Physiological Impact of Hypothermia:

The Good, the Bad and the Ugly

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Abstract

Hypothermia is defined as a core body temperature of < 35°C, and as body temperature is reduced the impact on physiological processes can be beneficial or detrimental. The beneficial effect of hypothermia enables circulation of cooled experimental animals to be interrupted for 1-2 h without creating harmful effects, while tolerance of circulation arrest in normothermia is between 4 and 5 min. This striking difference has attracted so many investigators, experimental as well as clinical, to this field, and this discovery was fundamental for introducing therapeutic hypothermia in modern clinical medicine in the 1950's. Together with the introduction of cardiopulmonary bypass, therapeutic hypothermia has been the cornerstone in the development of modern cardiac surgery. Therapeutic hypothermia also has an undisputed role as a protective agent in organ transplantation and as a therapeutic adjuvant for cerebral protection in neonatal encephalopathy. However, the introduction of therapeutic hypothermia for organ protection during neurosurgical procedures or as a scavenger after brain and spinal trauma has been less successful. In general, the best neuroprotection seems to be obtained by avoiding hyperthermia in injured patients. Accidental hypothermia occurs when endogenous temperature control mechanisms are incapable of maintaining core body temperature within physiologic limits and core temperature becomes dependent on ambient temperature. During hypothermia spontaneous circulation is considerably reduced and with deep and/or prolonged cooling, circulatory failure may occur, which may limit safe survival of the cooled patient. Challenges that limit safe rewarming of accidental hypothermia patients include cardiac arrhythmias, uncontrolled bleeding, and "rewarming shock".

Introduction

Humans are homeotherms, actively regulating our body temperature in response to the environment in which we live. The history of mankind reflects the history of human struggle for life against climatic change, where ambient temperature has always been a driving or life-threatening element. Although global warming is a general threat to mankind in modern times, history also tells us that since ancient times, human exposure to low ambient temperature has caused the loss of an enormous number of human lives, especially during war time. Such man-made human disasters, causing thousands upon thousands of lives among young soldiers, took place when Hannibal and his army crossed the Alps more than 2,200 years ago, during Napoleon's retreat from Moscow in 1812, and during Hitler's war against Russia, and his army's retreat from Stalingrad in 1944 - 45. These tragedies are well known examples of accidental hypothermia, but it was not until Fahrenheit invented the mercury thermometer in 1714 and its introduction as a clinical tool in 1866, that body temperature could actually be determined (213). Subsequently, hypothermia could be quantitatively categorized as a clinical diagnosis. However, hypothermia was first recognized only in extreme situations such as after immersion cooling to very low body temperatures, whereas less extreme conditions were not generally recognized and reported until the 1960s (74). Hypothermia was categorized by its diagnosis; thus, definitions were needed.

Hypothermia, definitions: The physiologic changes caused by cooling depend on the depth and duration of hypothermia. Hypothermia in humans is defined as a deliberate (therapeutic) or accidental lowering of core body temperature below 35°C, with further sub-classification as; mild (35-32°C), moderate (32-22°C), deep (22-8°C), or profound (<8°C) (146). In 1994 a new sub-classification followed as mild (35-32°C), moderate (32-28°C), severe (28-20°C), or profound (<20°C) (39). In 2009 Polderman (143) suggested a more simplified scaling as mild

(35-34°C), moderate (34-30°C), and severe (<30°C), which is now used by the American Heart Association. In the current text the scaling from 1994 is used. Hypothermia is also defined by its duration as acute (few hours), prolonged (several hours), or chronic (days or weeks) (Figure 1).

Fig. 1. *Hypothermia can be accidental, intentional and therapeutic.*

The Q_{10} temperature coefficient: The Q_{10} temperature coefficient is a measure of the temperature sensitivity of chemical reactions and biological processes (enzymatic and biochemical) in which an increase or decrease in temperature by 10°C causes a given change in the reaction rate or process. The Q_{10} of metabolic rates averages 2.2 in the mammalian brain (124) and about 2.0 in the whole body in therapeutic hypothermia during anesthesia (123). The protective role of hypothermia is created by a decrease in metabolic activity, and hence a decrease in O_2 consumption rate ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$). Accordingly, with moderate hypothermia (10°C reduction in core temperature), $\dot{V}O_2$ and $\dot{V}CO_2$ are approximately 50% of normothermic values. In conditions of profound hypothermia (30°C reduction in core temperature), the decrease in $\dot{V}O_2$ and $\dot{V}CO_2$ is even more pronounced. Thus, slowing $\dot{V}O_2$ and $\dot{V}CO_2$ by cooling can have a protective therapeutic effect.

Therapeutic Benefits of Hypothermia in Clinical Medicine – the "Good"

Despite the fear of accidental hypothermia, it had long been appreciated that by reducing core temperature the organism is much less sensitive to the detrimental effects of the external or internal environment than at normal body temperature. This fundamental property of therapeutic hypothermia enables circulation of cooled experimental animals to be interrupted for 1 - 2 h without creating harmful effects. This striking difference, between 4 and 5 min in

normothermia, and 2 h in profound hypothermia, has been the major factor that has attracted so many investigators, experimental as well as clinical, to this field. The potential curative and protective benefits of reduced body temperature were the background for launching therapeutic hypothermia as a new therapeutic tool in modern clinical medicine.

Therapeutic hypothermia: In early 20th century clinical medicine, therapeutic hypothermia was first introduced in the pioneering work of by Temple Fay (1895 – 1963) who used hypothermia to treat the spread of advanced cancer in humans. Patients were surface cooled to ~32°C and maintained at this low core temperature for up to 18 h before being rewarmed. However, despite an extensive effort to establish hypothermia as a new cancer treatment Fay's work did not receive appropriate acknowledgment (85).

Therapeutic hypothermia for myocardial protection during coronary artery surgery: By the 1950s, cardiac surgeons were looking for a method which enabled them to conduct surgical procedures on a quiescent heart. Therapeutic hypothermia appeared to serve this purpose by reducing whole body $\dot{V}O_2$ and $\dot{V}CO_2$, and cooling beyond 27°C to induce therapeutic hypothermic cardiac arrest (HCA), which caused an instant 80% reduction in myocardial $\dot{V}O_2$ (26). Thus, therapeutic hypothermia allowed the cardiac surgeon to complete the surgical procedure on a quiescent but metabolically protected heart. The technique was first introduced as immersion hypothermia in anesthetized patients. The technique permitted the surgeon 6-8 min of circulatory arrest in order to repair of simple defects based on a compromise between the time needed for heart repair and the brain's requirement for $\dot{V}O_2$. Consequently, low-flow pump oxygenators, forerunners to the modern heart-lung machine, or better the cardio-pulmonary bypass (CPB), were introduced, and HCA was achieved by blood cooling to 10-20°C (186), which increased the period of circulatory arrest to 30–60 min. Rapid chemical cardiac arrest before global myocardial ischemia with over 200 mM potassium, (cardioplegic

solution), introduced by Melrose et al. (119) in 1955, enabled a better post-ischemic recovery of cardiac function than simple aortic cross clamping. In these first years of modern cardiac surgery, myocardial protection was considered to be achieved by hypothermia in addition to one of numerous variants of cardioplegic solutions aimed at creating diastolic cardiac arrest. The cardioplegic solutions underwent considerable development aimed at adding myocardial protection during cardiac ischemia as well as during reperfusion and rewarming (31). Myocardial protection has long been considered key for successful recovery and improved outcomes for patients undergoing cardiopulmonary bypass requiring cardiac arrest. Over the past few decades different cardioplegic solutions have been diversified by pharmacological additives, blood cardioplegia, temperature modulation (warm; tepid), retrograde cardioplegia, controlled reperfusion, integrated cardioplegia, and pre-and postconditioning (214). Although first introduced by Melrose et al in 1955 (119) blood cardioplegia was later reintroduced (9, 66), and demonstrated experimentally and clinically to have potent protective effects against myocardial damage during ischemia and reperfusion (8). The advantages of blood cardioplegia were: 1) Greater oxygen-supply capacity (more aerobic metabolism), 2) rapid cardiac arrest in an oxygenated environment, 3) intermittent reoxygenation with delivery of cardioplegia solution, 4) whole blood which provides oncotic constituents that otherwise must be added as plasma protein, mannitol, or dextran, 5) greater acid-base balance capacity, and 6) numerous other positive effects as compared with crystalloid cardioplegia. However, the cold-blood cardioplegic solution also had disadvantages: 1) Increased viscosity causing disturbed coronary microcirculation, 2) leftward shift of oxygen dissociation curve causing decreased oxygen delivery in the peripheral tissue, 3) more frequent reinfusion to maintain asystole compared with the 4°C crystalloid cardioplegia, and 4) delayed postischemic recovery of cardiac function due to the hypothermia-induced depression of cardiac metabolism. Therefore, continuous normothermic blood cardioplegia was developed as a means of

