Therapeutic Hypothermia after Cardiac Arrest

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Introduction

Patients who are successfully resuscitated following cardiac arrest often present with what is now termed 'post-resuscitation disease' [1]. Most prominent, are post-resuscitation myocardial failure and ischemic brain damage. Although post-resuscitation myocardial dysfunction has been implicated as an important mechanism accounting for fatal outcomes after cardiac resuscitation [2–4], morbidity and mortality after successful cardiopulmonary resuscitation (CPR) largely also depends on recovery of neurologic function. As many as 30 % of survivors of cardiac arrest in fact manifest permanent brain damage [5–7]. The greatest post-resuscitation emphasis has been on long-term neurologically intact survival [8]. Evidence favoring correction of electrolyte and glucose abnormalities, control of post-resuscitation cardiac rate, rhythm, systemic blood pressure, and intravascular volumes are cited but objective proof of these interventions is still anedoctal. Of all interventions, the most persuasive benefits have followed the use of hypothermia [8].

Therapeutic hypothermia following return of spontaneous circulation was advocated for decades prior to its clinical acceptance [9]. More than a decade ago, it was reported that young and healthy people who underwent accidental deep hypothermia with cardiac arrest were able to survive with no or minimal cerebral impairment even after prolonged cardiac arrest [10]. The concept of hypothermia for reducing either or both ischemic and reperfusion injury of the brain represents a pioneering contribution of the late Professor Peter Safar and the persistence of his efforts through his students, and especially Professor Fritz Sterz [9, 11]. In 1996, Professor Safar and colleagues induced hypothermia by instilling Ringer's solution maintained at a temperature of 4 °C into the abdominal cavity of dogs after resuscitation from cardiac arrest. Cooling was maintained for 12 hours. Functional recovery was associated with minimal histological brain damage [9]. Two of the largest randomized clinical trials on systemic hypothermia published in 2002 [11, 12] objectively demonstrated improvements in neurological outcomes and, within a short 5 years, this therapeutic intervention has finally proved to be neuroprotective [8, 11, 12].

At present, therapeutic hypothermia has become a well-recognized useful tool in the physician's armamentarium for providing neuroprotection following cerebral ischemic events, including global cerebral ischemia following cardiac arrest. The International Liaison Committee and the American Heart Association (AHA) recommend post-resuscitation hypothermia in the range of 32°C to 34°C for between 12 and 24 hours in adult victims who are comatose following return of spontaneous circulation [8].

Effects of Hypothermia on Neurological Function Following Cardiac Arrest

Post-resuscitation neurological function largely depends on the duration of the arrest time, with no blood flow and development of ischemic injury. The severity of neurologic dysfunction after circulatory arrest also relates to the cerebral reperfusion disturbances observed during and after reperfusion following resuscitation. During ischemic episodes, there is increased blood viscosity and blood consequently stagnates within the microcirculation facilitating red cell aggregation. Constriction of blood vessels and perivascular edema have also been frequently observed [13, 14]. All these mechanisms may be implicated in increasing cerebral vascular resistance which culminates in marked impairment of reflow after return of spontaneous circulation and cerebral hypoperfusion, especially in the forebrain and cerebellar regions. Severe hypoperfusion to as low as 6 to 20 % of the normal level that developed in the first 10 to 20 minutes of reperfusion has been reported to last for at least 2 hours [15]. In a recent investigation performed in our laboratories [16], of special interest was the relationship between macro- and microvascular flows and the severity of brain tissue ischemia during and following cardiac arrest and return of spontaneous circulation. We reported that increases in cerebral cortical tissue PCO_2, a useful quantitative measurement of the metabolic severity of low flow states, were observed after onset of cardiac arrest and were progressive during (CPR). After return of spontaneous circulation, although macro- and microvascular flows were restored quite promptly, cerebral cortical ischemia was more slowly reversed. Hence, these studies pinpointed delays in reversal of brain ischemia after resuscitation with early brain protection such as initiating hypothermia during CPR rather than after resuscitation.

