Myocardial protection with mild hypothermia

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Abstract
Mild hypothermia, 32–35°C, is very potent at reducing myocardial infarct size in rabbits, dogs, sheep, pigs, and rats. The benefit is directly related to reduction in normothermic ischaemic time, supporting the relevance of early and rapid cooling. The cardioprotective effect of mild hypothermia is not limited to its recognized reduction of infarct size, but also results in conservation of post-ischaemic contractile function, prevention of no-reflow or microvascular obstruction, and ultimately attenuation of left ventricular remodelling. The mechanism of the anti-infarct effect does not appear to be related to diminished energy utilization and metabolic preservation, but rather to survival signalling that involves either the extracellular signal-regulated kinases and/or the Akt/phosphoinositide 3-kinase/mammalian target of rapamycin pathways. Initial clinical trials of hypothermia in patients with ST-segment elevation myocardial infarction were disappointing, probably because cooling was too slow to shorten normothermic ischaemic time appreciably. New approaches to more rapid cooling have recently been described and may soon be available for clinical use. Alternatively, it may be possible to pharmacologically mimic the protection provided by cooling soon after the onset of ischaemia with an activator of mild hypothermia signalling, e.g. extracellular signal-regulated kinase activator, that could be given by emergency medical personnel. Finally, the protection afforded by cooling can be added to that of pre- and post-conditioning because their mechanisms differ. Thus, myocardial salvage might be greatly increased by rapidly cooling patients as soon as possible and then giving a pharmacological post-conditioning agent immediately prior to reperfusion.

Keywords
Cardioprotection • Cooling • Extracellular signal-regulated kinase • Hypothermia

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1. Introduction
For several decades, severe (20–28°C) or profound hypothermia (<20°C) has been used to protect arrested hearts during cardiac surgery or for organ preservation. While severe hypothermia is detrimental to cardiac function, mild hypothermia (MH), 32–35°C, has little effect on the mechanical function of the in vivo beating heart, yet it is very protective against infarction during ischaemic insults. ¹–⁷ Historically, retroperfusion of the coronary sinus of ischaemic hearts with hypothermic blood minimized complications of reperfusion and reduced ultimate infarct size in dogs.⁸ Subsequently, reports have confirmed that MH during acute myocardial ischaemia is very cardioprotective in rabbits,⁹,¹⁰,¹¹,¹² dogs,¹³ swine,¹⁴,¹⁵ rats,¹⁶ and sheep.¹⁷ In most studies, the entire body was made hypothermic without apparent complications. These investigations expanded the potential therapeutic potential of MH, because it is already well documented to be neuroprotective and to improve survival in comatose patients resuscitated from cardiac arrest.¹⁸,¹⁹

In patients presenting with acute ST-segment elevation myocardial infarction (STEMI), the two first large-scale trials testing whole-body MH did not support an anti-infarct effect.²⁰,²¹ These failures were most probably a function of slow cooling rates, which delayed establishment of a mild hypothermic state until long after reperfusion had been induced. A recent clinical trial with a much more aggressive cooling protocol was more promising,²² and several trials are currently recruiting patients in order to further investigate MH in STEMI (e.g. studies identified as NCT00763828 and NCT01379261 in clinicaltrials.gov). This clinical activity, together with recent mechanistic studies showing that MH probably protects through a complex mechanism beyond energy preservation, reveals that cooling is still a hot topic for cardioprotection. In previous reviews or editorials, our groups²,³ and others³ have presented the overall background of...
the cardioprotective properties of MH. In the present review, we will focus on the aspects which are most critical for successful clinical translation of MH (e.g., importance of dosing and schedule of MH) and on the recent findings that, at least partly, unravel the mechanism of MH cardioprotection.\textsuperscript{24–27} Finally, we will evaluate pharmacological approaches that might mimic MH.

