Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs

MICHAEL W. DAE,1 DONG WEI GAO,1 DANIEL I. SESSLER,2 KAMEL CHAIR,3 AND CAROL A. STILLSON1
1Cardiovascular Research Institute, University of California, San Francisco, California 94143; and 2Outcomes Research Institute and Department of Anesthesiology, University of Louisville, Louisville, Kentucky 40202

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Dae, Michael W., Dong Wei Gao, Daniel I. Sessler, Kamel Chair, and Carol A. Stillson. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. Am J Physiol Heart Circ Physiol 282: H1584–H1591, 2002; 10.1152/ajpheart.00980.2001.—Mild hypothermia reduces myocardial infarct size in small animals; however, the extent of myocardial protection in large animals with greater thermal mass remains unknown. We evaluated the effects of mild endovascular cooling on myocardial temperature, infarct size, and cardiac output in 60- to 80-kg isoflurane-anesthetized pigs. We occluded the left anterior descending coronary artery for 60 min, followed by reperfusion for 3 h. An endovascular heat-exchange catheter was used to either lower core body temperature to 34°C (n = 11) or maintain temperature at 38°C (n = 11). Additional studies assessed myocardial viability and microvascular perfusion with 99mTc-sestamibi autoradiography. Endovascular cooling reduced infarct size compared with normothermia (9 ± 6% vs. 45 ± 8% of the area at risk; P < 0.001), whereas the area at risk was comparable (19 ± 3% vs. 20 ± 7%; P = 0.65). Salvaged myocardium showed normal sestamibi uptake, confirming intact microvascular flow and myocyte viability. Cardiac output was maintained in hypothermic hearts because of an increase in stroke volume, despite a decrease in heart rate. Mild endovascular cooling to 34°C lowers myocardial temperature sufficiently in human-sized hearts to cause a substantial cardioprotective effect, preserve microvascular flow, and maintain cardiac output. Hypothermia; ischemia-reperfusion injury; myocardial infarction; myocyte viability

Reperfusion remains the only established method to reduce infarct size during acute myocardial infarction. However, challenges to timely initiation of therapy still exist (2). Congestive heart failure remains a common clinical problem after reperfusion therapy for myocardial infarction (17). In addition, a significant number of patients show persistent ST segment elevation even after successful restoration of epicardial flow, consistent with microvascular injury (5). There is still a significant clinical need for other therapies to provide cell protection to allow greater salvage of myocardium before and after reperfusion (21).

Recent experimental studies demonstrated that only a mild decrease in myocardial temperature (2–5°C) can have a profound effect on myocardial infarct size (14, 17, 18). These mild levels of hypothermia are readily achieved in small animals, resulting in a decrease in infarct size even when instituted after coronary occlusion (9, 14). However, the extent to which mild hypothermia can provide myocardial cell protection in large animals, when instituted after the onset of ischemia, remains to be determined. This is not a trivial issue, because clinical trials of hypothermia are not likely to be undertaken without tests in a large animal model with coronary vasculature similar to that in humans.

Humans have considerable thermal mass. It is therefore difficult to cool adults rapidly without cardiopulmonary bypass. However, newly developed technology (endovascular heat-exchange catheters) can cool adults 2–4°C in only 30 min. A practical consequence is that it is now practical, for the first time, to use therapeutic hypothermia to treat myocardial infarction. As a prelude to human studies, we evaluated the extent of cardioprotection provided by mild endovascular hypothermia induced after coronary occlusion in 60- to 80-kg pigs. Pigs were chosen not only for size but also because of the lack of significant antegrade collateral blood flow (12). We tested the hypothesis that endovas-
cular cooling would reduce the temperature in deeply ischemic tissue in large hearts like those of humans rapidly and sufficiently enough to decrease infarct size. We also sought to address the question of what effects the combination of hypothermia and myocardial ischemia would have on cardiac output. Conflicting results have been reported that suggest myocardial depression (23) or inotropy (25) in the presence of hypothermia in normal hearts. The effects of hypothermia on myocardial function in ischemic hearts are not well studied.