preventing ischemia during the period of aortic clamping. In 1991, Lichtenstein et al. (107) presented ‘‘warm heart surgery’’ by suggesting safety and effectiveness of continuous normothermic blood cardioplegia. Since the introduction of normothermic blood cardioplegia many studies (1, 215, 216) have shown its superior effects on myocardial protection compared with those of conventional cold blood cardioplegia. However, during continuous normothermic blood cardioplegia infusion the presence of critical coronary stenoses may limit the delivery of O_2 to ischemic regions of the heart. In addition, for practical reasons the continuous infusion of cardioplegic solution needs to be interrupted during surgery. Such interruptions or inadequate distribution of normothermic cardioplegia may induce anaerobic metabolism and warm ischemic injury. However, Clafiore et al. (27) reported no difference in the cardioprotective effect between the intermittent warm and intermittent cold infusion groups in patients undergoing coronary bypass surgery. They therefore concluded that intermittent antegrade delivery of normothermic blood cardioplegia is a safe, reliable, and effective technique of myocardial protection (214). In addition, a new concept, tepid (29°C) blood cardioplegia was introduced by Hayashida et al. in 1994, as a safe and effective method of myocardial protection (83, 84). By reducing the heart temperature from 37°C to 29°C a buffer to ischemic injury is created when delivery of blood cardioplegia is nonhomogeneous or has to be interrupted.

However, later evaluations of the properties of the different cardioplegic solutions have suggested that other than inducing electrochemical arrest, the addition of high potassium cardioplegia solutions offers little or no *inherent* protection (52).

Therapeutic Hypothermia – an Incomplete Picture – the “Bad”

Myocardial protective effects. Hypothermia was long considered to create its protective effect by reducing metabolic rate and subsequent $\dot{V}O_2$ and $\dot{V}CO_2$ in the arrested heart, and the phrase "the colder, the better" was a well-known axiom (137). However, later basic physiological research has revealed that cardiac basal metabolism in the arrested heart is less reduced in response to whole body cooling beyond 27°C than first anticipated. At a core body temperature of ~27°C, spontaneous cardiac arrest occurs, even without adding a cardioplegic agent, and further cooling will have limited cardio-protective effects. Consequently, cold CPB used for conventional coronary bypass surgery is still used but at core body temperatures >30°C. New coronary surgical procedures have evolved, which unlike the conventional technique utilizing hypothermic cardioplegia and CPB, are accomplished on normothermic patients, known as off-pump bypass surgery or beating heart surgery. However, as conventional coronary surgery is considered as being a standardized procedure, a survey from 2017 disclosed considerable differences between surgical centers worldwide where core body temperatures of patients during bypass varied from 37.0 to 33.4°C across centers.

For cardiac reconstructive surgery, as well as for proximal aortic surgery, profound (<20°C) hypothermia and HCA is combined with antegrade or retrograde cerebral perfusion for neuroprotection. These techniques have evolved based on extensive research work (7, 59, 69, 220). In current clinical practice, HCA is performed at temperatures between 18 and 19°C, but the evidence to support any range of temperature is controversial (35, 162). In some institutions, there is now state-of-the-art consensus in favor of less hypothermia (110, 116), although some established medical institutions are warning against the use of less hypothermia (108, 110). Therefore, at the present time, there appears to be a lack of evidence and consensus opinion regarding the optimal temperature management strategy during CPB for proximal aortic - and reconstructive cardiovascular surgery. Thus, temperature management strategies during CPB

rely primarily on personal or institutional preference, rather than a solid scientific evidence (182).

Neuroprotective effects. The brain is the organ most sensitive to hypoxia and ischemia. The interpretation of tissue protection through hypothermia has been inherited through anecdotal stories about survivors, mostly children, successfully resuscitated without neurologic sequela, especially after submersion during wintertime. The neuroprotective effects of therapeutic hypothermia have been ascribed to the temperature-induced reduction in metabolic rate of neural tissue with the subsequent reduction in O_2 requirements and to the preservation of tissue pH and ATP, which promotes cellular homeostasis (5, 100, 118). Clinical and experimental results show protective effects of hypothermia during and after ischemic situations (157) by inhibiting the biosynthesis, release and uptake of several catecholamines and other excitotoxic neurotransmitters (136, 178, 181), especially glutamate and dopamine, thus preventing calcium overload and potential nerve tissue damage (37, 76). Other beneficial effects of hypothermia include preservation of the blood-brain barrier (10, 95), restitution of post-ischemic cerebral microcirculation (183), and possibly decreased intracranial pressure (104, 166). In addition to reducing metabolic rate and O_2 consumption, neuroprotective effects of therapeutic hypothermia during as well as after ischemia/reperfusion are ascribed to reduced reactive oxygen species (ROS) production, reduced production of inflammatory mediators, and inhibition of apoptosis during regional and global reperfusion of the brain (159). Randomized controlled trials in the early 2000s reported that the use of therapeutic hypothermia was associated with improved mortality and neurological outcomes (12, 89). However, although the neuroprotective mechanisms of hypothermia in different diseases vary and have yet to be fully determined, the neuroprotective role of hypothermia has been well established in experimental animals and in surviving patients after cardiac arrest (77, 179), hypoxic-ischemic encephalopathy (217), traumatic brain injury (106), and other diseases (219).

Despite extensive research, the optimal pH management strategy to guarantee the best neurologic outcome after cardiovascular procedures utilizing hypothermic CPB remains unknown. The two main clinically utilized strategies, alpha-stat and pH-stat, differ in their approach to the acid - base alterations that occur with hypothermia. The solubility of CO_2 and O_2 in water, and in blood and tissue, increases with cooling. If the concentration of gas is constant, the partial pressure of that gas will decrease. For CO_2, the effect is a constant factor of 4.5 percent per °C in blood and tissue, and independent on the level of pCO_2 or HCO_3. Consequently, as temperature falls, pH rises 0.0147 pH unit/°C, which is the Rosenthal factor (156). With alpha - stat management, the resulting alkalosis is left untouched during cooling, whereas with pH-stat management, carbon dioxide needs to be added to the gaseous inflow of the cardio-pulmonary bypass circuit in order to adjust the pH to physiologic levels during normothermia. Clinical trials have documented positive effects of the pH - stat management strategy on cerebral outcome after deep hypothermic circulatory arrest in the pediatric populations (55). The positive clinical effects in this population group has been attributed increased vasodilation (56) and better preservation of cerebral vascular autoregulation after this surgical procedure (129) when applying the pH-stat strategy. In the adult population, differences in outcome when comparing these two different strategies have not yet been documented, and in both clinical and experimental arenas no clear consensus exists (Figure 2).

Neurosurgery. Despite an overwhelming history demonstrating the potential benefit of hypothermia to rescue and preserve the brain and spinal cord after injury or disease, clinical trials over the past 50 years have failed to show a convincing benefit over controlled normothermia. The ebb and flow of neurosurgical interest in hypothermia that has since persisted reflects the continuing struggle to utilize neuroprotective benefits of cooling while minimizing the systemic side effects (24). For advanced brain surgery, cooling on CPB to profound (<20°C) therapeutic hypothermia, combined with maintained global circulatory arrest

during the surgical procedure, has until recently been routinely used. However, newer techniques favor the use of low pressure/low blood flow cerebral shunts during brain surgery and less cooling.