2. Mild hypothermia: why, when, and how

2.1 Cardioprotection and infarct reduction

Myocardial temperature is an independent predictor of infarct size in animal models of acute myocardial ischaemia.\textsuperscript{1,2,6} This was first shown by Chien et al.\textsuperscript{1} in anaesthetized rabbits subjected to 30 min of coronary artery occlusion, in which cardiac temperature was varied between 35 and 42 °C. The left panel of Figure 1 summarizes several reports of hypothermia with different target temperatures in rabbits experiencing a similar duration of myocardial ischaemia followed by reperfusion.\textsuperscript{5,10,28–30} The figure clearly illustrates that the relationship between infarct size and cardiac temperature established by Chien et al.\textsuperscript{1} agrees with that observed in subsequent studies. A similar relationship between ischaemic temperature and infarct size was found in dogs,\textsuperscript{6} pigs,\textsuperscript{2} and sheep,\textsuperscript{31} as shown in the right panel of Figure 1. In these studies, most investigators induced hypothermia very early during the ischaemic episode, therefore significantly shortening normothermic ischaemic time.\textsuperscript{1,2,6} Several studies investigated the required timing of initiation and duration of MH that would lead to cardioprotection.\textsuperscript{5,9,10,14,15,28,29,32} These reports have previously been reviewed extensively and indicated that the benefit afforded by MH varied inversely with how quickly after the onset of ischaemia it was established.\textsuperscript{5,9,10,14,15,28,29,32} In order to illustrate the cardioprotective window of MH, we merged results of published studies in anesthetized rabbits subjected to 30 min of regional myocardial ischaemia (Figure 2, left panel). As can be seen clearly, the benefit of hypothermia increases progressively as normothermic ischaemic time diminishes. The relationship is shifted upwards in a parallel fashion as the magnitude of cooling is intensified from 35 to 32 °C. Finally, the regression lines project to zero salvage when cooling is initiated after 40 min of occlusion.\textsuperscript{33} Recently, Göteborg et al.\textsuperscript{34} critically tested whether any benefit could be obtained by cooling only at reperfusion in pigs. Very rapid cooling (cold intravenous saline plus endovascular cooling probe) was begun after 40 min of coronary occlusion. Five minutes later, the heart was reperfused. In normothermic hearts, reperfusion was begun immediately after only 40 min of coronary occlusion. Despite 5 min of additional ischaemia in hypothermic hearts, infarct size was significantly reduced by a modest amount, indicating a specific effect on reperfusion injury because both groups were subjected to 40 min of normothermic ischaemia. When cooling was begun immediately after the onset of reperfusion, no protection was seen, indicating that cooling exerted its protection either shortly before or at reperfusion. This is an important point, because it is much easier to have STEMI patients cooled at the time of reperfusion, suggesting that in rabbits hypothermia targets an ischaemic injury but has little or no direct effect against reperfusion injury. The right panel of Figure 2 demonstrates a similar relationship in pigs. It is striking that the protective effect of hypothermia seems to be more pronounced in hearts with coronary occlusions of longer duration. Interestingly, the protection is negligible if cooling is initiated at the onset of reperfusion after a 40 min coronary occlusion, whereas there is some salvage if cooling is induced after 60 min of occlusion.\textsuperscript{33}
salvage kinases' in rabbits, that does not seem to be the case in pigs. Whether the human heart will respond like the pig or the rabbit is unknown, but in the two failed clinical trials significant protection was reported in subgroups in which significant cooling was already present at reperfusion (see section 4). While the debate continues on the benefit of MH against reperfusion injury, all investigators agree on the value of cooling during the ischaemic period. Reducing the temperature by a mere 3°C reduces infarct size by an amount comparable to ischaemic preconditioning.

2.2 Cardioprotection, myocardial contractile function, and ventricular remodelling

In non-ischaemic beating hearts, MH is associated with decreased heart rate, while mean arterial pressure remains unchanged. Post et al. assessed left ventricular performance with pressure-volume loops and cardiac output measurements in pigs cooled to 33°C. Heart rate and whole-body oxygen consumption decreased during hypothermia, whereas cardiac output did not change. Hypothermia was associated with impaired relaxation but a positive inotropic effect, as had previously been shown in dog hearts. The proposed mechanisms include increased Ca²⁺ sensitivity of myofilament proteins and improved Ca²⁺-activated force generation.

