Preclinical Trial of a Radiant Heat Device for Whole-Body Hyperthermia Using a Porcine Model

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ABSTRACT

After review of the published clinical experience with systemic hyperthermia, we concluded that a simple system which controls radiant heat balance to supplement metabolic heat might provide several advantages, including: (a) decreased morbidity; (b) elimination of the requirement for general anesthesia; (c) improved patient comfort; and (d) favorable cost-benefit considerations.

We have tested a prototype radiant heat device for whole-body hyperthermia (WBH) in patients with disseminated cancer. From preclinical evaluation of this device, the lightly anesthetized pig was found to be an ideal model for WBH. This species has physiological characteristics closely resembling those of humans. The pig's core, pulmonary artery, liver, rectal, and esophageal temperatures were raised to 41.8° in 80 to 90 min. The air temperatures near the chamber wall never exceeded 65° while the air temperature adjacent to the animal was 46°. Skin temperatures were approximately 42.5° at a core temperature of 41.8°. Once the core temperature is raised to 41.8°, this temperature is maintainable for ~3.5 hr without additional external heating if evaporative losses are controlled.

Prolonged WBH was accomplished with light sedation and without the requirement for endotracheal intubation. No significant acute toxicity was encountered in a series of 6 pigs undergoing 9 separate exposures to WBH. From these results, we conclude that our radiant heat apparatus is feasible for clinical trials. Additionally, the use of the pig as an appropriate animal model for further physiological and pharmacological WBH studies is strongly recommended.

INTRODUCTION

WBH is presently the subject of intense interest as a treatment modality for patients with disseminated cancer. In Phase I trials of WBH in humans, core temperatures have been maintained at 41 to 42° for several hr with acceptable morbidity (2, 4, 8, 11-15, 18, 20, 21). However, it is generally conceded that current technologies for WBH share a number of undesirable features, including cumbersome equipment, a requirement for general anesthesia, and difficulties with respect to temperature regulation and monitoring (1, 3, 9, 19).

Based on the published clinical experience with systemic hyperthermia, we concluded that a simple system which controls radiant heat balance might eliminate some of the undesirable features of existing WBH technologies (6). Systems utilizing an intense radiant energy flux obtained from incandescent bulbs have been used to produce WBH in man (8, 21) and in the pig (7). The use of incandescent bulbs is associated with erythema and burning of the skin. A critical difference between the incandescent bulb devices and our apparatus is the surface temperature of the radiant energy source; in bulbs, the temperature exceeds 1500° while our design uses a 70° wall. The radiant energy from the surface of our device is primarily absorbed by solid surfaces, e.g., the pig, the stretcher, etc., and does not increase air temperature directly. Increases in air temperature occur due to convection at the box surface and at the skin of the subject. The air temperature in the device is such that skin temperature never exceeds 42.5°, which is below the pain threshold. We have developed a prototype radiant heat device and conducted preclinical trials utilizing a porcine model.

We selected the porcine model for our preclinical trials because both the pig and the human display: comparable size and fat distribution; comparable hepatic and cardiovascular physiology; similar temperature regulation via skin convective losses and via evaporative losses by respiration; and similar response to anesthetic agents.

MATERIALS AND METHODS

Animals. Young female Yorkshire Cross pigs (45 to 70 kg) were purchased from the University of Wisconsin Experimental Farms.

Anesthesia. Anesthesia sufficient to immobilize the animals and to eliminate the discomfort associated with invasive procedures was used. Ketamine (20 mg/kg) was administered i.m. as a preanesthetic. After the animals became tranquilized, atropine (15 µg/kg) was administered s.c. to control p.o. secretions. Thiopental (1 to 3 mg/kg) was administered i.v. by intermittent bolus injections in order to maintain sedation.

A catheter placement in superficial veins or in the superior vena cava provided vascular access. A solution containing 5% glucose and 0.225% sodium chloride was infused at a rate of approximately 40 ml/hr. Urinary bladder catheterization and endotracheal intubation were not required.

WBH RHD. The prototype WBH RHD (Chart 1) was provided by Enthermics Inc., Brookfield, Wis. (patent pending). The device includes a housing of stainless steel sheeting mounted on a framework of rectangular stainless steel tubes. An internal chamber with a cylindrical wall formed of 1.22-mm-thick copper and sealed at one end by a disc formed of similar material is approximately 2 m long by 0.9 m in diameter. This chamber is suitable for receiving the body of a subject placed on a stretcher and inserted into the chamber. The stretcher is mounted on rails to permit easy movement in and out of the chamber.