Traumatic brain injury. Traumatic brain injury can be divided into primary and secondary injury. The primary injury is the consequence of mechanical damage of brain tissue during the initial trauma, like a skull fracture, cerebral contusion, epidural or subdural hematomas, or traumatic subarachnoid hemorrhage (4). The subsequent secondary brain injury is the consequence of oxidative stress, hypoxic/ischemic injury, inflammation and cerebral tissue edema, factors that all may lead to further neurological injury (5). Management of traumatic brain injury is composed of neuro-intensive treatment which is aimed at treating and preventing secondary brain injury from taking place. Neuro-surgical procedures directed at maintaining intracerebral pressure within physiologic boarders to secure improved cerebral oxygenation, and cerebral blood flow are central elements (4, 5). An alternative to neurosurgical intervention to reduce intra-cerebral pressure has been the induction of a pentobarbital coma, which additionally reduces cerebral metabolism and oxygen consumption. Subsequently, a reduction of cerebral blood flow may take place, in addition to a decrease in neuro-excitotoxicity by reducing the release of glutamate and aspartate in brain tissue (4, 12, 13). Over the years, animal experiments have documented promising results by use of induced hypothermia to mitigate secondary brain injury by reducing cerebral metabolic demands, inflammation, excitotoxicity, lipid peroxidation, and cell death (44, 51, 64). However, in contrast to the beneficial effects of induced hypothermia in preclinical experiments, three large multicenter randomized controlled human studies have failed to show beneficial effects of hypothermia (33°C) to prevent secondary brain injury (4, 33, 34). In children, the use of induced hypothermia has been shown to have

worsening outcomes with an increase in mortality (75). In adults, data are conflicting and the use of therapeutic hypothermia is not currently recommended for prophylactic or routine use in traumatic brain injury (13).

Therapeutic hypothermia after out-of-hospital cardiac arrest. Over the past 20 years, therapeutic hypothermia has been used almost routinely as a part of post cardiac arrest care in resuscitated comatose patients (159). Two international studies published in 2002 (12, 89) showed significantly increased survival to discharge after 24 h of treatment with induced hypothermia (32–34ºC) versus normothermia, to prevent the development of encephalopathy in comatose survivors after prehospital cardiac arrest. As a consequence, the 2010 American Heart Association guidelines recommended hypothermia (32°C to 34°C) as part of post cardiac arrest care in resuscitated patients (138). Later, the neuroprotective effects of therapeutic hypothermia in survivors have been evaluated. In 2013, the targeted temperature management (TTM) trial compared effects of 33°C vs. 36°C core temperature on outcome and found no differences (132). Therefore, the 2015 American Heart Association/International Liaison Committee on Resuscitation guidelines changed their recommendation of core temperature intervention from 32°C to 36°C (25, 28, 53). In cardiac arrest patients with a non-shockable rhythm the HYPERION trial (TTM for Cardiac Arrest with Nonshockable Rhythm) showed an improvement in neurological outcomes in patients assigned to therapeutic hypothermia when compared with normothermia (103). An updated meta-analysis from 2020 compared the efficacy of therapeutic hypothermia in post cardiac arrest patients. The analysis included the HYPERION trial and concluded that therapeutic hypothermia was associated with improved neurological outcomes in all patients sustaining cardiac arrest and with decreased mortality in patients with initial shockable rhythm (159). Despite promising results, the CARES group (Cardiac Arrest Registry to Enhance Survival surveillance group) reported a declining trend in the years 2013 to 2016 in the use of therapeutic hypothermia for this patient group (25). In a

recent publication from 2021 (38) no difference in survival after cardiac arrest was reported in a group treated with induced hypothermia (33°C) versus normothermia. However, knowledge gaps are evident with respect to neuro-protective effects of therapeutic hypothermia after cardiac arrest. To determine the efficacy and safety of this treatment, more questions need to be addressed.

Hypoxic- ischemic encephalopathy. Previously, apart from systemic supportive care, neonatologists had little to offer neonates with hypoxic-ischemic encephalopathy. However, the neuroprotective effects of therapeutic, moderate hypothermia used over the past decade to counteract hypoxic-ischemic encephalopathy in term infants, have shown that cooling reduces mortality without increasing major disability in survivors. Hypothermia reduces risk of death and disability in infants with moderate to severe hypoxic-ischemic encephalopathy (32, 57, 92, 94). The treatment should be instituted in term and late preterm infants with moderate-to-severe hypoxic ischemic encephalopathy by use of mild hypothermia (33.5°C - 35.0°C). Clinical data correlate outcome to the early (180 - 360 min) initiation of this therapy (25). A systematic Cochrane review from 2013 (92), evaluating 11 randomized controlled trials including 1,505 infants, concluded that therapeutic hypothermia is beneficial in term and late preterm newborns with hypoxic-ischemic encephalopathy. Ongoing trials aim at determining the appropriate techniques of cooling, including refinement of patient selection, duration of cooling, and method of providing therapeutic hypothermia for this patient group. The pathophysiology of hypoxic-ischemic encephalopathy is now better understood, and treatment with hypothermia has now become the foundation of therapy (54).

Hypothermia in organ preservation. Since the introduction of transplantation medicine in the 1960s, therapeutic hypothermia (0°C – 10°C) has been standard procedure to protect donor organs against the harmful effects of ischemia/hypoxia, after surgical removal from the donor.

However, it was recognized early that simple cooling an organ *per se* is not sufficient to provide good preservation. Early attempts to use blood-based solutions, even hemodiluted to reduce viscosity, was considered futile. Hypothermia was found to be associated with an increase in blood viscosity that contributes to red blood cells occluding the microvasculature ("sludging") as well as causing detrimental coagulopathies (11, 43, 93, 125, 180). It was concluded that red cell sludging had serious consequences for the microcirculation in organs during hypothermia as well as during reperfusion in the recipient. Animal experiments showed increased survival during profound hypothermia under CPB combined with exsanguination and substitution with acellular solutions, and successful rewarming with autotransfusion after prolonged hypothermia (187). As a consequence, the development of specialized storage solutions was the primary factor in the evolution of hypothermic organ preservation technology. Central elements were careful control of the extracellular environment of the component cells achieved by vascular flush or perfusion to counteract the detrimental effects of cooling. The prevailing explanation of cold-induced cell swelling (intracellular edema) has been the temperature - dependent decrease in the activity of the Na^+, K^+-ATPase pump (58) causing an increase in cytosolic Na^+ concentration ($[Na^+]_{cyt}$) (16, 169) and subsequent water retention. Also, the elevated $[Na^+]_{cyt}$ will retard Ca^{2+} extrusion by reversing the Na^+/Ca^{2+} exchange system, which may contribute to cytosolic Ca^{2+} overload, especially in cardiac cells. Interestingly, new and alternative theories have evolved to explain cold-induced cell swelling in donor organs, such as in the heart, (114) during cold storage. Extensive research (152) has disclosed an increase in intracellular chelatable iron ions, of unknown origin, (14, 17, 18, 114, 122, 130, 151) leading to the formation of highly reactive oxygen species (14, 140, 141, 221), which takes place within the first hours of cold incubation. This cold-induced injury is known to primarily target mitochondria and induce mitochondrial permeability transition, (139, 151) finally leading to apoptosis and cell swelling, which may predominate during rewarming (153, 161, 203). The

addition of iron chelators effectively inhibits this pathway of cold-induced mitochondrial injury and may pave the way for better preservation of organs during hypothermia in the future. Together, these discoveries of hypothermia-induced organ damage were previously ascribed to reperfusion injury (41, 142).

What made therapeutic hypothermia in cardiac surgery a success story? For comparison, over the same time span the overwhelmingly large number of successful cardiac procedures conducted using therapeutic hypothermia is far greater than for any other patient categories. A reduction in the use of therapeutic hypothermia in cardiac surgery patients over the past 20 years has not been due to clear side effects of hypothermia, although these are well described. Rather, the use of hypothermia in these cardiac surgery procedures has provided insight and experience to develop newer surgical techniques that are simpler, less cost consuming, and equally safe compared to the use of hypothermia. From a physiological perspective, the safe use of hypothermia in cardiac surgery appears to be the consequence of at least two essential effects achieved during HCA: The temperature-induced reduction in myocardial metabolism, and the temporarily "switched off" in cardiac function. Together these physiological changes lead to a substantially reduction in O_2 consumption (~ 80 %) during cardiac surgical interventions. The additional use of a cardioplegic agent, which temporarily terminates cardiac function by creating a chemical diastolic cardiac arrest has definite protective properties over the previous use of cooling only, to induce HCA, where cardiac arrest often was preceded by O_2 consuming arrhythmias. Last, but not least, a cardioplegic agent will maintain cardiac arrest throughout the hypothermia period and prevent occurrence of ventricular fibrillation as may take place when using plain HCA. No other body organ will experience a similar level of physiological shift in VO_2 in response to temperature reduction only. Body organ function is reduced in response to a reduction in temperature, but unlike the heart, function in the other

organs will be practically closed down first at very low core temperatures, temperatures below which HCA has taken place whereby spontaneous circulation has ceased and these organs are prone to ischemia and hypoxia. In contrast, during cardiac surgery with cardiac arrest, organ blood flow and O_2 support is provided by the CPB. Except for induced hypothermia applied before elective brain surgery, in the other cases discussed above, hypothermia is applied after the organ insult has taken place, but we expect that the organism will benefit from the same organ protective effects if applied first during the recovery and reperfusion process.