METHODS

Experimental preparation. The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1996). All protocols were approved by the institutional Committee on Animal Research. Pigs of either sex weighing 60–80 kg were preanesthetized with intramuscular ketamine (20 mg/kg), xylazine (2 mg/kg), and atropine (0.04 mg/kg), intubated, and mechanically ventilated with a mixture of isoflurane (1–4%) and oxygen. Electrocardiogram (ECG) and femoral arterial pressure were monitored continuously. A median sternotomy was performed, and the pericardium was opened. Core body temperature (distal esophageal) was monitored along with additional temperature measurements in the left atrial blood pool and left ventricular myocardium in the area at risk (AAR). Myocardial temperature was measured with a 22-gauge needle thermistor (Mallinckrodt Medical, St. Louis, MO) placed directly into the AAR. Left atrial temperature was measured from a thermistor wire (Cornerstone Sensors, Vista, CA) inserted into the left atrial blood pool via a purse-string suture through the left atrial appendage. Esophageal temperature was measured with a 9-Fr multipurpose Series 400 thermistor temperature probe (Mallinckrodt Medical) placed into the lower esophagus. A silk suture was placed around the left anterior descending coronary artery (LAD) approximately one-third of the distance from the apex to allow occlusion and reperfusion of the vessel. Heparin (200 IU/kg) and a lidocaine bolus (2 mg/kg) were given intravenously before coronary occlusion. Lidocaine was subsequently infused at a rate of 50 μg·kg⁻¹·min⁻¹. A supplemental dose of heparin (100 IU/kg) was given just before reperfusion.

Endovascular cooling. A heat-exchange balloon catheter (SetPoint System; Radiant Medical, Redwood City, CA) was inserted into the femoral vein and advanced into the inferior vena cava. The catheter consists of a triple-lobed, helically wound, heparin-coated balloon mounted on the distal portion of a multilumen shaft (Fig. 1). The shaft has an inflow lumen, an outflow lumen, and a guidewire lumen. The catheter with the unexpanded balloon has a 9.2-Fr diameter and is inserted through a 10-Fr introducer sheath, which is placed percutaneously into the femoral vein. The catheter is advanced over a guidewire until the distal tip is located at the level of the diaphragm. The balloon is expanded by circulating saline through the lumens. The fully expanded balloon diameter is 8.25 mm and is estimated to occupy 8–10% of the cross-sectional area of the inferior vena cava without causing any clinically important obstruction of normal blood flow. The catheter is connected via insulated fluid lines to a peripheral cassette consisting of a pump that circulates the saline and a thin-walled heat-exchange bag that lies on a thermal transfer plate that is cooled or heated by a solid-state thermoelectric module. This cools or warms the saline circulating through the heat-exchange element of the cassette without administration of fluids to the subject.

Assessment of myocardial infarct size. A target temperature of 34°C was chosen after pilot studies showed the ability to lower core body temperature 4°C after ~40 min of maximal cooling with the endovascular technique. The catheter was used to induce hypothermia (34°C; n = 11) or maintain
normothermia (38°C; n = 11). Hypothermia and normothermia control studies were alternated. The LAD was occluded for 60 min and then released. The surface ECG was monitored continuously, whereas epicardial color and regional wall motion were observed intermittently, to ensure that the hearts were ischemic during the entire 1-h duration of ischemia. Cooling was started 20 min after coronary occlusion and continued for 15 min after reperfusion, followed by gradual rewarming. Three hours after reperfusion, the coronary artery was reoccluded and 20 ml of blue dye (Unisperse Blue; Academy Materials, Mesa, AZ) was injected into the left ventricular cavity to delineate the AAR. The heart was then excised, cut into 5- to 10-mm-thick transverse slices, and photographed with a digital camera for subsequent determination of AAR. The fresh slices were immersed in 2% triphenyltetrazolium chloride (TTC) at 37°C for 10 min to delineate the infarct area and rephotographed. The slices were fixed in 10% buffered formalin until subsequent histological analysis. The digital photographs were coded and assessed blindly. Regions of interest were drawn around the AAR and infarct, and the areas were quantified with Image-Pro Plus software. AAR was expressed as percentage of the left ventricle, and infarct size was expressed as percentage of the AAR.

