A Pilot Study of Rapid Cooling by Cold Saline and Endovascular Cooling Before Reperfusion in Patients With ST-Elevation Myocardial Infarction

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Background—Experimental studies have shown that induction of hypothermia before reperfusion of acute coronary occlusion reduces infarct size. Previous clinical studies, however, have not been able to show this effect, which is believed to be mainly because therapeutic temperature was not reached before reperfusion in the majority of the patients. We aimed to evaluate the safety and feasibility of rapidly induced hypothermia by infusion of cold saline and endovascular cooling catheter before reperfusion in patients with acute myocardial infarction.

Methods and Results—Twenty patients with acute myocardial infarction scheduled to undergo primary percutaneous coronary intervention were enrolled in this prospective, randomized study. After 4±2 days, myocardium at risk and infarct size were assessed by cardiac magnetic resonance using T2-weighted imaging and late gadolinium enhancement imaging, respectively. A core body temperature of <35°C (34.7±0.3°C) was achieved before reperfusion without significant delay in door-to-balloon time (43±7 minutes versus 40±6 minutes, hypothermia versus control, P=0.12). Despite similar duration of ischemia (174±51 minutes versus 174±62 minutes, hypothermia versus control, P=1.00), infarct size normalized to myocardium at risk was reduced by 38% in the hypothermia group compared with the control group (29.8±12.6% versus 48.0±21.6%, P=0.041). This was supported by a significant decrease in both peak and cumulative release of Troponin T in the hypothermia group (P<0.01 and P<0.03, respectively).

Conclusions—The protocol demonstrates the ability to reach a core body temperature of <35°C before reperfusion in all patients without delaying primary percutaneous coronary intervention and that combination hypothermia as an adjunct therapy in acute myocardial infarction may reduce infarct size at 3 days as measured by MRI.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00417638.
(Circ Cardiovasc Interv. 2010;3:400-407.)

Key Words: hypothermia • myocardial infarction • MRI

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The 2 major clinical trials investigating mild hypothermia using endovascular cooling catheters as an adjunct therapy in AMI failed to show a reduction in IS.13,14 Post hoc analysis of the data in those trials have shown that only a minority of patients were hypothermic at onset of reperfusion, and the subgroup of patients who were cooled to a temperature of <35°C before reperfusion did have a significant reduction in IS. These findings are supported by experimental data showing that hypothermia, accomplished by a combination of an infusion of cold saline together with an endovascular cooling catheter, causes a reduction of IS if induced before reperfusion and not after.11 Therefore, the primary aim of this pilot study was to evaluate the safety and feasibility of rapidly induced hypothermia by infusion of cold saline and endovascular cooling catheter before reperfusion in patients with acute myocardial infarction.
study was to evaluate the safety and feasibility of inducing hypothermia before reperfusion by a combination of infusion of cold saline and endovascular catheter cooling as an adjunct therapy in patients with a STEMI scheduled to undergo primary percutaneous coronary intervention (PCI). The secondary aim was to assess the effect of prereperfusion hypothermia on IS normalized to myocardium at risk (MaR), both assessed by cardiac magnetic resonance (CMR) and the effect of hypothermia on myocardial biomarker release. The data presented are from the predefined safety and feasibility part of the Rapid Intravascular Cooling in Myocardial Infarction as Adjunctive to Percutaneous Coronary Intervention study (RAPID-MI-ICE, ClinicalTrials.gov Identifier: NCT00417638).

Methods

Ethics
The present study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the ethics committee. All patients gave written informed consent before inclusion in the study.