The heart in HCA during surgery bears similarities with what takes place during the preservation of any organ prepared for organ transplantation. Organs like liver, pancreas, kidneys, and lungs, are all perfused with preservation solutions and maintained at profound hypothermia. All these organs are disconnected from the general circulation whereby specific organ function is further reduced, and also deprived of any hormonal influence or inflammatory cascade reactions during the relatively short (60 min) period of hypoxia/ischemia. By further comparison to the preservation of transplant organs, where the use of acellular preservation solution media is crucial: During cardiac surgery the acellular cold cardioplegic solution used may have positive preserving effects on the microcirculation during the ensuing reperfusion/warming of the heart. The same argument might be applied to support the use of warm blood cardioplegia, as well.

What is currently known? The use of therapeutic hypothermia has been a cornerstone in the development of modern cardiac surgery. By achieving HCA, the requirement of the hypothermic heart for oxygen is immediately reduced by ~ 90%. Meanwhile, CPB will circulate all other body organs with cold, oxygenated blood, which enables the surgeon to finalize cardiac reconstruction work within a safe time frame.

Therapeutic hypothermia has been extensively used in patients with traumatic brain injuries for neuroprotection as part of the ICU treatment. Except for its possible effects to reduce, or to prevent an increase in intracranial pressure in these patients, the protective effects of therapeutic hypothermia on brain tissue survival remains elusive. As for the potential neuroprotective effects offered by therapeutic hypothermia after cardiac arrest, the value of maintaining body temperature within physiologic limits, and especially to prevent fever, has been documented. This fact has given the prevailing conclusion that therapeutic hypothermia has no curative effects in patients with traumatic brain injury.

Since the introduction of transplantation medicine, cold storage (0°C – 10°C) has been standard procedure to protect donor organs. Hypothermia enhanced by appropriately designed preservation solutions is the basis for current standard practices and The University of Wisconsin cold storage solution remains the gold standard for organ preservation and prevention of cell swelling in harvested organs.

However, despite the inherited stories about the healing effects of induced hypothermia on multiple disease processes, clinical trials conducted over the past 50 years have failed to show any therapeutic effects of induced hypothermia over that of maintaining normothermia in most critical conditions (24).

What is unknown and what knowledge gaps exist? Optimal temperature for myocardial protection has not yet been decided. “The colder the better” has been disputed and warm cardiac surgery is an alternative. The previous universal appreciation of the myocardial protective effects of cardioplegic solutions have been questioned. Likewise, optimal temperature to achieve best organ protective effects during hypothermic cardiac arrest for cardiovascular reconstructive surgery remains unanswered.

Disclosure of previously unknown pathophysiologic mechanisms of cold-induced tissue injury indicate that better organ preservation can follow a change in the composition of

established donor organ preservation media. Extensive experimental research has disclosed significant cold-induced ROS production and mitochondrial damage in donor organs which will promote apoptosis during the subsequent re-implantation and warming in donors. This new knowledge opens up for refining the compositions of new storage solutions and techniques to better preserve donor organs during cold storage.

Accidental hypothermia/rewarming – the "ugly"

Accidental hypothermia. Unlike during therapeutic hypothermia in patients anesthetized for cardiac surgery, cooling in conscious human victims of accidental hypothermia creates a condition governed by physical stress of unknown duration and intensity. These physiologic responses are aimed at preventing a drop in core temperature in order to maintain body temperature homeostasis, where all body organs may experience near maximum physiological activity. In humans, cerebral function is gradually reduced during cooling of core body temperature below 35°C and unconsciousness is reported to occur if cooling falls below 33°C. After consciousness is lost, the psychological stress is aborted, and a marked reduction in O_2 consumption follows. During a further reduction in core body temperature, the drop in O_2 consumption follows a linear pattern governed by the Q_{10} effect. Body organs all have a similar Q_{10}, which for the whole body is 2.0, and for the brain is 2.2. Unlike the heart, other body organs will experience a gradual reduction in organ function and subsequent O_2 consumption during cooling as long as circulatory function is maintained. During cooling, the heart eventually will enter HCA leading to ischemia/hypoxia in all organs. During the ensuing rewarming and reperfusion process the level of restitution of organ function is dependent on time before rescue, quality of prehospital interventions, and rewarming methods used, before being categorized as successful or non-successful rewarming. One of the best known case reports of successful rewarming is from 1999 (71) where an experienced young female off-piste skier fell down in a

waterfall gully, ending up trapped and hanging upside down from her skies. Her head was out of the water, but she was continuously sprinkled with ice cold water. After evacuation she was lifeless and cardiopulmonary resuscitation was started and continued. Upon arrival at the hospital, her core body temperature was 13.7°C, and after the 9-h period that included evacuation, transport, and stabilization, her heart regained sinus rhythm during rewarming on CPB. At the time of follow-up 5 months after the accident, her mental function was excellent and she was gradually returning to work (71).

Therapeutic challenges related to accidental hypothermia and rewarming. In emergency medicine textbooks, rewarming from accidental hypothermia is listed with three therapeutic challenges: i) arrhythmias, ii) bleeding, and iii) rewarming shock (126). Of these, the occurrence of arrhythmias is a well-documented and the most feared symptom taking place in accidental hypothermic patients since it is known to be the precursor of HCA during cooling as well as during rewarming. Although being a well-recognized complication of accidental hypothermia in general, little clinical data exists on the effects of using anti-arrhythmic drugs. Case reports have suggested favorable anti-arrhythmic effects of the class III antiarrhythmic agent bretylium tosylate in accidental hypothermia patients, and a preclinical study documented its potential beneficial effects to prevent reentry arrhythmias (22). In collaboration with another research group, we recently reported that during cooling, as well as rewarming, by entering temperatures between 34 to 30°C the heart is subjected to a pro-arrhythmic period due to a temperature-induced prolongation of repolarization (48). This hypothermia-induced prolongation of repolarization, which is the background mechanism for making this temperature interval arrhythmogenic, is prevented either by rewarming or by further cooling. In a follow-up literature review, we confirmed the lack of clinical reports using pharmacologic anti-arrhythmic substances in accidental hypothermia, but new experimental work documents

the antiarrhythmic potential of bretylium, whereas drugs that prolong the QT-interval should be avoided (50).

Bleeding is another feared complication induced by reduced body core temperature. Bleeding is the consequence of a hypothermia-induced malfunction in the coagulation system and in blood platelets. The reason for this malfunction of the coagulation system, is that their enzyme driven cascade systems only can work within limited temperature constraints. As a consequence, a reduction in core temperature of multi-traumatized patients is a serious threat with close to 100 % mortality due to lack of bleeding control.

Rewarming shock is an ill-defined concept but related to a sudden and unexpected reduction in spontaneous circulatory function during rewarming. In its fulminant form, rewarming shock occurs during or shortly after rewarming, unrelated to the occurrence of arrhythmias. Unlike arrhythmias and bleeding, a general appreciation of rewarming shock is lacking, and our present understanding of the pathophysiologic mechanism(s) is limited. Rewarming shock is well described in case reports and in some textbooks, but the term rewarming shock is not regularly used in the literature. In most cases, patients rewarmed with a perfusing rhythm, cardiac output and blood pressure will increase spontaneously as a consequence of elevation of core temperature. However, the first clinical sign of an ensuing circulatory shock is stagnation, or reduction in cardiac output during rewarming, or shortly after, unrelated to any obvious or easily curable cause (111-113, 167, 170). The later onset rewarming shock is recognized as a rapid fall in blood pressure, caused by a sudden lowering of total peripheral resistance but unmatched by a compensatory rise in cardiac output (19). This unfavorable hemodynamic situation is fatal if left untreated but may be cured temporarily by interventions aimed at increasing peripheral resistance. In the textbook “Accidental Hypothermia “, by Maclean & Emsely-Smith (113) published in 1977, it is stated that the real causes of "rewarming shock" are not yet known. Even if the compromised cardiac output taking

place during or after rewarming is detected, treatment modalities are few. Pharmacologic interventions, mostly limited to the use of agents to support cardiovascular function, and i.v. volume therapy, are often not successful to withstand the progression of a fulminant circulatory collapse (113).

