Safety and Efficacy of Endovascular Cooling and Rewarming for Induction and Reversal of Hypothermia in Human-Sized Pigs

Michael W. Dae, MD; Dong Wei Gao, MD; Philip C. Ursell, MD; Carol A. Stillson, BA; Daniel I. Sessler, MD

Background and Purpose—Numerous studies indicate that mild hypothermia provides substantial neuroprotection. However, current systems transfer insufficient heat to rapidly vary core temperature. We thus evaluated the safety and efficacy of endovascular cooling and rewarming for the induction and reversal of hypothermia.

Methods—In 10 anesthetized pigs (weight, 66±2 kg), a heat-exchange balloon catheter was inserted into the inferior vena cava and used to cool to a core temperature of 32°C and then rewarmed to normothermia. Control animals had 38°C saline infused. Venous blood was sampled before, during, and after cooling. Three animals in each group were killed 1 week later, and the lungs and inferior vena cava were removed for gross and microscopic examination. In 5 additional animals, cardiac output was measured during cooling to 32°C.

Results—Body temperature in the hypothermic animals decreased at a rate of 4.5±0.4°C/h. Animals were subsequently rewarmed to 36.0±0.04°C at 2.5±0.2°C/h. There was no difference in heart rate between hypothermic and control animals, whereas systolic pressure decreased during cooling. Cardiac output was well maintained during cooling. There were no thermal effects on blood elements or blood vessels.

Conclusions—The endovascular heat-exchange system effectively cooled and rewarmed pigs with large thermal mass without producing any adverse effects on blood elements, blood vessel integrity, or cardiovascular function. (Stroke. 2003;34:734-738.)

Key Words: endovascular therapy | heating | hypothermia | neuroprotection | pigs

Animal studies overwhelmingly indicate that mild hypothermia provides substantial protection against cerebral ischemia¹,² and minimizes damage from acute myocardial ischemia.³ Two recent randomized clinical trials showed a significant improvement in outcomes in survivors of out-of-hospital cardiac arrest treated with mild hypothermia.⁴,⁵ Various methods have been used to induce core hypothermia and to ultimately rewarmon patients. Common approaches include cardiopulmonary bypass, application of circulating-water mattresses or blankets, immersion in cold water, and volume administration of cooled intravenous fluids, and lavage of body cavities. With the exception of cardiopulmonary bypass, which is highly invasive, none provides the ability to manipulate core body temperature sufficiently rapidly and precisely for routine clinical use. We thus evaluated the efficacy and safety of a novel endovascular heat-exchange system (SetPoint, Radiant Medical, Inc) in human-sized pigs.

Hypothermia reduces the metabolic rate of hypothermic tissues approximately 7%/°C and causes bradycardia.⁶ However, the effect of mild hypothermia on myocardial contractility remains controversial. For example, depressed left ventricular function has been reported with cooling to 25°C⁷ and at 34°C in hearts that were paced fairly rapidly.⁸ In contrast, others report that mild hypothermia improves contractility in normal hearts.⁹,¹⁰ We thus also evaluated the effects of endovascular cooling on cardiac output and systemic hemodynamic responses.

Materials and Methods

This investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health, publication No. 85-23, revised 1996. The Institutional Committee on Animal Research approved the protocol.

Endovascular Cooling

A heat-exchange balloon catheter (SetPoint System, Radiant Medical, Inc) 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, 25 cm in length, mounted on the distal portion of a multi-lumen shaft (Figure 1). The shaft has an inflow lumen, an outflow lumen, and a guidewire lumen. The catheter with the unexpanded balloon has a diameter of 9.2F and is...
Protocol

Ten pigs of either sex, weighing 60 to 70 kg (mean weight, 66±2 kg), were anesthetized with intramuscular ketamine (20 mg/kg), lidocaine (2 mg/kg), and atropine (0.04 mg/kg). Their tracheas were intubated and lungs mechanically ventilated with a mixture of isoflurane (1% to 4%) and oxygen. The heat-exchange catheter was inserted via the femoral vein and positioned properly in the inferior vena cava. Proper position was documented radiologically. The animals were not paralyzed, and no shivering was observed.

