising our roles meticulously over the duration of the study. There has been no compromise to the safety of the patients and there has been no trial related serious adverse events.

The prevention of shivering is the key to successfully administering TH in these patients. The anti-shivering regimen provided by the sponsor is a useful guide to ensuring that safe doses of anti-shivering medications are administered and in the correct order. Early signs of shivering can be identified from the ECG monitors, where the isoelectric line may demonstrate signs of micro-shivering. This then allows the clinical team to administer bolus doses of pethidine if clinically indicated. However, the patient's clinical condition and safety takes priority over shiver control. Therefore, it is essential to monitor patient's clinical condition before any pethidine bolus is administered. The application of multiple layers of blanket ensures maximum surface warming, as the skin is the largest organ for heat exchange, and if the skin perceives warmth, then it appears that shivering is minimised.

The efficient transfer of patient from the catheter lab to the ward is another key element to success as this is a time when active cooling needs to be turned off and therefore allows the potential for rebound hyperthermia. We introduced the administration of a 250ml of cold saline into our transfer regime to minimise temperature rebound. In addition, the CCU is pre-notified before transfer to ensure all equipment including Bair Hugger and TG cooling device can be re-started instantly on patient's arrival. The continuous presence of a clinician throughout the course of the patient monitoring during active cooling and passive rewarming adds to the safety of this trial; however this may be a challenge in a centre with limited resources.

With a well-trained team within this feasibility trial, it is possible to deliver 18 minutes of TH to STEMI patients prior to PPCI reperfusion without a significant prolongation of door to balloon times. This work paves the way for a larger RCT, where important clinical outcomes including left ventricular infarct size and function, patient safety, and mortality can be measured against standard PPCI care.

In summary, reperfusion injury is associated with an increase in morbidity and mortality. TH has shown promise particularly in patients presenting early with anterior STEMI. The delivery of TH in the conscious patient is challenging, and previous trials have been criticised by delaying reperfusion to allow for delivery of TH, the benefits of which may be cancelled out by the adverse effects of lengthening the symptom to reperfusion time. This review outlines our experience at a busy Heart Attack Centre, in delivery of TH in conscious STEMI without delaying reperfusion, albeit in the setting of a clinical trial. We hope that this review will help other centres deliver similar results, thus giving TH the best chance of succeeding in reducing the adverse of effects of reperfusion injury in STEMI.

Declaration of Interest

The study received funding from Zoll (USA) for equipment and material support.

5. Chapter 5: Discussion

5.1. COOLCATH

5.1.1. Key findings

Early targeted brain cooling in the cardiac catheterisation laboratory following cardiac arrest (COOLCATH) was designed as single centre RCT to investigate the efficacy of a novel intra-nasal cooling device, Rhinochill® over conventional surface cooling using Blanketrol for TH induction and also, its impact on clinical outcomes including hospital length of stay, neurological recovery and all-cause mortality at hospital discharge. Rhinochill® TH induction was associated with quicker time to reach target temperature of ≤34°C from randomisation for both modalities of tympanic and oesophageal measurements, although these times were not statistically significant. It was however noted that the rate of drop in tympanic temperature in the first hour was significantly quicker with Rhinochill® induction, suggesting more rapid and focussed brain cooling. These observations did not translate to superior clinical outcomes in patients receiving Rhinochill® induction including neurological recovery and survival to hospital discharge. Remarkably, the combined survival to hospital discharge was a remarkable 67.1%, which is better than previously reported (Bernard, Gray et al. 2002, Mooney, Unger et al. 2011, Castren, Nordberg et al. 2010)

Two landmark RCTs published in the New England Journal of Medicine in 2002 (Bernard, Gray et al. 2002, Hypothermia after Cardiac 2002) showed significant mortality and morbidity benefit in cardiac arrest patients treated with mild TH over control groups. Other retrospective studies also supported the positive outcomes of these studies and reinforced the fact that, delays in initiating TH was associated with worse clinical outcomes in this group of patients. (Sendelbach, Hearst et al. 2012, Mooney, Unger et al. 2011). The TTM trial published in 2013 raised some important questions about the therapeutic role of hypothermia in cardiac arrest patients (Nielsen, Wetterslev et al. 2013). In this large RCT, there was no significant difference in neurological recovery or mortality reported between patients managed at 33°C and 36°C. However, closer inspection of the study design suggested that the mean delay in initiation of cooling was 130 minutes and the mean time to reach target temperature of 34°C was 5 hours (Polderman, Varon 2015), which was quite substantial for TH induction and could offset any potential benefit that can be offered by hypothermia. Another possible explanation for the equivocal results in this study is that both groups (33°C and 36°C) had active temperature management unlike previous trial, where

temperature in the control group was not actively maintained (Hypothermia after Cardiac 2002) resulting higher temperatures.

The rationale for further research in this area derives from high incidence of mortality and morbidity associated with cardiac arrest, whether methods are employed to reduce core temperature or to prevent systemic pyrexia. In the TTM trial alone, more than 50% of the patients died or had poor neurological recovery at 6-month follow-up (Nielsen, Wetterslev et al. 2013). To the best of our knowledge, COOLCATH was the first reported RCT, where TH induction using Rhinochill® was investigated in cardiac catheter laboratory in the setting of cardiac arrest.

In the COOLCATH study, 74 adult cardiac arrest patients with ROSC were randomly allocated to induction with Rhinochill® or Blanketrol irrespective of their initial pre-arrest rhythm. Initial consent was obtained from a legal surrogate in accordance with the Helsinki declaration (The Helsinki Declaration of the World Medical Association (WMA). Ethical principles of medical research involving human subjects. 2014). Simultaneous temperature recordings were made from tympanic and oesophageal probes. Patients randomised to Rhinochill® induction received uninterrupted cooling from randomisation throughout coronary intervention and transfer to ICU and were transferred to Blanketrol maintenance cooling once target temperature of 34°C was achieved. Patients allocated to Blanketrol induction were also cooled from randomisation and throughout coronary intervention but interrupted during patient transfer from cardiac catheter laboratory to ICU as the machine only operates from mains electricity supply. Both groups of patients were maintained at <34°C for 24 hours, using standard sedation protocol as per trust guideline, before active rewarming was conducted at hourly increments of 0.25-0.5°C and sedation withdrawn. There were no differences in baseline characteristics between the 2 groups including pre-arrest rhythms, mean time of untreated cardiac arrest and median time to ROSC. Day-to-day clinical decisions including prognosis and withdrawal of treatment were taken by treating medical team, who were unaware of the trial intervention for TH induction. The follow up duration was till hospital discharge.

Despite efficient cooling profile in both Rhinochill® and Blanketrol induction, a substantial amount of time (1-2 hours) had elapsed between ROSC and initiation of cooling, during which considerable brain damage may already have occurred. This could partially explain the findings of the COOLCATH study although the sample size was not sufficiently powered to detect a significant difference in primary and secondary outcomes. An ongoing trial, PRINCESS (Nordberg, Taccone et al. 2013) is being conducted to investigate pre-ROSC targeted brain cooling in cardiac arrest patients

and is anticipated to address some vital questions regarding the optimal time for initiation of cooling to provide greater neuro-protection.

5.1.2. Latest guidelines on TH in cardiac arrest

Having assessed the safety and feasibility of mild hypothermia in human survivors of cardiac arrest, landmark RCTs conducted in Europe (Hypothermia after Cardiac 2002) and Australia (Bernard, Gray et al. 2002) showed morbidity and mortality benefit of TH in cardiac arrest survivors. Following the publication of these studies, several other studies and meta-analyses were conducted (Holzer, Bernard et al. 2005, Hachimi-Idrissi, Corne et al. 2001) which resulted in many governing bodies advocating the routine use of hypothermia in cardiac arrest survivors (Peberdy, Callaway et al. 2010, Nolan, Neumar et al. 2008, NICE, National Institute for Clinical Excellence March 2011). The TTM trial (Nielsen, Wetterslev et al. 2013) was conducted to establish whether beneficial effects of hypothermia observed in previous studies is attributable to targeted temperature management or fever prevention and it did not show any superiority of patients being maintained at 33°C compared to patients maintained at 36°C. The limitations of this study were discussed earlier. The latest AHA guideline has been updated to reflect the current body of evidence on the institution of hypothermia in the setting of cardiac arrest and it recommends that ‘all comatose adult patients with ROSC after cardiac arrest should have TTM, with target temperature between 32°C and 36°C selected and achieved and then maintained for at least 24hours’ (Donnino, Andersen et al. 2015).

5.1.3. Other important considerations about TH in cardiac arrest

5.1.3.1. Downtime, cooling the right patient and target temperature

Epidemiological data suggests majority of OHCA occur at home and only a fraction in public areas (Nicholas P, Virdi G, Fothergill R September 2013). Only about 1 in 5 patients are found to be in shockable rhythm (Nicholas P, Virdi G, Fothergill R September 2013). In the UK, EMS attempted to resuscitate an estimated 28,000 OHCA in 2013 (NHS England 2013) but the actual number of calls were much higher where resuscitation attempts were not made due to medical reasons, including presence of a valid do-not-attempt resuscitation form, already deceased before EMS arrival and other situations where resuscitation attempts would be considered futile (NHS England 2013). There are regional variations in success of attempted CPR and LAS claim to be one of the better performing emergency services both in terms of successful ROSC to hospital arrival and survival to hospital discharge in their latest report (Virdi G, Picton S, Fothergill R September 2015). In London, only 49.2% of all OHCA were witnessed by

bystanders and despite improved education and training, about 63.1% of patients received bystander CPR, which is an improvement compared to previous year (Virdi G, Picton S, Fothergill R September 2015). Therefore, a significant proportion of OHCA is unattended at the time of the cardiac arrest and does not receive CPR. Prolonged downtime (cardiac arrest without ROSC) results in increased duration of anoxia, which is inherently related to poor clinical outcome (Oddo, Ribordy et al. 2008).

Majority of the success of hypothermia in cardiac arrest both in terms of neurological recovery and mortality is derived from patients who had minimal downtime, received effective bystander CPR and had initial shockable rhythm (Hypothermia after Cardiac 2002, Castren, Nordberg et al. 2010, Bernard, Gray et al. 2002). However, if hypothermia is considered to be beneficial in the context of cardiac arrest, then wider application in patients with poorer prognosis also needs to be verified. One of the latest meta-analysis (Schenone, Cohen et al. 2016) used very generous selection criteria to include all comatose survivors of witnessed or unwitnessed cardiac arrest irrespective of pre-arrest rhythm, with or without shock and more lenient downtimes. The only notable exclusion criteria were those who did not reach target temperature during hypothermia treatment.

In this meta-analysis, the authors reported that there was no statistically significant heterogeneity between the groups and concluded that TH reduced mortality (odds ratio 0.51; 95% confidence interval 0.41-0.64) and improved odds of neurological recovery (odds ratio 2.48; 95% confidence interval 1.91-3.22), regardless of pre-arrest rhythm, length of downtime and bystander CPR. Based on these findings, the authors advocated wider application of TH in cardiac arrest. However, in practice, the clinical judgement of the physician should take precedence in deciding institution of TH as it is an additional resource consuming intervention and some patients may be at high risk of sustaining adverse events due to pre-morbid functional status.

Unlike other meta-analysis, the authors decided to analyse a further 3 studies separately that compared different targeted temperature management in cardiac arrest (Schenone, Cohen et al. 2016). Kim et al (Kim, Yang et al. 2011) compared outcomes at 32°C, 33°C and 34°C in comatose patients surviving cardiac arrest and found no difference in clinical outcome. It is important to note that, two thirds of the patients in this study had non-shockable rhythm on presentation and half of the patients had cardiac arrests from non-cardiac origin. A smaller pilot RCT (Lopez-de-Sa, Rey et al. 2012) investigated outcomes in patients managed at 32°C and 34°C for 24hrs followed by controlled rewarming for a further 24 hours. The authors found better 6 months survival rate in patients managed at 32°C ($p=0.03$) and better neurological recovery in

patients with initial shockable rhythm managed at 32°C (p=0.029). And finally, TTM study (Nielsen, Wetterslev et al. 2013) was also included in this section of the analysis, which was discussed earlier. Additionally, a pooled analysis of 34 hypothermia arms grouped by cooling temperature did not show any statistically significant morbidity or mortality benefit and therefore, this analysis did not support the superiority of one temperature over another.

5.1.3.2. Optimal initiation of cooling and duration of cooling

One of the major limitations in hypothermia intervention is the timing of initiation of therapy as the vast majority of cardiac arrests occur out of hospital, where the priority of the EMS is to restore circulation and transfer the patient to a place of safety to treat the underlying cause. Aside from Rhinochill® and institution of cold fluid, no other available cooling equipment is portable and therefore the feasibility of TH induction in public areas is very challenging. The equivocal results in the TTM trial can be explained by the notable delay in initiating hypothermia (mean 130 minutes) and mean time to reach target temperature of 34°C of 5 hours (Nielsen, Wetterslev et al. 2013). On the basis of our understanding of molecular mechanism of hypoxic brain injury, one could hypothesise that a substantial amount of damage already occurred and hypothermia could not exert any additional neuro-protection. Registry based data has shown that delay in initiating hypothermia is associated with poorer outcomes (Sendelbach, Hearst et al. 2012, Mooney, Unger et al. 2011).

A recently published Cochrane review investigated the current body of evidence to see if pre-hospital cooling is more beneficial than in-hospital cooling (Arrich, Holzer et al. 2016) . Seven RCTs met the selection criteria for inclusion in this analysis (Bernard, Smith et al. 2012, Bernard, Smith et al. 2010, Castren, Nordberg et al. 2010, Debaty, Maignan et al. 2014, Kim, Nichol et al. 2014, Kim, Olsufka et al. 2007, Kamarainen, Virkkunen et al. 2009). The findings of the studies were investigated individually because of the methodological differences and the risk of bias due to variation in cooling strategies. High level of inconsistency and low precision resulted in very lowly scores for the quality of evidence. The authors declared that the beneficial or harmful effect of pre-hospital cooling over in-hospital cooling remain inconclusive with current low quality evidence and therefore, warrants further robust research in this field to establish reproducible facts.

There is very limited data investigating different duration of targeted temperature management on mortality and neurological recovery (Donnino, Andersen et al. 2016). One retrospective registry based observational study compared temperature management at 33°C for 24hrs with 32°C for 72hrs in comatose asphyxial cardiac

arrest survivors and found no difference in neurological recovery or mortality at 30 day follow up (Lee, Lee et al. 2014). In the absence of robust data to establish optimal duration of temperature management, The AHA currently suggests active temperature management for 24hrs based on 2 largest RCTs in this field (Nielsen, Wetterslev et al. 2013, Hypothermia after Cardiac 2002).

5.1.3.3. Consenting the unconscious patient – ethical challenge

Obtaining consent for participation in research is one of the biggest challenges in unconscious patients in the setting of cardiac arrest. The national research ethics committee has made special exception in this situation for an interim consent to be obtained from a legal surrogate in accordance with declaration of the Helsinki (The Helsinki Declaration of the World Medical Association (WMA). Ethical principles of medical research involving human subjects. 2014) but advises to obtain a further prospective consent from the patient if and when patient makes sufficient neurological recovery.

The whole experience of the cardiac arrest is very traumatic for any immediate family or friend without any reasonable doubt, who attend with the patient and consenting for an unproven intervention require a very thoughtful and compassionate conversation between the clinician and the next of kin. Evidence from trial data suggest that the vast majority of legal surrogates consent to the patient participation if sufficient information is provided about the rationale for research. Supplementary appendix from one of the largest multi-centre trial in this field, TTM (Nielsen, Wetterslev et al. 2013) showed only 4 patients out of the 950 (0.4%) randomised were withdrawn due to withdrawal consent either by the legal surrogate or the patients themselves on regaining consciousness. However, it also reports that 160 participants of the original 1242 (12.8%) eligible were not included for randomisation because consent could not be obtained in a timely manner. This highlights the extremely challenging circumstances under which consent is obtained, which can also be at unsocial hours when the patient is admitted to hospital.

5.1.3.4. Measuring brain temperature more accurately

The direct measurement of brain temperature in targeted brain cooling would be ideal for research purposes to accurately assess the impact of TH but it poses real life challenges. First of all, the anatomical location of the brain means that an invasive approach needs to be adopted to obtain direct measurement of the brain temperature but it can only be done in unconscious patients. Furthermore, the brain temperature may have variations depending on site of measurement and especially in the context of

cooling when areas of hot and cold gradients become more prominent (Karaszewski, Wardlaw et al. 2006, Laptook, Shalak et al. 2001).

The correlation of core temperature as a surrogate for brain temperature has been subject to controversy. It has been reported that there is a difference in the range of 0.3°C to 2.1°C between rectal temperature and frontal lobe recordings (Rumana, Gopinath et al. 1998) and 0.7°C to 2.3°C between pulmonary artery and ventricular temperature recordings (Rossi, Zanier et al. 2001). Infrared tympanic temperature was used as a surrogate for brain temperature in our RCT (Islam, Hampton-Till et al. 2015). Whilst some studies supported this as a close surrogate (Mariak, Lewko et al. 1994), others have challenged its validity (Kirk, Rainey et al. 2009, Moran, Peter et al. 2007).