Radionuclide assessment of perfusion and viability. To determine that the TTC reaction was not influenced by hypothermia, potentially indicating preservation of substrates and not myocardial viability, we compared the distribution of myocardial perfusion and viability with 99mTc-sestamibi autoradiography to the distributions of viable and infarcted myocardium with TTC. We studied 11 additional animals at 3 h (3 hypothermic, 3 normothermic) and 5 days (3 hypothermic, 2 normothermic) after reperfusion. For the chronic survival animals, the occlusion and reperfusion protocol was performed as in the acute studies under sterile conditions. A remnant of the 2-0 silk suture was left in place on the epicardium to identify the site of occlusion at the time of restudy. The pericardium and chest were closed, and air was evacuated with a chest tube. Postanesthetic pain was treated with buprenorphine (0.01 mg/kg im) every 8 h, followed by buprenorphine (0.01 mg/kg im) every 8–12 h as needed. The animals were returned to the laboratory 5 days after infarction, preanesthetized, intubated, and placed on isoflurane anesthesia. The chest was opened via median sternotomy, and radionuclide injections were done as outlined below.

The animals were injected intravenously with 20 mCi of 99mTc-sestamibi, to assess myocardial perfusion and viability, followed by intravenous injection of 250 ml of 1% TTC, to assess infarct distribution, before blue dye injection. Myocardial slices including the AAR were embedded in optimum cutting temperature compound and frozen on powdered dry ice, and 20-μm sections were cut with a cryostat microtome. Representative sections were collected on glass coverslips and exposed to a storage phosphor imaging plate ( Molecular Dynamics) for 12 h. The plate was then scanned to acquire digital autoradiographs of the distribution of 99mTc-sestamibi. The tissue sections used to form the autoradiographs were then imaged with a flatbed scanner to assess the distribution of blue dye (AAR) and TTC for subsequent comparison to the sestamibi autoradiographs. Interpreters of the perfusion images were not blinded to the experimental groups.

Circulatory responses to endovascular cooling. After the first six animals per group for infarct size assessment, an additional five animals per group were added to assess the effects of mild endovascular cooling on cardiac output, heart rate, and systolic blood pressure (hypothermia, n = 5; normothermia, n = 5) in addition to infarct size. A prior pilot study in five normal animals showed consistent cardiac output responses to cooling. A median sternotomy was done as described in Experimental preparation. The pericardium was opened, and the ascending aorta was isolated. A 28-mm ultrasonic flow probe (Transonic Systems, Ithaca, NY) was filled with coupling gel and placed around the root of the ascending aorta. The flow probe was connected to a dual-channel flowmeter (model T206, Transonic Systems). Cardiac output data was digitized at 200 Hz with an analog-to-digital converter (Biopac Systems, Santa Barbara, CA) and then interfaced to a personal computer for continuous recording. Hemodynamic data were analyzed with the Acknowledge software package (Biopac Systems).

**Statistical analysis.** All data are expressed as means ± SD. AAR and infarct size were compared in the hypothermic and normothermic groups with two-tailed, unpaired t-tests. Hemodynamic results were expressed as a percentage of baseline. The single most clinically relevant quantity (e.g., the minimum cardiac output) was then extracted from multiple measurements on each animal. Heart rate (minimum achieved), stroke volume (maximum achieved), cardiac output (minimum achieved), and systolic blood pressure (minimum achieved) were compared between the hypothermia and control animals with two-tailed, unpaired t-tests at three time periods: from the start of cooling at 20 min after occlusion to 120 min after reperfusion, from the start of cooling at 20 min of occlusion to the end of occlusion at 60 min, and from 10 min after reperfusion to 120 min of reperfusion. It was thought that minimum cardiac output, heart rate, and systolic blood pressure reflect changes that are most clinically relevant for hemodynamic stability, whereas maximum stroke volume reflects the most relevant adaptive response to these minima. The time periods were chosen to assess circulatory stability during the overall procedure and the more selective periods during coronary occlusion and reperfusion. The time periods during coronary occlusion and reperfusion also correspond to the periods of most active cooling and rewarming, respectively. The last hour of reperfusion was excluded from analysis to avoid potential artifacts due to the stability of the open chest preparation over prolonged periods. P < 0.05 was considered significant.

**RESULTS**

Assessment of infarct size. One animal included in the hypothermia group fibrillated soon after occlusion, before cooling, and could not be defibrillated. One animal in each group developed ventricular fibrillation during reperfusion; however, both returned to sinus rhythm after epicardial defibrillation. Figure 2 shows left atrial blood pool, left ventricular, and esophageal temperatures. Mean left atrial blood pool temperature decreased to 33.8 ± 0.3°C, whereas mean myocardial temperature in the AAR decreased to 34.0 ± 0.4°C during cooling, similar to the esophageal temperature of 34.0 ± 0.2°C. Mean myocardial temperature was 38.3 ± 0.4°C in normothermic control animals (Fig. 2).