The positive inotropic and oxygen-sparing effects of hypothermia might be beneficial to the acutely failing heart. In ischaemia-induced cardiogenic shock in pigs, MH reduces acute mortality, improves haemodynamic parameters, and reduces metabolic acidosis. A mechanical benefit from hypothermia was also seen when cardiac output was maintained despite a reduction in heart rate in pigs subjected to 60 min of regional ischaemia. We investigated functional regional recovery within the risk zone during 30 min of ischaemia and 72 h of reperfusion in chronically instrumented rabbits. Hypothermia instituted with total liquid ventilation after onset of ischaemia allowed virtually complete recovery of regional contractility within 24 h of reperfusion. We also observed that cooling improved function in the first hour of reperfusion. This benefit was not related merely to infarct size reduction, because ischaemic preconditioning which induced similar tissue salvage did not improve regional contractility during the first hours of reperfusion. Infarct size and regional contractility after 3 h of reperfusion in different groups of rabbits protected by either cooling or ischaemic preconditioning are plotted in Figure 3. These data were obtained from different studies investigating algorithms of ischaemic preconditioning (either one or six cycles of ischaemia/reperfusion) or cooling (instituted at either the fifth or fifteenth minute of ischaemia). Regional contractility recovered to 60–70% of its pre-ischaemic value in both hypothermic groups, whereas contractility remained deeply depressed in all preconditioned hearts. This strongly suggests that hypothermia during ischaemia directly prevents myocardial stunning, whereas ischaemic preconditioning does not.

Mild hypothermia during ischaemia enhances left ventricular contractile function through inhibition of post-infarction ventricular remodelling in sheep experiencing 60 min of regional ischaemia. After 8 weeks, echocardiographic left ventricular ejection fraction was significantly increased by 38% in hearts whose temperature had been lowered to 37.5°C during ischaemia over that in control hearts maintained at 39.5°C. It is, however, unknown how much of this protection against remodelling was related to infarct size reduction alone, because infarct size was not measured acutely, nor was a group with a normothermic anti-infarct intervention, such as ischaemic preconditioning, included.

A beneficial effect of MH on acutely failing myocardium has also been reported following global ischaemia and cardiac arrest.
and that may involve the effect of MH on the central nervous system. Tsai et al. found that cooling only the head of pigs resuscitated after 10 min of ventricular fibrillation with intranasal evaporation of cold perfluorocarbons improved myocardial function. We also showed in a rabbit model of cardiac arrest that rapid whole-body cooling with liquid ventilation reduces myocardial infarction even when started after resuscitation, a protocol that would have little effect on infarction from regional myocardial ischaemia.

2.3 Blood vessel protection and no-reflow

While external cooling induces cutaneous vasoconstriction, MH does not adversely affect myocardial blood flow or epicardial coronary artery diameter in rabbits, dogs, and pigs subjected to myocardial ischaemia. Hypothermia may protect against vascular injury through reduction of the no-reflow phenomenon, as shown by Hale et al. and others. In rabbits subjected to 30 min of ischaemia, cooling started 10 min before reperfusion, for example, led to a 70% decrease in the extent of no-reflow. In pigs, rapid cooling, even when initiated after reperfusion, dramatically reduced microvascular obstruction. However, myocardial infarction was not reduced in these hearts despite reduced no-reflow. This suggests that hypothermia at reperfusion exerts clear vascular protection independent of any anti-infarct effect. Long-term benefits might occur from targeting no-reflow per se, because no-reflow may affect subsequent remodelling. Also, maintaining a viable vasculature could improve viability of seeded stem cells.