The simultaneous measurement of oesophageal temperature as a surrogate for core body temperature was also made in our RCT to better understand the overall temperature changes with treatment. Although targeted brain cooling preferentially cools the cerebral hemispheres, venous blood returning from the cooled brain is likely to reduce core body temperature as well (Harris BA 2005). Thus if oesophageal temperature was reduced with Rhinochill® during TH induction, one can speculate that the intracranial temperature has also been reduced.

In future trials, the direct non-invasive measurements of brain temperature by more complex techniques such as MRI spectroscopy, microwave radiometry and infrared spectroscopy can be explored in trials involving TH in cardiac arrest (Covaciu, Weis et al. 2011, Bakhsheshi, Lee 2014, Stauffer, Snow et al. 2014). Whilst these measures are more resource intensive, it will be worth investigating the practicality of application of these measuring tools in the setting of cardiac arrest to get a better understanding of the temperature fluctuations during targeted temperature management.

5.1.3.5. Neurological prognostication

Following a period of 24 hours of temperature management with active sedation as per AHA recommendation (Donnino, Andersen et al. 2016), routine practice is to actively rewarm patients in increments of 0.5°C per hour whilst simultaneously weaning off sedation to allow patients to regain consciousness. In the TTM trial (Nielsen, Wetterslev et al. 2013), active temperature management with an aim to keep temperature below 37.5°C continued for a total of 72hrs to prevent pyrexia. The patient is assessed by the treating physicians for signs of recovery and expertise from a neurologist is sought to assess and prognosticate in patients who remain in comatose.

Although hypothermia in cardiac arrest has been instituted for many decades and even found its place in historic algorithms and most recent ones (Safar 1964, Donnino,

Andersen et al. 2016), there remains scepticism on its wider application due to lack of robust and convincing evidence and in some cases, it may not be appropriate where patients are considered to be too high risk due to pre-morbid function. Hence, the vast majority of historic guidelines on prognostication are documented without taking hypothermia into consideration. In 1985, Levy et al produced a model of prognostication based on neurological examination of 210 patients who survived cerebral hypoxia-ischaemia (Levy, Caronna et al. 1985). They reported that indicators of poor outcome include absent pupillary reflexes on admission and lack of flexor or extensor motor responses and absent spontaneous eye movements that were neither orientating nor roving conjugate. A comprehensive set of guideline was published by the American Academy of Neurology in 2006 (Wijdicks, Hijdra et al. 2006), that incorporated the body of evidence published in the previous decade and expanded on recommendations from Levy et al (Levy, Caronna et al. 1985) on prognostication after cardiac arrest. In this guideline, the authors concluded that absence of pupillary light response, corneal reflexes, motor reflexes to painful stimuli and the presence of myoclonus status epilepticus; raised biochemical marker serum neuron-specific enolase and somatosensory evoked potential studies can reliably assist in predicting neurological recovery after cardiac arrest (Wijdicks, Hijdra et al. 2006). The role of neuroimaging to guide prognostication was less established in this guideline. Neurological prognostication is more challenging in patients who have been treated with hypothermia as it affects drug metabolism and also induces physiological changes and therefore, patients may not exhibit true neurological recovery at the time of assessment (Perman, Kirkpatrick et al. 2012).

5.1.3.5.1. Neurological examination

A neurological examination to assess pupillary and corneal reflexes and motor responses to painful stimuli can predict prognosis if performed within 1-3 days after cardiac arrest according to the American Academy of Neurology (AAN) guidelines published in 2006 (Wijdicks, Hijdra et al. 2006). However, neurological examination performed during active hypothermia institution may not reliably provide accurate assessment of neurological recovery as hypothermia induces many physiological changes that include delayed in drug metabolism at temperatures below 35°C (Polderman 2004) and therefore, the effects of sedation may mask the examination. One prospective trial seem to suggest that there are no differences in time to regaining consciousness between patients treated with hypothermia and those without (Fugate, Wijdicks et al. 2011) and found that the median time to awakening was 2 days in both groups. However, other researchers seem to suggest that an assessment at 72 hours may not provide an accurate assessment in any modalities of neurological examination

in patients treated with hypothermia (Rossetti, Oddo et al. 2010). The variations in these findings suggest that either a delayed assessment or addition of other tools may provide more realistic reflection of neurological prognostication in patients treated with hypothermia.

5.1.3.5.2. Neuroimaging

The AAN guideline published in 2006 suggested that neuroimaging has limited role in neurological prognostication in cardiac arrest survivors (Wijdicks, Hijdra et al. 2006). However, more recent developments especially in magnetic resonance imaging (MRI) with diffusion weighted imaging (DWI) have shown that poorer outcomes are associated with size, number and location of lesions performed within 3-5 days after index event in patients treated with hypothermia (Jarnum, Knutsson et al. 2009, Lang, Welte et al. 2002). The relative lack of data suggests that neuroimaging alone cannot provide sufficient information to prognosticate but can be used in conjunction with other assessments to support the diagnosis.

5.1.3.5.3. Electrophysiological studies

According to the AAN guideline (Wijdicks, Hijdra et al. 2006), the absence of N20 component of the somatosensory evoked potentials (SSEPs) on stimulation of the median nerve can predict poor outcome between 24-72 hours after the index event. Hypothermia has been shown to affect the altitude and the latency of the SSEPs (Lang, Welte et al. 2002). There is limited evidence on the validity of performing SSEPs in the setting of hypothermia to predict outcome and although considered to be a useful tool, it is resource intensive and may not be feasible to perform in the ICU. The presence of burst-suppression or generalised epileptiform activity on electroencephalograms (EEG) has also been associated with poor outcome according to the AAN guideline (Wijdicks, Hijdra et al. 2006). In the setting of hypothermia, one small prospective study revealed that patients with poor outcomes showed non-reactive or discontinuous burst-suppression activity on continuous EEG monitoring (Rossetti, Urbano et al. 2010). Again, the relative lack of data means that EEG alone cannot be used to prognosticate in cardiac arrest patients treated with hypothermia but can provide valuable information that can be used as an additional tool to guide patient management.

5.1.3.5.4. Status epilepticus

The presence of myoclonus status epilepticus within 24hrs of cardiac arrest indicates poor prognosis (Wijdicks, Hijdra et al. 2006). However, in the context of hypothermia, there have been isolated reports of favourable prognosis despite clinical manifestation of myoclonic seizures (Rossetti, Oddo et al. 2009). Other studies supported the poor prognosis associated with seizures even in patients treated with hypothermia (Al

Thenayan, Savard et al. 2008). As most patients remain under active sedation whilst receiving TH, seizure activity may be difficult to witness clinically but EEG can aid early recognition and further research is warranted to establish the usefulness of EEG in this setting.

5.1.3.5.5. Biomarkers

Neuron-specific enolase (NSE) is an enzyme released by neurons in response to hypoxic injury (Rundgren, Karlsson et al. 2009) and a level >33µg/L between 24-72 hours after cardiac arrest has been associated with poor outcome (Wijdicks, Hijdra et al. 2006). However, the threshold for poor prognosis in patients treated with hypothermia has been debated (Daubin, Quentin et al. 2011) perhaps related to the timing of sampling and therefore, although high levels of NSE can give some indication on prognosis, it cannot be used in isolation based on current body of evidence.

5.1.4. Future directions and conclusions

Despite all recent controversies regarding hypothermia institution in cardiac arrest, epidemiological studies repeatedly confirmed the high incidence of morbidity and mortality associated with this life changing event in the presence or absence of hypothermia (Mozaffarian, Benjamin et al. 2015). In the latest consensus paper, the unadjusted survival to hospital discharge rate still stands at a meagre 8.6% (NHS England 2013). The relative lack of robust data in temperature management means that definite conclusions cannot be easily drawn from the current body of evidence. The observation from the TTM trial, the largest in this field (Nielsen, Wetterslev et al. 2013) was included in the latest meta-analysis published in 2016 (Schenone, Cohen et al. 2016) and it showed that, there is no difference in clinical outcome between various levels of active temperature management in the range of 33°C and 36°C. More importantly, this meta-analysis concluded that TH offers greater neuro-protection and mortality benefit compared to no temperature management.

The latest AHA guideline has been amended to reflect this observation (Donnino, Andersen et al. 2016). In this review the authors asked some very important questions and scrutinised the current body of evidence to provide meaningful answers. In response to question regarding mild hypothermia compared to no TTM in comatose survivors of OHCA, the authors recommend using TTM in patients with initial shockable rhythm (strong recommendation, low-quality evidence). The recommendation is weaker in comatose survivors of OHCA whose pre-arrest rhythm was non-shockable and for IHCA with any pre-arrest rhythm due to lack of robust data. The authors commented that the current data was indirectly obtained through extrapolation from studies focused on OHCA with shockable rhythm. Therefore, more research is warranted in this sub-

group of patients to establish if there is true reproducible therapeutic benefit of TH. Also in qualification of TTM between 32°C and 36°C, the authors outline that whether certain subgroup of patients would benefit from lower or higher temperature management remain unknown. For instance, the latest meta-analysis (Schenone, Cohen et al. 2016) suggested that there may be a potential beneficial role of lower TTM in non-shockable rhythm, but recommends verification with more robust research.

In response to question regarding early (pre-hospital) institution of TTM, the authors recommended against using large volume of cold saline to induce TH as it was associated with increased risk of pulmonary oedema and recurrence of cardiac arrest in one of the larger RCTs (Kim, Nichol et al. 2014). There is inadequate data investigating other modalities and strategies of TH induction in the pre-hospital setting and the authors have suggested that further research is required in this field. Indeed, one can speculate that it will be a noteworthy project to investigate an efficient and safe pre-hospital TH induction at 33°C with TTM at 36°C in the hospital setting on clinical outcome. For this to be feasible, the TH induction equipment need to be portable, least resource intensive and above all safe for application without incurring side effects as observed with cold fluids (Kim, Nichol et al. 2014).

And finally, the authors responded to the optimal duration TTM. In the absence of robust data, the authors recommended pursuing with 24hrs of active TTM based on the 2 largest RCTs in this field (Nielsen, Wetterslev et al. 2013, Hypothermia after Cardiac 2002). Again, there is knowledge gap in this aspect of temperature management and require further research to establish reliable and reproducible facts.

Authors from the TTM trial (Nielsen, Wetterslev et al. 2013) are embarking on a new and larger multicentre superiority trial, TTM2 (NCT02908308) in an attempt to answer some key questions that were raised from their original study. Highlights of these questions include whether faster and earlier cooling at 33°C improves clinical outcome and whether prevention of fever, without lowering core body temperature, provides adequate neuroprotection in cardiac arrest survivors.

The TTM2 is set up to investigate TTM at 33°C compared to normothermia with early treatment of fever (≥37.8°C). Outcome assessors and prognosticators will be blinded to the intervention; however healthcare providers will be unblinded at the time of application of intervention due to nature of the study. Patients allocated to 33°C will be cooled for 28hrs followed by 12hrs of controlled rewarming. In the normothermia (fever prevention group), pharmacological measures and physical cooling will be deployed at the recognition of temperature ≥37.8°C. Neurological recovery will be assessed in line with European Resuscitation Council's recommendations on neurological

prognostication. This trial will follow up patients up to 24months after inclusion in the study, although interim results will be reported at 6 months.

In theory, TTM2 trial is a major attempt to respond to key unanswered questions. However, one key observation from the study design is that, the deployment of TH at 33°C will still be started after hospital admission despite ROSC being achieved in the out of hospital setting. From TTM-1 (Nielsen, Wetterslev et al. 2013) it has been noted that considerable time is lost in patient transfer and initiation of intervention, during which substantial brain damage can occur. In other words, the true neuro-protective beneficial effect of TH at 33°C may still not be observed. The other observation is that, the authors mentioned TH induction method will include infusion of cold fluids despite current recommendations advocating against this due to risk of pulmonary oedema and recurrence of cardiac arrest (Kim, Nichol et al. 2014). Nonetheless, the outcome of this study is expected to influence wider adoption of TH in clinical practice and governing bodies will be reading the outcome of this study with a lot of interest.

In conclusion, TH has been around for many decades in the context of cardiac arrest and went through peaks and troughs in reporting success and failures over time. It will be far too naïve to deter from further research with hypothermia in cardiac arrest as there is still so many unknown, yet very important factors associated with this field of treatment. The extremely high incidence of morbidity and mortality associated with this condition provides an enormous impetus in its own merit to conduct further comprehensive and robust research within this field and perhaps, we can get more meaningful answers to the questions.

5.2. CARE

5.2.1. Key findings

Care after resuscitation (CARE) was set up as a non-randomised placebo controlled trial to investigate the impact of early psychological support for cardiac arrest survivors and their caregivers. The study was carried out in 2 phases using 2 groups of participants in a single tertiary centre. The focus of the first group was to establish the residual burden of emotional trauma, QoL and cognitive impairment at a mean 6 month after cardiac arrest who received standard rehabilitation care. In the second group, a comprehensive psychological support intervention was introduced from the outset to see if it made an impact on the wellbeing and cognitive function of the participants in a 6-month follow-up timescale. A recent study confirmed that short term unadjusted survival to hospital discharge of patients admitted with cardiac arrest was in the region of 67.1% and neurologically intact survival to hospital discharge was in the region of 55.7% (Islam, Hampton-Till et al. 2015) and therefore, any potential benefit of the CARE study would be available to the vast majority of cardiac arrest survivors and their caregivers.

Consecutive adult survivors of cardiac arrest with good neurological recovery defined by CPC grade 1-2 (Jennett, Bond 1975) and their caregivers were included in the study. Participants in group 1 were recruited using the hospital registry for cardiac arrest and Group 2 participants were recruited prospectively on hospital admission if they met the selection criteria. The latter group received detailed information leaflet, immediate referral to on-site psychiatrist, if appropriate, dedicated phone line to provide information regarding cardiac arrest on discharge and attendance at a focused cardiac arrest clinic, where physical health and psychological well-being were assessed and managed. Validated questionnaires were used to document assessments of QoL and cognitive function at defined time points.

Comparisons were made between Group 1 and Group 2 participants at 6-month follow-up and also a further comparison was made within Group 2 to compare baseline data with 6-month follow-up. Patients within Group 2 showed significant improvements in all domains of QoL assessment at 6 months except general health; however such improvement were not statistically significant when patients in Group 1 were compared with Group 2 patients. Caregivers within Group 2 also showed improvements in most domains of QoL assessment at 6-month follow-up without reaching statistical significance. No such trend was observed when caregivers in Group 1 were compared with caregivers in Group 2.

In terms of cognitive function, patients within Group 2 showed significant improvement when re-assessed at 6 months in one of the validated assessment tools but no difference was observed when Group 2 patients were compared with Group 1. Although the differences did not reach statistical significance, there was a trend towards improvement in cognitive function when caregivers within Group 2 were re-assessed at 6 months and similar comparison made with caregivers from Group 1.

In summary, the CARE study re-affirms presence of enormous emotional burden amongst cardiac arrest survivors and caregivers. Within the limitations of our small study, we were unable to demonstrate a benefit of the simple psychological intervention in cardiac arrest survivors and caregivers compared to those who received standard rehabilitation. However, our experience of looking after these participants has given us greater insight into understanding some of the very individual problems that they face. And clearly, there is a need more greater investment to address the concerns of this very important group of patients and their caregivers.

5.2.2. Relevant research in this field

The LAS reported a remarkable 32% survival to hospital discharge of witnessed OHCA with initial shockable rhythm compared to 5% over 10 years ago (Watson L: Virdi G, Fothergill R 2012). Better access to chain of survival is likely to result in improvement in cardiac arrest survival to hospital discharge rates and therefore, more people are expected to live with the unseen consequences of cardiac arrest. Beyond the physical health impacts, it has been reported that 50% patients suffer cognitive impairment, 50% develop fatigue, 35% live with emotional problems and 25% experience a reduced QoL (Moulaert, Verbunt et al. 2009, Wachelder, Moulaert et al. 2009).

The landmark trial in this field was carried out in Netherlands by Moulaert et al (Moulaert, van Heugten et al. 2015) where 185 patients were randomised to receiving intervention or standard care with an aim to better participation in society and improve QoL. They successfully reported that patients in the intervention group reported significant improvements in role emotional, mental health and general health components of the SF-36 and overall emotional state and anxiety levels at 12-month follow-up. Return to work rate was significantly better at 3-month follow-up but the difference in improvement could not hold at 12 months. Caregivers did not report improvement in QoL or emotional wellbeing at 12-month follow-up, which is similar to the finding in the CARE study described above.

Two further studies previously successfully investigated impact of psychological interventions in cardiac arrest survivors. Cowan et al conducted a prospective RCT investigating the impact of focused psychosocial therapy on cardiovascular mortality in

cardiac arrest survivors and found a significant reduction in mortality in patients receiving the intervention over a 2 year period (Cowan, Pike et al. 2001). Dougherty et al carried out a prospective RCT investigating the impact of 8 week educational telephone intervention aimed at improving the psychological wellbeing of cardiac arrest survivors who received ICD as part of their treatment (Dougherty, Thompson et al. 2005). They found that there was sustained improvement on patient concerns, reduced anxiety levels and better self-efficacy at 12-month follow-up in the intervention group. However, these groups did not carry out a cost-effectiveness analysis to see if this intervention should be incorporated into routine clinical practice.

