

# Hypothermia for Reduction of Myocardial Reperfusion Injury in Acute Myocardial Infarction

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CONTEMPORARY REVIEWS IN INTERVENTIONAL CARDIOLOGY

# Hypothermia for Reduction of Myocardial Reperfusion Injury in Acute Myocardial Infarction

## Closing the Translational Gap

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**ABSTRACT:** Myocardial reperfusion injury—triggered by an inevitable inflammatory response after reperfusion—may undo a considerable part of the myocardial salvage achieved through timely percutaneous coronary intervention in patients with acute myocardial infarction. Because infarct size is strongly correlated to mortality and risk of heart failure, the importance of endeavors for cardioprotective therapies to attenuate myocardial reperfusion injury and decrease infarct size remains undisputed. Myocardial reperfusion injury is the result of several complex nonlinear phenomena, and for a therapy to be effective, it should act on multiple targets involved in this injury. In this regard, hypothermia remains a promising treatment despite a number of negative randomized controlled trials in humans with acute myocardial infarction so far. To turn the tide for hypothermia in patients with acute myocardial infarction, sophisticated solutions for important limitations of systemic hypothermia should continue to be developed. In this review, we provide a comprehensive overview of the pathophysiology and clinical expression of myocardial reperfusion injury and discuss the current status and possible future of hypothermia for cardioprotection in patients with acute myocardial infarction.

**Key Words:** hypothermia ■ myocardial infarction ■ percutaneous coronary intervention ■ reperfusion

In ST-segment–elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) is currently the treatment of choice to restore blood flow to the ischemic myocardium and to limit infarct size (IS).<sup>1</sup> Subsequently, a decrease of IS translates to a lower rate of complications, such as heart failure and mortality.<sup>2</sup>

Paradoxically, revascularization of an occluded coronary artery in a patient with STEMI may also cause additional damage to cardiomyocytes that were still viable immediately before reperfusion. This myocardial reperfusion injury may undo a considerable part of the recovery of the ischemic myocardium achieved by primary PCI and consequently increases IS.<sup>3</sup> Most importantly, the major part of this reperfusion injury occurs within the first few minutes after reperfusion.<sup>3</sup>

The pathophysiology of myocardial reperfusion injury is still not completely understood. Multiple coexisting, interrelated, complex, and nonlinear phenomena occur

immediately after reperfusion with changes in biochemical processes and ultrastructure, resulting in irreversible damage of the initially surviving cardiomyocytes in the myocardium at risk (MaR), thereby annihilating part of the recovery.<sup>3</sup>

A major challenge in myocardial reperfusion injury is the translation of positive preclinical studies with experimental cardioprotective therapies to the clinical setting of patients with acute myocardial infarction (AMI). An important reason for failure in humans may be the fact that the cardioprotective strategies investigated are counteracting one of the multiple responsible mechanisms only.<sup>4</sup> Hypothermia acts upon multiple targets involved in reperfusion injury and thus seems to be a promising therapy.<sup>4</sup> In other organs, for example in ischemia-reperfusion brain injury after cardiac arrest, therapeutic hypothermia already proved to be effective, with reported target temperatures ranging from 33°C

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## Nonstandard Abbreviations and Acronyms

<b>AMI</b>	acute myocardial infarction
<b>CS</b>	cardiogenic shock
<b>IS</b>	infarct size
<b>MaR</b>	myocardium at risk
<b>MVO</b>	microvascular obstruction
<b>PCI</b>	percutaneous coronary intervention
<b>STEMI</b>	ST-segment–elevation myocardial infarction

to 36°C.<sup>5</sup> Unfortunately, for cardioprotection in patients with AMI, positive results of hypothermia have not been demonstrated yet.<sup>6–12</sup>

In this review, we discuss the clinical expression and pathophysiology of myocardial reperfusion injury and the role of therapeutic hypothermia for cardioprotection in patients with AMI.

## CLINICAL EXPRESSION AND PATHOPHYSIOLOGY OF MYOCARDIAL REPERFUSION INJURY

Myocardial reperfusion injury has been intensively investigated in many studies with controversial results. To understand the controversy, it is important to discuss its pathophysiology and clinical expression first.

Classically, myocardial reperfusion injury consist of 4 clinical features, that is, myocardial stunning, reperfusion-induced arrhythmias, the no-reflow phenomenon, and lethal myocardial reperfusion injury.<sup>3</sup> Since these undesirable phenomena mostly occur in the first minutes after reperfusion, it is suggestive that they are the result of reperfusion, confirming the true existence of myocardial reperfusion injury.