Hypothermia slows down most of the cerebral metabolic processes and, therefore, may inhibit deleterious biochemical or cerebrovascular events during reperfusion [17, 18]. Hypothermia also decreases damaging free radical production [18] and excitatory amino acid release [19] and instead promotes neuronal recovery after both focal and global brain ischemia.

Cerebral blood flow modifications in response to cooling are not as yet clearly understood. Previous studies have shown local or global decreases in blood reperfusion in the brain during whole body or selective brain cooling [20, 21]. This was explained as a direct result of the coupling between the local blood reperfusion and local metabolism that usually decreases when temperature drops. However, this coupling might be disrupted during ischemia [22]. In experimental models, Kuluz et al. [23] described increases in cerebral large vessel blood flow following selective brain cooling. In different settings, cooling of carotid artery preparations induced a reversible graded vasodilation and decreased or abolished the effect of vasocontractile neurotransmitters. Isometric tensions in rodent carotid artery strips were further assessed during stepwise cooling [24]. Lowering of the temperature, from 37 °C to 4 °C, induced a rapid and reproducible stepwise decrease in the arterial wall tone and when the temperature was reset to 37 °C, the tone rapidly returned to the basal level. Cooling also significantly reduced or totally abolished norepinephrine-induced contractions of the large cerebral vessels. In organs other than brain, hypothermia instead induced a clear-cut increase in basal tone of the smooth muscles of the blood vessels. Therefore, the basic mechanisms underlying hypothermic reactions of smooth muscle in blood vessels and other conduits of the body are regionally different and adjusted to serve the functional requirements of the organism when exposed

to hypothermia. In different settings, when cerebral perfusion was measured during hyperthermia, defined as increases of 4 °C from the basal temperature, carotid artery contraction and decreases in cerebral blood flow were observed [25].

Additional benefits of brain hypothermia are also identified in the ability of hypothermia to significantly reduce intracranial pressure (ICP) after restoration of flow and this might account for greater perfusion [26]. When ICP increases due to brain edema, neurons may be damaged thus jeopardizing cerebral perfusion. Induced hypothermia might, therefore, be considered to control increases in ICP, without compromising cerebral autoregulation [26, 27].

Effects of Hypothermia on Myocardial Function after Cardiac Arrest

More than 50 % of all patients initially resuscitated from cardiac arrest subsequently die before leaving the hospital. Studies in animals and in human patients support the notion that the majority of these deaths are due to impaired myocardial function primarily due to heart failure and/or recurrent ventricular fibrillation [28]. This high incidence of fatal outcomes related to post-resuscitation myocardial dysfunction has prompted research on options for myocardial preservation during cardiac arrest and resuscitation. In addition to neuroprotection [11, 12], hypothermia has also appeared to be an important intervention to protect the heart after cardiac arrest.

Hypothermia, in fact, has been shown to protect from ischemia-reperfusion injury [29], and to aid in diminishing myocardial infarct size in animal models of coronary artery occlusion [30, 31]. Such protection seemed to be mediated by increased nitric oxide (NO) generation via activation of protein kinase C-epsilon (PKCε) [29]. Hypothermia also reduced metabolic demand and high energy phosphate utilization in the myocardium [32], as well as oxygen utilization [33] with consequent reductions in ATP depletion [34]. In models of ischemia-reperfusion in cardiomyocytes, cooling prior to reperfusion conferred improved cell viability and attenuated a number of intracellular injury pathway mechanisms, including apoptotic enzymes, in comparison to reperfusion without cooling [29]. In settings of cardiac arrest, temperature preconditioning induced by short-term hypothermic perfusion and rewarming, protected hearts au pair to ischemic preconditioning [35]. Prior to inducing ischemia, hearts underwent cycles of hypothermic perfusion at 26°C interspersed with intervals of normothermic perfusion. During reperfusion following ischemia, hypothermia improved hemodynamic recovery, decreased arrhythmias, and reduced necrotic damage.

Moreover, rapid cooling has also been previously reported to lead to increases in mammalian cardiac muscle twitch force, probably related to increases in the calcium sensitivity of the myofilaments [36]. When we investigated the effects of a range of temperatures on ventricular myocyte contractility, we observed that decreases in perfusion temperatures were highly related to significant increases in myocyte contractility (unpublished data). Reductions in perfusion temperature were accompanied by corresponding increases in cell shortening percentage (**Fig. 1**).