Study Population
From March 2007 to October 2009, patients were enrolled in this prospective, randomized, single-center study to test the feasibility and safety of an infusion of cold saline together with endovascular hypothermia, using the Celsius Control System (Innercool Therapies Inc, San Diego, Calif) as an adjunct therapy in patients with an acute STEMI eligible for primary PCI. Men and women between 18 and 75 years of age who presented with an anterior or inferior STEMI with ST-segment elevation of >0.2 mV in 2 or more anatomically contiguous leads and a duration of symptoms of <6 hours were included. Patients with cardiac arrest, previous AMI, previous PCI or CABG, known congestive heart failure, end-stage kidney disease or hepatic failure, recent stroke, coagulopathy, pregnancy, or Killip class II through IV at presentation were excluded from the study.

Protocol
Figure 1 gives a time line of the protocol. Eligible patients were randomly assigned to hypothermia or to the control group in the cardiac catheterization laboratory before angiography. Sealed opaque envelopes that contained the study group assignment were opened after informed consent was obtained. Patients assigned to the hypothermia group were given 30 mg of oral buspirone. Meperidine was given as an intravenous loading dose of 1 mg/kg. The loading dose was reduced to 0.5 mg/kg if the patient had been given morphine before enrollment in the study. The loading dose was followed by a continuous infusion of meperidine at 30 mg/h. Additional 25-mg intravenous boluses doses of meperidine were given if the patient started to shiver. Shivering was further suppressed at the ward by skin warming using a forced-air warming blanket. Hypothermia was induced by forced infusion of 4° C cold saline using pressure bags. Volume administered was 1000 to 2000 mL at the physician’s discretion. A 14F introducer was inserted into the right femoral vein. Through the introducer, a 14F Celsius Control catheter (Innercool Therapies Inc) was placed into the inferior vena cava with the tip of the catheter at the level of the diaphragm. The target temperature was then set to 33°C. Core body temperature was measured using an integrated temperature probe in the cooling catheter. Cooling was maintained for 3 hours followed by passive warming to 36°C to 37°C during 3 hours. Loading doses of 500 mg of aspirin and 600 mg of clopidogrel were given to all patients before cardiac catheterization. After induction of hypothermia, a coronary angiogram was performed. Patients underwent PCI according to current standard of practice.

CMR Imaging
After 4±2 days, patients underwent a CMR examination in supine position using a 1.5-T system (Philips Intera CV, Philips, Best, The Netherlands) with a 5-element cardiac synergy coil. Initial scout images were acquired to locate the heart and the standard imaging planes. For visualization of the initial ischemic myocardium, T2-weighted short tau inversion recovery (STIR), turbo spin-echo images with a double inversion pulse for blood suppression were acquired in the short-axis view, covering the left ventricle from the base to apex. Image parameters for T2-weighted imaging were: echo...
time, 100 ms; repetition time, 2 heart beats; number of averages, 2; inversion time, 180 ms; and image resolution, 1.5×1.5×10 mm with no gap. Parallel imaging with SENSE=1 was used to minimize signal inhomogeneities caused by differences in coil sensitivity. For infarct visualization, late gadolinium enhancement (LGE) images were acquired 15 to 20 minutes after administration of 0.2 mmol/kg body weight of an extracellular gadolinium-based contrast agent (gadoteric acid, Gd-DOTA, Guerbet, Gotha Medical AB, Billdal, Sweden). The LGE images were acquired in the short-axis view, from base to apex, and in the 3 standard long-axis views (2-chamber, 4-chamber, and left ventricular outflow tract views), during breath-hold, using an ECG-triggered segmented inversion-recovery gradient recalled echo image sequence. Typical inversion-recovery gradient recalled echo sequence parameters were echo time, 1.2 ms; repetition time, 3.9 ms; image resolution, 1.5×1.5×8 mm with no gap; flip angle, 15°C; with acquisition every heart beat. The inversion time of typically 230 to 270 ms was manually adjusted to null the signal from remote myocardium.