The stretcher includes a headrest for the subject, a dependent panel that assists in sealing the chamber, and a handle by which the stretcher and subject are moved into and out of the chamber. A pair of insulated doors close the open end of the chamber. The doors are in the shape of an inverted L, to form an opening through which the neck of the subject extends. Hence, the subject's head remains...
Cardiac output was determined by a thermodilution technique using a computerized cardiac output computer (American Edwards Laboratories). This computer was also used for measurement of blood temperature. Electrocardiogram and respiratory monitoring were accomplished with standard transducers used in conjunction with the Beckman dynograph recorder. Thermal measurements of s.c. tissues and liver were obtained by placing thermocouples percutaneously (Model TH-6; Bailey Instruments, Saddie Brook, N. J.). Rectal, skin, esophageal, and ambient temperatures were measured using thermistors (Yellow Springs Instruments, Yellow Springs, Ohio) in conjunction with a digital thermometer (Model No. 5810; Digitec, Dayton, Ohio). Thermistors and thermocouples were cross-calibrated.

**Laboratory Determinations.** Anesthetic levels were determined by the clinical toxicology laboratory of the University of Wisconsin Hospitals using a standard gas chromatography method (details available upon request).

Hematological parameters were determined by the Hematology Laboratory of the University of Wisconsin Hospitals using standard clinical techniques. Samples were obtained immediately prior to hyperthermia treatment, at the peak hyperthermia treatment temperature (~41.8°), during the cooling period, at 24 hr and at 48 or 60 hr posttreatment, and at 7 or 10 days posttreatment. These studies included hematocrit, hemoglobin concentration, RBC count, WBC count, platelet count, prothrombin time, and activated partial thromboplastin time; normal values approximate those of humans.

Serum chemistry studies were performed by Raltech Scientific, a division of Ralston Purina, Madison, Wis., using automated standard clinical chemistry procedures. Samples were obtained immediately prior to treatment, at peak hyperthermia treatment temperature (~41.8°), during the cooling period, at 24 hr and at 48 or 60 hr posttreatment, and at 7 or 10 days posttreatment. These studies included: sodium, potassium, chloride, glucose, urea nitrogen, creatine, total protein, albumin, total bilirubin, calcium, phosphorus, magnesium, LDH, CPK, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and alkaline phosphatase. Normal porcine values for serum chemistries approximate those of humans.

**Postmortem Examinations.** Two animals were sacrificed 10 days following hyperthermia treatment. These animals were subjected only to gross examination. A third animal was sacrificed at 11 days posttreatment. Light microscopical sections were prepared from liver, spleen, muscle, heart, kidney, lung, intestine, skin, and s.c. tissue.

**RESULTS**

We observed no morbidity in a series of 6 animals undergoing 9 separate WBH experiments with our radiant heat device.

In each experiment, the animal was heated to a target core temperature of 41.8°. At this point, the animal was removed from the RHD. While there was an immediate drop in the skin temperature following removal from the RHD, the core temperature remained elevated in a stable plateau phase until active cooling was initiated with an alcohol bath.

Chart 2 illustrates an experiment involving a 70-kg animal placed in the RHD without preheating of the apparatus. In this and similar experiments conducted without preheating of the RHD, the heating time to a target core temperature of 41.8° was 120 min. Following removal from the RHD, the animal’s core temperature remained elevated without additional heating for 2 hr, at which time active cooling was initiated with an alcohol bath.

Chart 3 illustrates an experiment involving a second 70-kg animal placed in the RHD after preheating of the apparatus to a temperature of 65.0° adjacent to the chamber wall. In this and similar experiments conducted after preheating of the RHD, the heating time to a target core temperature of 41.8° was reduced to 80 min. We observed no apparent increased stress on the animal.
Chart 2. Responses of physiological parameters and temperatures (°) at different sites during WBH. Top, ambient temperatures in RHD; middle, respiratory rate, heart rate; bottom, rectal, dermal-abdominal, and heart temperatures measured in the pulmonary artery with a Swan Ganz catheter.

Chart 3. Data from an experiment in which the WBH RHD was preheated before the animal was placed in the device. The time to peak core temperature (°) is shorter than in Chart 2. Top, ambient temperatures in RHD; middle, respiratory rate (O) and heart rate (•); bottom, rectal, dermal-abdominal, and heart temperatures measured in the pulmonary artery with a Swan Ganz catheter.

Chart 4. This chart includes mean blood pressure and additional temperature (°) patterns. Top, ambient temperatures in RHD box; middle, mean blood pressure (BP) measured with arterial catheter, respiratory rate, and heart rate; bottom, rectal, liver, muscle, s.c. jowl (outside of box), and dermal-abdominal temperatures.

