Experimental paper

Induction, maintenance, and reversal of therapeutic hypothermia with an esophageal heat transfer device

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\textbf{A B S T R A C T}

\textit{Aim of the study:} To evaluate a novel esophageal heat transfer device for use in inducing, maintaining, and reversing hypothermia. We hypothesized that this device could successfully induce, maintain (within a 1 °C range of goal temperature), and reverse, mild therapeutic hypothermia in a large animal model over a 30-h treatment protocol.

\textit{Methods:} Five female Yorkshire swine, weighing a mean of 65 kg (range 61–70) kg each, were anesthetized with inhalational isoflurane via endotracheal intubation and instrumented. The esophageal device was connected to an external chiller and then placed into the esophagus and connected to wall suction. Reduction to goal temperature was achieved by setting the chiller to cooling mode, and a 24 h cooling protocol was completed before rewarming and recovering the animals. Histopathologic analysis was scheduled for 3–14 days after protocol completion.

\textit{Results:} Average baseline temperature for the 5 animals was 38.6 °C (range 38.1–39.2 °C). All swine were cooled successfully, with average rate of temperature decrease of 1.3 °C/h (range 1.1–1.9 °C/h). Standard deviation from goal temperature averaged 0.2 °C throughout the steady-state maintenance phase, and no treatment for shivering was necessary during the protocol. Histopathology of esophageal tissue showed no adverse effects from the device.

\textit{Conclusion:} A new esophageal heat transfer device successfully and safely induced, maintained, and reversed therapeutic hypothermia in large swine. Goal temperature was maintained within a narrow range, and thermogenic shivering did not occur. These findings suggest a useful new modality to induce therapeutic hypothermia.

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1. Introduction

Induction of hypothermia (a 4 °C decrease from baseline) demonstrably improves outcomes in at least two clinical conditions (adults resuscitated from cardiac arrest and neonates suffering from hypoxic ischemic encephalopathy), and appears to be of benefit in others.\textsuperscript{1–7} Nevertheless, the overall use of therapeutic hypothermia has remained relatively low.\textsuperscript{8–11} The most common methods currently used to induce hypothermia typically require skin contact (with blankets, pads, or ice packs, for example) or intravascular access (for the placement of intravascular cooling catheters); limitations or complexities inherent to these methods may contribute to the underuse of treatment.\textsuperscript{9}

Because new, less-complicated approaches to temperature control may improve adoption of therapeutic hypothermia, we...
evaluated a novel esophageal heat transfer device for use in inducing and maintaining hypothermia. This esophageal device is designed to replace the standard orogastric tube, maintaining its functionality for gastric suctioning and decompression, while additionally connecting to an external heat exchanger. Temperature-controlled water is supplied in a closed-circuit pathway of channels surrounding the central gastric access lumen, thereby enabling a transfer of heat to or from the patient.\textsuperscript{12,13} We hypothesized that this device could successfully induce, maintain (within a 1°C range of goal temperature), and reverse, mild therapeutic hypothermia in a large animal model over a 30-h treatment protocol.

2. Materials and methods

This was a prospective interventional study performed by an experienced research team under a protocol approved by the Institutional Animal Care Committee of the Minneapolis Medical Research Foundation Hennepin County Medical Center. The study utilized methods consistent with current veterinary and USDA standards, with a state-of-the-art, Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International-accredited vivarium. Animal care and handling was in accord with Office of Laboratory Animal Welfare guidance for humane care and use of animals and with regulations outlined in the USDA Animal Welfare Act (9 CFR Parts 1, 2 and 3) and the conditions specified in the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington DC, 1996). Animal experimentation was required to demonstrate the in vivo feasibility of safely and effectively inducing, maintaining, and reversing therapeutic hypothermia with this approach, because no alternative in vitro model can replicate the human cardiovascular physiology involved. The swine model was chosen for its similarity in size, physiology, and thoracic anatomy to humans, and because swine are a well-accepted model of the human cardiovascular system, with similar organ arrangement to humans (specifically with respect to the aorta, carotids, vena cava, azygos, and pulmonary vessels in relation to the esophagus). For this experiment, the swine did not undergo cardiac arrest, since the objective was to evaluate the performance and safety of the device, rather than the effectiveness of therapeutic hypothermia in treating post cardiac arrest neurologic injury.