**Image Analysis**

The analysis of MaR and IS was performed using a freely available postprocessing software (Segment, v.1.8 R0795; http://segment.heiberg.se).15 For assessment of MaR, the endocardial and epicardial borders were manually traced in each T2-weighted short-axis image. The myocardium with increased signal intensity was manually delineated, as previously described, by an experienced observer blinded to all other data.16 The MaR was expressed as a percentage of the left ventricular myocardium. The IS was assessed from the short-axis images and quantified using a previously described and validated semiautomatic method.17 The assessment of IS was performed by an observer blinded to all other data. In short, the endocardial and epicardial borders were manually traced in each LGE short-axis image. Thereafter, the hyperenhanced myocardium was automatically quantified using a computer algorithm, taking partial volume effects in the periphery of the infarction into account. In regions where the computer algorithm was clearly wrong, manual adjustments were made. IS was expressed as a percentage of the left ventricular myocardium. IS was subsequently expressed as percentage of MaR. Microvascular obstruction was defined as hypointense regions in the core of the infarction that had signal intensity less than the threshold for infarction. These regions were manually included in the infarct volume. The volume of microvascular obstruction (cm³) was calculated as the difference between the infarct volume before and after manual inclusion of regions of microvascular obstruction. The size of microvascular obstruction was expressed as percentage of IS.

**Biochemical Markers**

Creatine kinase (CK)MB and Troponin T were sampled on admission to the catheterization laboratory, and at 12 hours and 24 hours after admission. Peak values were defined as the highest measured value within 24 hours. The area under the curve (AUC) was calculated from the measurements. NT-proBNP was sampled at day 1.

**Statistics**

Calculations and statistics were performed using the GraphPad Prism 5.0 software (GraphPad Software Inc, La Jolla, Calif). The Fisher exact test was performed on categorical variables. Continuous variables were tested using Mann-Whitney U test with exact inference. Statistical significance was accepted at P<0.05.

**Role of the Funding Source**

The sponsor of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the article. The authors had full control of the data in the study and had final responsibility for the decision to submit for publication.

**Image Analysis**

**Table 1. Clinical and Angiographic Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothermia (n=9)</th>
<th>Control (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±10</td>
<td>58±7</td>
</tr>
<tr>
<td>Women</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Onset of symptoms to reperfusion, min</td>
<td>174±51</td>
<td>174±62</td>
</tr>
<tr>
<td>Door-to-balloon time, min</td>
<td>43±7</td>
<td>40±6</td>
</tr>
<tr>
<td>Initial TIMI flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>2/3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Successful revascularization</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>TIMI 3 flow after PCI</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Procedural time, min</td>
<td>55±24</td>
<td>40±18</td>
</tr>
<tr>
<td>Abciximab</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

P=NS for all comparisons. Data are presented as mean±SD.

**Results**

Twenty patients were enrolled in the study. There were no significant differences in baseline characteristics between the hypothermia group and the control group (Table 1). One patient in the normothermia group had a visible thrombus in the left main coronary artery and underwent emergency CABG after angiography had been performed and was therefore excluded from further analysis. One patient in the hypothermia group was prevented from immediate angiography because there was another STEMI patient at the catheterization laboratory, delaying cooling beyond the prespecified 6 hours duration of ischemia, and was therefore excluded from further analysis. Clinical and angiographic data are shown in Table 1. The time from onset of symptoms to reperfusion did not differ between the 2 groups (174±51 minutes versus 174±62 minutes, hypothermia versus control, P=1.00). Successful revascularization was performed in all patients. All patients who underwent PCI were stented. TIMI 3 flow was established in all patients. Thrombectomy was performed in 15 of 18 patients, with no difference between the groups.

