Physiological Studies of Whole-Body Hyperthermia of Dogs

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ABSTRACT

Whole body hyperthermia to 42°C was induced in five normal beagles, using a humidity- and temperature-controlled chamber. Core temperatures of 41.2°-43.0°C were achieved in 50 min and maintained for 60 min. Cardiopulmonary responses included marked tachypnea and tachycardia. Blood gases underwent progressive drops in both PO2 (mean, 117 torr) and PC02 (mean, 22 torr), suggesting the possibility of the development of a diffusion barrier during heating. Increased anion gaps in the face of respiratory alkalosis indicated that a metabolic acidosis developed in the heated dogs. Transient but significant drops in serum potassium and phosphorus were also observed during hyperthermia. Other physiological data, including serum chemistries, complete blood count, colony-forming units, and urine electrolyte excretion, did not change significantly.

INTRODUCTION

Whole-body hyperthermia has been used in the treatment of advanced and widespread cancers in humans and experimental animals with advanced disease (18, 26). Therapeutic effects have been documented for core temperatures of 41-42°C for several h. Methods for producing whole-body hyperthermia included hot wax baths (18), hot air cabinets (20), water blankets (1), space suits (4, 14), water bath (24), perfusion with extracorporeally heated blood (6, 9), and a radiant heat device (21). All these methods produce hyperthermia by the combination of reducing heat loss and the conduction of thermal energy into the body.

Despite the interest in whole-body hyperthermia for treatment of cancer, few studies have included extensive differential tissue thermometry to determine possible variability in tissue temperatures or to obtain detailed physiological data during heating. To circumvent some of the inherent difficulties in patient monitoring and some special requirements associated with many of these methods, a humidity- and temperature-controlled chamber for producing whole-body hyperthermia was evaluated in the dog. Because of the accessibility of the subject, this method permitted careful physiological measurements during hyperthermia treatment, as well as before and after hyperthermia. Specifically, it was of interest to know the uniformity and rate of tissue heating throughout the body, and the physiological and hematological response of dogs heated to 42°C prior to use of similar equipment for human cancer therapy.

MATERIALS AND METHODS

Animals. One female and four male adult beagle dogs (10 to 17 kg) were obtained from the Collaborative Radiological Health Laboratory of

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Whole-Body Hyperthermia Method. Whole-body hyperthermia was produced in a temperature- and humidity-controlled chamber obtained from the Donner Laboratory, University of California, Berkeley. The device is a Plexiglas chamber with 2 gasket-sealed openings, one at the front and one at the rear of the chamber for placement and positioning of the dog. Two smaller portals in the front of the chamber were used for sample collection during hyperthermia. Hand-operated wiper blades were used to clear condensation from the inside of the chamber for patient observation. Chamber temperature and humidity were controlled independently and were adjusted so that the core temperature of the dog would follow the planned heating curve and cooling curve (Chart 1).

RESULTS

During the 3 months of follow-up, there was no mortality in the 5 dogs undergoing whole-body hyperthermia. The acute morbidity was limited to a mild mucoid diarrhea and lethargy, both of which resolved in 2 to 3 days following whole-body hyperthermia. The temperature- and humidity-controlled chamber produced a readily reproducible heating curve, and a mean arterial blood temperature of 41.8°C was maintained with a range of 41.2-43°C (Chart 1). The time necessary to reach core temperatures of 42°C from 38°C was approximately 50 min, and the cooling time was approximately 35 min. Rate of tissue heating and uniformity of tissue heating was similar in all organs measured to the arterial temperature, except for thermistors located in the right lateral s.c. region (up side), midesophageal region, upper esophageal region, and tympanic membrane (Chart 2). Cardiopulmonary response to whole-body hyperthermia included a marked tachycardia and tachypnea (Chart 1, b and c). However, no significant arrhythmias were observed during the heating period. A modest rise in mean systolic blood pressure was observed during heating (Chart 1a). Arterial blood gases progressively dropped during heating, \( P_{\text{aCO}} \) dropped (mean, 117 torr) and \( P_{\text{aCO}} \) (mean of 22 torr) by the end of 60 min of heating (Table 1). Mean pH values ranged from 7.24 in the anesthetized, unventilated patient prior to heating, to 7.40 and 7.39 during hyperthermia. No significant changes in complete blood count were observed during heating, but an increase in the WBC was observed 24 h after whole-body hyperthermia. Leukocytosis components included a neutrophilia, lymphocytosis, and mono-
following whole-body hyperthermia (Table 2). Anion gaps calcu-
creased during heating, but returned to normal levels 24 h
after heating. Serum phosphorus and potassium levels de-
creased prior to heating in unanesthetized dogs
packed cell volume, serum creatinine, glucose, sodium, chloride,
alanine aminotransferase, creatinine phosphokinase, total biliru-
bin, magnesium, and alkaline phosphatase levels. Calcium and
total protein decreased prior to heating in unanesthetized dogs
and remained low during heating and 24 h following whole-body
hyperthermia. Serum phosphorus and potassium levels de-
creased during heating, but returned to normal levels 24 h
following whole-body hyperthermia (Table 2). Anion gaps calcu-
lated from concentrations of serum electrolytes (sodium potas-
sium, chloride, and bicarbonate) using the following formula:

\[
anion\ gap = (Na^+ + K^+) - (Cl^- + HCO_3^-)
\]

increased significantly during whole body hyperthermia when
compared to anesthetized, nonventilated prehyperthermia val-
ues. Urinary excretion of phosphorus, magnesium, and potas-
sium remained unchanged during whole-body hyperthermia. In-
creases in urinary excretion of calcium, sodium, and chloride
were observed in samples taken at the end of whole-body
hyperthermia, but returned to pretreatment levels 24 and 48 h
after whole-body hyperthermia.

