# Prospects for Mild Therapeutic Hypothermia and Improved CPR in Cardiopulmonary Cerebral Resuscitation

## By Michael G. Darwin on February 15, 2009

## Introduction

Each year in the United States there are ~450,00 deaths from myocardial infarction (MI) [1] (with 310,0006 these deaths occurring before the patient reaches the hospital) as a result of a non-perfusing arrhythmia, principally ventricular fibrillation.[2] This mode of sudden cardiac arrest<sup>1</sup> (SCA) is also responsible for the majority of the 190,000 in-hospital deaths from MI, which typically occur within the first 24 hours following admission.[3] Especially tragic is that 50% of these deaths occur in persons ~60 years of age or less.[4] An estimated additional 20,000 incidents of SCA occur as a result of asphyxiation, drowning, electrocution, and genetic or developmental predisposition to lethal arrhythmias (Wolf-Parkinson's White Syndrome, congenital thickening of the interventricular septum, and idiopathic arrhythmic disease) as well as other non-atherosclerosis causes. This latter category of SCA typically occurs in individuals whose mean age is less than 35.[5],[6]

At this time the principal treatments for SCA consist of initiation of manual,

'bystander' cardiopulmonary resuscitation, so-called Basic Cardiac Life Support (BCLS or BLS) followed by 'definitive' treatment of the arrhythmia beginning with defibrillation and the application of Advanced Cardiac Life Support (ACLS or ALS).[7]

**Figure 1-1 (right):** Mortality from sudden cardiac arrest (SCA)in 2004 as result of myocardial infarction compared to death from other 'high profile' causes of mortality in the US.



ACLS consists of the application of an algorithm of manual CPR, electrical defibrillation and pharmacologic therapy aimed at restoring a perfusing cardiac rhythm and adequate blood pressure and cardiac output to sustain life until definitive treatment of the underlying cause of the cardiac arrest can be achieved (e.g., coronary revascularization, implantation of an automatic defibrillator, or life-long anti-arrhythmic therapy).

<sup>&</sup>lt;sup>1</sup> The author rejects the conventional designation of 'sudden cardiac death' because it is inaccurate; death is, by definition, the irreversible loss of life. Acute cardiac arrest is not death and the nomenclature used to describe it should reflect that fact.

**Figure 1-2 (below):** Probability of survival as a function of time following cardiac arrest. [8]

As is shown in **Figure 1-6** below, the time to survival without neurological deficit following cardiac arrest in the absence of BCLS declines rapidly following a sigmoid curve with survival without neurological deficit being ~80-90% following 1 minute of arrest time, and less than 10% following 9 minutes of arrest.[8] Put another way, 50% of patients will experience significant morbidity or death following 4 minutes of circulatory arrest (**Figure 1-2**).

What is not shown in this graph is that the effect of immediate bystander CPR on survival is negligible in most studies [9],[10]





with the primary benefit being observed in patients who's time from the initiation of BCLS to successful cardiac resuscitation was greater than 8 minutes.[11] There is evidence in the literature that morbidity is improved with prompt by-stander CPR [12] providing that EMS response is also rapid, although this remains

controversial.[11],[13] A corollary of this is that the overall survival rate following SCA, with or without serious neurological morbidity, ranges between 1% (New York City, NY) [14] to 17% (Seattle, WA).[15] The mean survival (defined as survival to discharge from the hospital) in the United States as a whole is generally agreed to be at best 15% [16] with ~70% of these patients experiencing lasting neurological morbidity (ranging from 'mild' cognitive impairment to total incapacitation in the Persistent Vegetative State (PVS). [17],[18],[19]

The primary cause of non-survival in patients experiencing SCA is failed cardiac or cerebral resuscitation. Arguably, it is failed *cerebral resuscitation*, since most underlying causes of refractory cardiac arrest could be treated by 'bridging' supportive technologies such as emergency femoral-femoral cardiopulmonary bypass (CPB) until myocardial revascularization and hemodynamic stabilization were achieved. [20] When emergency CPB is applied to patients who are candidates for good neurological outcome, the survival rate is increased. [21],[22],[23],[24] However, these technologies are not typically used on patients who are unsuccessfully resuscitated (failed restoration of adequate cardiac rhythm and perfusion) because of the justified perception that irreversible brain damage would have occurred during the prolonged period of cardiac arrest or CPR/ACLS. [21] Similarly, it is for this reason that most attempts to achieve cardiopulmonary resuscitation in hospitalized patients who are not hypothermic or intoxicated with sedative drug are terminated after 15 minutes. [25],[26]

Within medicine it is widely understood that 'CPR doesn't really work' and that if the return of spontaneous circulation (ROSC) is not achieved within ~ 5 minutes of cardiac arrest, the chances for survival are slim, and the chances for survival absent neurological impairment are slimmer still. [8] The principal reason that conventional

CPR is not effective is that it fails to supply an adequate amount of flow at an adequate pressure. Cardiac output (CO) is typically ~1/3<sup>rd</sup> of the at-rest requirement (~1.5 versus ~4.5 liters per minute), and mean arterial pressure (MAP) is typically 25 mm Hg to 45 mm Hg; well short of the 60 mmHg required to sustain cerebral viability. [27],[28]

The condition of the typical sudden cardiac arrest (SCA) patient and the circumstances under which he experiences cardiac arrest are far from the ideal of a patient who is a candidate for emergency cardiopulmonary bypass (CPB) in hospital. The typical SCA patient is middle aged or elderly, often suffering from one or more co-morbidities (diabetes, obesity, COPD, hypertension), and, if subjected to prolonged CPR, will invariably have impaired gas exchange due accumulation of fluid in both the parenchyma and the air-spaces of the lungs (pulmonary edema with alveolar flooding). This occurs because closed chest CPR quickly causes pulmonary edema. [29],[30] As previously noted, even when the SCA patient is a 'good' candidate for salvage; someone who is relatively young and free of co-morbidities, CPR will likely prove futile due to cerebral ischemia-reperfusion injury and the post-resuscitation syndrome.

Over the past 25 years a vast number of therapeutic interventions have shown great promise in animal models of regional and global cerebral ischemia in the laboratory. [31],[32],[33],[34] In the last 6 years alone, over 1000 experimental papers and over 400 clinical articles on pharmacological neuroprotection have been published. [35],[36] However, with one exception, none of these interventions has been successfully applied clinically despite many attempts.

[37],[38],[39],[40],[41],[42],[43],[44] The sole exception to this frustrating debacle has been the introduction of mild therapeutic hypothermia (MTH) as the standard of care for a select (and very small) minority of SCA patients. [45],[46],[47],[48],[49],[50],[51]

#### Hypothermia as an Active Therapeutic Agent

Since the demonstration by Safar, et al., of the neuro-salvaging effects of mild systemic hypothermia after prolonged cardiac arrest in dogs [52],[53] there has been an explosion of translational research which has lead to a transformation in our understanding and application of mild hypothermia.[54], [55] Once seen solely as a *protective* tool which conferred benefit by reducing metabolism, it has become clear that mild hypothermia (33°C–35°C) [56] has *therapeutic effects* which appear to be primarily anti-inflammatory and anti-apoptotic in nature, and which operate independently of hypothermia's effect on metabolic rate. [57],[58] **Table 1-1** reviews some of the known pro-inflammatory factors inhibited or moderated by mild therapeutic hypothermia (MTH) and documents the supporting literature.

Reference	Model	Species	T (°C)	Factors
Takeda et al (2003)	Global	Gerbil	31 and 34	Anoxic depolarization
Busto et al (1989b)	Global	Rat	30 and 33	Glutamate
Dietrich et al (1990)	Global	Rat	30 and 33	BBB
Kawanishi (2003)	Hemorrhage	Rat	35	Edema; BBB; PMNL
Kawai et al (2000)	Focal	Rat	33	ICAM-1 mRNA; PMNL
Wang et al (2002)	Focal	Rat	30	ICAM-1; neutrophil and monocyte; microglia
Hamann et al (2004)	Focal	Rat	32 and 34	MMP-2; MMP-9; m-PA; t-PA

#### Table 1-1: Inhibition of Injury Cascades by Mild Therapeutic Hypothermia (MTH)

Karibe et al (1994a)	Focal	Rat	33	Ascorbate; glutathione		
Kader et al (1994)	Focal	Rat	33	NOS; nitrite		
Toyoda et al (1996)	Focal	Rat	30	Neutrophil		
Chopp et al (1992)	Global	Rat	30	HSP-70		
Mancuso et al (2000)	Focal	Rat	33	HSP-70; C-fos		
Tohyama et al (1998)	Focal	Rat	30	PKC		
Shimohata et al (2007a)	Focal	Rat	30	еРКС		
Harada et al (2002)	Global	Rat	32	CaM kinase II; PKC-a,b,g synaptosome		
Tsuchiya et al (2002)	Global	Mouse	33	Zn2+		
Phanithi et al (2000)	Focal	Rat	33	Fas; caspase-3		
Zhao et al (2007)	Focal	Rat	33	Cytochrome c and AIF		
Karabiyikoglu et al	Focal	Rat	33 intra or	iNOS; nNOS		
(2003)			post			
Wagner et al (2003)	Focal	Rat	33 post	BBB; MMP-9		
Inamasu et al (2000)	Focal	Rat	34.5 post	Neutrophil infiltration; microglia		
Horstmann et al (2003)	Stroke	Human	33 post	MMP-9		
Horiguchi et al (2003)	Global	Rat	32 post	Hydroxyl radical		
Han et al (2003)	Focal	Rat	33 post	NF-kB; iNOS; TNF-a		
Van Hemelrijck et al (2005)	Focal	Rat	34 post	Caspase-3; nNOS		
Inamasu et al (2000)	Focal	Rat	34.5 post	Bax		
Friedman et al (2001)	Global	Rat	30 intra/post	GluR1A; GluR2B; GluR3C; NMDAR1		
Ohta et al (2007)	Focal	Rat	35 post	Inflammatory genes: osteopontin, early growth response-1, and macrophage inflammatory protein-3a		
Luo et al (2007)	Focal	Rat	33 post	Base-excision repair pathway		
Preston & Webster (2004)	Global	Rat	32 post	BBB		
Liebetrau et al (2004)	Focal	Rat	32 post	Calpain		
Hu et al (2008)	Global	Rat	32 pre/post	of GluR6-PSD95-MLK3 signaling module		
Deng et al (2003)	Focal	Rat	33 post	ICAM-1		
Karabiyikoglu et al (2003)	Focal	Rat	33 post	nNOS; iNOS and peroxynitrite		
AIF, apoptosis-inducing factor; BBB, blood-brain barrier;; HSP-70, heat-shock protein-70; iNOS, inducible nitric oxide synthase; intra, intraischemic hypothermia: MMP-9, matrix metalloprotease-9; M, mouse; NF-kB, nuclear transcription factor kB; NOS,						

intra, intraischemic hypothermia; MMP-9, matrix metalloprotease-9; M, mouse; NF-kB, nuclear transcription factor kB; NOS, nitric oxide synthesis; nNOS, neuronal nitric oxide synthase; PKC, protein kinase C; PMNL, polymorphonuclear leukocytes; post, postischemic hypothermia; R, rat; S, species; T(1C), intraischemic temperature, unless specified; TNF-a, tumor necrosis factor-a. Reproduced with modifications from Zhao, H., Steinberg, GK, Sapolsky, RM., General versus specific actions of mild-moderate hypothermia in attenuating cerebral ischemic damage. J Cerebr Blood Flow Metab, 2007. **27**: p. 1879-1894.