5.2.3. Cost effectiveness of neurologically focussed follow up

The success of implementing a simple comprehensive intervention in improving the emotional state and QoL of cardiac arrest survivors (Moulaert, van Heugten et al. 2015) prompted authors to evaluate its cost effectiveness to help advocate routine incorporation into clinical practice. The findings were published recently in the journal of Resuscitation (Moulaert, Goossens et al. 2016). In addition to standard rehabilitation, patients and caregivers in the intervention group received between 1-6 face-to-face consultations with a trained nurse at patients' homes or at an outpatient clinic, depending on individual circumstances of the patient and caregiver. During these consultations, an assessment of the cognitive function and emotional wellbeing was made using validated questionnaires, verbal and written information on cardiac arrest and neurological consequences provided, self-management promoted and referred to a specialist if clinically warranted. Follow-up meetings were carried out by research assistants at 2 weeks, 3 months and 1 year to evaluate effectiveness of the intervention over the control group.

A comprehensive cost analysis was carried out to include intervention costs, direct costs such as healthcare costs, patient and family costs and indirect costs such as productivity losses using monthly cost diaries. In the economic evaluation, 136 patients were included for whom all cost data was available (Intervention n=72; Control n=64). The economic evaluation consisted of a cost-utility analysis and a cost effectiveness analysis.

The direct medical costs were significantly lower in the intervention group for many routine hospital visits but the cost of out-patient rehabilitation and admission in a psychiatry hospital was higher. The mean cost of providing the intervention in the year was €127. There were no significant differences in the overall costs between the 2 groups. The incremental cost effectiveness ratio supported the cost effectiveness of the

intervention and the probability of the intervention being cost effective was in excess of 54%. The authors concluded that, the results were robust and it demonstrated positive societal economic effects and is cost effective. Based on these findings, the authors recommend incorporation of this intervention into routine medical practice.

5.2.4. Conclusion and Future direction

The National Institute of Clinical Excellence (NICE) recommend routine review of patients discharged from critical care units within 2-3 months by means of a face-to-face consultation by an appropriately skilled health care professional, to carry out a functional assessment (NICE, National Institute for Clinical Excellence 2013). The recommendation extends to advocate referral to specialist services if there is concern regarding rate of recovery or development of unanticipated physical or non-physical comorbidity. Elaboration of the symptoms of non-physical comorbidity includes development of anxiety, depression, cognitive impairment and PTSD. Therefore, based on this guideline and the evidence presented in earlier sections, a business case can be put forward to implement simple psychological intervention to improve QoL and emotional wellbeing of cardiac arrest survivors. Although it is likely to be more resource intensive, it will be worth including patients whose neurological recovery remain compromised at CPC level 3 (Jennett, Bond 1975) as these are the group who are most likely to benefit from any proven psychological intervention along with their caregivers.

At the Essex CTC, since the conclusion of the CARE study, a regular CARE clinic is being held whereby cardiac arrest survivors and their caregivers are offered comprehensive support and information regarding coping strategies. Patients and any caregivers identified to be at risk of or suffering from psychological trauma such as PTSD, are now offered formal consultation with a clinical psychologist who offer specialist support for this important group of individuals. Going forward, we want to expand the services to include patients with poorer neurological recovery (CPC 3-5) and their caregivers to be offered the professional psychological support. Inevitably, this will be challenging as it is likely that these group of individuals may have restricted mobility and impaired cognitive function. The caregivers of these cardiac arrest survivors are likely to suffer prolonged and protracted period of psychological trauma in the form of depression, anxiety and PTSD and there is every reason to offer them a helping hand to enable them to re-integrate them into society. Their care needs may be unique and specific to the environment that they live in. Hence, any support being offered may need to be individualised for their needs.

In the long term, we hope to form a focus group in collaboration with the resuscitation council such that the CARE model can be expanded across the nation and the beneficial effects of our ground work can reach far and wide. Needless to say, the expansion of the services will require more financial and human resources; but as shown in the latest analysis by Moulaert et al (Moulaert, Goossens et al. 2016), attempts to help survivors of cardiac arrest and their caregivers reintegrate into society are cost effective.

5.3. COOLAMI

5.3.1. Key findings

The COOLAMI case series was carried out as a prospective study to evaluate the feasibility of simultaneously administering TH in patients presenting with STEMI in a tertiary UK heart attack centre, specifically looking at team dynamics, reducing door to balloon time and recording any adverse incidents related to trial intervention. The trial was found to be feasible as evidenced by a similar average door to balloon times for the first 11 patients recruited to this study being 38 minutes in comparison to a mean of 37 minutes for all patients presenting with STEMI at the Essex CTC in 2014. In the CHILL MI trial the door to balloon time was delayed by an average of 9 minutes (Erlinge, Gotberg et al. 2014).

Independent monitoring of our data suggested that the door to balloon time and general team efficiency improved with time. There has been no trial related adverse event and no compromise to patient care as a result of participation in this study. One of the major challenges of conducting this study was shiver management in conscious patients, which was discussed in introduction. Through strict adherence to trial protocol regarding shiver management, early recognition from ECG changes, we were able to deliver a cooling regimen to our patients effectively without any early termination due to shivering.

5.3.2. Conclusion and future direction

Animal studies have shown that TH can reduce left ventricular infarct size by up to 80% if instituted early before reperfusion in the setting coronary artery occlusion (Dixon, Whitbourn et al. 2002, Gotberg, Olivecrona et al. 2008a, Erlinge 2011). Human trials to date have not been so promising to date. The CHILL MI was the latest RCT conducted by Erlinge et al (Erlinge, Gotberg et al. 2014) and found no significant difference in overall infarct size in patients treated with TH. However, subgroup analysis of patients presenting with anterior STEMI within 4 hours, showed that TH reduced infarct size by 33% and a significant reduction in incidence of heart failure was also reported.

A structured literature review was recently published looking at the feasibility, safety and efficacy of TH in the setting of STEMI (Saunderson, Chowdhary et al. 2016). The authors commented that with exception of one trial (Nichol, Strickland et al. 2015) where they used peritoneal lavage, all other studies were considered feasible. The higher MACE rate in the VELOCITY trial (Nichol, Strickland et al. 2015) was driven by

higher rate of stent thrombosis but it was interesting to note that a third of the patients in this trial were administered clopidogrel which has been reported to have worse anti-platelet function in the context of hypothermia (Bednar, Kroupa et al. 2016). The authors also pointed out the lack of overall success for TH in STEMI can be explained by delayed presentation from symptom onset and only about 75% patients reaching target temperature of ≤35°C prior to reperfusion in the larger trials (Erlinge, Gotberg et al. 2014). Therefore future trials should aim to establish if more rapid and efficient TH to ensure target temperature of ≤35°C is reached before reperfusion without causing delay in PPCI can translate into reduction in infarct size and sustained improvement in left ventricular ejection fraction.

The recently conducted COOL AMI EU pilot trial using Zoll Proteus intravascular temperature management (IVTM) system demonstrated rapid and safe cooling of patients presenting with anterior STEMI to 33.6°C prior to reperfusion and this was associated with a non-significant, yet notable 7.1% absolute and 30% relative reduction in infarct size (Noc, Erlinge et al. 2017). This pilot trial was not powered to show difference in clinical outcome.

The COOL AMI EU pivotal trial (NCT03173313) is a larger statistically powered trial designed to investigate whether simultaneous TH with PPCI results in reduction in infarct size. In this multicentre trial, 468 patients presenting with anterior and inferior STEMI will be randomly allocated in a 1:1 manner to PPCI plus simultaneous endovascular cooling with Zoll Proteus IVTM device and the results will be compared with standard treatment with PPCI alone. Infarct size will be measured with cardiac MRI scan 4-6 weeks after initial presentation. The results of this trial will be eagerly awaited as it is expected to generate important insight into the future role of TH in STEMI.

Appendix 1.1 COOLCATH Selection Criteria

Patient Inclusion Criteria

1) ≥ 18 years old
2) Post cardiac arrest with ROSC
3) Planning to receive therapeutic hypothermia as part of post- cardiac arrest care

Patient Exclusion Criteria

1) Cardiac arrest caused by trauma, head injury, massive haemorrhage, drug overdose, cerebrovascular accident, drowning, electric shock or hanging.
2) Already hypothermic (<34°C)
3) Nasal obstruction preventing the insertion of a nasal catheter
4) Patients without established definitive airway
5) Do Not Attempt to Resuscitate (DNAR) orders
6) Known terminal illness (eg. malignancy in the end stages)
7) Known or obvious pregnancy
8) Known coagulation disorder (except those induced by medication eg. thrombolytics)
9) Known O_2- dependency

Appendix 1.2 CPC Scale

CPC Scale	**Interpretation**
1	Good cerebral performance or minor disability
2	Moderate disability
3	Severe disability
4	Coma or vegetative state
5	Brain Death

Appendix 1.3: CARE Questionnaires

SF-36 Questionnaire adopted from RAND

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. **Compared to one year ago**, how would you rate your health in general **now**?	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing **several** flights of stairs	[1]	[2]	[3]
7. Climbing **one** flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking **more than a mile**	[1]	[2]	[3]
10. Walking **several blocks**	[1]	[2]	[3]
11. Walking **one block**	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(Circle One Number)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

21. How much **bodily** pain have you had during the **past 4 weeks**?

(Circle One Number)

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

22. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks** . . .

(Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6

29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

How TRUE or FALSE is <u>each</u> of the following statements for you.

(Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

The Cognitive Failures Questionnaire (Broadbent et al 1982)

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the past 6 months. Please circle the appropriate number.

		Very often	Quite often	Occasion - ally	Very rarely	Never
1.	Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2.	Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3.	Do you fail to notice signposts on the road?	4	3	2	1	0
4.	Do you find you confuse right and left when giving directions?	4	3	2	1	0
5.	Do you bump into people?	4	3	2	1	0
6.	Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
7.	Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8.	Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9.	Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10.	Do you lose your temper and regret it?	4	3	2	1	0
11.	Do you leave important letters unanswered for days?	4	3	2	1	0

		Very often	Quite often	Occasion - ally	Very rarely	Never
12.	Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13.	Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
14.	Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15.	Do you have trouble making up your mind?	4	3	2	1	0
16.	Do you find you forget appointments?	4	3	2	1	0
17.	Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18.	Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19.	Do you daydream when you ought to be listening to something?	4	3	2	1	0
20.	Do you find you forget people's names?	4	3	2	1	0
21.	Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22.	Do you find you can't quite remember something although	4	3	2	1	0

	it's "on the tip of your tongue"?					
		Very often	Quite often	Occasion - ally	Very rarely	Never
23.	Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24.	Do you drop things?	4	3	2	1	0
25.	Do you find you can't think of anything to say?	4	3	2	1	0

References

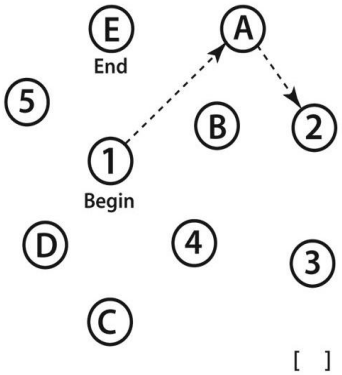
Broadbent, D.E., Cooper, P.F., FitzGerald, P., & Parkes, K.R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. *British Journal of Clinical Psychology*, *21*, 1-16.

Montreal Cognitive Assessment Tool

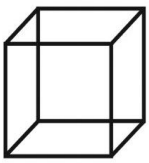
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube

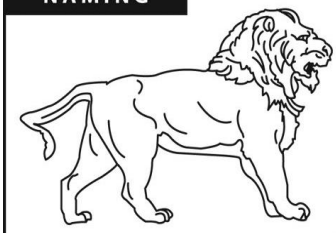


[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands __/5

NAMING



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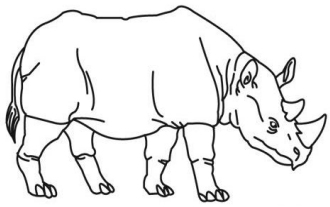

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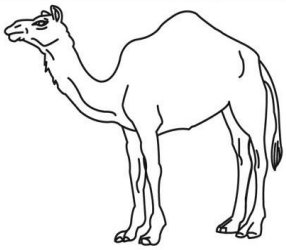

[ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

 www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

The Essex
Cardiothoracic Centre

Appendix 1.4 Life after Cardiac arrest Leaflet

This information leaflet is intended for cardiac arrest survivors, their family members and caregivers. It provides information on the possible consequences of cardiac arrest, including potential changes in cognitive function, emotion and behaviour and how this can affect your daily living. It also offers expert advice about how to deal with these changes. We advise you to use what is relevant to you, as all the information may not be relevant to you.

Patient Information

Cardiac arrest is defined as the sudden termination of the pumping action of the heart, which can be life threatening in the absence of prompt resuscitation. The brain is heavily dependent on the heart to receive blood and oxygen supply that are required for its function. During a cardiac arrest, the brain is at risk of sustaining damage, as it is completely deprived of blood supply. Brain damage can result in variable levels of consciousness, movement disorders and impairment of cognitive function. Hence, the consequence of a cardiac arrest is not limited to problems in the heart but has significant implications in brain function, which can subsequently affect quality of life in patients who survive this life changing event.

During the first few months after cardiac arrest, most of the recovery of your brain will occur. You will notice these improvements. However, some consequences like emotional wellbeing and cognitive function may not improve in the short term. These are usually the 'invisible consequences' of cardiac arrest. It is important to consider whether you experience these problems, which may be difficult to recognise. Your family members, friends or a healthcare professional can help you to find out which changes have occurred in your functioning.

Changes in thinking

When brain has suffered damage, the total capacity of brain function and speed of thinking can be diminished. In the next section, you will read common examples of changes in thinking, together with some tips.

- **Forgetfulness:** It is not possible to remember everything as you used to. Information from the past is often remembered well. In contrast, remembering new information has become more difficult.

Tip: Use a diary. This will unburden your brain and prevent you from forgetting things.

- **Slowness:** Thinking goes slower and daily activities take more time and energy.
  Tip: Make sure to plan enough time for the things you want to do. Make choice and try to say 'no'.
- **Concentration:** It is difficult to focus your attention
  Tip: Try to work in a quiet environment to avoid being distracted and improve your performance.
- **Multi-tasking:** It has become difficult to do two things at once such as cooking and talking.
  Tip: Plan your activities one after the other instead of at the same time.
- **Planning:** Planning, organising and keeping an overview are more difficult now.
  Tip: Plan beforehand how you are going to execute your activities, write this down and look at it regularly.
- **Fatigue:** Activities which were easy before will now take more energy. You feel tired more quickly.
  Tip: Try to break your activities into smaller ones and take regular breaks
- **Agitation:** You can feel exhausted more easily. This can lead to irritation or agitation.
  Tip: The tips above will help will diminish the chance of becoming agitated.

Changed feelings

The memories of the cardiac arrest itself are rare, but the fact that it happened can make one feel very anxious. Often people are afraid of a recurrence of the event and this can lead to avoidance of certain activities, which in itself generates more fear and insecurity. It is better to pick up your activities gradually which gives you more confidence in your functioning. Occasionally, you may benefit from talking to a health care professional who may be able to offer expert advice about dealing with this situation. Feelings of depression are also quite common and can emerge even after a few months. It is important to find out whether this is the case for you. Treating depression is possible and can consist of counselling and/or medication.

Changes in behaviour

Brain damage can lead to changes in behaviour, which is can be very diverse. Some people can become impulsive, easily agitated or disinhibited, while others can become

more passive and show lack of initiative. Sometimes the person is not aware of these changes, which can be a burden to family members and caregivers.

Relaxation

It is vital to find time to relax especially as usual daily activities can be more stressful, than before cardiac arrest. Physical activity is a form of relaxation, as it has a positive influence on endurance and health. Other people relax by listening to music or performing another leisure activity. It can also help just to do nothing for a while.

Family members and caregivers

A cardiac arrest is a major life changing event not only for the patient but also close family members, friends and caregivers. On the one hand, you are happy that he/she survived the cardiac arrest; on the other hand there can be fear and grief about the things cardiac arrest has changed.

Different person

A cardiac arrest can change your close relative or friend. Some partners say ‘He is not the same person anymore’ or ‘I have another wife now’. This can indeed be the case if the cardiac arrest led to brain damage, which changes the way in which one feels, thinks or behaves. This can lead to changes in relationship. You may have to take on additional responsibilities, which can be quite stressful. Sometimes changes occur within the relationship itself or in the area of intimacy or sexuality. It is important to talk about these changes to try to find solutions. A health care professional can help you with that.

Take care of yourself

Family members and caregivers can be worried about recurrence of the cardiac arrest. Sometimes these worries can be so pronounced that the person who had the cardiac arrest is never left alone. This is not necessarily the best solution for everyone involved. It is important to try and regain confidence, which may take time.