The size of the AAR was comparable in the hypothermic (n = 11) and normothermic (n = 11) animals (19 ± 3% vs. 20 ± 7%; P = 0.65). However, infarct size was reduced in the hypothermic animals (9 ± 6% vs. 45 ± 8%; P < 0.0001). When the animal that fibrillated before cooling is assigned the worst infarct value in the
hypothermic group and included in the analysis, the results remain highly significant \((11 \pm 6\% \text{ vs. } 45 \pm 8\%; P < 0.0001)\). Figure 3 shows the relationship between AAR and infarct size in the normothermic controls; however, hypothermia altered this relationship and showed smaller infarcts at all sizes of AAR.

**Radionuclide assessment of myocardial perfusion and viability.** The distribution of sestamibi uptake closely correlated with the distribution of TTC, providing concordant patterns of viable myocardium. Sestamibi uptake was more uniform in hypothermic hearts, with scattered islands of reduced activity at the endocardium (Fig. 4). In contrast, dense, extensive sestamibi perfusion defects were present in the normothermic controls (Fig. 4). Imaging results were similar in the animals studied 5 days after reperfusion (data not shown).

**Circulatory responses to endovascular cooling.** Figure 5 shows the physiological responses in hypothermia and control animals during coronary occlusion and reperfusion, expressed as a percentage of baseline. Statistical comparisons are shown in Table 1. Heart rate decreased significantly in response to cooling relative to the control animals (Fig. 5; Table 1). Stroke volume, however, significantly increased in response to cooling compared with controls (Fig. 5; Table 1). As a result of the significant increase in stroke volume, cardiac output was maintained in the hypothermia group despite the decrease in heart rate and there was no significant difference compared with the controls (Fig. 5; Table 1). Systolic blood pressure showed a significant decrease during cooling compared with the controls but showed no difference during the reperfusion period as the animals were rewarmed (Fig. 5; Table 1).

**DISCUSSION**

The results of this study demonstrate that deeply ischemic segments in a heart similar in size to that of humans can be cooled effectively, in the absence of antegrade collateral flow, with endovascular techniques. Endovascular cooling resulted in not only a substantial degree of myocardial protection but also maintenance of cardiac output during ischemia and reperfusion. In addition, there was no increase in arrhythmogenesis compared with the normothermic control animals.

Recent studies in small animal models showed reductions in infarct size with the institution of hypothermia after coronary occlusion (9, 14). Hale et al. (9) showed a 50% reduction in infarct size when topical cooling to \(-33^\circ\text{C}\) was applied directly to the myocardium 10 min after the start of a 30-min occlusion in rabbits. Miki et al. (14) showed an 80% reduction in infarct size with blood pool cooling to \(32^\circ\text{C}\) starting 10
min after a 30-min occlusion in rabbits. We found an 80% reduction in infarct size with endovascular cooling to 34°C starting 20 min after a 60-min occlusion in pigs. The current study is the first to show myocardial protection in a large, human-sized animal model with endovascular cooling. It is noteworthy that during coronary occlusion, in the absence of antegrade coronary flow, myocardial temperature in the AAR closely followed left atrial blood pool temperature. The ischemic myocardium was thus cooled by conduction from the blood pool, not from antegrade flow. This may represent an advantage over pharmacological approaches to providing cell protection where drug delivery may not be sufficient in collateral-poor regions. Body surface cooling methods are too slow to lower myocardial temperature quickly, whereas techniques such as cardiopulmonary bypass are too cumbersome to be done in the clinical setting. Other methods of establishing hypothermia have been used, such as perfusion of cold saline into the pericardial space.

Viability results obtained by TTC were confirmed by results obtained from sestamibi autoradiography. Our study provides evidence that both myocytes and microvascularity were protected by cooling, as supported by uniform delivery and extraction of sestamibi, a perfusion and viability tracer. Sestamibi results were similar in animals that were reperfused for 3 h and 5 days.