**Hypothermia Treatment**

Baseline temperature was similar in the 2 groups (36.8±0.7°C versus 36.5±0.6°C, hypothermia versus control, P=0.87). The time line at the catheterization laboratory and measurements of core body temperature are shown in Figure 1. Door-to-balloon time was 43±7 minutes in the hypothermia group and 40±6 minutes in the normothermia group, indicating that induction of hypothermia did not cause any significant delay of time to reperfusion (P=0.12) (Figure 2).
After random assignment to the hypothermia group, cold saline was given 29±6 minutes before reperfusion. An endovascular cooling catheter was inserted and endovascular hypothermia treatment was initiated 15±3 minutes before reperfusion. A core body temperature of <35°C was achieved in 10±7 minutes after onset of endovascular hypothermia treatment. Average temperature at reperfusion was 34.7±0.3°C (Figure 1). At the time of reperfusion, a core body temperature of <35°C was achieved in 9 of 9 patients (100%). For 1 patient in the hypothermia group, cold saline was the only cooling source because no endovascular cooling was possible because of technical problems. The volume of cold saline given was 1540±430 mL. Intravenous meperidine was given at the catheterization laboratory to prevent shivering. Mean dose was 106 mg (range, 60 to 150 mg).

Clinical Events/Safety
There were no significant differences between the groups with regard to clinical events (Table 2). Combination hypothermia was well tolerated in all patients, and no heart failure was seen in the hypothermia group, whereas 3 patients in the control group had clinical signs of heart failure (P=0.21). NT-proBNP was analyzed on day 1 after the infarct. There was no difference among the groups (hypothermia, 1275±651 ng/L versus control, 1350±930 ng/L; P=0.99) (Figure 3). In the hypothermia group, 2 patients had fever, cough, focal crepitations on lung auscultation, C-reactive protein (CRP) >100 mg/L, and had no signs of congestion on chest radiography, whereas 1 patient had fever, CRP >100 mg/L, and had no signs of congestion on chest radiography. All 3 patients’ symptoms and CRP elevations resolved on treatment with antibiotics. No suspected infections were observed in the normothermia group. There was no statistical difference between the groups with respect to occurrence of infection (P=0.21). The 30-day major adverse coronary event rate was 0% in both groups.

Assessment of MaR and IS
There was no difference between the hypothermia and control groups with regard to the timing of the MR examination (2.8±0.8 versus 3.2±1.0 days, hypothermia versus control, P=0.19) MaR assessed by T2-weighted CMR was 44±8% and 43±8% of left ventricular mass in the hypothermia group and control group, respectively (P=0.65; Figure 4A). Hypothermia caused a 38% reduction in IS normalized to MaR (29.8±12.6% versus 48.0±21.7%, hypothermia versus control, P=0.041, Figure 4B). IS alone was not statistically significant different between the 2 groups, although a trend toward a reduction in IS was seen (13.7±6.4% versus 20.5±10.0%, hypothermia versus control, P=0.08, Figure 4C). In patients with a TIMI 0 flow before reperfusion, hypothermia caused a 57% reduction in IS normalized to MaR (24.7±16.0 versus 56.9±16.1%, hypothermia [n=7] versus control [n=8], P=0.02). The study was not powered to study the effects on infarcts in different coronary artery territories, and no such statistical comparison was made. The IS normalized to MaR in left anterior descending infarcts was 33.4±11.6 (n=6) versus 45.0±23.0% (n=7), hypothermia versus control. IS normalized to MaR in the right coronary artery infarcts was 18.9±11.3 (n=3) versus 57.2±29.1% (n=2), hypothermia versus control. In the hypothermia group, a patchy appearance of the myocardial infarctions was observed in several patients. In the control group, the infarctions were more homogeneous in appearance (Figure 5). For 1 patient in each group, the T2-weighted images did not allow for assessment of MaR because of poor image quality. The 2 patients were included in the analysis of IS but not in the

Table 2. Clinical Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothermia (n=9)</th>
<th>Control (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day mortality</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30-Day major adverse coronary events</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Ventricular tachycardia/fibrillation</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

P=NS for all comparisons. Data are presented as mean±SD.
The size of microvascular obstruction was 0.8 ± 1.5% versus 1.9 ± 3.4%, hypothermia versus control (P = 0.24), and did not differ between the groups.