Being a partner or a close relative, it is important that you also take care of your own health. Strain and depression are often seen in caregivers. Try to notice when you feel burdened and ask for help. Try to arrange some leisure time and relaxation for yourself. Finding a balance between activity and rest is also a challenge for the caregivers.

References

The Helsinki Declaration of the World Medical Association (WMA). Ethical principles of medical research involving human subjects. 2014. *Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego,* **36**(215), pp. 298-301.

The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. 1985. *The New England journal of medicine,* **312**(14), pp. 932-936.

AL THENAYAN, E., SAVARD, M., SHARPE, M., NORTON, L. and YOUNG, B., 2008. Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. *Neurology,* **71**(19), pp. 1535-1537.

ALBERTINE, K.H., WEYRICH, A.S., MA, X.L., LEFER, D.J., BECKER, L.C. and LEFER, A.M., 1994. Quantification of neutrophil migration following myocardial ischemia and reperfusion in cats and dogs. *Journal of leukocyte biology,* **55**(5), pp. 557-566.

ALLOATTI, G., MONTRUCCHIO, G., EMANUELLI, G. and CAMUSSI, G., 1992. Platelet-activating factor (PAF) induces platelet/neutrophil co-operation during myocardial reperfusion. *Journal of Molecular and Cellular Cardiology,* **24**(2), pp. 163-171.

AMES, A.,3rd, WRIGHT, R.L., KOWADA, M., THURSTON, J.M. and MAJNO, G., 1968. Cerebral ischemia. II. The no-reflow phenomenon. *The American journal of pathology,* **52**(2), pp. 437-453.

ANDERSSON, A.E., ROSEN, H. and SUNNERHAGEN, K.S., 2015. Life after cardiac arrest: A very long term follow up. *Resuscitation,* **91**, pp. 99-103.

ARRICH, J., HOLZER, M., HAVEL, C., WARENITS, A.M. and HERKNER, H., 2016. Pre-hospital versus in-hospital initiation of cooling for survival and neuroprotection after out-of-hospital cardiac arrest. *The Cochrane database of systematic reviews,* **3**, pp. CD010570.

AUTHORS/TASK FORCE MEMBERS, WINDECKER, S., KOLH, P., ALFONSO, F., COLLET, J.P., CREMER, J., FALK, V., FILIPPATOS, G., HAMM, C., HEAD, S.J., JUNI, P., KAPPETEIN, A.P., KASTRATI, A., KNUUTI, J., LANDMESSER, U., LAUFER, G., NEUMANN, F.J., RICHTER, D.J., SCHAUERTE, P., SOUSA UVA, M., STEFANINI, G.G., TAGGART, D.P., TORRACCA, L., VALGIMIGLI, M., WIJNS, W. and WITKOWSKI, A., 2014. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *European heart journal,* **35**(37), pp. 2541-2619.

BACK, T., HEMMEN, T. and SCHULER, O.G., 2004. Lesion evolution in cerebral ischemia. *Journal of neurology,* **251**(4), pp. 388-397.

BAFFES, T.G., 1958. Hypothermia in Cardiovascular Surgery. *Journal of the National Medical Association,* **50**(6), pp. 426-428.

BAKHSHESHI, M.F. and LEE, T.Y., 2014. Non-invasive monitoring of brain temperature by near-infrared spectroscopy. *Temperature (Austin, Tex.),* **2**(1), pp. 31-32.

BEDNAR, F., KROUPA, J., ONDRAKOVA, M., OSMANCIK, P., KOPA, M. and MOTOVSKA, Z., 2016. Antiplatelet efficacy of P2Y12 inhibitors (prasugrel, ticagrelor, clopidogrel) in patients treated with mild therapeutic hypothermia after cardiac arrest due to acute myocardial infarction. *Journal of thrombosis and thrombolysis,* **41**(4), pp. 549-555.

BEESEMS, S.G., WITTEBROOD, K.M., DE HAAN, R.J. and KOSTER, R.W., 2014. Cognitive function and quality of life after successful resuscitation from cardiac arrest. *Resuscitation,* **85**(9), pp. 1269-1274.

BENECHILL INTERNATIONAL AG, , RhinoChill Intranasal Cooling System. Available: http://www.benechill.com/wp/rhinochill-trade/rhinochill-device/.

BENSON, D.W., WILLIAMS, G.R.,Jr, SPENCER, F.C. and YATES, A.J., 1959. The use of hypothermia after cardiac arrest. *Anesthesia and Analgesia,* **38**, pp. 423-428.

BERDOWSKI, J., BERG, R.A., TIJSSEN, J.G. and KOSTER, R.W., 2010. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation,* **81**(11), pp. 1479-1487.

BERGER, P.B., ELLIS, S.G., HOLMES, D.R.,Jr, GRANGER, C.B., CRIGER, D.A., BETRIU, A., TOPOL, E.J. and CALIFF, R.M., 1999. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. *Circulation,* **100**(1), pp. 14-20.

BERNARD, S.A., SMITH, K., CAMERON, P., MASCI, K., TAYLOR, D.M., COOPER, D.J., KELLY, A.M., SILVESTER, W. and RAPID INFUSION OF COLD HARTMANNS (RICH) INVESTIGATORS, 2010. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. *Circulation,* **122**(7), pp. 737-742.

BERNARD, S.A., SMITH, K., CAMERON, P., MASCI, K., TAYLOR, D.M., COOPER, D.J., KELLY, A.M., SILVESTER, W. and RAPID INFUSION OF COLD HARTMANNS INVESTIGATORS, 2012. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest*. *Critical Care Medicine,* **40**(3), pp. 747-753.

BERNARD, S.A., SMITH, K., FINN, J., HEIN, C., GRANTHAM, H., BRAY, J.E., DEASY, C., STEPHENSON, M., WILLIAMS, T.A., STRANEY, L.D., BRINK, D., LARSEN, R., COTTON, C. and CAMERON, P., 2016. Induction of Therapeutic Hypothermia During Out-of-Hospital Cardiac Arrest Using a Rapid Infusion of Cold Saline: The RINSE Trial (Rapid Infusion of Cold Normal Saline). *Circulation,* **134**(11), pp. 797-805.

BERNARD, S.A., GRAY, T.W., BUIST, M.D., JONES, B.M., SILVESTER, W., GUTTERIDGE, G. and SMITH, K., 2002. Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. *N Engl J Med,* **346**(8), pp. 557-563.

BIGELOW, W.G. and MCBIRINIE, J.E., 1953. Further experiences with hypothermia for intracardiac surgery in monkeys and groundhogs. *Annals of Surgery,* **137**(3), pp. 361-365.

BLATT, A., ELBAZ-GREENER, G.A., MIZRACHI, A., J'BARA, Z., TARABOULOS, T., LITOVCHIK, I., VERED, Z. and MINHA, S., 2015. Adjunctive mild hypothermia therapy to primary percutaneous coronary intervention in patients with ST segment elevation myocardial infarction complicated with cardiogenic shock: A pilot feasibility study. *Cardiology journal,* **22**(3), pp. 285-289.

BOGAERT, J., KALANTZI, M., RADEMAKERS, F.E., DYMARKOWSKI, S. and JANSSENS, S., 2007. Determinants and impact of microvascular obstruction in successfully reperfused ST-segment elevation myocardial infarction. Assessment by magnetic resonance imaging. *European radiology,* **17**(10), pp. 2572-2580.

BOLLI, R., JEROUDI, M.O., PATEL, B.S., DUBOSE, C.M., LAI, E.K., ROBERTS, R. and MCCAY, P.B., 1989. Direct evidence that oxygen-derived free radicals contribute to postischemic myocardial dysfunction in the intact dog. *Proceedings of the National Academy of Sciences of the United States of America,* **86**(12), pp. 4695-4699.

BOPASSA, J.C., VANDROUX, D., OVIZE, M. and FERRERA, R., 2006. Controlled reperfusion after hypothermic heart preservation inhibits mitochondrial permeability transition-pore opening and enhances functional recovery. *American journal of physiology.Heart and circulatory physiology,* **291**(5), pp. H2265-71.

BOTTIGER, B.W., SCHMITZ, B., WIESSNER, C., VOGEL, P. and HOSSMANN, K.A., 1998. Neuronal stress response and neuronal cell damage after cardiocirculatory arrest in rats. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* **18**(10), pp. 1077-1087.

BROADBENT, D.E., COOPER, P.F., FITZGERALD, P. and PARKES, K.R., 1982. The Cognitive Failures Questionnaire (CFQ) and its correlates. *The British journal of clinical psychology / the British Psychological Society,* **21 (Pt 1)**(Pt 1), pp. 1-16.

BROOKES, P.S., YOON, Y., ROBOTHAM, J.L., ANDERS, M.W. and SHEU, S.S., 2004. Calcium, ATP, and ROS: a mitochondrial love-hate triangle. *American journal of physiology.Cell physiology,* **287**(4), pp. C817-33.

BUNCH, T.J., WHITE, R.D., KHAN, A.H. and PACKER, D.L., 2004. Impact of age on long-term survival and quality of life following out-of-hospital cardiac arrest. *Critical Care Medicine,* **32**(4), pp. 963-967.

BURNS, R.J., GIBBONS, R.J., YI, Q., ROBERTS, R.S., MILLER, T.D., SCHAER, G.L., ANDERSON, J.L., YUSUF, S. and CORE STUDY INVESTIGATORS, 2002. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. *Journal of the American College of Cardiology,* **39**(1), pp. 30-36.

BUSL, K.M. and GREER, D.M., 2010. Hypoxic-ischemic brain injury: pathophysiology, neuropathology and mechanisms. *NeuroRehabilitation,* **26**(1), pp. 5-13.

BUSTO, R., DIETRICH, W.D., GLOBUS, M.Y. and GINSBERG, M.D., 1989. The importance of brain temperature in cerebral ischemic injury. *Stroke; a journal of cerebral circulation,* **20**(8), pp. 1113-1114.

BUSTO, R., DIETRICH, W.D., GLOBUS, M.Y., VALDES, I., SCHEINBERG, P. and GINSBERG, M.D., 1987. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* **7**(6), pp. 729-738.

CANADIAN CARDIOVASCULAR SOCIETY, AMERICAN ACADEMY OF FAMILY PHYSICIANS, AMERICAN COLLEGE OF CARDIOLOGY, AMERICAN HEART ASSOCIATION, ANTMAN, E.M., HAND, M., ARMSTRONG, P.W., BATES, E.R., GREEN, L.A., HALASYAMANI, L.K., HOCHMAN, J.S.,

KRUMHOLZ, H.M., LAMAS, G.A., MULLANY, C.J., PEARLE, D.L., SLOAN, M.A., SMITH, S.C.,Jr, ANBE, D.T., KUSHNER, F.G., ORNATO, J.P., PEARLE, D.L., SLOAN, M.A., JACOBS, A.K., ADAMS, C.D., ANDERSON, J.L., BULLER, C.E., CREAGER, M.A., ETTINGER, S.M., HALPERIN, J.L., HUNT, S.A., LYTLE, B.W., NISHIMURA, R., PAGE, R.L., RIEGEL, B., TARKINGTON, L.G. and YANCY, C.W., 2008. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology,* **51**(2), pp. 210-247.

CASTREN, M., NORDBERG, P., SVENSSON, L., TACCONE, F., VINCENT, J.L., DESRUELLES, D., EICHWEDE, F., MOLS, P., SCHWAB, T., VERGNION, M., STORM, C., PESENTI, A., PACHL, J., GUERISSE, F., ELSTE, T., ROESSLER, M., FRITZ, H., DURNEZ, P., BUSCH, H.J., INDERBITZEN, B. and BARBUT, D., 2010. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). *Circulation,* **122**(7), pp. 729-736.

CHEN, J., CRISPIN, J.C., TEDDER, T.F., DALLE LUCCA, J. and TSOKOS, G.C., 2009. B cells contribute to ischemia/reperfusion-mediated tissue injury. *Journal of Autoimmunity,* **32**(3-4), pp. 195-200.

CHENG, C., MATSUKAWA, T., SESSLER, D.I., OZAKI, M., KURZ, A., MERRIFIELD, B., LIN, H. and OLOFSSON, P., 1995. Increasing mean skin temperature linearly reduces the core-temperature thresholds for vasoconstriction and shivering in humans. *Anesthesiology,* **82**(5), pp. 1160-1168.

CHIEN, G.L., WOLFF, R.A., DAVIS, R.F. and VAN WINKLE, D.M., 1994. "Normothermic range" temperature affects myocardial infarct size. *Cardiovascular research,* **28**(7), pp. 1014-1017.

CHOPP, M., KNIGHT, R., TIDWELL, C.D., HELPERN, J.A., BROWN, E. and WELCH, K.M., 1989. The metabolic effects of mild hypothermia on global cerebral ischemia and recirculation in the cat: comparison to normothermia and hyperthermia. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* **9**(2), pp. 141-148.

CHRISTIAN, T.F., SCHWARTZ, R.S. and GIBBONS, R.J., 1992. Determinants of infarct size in reperfusion therapy for acute myocardial infarction. *Circulation,* **86**(1), pp. 81-90.

CINCINNATI SUB-ZERO PRODUCTS, I., , Blanketrol® III Body Temperature Regulation System. Available: http://www.cszmedical.com/Products/Hyper-Hypothermia/Blanketrol-III.aspx.

COHEN, A., GUYON, P., JOHNSON, N., CHAUVEL, C., LOGEART, D., COSTAGLIOLA, D. and VALTY, J., 1995. Hemodynamic criteria for diagnosis of right ventricular ischemia associated with inferior wall left ventricular acute myocardial infarction. *The American Journal of Cardiology,* **76**(4), pp. 220-225.

CORBETT, R., LAPTOOK, A. and WEATHERALL, P., 1997. Noninvasive measurements of human brain temperature using volume-localized proton magnetic resonance spectroscopy. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* **17**(4), pp. 363-369.

COVACIU, L., WEIS, J., BENGTSSON, C., ALLERS, M., LUNDERQUIST, A., AHLSTROM, H. and RUBERTSSON, S., 2011. Brain temperature in volunteers subjected to intranasal cooling. *Intensive care medicine,* **37**(8), pp. 1277-1284.

COWAN, M.J., PIKE, K.C. and BUDZYNSKI, H.K., 2001. Psychosocial nursing therapy following sudden cardiac arrest: impact on two-year survival. *Nursing research,* **50**(2), pp. 68-76.

CROMPTON, M., COSTI, A. and HAYAT, L., 1987. Evidence for the presence of a reversible Ca2+-dependent pore activated by oxidative stress in heart mitochondria. *The Biochemical journal,* **245**(3), pp. 915-918.

CRONIER, P., VIGNON, P., BOUFERRACHE, K., AEGERTER, P., CHARRON, C., TEMPLIER, F., CASTRO, S., EL MAHMOUD, R., LORY, C., PICHON, N., DUBOURG, O. and VIEILLARD-BARON, A., 2011. Impact of routine percutaneous coronary intervention after out-of-hospital cardiac arrest due to ventricular fibrillation. *Critical Care (London, England),* **15**(3), pp. R122.

CRUMRINE, R.C. and LAMANNA, J.C., 1991. Regional cerebral metabolites, blood flow, plasma volume, and mean transit time in total cerebral ischemia in the rat. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* **11**(2), pp. 272-282.

DAE, M.W., GAO, D.W., SESSLER, D.I., CHAIR, K. and STILLSON, C.A., 2002. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. *American journal of physiology.Heart and circulatory physiology,* **282**(5), pp. H1584-91.

DAUBIN, C., QUENTIN, C., ALLOUCHE, S., ETARD, O., GAILLARD, C., SEGUIN, A., VALETTE, X., PARIENTI, J.J., PREVOST, F., RAMAKERS, M., TERZI, N., CHARBONNEAU, P. and DU CHEYRON, D., 2011. Serum neuron-specific enolase as predictor of outcome in comatose cardiac-arrest survivors: a prospective cohort study. *BMC cardiovascular disorders,* **11**, pp. 48-2261-11-48.

DAVE, R.H., HALE, S.L. and KLONER, R.A., 1998. Hypothermic, closed circuit pericardioperfusion: a potential cardioprotective technique in acute regional ischemia. *Journal of the American College of Cardiology,* **31**(7), pp. 1667-1671.

DAVIES, M.J., 1992. Anatomic features in victims of sudden coronary death. Coronary artery pathology. *Circulation,* **85**(1 Suppl), pp. I19-24.

DE VOS, R., DE HAES, H.C., KOSTER, R.W. and DE HAAN, R.J., 1999. Quality of survival after cardiopulmonary resuscitation. *Archives of Internal Medicine,* **159**(3), pp. 249-254.

DEBATY, G., MAIGNAN, M., SAVARY, D., KOCH, F.X., RUCKLY, S., DURAND, M., PICARD, J., ESCALLIER, C., CHOUQUER, R., SANTRE, C., MINET, C., GUERGOUR, D., HAMMER, L., BOUVAIST, H., BELLE, L., ADRIE, C., PAYEN, J.F., CARPENTIER, F., GUEUGNIAUD, P.Y., DANEL, V. and TIMSIT, J.F., 2014. Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. *Intensive care medicine,* **40**(12), pp. 1832-1842.