Table 1-1: Intraischemic hypothermia delays or attenuates both ATP depletion (Ibayashi et al. 2000: Sutton et al. 1991: Welsh et al. 1990) and anoxic depolarization (Bart et al. 1998: Nakashima and Todd, 1996; Takeda, et al, 2003), it also blocks glutamate release (Busto et al, 1989b; Patel et al, 1994; Winfree et al, 1996), suppresses inflammation (Kawai et al, 2000; Wang et al, 2002), maintains the integrity of the BBB (Dietrich et al, 1990; Huang et al, 1999; Kawanishi, 2003), reduces free radical production (Maier et al, 2002), inhibits protein kinase C translocation (Cardell et al, 1991; Shimohata et al, 2007a, b; Tohyama et al, 1998), inhibits matrix metalloproteinase expression (Hamann et al, 2004), and blocks both necrosis and apoptosis. Intraischemic hypothermia also preserves the base-excision repair pathway, which repairs oxidative damage (Luo et al, 2007). In addition to those cascades directly associated with neuronal injury, hypothermia further blocks astrocyte activity and inhibits white matter injury (Colbourne et al, 1997; Dempsey et al, 1987; Kimura et al, 2002). Similarly, postischemic hypothermia blocks free radical generation (Horiguchi et al, 2003), attenuates inflammation (Horstmann et al. 2003: Ohta et al. 2007), prevents BBB permeability (Preston and Webster, 2004), and suppresses caspase activities (Van Hemelrijck et al, 2005). Indeed, a browse through the literature gives an overwhelming impression that hypothermia seems to block every damaging event associated with necrosis or apoptosis. One reason for this impression of pan-inhibition may lie in the causality of ischemic damage. For example, is the inflammatory response the cause of tissue damage or is it induced by brain injury? If it is the latter, then since hypothermia prevents tissue damage, it certainly also prevents the inflammatory response.

– Zhao, H., Steinberg, GK, Sapolsky, RM., General versus specific actions of mildmoderate hypothermia in attenuating cerebral ischemic damage. J Cerebr Blood Flow Metab, 2007. 27: p. 1879-1894.

The journey from the laboratory to the clinic for MTH has been long and difficult. Seven years after the publication of the prospective randomized trials clearly showing that MTH improves survival and neurological outcome in out-of-hospital cardiac arrest patients, and 6 years after the ILCOR and AHA Guidelines [59] recommended that: "Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF)," [49] only a minority of SCA patients are being treated with MTH. In surveys of emergency and critical care physicians conducted in 2005 and 2006, 74% of those responding in the US [60] and 64% of the international respondents indicated they had never used MTH. [61],[62] The use of pre-hospital, in-field MTH, is virtually nonexistent.[63]

No doubt, the commonly cited 'obstacles' of lack of institutional protocols, lack of physician education about the benefits and guideline changes, as well as the inevitable inertia that accompanies any paradigm shift in treatment are playing a significant role in the failure of MTH to become the practiced standard of care for the post resuscitation syndrome. [64],[60] However, what is not being said, or considered, is that while MTH as currently practiced represents a large relative improvement in outcome, the benefits are still modest in absolute terms. Only a miniscule subgroup of SCA patients currently can benefit from MTH; and even in its

best clinical implementation MTH still fails to rescue ~60% of that sub-group of SCA patients to whom it is applied. [65],[66],[67],[68],[69] This is in stark contrast to what can be achieved with MTH in ameliorating post-ischemic encephalopathy in the laboratory, where post-resuscitation MTH consistently provides rescue with stunning efficacy. [70],[71]



Figure 1-3: The impact of a delay of 10 min in inducing MHT is a dog model of cardiac arrest followed by 3 min of systemic ischemia, 7 minutes of mechanical CPR and 50 minutes of advanced life support. Hypothermia to 34°C was induced beginning at 10 min post arrest in the early hypothermia group and at 20 min post arrest in the delayed hypothermia group . In the early hypotherrmia group group, 5 of 7 surviving dogs were functionally normal (OPC 1 or 2), 1 had OPC 3, and 1 had OPC 4 (coma) at 96 hours of recovery. Histologically, 4 of 8 dogs in this group were normal (HDS 0), 1 had HDS 16, 1 had 22, and 1 had 98. The only surviving dog in the DH group was functionally normal at 96 hours (OPC 1, NDS 0) with an HDS of score of 32 (mild injury) Due to early mortality only two other dogs in the delayed hypothermia group were evaluated histologically and their HDS scores 38 and 45, respectively. Dogs in this study were scored by 'overall performance categories' (OPC: 1=normal, 2=moderate disability, 3=severe disability but conscious, 4=coma, and 5=death) Neurological function and neurological deficit scores (NDS; 0% to 10%=normal, 100%=brain death). [72],[73] Histological damage scores were obtained by neuropathological examination of 19 distcrete brain regions for severity and extent of ischemic neuronal changes, infarcts, and edema. A total brain histological damage score (HDS) >40 represented moderate damage, and HDS >100 represented severe damag.[74] Redrawn from Nozari, A., et al., Critical time

## window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. Circulation, 2006. **113**(23): p. 2690-6.

The primary obstacle to realizing this bonanza in translation research has been the practical impossibility of achieving systemic cooling within the narrow therapeutic window demonstrated in animal models of SCA and cardiopulmonary resuscitation. [75],[67],[65],[66],[67],[68],[69] If the clinical outcome of MTH was even half that achievable in the laboratory, widespread application would likely have been rapid and uniform; there is rarely resistance to the 'miraculous' if it is simple, easy to understand, biophysically well characterized and highly cost-effective. MTH applied immediately post ROSC would be all of these things.<sup>2</sup>



The data in **Figures 1-3 and 1-4** exemplify what is possible when MTH is induced within its optimum therapeutic window of 0-15 min post ROSC, versus a delay of even 10 minutes. In this study by Nozari, et al., of PeterSafar's group, [71] VF was electrically induced in 17 dogs, all of whom were subjected to a period of 3 minutes of no flow beginning when the MAP dropped below 30 mm Hg, followed by 7 minutes of mechanical CPR and 50 minutes of advanced life support during which time VF was maintained and mechanical CPR was continued. Nine animals were treated with rapid (early) induction of MTH to 34°C starting at 10 min post arrest (EH group) (concurrent with the start of ALS to simulate the time course of arrival of EMS paramedics) using a combination of cold IV saline and veno-venous heat exchange. Induction of hypothermia was not



**Figure 1-5:** Results of a study of 48 cardiac arrest patients treated with MTH via endovascular cooling. A strong correlation was found between rapidity of cooling and both neurological outcome and serum neuron specific enolase levels. Left: Time course of MTH among patients with good and poor neurological outcome. The curves indicate the course of mean body core temperature during MTH among patients with good ( $\blacksquare$ ) and those with poor ( $\blacktriangle$ ) outcome as well as in the entire (-) patient group. Right: Correlation between time to coldest temperature (minutes) and the maximum NSE values (µg/L). Normal serum NSE is 9.6±0.7 µg/L. Redrawn from Wolff B, et al., Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest, Int J Cardiol (2008).

begun until 20 min post arrest in the delayed hypothermia group (DH group) which consisted of 8 dogs. Target core temperature was achieved at  $6.0\pm2.7$  minutes after the initiation of cooling (3.5 minutes after the start of veno-venous cooling) in both groups. The delay from arrest to reaching ~34°C was 16.6 min in the EH group and 25.4 minutes in the DH group.

After 60 minutes of VF, ROSC was achieved with cardiopulmonary bypass for 4 hours, and intensive care was given for 96 hours. In the early hypothermia group, 7 of 9 dogs survived to 96 hours, 5 with good neurological outcome. By contrast, in the delayed hypothermia group, 7 of 8 dogs died of multiple organ failure within 37 hours (P=0.012); 3 animals died from secondary VF that was resistant to CPR with antiarrhythmic treatment and repeated defibrillations. Only one dog in the EH group died, and that animal succumbed to single organ failure; pulmonary edema with hemoptysis. This study extends the previous work by this group documnting an optimum therapeutic window for MHT (in dogs) of ~10-15 min. [76],[76],[77] The therapeutic window of MTH after cardiac arrest has been demonstrated to be similarly short in other species. [78],[79],[80],[81]

The dramatic efficacy of MTH in the laboratory made quick converts of the pioneering researcher-clinicians who forged ahead with the application of MTH to SCA in the clinic precisely because it was dramatic; indeed it was as close to the miraculous as interventions in medicine come. The real barrier to translating that 'miracle' to everyday practice has been the seemingly intractable problem of achieving cooling over the same time course that has proven so effective in the research setting.