Although not fully understood, hypothermic protection of ischemic myocardium is associated with preservation of high-energy phosphates, which may facilitate the maintenance of membrane integrity during ischemia. The mechanism is not related to hypothermia-induced bradycardia because the effects persist when heart rate is maintained with pacing. Whether hypothermia protection is protective during

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Fig. 4. Tc-sestamibi autoradiographs (top) and corresponding tissue sections showing AAR and triphenyltetrazolium chloride (TTC) (bottom). The hypothermic heart (left) achieved a temperature of 33.7°C at the nadir of hypothermia. There is uniform sestamibi uptake, indicating intact microvascular perfusion and myocyte viability, and TTC positivity (red) in the AAR. The normothermic heart (right) was maintained at a temperature of 38.2°C. There is a dense sestamibi perfusion defect that corresponds to the TTC-negative region shown at the bottom, indicating infarction.
Fig. 5. Heart rate, stroke volume, cardiac output, and systolic blood pressure (BP) in hypothermic pigs (●; n = 5) and normothermic controls (○; n = 5) during coronary occlusion (OC) and reperfusion (RP). Values are expressed as % of baseline. Statistical comparisons are shown in Table 1.
Table 1. Circulatory responses in hypothermic and normothermic animals.

<table>
<thead>
<tr>
<th>Time Group</th>
<th>Min HR</th>
<th>Max SV</th>
<th>Min CO</th>
<th>Min SBP</th>
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<tr>
<td>OC20–RP120</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypo</td>
<td>76 ± 10</td>
<td>119 ± 14</td>
<td>82 ± 9</td>
<td>75 ± 4</td>
</tr>
<tr>
<td>Normo</td>
<td>93 ± 10</td>
<td>97 ± 12</td>
<td>78 ± 10</td>
<td>75 ± 14</td>
</tr>
<tr>
<td>Diff</td>
<td>−32 to −3</td>
<td>3 to 41</td>
<td>−10 to 18</td>
<td>−15 to 14</td>
</tr>
<tr>
<td>P</td>
<td>0.022</td>
<td>0.031</td>
<td>0.55</td>
<td>0.95</td>
</tr>
<tr>
<td>OC20–OC60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo</td>
<td>80 ± 9</td>
<td>115 ± 18</td>
<td>87 ± 13</td>
<td>78 ± 5</td>
</tr>
<tr>
<td>Normo</td>
<td>98 ± 9</td>
<td>96 ± 6</td>
<td>86 ± 11</td>
<td>91 ± 5</td>
</tr>
<tr>
<td>Diff</td>
<td>−18</td>
<td>19</td>
<td>1</td>
<td>−12</td>
</tr>
<tr>
<td>95% CI</td>
<td>−30 to −5</td>
<td>−1 to 38</td>
<td>−16 to 18</td>
<td>−19 to −6</td>
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<tr>
<td>P</td>
<td>0.012</td>
<td>0.055</td>
<td>0.90</td>
<td>0.003</td>
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<tr>
<td>RP10–RP120</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo</td>
<td>78 ± 12</td>
<td>118 ± 13</td>
<td>82 ± 9</td>
<td>75 ± 4</td>
</tr>
<tr>
<td>Normo</td>
<td>93 ± 10</td>
<td>92 ± 10</td>
<td>78 ± 10</td>
<td>75 ± 13</td>
</tr>
<tr>
<td>Diff</td>
<td>−16</td>
<td>26</td>
<td>4</td>
<td>−0.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>−31 to 0</td>
<td>9 to 43</td>
<td>−10 to 18</td>
<td>−15 to 14</td>
</tr>
<tr>
<td>P</td>
<td>0.051</td>
<td>0.007</td>
<td>0.49</td>
<td>0.95</td>
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</table>

Values (in % baseline) are means ± SD; n = 5 hypothermic (Hypo) and 5 normothermic (Normo) pigs. Shown are magnitude of differences between groups (Diff), 95% confidence intervals (CI) and P values. Q = OC20–RP120, start of cooling at 20 min after occlusion (OC) to 120 min after reperfusion (RP); OC20–OC60, start of cooling at 20 min after OC to end of OC at 60 min; RP10–RP120, from 10 min after RP to 120 min after RP; HR, heart rate; SV, stroke volume; CO, cardiac output; SBP, systolic blood pressure.

In ischemic periods beyond 60 min cannot be determined by our results. Hale et al. (11) showed cardioprotection with hypothermia for up to 60 min of ischemia in rabbit myocardium. Miki et al. (14) established that 32°C was more effective than 35°C when the onset of cooling was delayed in rabbit myocardium.