DEMPSEY, R.J., COMBS, D.J., MALEY, M.E., COWEN, D.E., ROY, M.W. and DONALDSON, D.L., 1987. Moderate hypothermia reduces postischemic edema development and leukotriene production. *Neurosurgery,* **21**(2), pp. 177-181.

DEYE, N., CARIOU, A., GIRARDIE, P., PICHON, N., MEGARBANE, B., MIDEZ, P., TONNELIER, J.M., BOULAIN, T., OUTIN, H., DELAHAYE, A., CRAVOISY, A., MERCAT, A., BLANC, P., SANTRE, C., QUINTARD, H., BRIVET, F., CHARPENTIER, J., GARRIGUE, D., FRANCOIS, B., QUENOT, J.P., VINCENT, F., GUEUGNIAUD, P.Y., MIRA, J.P., CARLI, P., VICAUT, E., BAUD, F.J. and CLINICAL AND ECONOMICAL IMPACT OF ENDOVASCULAR COOLING IN THE MANAGEMENT OF CARDIAC ARREST (ICEREA) STUDY GROUP, 2015. Endovascular Versus External Targeted Temperature

Management for Patients With Out-of-Hospital Cardiac Arrest: A Randomized, Controlled Study. *Circulation,* **132**(3), pp. 182-193.

DIETRICH, W.D., BUSTO, R., ALONSO, O., GLOBUS, M.Y. and GINSBERG, M.D., 1993. Intraischemic but not postischemic brain hypothermia protects chronically following global forebrain ischemia in rats. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* **13**(4), pp. 541-549.

DIXON, S.R., WHITBOURN, R.J., DAE, M.W., GRUBE, E., SHERMAN, W., SCHAER, G.L., JENKINS, J.S., BAIM, D.S., GIBBONS, R.J., KUNTZ, R.E., POPMA, J.J., NGUYEN, T.T. and O'NEILL, W.W., 2002. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. *Journal of the American College of Cardiology,* **40**(11), pp. 1928-1934.

DON, C.W., LONGSTRETH, W.T.,Jr, MAYNARD, C., OLSUFKA, M., NICHOL, G., RAY, T., KUPCHIK, N., DEEM, S., COPASS, M.K., COBB, L.A. and KIM, F., 2009. Active surface cooling protocol to induce mild therapeutic hypothermia after out-of-hospital cardiac arrest: a retrospective before-and-after comparison in a single hospital. *Critical Care Medicine,* **37**(12), pp. 3062-3069.

DONNINO, M.W., ANDERSEN, L.W., BERG, K.M., REYNOLDS, J.C., NOLAN, J.P., MORLEY, P.T., LANG, E., COCCHI, M.N., XANTHOS, T., CALLAWAY, C.W., SOAR, J. and ILCOR ALS TASK FORCE, 2016. Temperature Management After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Resuscitation,* **98**, pp. 97-104.

DONNINO, M.W., ANDERSEN, L.W., BERG, K.M., REYNOLDS, J.C., NOLAN, J.P., MORLEY, P.T., LANG, E., COCCHI, M.N., XANTHOS, T., CALLAWAY, C.W., SOAR, J. and ILCOR ALS TASK FORCE, 2015. Temperature Management After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Circulation,* **132**(25), pp. 2448-2456.

DOOLITTLE, N.D. and SAUVE, M.J., 1995. Impact of aborted sudden cardiac death on survivors and their spouses: the phenomenon of different reference points. *American Journal of Critical Care : An Official Publication, American Association of Critical-Care Nurses,* **4**(5), pp. 389-396.

DOUGHERTY, C.M., THOMPSON, E.A. and LEWIS, F.M., 2005. Long-term outcomes of a telephone intervention after an ICD. *Pacing and clinical electrophysiology : PACE,* **28**(11), pp. 1157-1167.

DUMAS, F., CARIOU, A., MANZO-SILBERMAN, S., GRIMALDI, D., VIVIEN, B., ROSENCHER, J., EMPANA, J.P., CARLI, P., MIRA, J.P., JOUVEN, X. and SPAULDING, C., 2010. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. *Circulation.Cardiovascular interventions,* **3**(3), pp. 200-207.

ENDOH, M., MAIESE, K. and WAGNER, J., 1994. Expression of the inducible form of nitric oxide synthase by reactive astrocytes after transient global ischemia. *Brain research,* **651**(1-2), pp. 92-100.

ENTMAN, M.L. and SMITH, C.W., 1994. Postreperfusion inflammation: a model for reaction to injury in cardiovascular disease. *Cardiovascular research,* **28**(9), pp. 1301-1311.

ERECINSKA, M., THORESEN, M. and SILVER, I.A., 2003. Effects of hypothermia on energy metabolism in Mammalian central nervous system. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* **23**(5), pp. 513-530.

ERLINGE, D., 2011. A Review of Mild Hypothermia as an Adjunctive Treatment for ST-Elevation Myocardial Infarction. *Therapeutic hypothermia and temperature management,* **1**(3), pp. 129-141.

ERLINGE, D., GOTBERG, M., GRINES, C., DIXON, S., BARAN, K., KANDZARI, D. and OLIVECRONA, G.K., 2013. A pooled analysis of the effect of endovascular cooling on infarct size in patients with ST-elevation myocardial infarction. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology,* **8**(12), pp. 1435-1440.

ERLINGE, D., GOTBERG, M., LANG, I., HOLZER, M., NOC, M., CLEMMENSEN, P., JENSEN, U., METZLER, B., JAMES, S., BOTKER, H.E., OMEROVIC, E., ENGBLOM, H., CARLSSON, M., ARHEDEN, H., OSTLUND, O., WALLENTIN, L., HARNEK, J. and OLIVECRONA, G.K., 2014. Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. The CHILL-MI trial: a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. *Journal of the American College of Cardiology,* **63**(18), pp. 1857-1865.

ERLINGE, D., GOTBERG, M., NOC, M., LANG, I., HOLZER, M., CLEMMENSEN, P., JENSEN, U., METZLER, B., JAMES, S., BOTKER, H.E., OMEROVIC, E., KOUL, S., ENGBLOM, H., CARLSSON, M., ARHEDEN, H., OSTLUND, O., WALLENTIN, L., KLOS, B., HARNEK, J. and OLIVECRONA, G.K., 2015. Therapeutic hypothermia for the treatment of acute myocardial infarction-combined analysis of the RAPID MI-ICE and the CHILL-MI trials. *Therapeutic hypothermia and temperature management,* **5**(2), pp. 77-84.

ERLINGE, D., GÖTBERG, M., LANG, I., HOLZER, M., NOC, M., CLEMMENSEN, P., JENSEN, U., METZLER, B., JAMES, S., BÖTKER, H.E., OMEROVIC, E., ENGBLOM, H., CARLSSON, M., ARHEDEN, H., ÖSTLUND, O., WALLENTIN, L., HARNEK, J. and OLIVECRONA, G.K., 2014. Rapid Endovascular Catheter Core Cooling Combined With Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction: The CHILL-MI Trial: A Randomized Controlled Study of the Use of Central Venous Catheter Core Cooling Combined With Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction. *Journal of the American College of Cardiology,* **63**(18), pp. 1857-1865.

FAY, T., 1959. Early experiences with local and generalized refrigeration of the human brain. *Journal of neurosurgery,* **16**(3), pp. 239-59; discussion 259-60.

FELBERG, R.A., KRIEGER, D.W., CHUANG, R., PERSSE, D.E., BURGIN, W.S., HICKENBOTTOM, S.L., MORGENSTERN, L.B., ROSALES, O. and GROTTA, J.C., 2001. Hypothermia after cardiac arrest: feasibility and safety of an external cooling protocol. *Circulation,* **104**(15), pp. 1799-1804.

FISCHER, E.G. and AMES, A., 1972. Studies on mechanisms of impairment of cerebral circulation following ischemia: effect of hemodilution and perfusion pressure. *Stroke; a journal of cerebral circulation,* **3**(5), pp. 538-542.

FUGATE, J.E., WIJDICKS, E.F., WHITE, R.D. and RABINSTEIN, A.A., 2011. Does therapeutic hypothermia affect time to awakening in cardiac arrest survivors? *Neurology,* **77**(14), pp. 1346-1350.

GAMPER, G., WILLEIT, M., STERZ, F., HERKNER, H., ZOUFALY, A., HORNIK, K., HAVEL, C. and LAGGNER, A.N., 2004. Life after death: posttraumatic stress disorder in survivors of cardiac arrest--prevalence, associated factors, and the influence of sedation and analgesia. *Critical Care Medicine,* **32**(2), pp. 378-383.

GENTLEMAN ROBERT, 2013. *R: A language and environment for statistical computing.* Vienna, Austria: R foundation for statisitical computing.

GILLIES, M.A., PRATT, R., WHITELEY, C., BORG, J., BEALE, R.J. and TIBBY, S.M., 2010. Therapeutic hypothermia after cardiac arrest: a retrospective comparison of surface and endovascular cooling techniques. *Resuscitation,* **81**(9), pp. 1117-1122.

GINSBERG, M.D. and MYERS, R.E., 1972. The topography of impaired microvascular perfusion in the primate brain following total circulatory arrest. *Neurology,* **22**(10), pp. 998-1011.

GOLL, D.E., THOMPSON, V.F., LI, H., WEI, W. and CONG, J., 2003. The calpain system. *Physiological Reviews,* **83**(3), pp. 731-801.

GOTBERG, M., OLIVECRONA, G.K., ENGBLOM, H., UGANDER, M., VAN DER PALS, J., HEIBERG, E., ARHEDEN, H. and ERLINGE, D., 2008a. Rapid short-duration hypothermia with cold saline and endovascular cooling before reperfusion reduces microvascular obstruction and myocardial infarct size. *BMC cardiovascular disorders,* **8**, pp. 7-2261-8-7.

GOTBERG, M., OLIVECRONA, G.K., KOUL, S., CARLSSON, M., ENGBLOM, H., UGANDER, M., VAN DER PALS, J., ALGOTSSON, L., ARHEDEN, H. and ERLINGE, D., 2010. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. *Circulation.Cardiovascular interventions,* **3**(5), pp. 400-407.

GOTBERG, M., VAN DER PALS, J., GOTBERG, M., OLIVECRONA, G.K., KANSKI, M., KOUL, S., OTTO, A., ENGBLOM, H., UGANDER, M., ARHEDEN, H. and ERLINGE, D., 2011. Optimal timing of hypothermia in relation to myocardial reperfusion. *Basic research in cardiology,* **106**(5), pp. 697-708.

GOTBERG, M., OLIVECRONA, G., ENGBLOM, H., UGANDER, M., VAN, D.P., HEIBERG, E., ARHEDEN, H. and ERLINGE, D., 2008b. Rapid short-duration hypothermia with cold saline and endovascular cooling before reperfusion reduces microvascular obstruction and myocardial infarct size. *BMC Cardiovascular Disorders,* **8**(1), pp. 7.

GRANJA, C., CABRAL, G., PINTO, A.T. and COSTA-PEREIRA, A., 2002. Quality of life 6-months after cardiac arrest. *Resuscitation,* **55**(1), pp. 37-44.

GRASNER, J.T., HERLITZ, J., KOSTER, R.W., ROSELL-ORTIZ, F., STAMATAKIS, L. and BOSSAERT, L., 2011. Quality management in resuscitation--towards a European cardiac arrest registry (EuReCa). *Resuscitation,* **82**(8), pp. 989-994.

GRIFFITHS, E.J. and HALESTRAP, A.P., 1995. Mitochondrial non-specific pores remain closed during cardiac ischaemia, but open upon reperfusion. *The Biochemical journal,* **307 (Pt 1)**(Pt 1), pp. 93-98.

GRIFFITHS, E.J. and HALESTRAP, A.P., 1993. Protection by Cyclosporin A of ischemia/reperfusion-induced damage in isolated rat hearts. *Journal of Molecular and Cellular Cardiology,* **25**(12), pp. 1461-1469.

GRINES CL, 2004. *ICE IT: Intravascular cooling adjunctive to percutaneous coronary intervention for acute myocardial infarction*, 2004 2004, Transcatheter cardiovascular therapeutics.

GRUBB, N.R., FOX, K.A., SMITH, K., BEST, J., BLANE, A., EBMEIER, K.P., GLABUS, M.F. and O'CARROLL, R.E., 2000. Memory impairment in out-of-hospital cardiac arrest survivors is associated with global reduction in brain volume, not focal hippocampal injury. *Stroke; a journal of cerebral circulation,* **31**(7), pp. 1509-1514.

GRUNAU, B., REYNOLDS, J.C., SCHEUERMEYER, F.X., STENSTROM, R., PENNINGTON, S., CHEUNG, C., LI, J., HABIBI, M., RAMANATHAN, K., BARBIC, D. and CHRISTENSON, J., 2016. Comparing the prognosis of those with initial shockable and non-shockable rhythms with increasing durations of CPR: Informing minimum durations of resuscitation. *Resuscitation,* **101**, pp. 50-56.

HACHIMI-IDRISSI, S., CORNE, L., EBINGER, G., MICHOTTE, Y. and HUYGHENS, L., 2001. Mild hypothermia induced by a helmet device: a clinical feasibility study. *Resuscitation,* **51**(3), pp. 275-281.

HALE, S.L., DAE, M.W. and KLONER, R.A., 2003. Hypothermia during reperfusion limits 'no-reflow' injury in a rabbit model of acute myocardial infarction. *Cardiovascular research,* **59**(3), pp. 715-722.

HALE, S.L. and KLONER, R.A., 1997. Myocardial temperature in acute myocardial infarction: protection with mild regional hypothermia. *The American Journal of Physiology,* **273**(1 Pt 2), pp. H220-7.

HARRIS BA, A.P., 2005. Direct Brain Cooling

. In: S.D. MAYER SA, ed, *Therapeutic hypothermia.* New York, NY: Marcel Dekker, pp. 323.

HARRIS, O.A., MUH, C.R., SURLES, M.C., PAN, Y., ROZYCKI, G., MACLEOD, J. and EASLEY, K., 2009. Discrete cerebral hypothermia in the management of traumatic brain injury: a randomized controlled trial. *Journal of neurosurgery,* **110**(6), pp. 1256-1264.

HARUKUNI, I. and BHARDWAJ, A., 2006. Mechanisms of brain injury after global cerebral ischemia. *Neurologic clinics,* **24**(1), pp. 1-21.

HAUSENLOY, D.J., DUCHEN, M.R. and YELLON, D.M., 2003. Inhibiting mitochondrial permeability transition pore opening at reperfusion protects against ischaemia-reperfusion injury. *Cardiovascular research,* **60**(3), pp. 617-625.

HEYNDRICKX, G.R., MILLARD, R.W., MCRITCHIE, R.J., MAROKO, P.R. and VATNER, S.F., 1975. Regional myocardial functional and electrophysiological alterations after brief coronary artery occlusion in conscious dogs. *The Journal of clinical investigation,* **56**(4), pp. 978-985.

HOFGREN, C., LUNDGREN-NILSSON, A., ESBJORNSSON, E. and SUNNERHAGEN, K.S., 2008. Two years after cardiac arrest; cognitive status, ADL function and living situation. *Brain injury,* **22**(12), pp. 972-978.

HOLZER, M., BERNARD, S.A., HACHIMI-IDRISSI, S., ROINE, R.O., STERZ, F., MULLNER, M. and COLLABORATIVE GROUP ON INDUCED HYPOTHERMIA FOR NEUROPROTECTION AFTER CARDIAC ARREST, 2005. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Critical Care Medicine,* **33**(2), pp. 414-418.

HOSSMANN, K.A., 1997. Reperfusion of the brain after global ischemia: hemodynamic disturbances. *Shock (Augusta, Ga.),* **8**(2), pp. 95-101; discussion 102-3.

HOSSMANN, K.A. and ZIMMERMANN, V., 1974. Resuscitation of the monkey brain after 1 h complete ischemia. I. Physiological and morphological observations. *Brain research,* **81**(1), pp. 59-74.

HOXWORTH, J.M., XU, K., ZHOU, Y., LUST, W.D. and LAMANNA, J.C., 1999. Cerebral metabolic profile, selective neuron loss, and survival of acute and chronic hyperglycemic rats following cardiac arrest and resuscitation. *Brain research,* **821**(2), pp. 467-479.

HUANG, C.H., CHEN, H.W., TSAI, M.S., HSU, C.Y., PENG, R.H., WANG, T.D., CHANG, W.T. and CHEN, W.J., 2009. Antiapoptotic cardioprotective effect of hypothermia treatment against oxidative stress injuries. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine,* **16**(9), pp. 872-880.

HYPOTHERMIA AFTER CARDIAC, A.S., 2002. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *The New England journal of medicine,* **346**(8), pp. 549-56.

INOUE, K., ANDO, S., GYUAN, F. and TAKABA, T., 2003. A study of the myocardial protective effect of rapid cooling based on intracellular Ca, intracellular pH, and HSP70. *Annals of Thoracic and Cardiovascular Surgery : Official Journal of the Association of Thoracic and Cardiovascular Surgeons of Asia,* **9**(5), pp. 301-306.