Saline was perfused through the catheter to produce systemic cooling or warming. Saline temperature ranged between 4°C and 45°C, as necessary. In the hypothermic group, the animals were cooled to an esophageal temperature of 32°C (n=5), maintained at 32°C for 1 hour, then rewarmed to 36°C because this is a temperature beyond the shivering threshold and the temperature at which patients are often extubated. The body’s metabolism can raise temperature the remainder of the way to normothermia. This also avoids the potential for transient hyperthermia. In the normothermic control animals (n=5), 38°C saline was infused into the catheter, the catheter was scaled, and the animals were maintained at normothermia throughout the remainder of the experiment with the use of a forced-air warming blanket (Bair Hugger, Augustine Medical, Inc.).

The effects of mild endovascular hypothermia on cardiac output were assessed in 5 additional animals. A median sternotomy was performed after induction of anesthesia as described above. The pericardium was opened, and the aorta was isolated. A 28-mm ultrasonic flow probe (Transonic Systems, Inc) was filled with coupling gel and placed around the root of the ascending aorta. Core body temperature was then decreased to 32°C and immediately rewarmed to 37°C. The flow probe was connected to a dual-channel flowmeter (model T206, Transonic Systems, Inc). Cardiac output was digitized at 200 Hz with an analog-to-digital converter (Biopac Systems, Inc) and recorded continuously on a computer. Hemodynamic data were similarly recorded and analyzed with the use of Acknowledge software (Biopac Systems, Inc).

Measurements

Heart rate from the ECG, femoral arterial pressure, and arterial oxygen saturation (pulse oximetry) were monitored continuously. Distal esophageal temperature was measured continuously with a 9F multipurpose series 400 thermistor temperature probe (Tyco-Mallinckrodt, Inc) interfaced with the SetPoint system. The accuracy of this system is near 0.1°C.

Blood samples were removed from the femoral vein at baseline, after 30 minutes at 32°C, and at the end of rewarming. Samples were removed at comparable times in the controls. Analyses included white blood cell (WBC) count, platelet count, and plasma-free hemoglobin. Samples were analyzed for complete blood cell count and platelet count (IDEXX Veterinary Services) and plasma-free hemoglobin to assess hemolysis (Analytixs, Inc).

After rewarming (or a comparable time in the normothermic animals), the femoral vein and the catheters and sheaths were removed surgically in a single specimen in 2 of the animals from each group. The catheters were rinsed under a gentle stream of saline to remove blood and were assessed visually for the presence of thrombus. The saline wash-off was captured in a basin and assessed visually for thrombus.

In the remaining 6 animals, the catheters were removed through the sheath in the femoral vein. These 6 animals (3 in the hypothermia group and 3 control) were allowed to recover from anesthesia and killed 7±1 days later. The inferior vena cava and the lungs were removed and examined grossly and histologically for evidence of endothelial injury and pulmonary emboli, respectively. The pulmonary vasculature was examined grossly for evidence of pulmonary emboli by an observer unaware of the experimental treatment (hypothermia or normothermia). Samples of the inferior vena cava were removed from the subdiaphragmatic region, fixed in 10% formalin, and subjected to histological analysis. Five random samples of lung parenchyma were removed from each animal (n=15 each for the hypothermic and normothermic animals), fixed in 10% formalin, and processed for histological analysis with hematoxylin and eosin staining. All histological samples were coded and assessed by a pathologist who was blinded to treatment status of the animal.

Statistical Analysis

For comparison of hemodynamic responses in the hypothermic versus control groups, hemodynamic variables were expressed as a percentage of baseline. The single most clinically relevant quantity (minimum heart rate and minimum systolic blood pressure) was then extracted from multiple measurements on each animal. Heart rate (minimum achieved) and systolic pressure (minimum achieved) were compared between the hypothermic and control animals with 2-tailed, unpaired t tests at 3 time periods: during cooling, during maintenance of hypothermia, and during rewarming. For the hemodynamic responses to cooling in the open-chest pigs (cardiac output, heart rate, and systolic pressure), results were expressed as percentage of baseline. Statistical changes were assessed compared with the baseline value by paired t tests. WBC count, platelet count, and plasma-free hemoglobin before and after the study were compared with 2-tailed, paired t tests. Thermal stability at the target core temperature was characterized by the standard deviations of the measurements recorded during this period. The rates of cooling and rewarmed were evaluated with linear regression. Results are expressed as mean±SD; P<0.05 was considered statistically significant.