### Myocardial Stunning

In the absence of reperfusion, the ischemic myocardium will get infarcted as a result of necrosis of cardiomyocytes. In such case, the MaR will become infarcted almost completely (Figure 1). By timely revascularization, part of the MaR will be salvaged because not all cardiomyocytes at risk have been irreversibly injured yet (Figure 1).<sup>13</sup> However, because of (reversible) abnormalities in biochemical processes and ultrastructure, part of the salvaged myocardium is unable to fulfill its contractile function for a prolonged period after reperfusion, despite return of normal or near-normal perfusion.<sup>14</sup> This is called myocardial stunning and can be observed in >50% of patients with STEMI who are treated with reperfusion therapy.<sup>15</sup> Although myocardial stunning is transient in nature, it may contribute to the development of heart failure in the

acute phase of AMI. Myocardial stunning increases the risk of cardiogenic shock (CS). Application of vasopressors and inotropes can be considered to maintain tissue perfusion. In case of refractory CS, mechanical circulatory assist devices can be used in selected cases as a bridge to recovery. In most patients, this stunned myocardium recovers within 2 weeks, regaining its contractile function.<sup>15</sup>

### Reperfusion-Induced Arrhythmias

The electrical changes seen after reperfusion include ventricular arrhythmias and are potentially harmful.<sup>16</sup> Although infrequent and often self-terminating, these ventricular arrhythmias occasionally require treatment with antiarrhythmic drugs and defibrillation.<sup>17</sup>

Historically, accelerated idioventricular rhythm was considered an encouraging sign, indicating the moment of reperfusion. It is the most frequent arrhythmia seen during primary PCI and is observed in >50% of patients with reperfused STEMI.<sup>18</sup> Nowadays, it is believed to be an expression of myocardial reperfusion injury and is adversely correlated to IS.<sup>18</sup>

### No-Reflow Phenomenon

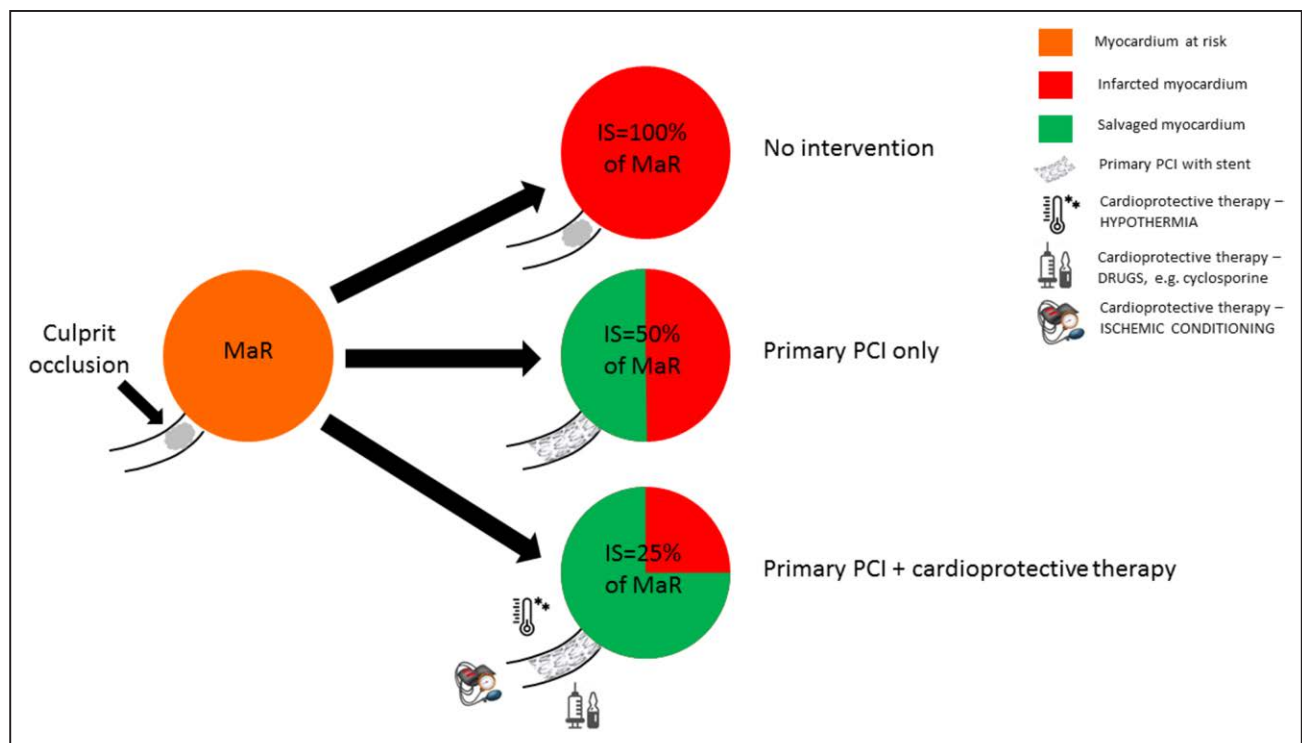
It is hypothesized that the no-reflow phenomenon, observed after reperfusion, is caused by interstitial edema and obstructive swelling of endothelial cells resulting in compression of the microvasculature. Together with the infiltration and capillary plugging of leukocytes, this may further impair microvascular blood flow.<sup>19</sup> Consequently, the terminology no-reflow phenomenon and microvascular obstruction (MVO) are often used interchangeably.