INSERTE, J., GARCIA-DORADO, D., HERNANDO, V. and SOLER-SOLER, J., 2005. Calpain-mediated impairment of Na+/K+-ATPase activity during early reperfusion contributes to cell death after myocardial ischemia. *Circulation research,* **97**(5), pp. 465-473.

ISLAM, S., HAMPTON-TILL, J., WATSON, N., MANNAKKARA, N.N., HAMARNEH, A., WEBBER, T., MAGEE, N., ABBEY, L., JAGATHESAN, R., KABIR, A., SAYER, J., ROBINSON, N., AGGARWAL, R., CLESHAM, G., KELLY, P., GAMMA, R., TANG, K., DAVIES, J.R. and KEEBLE, T.R., 2015. Early targeted brain COOLing in the cardiac CATHeterisation laboratory following cardiac arrest (COOLCATH). *Resuscitation,* **97**, pp. 61-67.

ITO, H., 2006. No-reflow phenomenon and prognosis in patients with acute myocardial infarction. *Nature clinical practice.Cardiovascular medicine,* **3**(9), pp. 499-506.

JARNUM, H., KNUTSSON, L., RUNDGREN, M., SIEMUND, R., ENGLUND, E., FRIBERG, H. and LARSSON, E.M., 2009. Diffusion and perfusion MRI of the brain in comatose patients treated with mild hypothermia after cardiac arrest: a prospective observational study. *Resuscitation,* **80**(4), pp. 425-430.

JENNETT, B. and BOND, M., 1975. Assessment of outcome after severe brain damage. *Lancet,* **1**(7905), pp. 480-484.

JENNINGS, R.B., SOMMERS, H.M., SMYTH, G.A., FLACK, H.A. and LINN, H., 1960. Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. *Archives of Pathology,* **70**, pp. 68-78.

JOHNSON, G.,3rd, TSAO, P.S. and LEFER, A.M., 1991. Cardioprotective effects of authentic nitric oxide in myocardial ischemia with reperfusion. *Critical Care Medicine,* **19**(2), pp. 244-252.

JONES, S.P., GIROD, W.G., PALAZZO, A.J., GRANGER, D.N., GRISHAM, M.B., JOURD'HEUIL, D., HUANG, P.L. and LEFER, D.J., 1999. Myocardial ischemia-reperfusion injury is exacerbated in absence of endothelial cell nitric oxide synthase. *The American Journal of Physiology,* **276**(5 Pt 2), pp. H1567-73.

JORDAN, J.E., ZHAO, Z.Q. and VINTEN-JOHANSEN, J., 1999. The role of neutrophils in myocardial ischemia-reperfusion injury. *Cardiovascular research,* **43**(4), pp. 860-878.

JULAYANONT, P., TANGWONGCHAI, S., HEMRUNGROJN, S., TUNVIRACHAISAKUL, C., PHANTHUMCHINDA, K., HONGSAWAT, J., SUWICHANARAKUL, P., THANASIRORAT, S. and NASREDDINE, Z.S., 2015. The Montreal Cognitive Assessment-Basic: A Screening Tool for Mild Cognitive Impairment in Illiterate and Low-Educated Elderly Adults. *Journal of the American Geriatrics Society,* **63**(12), pp. 2550-2554.

KAMARAINEN, A., VIRKKUNEN, I., TENHUNEN, J., YLI-HANKALA, A. and SILFVAST, T., 2009. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial. *Acta Anaesthesiologica Scandinavica,* **53**(7), pp. 900-907.

KANDZARI, D.E., CHU, A., BRODIE, B.R., STUCKEY, T.A., HERMILLER, J.B., VETROVEC, G.W., HANNAN, K.L., KRUCOFF, M.W., CHRISTENSON, R.H., GIBBONS, R.J., SIGMON, K.N., GARG, J., HASSELBLAD, V., COLLINS, K., HARRINGTON, R.A., BERGER, P.B., CHRONOS, N.A., HOCHMAN, J.S. and CALIFF, R.M., 2004. Feasibility of endovascular cooling as an adjunct to primary percutaneous coronary intervention (results of the LOWTEMP pilot study). *The American Journal of Cardiology,* **93**(5), pp. 636-639.

KANE, D.J., ORD, T., ANTON, R. and BREDESEN, D.E., 1995. Expression of bcl-2 inhibits necrotic neural cell death. *Journal of neuroscience research,* **40**(2), pp. 269-275.

KARASZEWSKI, B., WARDLAW, J.M., MARSHALL, I., CVORO, V., WARTOLOWSKA, K., HAGA, K., ARMITAGE, P.A., BASTIN, M.E. and DENNIS, M.S., 2006. Measurement of brain temperature with magnetic resonance spectroscopy in acute ischemic stroke. *Annals of Neurology,* **60**(4), pp. 438-446.

KASUYA, R.T., POLGAR-BAILEY, P. and TAKEUCHI, R., 2000. Caregiver burden and burnout. A guide for primary care physicians. *Postgraduate medicine,* **108**(7), pp. 119-123.

KATSURA, K., RODRIGUEZ DE TURCO, E.B., FOLBERGROVA, J., BAZAN, N.G. and SIESJO, B.K., 1993. Coupling among energy failure, loss of ion homeostasis, and phospholipase A2 and C activation during ischemia. *Journal of neurochemistry,* **61**(5), pp. 1677-1684.

KHOT, S. and TIRSCHWELL, D.L., 2006. Long-term neurological complications after hypoxic-ischemic encephalopathy. *Seminars in neurology,* **26**(4), pp. 422-431.

KIM, F., NICHOL, G., MAYNARD, C., HALLSTROM, A., KUDENCHUK, P.J., REA, T., COPASS, M.K., CARLBOM, D., DEEM, S., LONGSTRETH, W.T.,Jr, OLSUFKA, M. and COBB, L.A., 2014. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *Jama,* **311**(1), pp. 45-52.

KIM, F., OLSUFKA, M., LONGSTRETH, W.T.,Jr, MAYNARD, C., CARLBOM, D., DEEM, S., KUDENCHUK, P., COPASS, M.K. and COBB, L.A., 2007. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. *Circulation,* **115**(24), pp. 3064-3070.

KIM, J.S., JIN, Y. and LEMASTERS, J.J., 2006. Reactive oxygen species, but not Ca2+ overloading, trigger pH- and mitochondrial permeability transition-dependent death of adult rat myocytes after ischemia-reperfusion. *American journal of physiology.Heart and circulatory physiology,* **290**(5), pp. H2024-34.

KIRK, D., RAINEY, T., VAIL, A. and CHILDS, C., 2009. Infra-red thermometry: the reliability of tympanic and temporal artery readings for predicting brain temperature after severe traumatic brain injury. *Critical Care (London, England),* **13**(3), pp. R81.

KLONER, R.A., 1993. Does reperfusion injury exist in humans? *Journal of the American College of Cardiology,* **21**(2), pp. 537-545.

KRUG, A., DU MESNIL DE, R. and KORB, G., 1966. Blood supply of the myocardium after temporary coronary occlusion. *Circulation research,* **19**(1), pp. 57-62.

KUBOYAMA, K., SAFAR, P., RADOVSKY, A., TISHERMAN, S.A., STEZOSKI, S.W. and ALEXANDER, H., 1993. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. *Critical Care Medicine,* **21**(9), pp. 1348-1358.

KUFFLER, D.P., 2012. Maximizing neuroprotection: where do we stand? *Therapeutics and clinical risk management,* **8**, pp. 185-194.

LADILOV, Y.V., SIEGMUND, B. and PIPER, H.M., 1995. Protection of reoxygenated cardiomyocytes against hypercontracture by inhibition of Na+/H+ exchange. *The American Journal of Physiology,* **268**(4 Pt 2), pp. H1531-9.

LAMBERT, L., BROWN, K., SEGAL, E., BROPHY, J., RODES-CABAU, J. and BOGATY, P., 2010. Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. *Jama,* **303**(21), pp. 2148-2155.

LANG, M., WELTE, M., SYBEN, R. and HANSEN, D., 2002. Effects of hypothermia on median nerve somatosensory evoked potentials during spontaneous circulation. *Journal of neurosurgical anesthesiology,* **14**(2), pp. 141-145.

LAPIDUS, R.G. and SOKOLOVE, P.M., 1994. The mitochondrial permeability transition. Interactions of spermine, ADP, and inorganic phosphate. *The Journal of biological chemistry,* **269**(29), pp. 18931-18936.

LAPTOOK, A.R., SHALAK, L. and CORBETT, R.J., 2001. Differences in brain temperature and cerebral blood flow during selective head versus whole-body cooling. *Pediatrics,* **108**(5), pp. 1103-1110.

LARA-CELADOR, I., GONI-DE-CERIO, F., ALVAREZ, A. and HILARIO, E., 2013. Using the endocannabinoid system as a neuroprotective strategy in perinatal hypoxic-ischemic brain injury. *Neural regeneration research,* **8**(8), pp. 731-744.

LARSSON, I.M., WALLIN, E., RUBERTSSON, S. and KRISTOFFERZON, M.L., 2014. Health-related quality of life improves during the first six months after cardiac arrest and hypothermia treatment. *Resuscitation,* **85**(2), pp. 215-220.

LEE, B.K., LEE, S.J., JEUNG, K.W., LEE, H.Y., HEO, T. and MIN, Y.I., 2014. Outcome and adverse events with 72-hour cooling at 32 degrees C as compared to 24-hour cooling at 33 degrees C in comatose asphyxial arrest survivors. *The American Journal of Emergency Medicine,* **32**(4), pp. 297-301.

LEMASTERS, J.J., BOND, J.M., CHACON, E., HARPER, I.S., KAPLAN, S.H., OHATA, H., TROLLINGER, D.R., HERMAN, B. and CASCIO, W.E., 1996. The pH paradox in ischemia-reperfusion injury to cardiac myocytes. *EXS,* **76**, pp. 99-114.

LEONOV, Y., STERZ, F., SAFAR, P., RADOVSKY, A., OKU, K., TISHERMAN, S. and STEZOSKI, S.W., 1990. Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* **10**(1), pp. 57-70.

LEVY, D.E., CARONNA, J.J., SINGER, B.H., LAPINSKI, R.H., FRYDMAN, H. and PLUM, F., 1985. Predicting outcome from hypoxic-ischemic coma. *Jama,* **253**(10), pp. 1420-1426.

LIM, C., VERFAELLIE, M., SCHNYER, D., LAFLECHE, G. and ALEXANDER, M.P., 2014. Recovery, long-term cognitive outcome and quality of life following out-of-hospital cardiac arrest. *Journal of Rehabilitation Medicine,* **46**(7), pp. 691-697.

LINDNER, T.W., SOREIDE, E., NILSEN, O.B., TORUNN, M.W. and LOSSIUS, H.M., 2011. Good outcome in every fourth resuscitation attempt is achievable--an Utstein template report from the Stavanger region. *Resuscitation,* **82**(12), pp. 1508-1513.

LIPTON, P., 1999. Ischemic cell death in brain neurons. *Physiological Reviews,* **79**(4), pp. 1431-1568.

LUNDGREN-NILSSON, A., ROSEN, H., HOFGREN, C. and SUNNERHAGEN, K.S., 2005. The first year after successful cardiac resuscitation: function, activity, participation and quality of life. *Resuscitation,* **66**(3), pp. 285-289.

LY, H.Q., DENAULT, A., DUPUIS, J., VADEBONCOEUR, A., HAREL, F., ARSENAULT, A., GIBSON, C.M. and BONAN, R., 2005. A pilot study: the Noninvasive Surface Cooling Thermoregulatory System for Mild Hypothermia Induction in Acute Myocardial Infarction (the NICAMI Study). *American Heart Journal,* **150**(5), pp. 933.

MAENG, M., MORTENSEN, U.M., KRISTENSEN, J., KRISTIANSEN, S.B. and ANDERSEN, H.R., 2006. Hypothermia during reperfusion does not reduce myocardial infarct size in pigs. *Basic research in cardiology,* **101**(1), pp. 61-68.

MANNING, A.S. and HEARSE, D.J., 1984. Reperfusion-induced arrhythmias: mechanisms and prevention. *Journal of Molecular and Cellular Cardiology,* **16**(6), pp. 497-518.

MARIAK, Z., LEWKO, J., LUCZAJ, J., POLOCKI, B. and WHITE, M.D., 1994. The relationship between directly measured human cerebral and tympanic temperatures during changes in brain temperatures. *European journal of applied physiology and occupational physiology,* **69**(6), pp. 545-549.

MEHTA, J.L., NICHOLS, W.W. and MEHTA, P., 1988. Neutrophils as potential participants in acute myocardial ischemia: relevance to reperfusion. *Journal of the American College of Cardiology,* **11**(6), pp. 1309-1316.

MILLER, J.R. and MYERS, R.E., 1972. Neuropathology of systemic circulatory arrest in adult monkeys. *Neurology,* **22**(9), pp. 888-904.

MILLER, P., WIKOFF, R., GARRETT, M.J., MCMAHON, M. and SMITH, T., 1990. Regimen compliance two years after myocardial infarction. *Nursing research,* **39**(6), pp. 333-336.

MILLER, P.J. and WIKOFF, R., 1989. Spouses' psychosocial problems, resources, and marital functioning postmyocardial infarction. *Progress in cardiovascular nursing,* **4**(2), pp. 71-76.

MOKHTARANI, M., MAHGOUB, A.N., MORIOKA, N., DOUFAS, A.G., DAE, M., SHAUGHNESSY, T.E., BJORKSTEN, A.R. and SESSLER, D.I., 2001. Buspirone and meperidine synergistically reduce the shivering threshold. *Anesthesia and Analgesia,* **93**(5), pp. 1233-1239.

MOONEY, M.R., UNGER, B.T., BOLAND, L.L., BURKE, M.N., KEBED, K.Y., GRAHAM, K.J., HENRY, T.D., KATSIYIANNIS, W.T., SATTERLEE, P.A., SENDELBACH, S., HODGES, J.S. and PARHAM, W.M., 2011. Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling. *Circulation,* **124**(2), pp. 206-214.

MORAN, J.L., PETER, J.V., SOLOMON, P.J., GREALY, B., SMITH, T., ASHFORTH, W., WAKE, M., PEAKE, S.L. and PEISACH, A.R., 2007. Tympanic temperature measurements: are they reliable in the critically ill? A clinical study of measures of agreement. *Critical Care Medicine,* **35**(1), pp. 155-164.

MOULAERT, V.R., GOOSSENS, M., HEIJNDERS, I.L., VERBUNT, J.A. and HEUGTEN, C.M., 2016. Early neurologically focused follow-up after cardiac arrest is cost-effective: A trial-based economic evaluation. *Resuscitation,* **106**, pp. 30-36.

MOULAERT, V.R., VAN HEUGTEN, C.M., WINKENS, B., BAKX, W.G., DE KROM, M.C., GORGELS, T.P., WADE, D.T. and VERBUNT, J.A., 2015. Early neurologically-focused follow-up after cardiac arrest improves quality of life at one year: A randomised controlled trial. *International journal of cardiology,* **193**, pp. 8-16.

MOULAERT, V.R., VERBUNT, J.A., VAN HEUGTEN, C.M. and WADE, D.T., 2009. Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review. *Resuscitation,* **80**(3), pp. 297-305.

MOULAERT, V.R., WACHELDER, E.M., VERBUNT, J.A., WADE, D.T. and VAN HEUGTEN, C.M., 2010. Determinants of quality of life in survivors of cardiac arrest. *Journal of Rehabilitation Medicine,* **42**(6), pp. 553-558.

MOZAFFARIAN, D., BENJAMIN, E.J., GO, A.S., ARNETT, D.K., BLAHA, M.J., CUSHMAN, M., DE FERRANTI, S., DESPRES, J.P., FULLERTON, H.J., HOWARD, V.J., HUFFMAN, M.D., JUDD, S.E., KISSELA, B.M., LACKLAND, D.T., LICHTMAN, J.H., LISABETH, L.D., LIU, S., MACKEY, R.H., MATCHAR, D.B., MCGUIRE, D.K., MOHLER, E.R.,3rd, MOY, C.S., MUNTNER, P., MUSSOLINO,

M.E., NASIR, K., NEUMAR, R.W., NICHOL, G., PALANIAPPAN, L., PANDEY, D.K., REEVES, M.J., RODRIGUEZ, C.J., SORLIE, P.D., STEIN, J., TOWFIGHI, A., TURAN, T.N., VIRANI, S.S., WILLEY, J.Z., WOO, D., YEH, R.W., TURNER, M.B. and AMERICAN HEART ASSOCIATION STATISTICS COMMITTEE AND STROKE STATISTICS SUBCOMMITTEE, 2015. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation,* **131**(4), pp. e29-322.

MUELLER-BURKE, D., KOEHLER, R.C. and MARTIN, L.J., 2008. Rapid NMDA receptor phosphorylation and oxidative stress precede striatal neurodegeneration after hypoxic ischemia in newborn piglets and are attenuated with hypothermia. *International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience,* **26**(1), pp. 67-76.