The relative contribution of the protection afforded by hypothermia during the ischemic period versus the reperfusion period cannot be determined by our results. That so little damage was detected after 3 h of reperfusion in our study suggests that “reperfusion injury” was not a significant factor, however. It is generally believed that the events leading to reperfusion injury are established or “primed” during the ischemic period (3). Ultrastructural and functional assessment of myocardium have shown progressive damage over several hours of reperfusion (1). The time course of this damage is consistent with neutrophil accumulation and subsequent injury (1). It is noteworthy that hypothermia also inhibits neutrophil migration and activity (22). Hypothermia protection against reperfusion injury likely involves other mechanisms in addition to inhibition of inflammation, because evidence of cell protection during reperfusion has been seen in isolated cardiomyocyte preparations (24). Cell protection was lost, however, when induction of hypothermia was delayed >15 min after reperfusion (24).

There are conflicting reports concerning the effects of hypothermia on myocardial function. Depressed left ventricular function has been reported with cooling at 25°C (23) and at 34°C in hearts that were paced fairly rapidly (8). Other studies reported an increase in contractile function with mild hypothermia to a level of 31°C in normal hearts (25). As opposed to most inotropic agents, the increase in contractile function with hypothermia has been shown to occur without an increase in myocardial oxygen consumption (20). In the current study, cardiac output was maintained with cooling to 34°C during acute myocardial infarction compared with normothermia despite the decrease in heart rate because of the significant increase in stroke volume. An increase in filling due to a lower heart rate could explain the increase in stroke volume because of a Starling effect. However, this explanation seems unlikely to explain our findings, because pig myocardium is characterized by a positive force-frequency relation, which results in reduced rather than enhanced contractility at lower heart rates (25). In addition, the delayed relaxation associated with hypothermia might be expected to impair filling (25). Thus the increase in stroke volume seen in the current study is consistent with, but does not prove, increased contractility. Whether increased contractile function occurred in the remote nonischemic myocardium or in the ischemic bed cannot be determined from our results.

Clinical implications. It is well established that reperfusion is the most successful treatment for salvaging myocardium during acute infarction. However, numerous recent studies showed a persistence of ST segment elevation, consistent with microvascular injury and “no reflow,” in up to 36% of patients, despite the achievement of Thrombolysis in Myocardial Infarction grade 3 flow in the epicardial vessels (5). The duration of ischemia has been shown to be an important determinant for the degree of microvascular damage in patients (13). Early institution of cooling, before reperfusion, may alter this relationship. Various adjunctive therapies to reduce infarct size in human myocardium have been largely unsuccessful to date. Our results would suggest that endovascular cooling may arrest or at least delay damage to ischemic myocardium, even in the absence of significant collateral flow, when instituted before reperfusion.

The protocol that we used may have relevance for myocardial infarction in humans. We instituted cooling at 20 min after coronary occlusion to arrest ischemic damage in pigs. This is far too brief an interval to be feasible in patients. However, myocardial infarction occurs much more rapidly in pig myocardium. After only 75 min of coronary occlusion, nearly all cells in the AAR are necrosed in pig hearts (12). Necrosis occurs much slower in human myocardium, where reperfusion therapy can save myocardium for up to 12 h after the onset of symptoms (21). The time window for salvage of human myocardium is therefore likely much longer. Milavetz et al. (15) showed that reperfusion up to 2 h after coronary occlusion in patients resulted in salvage of ~80% of myocardium in the AAR, regardless of the presence or absence of collateral flow. However, salvage was greatly dependent on collateral flow if reperfusion occurred beyond 2 h (15). Institution of hypothermia during this critical period of dependence...
on collateral flow may provide ischemic cell protection, as was found in collateral-deficient pig myocardium.

Several issues remain to be addressed before the clinical trials that are beyond the scope of the present study. Issues such as the safety of the endovascular heat-exchange catheter to blood elements and blood vessels must be addressed. Another issue to be addressed is the control of shivering in awake patients that are hypothermic.

In summary, we have shown a major reduction in myocardial infarct size, and preservation of cardiac output, by reducing blood temperature a few degrees in collateral-deficient pigs. The methods used to induce cooling in this large animal model are practical in humans and suggest that clinical trials to test the ability of mild hypothermia to reduce infarct size are feasible.

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REFERENCES