Currently, MVO is easily detectable *in vivo* by cardiovascular magnetic resonance imaging, using late gadolinium enhancement imaging.<sup>20</sup> MVO appears as unenhanced areas within the core of the contrast-enhanced regions (Figure 2). MVO is associated with worse prognosis, and therefore, it should be considered as an undesirable phenomenon after reperfusion, occurring in more than half of patients with reperfused STEMI.<sup>21</sup>

### Lethal Myocardial Reperfusion Injury

The cell death of cardiomyocytes that were still viable immediately before reperfusion is known as lethal myocardial reperfusion injury.<sup>3</sup>

During ischemia, the oxygen-depleted cardiomyocytes will switch to anaerobic glycolysis, resulting in ATP depletion and the accumulation of lactate.<sup>22</sup> Immediately after reperfusion, a quick restoration of the intracellular pH causes opening of the mitochondrial permeability transition pore, a key feature of myocardial reperfusion injury<sup>23</sup> (Figure 3). The opening of the mitochondrial permeability transition pore depolarizes the mitochondrial membrane



**Figure 1.** If in case of acute myocardial infarction, the occluded coronary artery is left untreated, the myocardium at risk (MaR) will almost entirely be infarcted.

Through early revascularization by primary percutaneous coronary intervention (PCI)  $\approx 50\%$  of the MaR will be salvaged. By adding a particular cardioprotective therapy, for example, hypothermia, a further decrease of infarct size (IS), up to 50%, has been observed in experimental studies.

and uncouples oxidative phosphorylation, resulting in progressive ATP depletion<sup>23–25</sup> (Figure 3).

Due to supraphysiological levels of intracellular calcium, caused by reactive oxygen species induced damage to the sarcoplasmic reticulum, hypercontracture of the myofibrils can be observed after reperfusion<sup>3,26</sup> (Figure 3). The latter, in combination with a state of ATP depletion, may result in cell death of myocytes that initially survived ischemia. This results in an increase of IS.<sup>3</sup>

Preclinical cardioprotection studies suggest that lethal myocardial reperfusion injury may account for up to 50% of the final IS.<sup>3</sup>

## LIMITING MYOCARDIAL REPERFUSION INJURY

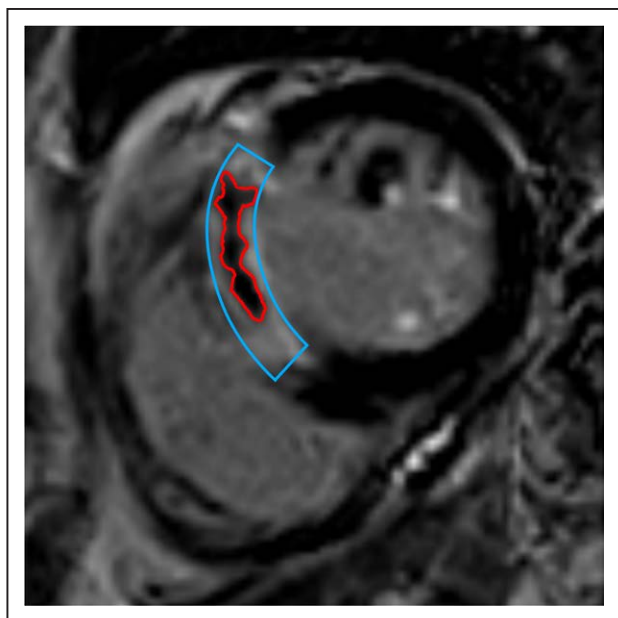
When considering whatever methodology to reduce myocardial reperfusion injury, it is paramount to realize that such injury occurs for the major part in the first minutes after reperfusion has been established.<sup>3,4</sup> Therefore, for a cardioprotective therapy to be effective and enhance myocardial salvage, 2 important issues should be taken into consideration. First, the agent or therapy should be administered before reperfusion. Second, administration should be distal to the occlusion in the coronary artery instead of systemic, to actually reach the MaR where it must deploy its protective effects.