MYERBURG RJ and CASTELLANOS A, 2001. Cardiac arrest and sudden cardiac death. In: BRAUNWALD E, ZIPES DP, LIBBY P, ed, *Heart Disease: A Textbook of Cardiovascular Medicine.* 6th edn. Philadelphia: W.B Saunders Company, pp. 890-931.

NAKASHIMA, K. and TODD, M.M., 1996. Effects of hypothermia on the rate of excitatory amino acid release after ischemic depolarization. *Stroke; a journal of cerebral circulation,* **27**(5), pp. 913-918.

NATIONAL INSTITUTE OF CLINICAL EXCELLENCE, February 2014-last update, The RhinoChill intranasal cooling system for reducing temperature after cardiac arrest. Available: https://www.nice.org.uk/advice/mib4/chapter/technology-overview.

NHS ENGLAND, 2013-last update, Ambulance quality indicators. Available: https://www.england.nhs.uk/statistics/statistical-work-areas/ambulance-quality-indicators/.

NICE, NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE, March 2011-last update, Therapeutic hypothermia following cardiac arrest. IPG386. Available: https://www.nice.org.uk/guidance/IPG386/chapter/1-Guidance.

NICE, NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE, December 2016, 2016-last update, Hypothermia: prevention and management in adults having surgery (CG65). Available: https://www.nice.org.uk/guidance/cg65/chapter/Recommendations#perioperative-care.

NICE, NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE, 2013-last update, Rehabilitation after critical illness in adults CG83. Available: https://www.nice.org.uk/guidance/cg83/chapter/1-Guidance.

NICHOL, G., GUFFEY, D., STIELL, I.G., LEROUX, B., CHESKES, S., IDRIS, A., KUDENCHUK, P.J., MACPHEE, R.S., WITTWER, L., RITTENBERGER, J.C., REA, T.D., SHEEHAN, K., RAC, V.E., RAINA, K., GORMAN, K., AUFDERHEIDE, T. and RESUSCITATION OUTCOMES CONSORTIUM INVESTIGATORS, 2015. Post-discharge outcomes after resuscitation from out-of-hospital cardiac arrest: A ROC PRIMED substudy. *Resuscitation,* **93**, pp. 74-81.

NICHOL, G., STRICKLAND, W., SHAVELLE, D., MAEHARA, A., BEN-YEHUDA, O., GENEREUX, P., DRESSLER, O., PARVATANENI, R., NICHOLS, M., MCPHERSON, J., BARBEAU, G., LADDU, A., ELROD, J.A., TULLY, G.W., IVANHOE, R., STONE, G.W. and VELOCITY INVESTIGATORS, 2015. Prospective, multicenter, randomized, controlled pilot trial of peritoneal hypothermia in patients with ST-segment- elevation myocardial infarction. *Circulation.Cardiovascular interventions,* **8**(3), pp. e001965.

NICHOLAS P, VIRDI G, FOTHERGILL R, September 2013-last update, Cardiac Arrest Annual Report: 2012/13. Available: file://anglia.local/fs/StudentsHome/SABI100/My%20Documents/My%20Downloads/Cardiac%20Arrest%20Annual%20Report%202012-13%20FINAL%20(external).pdf.

NICHOLS, W.W., MEHTA, J.L., THOMPSON, L. and DONNELLY, W.H., 1988. Synergistic effects of LTC4 and TxA2 on coronary flow and myocardial function. *The American Journal of Physiology,* **255**(1 Pt 2), pp. H153-9.

NIELSEN, N., WETTERSLEV, J., CRONBERG, T., ERLINGE, D., GASCHE, Y., HASSAGER, C., HORN, J., HOVDENES, J., KJAERGAARD, J., KUIPER, M., PELLIS, T., STAMMET, P., WANSCHER, M., WISE, M.P., ÅNEMAN, A., AL-SUBAIE, N., BOESGAARD, S., BRO-JEPPESEN, J., BRUNETTI, I., BUGGE, J.F., HINGSTON, C.D., JUFFERMANS, N.P., KOOPMANS, M., KØBER, L., LANGØRGEN, J., LILJA, G., MØLLER, J.E., RUNDGREN, M., RYLANDER, C., SMID, O., WERER, C., WINKEL, P. and FRIBERG, H., 2013. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. *N Engl J Med,* **369**(23), pp. 2197-2206.

NING, X.H., CHI, E.Y., BUROKER, N.E., CHEN, S.H., XU, C.S., TIEN, Y.T., HYYTI, O.M., GE, M. and PORTMAN, M.A., 2007. Moderate hypothermia (30 degrees C) maintains myocardial integrity and modifies response of cell survival proteins after reperfusion. *American journal of physiology.Heart and circulatory physiology,* **293**(4), pp. H2119-28.

NING, X.H., XU, C.S., SONG, Y.C., XIAO, Y., HU, Y.J., LUPINETTI, F.M. and PORTMAN, M.A., 1998. Hypothermia preserves function and signaling for mitochondrial biogenesis during subsequent ischemia. *The American Journal of Physiology,* **274**(3 Pt 2), pp. H786-93.

NOC, M., ERLINGE, D., NESKOVIC, A.N., KAFEDZIC, S., MERKELY, B., ZIMA, E., FISTER, M., PETROVIC, M., CANKOVIC, M., VERESS, G., LAANMETS, P., PERN, T., VUKCEVIC, V., DEDOVIC, V., SREDNIAWA, B., SWIATKOWSKI, A., KEEBLE, T.R., DAVIES, J.R., WARENITS, A.M., OLIVECRONA, G., PERUGA, J.Z., CISZEWSKI, M., HORVATH, I., EDES, I., NAGY, G.G., ARADI, D. and HOLZER, M., 2017. COOL AMI EU pilot trial: a multicentre, prospective, randomised controlled trial to assess cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology,* **13**(5), pp. e531-e539.

NOC, M., FAJADET, J., LASSEN, J.F., KALA, P., MACCARTHY, P., OLIVECRONA, G.K., WINDECKER, S., SPAULDING, C., EUROPEAN ASSOCIATION FOR PERCUTANEOUS CARDIOVASCULAR INTERVENTIONS (EAPCI) and STENT FOR LIFE (SFL) GROUP, 2014. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European association for percutaneous cardiovascular interventions (EAPCI)/stent for life (SFL) groups. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology,* **10**(1), pp. 31-37.

NOGUCHI, K., MATSUMOTO, N., SHIOZAKI, T., TASAKI, O., OGURA, H., KUWAGATA, Y., SUGIMOTO, H. and SEIYAMA, A., 2011. Effects of timing and duration of hypothermia on survival in an experimental gerbil model of global ischaemia. *Resuscitation,* **82**(4), pp. 481-486.

NOLAN, J., SOAR, J. and EIKELAND, H., 2006. The chain of survival. *Resuscitation,* **71**(3), pp. 270-271.

NOLAN, J.P., NEUMAR, R.W., ADRIE, C., AIBIKI, M., BERG, R.A., BOTTIGER, B.W., CALLAWAY, C., CLARK, R.S., GEOCADIN, R.G., JAUCH, E.C., KERN, K.B., LAURENT, I., LONGSTRETH, W.T.,

MERCHANT, R.M., MORLEY, P., MORRISON, L.J., NADKARNI, V., PEBERDY, M.A., RIVERS, E.P., RODRIGUEZ-NUNEZ, A., SELLKE, F.W., SPAULDING, C., SUNDE, K. and HOEK, T.V., 2008. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. *Resuscitation,* **79**(3), pp. 350-379.

NOLAN, J.P., SOAR, J., SMITH, G.B., GWINNUTT, C., PARROTT, F., POWER, S., HARRISON, D.A., NIXON, E., ROWAN, K. and NATIONAL CARDIAC ARREST AUDIT, 2014. Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. *Resuscitation,* **85**(8), pp. 987-992.

NORDBERG, P., TACCONE, F.S., CASTREN, M., TRUHLAR, A., DESRUELLES, D., FORSBERG, S., HOLLENBERG, J., VINCENT, J.L. and SVENSOON, L., 2013. Design of the PRINCESS trial: pre-hospital resuscitation intra-nasal cooling effectiveness survival study (PRINCESS). *BMC emergency medicine,* **13**, pp. 21-227X-13-21.

ODDO, M., RIBORDY, V., FEIHL, F., ROSSETTI, A.O., SCHALLER, M.D., CHIOLERO, R. and LIAUDET, L., 2008. Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: a prospective study. *Critical Care Medicine,* **36**(8), pp. 2296-2301.

OLIVECRONA, G.K., GOTBERG, M., HARNEK, J., VAN DER PALS, J. and ERLINGE, D., 2007. Mild hypothermia reduces cardiac post-ischemic reactive hyperemia. *BMC cardiovascular disorders,* **7**, pp. 5.

O'NEILL, W.W., 2004. *Cooling as an adjunct to primary PCI for myocardial infarction*, 2004 2004, Transcatheter Cardiovascular Therapeutics.

OPIE, L.H., COMMERFORD, P.J., GERSH, B.J. and PFEFFER, M.A., 2006. Controversies in ventricular remodelling. *Lancet,* **367**(9507), pp. 356-367.

O'REILLY, S.M., GRUBB, N. and O'CARROLL, R.E., 2004. Long-term emotional consequences of in-hospital cardiac arrest and myocardial infarction. *The British journal of clinical psychology / the British Psychological Society,* **43**(Pt 1), pp. 83-95.

OTAKE, H., SHITE, J., PAREDES, O.L., SHINKE, T., YOSHIKAWA, R., TANINO, Y., WATANABE, S., OZAWA, T., MATSUMOTO, D., OGASAWARA, D. and YOKOYAMA, M., 2007. Catheter-based transcoronary myocardial hypothermia attenuates arrhythmia and myocardial necrosis in pigs with acute myocardial infarction. *Journal of the American College of Cardiology,* **49**(2), pp. 250-260.

PARDEE H. E. B., 1920.
An electrocardiographic sign of coronary artery obstruction. *Arch Intern Med,* **26**, pp. 244-257.

PEARLIN, L.I., MULLAN, J.T., SEMPLE, S.J. and SKAFF, M.M., 1990. Caregiving and the stress process: an overview of concepts and their measures. *The Gerontologist,* **30**(5), pp. 583-594.

PEBERDY, M.A., CALLAWAY, C.W., NEUMAR, R.W., GEOCADIN, R.G., ZIMMERMAN, J.L., DONNINO, M., GABRIELLI, A., SILVERS, S.M., ZARITSKY, A.L., MERCHANT, R., VANDEN HOEK, T.L., KRONICK, S.L. and AMERICAN HEART ASSOCIATION, 2010. Part 9: post-cardiac arrest care:

2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation,* **122**(18 Suppl 3), pp. S768-86.

PERMAN, S.M., KIRKPATRICK, J.N., REITSMA, A.M., GAIESKI, D.F., LAU, B., SMITH, T.M., LEARY, M., FUCHS, B.D., LEVINE, J.M., ABELLA, B.S., BECKER, L.B. and MERCHANT, R.M., 2012. Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia*. *Critical Care Medicine,* **40**(3), pp. 719-724.

PIANTADOSI, C.A. and ZHANG, J., 1996. Mitochondrial generation of reactive oxygen species after brain ischemia in the rat. *Stroke; a journal of cerebral circulation,* **27**(2), pp. 327-31; discussion 332.

PIPER, H.M., ABDALLAH, Y. and SCHAFER, C., 2004. The first minutes of reperfusion: a window of opportunity for cardioprotection. *Cardiovascular research,* **61**(3), pp. 365-371.

PIPER, H.M., GARCIA-DORADO, D. and OVIZE, M., 1998. A fresh look at reperfusion injury. *Cardiovascular research,* **38**(2), pp. 291-300.

POLDERMAN, K.H., 2009. Mechanisms of action, physiological effects, and complications of hypothermia. *Critical Care Medicine,* **37**(7 Suppl), pp. S186-202.

POLDERMAN, K.H., 2008. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet (London, England),* **371**(9628), pp. 1955-1969.

POLDERMAN, K.H., 2004. Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality--Part 2: Practical aspects and side effects. *Intensive care medicine,* **30**(5), pp. 757-769.

POLDERMAN, K.H. and HEROLD, I., 2009. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Critical Care Medicine,* **37**(3), pp. 1101-1120.

POLDERMAN, K.H. and VARON, J., 2015. How low should we go? Hypothermia or strict normothermia after cardiac arrest? *Circulation,* **131**(7), pp. 669-675.

PUNDIK, S., XU, K. and SUNDARARAJAN, S., 2012. Reperfusion brain injury: focus on cellular bioenergetics. *Neurology,* **79**(13 Suppl 1), pp. S44-51.

PUSSWALD, G., FERTL, E., FALTL, M. and AUFF, E., 2000. Neurological rehabilitation of severely disabled cardiac arrest survivors. Part II. Life situation of patients and families after treatment. *Resuscitation,* **47**(3), pp. 241-248.

PYCHA, C., CALABRESE, J.R., GULLEDGE, A.D. and MALONEY, J.D., 1990. Patient and spouse acceptance and adaptation to implantable cardioverter defibrillators. *Cleveland Clinic journal of medicine,* **57**(5), pp. 441-444.

RALEY-SUSMAN, K.M. and LIPTON, P., 1990. In vitro ischemia and protein synthesis in the rat hippocampal slice: the role of calcium and NMDA receptor activation. *Brain research,* **515**(1-2), pp. 27-38.

RAND AS PART OF THE MEDICAL OUTCOMES STUDY, , 36-Item Short Form Health Survey. Available: http://www.rand.org/health/surveys_tools/mos/mos_core_36item_terms.html.

REICHENBACH, D.D., MOSS, N.S. and MEYER, E., 1977. Pathology of the heart in sudden cardiac death. *The American Journal of Cardiology,* **39**(6), pp. 865-872.

REIMER, K.A., LOWE, J.E., RASMUSSEN, M.M. and JENNINGS, R.B., 1977. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation,* **56**(5), pp. 786-794.

ROINE, R.O., KAJASTE, S. and KASTE, M., 1993. Neuropsychological sequelae of cardiac arrest. *Jama,* **269**(2), pp. 237-242.

ROSOMOFF, H.L. and HOLADAY, D.A., 1954. Cerebral blood flow and cerebral oxygen consumption during hypothermia. *The American Journal of Physiology,* **179**(1), pp. 85-88.

ROSSETTI, A.O., ODDO, M., LIAUDET, L. and KAPLAN, P.W., 2009. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. *Neurology,* **72**(8), pp. 744-749.

ROSSETTI, A.O., ODDO, M., LOGROSCINO, G. and KAPLAN, P.W., 2010. Prognostication after cardiac arrest and hypothermia: a prospective study. *Annals of Neurology,* **67**(3), pp. 301-307.

ROSSETTI, A.O., URBANO, L.A., DELODDER, F., KAPLAN, P.W. and ODDO, M., 2010. Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. *Critical Care (London, England),* **14**(5), pp. R173.

ROSSI, S., ZANIER, E.R., MAURI, I., COLUMBO, A. and STOCCHETTI, N., 2001. Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage. *Journal of neurology, neurosurgery, and psychiatry,* **71**(4), pp. 448-454.

ROWE, G.T., MANSON, N.H., CAPLAN, M. and HESS, M.L., 1983. Hydrogen peroxide and hydroxyl radical mediation of activated leukocyte depression of cardiac sarcoplasmic reticulum. Participation of the cyclooxygenase pathway. *Circulation research,* **53**(5), pp. 584-591.

RUMANA, C.S., GOPINATH, S.P., UZURA, M., VALADKA, A.B. and ROBERTSON, C.S., 1998. Brain temperature exceeds systemic temperature in head-injured patients. *Critical Care Medicine,* **26**(3), pp. 562-567.

RUNDGREN, M., KARLSSON, T., NIELSEN, N., CRONBERG, T., JOHNSSON, P. and FRIBERG, H., 2009. Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia. *Resuscitation,* **80**(7), pp. 784-789.

SAFAR, P., 1964. Community-Wide Cardiopulmonary Resuscitation. *Journal of the Iowa Medical Society,* **54**, pp. 629-635.

SAIA, F., GRIGIONI, F., MARZOCCHI, A. and BRANZI, A., 2010. Management of acute left ventricular dysfunction after primary percutaneous coronary intervention for ST elevation acute myocardial infarction. *American Heart Journal,* **160**(6 Suppl), pp. S16-21.

SANER, H., BORNER RODRIGUEZ, E., KUMMER-BANGERTER, A., SCHUPPEL, R. and VON PLANTA, M., 2002. Quality of life in long-term survivors of out-of-hospital cardiac arrest. *Resuscitation,* **53**(1), pp. 7-13.

SAUNDERSON, C.E., CHOWDHARY, A., BROGAN, R.A., BATIN, P.D. and GALE, C.P., 2016. In an era of rapid STEMI reperfusion with Primary Percutaneous Coronary Intervention is there a

role for adjunct therapeutic hypothermia? A structured literature review. *International journal of cardiology,* **223**, pp. 883-890.