2.4 How can myocardium be cooled quickly?

To obtain maximal benefit, a patient’s normothermic ischaemic time should be minimized. Hypothermic treatment should be begun as soon after the onset of ischaemia as possible, and body temperature should be lowered as rapidly as possible. The different approaches that could be used for induction of MH have been extensively described in previous reviews in both experimental and clinical settings. Experimental reports with MH in animal models of coronary occlusion have used topical epicardial cooling, intracoronary administration of cold fluids, surface skin cooling, or endovascular thermodes, either alone or combined with the infusion of a large volume of cold fluid. Among these different studies, the anti-infarct effect of MH was directly related to the ability to offer hypothermia early during ischaemia through an early institution of the cooling strategy and/or through fast cooling. In order to increase the benefit further and still reduce infarct size when cooling was started later during the ischaemic process, cardiac ultra-fast cooling strategies have been examined in animals with extracorporeal blood cooling, total liquid ventilation with temperature-controlled perfluorocarbons and pericardoperfusion with cold fluids.
3. Mechanism of cooling-induced cardioprotection

3.1 Mild hypothermia does not act only through energy preservation

The mechanism of the cardioprotective effect of MH (>30°C) in beating hearts has received much less attention than that of deeper hypothermia and cold cardioplegia (typically 4°C). During the latter, metabolism is dramatically reduced, and acidosis and cellular calcium and sodium overload are dramatically attenuated because contractile activity is arrested along with most enzymatic activity. The sarcoplasmic Na⁺–Ca²⁺ exchanger is inhibited, while the Na⁺–H⁺ exchanger is paradoxically activated. Importantly, cold cardioplegia prevents mitochondrial calcium overload during ischaemia, as well as post-ischaemic generation of reactive oxygen species (ROS). As recently reviewed, deep hypothermia blunts virtually all known deleterious aspects of ischaemia, including ATP depletion, calcium overload, and ROS production at reperfusion.

During MH (>30°C), modest preservation of high-energy phosphates has also been evident during myocardial ischaemia in rabbits, and dogs. This is accompanied by decreased glucose consumption and lactate accumulation. However, these metabolic alterations cannot entirely explain the protection afforded by MH. There is a sharp threshold for ATP preservation that varies between 30 and 34°C, yet cooling to 35°C is still very protective. This suggests that protection must involve effects other than energy preservation alone. Activation of one or more protective signalling pathways, much as those seen in ischaemic preconditioning, has recently been proposed to accompany hypothermia (Table 1).

3.2 Mild hypothermia initiates protective signal transduction

Ning et al. investigated the effect of pre-ischaemic cooling to 31°C in isolated rabbit hearts prior to 120 min of global ischaemia with cardioplegia at 34°C. This not only preserved ATP levels but also mRNA levels of adenine nucleotide translocase isoform 1 and PPAR-β, suggesting a possible effect on mitochondrial biogenesis. Unfortunately, the study was complicated by the addition of cardioplegia, which is itself cardioprotective. These authors also showed that 120 min of cardioplegic arrest at 30°C led to elevated expression of hypoxia-
inducible factor 1α, haem oxygenase 1, peroxisome proliferator-activated receptor-β and Akt-1 compared with 34°C. This further supported the attractive hypothesis of a role for signal transduction in the action of hypothermia.

