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Intracoronary Hypothermia Before Reperfusion to Reduce Reperfusion Injury in Acute Myocardial Infarction: A Novel Hypothesis and Technique

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Because current reperfusion strategies in acute myocardial infarction (AMI) seem to be exhausted in terms of additional mortality benefit, there remains a need for new methods to attenuate reperfusion injury and, thereby, further reduce myocardial infarct size and improve long-term survival. Therapeutic hypothermia (32–35°C) diminishes reperfusion injury and reduces infarct size in a variety of animal models of AMI if provided before reperfusion. In human studies this reduction has not been confirmed so far, most likely because systemic cooling acts slowly, and therefore, the target temperature is not reached in time or at all in a substantial number of patients. Furthermore, systemic cooling can cause adverse effects such as severe shivering, volume overload, and an enhanced adrenergic state. In most randomized clinical trials, however, subgroups of patients with anterior myocardial infarction that reached the target temperature before reperfusion did show a reduction in infarct size. To transform therapeutic hypothermia into a clinically feasible treatment for AMI, its method must be modified. An ideal technique should be quick enough to achieve sufficient myocardial hypothermia before reperfusion, without significant delay and without the adverse effects of systemic cooling. In this review, we propose a novel, potentially feasible method of selective intracoronary hypothermia to overcome the problems encountered with prior techniques.

Keywords: intracoronary hypothermia, primary percutaneous coronary intervention, myocardial reperfusion injury, acute myocardial infarction

Introduction

IN THIS REVIEW we propose a novel hypothesis and introduce a new technique regarding therapeutic hypothermia in patients with acute myocardial infarction (AMI). Our theory explains the negative results in prior randomized trials in humans and leads naturally to a new method with the potential to overcome previous limitations. Importantly, the method proposed in this study can be performed within the routine of primary percutaneous coronary intervention (PPCI) and with standard PCI equipment.

Damage to the myocardium in AMI results from two processes that share several harmful mechanisms: acute ischemic injury on the one hand and subsequent myocardial reperfusion injury on the other hand (Fordyce *et al.*, 2015). Therapies to reduce acute ischemic injury, primarily by PPCI, have significantly improved the prognosis of patients

with AMI and have been widely incorporated into clinical practice (American College of Emergency Physicians *et al.*, 2013). However, given the plateau in outcomes after AMI, these gains seem to have been exhausted (Kapur and Karas, 2015). Consequently, attention must naturally shift to therapies targeting myocardial reperfusion injury to obtain further reductions in infarct size. The motivation for improving care is clear, as coronary artery disease, especially AMI, remains the leading cause of death in the world (Nabel and Braunwald, 2012; Go *et al.*, 2014). In AMI patients, infarct size relates directly to short- and long-term mortality and to the development of chronic heart failure (Kaul *et al.*, 2013; Stone *et al.*, 2016). Therefore, limiting infarct size is of paramount importance.

Despite a large number of successful animal studies in recent years using cardioprotective strategies to reduce myocardial reperfusion injury, translation to clinical practice

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has been difficult and has failed so far (Apex Ami Investigators *et al.*, 2007; Kim *et al.*, 2010; Voors *et al.*, 2010; Ludman *et al.*, 2011; Selker *et al.*, 2012; Lincoff *et al.*, 2014; Cung *et al.*, 2015). The reasons for failure are unique to each strategy, and in this study we focus our attention on therapeutic hypothermia.

We start with a general review of therapeutic hypothermia in AMI before turning attention to our novel hypothesis and method of locally delivered and controlled myocardial cooling before reperfusion.

Hypothermia in Acute Myocardial Infarction

In AMI final damage to the myocardium equals necrosis during vessel occlusion plus injury induced by the subsequent reperfusion. Myocardial reperfusion injury refers to cardiomyocyte death that paradoxically results from reperfusion of the jeopardized myocardium and may account for 25–50% of the final infarct size (Yellon and Hausenloy, 2007; Frohlich *et al.*, 2013). Currently there exists no effective therapy for preventing myocardial reperfusion injury in patients with AMI, making it a plausible therapeutic target for novel cardioprotective strategies (Cung *et al.*, 2015).