2.1. Anesthesia, preparation, and monitoring

Five female Yorkshire Crossbred Swine with a mean weight of 65 kg (range 61–70 kg), were selected for this study. This number was chosen after including input from the U.S. Food and Drug Administration, and by attempting to balance a desire to demonstrate efficacy while identifying significant safety findings within the constraints of the funding available for this study; however, no formal estimates of precision on performance parameters were undertaken a priori. After acclimation to the facility for at least 2 days, and with 12 h food restriction but free access to water before the investigation, swine were pre-medicated with intramuscular ketamine (10–15 mg/kg of Ketaset, Fort Dodge Animal Health, Fort Dodge, Iowa) followed by inhaled isoflurane at 0.6–2.5%. The swine were endotracheally intubated with a size 7.0 endotracheal tube. Normal saline (warmed to ∼37°C) was infused through the intravenous heparin bolus (100 units/kg) and 500 units of heparin every hour until the study was completed. Using aseptic surgical conditions, a micromanometer-tipped (Mikro-Tip Transducer, Millar Instruments, Houston, Texas) catheter was placed at the right femoral artery to the beginning of the descending thoracic aorta to obtain central aortic blood pressure, and an intravascular thermistor was placed at the left femoral vein and advanced to the inferior vena cava to obtain core swine temperature. Surface electrocardiographic tracings were continuously recorded, and all data was recorded with a digital recording system (BIOPAC MP 150, BIOPAC Systems, Inc., CA, USA). End tidal CO2 (ETCO2), tidal volume, minute ventilation, and blood oxygen saturation were continuously measured with a respiratory monitor (CO2SMO Plus, Novametrix Medical Systems, Wallingford, Connecticut).

2.2. Measurements

Temperature was recorded continuously via an intravascular Biopac TSD202A Fast Response Thermistor. In addition, temperature measurements were obtained and manually recorded via rectal thermistor and temperature-sensing Foley catheter (Bard Medical) placed either in the bladder or in the vaginal vault. Bladder catheter placement was trans-urethral in two swine and suprapubic in three. Temperatures from all sensors were recorded manually at 15 min intervals during active cooling and rewarming, and at 30 min intervals during the 24 h of steady-state period. Serum blood chemistries via arterial blood gas analysis were measured at intervals throughout the 30 h protocol.

2.3. Experimental protocol

The esophageal heat transfer device (Fig. 1) is designed to be placed through the mouth into the esophagus, and is made of extruded medical-grade silicone, similar in size and shape to a large orogastric or Ewald tube (70 cm length and 1.2 cm diameter). Within the device are lumens to provide pathways for the flow of water from an external heat exchanger, and a central lumen to allow suction and decompression of the stomach. The thin walls of the device allow adequate heat transfer while still remaining rigid enough to prevent ballooning, and the flow of water internally is parallel countercurrent.

After anesthesia and preparation, the esophageal heat transfer device was connected to an external heat exchange unit (Gaymar Medi-Therm III, Gaymar industries, Inc., Orchard Park, New York). The chiller, which uses distilled water as the coolant, was turned on to begin circulating coolant through the device. The tip of the device was lubricated with a water soluble lubricant and inserted through the oropharynx into the esophagus to the depth determined by external measurement in a similar fashion to the placement of standard orogastric tubes. Confirmation of adequate placement was confirmed by auscultation of stomach sounds during insufflation of air via syringe, successful withdrawal of stomach contents through the central gastric access pathway within the device, and
fluoroscopic imaging to provide visual confirmation of placement. Low intermittent wall suction was then connected to the gastric outlet to provide gastric decompression.

After tracheal injury from prolonged contact with the endotracheal tube cuff balloon was discovered on necropsy of the second study animal, the protocol was amended to include the recommended practice during prolonged tracheal intubation of periodically measuring endotracheal tube cuff balloon pressure and maintaining balloon pressure less than 20 cm H2O.

2.4. Cooling

After the completion of swine preparation, instrumentation, and placement of the esophageal heat transfer device, the chiller was set to cooling mode to initiate induction of hypothermia. The cooling objective was a reduction in body temperature to that of mild therapeutic hypothermia (4°C below normal body temperature).

2.5. Maintenance

Upon reaching goal temperature, each animal was then maintained at that goal temperature via the external chiller for a total of 24 h from the start of cooling. During this time, the swine were manually rotated from one side to the other every 4 h to prevent pressure injuries to skin.

2.6. Warming and recovery

Twenty-four hours after the start of cooling, rewarming was initiated by setting the chiller to warming mode. Swine were left uncovered for at least the first 2 h of warming to establish the rewarming capability of the esophageal heat transfer device, but passive warming was added with blankets subsequently to support more rapid rewarming and recovery of the animals. Once swine temperature surpassed 36°C, recovery procedures were initiated, monitoring instruments were removed, and weaning of isoflurane commenced. Swine were extubated once assessed for their ability to maintain independent respiratory effort with adequate arterial saturation (>92%) and end tidal CO2 production (>32 mmHg), and transferred to their cages while spontaneously breathing and slightly sedated for additional monitoring every 20 min for 2 h before being left alone overnight. Animals were given an intramuscular analgesic injection of non-steroidal anti-inflammatory medication (Flunixin) at recovery as well as the day after, and had free access to water and food.