All these effects of hypothermia may contribute to the explanation of more recent observations of increased myocardial contractility following cooling treatment after cardiac arrest. In isolated hearts perfused and exposed to mild or moderate hypothermia during 120 minutes of ischemia, moderate hypothermia suppressed anaerobic metabolism during ischemia and significantly diminished left ventricular end-

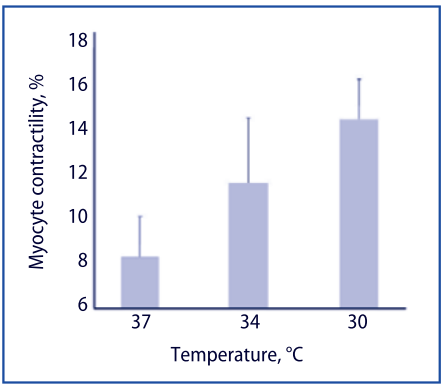

Fig. 1. Myocyte contractility expressed in % of baseline length during different perfusion temperatures.

diastolic pressure at the end of ischemia. Hypothermia therefore contributed to the preservation of myocardial function, coronary flow, and oxygen consumption compared with normal control hearts [37]. Interesting data, highlighting improvements of myocardial contractility in animals that received hypothermia treatment following cardiac arrest, have been recently published by Zhao et al [38]. In these experiments, hypothermic cardiovascular reperfusion resulted in considerably greater cardiac output with concomitant lesser systolic and diastolic myocardial dysfunction during the post-arrest period. Accordingly, we have recently confirmed, employing a different method of cooling to provide rapid selective head cooling initiated during CPR, improvements not only on post-resuscitation neurological outcome but also increases in coronary perfusion pressure during chest compressions, with consequent greater success of resuscitation and better post-resuscitation myocardial function and survival [39–41].

Finally, hypothermia has been reported to reduce the defibrillation threshold to terminate ventricular fibrillation [42]. Boddicker et al. [32] demonstrated that moderate or severe systemic hypothermia, induced by surrounding the head, thorax, and abdomen with ice, prior to resuscitation, improved the success of defibrillation and return of spontaneous circulation in a prolonged porcine model of cardiac arrest. Severe surface hypothermia facilitated transthoracic defibrillation through modifications in mechanical and electrophysiological myocardium properties, shown by increases in thoracic impedance with a decrease in current.

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Timing and Methods for Inducing Hypothermia

Currently, hypothermic treatment is initiated during the post-resuscitation period in order to minimize reperfusion injury following ischemia. However, several experimental investigations have raised the importance of starting hypothermia as soon as possible and have also suggested that intra-arrest hypothermia may provide additional survival benefits [38–41, 43, 44]. The theoretical advantages of earlier cooling include decreasing reperfusion related injury mechanisms, attenuation of the oxidant burst seen within minutes of normothermic reperfusion, and inhibition of reperfusion related apoptosis [45].

When mild cerebral hypothermia was induced in pigs immediately after return of spontaneous circulation, improved cerebral functional and morphologic outcomes

were observed in contrast to animals not subjected to cooling, whereas a delay of as little as 15 minutes in initiation of cooling after reperfusion slightly decreased tissue damage but did not improve functional outcome [46]. Subsequently, when hypothermia was initiated during cardiac arrest, early cooling not only improved neurological outcome but also yielded better 72-hour survival, in contrast to delayed hypothermia and normothermic resuscitation [44]. Even when resuscitative efforts were delayed in order to facilitate external surface cooling before initiation of CPR, better hemodynamics, survival and neurological function have been reported [38].