In an outcome analysis from 2001 of severe accidental hypothermia patients treated in an ICU, circulatory shock, requiring treatment with vasoactive drugs was found to be an independent risk factor for mortality greater than 60 % (205). This epidemiologic analysis is in support of both the existence of, and the severity of rewarming shock, which may take place when warming accidental hypothermia patients, as described in numerous clinical case reports. As already stated, our present understanding of the pathophysiologic mechanism(s) of rewarming shock is limited, but suggests it is related to the occurrence of an acute cardiac failure, created during the exposure to hypothermia (112, 144, 146, 147).

Rewarming shock - new insights from animal models of hypothermia/rewarming. Despite the protective role of hypothermia on tissue survival, profound and prolonged cooling eventually leads to circulatory failure during hypothermia, and this is probably the main factor limiting the safe survival of cooled organisms with maintained spontaneous circulation. Early researchers (144, 145) found that survival time was closely related to the extent of reduction in core temperature, and to the duration of hypothermia. It was observed that animals cooled to 15°C would live at this temperature for 9-10 h, but safe rewarming would follow only if rewarming was started during the initial 5 h. If rewarming was attempted after 5 h, animals would die as soon as core temperature reached 25°C to 28°C. It was speculated that rewarming shock leading to death was due to an increase in peripheral resistance brought about by a marked hemo-concentration, a compromised capillary perfusion, a decrease in venous return, and acute cardiac failure.

To provide evidence for “the safe use of hypothermia in cardiac surgery” in the 1950’s, extensive research into the physiology of hypothermia was conducted (18, 19, 208). The interaction between the depth of hypothermia and duration were explored before the introduction of CPB (60) . Specifically, there was a series of step-by-step laboratory and clinical investigations pragmatically focused on the compromises between the time needed for heart repair and the brain's requirement for oxygen (168). An important contribution was the pioneering work by Bigelow et al. in 1950. Using a dog model of immersion cooling to 18°C - 20°C, followed by immediate immersion rewarming, these investigators reported a significant reduction in cardiac output after rewarming (18, 19, 60, 149). This finding was consistent with subsequent experiments showing that a reduced cardiac output after rewarming is the consequence of the post-hypothermic cardiac dysfunction (rewarming shock), which occurs during rewarming in the intact animal heart in a non-arrested state (23, 61, 148, 158, 173, 194, 198).

When the spontaneous work of the heart was assumed by the cardiac pump during CPB surgery, post-hypothermic cardiac dysfunction (rewarming shock) appeared to be eliminated. Thus, any pathophysiology of post-operative cardiac dysfunction was attributed to the preceding period of ischemia-reperfusion during cardiac surgery and not to the exposure to hypothermia (120). As a result, post-hypothermic cardiac dysfunction is considered to be a clinical challenge only when rewarming victims of accidental hypothermia. A determination of the pathophysiological mechanism(s) underlying hypothermia-induced cardiac dysfunction will be critical to comprehensively treat hypothermia-induced myocardial failure in the clinical setting. Therefore, our research group has since the early 1990’s, conducted experimental studies to further explore cardiovascular function during experimental hypothermia and rewarming. Initially, these studies were conducted by use of intact animal models (193, 200, 201). From studies using a dog model (192, 194, 199), we found that

rewarming from moderate hypothermia induced depression of cardiovascular function in parallel with a marked reduction in myocardial blood flow, despite the presence of an intact coronary endothelial function (192). These results indicated a direct influence of hypothermia/rewarming on myocardial contractile function. These studies were inspired by the original work of Bigelow et al. (18, 19, 60, 149), and our results are consistent with their findings of reduced myocardial function after rewarming. Similar results were observed using an intact rat model (195, 198) in which we showed deterioration of myocardial mechanical function and a shift in energy metabolism. Thus, it is likely that the heart is an important target of hypothermia and rewarming *in vivo*, with cardiac dysfunction contributing to the development of a circulatory collapse after rewarming. By use of contemporary invasive hemodynamic monitoring techniques in the intact dog, rat, mouse and pig models (62, 63, 204), results have consistently revealed that the hypothermia and rewarming cause direct effects on myocardial excitation-contraction coupling and actin-myosin interaction (63, 80, 199). These effects most likely explain the depression in left ventricular contractile function after rewarming, which underlies the reduction of cardiac output and systemic arterial pressure (190). These models have also been used to screen the potential beneficial effects of different pharmacologic interventions to alleviate hypothermia-rewarming induced cardiac dysfunction *in vivo* (45, 47, 49, 62, 98, 133, 196, 197).

To unravel the basic pathophysiological mechanism(s) of hypothermia-rewarming related cardiac dysfunction, investigations have focused on excitation-contraction coupling and muscle force generation in cardiomyocytes. Impaired regulation of $[Ca^{2+}]_{cyt}$ is a key factor in the pathophysiology of heart failure during normothermia (206), which also appears to be the case during hypothermia. Normally, basal $[Ca^{2+}]_{cyt}$ is maintained at low levels and increases only transiently in response to electrical stimulation. The amplitude and duration of evoked $[Ca^{2+}]_{cyt}$ transients are proportionally transduced into contractile responses via troponin-based

thin filament regulation, specifically $[Ca^{2+}]_{cyt}$ binding to cardiac troponin C (cTnC) and removal of the steric hinderance posed by troponin I (cTnI) (15). Hypothermia appears to disturb the mechanisms underlying sarcoplasmic reticulum (SR) Ca^{2+} release and reuptake, thereby increasing the amplitude and prolonging the duration of the evoked $[Ca^{2+}]_{cyt}$ response to electrical stimulation. With the increased amplitude and duration of the $[Ca^{2+}]_{cyt}$ transient, the contractile response of cardiac myocytes is also increased during hypothermia. These seemingly contradictory functional changes in cardiac myocytes are already observed when core body temperature is reduced from 36°C to 30°C (101). The increased amplitude and prolonged duration of the evoked $[Ca^{2+}]_{cyt}$ transient is dysfunctional over time in that it can lead to a Ca^{2+} overload (185, 206). Hypothermia-induced alterations in the transient $[Ca^{2+}]_{cyt}$ response can also be attributed to changes in other cellular components of ionic balance within cardiac myocytes. For example, hypothermia affects the Na^+, K^+-ATPase pump (91, 174), the Na^+/Ca^{2+}-exchanger (169), and the sarcoplasmic-endoplasmic reticulum ATPase (SERCA2) pump (102). The biphasic course in cardiac function in response to increased $[Ca^{2+}]_{cyt}$ has been documented in experiments using isolated hypothermic hearts (17, 68, 73, 109, 150, 165, 169, 171, 174-177, 221, 222), as well as in intact animals (99, 211), and in isolated cardiac myocytes (79, 163).

The resulting $[Ca^{2+}]_{cyt}$ overload during hypothermia might negatively impact the contractile response over time through downstream effects (206). Elevated $[Ca^{2+}]_{cyt}$ increases energy consumption by activating ATP-dependent cross-bridge cycling, and ATP-dependent Ca^{2+} pumps in the SR and sarcolemma (14). The hypothermia-induced increase in ATP consumption will eventually cause mitochondrial depolarization, an uncoupling of oxidative phosphorylation, ROS formation, compromised energy production, mitochondrial swelling, and cell death (6, 14, 30, 40, 42, 70, 72, 78, 88, 105, 154, 155, 184, 198, 199). Using electron microscopy and morphometry, we were able to quantify and categorize myocardial

mitochondrial damage after rewarming following a 4-h period at 15-13°C with spontaneous circulation (200). Altered mitochondria with electron-dense inclusions constituted 20% of total mitochondrial volume, and this finding corresponds with findings of altered mitochondrial function with significant loss of high energy phosphates in our comparable experimental work (198). In isolated cells showing hypothermia-rewarming induced disruption of myocardial excitation-contraction coupling, we found that mitigating excessive ROS formation by antioxidant treatment during hypothermia ameliorated myocardial dysfunction (164) (Figure 3).