A number of therapeutic approaches have been investigated to attenuate myocardial reperfusion injury.<sup>3,4</sup> These include intravenous administration of drugs (eg, cyclosporine and adenosine) before reperfusion by primary PCI, ischemic preconditioning and postconditioning (whether or not remote) and systemic hypothermia. For all of these approaches, favorable outcome has been described experimentally but none of them proved to decrease IS in prospective randomized controlled trials in humans, most likely because the above-mentioned issues were insufficiently met. This is also the case with systemic hypothermia, as will be discussed below.

## HYPOTHERMIA AND MYOCARDIAL REPERFUSION INJURY

The understanding of the cardioprotective effects of hypothermia is mainly extrapolated from experimental studies and from the use of hypothermia for other indications, for example, in ischemia-reperfusion brain injury after cardiac arrest or for cardioprotection during cardiac surgery, although the mechanisms might be different.

Initially, the cardioprotective effect of hypothermia was considered to be a direct consequence of reduced metabolism and energy preservation. Although the latter may well be true, hypothermia does not decrease the accumulation of intracellular lactate.<sup>27,28</sup> By treatment



**Figure 2.** An example of a cardiovascular magnetic resonance imaging study (late gadolinium enhancement sequence) of a patient with large anterior wall ST-segment-elevation myocardial infarction after reperfusion from the ongoing EURO-ICE study (European Intracoronary Cooling Evaluation in Patients With STEMI).

In the core of the contrast-enhanced region (traced in blue), an unenhanced area can be observed (traced in red), corresponding to microvascular obstruction.

with hypothermia, the prohibitory effect of a lower pH on mitochondrial permeability transition pore opening would still be present, accompanied by preservation of ATP. Hypothermia affects multiple signaling pathways (eg, Akt) and decreases the release of reactive oxygen species during ischemia and upon reperfusion.<sup>29–31</sup> Importantly, less cytosolic calcium and mitochondrial calcium overload is observed.<sup>32</sup> Ultimately, hypothermia would preserve mitochondrial function and prevent the hypercontractile state of the myofibrils.

### Myocardial Stunning and Hypothermia

Myocardial contractility in general and occurrence of stunning, in particular, are influenced by temperature in both positive and negative ways. In case of mild hypothermia (32 °C–35 °C), myocardial contractility is better preserved directly after reperfusion.<sup>28,33</sup> A further drop in myocardial temperature in case of severe hypothermia (20 °C–28 °C) results in a significant depression of left ventricular function and myocardial contractility.<sup>34</sup> In the SHOCK-COOL trial (Mild Hypothermia in Cardiogenic Shock Complicating Myocardial Infarction), patients with CS undergoing primary PCI were randomized to (systemic) mild therapeutic hypothermia (33 °C) or control with no difference in both cardiac power index (has strong correlation with mortality in CS) and mortality (overall 55%).<sup>35</sup>

Unfortunately, imaging outcome parameters were not available. It would be of interest to determine recovery of left ventricular function over time in hypothermia-treated survivors of patients with STEMI complicated by CS.

### Reperfusion-Induced Arrhythmias and Hypothermia

Hypothermia increases the chance of self-termination of ventricular tachycardia/fibrillation.<sup>36</sup> This becomes even more clear in case of regional hypothermia. In isolated Langendorff-perfused rabbit hearts, 48% versus 0% of sustained ventricular tachycardia's self-terminated in hypothermia-treated hearts compared with controls, respectively.<sup>37</sup> Figure 4 demonstrates the effect of regional hypothermia on ventricular arrhythmias in a patient from the ongoing EURO-ICE trial (European Intracoronary Cooling Evaluation in Patients With STEMI; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03447834).<sup>38</sup> The beat-to-beat heart rate of a patient with anterior wall STEMI during primary PCI is displayed along with the simultaneously recorded intracoronary temperature. During hypothermia, a decrease of ventricular tachyarrhythmia's could be detected. The interaction becomes even more pronounced after rewarming, at which point the ventricular tachyarrhythmia's quickly reappear.