These findings support the concept that post-resuscitation injury processes begin immediately after return of spontaneous circulation, and that intra-arrest cooling might serve as a useful therapeutic approach to improve both cerebral outcome and finally survival. The beneficial effects of early initiation of hypothermia on survival and outcomes of CPR have been further confirmed in the clinical scenario. The institution of hypothermic treatment based on a 'control of the time to target temperature', so as to achieve mild hypothermic temperature as fast as possible, was associated with reduced hypoxic brain injury and favored better neurologic outcome in resuscitated victims of cardiac arrest [47]. Therefore, although delayed hospital cooling has been demonstrated to improve outcomes after cardiac arrest, in-field cooling started immediately after return of spontaneous circulation has the potential to be more beneficial. When victims of out of hospital cardiac arrest were randomized to receive intravenous infusion of up to 2 l of 4 °C normal saline in the field, mean temperature decreased over 1.24 °C reaching an average temperature of 34.7 °C prior to hospital arrival. This in-field cooling was not associated with adverse consequences in terms of blood pressure, heart rate, arterial oxygenation, or evidence of pulmonary edema, and instead was associated with improvement regarding awakening and survival to hospital discharge [48].

Traditionally, hypothermia has been accomplished by two methods. The first is 'external cooling', which employs cold packs or cooling blankets and sophisticated machines with automatic feedback control; the second is 'internal cooling', which uses cold intravenous infusions, intravascular cooling catheters, body cavity lavage, extra-corporeal circuits, and, more recently, selective brain cooling. Other non-invasive methods include drugs and cold liquid ventilation. Improved cooling technologies have resulted in earlier attainment of target temperature and even more robust clinical benefits in the management of the survivors of cardiac arrest. Most of these methods are quite invasive and are still at an experimental stage. The optimal timing and technique for the induction of hypothermia after cardiac arrest have not as yet been defined, and are currently a major topic of ongoing research. External methods cool first the skin and peripheral compartments of the body and internal methods cool the blood, thus directly cooling the core compartment of the body. These methods are, however, slow to achieve significant cooling of the brain because they are targeted at cooling the entire body, rather than the injured cerebral area. A reduction in brain temperature of as little as 2 °C has been shown to reduce ischemic damage and significantly improves outcomes in patients with stroke, head injuries or after cardiac arrest. The major challenge facing clinicians is represented by the need to maximize the protective effects of brain hypothermia and thereby the time to delivery of this type of treatment. Cooling the entire body or the total arterial blood to achieve a temperature reduction in the brain may not be necessary, since the brain receives only 20 % of the resting cardiac output. The long cooling period may be reduced if only the head is cooled. Selective brain hypothermia using different devices has, therefore, been proposed [22, 39]. In our recent experience, we uti-

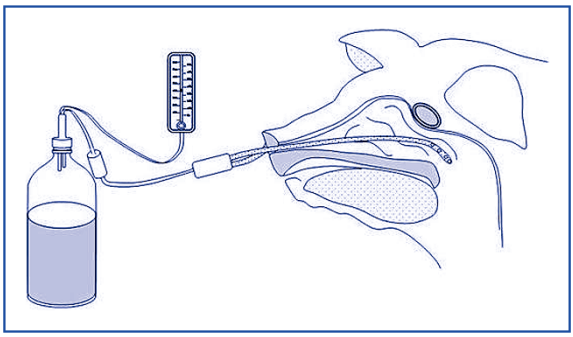

Fig. 2. Schematic representation of the system for head cooling (BeneChill Inc., San Diego, CA) applied in a pig.

lize the nasopharynx cavity to induce hypothermia. A chemically and biologically inert volatile fluorocarbon is vaporized and propelled into the nasopharynx by oxygen where it produces evaporative cooling. This natural cavity into the head takes advantage of overcoming the obstacle of cooling the brain through the skull. This approach can, therefore, significantly cool the nasopharynx cavity and offers the ability to cool the brain more quickly via direct conductive mechanisms and indirect hematogenous mechanisms (**Fig. 2**).