Results

Core temperature was stable before onset of experimental cooling. Figure 2 shows core temperature and catheter saline
temperature in a typical study during cooling and rewarming. During cooling (n=5), saline inlet temperature decreased to 6.4±4.1°C (range, 3.1°C to 11.8°C). This decreased core (esophageal) body temperature from 37.4±0.9°C to 32.1±0.1°C in 71±25 minutes. The cooling rate averaged 4.5±0.4°C/h. Near the end of the maintenance period, at a core temperature of 32.1±0.1°C, saline inlet temperature averaged 27.4±1.8°C. During rewarming, saline inlet temperature increased to 45.1±0.2°C (range, 45.0°C to 45.5°C). This increased core body temperature to 36.0±0.04°C at a rate of 2.5±0.2°C/h. Core body temperature in the controls (n=5) averaged 38.1±1.1°C (range, 36.9°C to 39.5°C). There were no differences in heart rate between the hypothermic and control animals. Systolic blood pressure was significantly decreased in the hypothermic animals, relative to the controls, during cooling and maintenance of hypothermia but not during rewarming (Figure 3, Table 1). Systolic pressure decreased from 109±18 to 82±11 mm Hg at 32°C (mean arterial pressure decreased from 78±13 to 62±9 mm Hg) (P<0.05 for both). In the open-chest animals, cardiac output did not change, whereas heart rate and systolic pressure decreased compared with baseline (Figure 4).

The platelet count, WBC count, and plasma-free hemoglobin concentration were similar in the hypothermic and normothermic animals and did not change significantly during the course of the study (Table 2). No thrombus was observed on the surface of the catheters from the animals in either temperature group.

One week after surgery, there was no gross evidence of pulmonary emboli in either the hypothermic or control animals. The absence of emboli was confirmed microscopically in the random samples taken from the lungs of each of 6 animals (hypothermia, n=15; control, n=15). Furthermore, there was no microscopic evidence of infarction.

No evidence of thrombus was found in the full length of the inferior vena cava from the diaphragm to the femoral vein in either hypothermic or control animals. There was no gross evidence of damage to the inferior vena cava in either the hypothermic (n=3) or control (n=3) animals. Additionally, microscopic evaluation of the 5 random samples from each inferior vena cava (hypothermia, n=15; control, n=15) revealed no microscopic pathology suggestive of damage to the vessel.

Discussion
Mild hypothermia is a promising therapy for neuroprotection; however, current methods for cooling are not ideal. Humans have considerable thermal mass. As a result, induction of core hypothermia with the use of surface cooling is a relatively
TABLE 1. Circulatory Responses in Hypothermic and Normothermic Animals

<table>
<thead>
<tr>
<th></th>
<th>Cooling</th>
<th>Maintenance</th>
<th>Rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo</td>
<td>88±6</td>
<td>95±13</td>
<td>93±14</td>
</tr>
<tr>
<td>Normo</td>
<td>91±2</td>
<td>88±3</td>
<td>89±6</td>
</tr>
<tr>
<td>Diff</td>
<td>-3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>95% CI</td>
<td>-10 to 5</td>
<td>-7 to 21</td>
<td>-12 to 20</td>
</tr>
<tr>
<td>$P$</td>
<td>0.32</td>
<td>0.27</td>
<td>0.57</td>
</tr>
<tr>
<td>Min SBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo</td>
<td>74±13</td>
<td>68±14</td>
<td>66±20</td>
</tr>
<tr>
<td>Normo</td>
<td>98±11</td>
<td>88±5</td>
<td>81±5</td>
</tr>
<tr>
<td>Diff</td>
<td>-24</td>
<td>-20</td>
<td>-15</td>
</tr>
<tr>
<td>95% CI</td>
<td>-42 to -6</td>
<td>-35 to -5</td>
<td>-36 to 6</td>
</tr>
<tr>
<td>$P$</td>
<td>0.014</td>
<td>0.017</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Values (in % baseline) are mean±SD; hypothermic (Hypo; n=5) and normothermic (Normo; n=5) pigs. Shown are magnitude of differences between groups (Diff), 95% confidence intervals (CI), and $P$ values. HR indicates heart rate; SBP, systolic blood pressure.

Figure 4. Cardiac output (CO), heart rate (HR), and systolic blood pressure (SBP) at each temperature during cooling from 38°C to 32°C and rewarming to 36°C (n=5). *$P<0.05$ compared with baseline. Baseline values: CO, 3.8±0.7 L/min; HR, 84±6 bpm; SBP, 88±8 mm Hg.