During rewarming, the amplitude and duration of the evoked $[Ca^{2+}]_{cyt}$ transient returns to normothermic levels. Thus, it does not appear that the decrease in contractility of cardiac myocytes (heart failure) in rewarming shock can be solely attributed to dysregulation of $[Ca^{2+}]_{cyt}$ release and reuptake. Instead, the contractile sensitivity of cardiac myocytes to $[Ca^{2+}]_{cyt}$ (Ca^{2+} sensitivity) is reduced during rewarming shock (82). Another mechanism that underlies a reduction in force generation independent of $[Ca^{2+}]_{cyt}$ levels is the effect of an increased phosphorylation of cTnI, leading to reduced Ca^{2+} sensitivity of the contractile response (172). The phosphorylation of cTnI serine at residues 23 and 24 is mediated by protein kinase A (PKA) alters the molecular conformation of cTnI and serves to accelerate relaxation and cross bridge cycle kinetics (96). The ser-23 site may be constitutively phosphorylated, while phosphorylation of ser-24 may have more functional importance (218). Importantly, the interaction between myosin and actin to form cross bridges is more likely when ser-24 of cTnI is not phosphorylated (115), and phosphorylation of cTnI reduces the Ca^{2+} binding affinity of TnC.

Using an intact rat model of accidental hypothermia-rewarming, we showed that the Ca^{2+} sensitizer levosimendan, which targets cTnC, mitigated the ~60% reduction in cardiac

output after rewarming (45). By comparing wild type vs. transgenic mice, expressing slow skeletal TnI (ssTnI) that lacks the Ser23/24 phosphorylation sites, we showed that hypothermia-rewarming induced cardiac dysfunction was mitigated when phosphorylation of cTnI at Ser23/24 was prevented in transgenic mice (191). Furthermore, in rat papillary muscle, which was continuously paced during 1.5-h period of hypothermia (15°C) to mimic the beating heart in accidental hypothermia, the cardiac contractile response was reduced after rewarming despite normal evoked $[Ca^{2+}]_{cyt}$ responses reflecting a reduction in Ca^{2+} sensitivity (81). Importantly, in this model of rewarming shock, PKA-dependent phosphorylation of cTnI at ser23/24 increased. Similar findings were observed using an isolated rat cardiac myocyte preparation subjected to a similar period of hypothermia (15°C) (163). In this preparation, evoked $[Ca^{2+}]_{cyt}$ and contractile (sarcomere length shortening) responses were simultaneously measured and reduced Ca^{2+} sensitivity was demonstrated by a rightward shift in the phase-loop plots of $[Ca^{2+}]_{cyt}$ and contractile responses. In cardiac myocytes, reduced Ca^{2+} sensitivity was associated with cTnI phosphorylation at ser23/24 and activation of PKA. We also confirmed that during hypothermia, the amplitude of the evoked $[Ca^{2+}]_{cyto}$ transients increased and the duration was prolonged, and there was an elevation of basal $[Ca^{2+}]_{cyt,}$ which may underlie hypothermia-induced Ca^{2+} overload. However, immediately after rewarming the evoked $[Ca^{2+}]_{cyt}$ response returned to pre-hypothermia levels. Importantly, if the isolated cardiac myocytes were left unstimulated during hypothermia, the reduction in Ca^{2+} sensitivity and cTnI phosphorylation were mitigated (79). These results are relevant to cardiac surgery, where the heart is arrested during hypothermia. One may argue that due to HCA, in addition to potential protective effects of a chemical cardioplegic agent, during cardiac surgery the heart is protected from elevation of basal $[Ca^{2+}]_{cyt}$, changes in Ca^{2+} sensitivity and cTnI phosphorylation and thus, to post-hypothermic cardiac dysfunction (Figure 4).

Case stories of accidental hypothermia patients with cardiac arrest have reported complete restitution of neurologic function after up to 6 h of pre-hospital resuscitation and in-hospital rewarming (71, 87, 117, 209, 210). These reports of favorable outcomes appear to be linked to the quality of pre-hospital emergency medical treatment provided including the early initiation and continued use of cardiopulmonary resuscitation in accordance to the latest international guidelines (127, 188). In an attempt to document effects of cardiopulmonary resuscitation on cardiac output, blood pressure, O_2 transport and O_2 consumption, and regional blood flow, our established porcine model of experimental hypothermia (204) was equipped with an automated chest compression device to perform cardiopulmonary resuscitation for hypothermic cardiac arrest. We found that, compared to spontaneous circulation at normothermia, 3 h of continuous resuscitation at 27°C provided limited but sufficient O_2 delivery to maintain aerobic metabolism in essential organs (135). Based on promising clinical reports (21, 128, 160), the use of extracorporal membrane oxygenation for rewarming from accidental hypothermia has been recommended. We, therefore, added rewarming using extracorporal membrane oxygenation following 3-h continuous cardiopulmonary resuscitation to our model. Results showed sustained lower levels of cardiac output and blood pressure, maintained aerobic metabolism, restoration of blood flow to the heart and brain, and this rewarming method created a "shockable" cardiac rhythm (134). Due to the appearance of hypothermia-induced cardiac dysfunction in our animals after rewarming, extracorporeal circulation for cardio/respiratory support must be continued for days, if needed, similar to the accidental hypothermia patients rewarmed with this technique (128, 160), in order to re-establish a perfusing rhythm.

Rewarming following hypothermic cardiac arrest and reperfusion after normothermic ischemia/hypoxia share the same treatment strategy; to restore blood flow at the macro-vascular level in an attempt to optimize blood flow at the micro-vascular level to minimize end organ

dysfunction. However, all reperfused organs are exposed to complex pathophysiologic processes causing uneven alterations in organ function, collectively termed the post-cardiac arrest syndrome (131). This syndrome may also involve systemic inflammatory reactions and cross-talk pathways between inflammation and the coagulation/fibrinolysis reactions. Hypoxic/ischemic insult is believed to be the leading cause of postoperative neuronal death that subsequently results in long-term neurologic disability. The ischemia/reperfusion concept during normothermic conditions has been extensively covered elsewhere (212), but also numerous experimental as well as clinical studies have documented that hypothermia, accidental as well as therapeutic, and rewarming may create cellular stress - responses (3, 20, 29, 65, 67, 86, 90, 121, 189, 207), which are central in the pathophysiology of hypothermia-rewarming and potentially available for future therapeutic interventions. Using a rat model, we demonstrated that resuscitation following severe hypothermia is associated with myocardial cellular stress response that involves activation of nuclear factor kappa B - signaling and induction of autophagy. Furthermore, the majority of changes in gene expression were found to be induced during the rewarming phase suggesting that key events in the pathogenesis of rewarming shock occur during rewarming, making them amenable to therapeutic interventions (46, 97, 99, 202, 211).

What is currently known? Due to better prehospital diagnosis and interventions, the survival rate of accidental hypothermia patients with a perfusing rhythm has increased from only 20-48 % surviving 20 years ago to the present survival rate of 68-72 %. Mortality is related to the occurrence of arrhythmias, bleeding, and acute cardiac failure (rewarming shock) during rewarming. In contrast, mortality of accidental hypothermia patients in cardiac arrest are as high as 70 % and have remained more or less unchanged over the same time period. However, recent patient data report increased survival in the latter patient group after using contemporary invasive rewarming techniques

What is unknown and what knowledge gaps exist? There is a general lack of detailed insight regarding the mechanism(s) of organ dysfunction created during hypothermia. Better insight in these pathophysiologic mechanisms is needed for creating better rewarming techniques. Likewise, this new insight is a prerequisite to manage early recognition of symptoms, and to start early interventions against life threatening situations, with background in hypothermia-induced acute organ failure during rewarming.

Epilogue. Philosophically, one may argue that from the fact that homoeothermic species are equipped with so many protective mechanisms to regulate core body temperature within close temperature limits, and spend so much energy on maintaining thermoregulation, possible beneficial physiological effects from reducing core temperature beyond these limits appear limited. In our survey, we find only three clinical situations where there may be a benefit from the use of in therapeutic hypothermia: 1) hypothermic cardiac arrest during heart surgery, 2) single donor organs maintained at lower temperature during donation and transportation before being transplanted in the recipient, and 3) neuroprotective effects of therapeutic hypothermia to counteract hypoxic-ischemic encephalopathy in premature and newborn babies. Therefore, one may explore similarities between these organs with respect to how they are treated during exposure to therapeutic hypothermia. In cardiac surgery heart function is terminated due to the combined effects of low temperature and a chemical cardioplegic agent. The cold, arrested heart is thus isolated from the pathophysiological processes related to continued activity, which may otherwise harm the intact, hypothermic, working heart. Similarly, the single organ harvested for transplantation (mostly kidneys, liver, pancreas, lungs, and heart) is kept at a very low temperature (0°C – 10°C), in which the protective effects of hypothermia are mediated by reduced O_2 consumption in parallel with reduced organ function. In each of these examples, the organs are disconnected from the general circulation, they are isolated from hormonal and

whole-body immunologic interactions, and they are relieved from their normal energy requiring physiological function.