Preliminary Experience with Selective Brain Cooling: Effects on Neurological and Myocardial Functions

When pigs were cooled coincident with onset of CPR, the jugular venous temperature was reduced from 38 °C to 34 °C over 5 minutes. The likelihood of successful defibrillation after 10 minutes of untreated cardiac arrest and 5 minutes of CPR was significantly increased with head cooling. Eight cooled animals survived for 96 hours with full neurological recovery. Only 2 of 8 normothermic controls survived and both had persistent neurological deficits. Quite unexpectedly and in the absence of more than a 1.3 °C decrease in body temperature over the ensuing hour, left ventricular systolic function, reflected by ejection fraction and fractional area change together with left ventricular diastolic function, represented by isovolumic relaxation time and E/E' ratio, were significantly better in head cooled animals (**Fig. 3**) [39, 40]. Several mechanisms may have contributed to the observed improvement in myocardial performance. The cooled animals had a higher defibrillation success rate ($p = 0.034$), required a shorter duration of CPR ($p = 0.01$) and a lesser total dose of epinephrine ($p = 0.009$), in comparison to the control group. Greater post-resuscitation hemodynamic stability was also observed in cooled animals. Immediately post-return of spontaneous circulation, arterial pressures and coronary perfusion pressures, in fact, increased in cooled animals and were significantly greater compared to control animals, in which pressures decreased. Brain cooling during CPR therefore improved myocardial perfusion and this was reflected in less recurrent ventricular fibrillation and ultimately in improvements in myocardial performance (**Table 1**).

These beneficial effects on ease of defibrillation and a more benign post-resuscitation course were subsequently confirmed in animals in which the duration of untreated cardiac arrest was extended to 15 minutes [41]. Also unexpectedly there

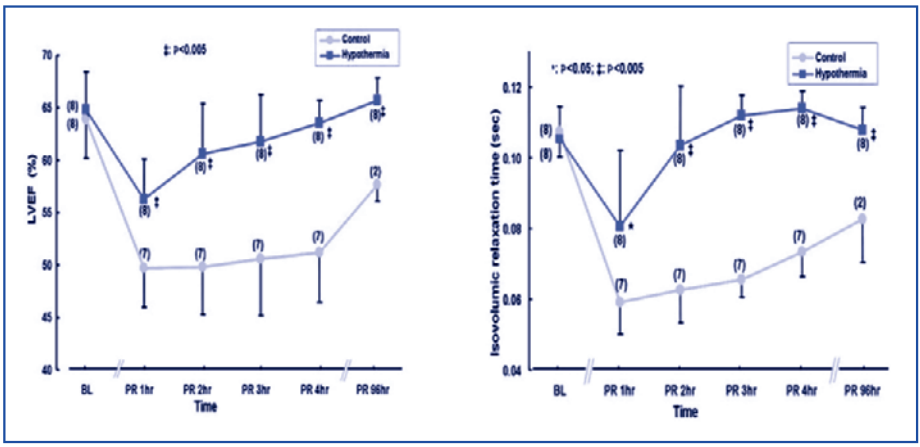

Fig. 3. Post-resuscitation left ventricular ejection fraction (LVEF) and isovolumic relaxation time. BL: baseline; PR: post-resuscitation.

Table 1. Effects of head cooling on post-resuscitation hemodynamics.

	Control (8)	Head Cooled (8)	p value
Brain temperature, °C			
Baseline	38 ± 0.3	38.01 ± 0.3	NS
Post-resuscitation	38.3 ± 0.2	35.8 ± 2.3	0.016
Core temperature, °C			
Baseline	37.9 ± 0.1	38 ± 0.3	NS
Post-resuscitation	38.1 ± 0.3	38 ± 0.3	NS
Number of recurrent VF	12 ± 7	6 ± 4	0.05
Coronary perfusion pressure, mmHg			
Baseline	73 ± 11	73 ± 14	NS
Post-resuscitation	30 ± 17	61 ± 25	0.009
Mean arterial pressure, mmHg			
Baseline	119 ± 12	119 ± 11	NS
Post-resuscitation	71 ± 23	130 ± 6	< 0.001

VF: ventricular fibrillation

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was a remarkably higher coronary perfusion pressure in head cooled animals and this was consistent with greater success of defibrillation ($p < 0.01$).