In contrast, in closed-chest anesthetized landrace pigs, systemic hypothermia rendered the atria more susceptible to atrial fibrillation.<sup>39</sup> Moreover, this effect has also been observed in the COOL AMI EU pilot trial (A Multicenter, Prospective, Randomized Controlled Trial To Assess Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients With Acute Myocardial Infarction).<sup>11</sup>

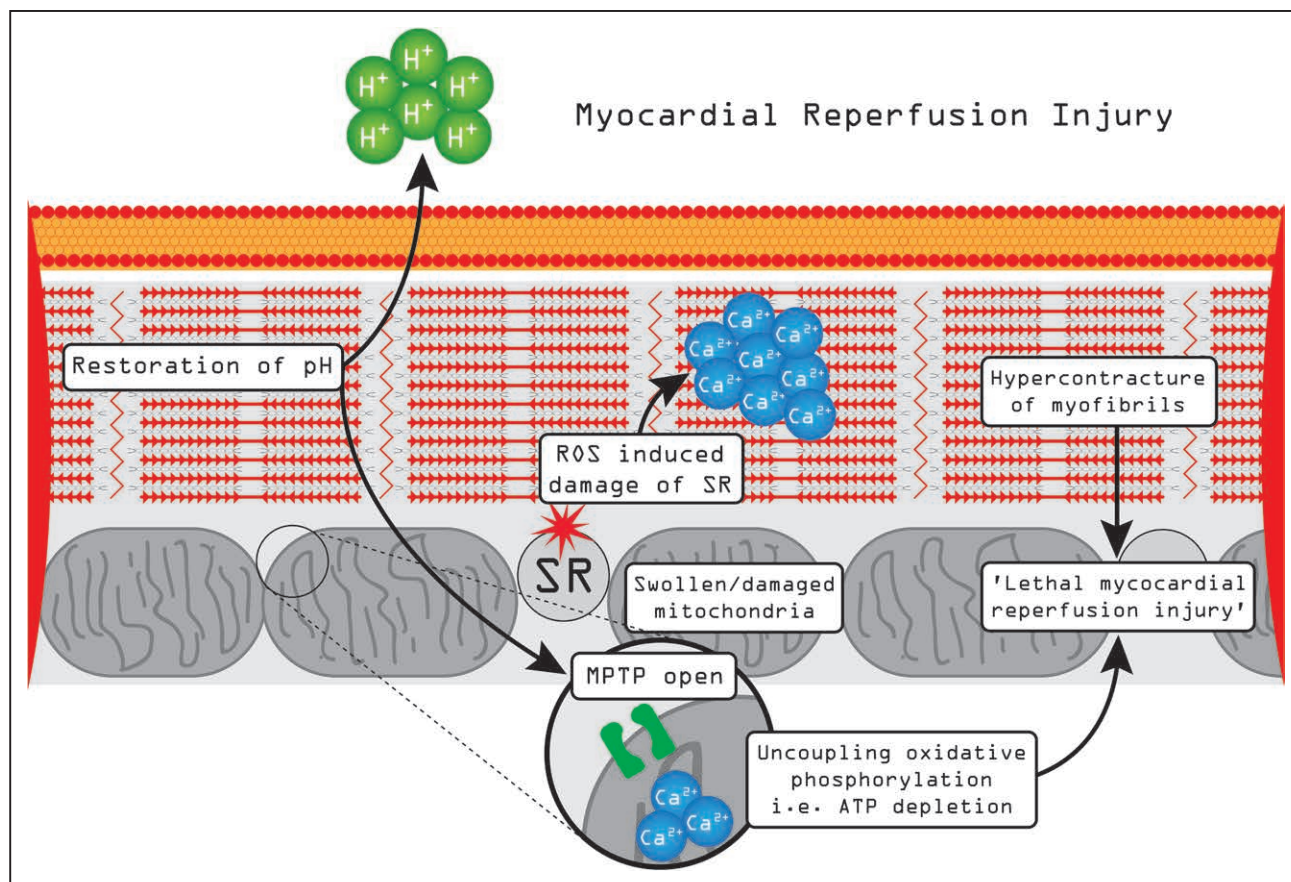
### No-Reflow Phenomenon and Hypothermia

The microvasculature is sensitive to the protective effects of hypothermia. Although it is not clear yet whether this is solely the result of limiting edema or if it is more complex, in preclinical studies of an AMI model, it has been well demonstrated that hypothermia attenuates MVO.<sup>40,41</sup> As with IS, this effect of hypothermia has not yet been confirmed in humans (Table).

### Lethal Myocardial Reperfusion Injury and Hypothermia

Many animal studies already demonstrated a decrease of IS in AMI models, when treated with hypothermia.<sup>40,42,43</sup> However, such results could not be confirmed in randomized controlled trials involving patients with AMI (Table). The limitations of these studies will be discussed below.