The problem is that the optimum therapeutic window for the treatment of cerebral ischemia-reperfusion injury appears to be in the range of 0 to 15 minutes post ROSC. One of the first follow-up studies on MTH carried out by Safar, et al., demonstrated that in a standardized model of cardiac arrest in dogs a delay in the application MTH of as little as15 min after ROSC abolished most of the benefit. [77],[82] While the work of Bernard, et al., [46] and that of the Hypothermia After Cardiac Arrest Study Group [48] demonstrated that delays in cooling of up to 2-3 hours post ROSC in humans still have sufficient clinical utility to justify the routine application of MTH in a selected group of SCA patients, this benefit is marginal when contrasted to that achievable in the laboratory when MTH is rapidly induced during the first 15 minutes after ROSC.[77] Thus, the optimum clinical benefit of MTH in

ischemic and very likely traumatic CNS injury, requires the ability to achieve very rapid core cooling. [83]



**Figure 1-6:** Survival after cardiac arrest declines rapidly as a function of time to ROSC, exhibiting the sigmoidal curve shown at left, above ( $\blacksquare > \blacksquare$ ), with essentially all patients failing to survive with normal mentation after arrest intervals of  $\cong$  10 min. Application of MTH ( $\blacksquare$ ) within the window of  $\cong$  15 min offers the promise of squaring the survival curve in SCA of  $\cong$  10 min duration yielding a survival rate of ~65-70% with little or no neurological deficit. Application of deep (10-22°C) or profound hypothermia (5-9°C) ( $\blacksquare$ ) may allow survival after intervals of as long as 1-2 hours of CPR. Graphic by M.G. Darwin

In the clinical arena the time to reach the target core temperature under 'good' circumstances is in the range of 3-4 hrs; not 10 to 30 min, as is the case in the laboratory. Even with such long delays in cooling the adverse effect of delay is still present. Wolf, et al., recently published a study of 49 out of hospital cardiac arrest patients who were treated with MTH (32.0-34.0°C; with a target temperature of 33.0°C) of 24 h duration using endovascular cooling. [69] The study endpoints were neurological outcome on discharge from hospital and serum neuron specific enolase (NSE) levels (a sensitive and specific marker of neuroinjury) at 24 h intervals to 3 days (**Figure 1-5**).



**Figure 1-7:** The graph above shows the hypothesized relative effect on survival of effectively administered CPR started at 5 min post-arrest followed by defibrillation at 6 min and ACLS at 8 min post arrest (~30% survival). The light blue shaded area of this graph shows the expected improvement in survival if MTH is induced at the start of ACLS (8 min post-arrest) and target temperature is reached by 15 min post ROSC. The dark blue shaded area shows the potential of Emergency Preservation resuscitation (EPR) using moderate (10-22°C) or profound (5-9°C) hypothermia to not only square the curve of survival with CPR, but to facilitate survival in patients who would otherwise not benefit from either BCLS or ACLS (i.e., refractory to defibrillation, hypovolemic, etc.). Graphic by M.G. Darwin

As is the case in laboratory studies of MTH in cardiac arrest in dogs, Wolff, et al., found that neurological outcomes were binary, with no patients who survived experiencing moderate degrees of disability; patients either recovered well with no or mild neurological impairment, or experienced severe disability (n = 1) coma or PVS (n = 6). Twenty-eight patients were discharged with a good outcome and a strong correlation was found between good outcome and the time interval from the start of cooling to the lowest temperature (p = .035) and a less robust correlation with the time to reach target temperature (p = .071). Similarly, NSE levels were found to correlate well with the time required to reach the lowest temperature achieved in each patient (**Figure 1-5**).

Even with delays in the start of cooling that averaged 2.5 hrs; and a mean time to reach target core temperature of 6.8 hrs, additional injury accruing from slowness in cooling was still clinically and biologically apparent. Despite the homogeneity of the patients, their arrest times, and their course of treatment, ~60% of the patients in this study either did not survive, or were comatose or PVS.

## The Benefits and Limits of 'Delayed' MTH: Real World Experience

To understand the benefits and limits of MTH when it is aggressively and competently implemented with currently available technology, it would be hard to find a better example than that of Wake County, SC. Wake County is located in the northeast central region of North Carolina and is part of the Research Triangle metropolitan area, which consists of Raleigh, Durham, Chapel Hill, and surrounding urban and suburban areas. The area serviced by the Wake County Emergency Medical System (Wake EMS) has a population of 832,970 (as of 2007). The Wake County EMS operates 35 ambulances from 23 locations with 825 ALS personnel; ambulances are staffed with two paramedics 95% of the time, and there is always one paramedic responding. [84] In 2002 the Wake EMS answered more than 50,000 medical requests for service. Based on the latest national data, Wake County ranks third in the US for recovery from "survivable" cardiac arrests (primarily ventricular fibrillation-ventricular tachycardia). Nationally, the average survival rate is 17% for patients presenting with these arrhythmias.

#### Figure 1-8 (right):

Improvement in overall survival of patients in cardiac arrest in response to the phased introduction of CPR per AHA 2005 Guidelines, use of an impedance threshold device (ITD) and in-field induction of MTH.[85]

Beginning in January 2004 Wake EMS initiated a study to evaluate the efficacy of CPR as they



then practiced it, and to evaluate the effectiveness of the impending change in the American Heart association (AHA) guidelines for CPR, the introduction of an impedance threshold valve (the ResQPod<sup>™</sup>) and Wake EMS' planned implementation of the ILCOR Guidelines for post-arrest MTH. [85],[86] From January 2004 until April of 2005, Wake EMS personnel employed the then extant AHA guidelines, which mandated an emphasis on intubation and a 15:2 compression-to-ventilation ratio; with interruption of chest compressions for ventilation. This period constituted the baseline of the study, and data were collected per protocol; *not gathered retrospectively.* 

During the baseline period survival to discharge from hospital was 2.4% for all patients given CPR and 12.1% for patients with ventricular fibrillation-ventricular tachycardia (VF-VT) arrhythmias. In April 2005, Wake EMS implemented continuous cardiac compression CPR with a 30:2 compression-to-ventilation ratio with emphasis on no, or very minimal, interruption of chest compressions. After 12 months, the overall survival rate had risen to 4%; and had more than doubled to 21.8% for patients who presented in VF-VT.

In April 2006, Wake EMS added the use of an impedance threshold device (ITD) to improve cerebral and coronary perfusion during CPR. Introduction of the ITD resulted in an increase in overall survival to 4.5% and an increase in the survival of patients with VF-VT to 28.5%.

#### Figure 1-9 (right):

Dramatic improvement in neurologically intact survival as a result of the phased introduction of CPR per AHA 2005 Guidelines, use of an impedance threshold device (ITD) and infield induction of MTH.[85]

The final phase of the investigative protocol



began in October of 2006 when Wake EMS added in-field induction of MTH to the two previous interventions. MTH was induced using a combination of external cooling employing ammonium nitrate-water eutectic 'instant cold packs' applied to the axilla and groin, and cold IV saline (1-2°C, 30mL/kg to a maximum of 2 liters) given rapidly via two large bore catheters and/or intraosseous infusion. Criteria for induction of hypothermia were that the patient have ROSC and show no return of consciousness (Glasgow Coma Score (GCS) <8). Induction of hypothermia was initiated two to three minutes after ROSC. There was heavy emphasis on avoiding over-ventilation and on attempting to maintain end-tidal  $CO_2$  (EtCO<sub>2</sub>) at a minimum of 40 mm Hg. Patients undergoing MTH were sedated with etomidate, paralyzed with vercuronium and given a titrated dopamine drip to maintain mean arterial pressure (MAP) between 90-100 mm Hg. The mean time to target temperature (34°C) in this study was extraordinarily short: 68 minutes (95% CI 47 to 88); compared to the 2-3 hours typically required to induce MTH.

With the combination of continuous compression CPR, use of the ITD and prompt application of MTH, survival rates for the 12 months from October of 2006 to October 2007 had increase to 6.7% overall and 37.4% for patients with VF-VT. The odds of overall survival increased three-fold (95% CI 1.7 to 5.0) and the odds of survival for patients in VF-VT increased 4.3-fold (95% CI 2.2 to 8.6) from the beginning of the

study (**Figures 1-8 and 1-10**). The probability of a good neurological outcome increased from 20% at baseline to 80% at the conclusion of the study (**Figure 1-9**). In multivariate analysis, the odds ratios for survival for each phase of implementation were as follows:

**Figure 1-10 (right):** *Multivariate odds for all factors in outcome evaluated during the* 

Multivariate Odds of Survival Wake County, SC Experience					
Factor	Odds	95% CI			
Age	0.97	0.96-0.98			
Residence	0.50	0.31-0.82			
Bystander CPR	2.18	1.34-3.54			
New CPR	2.37	1.10-4.96			
ITD	2.99	1.29-6.95			
Hypothermia	3.67	1.86-7.26			

а

Wake EMS study. MTH was by far the most powerful intervention. As in most previous studies of survival factors associated with CPR age and residence (home versus extended care or assisted living facility) had only modest impact on survival.[85]

- New CPR protocol: 2.13 (95% CI 1.12 to 4.04)
- Addition of impedance threshold device: 2.33 (95% CI 1.09 to 5.00)
- Addition of early hypothermia: 3.99 (95% CI 2.19 to 7.27)
- Patients who received bystander CPR 1.79-fold (95% CI 1.18 to 2.72) more likely to survive.

**Figure 1-11 (right):** The Engel-15 portable, (compressor-type) refrigerator/freezer has a 14 L capacity, weighs 11.5 kg and can maintain 12-13 liters of saline at 1-2°C at ambient temperatures as high as 40°C . It retails for ~\$380 US. [Photo courtesy of Engel, Ltd., Australia]



Interestingly, all three elements of the Wake EMS protocol were implemented at a cost of less than \$200 per patient. Due to budget

constraints, Wake EMS chose simple, inexpensive commercial products for refrigeration of IV fluid and implementation of external cooling, as opposed to more costly products developed specifically for medical application, such as the EMCOOLS surface cooling system (Emergency Medical Cooling Systems, AG, Austria). Saline was kept at the requisite temperature of 1-2°C with a compact, 12V operated, consumer travel refrigerator/freezer (**Figure: 1-11**, Engel-15: http://www.i-m-d.com/) and surface cooling was with generic ammonium nitrate cooling packs.