The mechanism by which selective brain cooling improved the likelihood of return of spontaneous circulation is not fully understood. It is conceivable that targeted cooling of the underside of the brain using nasopharyngeal cooling alters the firing rates of efferent autonomic nerves in the cervical chain. Inhibition of sympathetic firing during systemic hypothermia has been reported previously as temperature was reduced from 38°C to 31°C [49]. Experimental studies in healthy volunteers demonstrated that plasma norepinephrine and total peripheral resistances were reduced during moderately cold head immersion for 20 minutes. Moreover, hypothermia has been reported to attenuate ischemia-induced release of norepinephrine

and acetylcholine [50]. The paraventricular nucleus of the hypothalamus is a focal point in the complex of interacting systems regulating stress response and, in our model, those brain regions were close to the source of cooling. When we measured plasma norepinephrine concentration during CPR prior to return of spontaneous circulation, it was lower in the cooled animals than in the control animals.

In assessing the critical perfusion condition during and after resuscitation from cardiac arrest, both investigators and clinicians have focused on pressure and blood flow through large vessels and specifically arterial and large venous vessels and cardiac output. CPR interventions and especially chest compressions focused on increasing and maintaining optimal pressures so as to favor large vessel supplies to the brain and the heart. With the advent of methods by which microvessels and especially capillaries are visualized, it has become apparent that large vessel pressures and flows alone may not be predictive of the extent to which microvessels and, therefore, tissues are perfused. Yet, it is the microvessels and specifically the capillaries, which serve as the ultimate exchange sites for vital metabolites. In a preliminary study in pigs, we have addressed effects of selective head cooling on cerebral microcirculatory flows in relation to carotid blood flows. After 4 minutes of untreated ventricular fibrillation and 4 minutes of CPR, carotid artery diameters and flows increased during selective head cooling, even though cardiac output was not changed in comparison to controls at that time point. The increases in carotid blood flows were associated with concurrent increases in the numbers of perfused capillaries visualized in the cerebral cortex (Fig. 4).

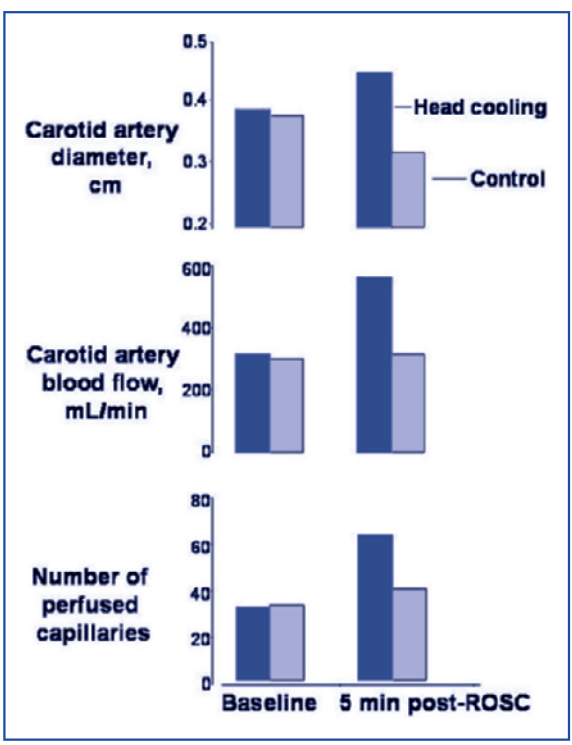

Fig. 4. Carotid artery diameter and flow and number of perfused cerebral cortical microvessels in animals resuscitated from cardiac arrest and subjected to head cooling or control. ROSC: return of spontaneous circulation

Conclusion

Over the past few years, the implementation of therapeutic hypothermia has provided an exciting opportunity toward improving neurological outcome from out-of-hospital cardiac arrest. The pioneering approaches of Doctor Safar, more than a decade ago, to introduce hypothermia as a valid treatment to reduce ischemic brain injury following cardiac arrest, represented the initial steps toward its affirmation as useful neuroprotective treatment. The need to initiate hypothermia as soon as possible following resuscitation has now been clearly recognized. However, there are compelling data suggesting the importance to begin hypothermia during the intra-arrest period and resuscitative maneuvers. This approach may provide significant additional survival benefits. Early initiation of therapeutic hypothermia is, in fact, emerging as a method able to preserve not only cerebral function but also myocardial function and, therefore, improve survival after resuscitation from cardiac arrest.

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