In murine cardiomyocytes subjected to 90 min of simulated ischaemia at 32°C, the protection afforded by hypothermia applied 10 min before and maintained during 1 h of reoxygenation was abolished by pharmacological inhibition of Akt and nitric oxide (NO) synthase but not by a cyclic GMP inhibitor. Hypothermia also attenuated ROS generation at reoxygenation, increased NO, and maintained mitochondrial membrane potential, while increasing phosphorylated Akt during ischaemia and enhancing phosphorylation of heat shock protein 27 (HSP27), a regulator of Akt. This study finally proposed a signalling pathway involving Akt/HSP27 phosphorylation and enhanced NO generation or phosphoinositide 3-kinase (PI3K) with Akt-activation with wortmannin. The protection given by hypothermia against infarction was not affected when NO production was blocked with Nω-nitro-l-arginine methyl ester or Akt activation with wortmannin. The protection given by cooling was also not affected by pharmacological inhibition of protein kinase C, a key kinase in preconditioning; however, inhibition of extracellular signal-regulated kinase (ERK) totally abolished anti-infarct effect of cooling (Figure 4). Moreover, the ischaemic rather than the reperfusion phase was shown to be the critical time when ERK had to be active to elicit protection. The above studies showing the role of the NO/Akt/PI3K/mTOR pathway were notably performed in isolated cells with hypothermia targeting the reperfusion phase, or in isolated rat hearts after global ischaemia. We previously emphasized, however, that the effect of hypothermia against reperfusion injury is modest at best when evaluated after regional myocardial ischaemia in vivo. Accordingly, we recently investigated the mechanism by which MH targets injury in a mouse model of myocardial ischaemia.26 Further proposed that this pathway could involve inhibition of the mammalian target of rapamycin (mTOR), either directly or through AMP-activated protein kinase. This was shown by the differential phosphorylation of the mTOR targets 70S6K and eEF2 and by the increase in phosphorylated AMPK after 60 min of simulated ischaemia in cardiomyocytes isolated from 1- to 2-day-old mice. In this model, cell death was minimal at the end of simulated ischaemia, while it was dramatically accelerated during 3 h of subsequent reperfusion (4 vs. 39%). Importantly, the results were confirmed in vivo in a mouse model of cardiac arrest with therapeutic hypothermia after resuscitation. Interestingly, the effect of MH could be mimicked by the pharmacological inhibition of mTOR with rapamycin, offering a promising therapeutic perspective.

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afforded by cooling against ischaemic injury in normothermic conditions, which would eliminate the logistical nightmare of trying rapidly to cool the acutely ill cardiac patient.

In a subsequent report, we tested whether MH-activated signalling was triggered by occupation of G protein-coupled receptors through an increased release of adenosine or opioids. However, pharmacological inhibition of either of these receptors did not affect the protection afforded by hypothermia in in situ rabbit hearts. The mechanism by which cooling activates its protective pathway is presently unknown. The central nervous system is probably not involved, because protection occurs in isolated hearts, and with local cooling of the in vivo heart. One possibility is the widely distributed transient receptor potential (TRP) channels, which are used to sense temperature in the central nervous system and have unknown function in non-neural tissues. The TRPV4 channel is highly temperature sensitive, however, cooling of cardiomyocytes from TRPV4 knockout mice still activated ERK (J.M. Downey and M.V. Cohen, unpublished data). There are other TRP channel types, many of which are also temperature sensitive.

### 3.3 Possible end-effectors and perspectives

It would be instructive to identify the end-effector of the protection afforded by hypothermia. It was shown that MH (32°C) inhibited calcium-induced mitochondrial permeability transition pore (mPTP) formation in ventricular samples from ischaemic rabbit hearts. This was observed in mitochondria isolated from hearts subjected to either only 30 min of in vivo ischaemia, or to a similar period of ischaemia followed by 10 min of reperfusion. This again shows that reperfusion is not mandatory for MH protection. While mPTPs may form only during reperfusion, it is the injury during ischaemia that causes them to do so in the first place. One cannot have reperfusion injury without ischaemic injury.