TABLE 2. Hematologic Responses in Hypothermic and Normothermic Animals

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Cooling</th>
<th>Rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count, in thousands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo</td>
<td>389±33</td>
<td>347±34</td>
<td>374±76</td>
</tr>
<tr>
<td>Normo</td>
<td>317±89</td>
<td>311±68</td>
<td>300±51</td>
</tr>
<tr>
<td>WBCs, in thousands/µL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo</td>
<td>18.9±1.9</td>
<td>16.4±3.9</td>
<td>16.3±3.8</td>
</tr>
<tr>
<td>Normo</td>
<td>16.4±3.5</td>
<td>16.1±3.0</td>
<td>14.3±4.3</td>
</tr>
<tr>
<td>PFHB, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo</td>
<td>2.7±0.6</td>
<td>3.2±2.0</td>
<td>2.7±1.4</td>
</tr>
<tr>
<td>Normo</td>
<td>2.4±0.5</td>
<td>2.7±1.6</td>
<td>2.9±1.0</td>
</tr>
</tbody>
</table>

Hypo indicates hypothermic; Normo, normothermic; PFHB, plasma-free hemoglobin.

slow process. For example, in the recent Hypothermia After Cardiac Arrest trial, the target temperature of 32°C to 34°C was reached an average of 8 hours after the restoration of spontaneous circulation. An additional problem with surface cooling, and the consequent large thermal gradients between the peripheral and core compartments, is overshoot of the target temperature. This was problematic in a recent study of surface-induced hypothermia used to treat patients with acute ischemic stroke. It is therefore difficult to rapidly cool adults without cardiopulmonary bypass.

Endovascular heat exchange represents a novel and efficient means of inducing hypothermia that is applicable in the clinical environment. In the present study the target temperature of 32°C was reached in approximately 1 hour, and core temperature was precisely maintained at the target core temperature, indicating that the computerized control system was effective. The saline-to-blood temperature gradient was considerably less during rewarming than during cooling (13°C versus 31°C) because greater saline temperatures might have damaged red blood cells or coagulation elements. The rewarming rate was thus less than the cooling rate (2.5±0.2°C/h versus 4.5±0.4°C/h). However, slow controlled rewarming will likely be necessary when hypothermia is used for neuroprotection or control of intracranial pressure. Cooling rates may be less in clinical studies in which surface warming is used to inhibit shivering during core cooling. Another issue relates to the fact that the animals were studied under general anesthesia. As a result, the metabolic generation of heat may have been reduced compared with what might occur in some clinical situations in humans. Thus, the observed rate of cooling may be less pronounced in the absence of deep anesthesia.

Cooling and warming with the use of the SetPoint catheter had no effect on platelet count or WBC count and produced no evidence of hemolysis. There was no evidence for thermal injury to blood vessels or blood elements in vivo. Similarly, there was no evidence for deep venous thrombosis after in vivo use of the SetPoint catheter, nor were we able to detect any gross or microscopic pulmonary emboli. We thus conclude that the catheter is clinically biocompatible and does not provoke obvious complications. Clinical trials will involve cooling for longer durations, and any new safety concerns related to the longer duration will have to be addressed. Our study assessed the acute responses to cooling (approximately 1 hour to cool, an additional 1 hour of maintenance, and 2 hours of rewarming). No adverse events were noted in this preliminary study. We chose 32°C because
this likely represents the low end of the target temperature that will be used in clinical trials. Animal studies have shown significant neuroprotection at this temperature, and cardiac arrhythmia is not considered to be an issue until a level of 30°C is reached.

Blood pressure was decreased during cooling relative to the controls. However, pressure tended to decrease in both groups, partly related to the effects of general anesthesia. Blood pressure responses to endovascular cooling during general anesthesia must be further evaluated in clinical trials. Cooling in awake, sedated patients may result in different blood pressure responses from those in anesthetized patients. Cardiac output was maintained with cooling to 32°C despite a decrease in heart rate. Stroke volume therefore likely did not decrease. Although prior studies suggest that hypothermia increases contractility and does so without a concomitant increase in myocardial oxygen consumption, we can only conclude from our data that hypothermia does not appear to severely compromise cardiac function in this model.

An obvious limitation of our study is that we evaluated pigs rather than humans. However, the pigs were similar in size to adult humans. Furthermore, the vascular system in pigs and humans is similar. It is thus unlikely that heat transfer rates or biocompatibility will differ markedly in humans. Issues such as control of shivering will need to be addressed before application of endovascular cooling in awake patients is attempted.

In summary, the endovascular heat-exchange system effectively cooled and rewarmed pigs with large thermal mass. Cardiac output was well maintained during hypothermia to 32°C. There were no adverse effects on blood elements or blood vessels associated with the ranges of saline temperature used for heat exchange. These findings suggest that endovascular thermal management may prove useful in humans.

Acknowledgments
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