**Biochemical Markers**

Peak Troponin T was reduced by 43% in the hypothermia group compared with the control group (3.9 ± 2.5 µg/L versus 6.9 ± 2.8 µg/L, P = 0.01) (Figure 6A). Furthermore, the AUC for Troponin T was reduced by 41% in the hypothermia group compared with the control group (67.7 ± 40.3 versus 113.8 ± 47.2, P = 0.03) (Figure 6B). Peak CKMB, however, did not differ between the groups, although a trend to a reduction was observed in the hypothermia group (273 ± 196 µg/L versus 343 ± 153 µg/L, hypothermia versus control, P = 0.17) (Figure 6C). The AUC for CKMB did not either show a significant difference between the groups, although a similar trend was observed (hypothermia 3978 ± 3083 versus control 5358 ± 2544, P = 0.15) (Figure 6D). Several patients in both groups had a peak CKMB > 500 µg/L, which was the upper limit of detection in the analysis. No patient reached the upper limit for Troponin T, which may explain the disparity between the reduction in CKMB versus Troponin T in the hypothermia group.
Discussion

The present study demonstrates that using a combination of an infusion of cold saline together with an endovascular cooling catheter to induce mild hypothermia in STEMI is feasible. Furthermore, there was a significant reduction in IS normalized to MaR as assessed by CMR and in Troponin T release in the hypothermia group compared with the patients who were reperfused at normothermic conditions.

Safety

The safety of using endovascular cooling alone has previously been demonstrated in awake patients with AMI. The rationale of using a combination of cold saline together with endovascular cooling was to achieve a rapid induction of hypothermia without delaying reperfusion therapy. Previous data indicate the necessity of inducing hypothermia before reperfusion to reduce IS. However, an intravenous infusion of cold saline could possibly lead to an increase in acute heart failure and pulmonary congestion in patients with AMI. In this population without previous congestive heart failure although with relatively large ischemic areas (43% to 44% of left ventricular mass), no clinical signs of heart failure or pulmonary congestion were observed in the hypothermia group. In the control group, however, 3 patients had clinical signs of heart failure and 2 patients had ventricular arrhythmia during the early postinfarction period. Furthermore, the groups had similar NT-proBNP values at day 1, indicating that the administration of cold saline did not adversely affect left ventricular load the day after intervention. Clinical event rate was low and did not differ between the groups.

Meperidine and buspirone were chosen to suppress shivering because they act synergistically without causing respiratory depression. Furthermore, the drugs have been used in previous clinical trials with a high tolerability in awake patients with AMI. In this study, hypothermia was well tolerated, and treatment was not discontinued in any patients because of shivering.

Feasibility

In a previous experimental study, we have demonstrated that a combination of cold saline infusion and an endovascular cooling catheter can accomplish a reduction in core body temperature to \( \frac{35}{\circ} \)C within 5 to 10 minutes in 40- to 50-kg pigs. Furthermore, inducing hypothermia before reperfusion led to a 43% reduction in IS, whereas inducing hypothermia after the onset of reperfusion did not affect IS. The present study has shown that inducing hypothermia with a combination of cold saline infusion and endovascular cooling is clinically feasible and can be used to obtain a rapid reduction in core body temperature in patients with STEMI without delaying time to reperfusion.

IS and Biochemical Markers

Although the present safety and feasibility study was not primarily designed or powered to demonstrate a difference in IS between the hypothermia and control groups, a significant reduction (38%) in IS normalized to MaR was observed. There was, however, no statistically significant difference between the 2 groups with regard to IS alone, even though there was a clear trend toward a reduction in the hypothermia group. This reflects the importance and strength of being able to assess IS in relation to MaR. Using CMR for assessing MaR in relation to IS has recently been validated in patients with AMI and used to describe the natural course of infarct evolution in humans. Thus, this methodology could potentially be used to reduce the sample size needed in clinical trials to show significant effects of cardioprotective interventions. The observed difference in IS as assessed by CMR between the groups was further supported by the significant difference in peak and cumulative Troponin T release.