The Wake County EMS program is extraordinary in every way. It represents the best application of the best available technology by arguably some of the best medical and paramedical personnel in the US. The mean time to target temperature of 68 minutes is unprecedented in any clinical study employing MTH. Of the 359 patients who participated in the study (all comers) after MTH was in place; 25 survived. In the subgroup of 93 patients who presented with VF-VT; 34 survived, with 78% or 27 patients being discharged with a good neurological outcome. Put another way 92% of patients who presented under the most favourable circumstances (VF-VT), treated with the best currently available interventions, at the fastest rate of cooling so far reported, failed to survive or did so with profound neurological debility.

The primary difference between the survivors and the profoundly disabled or dead was the development of the post-resuscitation syndrome and the primary reason for this complication was not comorbidity, or delay in paramedical assistance, but rather delay in the rapidity of cooling which, if achieved within the first 15 min post ROSC, would have offered the prospect of neurologically intact survival in the range of 70-80% in patients presenting with VF-VT, and 30-40% in all comers.

These interventions, remarkable achievements that they are, do not escape from the harsh reality that the 400% increase in survival from cardiac arrest in Wake County,

when expressed in absolute terms, means that the number of lives saved increased from ~5 to 25 - out of 395 SCA patients; a huge relative gain, but a comparatively small increase in the absolute number and percentage of lives saved, and minds salvaged. The true life saving potential of MTH remains elusive by virtue of its exceedingly small therapeutic window.

## The Problem of Heat Exchange

Because of this minute therapeutic window, there is a pressing need to achieve rapid and durable core cooling of patients during CPR by simple, easily accessible means. External cooling is only effective at reducing core temperatures by 0.15 to 0.25°C/min in the average patient undergoing CPR (**Figure 1-12**) and this is achieved only by complete immersion of patients in a stirred ice water bath.



#### Efficacy of External Cooling in Four Cryopatients<sup>3</sup>

<sup>&</sup>lt;sup>3</sup>Data on cooling of humans during CPR is, of necessity, derived from the human cryopreservation program; implemented in the United States starting in 1967 as a controversial effort to achieve a form of 'medical time travel' for individuals experiencing medico-legal, but not biological death.

**Figure 1-12 (above):** Comparison of the cooling rates of four cryopatients. Immediately following pronouncement of medico-legal death patients were given closed chest mechanical cardiopulmonary support and placed in a stirred ice water bath for induction of hypothermia. Epinephrine was administered as per ACLS guidelines; thus peripheral vasoconstriction would be expected to be comparable to that seen in the typical SCA patient undergoing cardiac resuscitation.

The most effective external cooling achieved by a commercial system using direct, whole body surface cooling employing circulation of ice water (ThermoSuit, <sup>™</sup> Life Recovery Systems, Kinnelon, NJ) is probably the work of Janata, et al., using human human-sized swine.[87]

They were able to achieve core cooling at a rate of 0.3°C/min; however it is important to note that the animals in this study were not in cardiac arrest while undergoing CPR in the presence of profoundly peripherally vasoconstricting agents, such as epinephrine or vasopressin; as would usually be the case during ACLS in humans [59] and which is known to further slow surface cooling.[88]



**Figure 1-13:** The Life Recovery Systems ThermoSuit<sup>™</sup> employs direct ice water contact with the patient's skin to achieve the maximum possible rate of cooling by external means. The system consists of an inflatable insulating and water containment patient enclosure inside of which the patient rests on a mat of Dacron bonded polyester 'wool' which acts to diffuse and film water pumped over the dorsal surface of the patient's body. Water at 2-4°C is thin-filmed over the ventral surface of the body by a thin, transparent blanket with many hundreds of small perforations through which water under pressure pours out and over the patient. Cold water is recirculated over crushed or cubed ice in an insulated reservoir containing a disposable liner and pumps. Cooling is computer controlled via a thermistor which can be placed in any desired anatomical location. All patient contact items are single-use and disposable (including, as previously mentioned, the pumps) http://www.life-recovery.com/.

The obvious problems with this system are its bulk (**Figure 1-13**), likely high cost, lack of ease in field deployment (again related to its bulk and weight) and the intrinsic physiological problems associated with the induction of hypothermia via external cooling. As extensively discussed in *Section Two*, the mammalian body consists of multiple thermal compartments transiently 'isolated' from each other by differences in blood flow and heat conductivity. [89] Broadly, these compartments can be classified as strongly and weakly circulated (perfused); corresponding to the body core and periphery. The core tissues receive ~63% of the resting cardiac output (CO) but constitute only ~19% of the total body mass. By contrast, the peripheral tissues receive ~37% of the basal CO and constitute ~81% of the body's mass (**Figure 1-14**).

#### Figure 1-14: The

parenchymatous organs that comprise the visceral core of the body receive an aggregate of ~63% of resting the cardiac output while comprising only ~19% of the body mass. By contrast, the peripheral tissue mass which accounts for ~81% of body mass receive only ~19% of the cardiac output. External cooling profoundly chills peripheral tissues before significantly reducing core temperature. Values for organ and tissue masses were obtained from: IAEA. Compilation of anatomical, physiological and metabolic characteristics for a Reference Asian Man. Volumes 1 and 2. Report



IAEA-TECDOC-1005, (Vienna, Austria: International Atomic Energy Agency) (1998), Boecker, BB. References values for Basic Human Anatomical and physiological characteristics for use in radiation protection. Radiation Protection Dosimetry.105(1– 4): 571–574;2003, de la Grandmaison GL, Clairand I, Durigon M. Organ weight in 684 adult autopsies: new tables for a Caucasoid population. Forensic Sci Int. 2001 Jun 15;119(2):149-54 and Heymsfield SB, Gallagher D, Mayer L, Beetsch J, Pietrobelli A. Scaling of human body composition to stature: new insights into body mass index. Am J Clin Nutr 2007;86:82–91. Values for organ and tissue blood flows were obtained from: Williams, LR, Leggett, RW. Reference values for resting blood flow to organs of man. Clin Physiol Meas. 10:187-212;1989. Graphic by M.G. Darwin

## The Pathophysiology and Biophysical Limitations of External Cooling

The objective of MTH is to provide protection against ischemia-reperfusion injury to the brain, heart, kidneys and liver; the visceral organs that constitute the strongly circulated core of the body. The peripheral tissues (skin, skeletal muscle, connective tissues and bone) are at once much more resistant to ischemia and less well perfused. External cooling rapidly chills the ischemia-resistant peripheral tissues cooling them profoundly, while failing to provide protection to the vulnerable parenchymatous organs in the body core. This is not only undesirable in terms of its inefficiency; it also poses a number of hazards and risks. [90] Hypothermia is therapeutic in ischemia-reperfusion *because* it down-regulates the immune-inflammatory response; a response that is vital for host defense, wound healing and hemostasis. Hypothermia, like any major medical intervention that perturbs fundamental physiological processes, carries with it serious risks, as well as potential benefits. In both animals and humans, hypothermia is markedly immunosuppressive [91],[92] and interferes with the both the biochemistry of the clotting cascade and the production of platelets and clotting proteins. [93],[94]

In humans, perioperative minimal hypothermia (MinH) (36°C) increases the rate of wound infections [95] and prolongs hospitalization. [96] These effects occur in part due to the regional thermoregulatory vasoconstriction MinH induces; which in turn leads to reduced oxygen delivery to injured tissues, [97] inhibition of oxidative killing by neutrophils, [98] and reduced collagen deposition. [96] MinH induces significant suppression of mitogenic responses to Concanavalin A (con A), phytohemagqlutinin (PHA), and pokeweed mitogen (PWM) and these changes are known to persist for at least 48 h. The mitogens PHA and ConA activate T cells, whereas PWM stimulates both T and B cells, thus indicating that the suppressive effects of MinH involve a variety of lymphocyte subpopulations. Hypothermia of as little as 1°C significantly inhibits production of interlukins (IL-16, IL-2, IL-6) and TNFα in post-surgical patients, [99] and this suppression of cytokine production persists for least 24 hours, after even a brief post-operative hypothermic interval. [96] The inhibition of proinflammatory cytokine production by IL-16 and TNFα induce tissue factor, which is critical to angiogenesis, collagen elaboration and fibroblast activation; all essential processes in wound repair and hemostasis. [100],[101],[102] Significantly, many of these of adverse effects of post-operative MinH can be prevented by maintaining normothermia in the perioperative period. [96]

In the Hypothermia After Cardiac Arrest Study Group, patients treated with MTH experienced twice the incidence of sepsis. This finding is consistent with other studies where MinH and MTH were found to double the rate of post operative wound infection. [96] A recent meta-analysis of MTH for traumatic brain injury (TBI) found that the incidence of pneumonia was also doubled for patients undergoing MTH. [103]

External cooling causes greater perturbation in hemodynamics than does central cooling, [104] resulting in increased systemic vascular resistance and decreased cardiac index; a phenomenon observed in all of the patients in the Bernard, et al., study that employed MTH for post-arrest cerebral resuscitation. [46] This is particularly undesirable in the setting of MI, CHF and cardiogenic shock. For these reasons, as is the case with any potent therapy, careful attention must be paid to the dose-response curve, and overshoot or excessive regional cooling must be minimized or avoided. [105]

In patients cooled with ice packs and non-feedback controlled cooling blankets, there have been persistent and extensive problems with overshoot. In one study, 63% of patients overshot to <32°C, 28% to <31°C, and 13% were inadvertently cooled <30°C. [105] By contrast, patients in the European Resuscitation Council Hypothermia After Cardiac Arrest Registry who were cooled endovascularly had less overshoot (mean lowest temperature 32.9°C, IQR; 32.6°C to 33°C) when compared to patients cooled by other methods (mean lowest temperature 32.4°C, IQR: 31°C to 32.9°C). [106]

In part, the problem of overshoot in external cooling can be corrected by servocontrol of patient cooling. However, the fundamental problems of external cooling remain. Excessive cooling of poorly perfused peripheral tissues will inevitably result in 'after-drop' of core temperature as thermal equilibration occurs. This process is idiosyncratic and inherently difficult to model or predict. In large measure the speed and character of thermal equilibration between peripheral and central tissues will depend upon highly variable factors such as body morphology and composition, body surface area, cardiac output, regional blood flow distribution, and the administration of vasoactive medication such as ionotropes; with their attendant peripheral vasoconstriction.