To counteract hypoxic-ischemic encephalopathy newborns are treated with therapeutic hypothermia at a lower core temperature and kept at this low temperature for a much longer periods of time than otherwise attempted for neuroprotection in adults. But unlike in adults the outcome is undisputedly much better in newborns. It is well known that newborns are equipped with physiologically competent mechanisms that provide them with a much higher tolerance to survive any birth-related (accidental) hypothermia situation compared to adults or even older infants. Some of these inborn mechanisms are well described, e.g., cardiac myocytes in the newborn express a slow skeletal isoform of TnI (ss-TnI), which is later replaced by the adult cTnI isoform within only a few weeks after birth. It is well known that ss-TnI maintains its regulatory function down to very much lower temperatures as compared to cTnI. Inspired by this background knowledge we recently documented increased tolerance to 3-h hypothermia and rewarming, over wild type mice, by use of adult, transgenic ss-TnI mice (191). As a consequence of this increased cold tolerance, spontaneous cardiac activity in newborns is maintained at much lower temperatures than in adolescents, an important physiological mechanism to increase survival during accidental, birth-related, hypothermia. It is tempting to suggest that other essential body organs than the heart, like the brain, are provided with inherent biological mechanisms which promote organ specific cold tolerance at birth. A report described spontaneous restart of breathing during rewarming following experimental cooling to respiratory arrest in newborn animals. This inherent and well described (2) ability to restart breathing during rewarming was present in newborn rats and hamsters (36), but disappeared after the first three to four weeks of maturation, respectively, in these two species.

The overwhelming favorable effects of therapeutic hypothermia to withstand massive organ damage during/after hypoxic/ischemic events in animal experiments have so far been

difficult to recognize in randomized clinical trials elevating patient outcome data after applying therapeutic hypothermia in clinical therapy. Obvious explanations to this lack of therapeutic effects may be due to differences in species, hypothermia induced before start of hypoxia etc. However, the institution of therapeutic hypothermia as a treatment option in the clinical ICU situation is also quite different from starting a standardized hypothermia protocol on anesthetized experimental animals. It appears from the randomized clinical trials listed that in a clinical situation: 1) That the decision to start cooling may often be delayed, 2) effective cooling may not be tolerated in semi-comatose patients which also may not tolerate heavy sedation due to hemodynamic instability, 3) the occurrence of shivering, 4) lack of proper patient temperature monitoring, and, 5) inadvertent events causing hyperthermia during patient rewarming.

To optimize clinical effects of therapeutic hypothermia, as well as to optimize techniques for rewarming of accidental hypothermia patients, it appears fruitful to consider background knowledge and experience obtained from different temperature intervention techniques applied for multiple clinical therapeutic purposes. A good example would be to squint to techniques developed for organ preservation of donor organs where the use of preservation solutions are central. Background for the invention and use of preservation solutions was the early observation during animal experiments. These experiments demonstrated the benefits of perfusion with an acellular solution to counteract microvascular obstruction, which otherwise would appear when perfusing with whole blood, even during massive hemodilution. It appears fruitful to follow, or at least to consider, a similar approach when rewarming an accidental hypothermia patient using cardiopulmonary bypass, where reestablishment of organ reperfusion and microvascular integrity appears essential.

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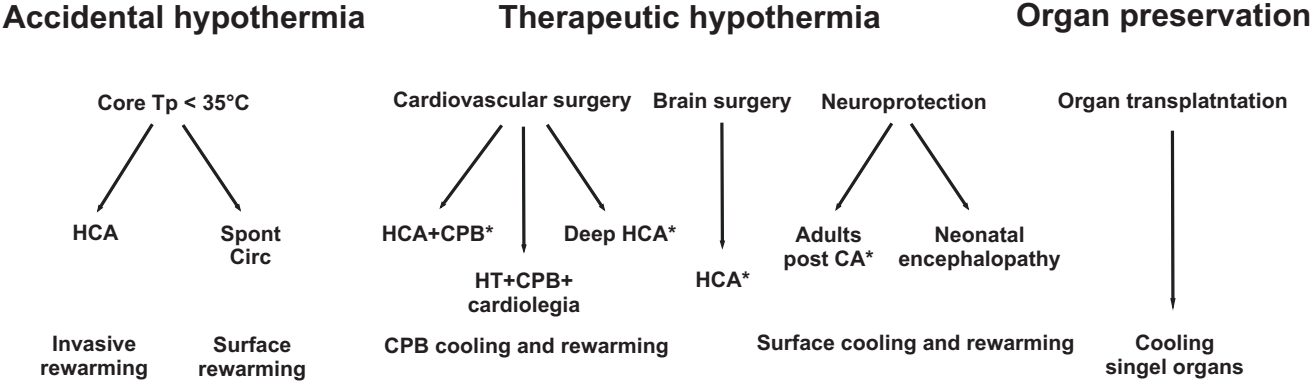

* Indicate the technique is no longer used/more seldome used or replaced by other therapeutic techniques not affecting core temperature.

FIGURE 1. Hypothermia can be accidental, intentional, and therapeutic
HCA, hypothermic cardiac arrest; CPB, cardiopulmonary bypass.

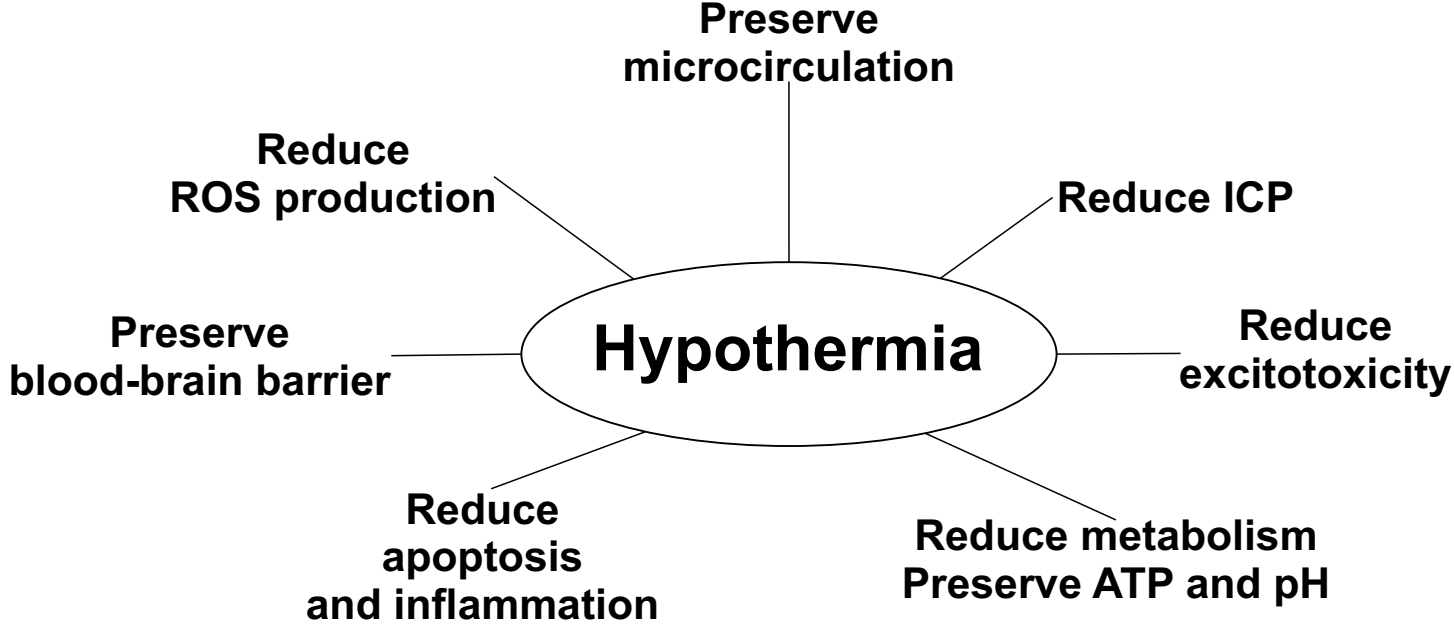

FIGURE 2. Neuroprotective effects of induced hypothermia
ROS, reactive oxygen species; ICP, intracerebral pressure.