SAUVE, M.J., DOOLITTLE, N., WALKER, J.A., PAUL, S.M. and SCHEINMAN, M.M., 1996. Factors associated with cognitive recovery after cardiopulmonary resuscitation. *American Journal of Critical Care : An Official Publication, American Association of Critical-Care Nurses,* **5**(2), pp. 127-139.

SAXENA, S., ORLEY, J. and WHOQOL GROUP, 1997. Quality of life assessment: The world health organization perspective. *European psychiatry : the journal of the Association of European Psychiatrists,* **12 Suppl 3**, pp. 263s-6s.

SCAFOUNDATION, 2014-last update, AHA releases 2015 Heart and Stroke Statistics. Available: http://www.sca-aware.org/sca-news/aha-releases-2015-heart-and-stroke-statistics.

SCHENONE, A.L., COHEN, A., PATARROYO, G., HARPER, L., WANG, X., SHISHEHBOR, M.H., MENON, V. and DUGGAL, A., 2016. Therapeutic hypothermia after cardiac arrest: A systematic review/meta-analysis exploring the impact of expanded criteria and targeted temperature. *Resuscitation,* .

SCHULZ, R. and BEACH, S.R., 1999. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *Jama,* **282**(23), pp. 2215-2219.

SENDELBACH, S., HEARST, M.O., JOHNSON, P.J., UNGER, B.T. and MOONEY, M.R., 2012. Effects of variation in temperature management on cerebral performance category scores in patients who received therapeutic hypothermia post cardiac arrest. *Resuscitation,* **83**(7), pp. 829-834.

SERRANO, C.V.,Jr, MIKHAIL, E.A., WANG, P., NOBLE, B., KUPPUSAMY, P. and ZWEIER, J.L., 1996. Superoxide and hydrogen peroxide induce CD18-mediated adhesion in the postischemic heart. *Biochimica et biophysica acta,* **1316**(3), pp. 191-202.

SILASI, G. and COLBOURNE, F., 2011. Therapeutic hypothermia influences cell genesis and survival in the rat hippocampus following global ischemia. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* **31**(8), pp. 1725-1735.

SIMKHOVICH, B.Z., HALE, S.L. and KLONER, R.A., 2004. Metabolic mechanism by which mild regional hypothermia preserves ischemic tissue. *Journal of cardiovascular pharmacology and therapeutics,* **9**(2), pp. 83-90.

SPAULDING, C.M., JOLY, L.M., ROSENBERG, A., MONCHI, M., WEBER, S.N., DHAINAUT, J.F. and CARLI, P., 1997. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *The New England journal of medicine,* **336**(23), pp. 1629-1633.

STAUFFER, P.R., SNOW, B.W., RODRIGUES, D.B., SALAHI, S., OLIVEIRA, T.R., REUDINK, D. and MACCARINI, P.F., 2014. Non-invasive measurement of brain temperature with microwave radiometry: demonstration in a head phantom and clinical case. *The neuroradiology journal,* **27**(1), pp. 3-12.

STEINBERG, S.F., 2013. Oxidative stress and sarcomeric proteins. *Circulation research,* **112**(2), pp. 393-405.

STEINKE, E.E., 2003. Sexual concerns of patients and partners after an implantable cardioverter defibrillator. *Dimensions of critical care nursing : DCCN,* **22**(2), pp. 89-96.

STUB, D., HENGEL, C., CHAN, W., JACKSON, D., SANDERS, K., DART, A.M., HILTON, A., PELLEGRINO, V., SHAW, J.A., DUFFY, S.J., BERNARD, S. and KAYE, D.M., 2011. Usefulness of cooling and coronary catheterization to improve survival in out-of-hospital cardiac arrest. *The American Journal of Cardiology,* **107**(4), pp. 522-527.

SUNDE, K., PYTTE, M., JACOBSEN, D., MANGSCHAU, A., JENSEN, L.P., SMEDSRUD, C., DRAEGNI, T. and STEEN, P.A., 2007. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation,* **73**(1), pp. 29-39.

TARLOV, A.R., WARE, J.E.,Jr, GREENFIELD, S., NELSON, E.C., PERRIN, E. and ZUBKOFF, M., 1989. The Medical Outcomes Study. An application of methods for monitoring the results of medical care. *Jama,* **262**(7), pp. 925-930.

TASK FORCE ON THE MANAGEMENT OF ST-SEGMENT ELEVATION ACUTE MYOCARDIAL INFARCTION OF THE EUROPEAN SOCIETY OF CARDIOLOGY (ESC), STEG, P.G., JAMES, S.K., ATAR, D., BADANO, L.P., BLOMSTROM-LUNDQVIST, C., BORGER, M.A., DI MARIO, C., DICKSTEIN, K., DUCROCQ, G., FERNANDEZ-AVILES, F., GERSHLICK, A.H., GIANNUZZI, P., HALVORSEN, S., HUBER, K., JUNI, P., KASTRATI, A., KNUUTI, J., LENZEN, M.J., MAHAFFEY, K.W., VALGIMIGLI, M., VAN 'T HOF, A., WIDIMSKY, P. and ZAHGER, D., 2012. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European heart journal,* **33**(20), pp. 2569-2619.

TESTORI, C., STERZ, F., DELLE-KARTH, G., MALZER, R., HOLZER, M., STRATIL, P., STOCKL, M., WEISER, C., VAN TULDER, R., GANGL, C., SEBALD, D., ZAJICEK, A., BUCHINGER, A. and LANG, I., 2013. Strategic target temperature management in myocardial infarction--a feasibility trial. *Heart (British Cardiac Society),* **99**(22), pp. 1663-1667.

THIM, T., HAGENSEN, M.K., BENTZON, J.F. and FALK, E., 2008. From vulnerable plaque to atherothrombosis. *Journal of internal medicine,* **263**(5), pp. 506-516.

TIMMER, J.R., BREET, N., SVILAAS, T., HAAKSMA, J., VAN GELDER, I.C. and ZIJLSTRA, F., 2010. Predictors of ventricular tachyarrhythmia in high-risk myocardial infarction patients treated with primary coronary intervention. *Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation,* **18**(3), pp. 122-128.

TISSIER, R., CHENOUNE, M., PONS, S., ZINI, R., DARBERA, L., LIDOUREN, F., GHALEH, B., BERDEAUX, A. and MORIN, D., 2013. Mild hypothermia reduces per-ischemic reactive oxygen species production and preserves mitochondrial respiratory complexes. *Resuscitation,* **84**(2), pp. 249-255.

TISSIER, R., COUVREUR, N., GHALEH, B., BRUNEVAL, P., LIDOUREN, F., MORIN, D., ZINI, R., BIZE, A., CHENOUNE, M., BELAIR, M.F., MANDET, C., DOUHERET, M., DUBOIS-RANDE, J.L., PARKER, J.C., COHEN, M.V., DOWNEY, J.M. and BERDEAUX, A., 2009. Rapid cooling preserves the ischaemic myocardium against mitochondrial damage and left ventricular dysfunction. *Cardiovascular research,* **83**(2), pp. 345-353.

TORGERSEN, J., STRAND, K., BJELLAND, T.W., KLEPSTAD, P., KVALE, R., SOREIDE, E., WENTZEL-LARSEN, T. and FLAATTEN, H., 2010. Cognitive dysfunction and health-related quality of life after a cardiac arrest and therapeutic hypothermia. *Acta Anaesthesiologica Scandinavica,* **54**(6), pp. 721-728.

TOWNSEND, N., WICKRAMASINGHE, K., BHATNAGAR, P., SMOLINA, K., NICHOLS M, LEAL J, R, L.-F. & RAYNER, M., 2012.
Coronary heart disease statistics 2012 edition. 2012 edn. London: British Heart Foundation Health Promotion Research Group.

TVEITA, T., MORTENSEN, E., HEVROY, O., REFSUM, H. and YTREHUS, K., 1994. Experimental hypothermia: effects of core cooling and rewarming on hemodynamics, coronary blood flow, and myocardial metabolism in dogs. *Anesthesia and Analgesia,* **79**(2), pp. 212-218.

VAN ALEM, A.P., DE VOS, R., SCHMAND, B. and KOSTER, R.W., 2004. Cognitive impairment in survivors of out-of-hospital cardiac arrest. *American Heart Journal,* **148**(3), pp. 416-421.

VARON, J. and ACOSTA, P., 2008. Therapeutic hypothermia: past, present, and future. *Chest,* **133**(5), pp. 1267-1274.

VIRDI G, PICTON S, FOTHERGILL R, September 2015-last update, Cardiac Arrest Annual Report: 2014/15. Available: file://anglia.local/fs/StudentsHome/SABI100/My%20Documents/My%20Downloads/LAS%20Cardiac%20Arrest%20Annual%20Report%202014-15%20(1).pdf.

WACHELDER, E.M., MOULAERT, V.R., VAN HEUGTEN, C., VERBUNT, J.A., BEKKERS, S.C. and WADE, D.T., 2009. Life after survival: long-term daily functioning and quality of life after an out-of-hospital cardiac arrest. *Resuscitation,* **80**(5), pp. 517-522.

WAGNER, S.R.,4th and LANIER, W.L., 1994. Metabolism of glucose, glycogen, and high-energy phosphates during complete cerebral ischemia. A comparison of normoglycemic, chronically hyperglycemic diabetic, and acutely hyperglycemic nondiabetic rats. *Anesthesiology,* **81**(6), pp. 1516-1526.

WALPOTH, B.H., LOCHER, T., LEUPI, F., SCHUPBACH, P., MUHLEMANN, W. and ALTHAUS, U., 1990. Accidental deep hypothermia with cardiopulmonary arrest: extracorporeal blood rewarming in 11 patients. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery,* **4**(7), pp. 390-393.

WALPOTH, B.H., WALPOTH-ASLAN, B.N., MATTLE, H.P., RADANOV, B.P., SCHROTH, G., SCHAEFFLER, L., FISCHER, A.P., VON SEGESSER, L. and ALTHAUS, U., 1997. Outcome of survivors of accidental deep hypothermia and circulatory arrest treated with extracorporeal blood warming. *The New England journal of medicine,* **337**(21), pp. 1500-1505.

WAN, S., LECLERC, J.L. and VINCENT, J.L., 1997. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. *Chest,* **112**(3), pp. 676-692.

WANG, H., OLIVERO, W., WANG, D. and LANZINO, G., 2006. Cold as a therapeutic agent. *Acta Neurochirurgica,* **148**(5), pp. 565-70; discussion 569-70.

WANG, X.P., LIN, Q.M., ZHAO, S., LIN, S.R. and CHEN, F., 2013. Therapeutic benefits of mild hypothermia in patients successfully resuscitated from cardiac arrest: A meta-analysis. *World journal of emergency medicine,* **4**(4), pp. 260-265.

WATSON L: VIRDI G and FOTHERGILL R, 2012-last update, London's cardiac arrest survival rate highest in country. Available: http://www.londonambulance.nhs.uk/news/news_releases_and_statements/londons_cardiac_arrest_suriva.aspx?lang=en-gb.

WEAVER, W.D., HILL, D., FAHRENBRUCH, C.E., COPASS, M.K., MARTIN, J.S., COBB, L.A. and HALLSTROM, A.P., 1988. Use of the Automatic External Defibrillator in the Management of Out-of-Hospital Cardiac Arrest. *N Engl J Med,* **319**(11), pp. 661-666.

WEISS, S.J., 1989. Tissue destruction by neutrophils. *The New England journal of medicine,* **320**(6), pp. 365-376.

WHO, 2001-last update, International Classification of Functioning, Disability and Health ICF. Available: http://apps.who.int/gb/archive/pdf_files/WHA54/ea54r21.pdf?ua=1.

WHO, 1993-last update, The ICD-10 Classification of Mental and Behavioural Disorders. Available: http://www.who.int/classifications/icd/en/GRNBOOK.pdf.

WHO FACTSHEET 2016, September 2016-last update, The World Health Organisation Cardiovascular Disease Factsheet. Available: http://www.who.int/mediacentre/factsheets/fs317/en/.

WIJDICKS, E.F., HIJDRA, A., YOUNG, G.B., BASSETTI, C.L., WIEBE, S. and QUALITY STANDARDS SUBCOMMITTEE OF THE AMERICAN ACADEMY OF NEUROLOGY, 2006. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology,* **67**(2), pp. 203-210.

WILDER SCHAAF, K.P., ARTMAN, L.K., PEBERDY, M.A., WALKER, W.C., ORNATO, J.P., GOSSIP, M.R., KREUTZER, J.S. and VIRGINIA COMMONWEALTH UNIVERSITY ARCTIC INVESTIGATORS, 2013. Anxiety, depression, and PTSD following cardiac arrest: a systematic review of the literature. *Resuscitation,* **84**(7), pp. 873-877.

WILLIAMS, G.R.,Jr and SPENCER, F.C., 1958. The clinical use of hypothermia following cardiac arrest. *Annals of Surgery,* **148**(3), pp. 462-468.

WILSON, M., STANIFORTH, A., TILL, R., DAS NAIR, R. and VESEY, P., 2014. The psychosocial outcomes of anoxic brain injury following cardiac arrest. *Resuscitation,* **85**(6), pp. 795-800.

WU, E., ORTIZ, J.T., TEJEDOR, P., LEE, D.C., BUCCIARELLI-DUCCI, C., KANSAL, P., CARR, J.C., HOLLY, T.A., LLOYD-JONES, D., KLOCKE, F.J. and BONOW, R.O., 2008. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. *Heart (British Cardiac Society),* **94**(6), pp. 730-736.

XIE, Y., ZACHARIAS, E., HOFF, P. and TEGTMEIER, F., 1995. Ion channel involvement in anoxic depolarization induced by cardiac arrest in rat brain. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* **15**(4), pp. 587-594.

YANG, Z., DAY, Y.J., TOUFEKTSIAN, M.C., XU, Y., RAMOS, S.I., MARSHALL, M.A., FRENCH, B.A. and LINDEN, J., 2006. Myocardial infarct-sparing effect of adenosine A2A receptor activation is due to its action on CD4+ T lymphocytes. *Circulation,* **114**(19), pp. 2056-2064.

YELLON, D.M. and HAUSENLOY, D.J., 2007. Myocardial reperfusion injury. *The New England journal of medicine,* **357**(11), pp. 1121-1135.

YENARI, M.A. and HAN, H.S., 2012. Neuroprotective mechanisms of hypothermia in brain ischaemia. *Nature reviews.Neuroscience,* **13**(4), pp. 267-278.

YU, T., BARBUT, D., RISTAGNO, G., CHO, J.H., SUN, S., LI, Y., WEIL, M.H. and TANG, W., 2010. Survival and neurological outcomes after nasopharyngeal cooling or peripheral vein cold saline infusion initiated during cardiopulmonary resuscitation in a porcine model of prolonged cardiac arrest. *Critical Care Medicine,* **38**(3), pp. 916-921.

ZEINER, A., HOLZER, M., STERZ, F., BEHRINGER, W., SCHORKHUBER, W., MULLNER, M., FRASS, M., SIOSTRZONEK, P., RATHEISER, K., KAFF, A. and LAGGNER, A.N., 2000. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. *Stroke; a journal of cerebral circulation,* **31**(1), pp. 86-94.

ZHANG, H., XU, G., ZHANG, J., MURONG, S., MEI, Y. and TONG, E., 2010. Mild hypothermia reduces ischemic neuron death via altering the expression of p53 and bcl-2. *Neurological research,* **32**(4), pp. 384-389.

ZHAO, Q.J., ZHANG, X.G. and WANG, L.X., 2011. Mild hypothermia therapy reduces blood glucose and lactate and improves neurologic outcomes in patients with severe traumatic brain injury. *Journal of critical care,* **26**(3), pp. 311-315.

ZHAO, Z.Q., VELEZ, D.A., WANG, N.P., HEWAN-LOWE, K.O., NAKAMURA, M., GUYTON, R.A. and VINTEN-JOHANSEN, J., 2001. Progressively developed myocardial apoptotic cell death during late phase of reperfusion. *Apoptosis : An International Journal on Programmed Cell Death,* **6**(4), pp. 279-290.

ZIMMERLI, M., TISLJAR, K., BALESTRA, G.M., LANGEWITZ, W., MARSCH, S. and HUNZIKER, S., 2014. Prevalence and risk factors for post-traumatic stress disorder in relatives of out-of-hospital cardiac arrest patients. *Resuscitation,* **85**(6), pp. 801-808.

ZIMMET, J.M. and HARE, J.M., 2006. Nitroso-redox interactions in the cardiovascular system. *Circulation,* **114**(14), pp. 1531-1544.

ZITTA, K., MEYBOHM, P., BEIN, B., RODDE, C., STEINFATH, M., SCHOLZ, J. and ALBRECHT, M., 2010. Hypoxia-induced cell damage is reduced by mild hypothermia and postconditioning with catalase in-vitro: application of an enzyme based oxygen deficiency system. *European journal of pharmacology,* **628**(1-3), pp. 11-18.

ZOROV, D.B., JUHASZOVA, M., YANIV, Y., NUSS, H.B., WANG, S. and SOLLOTT, S.J., 2009. Regulation and pharmacology of the mitochondrial permeability transition pore. *Cardiovascular research,* **83**(2), pp. 213-225.