Hypothermia may blunt the damaging processes that occur during reperfusion injury. As opposed to pharmacological therapy that targets one specific pathway, hypothermia has simultaneous effects on multiple pathways involved in reperfusion injury (Herring *et al.*, 2014; Chavez *et al.*, 2017). Adequate myocardial hypothermia results in reduction of microvascular obstruction or no-reflow (Gotberg *et al.*, 2008; Hale *et al.*, 2013), inhibition of mPTP opening by adenosine triphosphate repletion, attenuation of reactive oxygen species formation, and induction of signal transduction pathways (Hausenloy *et al.*, 2002; Tissier *et al.*, 2012). Moreover, in the reperfusion phase hypothermia activates survival kinases (Akt) and heat-shock proteins (HSP27), thereby reducing the reperfusion-induced cell destruction phase (Ning *et al.*, 2007; Shao *et al.*, 2010).

In animal models of coronary artery occlusion and reperfusion, hypothermia has reliably and markedly reduced myocardial infarct size when initiated during myocardial ischemia but before the onset of reperfusion (Chien *et al.*, 1994; Hale and Kloner, 1997, 1998; Hale *et al.*, 1997, 2003; Kim *et al.*, 2005; Otake *et al.*, 2007; Gotberg *et al.*, 2008; Tissier *et al.*, 2009, 2012; Dai *et al.*, 2015; Herring *et al.*, 2015). Furthermore, there appears to be a relationship between the onset of hypothermia and the reduction in infarct size, varying from a 100% reduction if started before the onset of ischemia to no reduction if initiated after reperfusion (Maeng *et al.*, 2006; Gotberg *et al.*, 2008). These results suggest that hypothermia attenuates myocardial injury already in the ischemic (prereperfusion) phase. Hypothermia started at the onset of reperfusion (postreperfusion) phase did show an improvement in microvascular resistance thereby limiting no-reflow, but did not lead to a reduction in infarct size (Gotberg *et al.*, 2008; Hale *et al.*, 2013).

In summary, while hypothermia seems to be effective in limiting infarct size if achieved before reperfusion, much uncertainty exists with respect to its timing and the interval during which hypothermia should be continued. However, it can be concluded that at the moment of reperfusion, the myocardium of interest should be sufficiently cooled and this cooling should be continued until reperfusion is completed.

From theory to practice: human studies involving hypothermia

Despite significant myocardial salvage in animal studies, human studies in AMI have been negative so far (Villablanca *et al.*, 2016). This failure of translation seems to be due to a number of practical limitations that have hampered studies to reveal the true value of hypothermia to limit infarct size in humans.

In human studies different systemic cooling methods have been used, including endovascular cooling, infusion of cold saline, surface cooling, and intraperitoneal methods (Villablanca *et al.*, 2016). All these methods have four significant drawbacks. First, systemic cooling methods cannot guarantee that hypothermia will directly reach the endangered myocardium on time or at all, since the epicardial artery supplying that region is obstructed.

Second, systemic delivery of hypothermia can induce severe discomfort and shivering in conscious patients requiring sedative medications and artificial ventilation with their associated disadvantages. Furthermore, systemic hypothermia may enhance the adrenergic state, which increases systemic oxygen consumption maintaining the ischemic cycle (Polderman, 2009).

Third, since humans have a large body mass, reaching a systemic target temperature of 4°C below body temperature not only requires a relatively long time, and therefore unacceptably prolongs symptom-to-reperfusion time, but also requires a large amount of cold fluid to cool the whole body, potentially leading to pulmonary edema in a hemodynamically compromised patient. Exploratory *post hoc* analysis and a meta-analysis of hypothermia trials found that the small subgroup of patients who were cooled to a temperature of <35°C before reperfusion experienced a significant reduction in infarct size (Villablanca *et al.*, 2016). Since there is a clear benefit with lower temperatures in terms of reduction of infarct size, most likely the lowest effective temperature is preferable, within the safe zone. That goal temperature should be achieved quickly, within minutes.

Fourth, the inability to monitor the distal temperature and titrate the therapy to a target level remains another severe barrier to translating animal models to human trials. At least some direct feedback on the temperature in the infarcted and cooled area is mandatory to guide adequate and safe treatment.