**Figure 3. Pathophysiology of myocardial reperfusion injury. Ultimately, ATP depletion and hypercontracture of myofibrils result in lethal myocardial reperfusion injury.**

Ca<sup>2+</sup> indicates calcium ion; H<sup>+</sup>, hydrogen ion; MPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species; and SR, sarcoplasmic reticulum.

## LIMITATIONS OF PREVIOUS HYPOTHERMIA TRIALS

At least 6 randomized controlled trials have studied hypothermia for AMI, which were all negative for the primary end point, either IS or IS/MaR (Table). Only a patient-level pooled meta-analysis by Dae et al<sup>44</sup> demonstrated an absolute reduction of IS by 6.5% (relative reduction of 30%) in a subgroup of patients with anterior wall infarction, cooled to <35°C before reperfusion. It can, therefore, still be hypothesized that hypothermia could decrease IS, as also evidenced by experimental studies, if at least a number of limitations and pitfalls can be overcome.

What then, are the fundamental differences in this respect between experimental and human studies? Why does hypothermia work in animals and not in humans? All studies investigating systemic hypothermia in humans with AMI were fundamentally limited because of one or more of the following reasons:

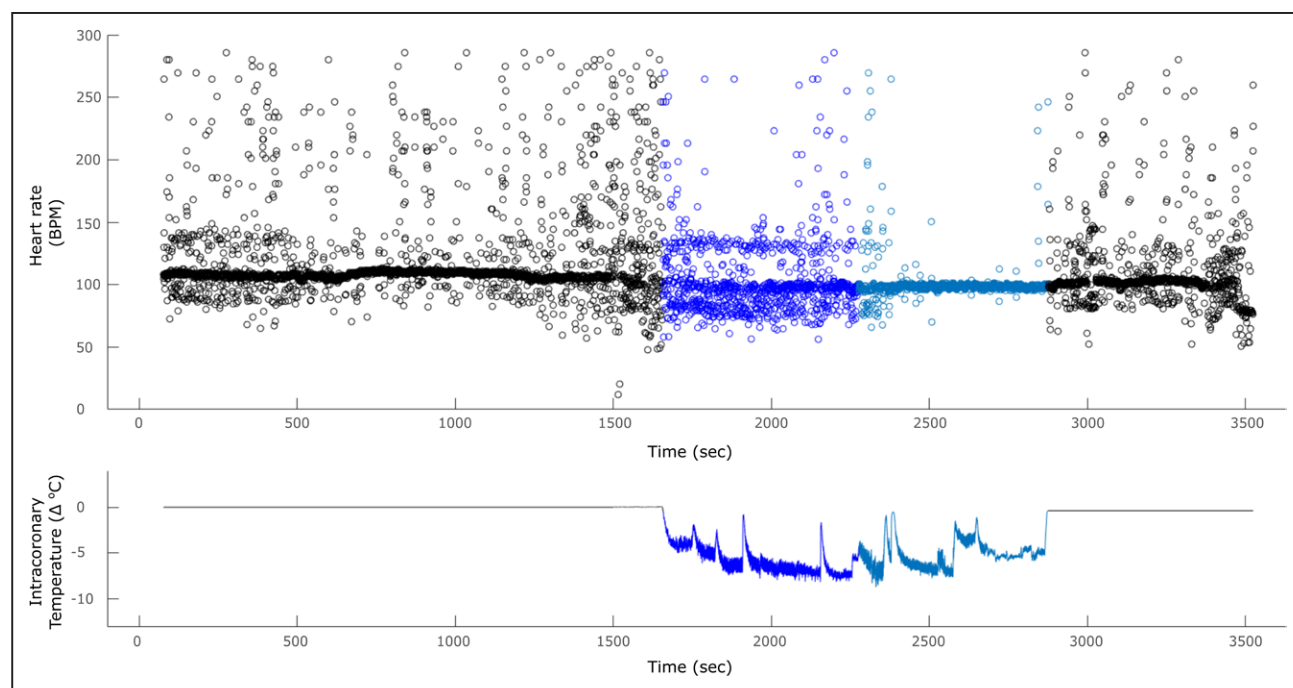
1. Inability to cool fast enough, that is, before reperfusion and without delaying reperfusion too long, so that ischemic time is increased only minimally. It is obvious that cooling methods, that intent to cool

the entire body are by definition time consuming. Although endovascular cooling is much faster than surface cooling, this delay is at the expense of the benefit achieved by hypothermia.