When the tissues of non-hibernating (or unprepared hibernating mammals) are cooled to ≤20°C a wide range of deleterious changes occur. The saturated fats which comprise cell membrane lipids undergo phase change, resulting in red and white blood cell rigidity; with accompanying inability to deform and pass through capillaries. Red cell aggregation also occurs and this, in association with reduced flow as a result of vasoconstriction, results in blood sludging and failure of the microcirculation. [107],[108] Profound hypothermia, either local or systemic, results in hemoconcentration as a consequence of translocation of vascular water and electrolyte to the interstitial space. [109],[104],[110],[111],[112] This hemoconcentration further exacerbates regional ischemia in deeply chilled tissues.

Independent of injury from the freezing of water, moderate, profound or ultraprofound hypothermia is known to cause cellular damage which is referred to as 'chilling injury.' Chilling injury appears to be a multifactorial process in which alterations of membrane structure (reorganization of lamellar lipid sheets with lateral phase separation between regions of gel phase and regions of liquid crystal phase result in loss of membrane integrity), [113],[114] failure of ion pumping (with consequent disruption of cellular ionic homeostasis), [115],[116] depolymerisation of some elements of the cytoskeleton, [117],[118] generation of free radicals, [119],[120] and metabolic disruption due to selective inactivation of critical enzymes [121] all appear to play a role.

Cooling of tissues to 5°C for as little as 1 hour has been shown to cause microvascular endothelial damage similar to that observed in ischemia-reperfusion injury; loss of endothelial cell tight junctions, infiltration of capillary and venule walls with leukocytes, and frank extravasation of red cells from injured vessels. [122] A possible reason for the similarity in the histological appearance of chilling injury with ischemia-reperfusion injury may be due to the fact that both types of injury appear to be caused, at least in part, by reactive oxygen species and by disruption of the cytoskeleton.

The molecular changes induced by moderate, profound and ultraprofound hypothermia may also directly compromise endothelial cell integrity. For example,

chilling of several types of epithelial cells has been shown to result in disassembly (depolymerisation) of the intracellular microtubules resulting in compromise of the polarized membrane expression and function of some transport proteins in these cells. [123] These functions are slow to return to normal ( $\cong$ 20 hr) and are associated with prolonged dysfunction of allografts that have undergone cold preservation storage. [124],[125]

Deep cooling of the peripheral tissues may also result in immunosuppresion in chilled limbs and skin, and possibly impaired hematopoiesis due to localized moderate hypothermia in bone marrow in the cranium, sternum, vertebrae, and to a lesser extent, in the pelvis. [In children, the long bones are the principal repository of hematocytoblasts, and this marrow would also be disproportionately chilled during external cooling.] In contrast to the anti-inflammatory effect of MTH, systemic hypothermia to  $\leq 28^{\circ}$ C, either accidental or induced, has been shown to increase levels of pro-inflammatory cytokines.

Core cooling is thus the gold standard for the induction of systemic hypothermia (mild, moderate, profound or ultraprofound) and external (peripheral) cooling should be used only where there is no other alternative for achieving truly rapid cooling, or maintaining it for the required 24-48 hours following induction.

## **Consideration of Invasive Core Cooling Methods**

Figure 1-15 (right): Typical (idealized) cooling and rewarming curve achievable with maximum extracorporeal (cardiopulmonary bypass) cooling.

Extracorporeal cooling via cardiopulmonary bypass (CPB) [126] or high flow veno-venous heat exchange [127],[128] allows for cooling rates of 0.8°C/min to 1.0°C/min (**Figure 1-15**) However, it cannot be applied rapidly enough given existing logistic and regulatory



constraints. CPB requires complex hardware and highly skilled personnel who must maintain their clinical reflexes by practicing perfusion on a regular (preferably daily or at least weekly) basis. Even in centers of excellence, with a highly skilled, rapidresponse CPB team at the ready (including a well-practiced surgeon or cardiologist), the soonest CPB can be initiated after cardiac arrest is typically 15-20 minutes. [129],[130]

The use of emergency CPB applied in this time frame is largely confined to patients undergoing cardiac catheterization and/or revascularization (i.e., angioplasty or stent placement) who arrest in the cardiac catheterization lab. When such patients experience cardiac arrest that is refractory to treatment with drugs and defibrillation - they are usually otherwise healthy – they have normally functioning lungs, normal

fluid balance and fluid distribution (are neither dehydrated nor edematous from fluid overload), and have failure of a only a single organ – the heart. Even under such 'ideal' conditions, CPR is often inadequate to maintain brain viability during the brief interval between cardiac arrest and the start of CPB.

While veno-venous extracorporeal cooling is less technically demanding, it still requires skill-intensive vascular access under field conditions, and reported rates of cooling are modest; ~0.012°C/min. [131],[87] Both of these techniques may require anticoagulation, and certainly require coagulation monitoring; which again is a barrier to in-field application.

Administration of large volumes (40mL/kg) of chilled intravenous fluid has also been used to reduce core temperature in the field in patients undergoing CPR. However this method is extremely slow (~0.058°C/min) [132],[133],[134], and is sharply constrained by the maximum volume of fluid that can be administered.



**Figure 1-16 (left):** Cryopatient undergoing ECMO and blood washout in the home. Even under ideal circumstances cardiopulmonary bypass takes in excess of 30 minutes to initiate.

The effectiveness of intravascular fluid administration in achieving

durable core cooling is also a function of body composition. Obesity, which has become epidemic in the developed world, is now rapidly becoming a global problem with 1.1 billion adults worldwide classified as overweight, and 312 million of them as obese by the World Health Organization (WHO). [135] Vascular volume does not increase proportionally with increases in body weight; in fact, the vascular volume to body weight ratio falls toward an asymptotic value of approximately 45 ml/kg in the obese human.[136] Thus, the use of cold intravenous infusions will necessarily be even less effective in the obese than might be expected, since the maximum volume of fluid that may be safely given does not increase linearly with body weight. Fat is also an extraordinarily good insulator, and obesity often unfavorably alters body surface to volume area. All of these factors combine to dramatically reduce the speed and overall effectiveness of external cooling.

The limits of efficiency of core cooling that can be achieved by irrigating the peritoneal or pleural spaces with cold liquid are in the range of 0.05 to 0.3°C/min [137],[138] and both of these techniques are invasive, require considerable technical skill, and carry with them risks of serious iatrogenic consequences.

As noted earlier, the ideal way to address these needs would be extracorporeal membrane oxygenation (ECMO) and cooling. However, the practicality of rapidly bringing this demanding technology to bear in the EMS setting is currently negligible. Surgery (or time-consuming percutaneous vascular access; at or beyond the optimum therapeutic window of 15 min post ROSC) is required to access the

circulation and this cannot be accomplished under field conditions. Experience with emergent initiation of ECMO in patients presenting for experimental cryopreservation (**Figure 1-16**) are probably representative of the time required to achieve extracorporeal support under field conditions for patients with SCA. Such patients typically experience a delay of 60 to 80 minutes (and not infrequently longer) after the initiation of closed chest CPR before the application of CPB, even under optimum circumstances. [139],[140],[141]

Thus, what is needed for patients who have suffered prolonged ( $\geq$ 5 min) cardiac arrest, or in whom ROSC cannot be effectively established, is the ability to rapidly induce hypothermia via core cooling *simply and noninvasively*. In addition to moderating the injury cascade initiated by ischemia-reperfusion, mild (33-35°C) or moderate (28-32°C) hypothermia can indirectly act to improve gas exchange and hemodynamics by bringing the patient's cerebral and systemic metabolic demands closer to those that can be delivered by CPR.

## **Exsanguinating Trauma Resulting in Cardiac Arrest**

Closely related in pathophysiology to prolonged normothermic ischemia secondary to SCA, is cardiac arrest secondary to exsanguinating trauma. It is estimated that ~20,000 US civilians a year die as result of hemorrhage from abdominal and thoracic injuries [36], or from poly-trauma. In developing nations this problem is even more severe as a disproportionate amount of trauma occurs in rural settings remote from tertiary care facilities; and with no helicopter or other airlift infrastructure available to shorten this interval.

Similarly, approximately 20% of the battlefield casualties who fail to reach tertiary care facilities die from intractable hemorrhage on the battlefield or during transport.[142],[143],[144],[145],[146] The US military, under the auspices of DARPA, has been funding a multimillion project to achieve ~30 minutes of battlefield 'suspended animation' using chilled, drug containing crystalloid solutions, to solve this major cause of war-related mortality [37] and preliminary studies have been positive. [147],[128],[147]

Cardiac arrest secondary to exsanguinating trauma offers a unique opportunity for intervention in the pathophysiological cascade of cardiac arrest. Because blood loss and deterioration of the patient to the agonal state occur over a time course of minutes, to an hour or longer, it is possible to begin induction of hypothermia before cardiac arrest occurs; potentially allowing for the opportunity to prevent many of the foreseeable irreversible pathological events which occur during ischemia as a result of cardiac arrest.