Future Directions

Synthesizing the above points, we can logically conclude that the following conditions are paramount for therapeutic hypothermia to enter clinical practice during the rapid and catheter-based modern treatment of AMI.

First, hypothermic protection must act at the location where harmful processes occur, namely within the infarct area, preferably not affecting the adjacent myocardium. The culprit and occluded coronary artery, however, may prevent local administration of hypothermia to the required territory and, thus, represents the first hurdle to be overcome. Second, the target temperature of the myocardium should be reached quickly and before the onset of reperfusion, that is, within minutes. Third, the application of hypothermia should be easy to apply within the routine practice of PPCI and not delay time to reperfusion too much. Fourth, and most importantly, the

degree of temperature decrease in the distal coronary artery and myocardium should be monitored precisely to prevent too low or insufficient hypothermia and to achieve a tissue temperature of $\sim 4^{\circ}\text{C}$ below body temperature.

Intracoronary hypothermia

To cool quickly and to overcome the adverse effects of systemic hypothermia, intracoronary administration of cold saline selectively to the infarct area appears both logical and necessary. Kim *et al.* (2005) described an intracoronary infusion of cold saline in pigs with AMI in 2005. In their study, no hemodynamic compromise or arrhythmia was observed, and a correlation between intracoronary and intramyocardial

temperature was established. Otake *et al.* (2007) showed an intracoronary infusion of cold saline to be safe and to reduce infarct size in a pig model of AMI. Application in humans of intracoronary cold saline infusion or other local hypothermia methods selectively to the infarct area has not been studied so far.

We recently evaluated the safety of intracoronary delivery of hypothermia by retrospectively analyzing data from two clinical trials in which intracoronary saline administration at room temperature was used to perform coronary flow measurements by thermodilution. Coronary temperature in these studies decreased by $0.5\text{--}6^{\circ}\text{C}$. No adverse effects, apart from short-lasting second degree atrioventricular block (AV-block) in a few patients with measurement in the RCA, were noted (Otterspoor *et al.*, 2016).

FIG. 1. Visualization of the infarct area by infrared camera before (*upper image*) and during (*lower image*) selective infusion of cold saline through the balloon catheter in the occluded coronary artery. During cold saline infusion the infarct area becomes hypothermic, while the adjacent myocardium is not affected as also confirmed by needle thermistors visible in the image (Otterspoor *et al.*, 2017).

FIG. 2. Schematic drawing of the setup used in the pilot study in humans. Through the infusion pump cold saline is administered through the lumen of an over-the-wire balloon (OTWB) catheter. The distal intracoronary temperature is closely monitored by a pressure/temperature wire in the distal coronary artery connected to an analyzer and adjustments to the flow of the cold saline can be made instantly.

Based upon these observations, we developed a clinically feasible method for induction and maintenance of therapeutic myocardial hypothermia using standard PCI equipment. This method was investigated first in the isolated beating pig heart (Otterspoor *et al.*, 2017).

In that study, an over-the-wire balloon (OTWB) was advanced over a regular guidewire and inflated to 4 atm in the coronary artery to create an occlusion. Thereafter, the regular guidewire was removed and an infusion of saline started through the central lumen of the balloon while the balloon remained inflated. An additional pressure/temperature wire was then placed in the distal coronary artery and used to monitor the intracoronary temperature, and thereby, also the temperature of the distal endangered myocardium. Simultaneously, coronary pressure distal to the occlusion was monitored to prevent pressure overload in the coronary artery and myocardium. It should be noted that, in an attempt to mimic physiological circumstances inside the human body, the isolated beating pig heart model was submerged in a warm water bath equaling body temperature. Moreover, the isolated beating pig heart model is a laboratory setup in which the heart is fully functional and achieves a cardiac output similar to “normal” conditions, in contrast to a Langendorff setup. Coronary blood flow is maximal in the nonoccluded coronary artery and myocardium adjacent to the infarct area. Therefore, we believe that heat exchange mimics the *in vivo* situation in humans. Using multiple needle thermistors placed under the guidance of infrared camera recordings, it was confirmed that hypothermia just acted locally within the myocardium at risk (Fig. 1). Simultaneously, to reach the target temperature of 4°C below body temperature throughout the infarct area, dose finding experiments determined an