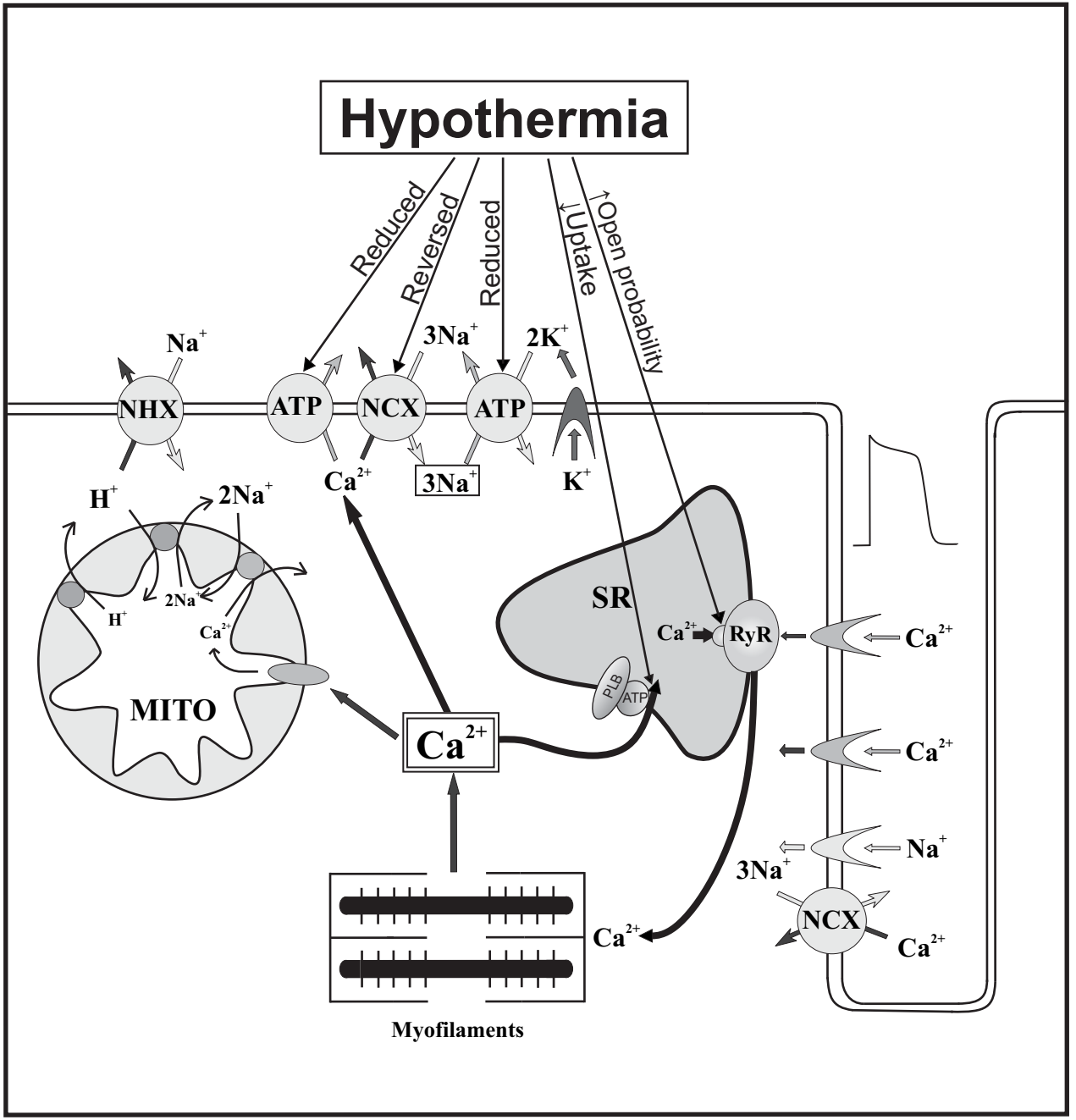

FIGURE 3. The classic theories to explain hypothermia-induced cell edema and calcium overload
SR, sarcoplasmic reticulum; RyR, ryanodine receptor; PLB, phospholamban; NCX, Na^+ /$Ca2^+$ exchanger.

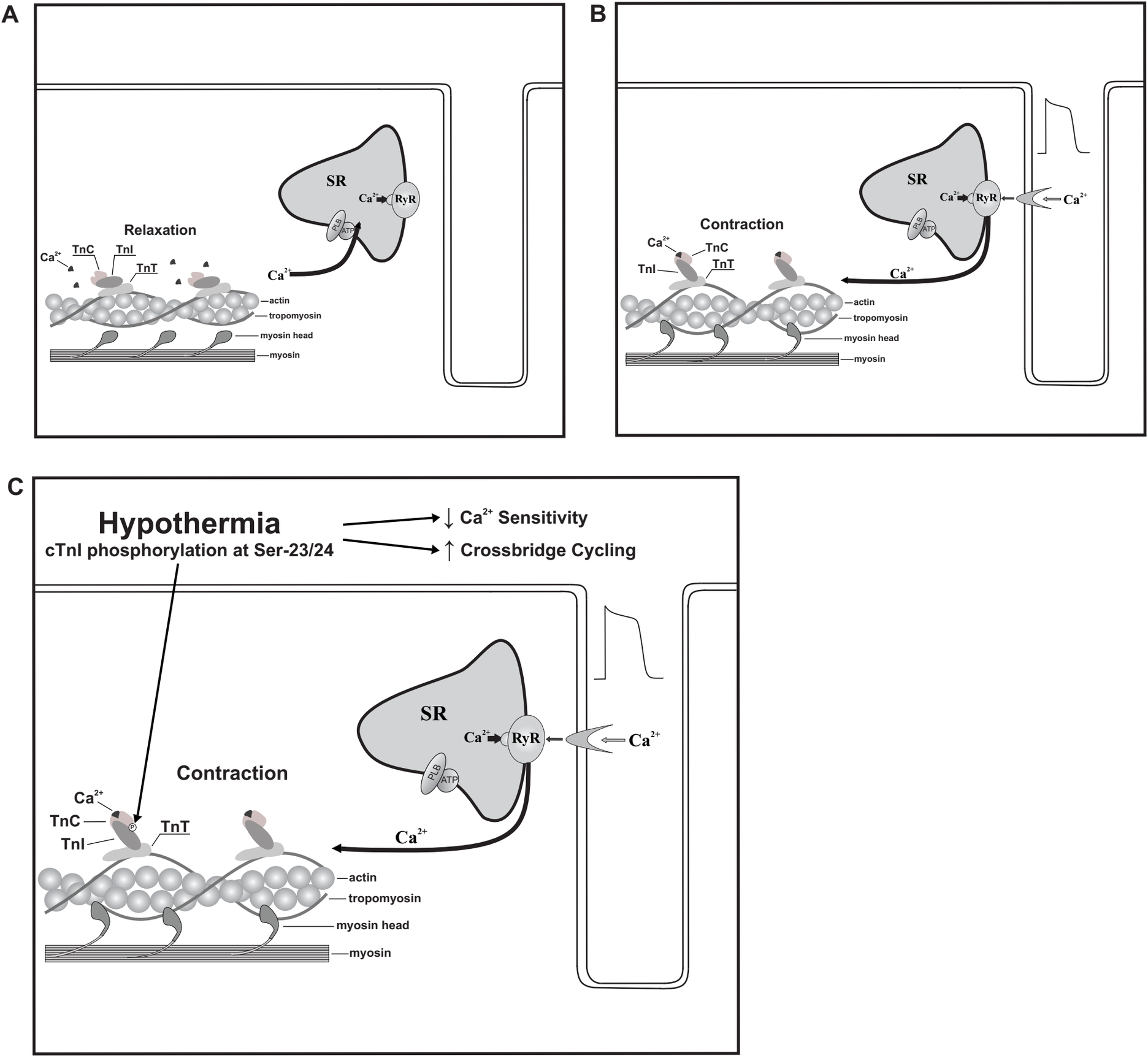

FIGURE 4. Cardiac cell excitation-contraction-coupling
A and B: cardiac cell excitation-contraction-coupling in response to sarcolemma membrane depolarization, calcium-induced sarcoplasmic reticulum (SR) calcium release, Ca^{2+}-induced changes in actin-myosin-tropomyosin interaction, and cytoplasmic Ca^{2+}-induced change in conformation between cardiac troponin C (cTnC) and cardiac troponin I (cTnI).
C: hypothermia-induced protein kinase A (PKA) mediated increase in cTnI phosphorylation at Ser23/24 to decrease Ca^{2+} sensitivity of cTnC and increase cross bridge cycling. RyR, ryanodine receptor; PLB, phospholamban.