Beyond inhibition or moderation of the injury cascade attendant to ischemiareperfusion injury, deep (15-27°C) profound (5-14°C) or ultra-profound (5-0°C) hypothermia offers the prospect of acting as a bridge to definitive therapy in cases of uncontrolled hemorrhage in both the military and civilian settings, as well as in cases of cardiac arrest that are refractory to prompt defibrillation and that require prolonged CPR until CPB can be initiated and coronary revascularization or application of long-term circulatory support (i.e., left ventricular assist device (LVAD) or total artificial heart (TAH)) can be implemented. This was the vision of one of the fathers of CPR and the discoverer of MTH, Dr. Peter Safar. Safer envisioned a time in the near tomorrow when patients who were not salvageable in the field would be placed into what he termed a 'metabolic lock-box' and preserved until definitive therapy could be applied in hospital. His formal name for this paradigm was 'emergency preservation and resuscitation' (EPR). [148]

As is the case with truly effective implementation of MTH in cardiac arrest or neurotrauma the principal barrier to EPR is safe, rapid and easily implemented core cooling. This barrier will have to be overcome before MTH can be applied clinically in a meaningful time frame. Alternatively, or complementarily, induction of a profound reduction in metabolism via the use of pharmacological means may provide an immediately applicable method for achieving neurosalvage in SCA patients. [149, 150]

## References

- 1. American-Heart-Association, *Heart Disease and Stroke Statistics 2008 Update.*. 2008, American Heart Association: Dallas, Texas.
- 2. de Vreede-Swagemakers, J., et al., *Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. .* J Am Coll Cardiol, 1997. **30**: p. 1500-5.
- 3. American-Heart-Association-and-National-Research-Council, Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JJ Amer Med Assoc, 1974. **227(suppl)**: p. 833-68.
- 4. Sakai, A., Sudden deaths among male employees: a six-year epidemiological survey. J Cardiol, 1990. **20**: p. 957-61.
- 5. Safranek, D., Eisenberg, MS, Larsen, MP., *The epidemiology of cardiac arrest in young adults.* Ann Emerg Med, 1992. **21**: p. 1102-6.
- 6. Viskin, S., Belhassen, B., *Idiopathic ventricular fibrillation.* American Heart Journal, 1990. **120**: p. 661 671.
- 7. Skogvoll, E., et al., *Out-of-hospital cardiopulmonary resuscitation: a population-based Norwegian study of incidence and survival.* . Eur J Emerg Med, 1999. **6**: p. 323-30.
- 8. Weale, F., *The efficacy of cardiac massage.* Lancet, 1960. **1**: p. 990-96.
- 9. Eisenberg, M., *Cardiac Arrest and Resuscitation: A tale of 29 cities.* Ann of Emer Med, 1990. **19**: p. 179-86.
- 10. Kentsch, M., et al., *Early prediction of prognosis in out-of-hospital cardiac arrest.* Intensive Care Med, 1990. **16**: p. 378-83.
- 11. Troiano, P., et al., *The effect of bystander CPR on neurologic outcome in survivors of prehospital cardiac arrests.* Resuscitation, 1989. **17**: p. 91-8.
- 12. Bossaert, L., Van Hoeyweghen, R., *Bystander cardiopulmonary resuscitation* (*CPR*) *in out-of-hospital cardiac arrest. The Cerebral Resuscitation Study Group.*. Resuscitation, 1989. **17(Suppl)**: p. S55-69; discussion S199-206.
- 13. Stueven, H., et al., *Bystander/first responder CPR: ten years experience in a paramedic system.* Ann Emerg Med, 1986. **15**: p. 707-10.
- 14. Lombardi, G., Gallagher, J, Gennis, P., *Outcome of out-of-hospital cardiac* arrest in New York City. The Pre- Hospital Arrest Survival Evaluation (PHASE) Study [see comments]. JAMA, 1994. **271**: p. 678-83.
- 15. McCarthy, M., *Looking after your neighbors Seattle-style.* Lancet, 1998. **351**: p. 732.

- 16. Hayward, M., *Cardiopulmonary resuscitation: are practitioners being realistic?* Br J Nurs, 1999. **8**: p. 810-4.
- 17. Bengtsson, M., *A psychiatric-psychosocial investigation of patients who had survived circulatory arrest.* Acta Psychiat Scan, 1969. **45**: p. 327.
- 18. Roewer, N., Kloss, T, Puschel, K., *Long-term result and quality of life following preclinical cardiopulmonary resuscitation.* Anasth Intensivther Notfallmed, 1985. **20**: p. 244-50.
- 19. de Vos, R., *Quality of life after cardiopulmonary resuscitation.* Resuscitation, 1997. **35**: p. 231-6.
- 20. Phillips, S., *Resuscitation for cardiogenic shock with extracorporeal membrane oxygenation systems.* Semin Thorac Cardiovasc Surg, 1994. **6**: p. 131-5.
- 21. Younger, J., et al., *Extracorporeal resuscitation of cardiac arrest [see comments].* Acad Emerg Med, 1999. **6**: p. 700-7.
- 22. Matsuwaka, R., et al., *Emergency percutaneous cardiopulmonary support for patients with cardiac arrest or severe cardiogenic shock.* Nippon Kyobu Geka Gakkai Zasshi, 1996. **44**: p. 2006-10.
- 23. Myerburg, R., *Clinical, electrophysiologic, and hemodynamic profiles of patients resuscitated from pre-hospital cardiac arrest.*. Amer J Med, 1980. **68**: p. 568.
- 24. Safar, P., Abramson, NS, Angelos, M, et al., *Emergency cardiopulmonary bypass for resuscitation from prolonged cardiac arrest.* Am J Emerg Med, 1990. **8**: p. 55-67.
- 25. Peterson, M., et al., *Outcome after cardiopulmonary resuscitation in a medical intensive care unit.* Chest, 1991. **100**: p. 168-74.
- 26. Gener, J., et al., *Immediate and 1-year survival after cardiopulmonary resuscitation at an intensive care unit*. Med Clin (Barc), 1989. **93**: p. 445-8.
- 27. Rubertsson, S., et al., *Blood flow and perfusion pressure during open-chest versus closed-chest cardiopulmonary resuscitation in pigs.* Am J Emerg Med, 1984. **23**: p. 568-571.
- 28. Bircher, N., Safar, P., *Open-chest CPR: An old method whose time has returned.* Am J Emerg Med, 1984. **2**: p. 568-71.
- 29. McDonald, J., Systolic and mean arterial pressures during manual and mechanical CPR in humans. Ann Emerg Med, 1982. **11**: p. 292-5.
- 30. Ornato, J., et al., *Measurement of ventilation during cardiopulmonary resuscitation.* Crit Care Med., 1983. **1**: p. 79-82.
- 31. Kim, H., et al., *Amelioration of impaired cerebral metabolism after severe acidotic ischemia by tirilazad post-treatment in dogs.*. Stroke, 1996. **27**: p. 114-21.
- 32. Iwatsuki, N., et al., *Hyperbaric oxygen combined with nicardipine administration accelerates neurologic recovery after cerebral ischemia in a canine model.*. Crit Care Med, 1994. **22**: p. 858-63.
- 33. Cervantes, M., Moralı´, G, Letechipı´a-Vallejo, G., *Melatonin and ischemia reperfusion injury of the brain.* J. Pineal Res, 2008. **45**: p. 1-7.
- Krep, H., Bernd W, Bottiger, BW, et al., *Time course of circulatory and metabolic recovery of cat brain after cardiac arrest assessed by perfusion-and diffusion-weighted imaging and MR-spectroscopy.* Resuscitation, 2003. 58: p. 337-348.
- 35. DeGraba, T., Pettigrew, C., *Why do neroprotectivedrugs work in animals but not in humans?* Neurologic Clinics, 2000. **18**: p. 475-493.

- 36. Ginsberg, M., Adventures in the Pathophysiology of Brain Ischemia: Penumbra, Gene Expression, Neuroprotection. The 2002 Thomas Willis Lecture. Stroke, 2003. **34**: p. 214-223.
- 37. Cheng, J., Al-Khoury, L, Zivin, JA., *Neuroprotection for Ischemic Stroke: Two Decades of Success and Failure.* NeuroRX, 2004. **1**: p. 36-45.
- 38. Roine, R.O., et al., *Nimodipine after resuscitation from out-of-hospital ventricular fibrillation. A placebo-controlled, double-blind, randomized trial.* JAMA, 1990. **264**(24): p. 3171-3177.
- 39. Longstreth, W.T., Jr., et al., *Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest.* Neurology, 2002. **59**(4): p. 506-514.
- 40. Landau, W.M., et al., *Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest.* Neurology, 2003. **60**(11): p. 1868-1869.
- 41. Halstrom, A., Rea, TD, et al., *Manual chest compression vs use of an automated chest compression device during resuscitation following out-of-hospital cardiac arrest: a randomized trial.* JAMA, 2006. **295**: p. 2620-8.
- 42. Lafuente-Lafuente, C., Melero-Bascones, M., *Active chest compressiondecompression for cardiopulmonary resuscitation.* Cochrane Database Syst Rev., 2004. (2):CD002751.
- 43. Aung, K., Htay, T., Vasopressin for cardiac arrest: a systematic review and meta-analysis. Arch Intern Med, 2005. **10**: p. 17-24.
- 44. Callaham, M., Madsen, CD, Barton, CW, Saunders, CE, Pointer, J., *A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest.* JAMA, 1992. **268**: p. 2667-72.
- 45. Rincon, F., Mayer, SA., *Therapeutic hypothermia for brain injury after cardiac arrest.* . Semin Neurol 2006. **26**: p. 387-395.
- Bernard, S., Gray, TW, Buist, MD, et al., *Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.* N Engl J Med, 2002.
   346: p. 557-563.
- 47. Liu, L. and M.A. Yenari, *Therapeutic hypothermia: neuroprotective mechanisms.* Front Biosci, 2007. **12**: p. 816-25.
- 48. The-Hypothermia-after-Cardiac-Arrest-Study-Group, *Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest.* N Engl J Med, 2002. **346**: p. 549-556.
- 49. Nolan, J., Morley, PT, Vanden Hoek, TL, Hickey, RW., *Therapeutic* Hypothermia After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. Circulation, 2003. **108**: p. 118-121.
- 50. Arrich, J., *Clinical application of mild therapeutic hypothermia after cardiac arrest.* Crit Care Med, 2007. **35**(4): p. 1041-7.
- 51. Sandroni, C., et al., *In-hospital cardiac arrest: incidence, prognosis and possible measures to improve survival.* Intensive Care Med, 2007. **33**(2): p. 237-45.
- 52. Safar, P., *Resuscitation from clinical death: Pathophysiologic limits and therapeutic potentials.* Crit Care Med, 1988. **16**: p. 923-941.
- 53. Safar, P., et al., *Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion.* Stroke, 1996. **27**(1): p. 105-13.