2.7. Histopathological analysis

Swine were scheduled for sacrifice at either 3 or 14 days after recovery for gross pathological and histological analysis, with particular attention to the integrity of esophageal mucosal tissue and adjacent organs after the experimental temperature modification. The time points for analysis were determined from guidance offered by the U.S. Food and Drug Administration, with analyses performed by an independent board-certified and licensed veterinarian and by an independent board-certified and licensed veterinary pathologist.

2.8. Data

The outcome measure was swine temperature, with specific attention to the rates of temperature change during cooling and warming, as well as the variation around goal temperature during steady-state maintenance of hypothermia. Data are reported graphically as means, with standard deviation error bars, with variation around goal temperature reported as the standard deviation of temperature measurements.

3. Results

Five swine were studied from April to June 2012 according to the experimental protocol. The weight of each animal, along with temperature at baseline prior to preparation, temperature at start of cooling, goal temperature, cooling rate, and variation around goal temperature at steady-state, are shown in Table 1. Fig. 2 shows temperature versus time plots for the 5 animals.

3.1. Cooling

Placement time for the esophageal heat transfer device was minimal, typically taking less than 1 min to pass the device through the oropharynx, into the esophagus, and to the stomach. All 5 swine were cooled successfully, with average baseline temperature prior to initiation of inhalational anesthesia for the 5 animals of 38.6°C (range 38.1–39.2°C) (Table 1). After anesthesia, swine temperature dropped an average of 1.2°C (range 0.3–2.6°C) due to heat losses that are known to occur from inhalational anesthesia and also during animal preparation and exposure for vascular access; this drop was largest for the first subject (2.6°C), due to a longer than expected preparation time as the team performed the protocol for the first time. The average rate of temperature decrease was 1.3°C/h (range 1.1–1.9°C/h).

Although our protocol included the option to use pancuronium if needed to stop thermogenic shivering (which is known to prevent successful induction of hypothermia), none occurred in any of the study subjects. Consequently, no swine received pancuronium during any stage (cooling, maintenance, or warming) of the protocol.

3.2. Maintenance

Average deviation from goal temperature was 0.2°C, (range 0.03–0.48°C) across all animals during the maintenance phase of the study (Table 1). Swine #5 had the largest standard deviation around goal temperature, due to problems encountered with the connector on the temperature probe, which had been sterilized and re-used between subjects.

3.3. Warming

Because swine had not suffered cardiac arrest and were not being treated with hypothermia for its known therapeutic benefits (in which slow rewarming is necessary to optimize outcome), swine were rewarmed at the maximum rate provided by the esophageal heat transfer device. Warming rates during the first 2 h (using only the esophageal heat transfer device) averaged 0.4°C/h (range 0.25–0.6°C/h).

3.4. Recovery and histopathology

All swine were recovered from anesthesia successfully and transferred to cages while spontaneously breathing; however, Swine #2 was noted to have labored breathing and suffered a respiratory arrest approximately 4 h after completion of the protocol. At necropsy, this was found to be due to tracheal edema and tissue damage induced by the prolonged pressure contacting the trachea with the inflated endotracheal tube balloon. A lesser degree of tracheal mucosal impact was then found at scheduled necropsy of Swine #1. This problem was addressed by incorporating current recommendations to measure and limit endotracheal
tube cuff balloon pressure to less than 20 cm H2O during prolonged intubation.14

With the exception of Swine #2, all animals were recovered successfully from anesthesia and returned to normal behavioral, eating, and drinking habits. Three swine were sacrificed 3 days after the experimental protocol, and one swine was sacrificed 14 days after the protocol for gross pathological and histological analysis. Multiple sections of each esophagus were taken (cranial, mid-cranial, mid, mid-caudal, caudal, and gastroesophageal junction), and other than mild changes related to gastric acid reflux and retention after the respiratory arrest of Swine #2, no adverse effects from the esophageal heat transfer device were identified in gross or histological analyses (Fig. 3).

4. Discussion

This study adds further evidence to an initial proof of concept study12 that modifying and controlling temperature via heat transfer through the esophagus is effective and safe. The design of the esophageal heat transfer device takes advantage of the robust heat transfer environment surrounding the esophagus via the extensive blood flow from the nearby vena cava, aorta, heart, pulmonary, and aygos vessels. Because the esophagus is surrounded by this large volume of blood flow, the available heat transfer capacity (via conduction across the esophagus and subsequent convection through surrounding blood flow) is large and the effective heat transfer coefficient is not likely to be diminished with temperature reduction as it is with skin during surface cooling.