2. Inability to reach the target temperature. In some patients, the target temperature was not reached before reperfusion or not at all.<sup>9,10</sup>
3. Inability to cool the MaR selectively. In fact, with any systemic approach, the whole body is cooled but no direct cooling occurs where it is most needed, that is, the myocardium distal to the occluded artery.
4. Side effects due to systemic hypothermia, for example, shivering that necessitates the need for antishivering medication in all patients,<sup>6,8-11</sup> atrial arrhythmia,<sup>11</sup> and enhanced adrenergic response due to hypothermia-induced catecholamine release.<sup>45,46</sup>

Beside these conceptual limitations of systemic hypothermia, other practical aspects may also have contributed to the failure of hypothermia trials in AMI so far:

5. All studies investigating systemic hypothermia, included patients without knowing Thrombolysis in Myocardial Infarction grade flow since it was obliged to start cooling before the angiogram was performed. Therefore, up to 30% of patients



**Figure 4. Beat-to-beat heartrate (measured through the R-R interval with the previous heartbeat) during primary percutaneous coronary intervention in combination with selective intracoronary hypothermia of a patient with large anterior wall ST-segment-elevation myocardial infarction (STEMI) from the ongoing EURO-ICE study (European Intracoronary Cooling Evaluation in Patients With STEMI).**

During the hypothermic interval (blue/turquoise), a remarkable decrease of the fast heartrates, that is, ventricular tachyarrhythmia's, can be observed. After termination of the hypothermia protocol and the temperature restores to normal, the ventricular tachyarrhythmia's quickly reappear.

with AMI were included in whom reperfusion had already occurred.<sup>6,8–11</sup> Since myocardial reperfusion injury occurs in the first minutes after reperfusion, a potential effect of hypothermia in these patients could not be expected.

- Wrong assumptions for calculation of study power. Due to an overestimation of the presumed effect of hypothermia on IS, too few patients were enrolled to demonstrate a significant decrease of IS.<sup>6,8,10–12</sup>

These limitations may explain why randomized controlled trials do not support the use of systemic hypothermia as a way of cardioprotection in patients with AMI.

## HOW TO CONTINUE WITH HYPOTHERMIA IN AMI

One of the fundamental ideas presented in this review is that reperfusion induces an (uncontrolled) inflammatory response, intended to promote healing but unfortunately exceeding its goal which leads to inflow and sequestration of leucocytes, release of damaging reactive oxygen species and intracellular and interstitial edema.

Hypothermia to reduce myocardial reperfusion injury is very logical since it implicates multiple anti-inflammatory characteristics. This is supported by numerous experimental studies. Among others, hypothermia targets the inflammation, limits edema and thereby

no-reflow, it decreases release of reactive oxygen species and decreases metabolic demand of critically ischemic myocardium. In AMI, the translation of experimental data to humans is cumbersome however, and to be successful, the earlier mentioned limitations should be overcome.

Recently, a new method of selective intracoronary hypothermia was developed.<sup>47,48</sup> Selective intracoronary hypothermia overcomes most of the earlier mentioned limitations of systemic hypothermia. By infusing saline (room temperature, 22 °C) distal to the occlusion through the central lumen of an inflated over-the-wire balloon, the MaR is selectively cooled off without affecting the adjacent healthy myocardium. While the MaR is cooled off by 4 °C to 6 °C below body temperature, the immediately adjacent myocardium only has a temperature decrease of 0.2 °C.<sup>47</sup> After 7 to 10 minutes, the balloon is deflated, and reperfusion in the (cooled) myocardium is allowed while infusion continues for 10 minutes with cold saline (3 °C) to compensate for the recovered warm blood flow.

In the ongoing EURO-ICE trial, which is a European multicenter, randomized controlled, proof-of-principle study, the effect of selective intracoronary hypothermia during primary PCI is being investigated in patients with anterior wall STEMI.<sup>38</sup>

Although we believe that selective intracoronary hypothermia is the logical next step in the evolution of