We observed that several infarctions were patchy in appearance in the hypothermia group. This phenomenon with a scattered myocardial salvage has been described by us previously in an experimental hypothermia study. It is also in agreement with Dae et al., who described scattered islands of
reduced Sestamibi uptake in pig hearts when assessing IS with SPECT in pigs subject to endovascular hypothermia. The pattern differs from the classic wave front pattern in infarct progression previously described by Reimer and Jennings.23 The long-term significance of the observed patchy infarction pattern is not known. In a previous experimental study, hypothermia treatment reduced the extent of microvascular obstruction within the infarct.11 In this study, the occurrence of microvascular obstruction was low in both groups and did not differ between the hypothermia group and the control group. This study was too small to establish whether hypothermia reduces microvascular obstruction in patients with AMI.

Limitations

The primary aim of this study was to assess the safety and feasibility of hypothermia in AMI. IS normalized to Mar was a secondary end point, and even though a significant reduction was observed, these results should be interpreted with caution due to the small study sample. It cannot be excluded that part of the hyperenhanced myocardium on CMR acquired at 4–2 days can be due to edema, because it has recently been shown that there is a significant decrease in hyperenhanced myocardium during the first week after infarction.23,24 There was, however, no difference in the timing of the MR examination between the hypothermic patients and the control patients, and thus the effect of IS reduction in the hypothermia group cannot be attributed to the changes in IS during the first week after infarction. Although no complications of combination hypothermia was observed in the patients in this pilot study, larger studies are required before it can be concluded that this regime is safe in patients with large myocardial infarction, especially given the potential risks of volume overload and arrhythmias.

Conclusion

The results of the present study indicate that it is clinically feasible to induce hypothermia by using a combination of cold saline infusion and endovascular cooling before reperfusion in awake STEMI patients without delaying time to reperfusion. Even though preperfusion hypothermia was shown to reduce IS as assessed by CMR and Troponin T release, larger clinical studies are needed to verify these findings and to assess possible long-term clinical benefit for the patients.

Acknowledgments

We thank Fredrik Scherstén, MD, PhD, for performing an independent adjudication on the clinical data of the study.

Sources of Funding

This study was supported by the Swedish Research Council, the Swedish Heart and Lung Foundation, and the Vascular Wall program (Lund University Faculty of Medicine). Dr Erlinge holds the Lars Werkö distinguished research fellowship from the Swedish Heart and Lung Foundation. The study was funded by a grant from Innercool Therapies Inc, San Diego, Calif, covering the use of the Celsius Control cooling console and the cost of CMR evaluation.

Disclosures

None.

References
20. Mokhtarani M, Mahgoub AN, Morioka N, Doufas AG, Dae M, Shaughnessy TE, Bjorksten AR, Sessler DI. Buspirone and meperidine
Clinical Perspective

The use of endovascular hypothermia in awake patients with acute myocardial infarction has previously been evaluated in the clinical trials ICE-IT and COOL-MI. The trials failed to show a benefit of hypothermia in reducing infarct size. A major problem was that the induction of hypothermia was too slow and only a minority of patients reached target temperature before reperfusion (percutaneous coronary intervention). In this pilot study, a combination of an infusion of cold saline with an endovascular cooling catheter was evaluated in awake patients with acute myocardial infarction. All patients reached a core body temperature of <35°C without any significant delay in reperfusion therapy, and no increase in heart failure or pulmonary congestion was observed as the result of the hypothermia therapy. Furthermore, a significant reduction in infarct size and Troponin-T levels was observed. Although these promising results must be verified in a larger trial, hypothermia may be a promising candidate for adjunct therapy to revascularization in patients with acute myocardial infarction.
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Circ Cardiovasc Interv. 2010;3:400-407; originally published online August 24, 2010;
doi: 10.1161/CIRCINTERVENTIONS.110.957902

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