Chart 5. This chart includes additional cardiovascular parameters. Top, cardiac output, mean pulmonary artery pressure, and wedge pulmonary artery pressure measured with a Swan Ganz catheter; middle, heart rate; bottom, rectal and pulmonary artery temperature (°).

Chart 5 illustrates an experiment involving a fourth 70-kg animal in which cardiac output, mean pulmonary arterial pressure, and pulmonary arterial wedge pressure were monitored throughout the period of WBH treatment. This experiment confirms our repeated clinical observations regarding the stability of the pig's cardiovascular system during WBH treatment. Note that in this experiment the heating time to a target core temperature of 41.8° was prolonged. In this experiment, repeated bolus infusions of 0.9% sodium chloride solution at 0° were utilized in

animal's respiratory or cardiovascular systems with the faster heating time.

Chart 4 illustrates an experiment involving a third 70-kg animal in which the mean arterial blood pressure and various tissue temperatures were monitored throughout the period of WBH treatment. The mean arterial blood pressure remained stable throughout the course of this experiment. The liver temperature-time pattern was qualitatively similar to that found for rectal (core) temperature. In separate experiments, vaginal and axillary temperatures also were observed to closely parallel the core temperature, as determined by rectal probe or cardiac catheter. Esophageal probes in these animal experiments have not provided reliable temperature data.
obtaining the serial cardiac output determinations. Previous studies have indicated that cold 0.9% saline infusions exert a disturbing influence on thermoregulatory mechanisms (5, 7) that may have contributed to the delay in heating.

A transient elevation in the WBC count to approximately 20 to 30% above base-line values at 24 and 48 hr was the only significant hematological change in any of our experiments. Similarly, consistent transient rises in the CPK and LDH, which were respectively related to changes in skeletal muscle and hepatic isoenzyme levels, with no corresponding changes in cardiac isoenzyme levels were the only biochemical changes seen. Table 1 summarizes the serial biochemical determinations obtained in the experiment illustrated in Chart 5.

The gross postmortem examinations of 2 animals sacrificed at 10 days following WBH treatment revealed no significant abnormalities. Light microscopical sections from a third animal sacrificed at 11 days following WBH treatment revealed no significant histological abnormalities of the liver, spleen, muscle, heart, kidney, lung, intestine, skin, or s.c. tissues.

Because the metabolism of anesthetic agents administered during the course of WBH is of interest to our group, serum lidocaine levels were measured in the experiment illustrated in Chart 5. A single 100-mg bolus dose of lidocaine was administered at Time 0, followed by a continuous i.v. infusion of lidocaine at 4.0 mg/min for 1 hr and at 2.0 mg/min for the next 3 hr. The serum lidocaine levels during the entire course of this experiment were between 2 to 6 μg/ml, values which correspond to the therapeutic range for humans.

### DISCUSSION

When evaporative losses are controlled, radiant energy is the major component of heat exchange with the environment (12). Our results demonstrate an apparatus which by controlling radiant heat exchange can provide a simple and efficient means of delivering WBH in large (~70 kg) animals.

Table 2 summarizes a theoretical heat balance of a 70-kg man subjected to WBH utilizing a radiant heat device. Under normothermic conditions, radiation is the major component of energy loss required to compensate for the energy gain produced by metabolism. The second line of Table 2 shows that this normal heat loss becomes a dominant radiant heat gain when a human is exposed to a radiating surface at 55° with evaporative losses minimized by a water-saturated environment. In addition, there is a nonlinear increase in the BMR as the core temperature (Tcore) rises. This nonlinear increase in the BMR is described by the equation

\[ \text{BMR}_{\text{Tcore}} = 85 \times (1.07)^{T_{\text{core}} - 37} \]

(10, 12). At the point in time when a core temperature of 41.8° has been achieved, the BMR will have doubled from 85 to 162 watts.