**Table. Schematic Overview of Published Systemic Hypothermia Trials in Humans With Acute Myocardial Infarction**

Study (year)	No. of patients	Anterior MI (% of total)	Hypothermia technique	Target temperature	No. of patients achieving target temperature (% of hypothermia arm)	No. of patients with TIMI flow grade 2 or 3 at initial angiography (% of hypothermia arm)	Imaging modality	Infarct size-hypothermia vs control in % of LVM (P value)	MVO-hypothermia vs control in % of LVM (P value)
COOL-MI I pilot <sup>6</sup> (2002)	42	19 (45)	Endovascular	33°C	21 (100)	5 (24)	SPECT	2 vs 8 (P=0.80)	N/R*
NICAMI <sup>7</sup> (2005)	9	3 (33)	Surface	34.5°C	9 (100)	2 (22)	SPECT	23†	N/R*
RAPID-MHCE <sup>8</sup> (2010)	20	13 (72)	Endovascular+cold saline infusion	33°C	9 (90)	2 (20)	CMR	13.7 vs 20.5 (P=0.08) 29.8 vs 48.0‡ (P=0.041)	0.8 vs 1.9 (P=0.24)
CHILL-MI <sup>9</sup> (2014)	120	51 (42)	Endovascular +cold saline infusion	33°C	46 (76)	7 (11)	CMR	40.5 vs 46.6‡ (P=0.15)	0.26 vs 0.12 (P=0.79)
VELOCITY <sup>10</sup> (2015)	54	25 (46)	Peritoneal lavage	32.5°C	24 (85)	5 (18)	CMR	17.2 vs 16.1 (P=0.54) 67.3 vs 55.8‡ (P=0.36)	0 vs 0 (P=0.64)
COOL AMI EU pilot <sup>11</sup> (2017)	50	50 (100)	Endovascular+cold saline infusion	32°C	23 (92)	2 (8)	CMR	16.7 vs 23.8 (P=0.31)	2.2 vs 2.5 (P=0.96)
COOL-MI InCor <sup>12</sup> (2020)	50	19 (38)	Endovascular+cold saline infusion	32°C	35 (100)	5 (10)	CMR	13.9 vs 13.8 (P=0.801)	N/R*

CHILL-MI indicates Rapid Endovascular Catheter Core Cooling Combined With Cold Saline as an Adjunct to Percutaneous Coronary Intervention For the Treatment of Acute Myocardial Infarction; CMR, cardiovascular magnetic resonance; COOL AMI EU, A Multicentre, Prospective, Randomised Controlled Trial to Assess Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients With Acute Myocardial Infarction; COOL-MI, Induction of Mild Systemic Hypothermia With Endovascular Cooling During Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction; COOL-MI InCor, Cooling as an Adjunctive Therapy to Percutaneous Intervention in Acute Myocardial Infarction; COOL-MI InCor Trial, LVM, left ventricular mass; MI, myocardial infarction; MVO, microvascular obstruction; NICAMI, A Pilot Study: The Noninvasive Surface Cooling Thermoregulatory System for Mild Hypothermia Induction in Acute Myocardial Infarction; RAPID-MHCE, A Pilot Study of Rapid Cooling by Cold Saline and Endovascular Cooling Before Reperfusion in Patients With ST-Elevation Myocardial Infarction; SPECT, single photon emission computed tomography; TIMI, Thrombolysis in Myocardial Infarction; and VELOCITY, Prospective, Multicenter, Randomized, Controlled Pilot Trial of Peritoneal Hypothermia in Patients With ST-Segment-Elevation Myocardial Infarction.

\*Not reported.

†No control arm in study.

‡Infarct size as a percentage of myocardium at risk.



therapeutic hypothermia in AMI during primary PCI, we are aware of the uncertainties that still remain. The duration and depth of cooling to attenuate myocardial reperfusion injury are still unclear, and this obviously needs clarification to make hypothermia more effective. If prolonged duration of hypothermia seems necessary, additional methods beyond the procedure of primary PCI itself should be developed and studied. This can be done by prolonged cooling itself or by adding pharmacological stimuli with a comparable effect to hypothermia, the so-called hypothermia in a syringe,<sup>49</sup> the latter route of course being the most practical from a clinical point of view.

Although selective hypothermia might be promising, it should be considered that its effects could be further enhanced by combining it with other cardioprotective therapies, such as administration of intracoronary anti-inflammatory drugs (easily to combine with the intracoronary cold saline infusion), preconditioning and postconditioning or left ventricular unloading before reperfusion. Further studies on such combinations are mandatory to clarify this position.

Either way, it is paramount in this respect that any additional drug should be present in the MaR before reperfusion injury occurs.

## CONCLUSIONS

A further decrease of IS in patients with AMI as an adjunct therapy to primary PCI, can be accomplished if myocardial reperfusion injury is attenuated. Hypothermia, although hampered so far by conflicting results between experimental and human studies, remains a promising therapy to decrease IS because it acts on multiple targets involved in myocardial reperfusion injury. To close this translational gap, the importance of endeavors to find new approaches that overcome the conceptual and practical limitations of current cooling techniques remains undisputed.

## ARTICLE INFORMATION

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### Disclosures

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