The exact mechanism by which MH attenuates mPTP formation is not known, but many hypotheses are plausible. While this was not directly shown, the sensitivity to mPTP formation could be directly attenuated by the effect of MH on ATP depletion and reactive oxygen species generation. The previously described signalling components proposed for the protection afforded by hypothermia (ERK, NO, and Akt) are also all known to inhibit mPTP through the pathway used by pre- and post-conditioning. Targeting mPTP opening with direct inhibitors, such as ciclosporin, is known to be highly cardioprotective. One might further wonder whether other regulators of mPTP formation, such as the Akt target glycogen synthase kinase-3β (GSK-3β), could be involved in MH cardioprotection. The non-phosphorylated active form of GSK-3β is indeed known to phosphorylate the voltage-dependent anion channel, thereby releasing hexokinase and triggering mPTP opening. To our knowledge, there is no evidence for a direct role of GSK-3β in MH cardioprotection. However, profound hypothermia (15°C) has been shown to elevate several downstream targets of Akt, including phosphorylated GSK-3β (inactive), phosphorylated Bad (inactive), β-catenine, and Bcl-2 in a rodent model of haemorrhagic shock with subsequent cardiopulmonary bypass. This was importantly associated with a decreased activity of myocardial caspase-3, as also shown in animal models of cardiac arrest with post-resuscitation MH. In rats subjected to moderate hypothermia (30°C) after focal brain ischaemia, it was also shown that GSK-3β was dephosphorylated in hypothermic but not normothermic brains after stroke. This was accompanied by an attenuation of the β-catenin degradation in the ischaemic penumbra, and may ultimately result in an increased expression of pro-survival genes and preserved cell—cell adhesion.

One might speculate that another candidate for the mediation of the cardioprotective effect of MH could be the mitochondrial ATP-dependent potassium channel (mKATP), because cross-talk with the signalling components of MH (e.g. Akt, PI3K, and ERK) is well established during pre- and post-conditioning. However, this speculation is not supported by the decreased sensitivity towards opening of myocardial KATP channels with nicorandil when temperature is decreased in guinea pig ventricular myocytes during patch-clamp experiments. For example, the time needed to open this channel was 2.3 ± 1.0 min at 35°C vs. 9.4 ± 10.2 min at 25°C.

Despite sharing some signalling components, pre-/post-conditioning and hypothermia have major mechanistic differences. Mild hypothermia protects primarily when applied during the ischaemic period and is likely to do so by preventing ischaemic injury that either kills cells outright or programmes them for mPTP formation in surviving cells when the heart is reperfused. Accordingly, giving an ERK inhibitor immediately prior to reperfusion has no effect on the protection from MH but will completely abolish the protection afforded by pre or post-conditioning. In preconditioned hearts, survival kinases (including PI3K/Akt and ERK) somehow directly inhibit mPTP formation during reperfusion in cells in which prior ischaemia has programmed them to open. It is not known how ERK can be involved in both mechanisms and behave so differently. Perhaps differ-
temperature of $34.7 \pm 0.3 \, ^\circ\text{C}$ was achieved before reperfusion without any significant delay in door-to-balloon time. This was associated with an infarct size of $29.8 \pm 12.6\%$ of the ischaemic zone in the hypothermia group, whereas it was $48.0 \pm 21.6\%$ in the normothermic control group. The study also demonstrated that it is possible to induce hypothermia efficiently before reperfusion without delaying primary percutaneous coronary intervention. A much larger study will be needed to verify these results.

5. Conclusion

Mild hypothermia is very cardioprotective in animal models of myocardial infarction. The benefit is directly related to reduction in normothermic ischaemic time and depth of hypothermia, supporting the importance of early and rapid cooling. New evidence suggests that the protection afforded by MH does not involve energy and metabolic preservation as much as activation of pro-survival signalling pathways. Reduction of injury during ischaemia seems to reduce the proclivity for lethal mPTPs to form during reperfusion. Further studies are still needed to unravel exactly how these kinases protect ischaemic hearts. As the protection given by MH appears to involve signalling, it may ultimately be possible to replace the cumbersome cooling apparatus with a simple drug. Also, because the mechanism of protection by MH differs from that of ischaemic post-conditioning, it should be possible to add MH and post-conditioning to produce ‘super protection’. In patients with STEMI, the first clinical trials with hypothermia were disappointing, presumably because of slow rates of cooling. As the technology for inducing more rapid cooling has markedly improved, future clinical trials will hopefully translate the success of MH in experimental infarction models successfully to the STEMI patient.

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