The third line of Table 2 shows how this change in the BMR can result in a stable elevated core temperature and a new heat balance when a 70-kg man is removed from the RHD after reaching a target core temperature of 41.8° (once again assuming that evaporative losses are minimized). The increased body

### Table 1

Porcine serum chemistries pre- and post-WBH

<table>
<thead>
<tr>
<th>Study</th>
<th>Pre-WBH base line</th>
<th>On cooling 24 hr</th>
<th>48 hr</th>
<th>10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>110.4 mg/dl</td>
<td>167.6</td>
<td>230.9</td>
<td>110.7</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>11.8 mg/dl</td>
<td>15.7</td>
<td>25.5</td>
<td>15.8</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0 mg/dl</td>
<td>1.3</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Total protein</td>
<td>6.0 g/dl</td>
<td>6.0</td>
<td>6.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.3 g/dl</td>
<td>3.3</td>
<td>3.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.2 mg/dl</td>
<td>0.3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>LDH</td>
<td>315.0 IU/liter</td>
<td>284.0</td>
<td>474.0</td>
<td>447.0</td>
</tr>
<tr>
<td>CPK</td>
<td>1085.0 IU/liter</td>
<td>1371.0</td>
<td>2739.0</td>
<td>3663.0</td>
</tr>
<tr>
<td>Glutamic oxaloacetic transaminase</td>
<td>24.0 IU/liter</td>
<td>33.0</td>
<td>54.0</td>
<td>56.0</td>
</tr>
<tr>
<td>Glutamic pyruvic transaminase</td>
<td>23.0 IU/liter</td>
<td>26.0</td>
<td>35.0</td>
<td>37.0</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>52.0 IU/liter</td>
<td>57.0</td>
<td>78.0</td>
<td>53.0</td>
</tr>
<tr>
<td>Calcium</td>
<td>9.2 mg/dl</td>
<td>8.0</td>
<td>9.9</td>
<td>10.1</td>
</tr>
<tr>
<td>Phosphorous</td>
<td>7.3 mg/dl</td>
<td>7.9</td>
<td>10.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.6 mg/dl</td>
<td>1.7</td>
<td>2.0</td>
<td>1.8</td>
</tr>
</tbody>
</table>

| *a* Values obtained in experiment illustrated in Chart 5.
| *b* Isozyme studies for a cardiac contribution to LDH or CPK at all time points were negative.
| *c* Base-line values are typically 400; prior to obtaining this sample the pig had had i.m. injections and surgery to place a catheter in the jugular vein.

### Table 2

Theoretical heat balance for WBH in a 70-kg man subjected to WBH utilizing a RHD

<table>
<thead>
<tr>
<th>Temperature (°)</th>
<th>Heat exchange (watts)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>Skin</td>
</tr>
<tr>
<td>Normothermic</td>
<td>37.0</td>
</tr>
<tr>
<td>In RHD</td>
<td>41.8</td>
</tr>
<tr>
<td>Out of RHD</td>
<td>41.8</td>
</tr>
</tbody>
</table>

| *a* One watt = 1.146 kcal/hr.
| *b* Calculations based upon equations in references (11) and (12).
| *c* Calculations based upon equations in references (5) and (12).
| *d* Evaporative losses minimized when in or out of RHD.
surface temperature results in a radiant heat loss that compensates for the increased BMR.

Our porcine model exhibited a thermal response to WBH that was the same as we predicted (6) for humans. Because the pig lacks eccrine sweat glands, maintenance of a water-saturated environment was not required. (A water-saturated atmosphere during heating is required for human use to limit evaporative heat losses.) Active cooling with an alcohol bath was necessary to rescue the animal from the plateau phase of hyperthermia at 41.8°. In clinical trials involving humans, we find that evaporative losses occurring outside of the radiant heat device can be minimized with the use of a blanket placed over the subject until termination of the hyperthermia plateau phase of hyperthermia is desired. At this point, removal of the blanket permits evaporation to occur and temperature to fall.

The transient elevations of WBC, glucose, LDH and CPK we observed have been described in WBH experiments involving human subjects (2, 4, 11, 13, 16). We did not observe the changes in serum calcium and phosphorus levels reported in the clinical trials referenced.

While we observed a tachycardia in response to hyperthermic stress, the cardiovascular status of the animals remained stable. Specifically, the alterations in systemic arterial pressure, pulmonary wedge pressure, or cardiac output seen in these experiments are less than expected from previous reports. No significant cardiac arrhythmias were encountered. This stability of the cardiovascular status during hyperthermic stress may reflect unique properties of the radiant heat apparatus utilized in our experiments or simply the normal physiological characteristics of our porcine model.

It is of historical interest to note that in the 1930’s Warren (21) treated several patients with a radiant heat device based upon incandescent bulbs without anesthesia. He did not report cardiovascular complications. Since this was at a time when i.v. fluid replacement was not available for the support of patients during prolonged exposures to WBH, we find his results striking.

In a previous study of WBH in pigs by Dickson et al. (7), incandescent bulbs were utilized as the radiant heat source in experiments or simply the normal physiological characteristics of our porcine model.

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