- 54. Polderman, K.H., *Hypothermia and neurological outcome after cardiac arrest: state of the art.* Eur J Anaesthesiol Suppl, 2008. **42**: p. 23-30.
- 55. Busto, R., Dietrich, WD, Globus, MY, et al., *Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury.* J Cereb Blood Flow Metab, 1987. **7**: p. 729-738.
- 56. Safar, P., Behringer, W., ed. *Brain resuscitation after cardiac arrest.* Textbook of neurointensive care., ed. A. Layon, Gabrielli, A, Friedman, WA (Eds). . 2001, WB Saunders: Philadelphia.
- 57. Shimohata, T., H. Zhao, and G.K. Steinberg, *Epsilon PKC may contribute to the protective effect of hypothermia in a rat focal cerebral ischemia model.* Stroke, 2007. **38**(2): p. 375-80.
- 58. Zhao, H., G.K. Steinberg, and R.M. Sapolsky, *General versus specific actions* of mild-moderate hypothermia in attenuating cerebral ischemic damage. J Cereb Blood Flow Metab, 2007. **27**(12): p. 1879-94.
- 59. American-Heart-Association, AHA CPR Guidelines: Part 7.2: Management of Cardiac Arrest. Circulation, 2005. **112:IV-58-IV-66**.
- 60. Abella, B., Rhee, JW, Huang, KN, et al., *Induced hypothermia is underused after resuscitation from cardiac arrest: A current practice survey.* Resuscitation, 2005. **64**: p. 181-186.
- 61. Merchant, R., Soar, J, Skrifvars, MB, et al., *Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest.* . Crit Care Med, 2006. **34**: p. 1935-1940.
- 62. Kennedy, J., Green, RS, Stenstrom, R., *The use of induced hypothermia after cardiac arrest: A survey of Canadian emergency physicians.* CJEM, 2008. **10**: p. 125-130.
- 63. Suffoletto, B., Salcido, DD, Menegazzi, JJ., Use of prehospital-induced hypothermia after out-of-hospital cardiac arrest: A Survey of the National Association of Emergency Medical Services Physicians. Prehosp Emerg Care, 2008. **12**: p. 52-56.
- 64. Alam, H., Just do it. Critical care medicine,, 2008. **36**: p. 2456-7.
- 65. Skulec, R., et al., *Induction of mild hypothermia in cardiac arrest survivors presenting with cardiogenic shock syndrome.* Acta Anaesthesiol Scand, 2008. **52**(2): p. 188-94.
- 66. Hay, A.W., et al., *Therapeutic hypothermia in comatose patients after out-ofhospital cardiac arrest.* Anaesthesia, 2008. **63**(1): p. 15-9.
- 67. Wolfrum, S., et al., *Mild therapeutic hypothermia in patients after out-ofhospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention.* Crit Care Med, 2008. **36**(6): p. 1780-6.
- 68. Bernard, S., *Therapeutic hypothermia after cardiac arrest: now a standard of care.* Crit Care Med, 2006. **34**(3): p. 923-4.
- 69. Wolff, B., et al., *Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest.* Int J Cardiol, 2008.
- 70. Nagel, Š., et al., *Therapeutic hypothermia in experimental models of focal and global cerebral ischemia and intracerebral hemorrhage.* Expert Rev Neurother, 2008. **8**(8): p. 1255-68.
- 71. Nozari, A., et al., *Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation.* Circulation, 2006.
  113(23): p. 2690-6.

- 72. Reich, H., et al., *Cardiac resuscitability with cardiopulmonary bypass after increasing ventricular fibrillation times in dogs.* Ann Emerg Med, 1990. **19**(8): p. 887-90.
- Angelos, M., P. Safar, and H. Reich, A comparison of cardiopulmonary resuscitation with cardiopulmonary bypass after prolonged cardiac arrest in dogs. Reperfusion pressures and neurologic recovery. Resuscitation, 1991. 21(2-3): p. 121-35.
- 74. Radovsky, A., et al., Regional prevalence and distribution of ischemic neurons in dog brains 96 hours after cardiac arrest of 0 to 20 minutes. Stroke, 1995.
  26(11): p. 2127-33; discussion 2133-4.
- 75. Thoresen, M., Wyatt, J. [see comments], *Keeping a cool head, post-hypoxic hypothermia: an old idea revisited.* Acta Paediatr 1997. **86**: p. 1029-33.
- 76. Nozari, A., et al., *Mild hypothermia during prolonged cardiopulmonary cerebral resuscitation increases conscious survival in dogs.* Crit Care Med, 2004. **32**(10): p. 2110-6.
- 77. Kuboyama, K., Safar, P, Radovsky, A, Tisherman, SA, Stezoski, SW, Alexander, H., *Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study* [see comments]. 21, 1993. **Crit Care Med**: p. 1348-58.
- 78. Takata, K., Takeda, Y, Sato T, Nakatsuka, H, Yokoyama, M, Morita, K., Effects of hypothermia for a short period on histologic outcome and extracellular glutamate concentration during and after cardiac arrest in rats. . Crit Care Med, 2005. **33**: p. 1340 -1345.
- 79. Abella B, Z.D., Alvarado J, Hamann K, Vanden Hoek T, Becker L., *Intra-arrest cooling improves outcomes in a murine cardiac arrest model.* Circulation, 2004. **109**: p. 2786 -2791.
- 80. Dietrich, W., Busto, R, Alonso, O, et al. 993, *Intraischemic but not* postischemic brain hypothermia protects chronically following global forebrain ischemia in rats. J Cerebr Blood Flow Metab, 1993. **13**: p. 541-549.
- 81. Maier, C.M., et al., *Delayed induction and long-term effects of mild hypothermia in a focal model of transient cerebral ischemia: neurological outcome and infarct size.* J Neurosurg, 2001. **94**(1): p. 90-6.
- 82. Marion, D., Leonov Y, Ginsberg, M, Katz, LM, Kochanek, PM, Lechleuthner, A, Nemoto, EM, Obrist, W, Safar, P, Sterz, F, Tisherman, SA, White, RJ, Xiao, F, Zar, H., *Resuscitative hypothermia.* Crit Care Med, 1996. **24**: p. S81-9.
- 83. Zivin, J., *Editorial comment.* Stroke, 1999. **30**: p. 1899.
- 84. Wake-County-Government, *Wake County Emergency Medical Services.* 2008, Wake County Government.
- 85. Hinchey, P., et al., Out-of-hospital cardiac arrest survival after the sequential implementation of 2005 AHA guidelines for compressions, ventilations, and induced hypothermia., in SAEM Meeting. 2008: Washington, D.C. .
- 86. Olson, J., Hinchey, P, Myers, B. (2006) *Wake County EMS Cools Down: System begins induced hypothermia of ROSC patients.* JEMS **Volume**,
- Bayegan, K., et al., Rapid non-invasive external cooling to induce mild therapeutic hypothermia in adult human-sized swine. Resuscitation, 2008. 76(2): p. 291-8.
- Kurz, A., Sessler, DI, Birnbauer, F, Illievich, U, Spiss, C., *Thermoregulatory vasoconstriction impairs active core cooling.* Anesthesiology 1995. 82: p. 870-6.

- 89. Stolwijk, J., Hardy, JD., ed. *Control of body temperature: Reactions to environmental agents.* In Handbook of Physiology., ed. e. Douglas HK. . 1977, American Physiological Society: Bethesda. 45-69.
- 90. Doufas, A., *Consequences of inadvertent perioperative hypothermia.* Best Pract Res Clin Anaesthesiol, 2003. **17**: p. 535-49.
- 91. Sheffield, C., Sessler, DI, Hunt, TK. , *Mild hypothermia during isoflurane anesthesia decreases resistance to E. coli dermal infection in guinea pigs.* Acta Anaesthesiol Scand, 1994. **38**: p. 201-5.
- 92. Lee, S., Battistella, FD, Go, K., *Hypothermia induces T-Cell production of immunosuppressive cytokines.* J Surg Res, 2001 **100**(4): p. 150-153.
- 93. Reed, R., Bracey, AW, Hudson, JD, Miller, TA, Fisher, RP., Hypothermia and blood coagulation: dissociation between enzyme activity and clotting factor levels. Circ Shock, 1990. **32**: p. 141-152.
- 94. Nirula, R., Gentilello, LM., ed. *Detrimental Effects of Hypothermia* Therapeutic Hypothermia., ed. S. Tisherman, Sterz, F. 2007, Springer US: New York.
- 95. Flores-Maldonado, A., Medina-Escobedo, CE, Rios-Rodriguez, HM, Fernandez-Dominguez, R., *Mild perioperative hypothermia and the risk of wound infection.* Arch Med Res, 2001. **32**: p. 227-231.
- 96. Kurz, A., Sessler, DI, Lenhardt, R., *Perioperative normothermia to reduce the incidence of surgical wound infection and shorten hospitalization.* N Engl J Med, 1996. **334**: p. 1209-15.
- 97. Sheffield, C., Sessler, DI, Hopf, HW, Schroeder, M, Moayeri, A, Hunt, TK, West, JM., *Centrally and locally mediated thermoregulatory responses alter subcutaneous oxygen tension.* Wouns Rep Reg 1997. **4**: p. 339-45.
- Wenisch, C., Narzt, E, Sessler, DI. Parschalk, B, Lenhardt, R, Kurz, A, Graninger, W., *Mild intraoperative hypothermia reduces production of reactive oxygen intermediates by polymorphonuclear leukocytes.* Anesth Analg, 1996.
   82: p. 810-6.
- 99. Beilin, B., Shavit, Y, Razumovsky, J, et al., *Effects of mild perioperative hypothermia on cellular immune responses.* Anesthesiology, 1998. **89**: p. 1133-1140.
- 100. Jyung, R., Mustoe, TA., *Role of cytokines in wound repair.* Clinical Application of Cytokines., ed. J. Oppenheim, Rossio, JL, Gearing, AJH, eds. 1993, New York: Oxford University Press.
- 101. Baigrie, R., Lamont, PM, Kwiatkowski, D, Dallman, MG, Morris, PG., Systemic cytokine response after major surgery. Br J Surg, 1992. **79**: p. 757-60.
- 102. Qwarnstrom, E., Page, RC, Gillis, S, Dower, SK., *Binding, internalization and intracellular localization of interleukin-1 beta in human diploid fibroblasts.* B Biol Chem, 1988;. **263:** p. 8261-9.
- Peterson, K., Carson, S, Carney, N., Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis. J Neurotrauma, 2008. 25(1): p. 62-71.
- 104. Hammersborga, S., Brekkea, KB, Haugena, OM, et al., *Surface cooling versus core cooling: Comparative studies of microvascular fluid- and protein-shifts in a porcine model.* Resuscitation, 2008. **79**: p. 292-300.
- Merchant, R., Abella, BS, Peberdy, MA, Soar, J, et al., *Therapeutic hypothermia after cardiac arrest: Unintentional overcooling is common using ice packs and conventional cooling blankets.* Crit Care Med, 2006.
   34[Suppl.]: p. S490-S494.