Prior mathematical models13 suggested the possibility of finding a higher cooling rate than we encountered; however, models utilizing Pennes bioheat transfer equation may overestimate the convective heat transfer coefficient.15 Nevertheless, the cooling rate achieved by the esophageal heat transfer device compares favorably with other approaches, exceeding those of most surface contact devices, and matching most reported rates of cooling in humans with intravascular catheters (0.6–1.7 °C/h, with most reports describing rates between 0.8 and 1.2 °C/h).16–23 In addition, because of the short time required for placement of the device (less than 1 min in our experience), the initiation of cooling can begin almost immediately after a decision is made to cool with this approach. Because placement is simple and analogous to that of standard orogastric tubes, a wide range of healthcare providers could also place the device without need for physician-level skills.

The lack of shivering seen in the test subjects was unexpected. Since skin surface receptors are known to play a significant role in the initiation of shivering,24 and skin counter-warming is recommended as an option to reduce or eliminate shivering, the induction of hypothermia through the esophagus may result in avoidance or

Table 1
Baseline weights, temperatures, and cooling rates of study subjects.

<table>
<thead>
<tr>
<th>Swine #</th>
<th>Weight (kg)</th>
<th>Baseline temperature (°C)</th>
<th>Goal temperature (°C)</th>
<th>Time to goal temperature (min)</th>
<th>Cooling rate (°C/h)</th>
<th>Standard deviation at steady state (°C)</th>
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<td>1</td>
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<td>39.2</td>
<td>35.2</td>
<td>150</td>
<td>1.08</td>
<td>0.28</td>
</tr>
<tr>
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<td>38.6</td>
<td>34.6</td>
<td>210</td>
<td>1.06</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Fig. 2. Temperature versus time plot for the 5 subjects. Vertical lines show initiation point of temperature control (cooling, maintenance, and reversal of hypothermia) with the esophageal heat transfer device.
In general, the cooling rate appeared to decrease with each study subject. Although we cannot firmly establish the reason for this, one possibility is that the fact that devices were reused between subjects, and that despite cleaning between uses, contaminant buildup on the inner or outer walls of the device could have contributed to diminished performance. The distilled water used in the heat exchanger for this experiment was not supplemented with the algacide recommended in the user manual, which may additionally have allowed biofilm buildup in the reused devices, adding further heat transfer resistance.

Limitations of this study include the fact that we started our cooling protocol from different start temperatures for each animal and targeted different goal temperatures. We initially planned to use the same fixed temperature goal for all subjects. However, because swine temperature at baseline varies more than in humans (ranging from 38°C to almost 40°C, with average of 38.8°C), after the first two subjects had been studied, we subsequently set goal temperature with this in mind, using a goal of 4°C from each animal’s baseline temperature prior to start of inhalational anesthesia. We opted for this approach because it avoided possible risks of subjecting animals to larger (>5°C) temperature decreases than typically needed in clinical use and the dangers inherent in temperatures approaching moderate, rather than mild, therapeutic hypothermia, yet still provided the necessary test of the device’s effectiveness in inducing mild therapeutic hypothermia. Moreover, equipoise still exists on what the optimal goal temperature should be in clinical use, with ongoing and recently completed trials evaluating this factor.25,26 Tracheal injury from extended contact with an endotracheal tube cuff balloon is a well-known phenomenon,27 but was unfortunately not anticipated by our group at the start of the study, since long-duration anesthesia and intubation of study subjects (a risk factor for tracheal injury) in survival studies is not commonly performed. We did not subject to the swine to cardiac arrest for this study. Although physiologic changes occur post cardiac arrest, because such a large percentage of total blood volume continues to circulate in close proximity to the esophagus (even in cases of reduced cardiac output), we would not expect dramatic changes in our results if swine were subjected to cardiac arrest prior to use.

5. Conclusions

A new esophageal device successfully induced, maintained, and reversed therapeutic hypothermia in large swine. Goal temperature was maintained within a very narrow range, and thermogenic shivering did not occur. These findings suggest a useful new modality to induce therapeutic hypothermia.

Conflict of interest

EK is an equity owner, and PS is an employee, of a company, Advanced Cooling Therapy, LLC, involved in the commercialization of temperature management devices and have filed patent applications relating to this technology. KL is the founder of, and AM and JR work for, a company, Advanced Circulatory Systems, Inc., developing resuscitative technology that is not related to this work. All other authors have no conflicts of interest related to this work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2013.06.019.

References


Fig. 3. Histopathology of mid-esophagus of swine at 3-day sacrifice (left) and of mid-esophagus of swine at 14-day sacrifice (right).