FIG. 3. Graphs from a 56-year-old male patient who presented with an acute anterior myocardial infarction and who was treated with intracoronary hypothermia. Cooling took place both for 10 minutes before opening the left anterior ascending arterial occlusion (occlusion phase) and also for 10 minutes after opening (reperfusion phase). The *upper part* of the figure indicates the stable systemic (red) and distal coronary pressures (green). The *lower part* shows the distal intracoronary temperature (blue). An intracoronary blood temperature of 6°C below body temperature was reached within 30 seconds and remained stable during the whole duration of the treatment protocol (20 minutes). The two spikes in the temperature curve just after 600 seconds are due to the changing of the saline from room temperature to 4°C.

infusion flow of 30 mL/min with an infusate temperature of 20°C during the occluded vessel phase and 4°C during the open vessel phase.

Following these findings in the beating pig heart, we started conducting a clinical pilot study in patients with AMI to evaluate the safety and feasibility of this novel technique (SINTAMI, ClinicalTrials.gov identifier NCT02753478). In contrast to previous human studies, the infusion of saline was selective and only local into the infarct area, thereby preventing the systemic effects of hypothermia. Using an inflated OTWB, reperfusion can be delayed while saline at room temperature is infused to cool the infarct area. During this occlusion phase saline at 20°C was infused for 10 minutes. Hereafter, the balloon was deflated allowing reperfusion with blood, and the temperature of the infused saline was lowered to 4°C because of the mixing with blood. This reperfusion phase also lasted for 10 minutes after which a stent was placed. The interventional team used a pressure/temperature wire to control the intracoronary temperature and titrate the infusion rate in real time during the procedure (Fig. 2). In contrast with the beating pig heart model, the infusion rate during the occlusion phase was started at 20 mL/min. This is because we observed that with 30 mL/min the coronary temperatures were often too low. Figure 3 shows a temperature curve of a subject enrolled in this study demonstrating the very fast induction and maintenance of the target intracoronary temperature.

Possible weaknesses of the intracoronary method

First, a possible complication of the intracoronary method could be the induction of AV-block due to hypothermia of the AV-node in patients with a right coronary artery occlusion. In the beating pig heart model, we only studied hearts with occlusions of left anterior descending artery. Second, another potential complication of selective intracoronary hypothermia through coronary infusion is the embolization of thrombus distal to the occlusion.

Third, applying the intracoronary method in the catheterization laboratory has to be feasible and should be easy to perform without significantly delaying the opening of the vessel. Fourth, important in its possible infarct reducing properties is the fact that the infarct area has to be cooled off before the start of reperfusion. Therefore, any reperfusion by passing the guidewire through the stenosis should be prevented or shortened by inflating the OTWB as soon as possible.

Fifth, during reperfusion, it is unknown how long hypothermia needs to be maintained for maximal benefit. It will be unrealizable to apply intracoronary infusion for hours after reperfusion.

We realize that it goes against the fundamental principle of “time is muscle” to intentionally delay symptom-to-reperfusion time for 10 minutes to achieve and maintain adequate cooling. However, this delay might be counterbalanced by the potentially beneficial effect of cooling. Considering these factors together, we expect that intracoronary hypothermia implicates an opportunity to decrease the infarct size compared to present standard therapy by PPCI alone.

Summary

Therapeutic hypothermia may attenuate reperfusion injury in patients with AMI if the target temperature is achieved

within the endangered myocardium before reperfusion starts. Using this technique most of the damaging processes that occur during reperfusion may be mitigated. Future studies should therefore use methods that lower the myocardial temperature quickly enough to reach the therapeutic target (4°C below body temperature) before the onset of reperfusion, while not prolonging time to reperfusion significantly and without inducing systemic side effects. This novel intracoronary method to deliver and control hypothermia selectively in the endangered myocardium seems logical, promising, safe, and feasible during PPCI and is already being further developed and explored.

Author Disclosure Statement

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