- 106. Al-Senani, F., Graffagnino, C, Grotta, JC, et al., *A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest.* . Resuscitation, 2004. **62**(2): p. 143-50.
- 107. Chen, R., Chien, S., *Hemodynamic functions and blood viscosity in surface hypothermia.* Am J Physiol Lung Cell Mol Physiol, 1978. **235**: p. H136-43.
- 108. Zarins, C., Skinner, DB., *Hemodynamics and blood flow distribution following prolonged circulation at 5 degrees C.* Am J Physiol., 1975. **229**: p. 275-8.
- 109. Hammersborga, S., Farstad, M, Haugen, O, Kvalheim, VL, Onarheim, H, Husby, P., *Time course variations of haemodynamics, plasma volume and microvascular fluid exchange following surface cooling: an experimental approach to accidental hypothermia.* Resuscitation, 2005. **65**: p. 211-9.
- 110. Lewis, T., Swelling of the human limbs in response to immersion in cold water. Clin Sci, 1939. **4**.
- 111. Farry, P., Prentice, NG, Hunter, AC, Wakelin, CA., *Ice treatment of injured ligament: an experimental model.* N Z Med J., 1980. **91**: p. 12-14.
- 112. Matthew, C., Sils, IV, Bastille, AM., *Tissue-specific extravasation of albuminbound Evans blue in hypothermic and rewarmed rats.* Can J Physiol Pharmacol, 2002. **80**(3): p. 233-243.
- 113. Kruuv, J., Glofcheski, D, Cheng, KH, Campbell, SD, Al-Qysi, HMA, Nolan, WT, Lepock, JR, *Factors influencing survival and growth of mammalian cells exposed to hypothermia. I. Effects of temperature and membrane lipid perturbers.* J Cell Physiol, 1983. **115**: p. 179-185.
- 114. Rule, G., Frim, J, Thompson, JE, Lepock, JR, Kruuv, J., *Theeffect of membrane lipid perturbers on survival of mammalian cells to cold.* Cryobiology 1978. **15**: p. 408-414.
- 115. Marsh, D., Lindell, SL, Fox, LE, Belzer, FO, Southard, JH., *Hypothermic preservation of hepatocytes. I. Role of cell swelling.* Cryobiology, 1989. **26**: p. 524-534.
- 116. McAnulty, J., Ametani, MS, Southard, JH, Belzer, FO., *Effect of hypothermia* on intracellular Ca21 in rabbit renal tubules suspended in UW-gluconate preservation solution. . Cryobiology, 1996. **33**: p. 196-204.
- 117. Breton, S., Brown, D., Cold-induced microtubule disruption and relocalization of membrane proteins in kidney epithelial cells. J Am Soc Nephrol, 1998. **9**: p. 155-166.
- 118. Stefanovich, P.E., RM, Sheehan, SJ, Tompkins, RG, Yarmush, ML., *Effects of hypothermia on the function, membrane integrity, and cytoskeletal structure of hepatocytes.* Cryobiology, 1995. **23**: p. 389-403.
- 119. Zieger, M., Glofcheski, DJ, Lepock, JR, Kruuv, J., *Factors influencing survival of mammalian cells exposed to hypothermia IV. Effects of iron chelation.* . Cryobiology, 1990. **27**: p. 452-464.
- Rauen, R., DeGroot, H., Cold induced release of reactive oxygen species asa decisive mediator of hypotherrmiainjury to cultured liver cells. Free Rad Biol & Med, 1998. 24(7/8): p. 1316-1323.
- 121. Hochachka, P., *Defense strategies against hypoxia and hypothermia.* Science 1986. **231**: p. 234-241.
- 122. Endrich, B., Hammersen F, Messmer, K., *Microvascular ultrastructure in non-freezing cold injury.* Res Exp Med, 1990. **190**: p. 365-79.

- 123. Verrey, F., Groscurth, P, Bolliger, UI., *Cytoskeletal disruption in A6 kidney cells: Impact on endo-exocytosis and NaCI transport regulation by antidiuretic hormone.* J Membr Bio, 1995. **145**: p. 193-204.
- 124. Hall, S., Komai, H, Reader, J, Haworth, SG., *Donor lung preservation: Effect* of cold preservation fluids on cultured pulmonary endothelial cells. . Am J Physiol Lung Cell Mol Physiol, 1994. **267**: p. L508-L5 I 7.
- 125. Breton, S., Brown, D., Cold-induced microtubule disruption and relocalization of membrane proteins inkidney epithelial cells. J Am Soc Nephrol, 1998. **9**: p. 155-66.
- 126. Reed, C., Clark, D, editors, ed. *Heat exchangers and hypothermia.* Cardiopulmonary Perfusion. 1975, Texas Medical Press, Inc.: Houston TX. 272–8.
- Furuse, M., Ohta, T, Ikenaga, T, et al., Effects of intravascular perfusion of cooled crystalloid solution on cold-induced brain injury using an extracorporeal cooling-filtration system. Acta Neurochir, 2003. 145: p. 983-993.
- 128. Behringer, W., et al., *Veno-venous extracorporeal blood shunt cooling to induce mild hypothermia in dog experiments and review of cooling methods.* Resuscitation, 2002. **54**(1): p. 89-98.
- 129. Overlie, P., *Emergency Use of Cardiopulmonary Bypass.* Journal of Interventional Cardiology, 1995. **8**: p. 239-247.
- 130. Kurusz, M., Zwischenberger, JB., *Percutaneous cardiopulmonary bypass for cardiac emergencies.* Perfusion, 2002. **17**: p. 269-77.
- Holzer, M., Behringer, W, Janata, A, Bayegan, K, Schima, H, Deckert, Z, Losert, U, Laggner, AN, Sterz, F., *Extracorporeal venovenous cooling for induction of mild hypothermia in human-sized swine.* Crit Care Med, 2005. 33: p. 1346-50.
- 132. Bernard, S., Buist, M, Monterio, O, Smith, K., *Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report.* Resuscitation, 2003. **56**: p. 9-13
- 133. Bernard, S., Rosalion, A., *Therapeutic hypothermia induced during cardiopulmonary resuscitation using large-volume, ice-cold intravenous fluid.* Resuscitation, 2008. **76**: p. 311 313.
- 134. Kamarainen, A., et al., *Prehospital induction of therapeutic hypothermia during CPR: a pilot study.* Resuscitation, 2008. **76**(3): p. 360-3.
- 135. Haslam, D., James, WP., Obesity. Lancet, 2005. 366: p. 1197-209.
- 136. Feldschuh, J., Enson, Y., *Prediction of the normal blood volume. Relation of blood volume to body habitus.* Circulation, 1977. **56**: p. 605 612.
- 137. Plaisier, B.R., *Thoracic lavage in accidental hypothermia with cardiac arrest*report of a case and review of the literature. Resuscitation, 2005. **66**(1): p. 99-104.
- 138. Xiao, F., P. Safar, and H. Alexander, *Peritoneal cooling for mild cerebral hypothermia after cardiac arrest in dogs.* Resuscitation, 1995. **30**(1): p. 51-9.
- 139. Darwin, M., Leaf, JD, Hixon, HL. *Neuropreservation of Alcor patient A-1068.* Cryonics 1986 [cited 7 2]; 17-32]. Available from: http://www.alcor.org/Library/html/casereport8504.html.
- 140. Darwin, M. Cryopreservation Patient Case Report: Arlene Francis Fried, A-1049. 2006 [cited 2007 07 June]; Available from: http://www.alcor.org/Library/html/fried.html.

- 141. Jones, T., *Cryopreservation case report: the cryopreservation of patient A-2063.* Cryonics, 2005. **26**(1): p. 10-12.
- 142. Bellamy, R., *The causes of death in conventional land warfare: Implications for combat casualty research.* Military Medicine, 1984. **149**: p. 55-62.
- 143. Bellamy, R., *Death on the battlefield and the role of first aid.* Military Medicine, 1987a. **152**: p. 634-35.
- 144. Bellamy, R., *Death on the battlefield and the role of first aid. Military Medicine.* 1987b. **152** p. 617-21.
- 145. Bellamy, R., *Trauma epidemiology of combat casualties.*, in *Presentation to Institute of Medicine Committee on Fluid Resuscitation for Combat Casualties.* 1998: Washington, D.C.
- 146. Bowen, T., Bellamy, RF, (eds). , *Emergency war Surgery: Second United States Revision of the Emergency War Surgery Handbook.* 1998, US Government printing Office: Washington, D.C.
- 147. Wu, X., et al., *Emergency preservation and resuscitation with profound hypothermia, oxygen, and glucose allows reliable neurological recovery after 3 h of cardiac arrest from rapid exsanguination in dogs.* J Cereb Blood Flow Metab, 2008. **28**(2): p. 302-11.
- 148. Tisherman, S., Rodriguez, A, Safar, P., *Therapeutic hypothermia in traumatology.* Surg Clin North Am, 1999. **79**: p. 1269-89.
- 149. Blackstone, E, Morrison, M, Roth, M. H2S Induces a Suspended Animation–Like State in Mice.2005. Science. 308: p. 215
- Elrod JW, Calvert JW, Morrison J, Doeller JE, Kraus DW, Tao L, Jiao X, Scalia R, Kiss L, Szabo C, et al. (2007) Proc Natl Acad Sci USA 104:15560– 15565.