**DISCUSSION**

The 5 dogs survived 42°C for 1 h. This was expected, based
on previous survival studies done in nonanesthetized dogs (11).

Smith *et al.* (22) reported diarrhea and weakness in human
patients following whole-body hyperthermia similar to that ob-
served in the dogs in this investigation. The temperature- and
humidity-controlled chamber reliably produced and maintained a
mean arterial temperature of 41.9°C, with an upper and lower
range during the 60-min period of 42.1–42.8°C. The mean heat-
up time from 38–42°C was 50 min. The mean cool-down time
from 42–38°C was 35 min. This was a shorter time period than
the 2 to 2.5 h required for the water blanket technique of Larkin
(13) and the radiant-heat device by Robins *et al.* (21), but may
have reflected the relatively larger surface area:volume ratio of
the dogs used in the present study. The maximum temperature
recorded in some locations in these dogs occasionally was as
great as 43°C for several min. Since these temperatures were
registered for only a brief period of time they were not con-
sidered life threatening. Frasier (9) found that humans undergoing
whole-body hyperthermia tolerated temperatures of 43.2°C for
15 to 30 min without harmful acute effects.

Dogs lack exocrine sweat glands and normally regulate body
heat by panting. Heat is lost by rapidly passing air over an air-
venous exchanger and a venous-arterial blood heat exchanger
located in the nasal cavity (7, 17). Because the dogs were
intubated, these systems for normal temperature control were
essentially eliminated. The principal means of producing hyper-
thermia is heat conducted from the heated humidified air in the
chamber and interference of heat loss from the metabolism of
the animal, which increases with a rise in core temperature (15).
Stabilization of core temperature at or near 42°C was accom-
plished by changing temperature and humidity so that heat
gained equaled heat lost. Similar mechanisms have been used
in other systems (4, 13, 21). Cooling resulted from radiant heat
loss and evaporation of moisture left on the surface of animals
from the water-saturated environment. A water-saturated envi-
ronment during heating may not have been required for dogs but
would be required in humans to limit heat loss through evapo-
ration; however, the water-saturated environment probably did
facilitate heat loss in the cooling phase of whole-body hyper-
thermia in these dogs. Thermistors located in the left lateral s.c.
tissues (up side), mid- and upper esophageal locations, and
 tympanic membrane had wide temperature ranges when com-
pared with other thermistor locations. These wide ranges were
attributed to the superficial location of the s.c. and tympanic
membrane thermistors and were more sensitive to chamber
temperatures. Consistently lower temperatures in the mid- and
upper esophageal thermistor locations reflected cooling from the
rapid movement of room temperature gases in the trachea.

The tachycardia associated with whole-body hyperthermia
was significant and greater in magnitude than those reported in
humans (4). Tachypnea associated with whole-body hyperther-
mia has been reported in the pig (21), in humans (25), and in the

<table>
<thead>
<tr>
<th>Time</th>
<th>PaO₂ (mmHg)</th>
<th>PaCO₂ (mmHg)</th>
<th>Arterial pH</th>
<th>Anion gap</th>
</tr>
</thead>
</table>
| 1 h preheat period (be-
gin heat up)           | 383 (410–350)* | 50 (49–56)  | 7.24 (7.20–7.27) | 11.8 (7.5–13.7) |
| Begin heat period (fol-
lowing heat up)        | 313 (477–173) | 30 (12–52)  | 7.34 (7.49–7.29) | 17.9 (29.5–6.5)  |
| End heat period        | 266 (391–131) | 28 (18–43)  | 7.39 (7.52–7.25) | 18.5 (24.4–5.5)  |

* Numbers in parentheses, range.
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Table 2

<table>
<thead>
<tr>
<th>Mean urinary excretion (ratio of creatinine/element)</th>
<th>Mean serum levels</th>
<th>Mean WBC/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phosphorus (mg/dl)</td>
<td>K+ (mg/dl)</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Preheat, unanesthetized</td>
<td>0.02</td>
<td>1.65</td>
</tr>
<tr>
<td>Preheat, anesthetized</td>
<td>0.07</td>
<td>3.0</td>
</tr>
<tr>
<td>Begin 42°C heating</td>
<td>0.06</td>
<td>3.8</td>
</tr>
<tr>
<td>End 42°C heating</td>
<td>0.13</td>
<td>3.2</td>
</tr>
<tr>
<td>Postheating</td>
<td>0.84</td>
<td>9.76</td>
</tr>
<tr>
<td></td>
<td>0.18</td>
<td>2.23</td>
</tr>
</tbody>
</table>

Dog (17). Tachypnea in the dogs in this study, although high, was consistent with that reported by Nemoto and Frankel (17) with hyperthermia.

Heat loss from the lungs is considered small under normal circumstances (15), but because of the high respiratory rate it undoubtedly contributed to the consistently lower temperatures observed in the upper and midesophageal regions. Since intrathoracic temperature would be important in the clinical application of whole-body hyperthermia, we are currently using an in-line heater in our respiratory system which has raised the measured esophageal temperature. The increased respiratory effort may have also been partially responsible for the observed metabolic acidosis. Increased levels of serum lactate have been reported in tachypneic dogs undergoing whole-body hyperthermia with normal PaO2 and hemoglobin saturation (8). Metabolic acidosis has also been observed in human patients with increased respiratory rates undergoing whole-body hyperthermia (15, 25). The drop in Pco2 during whole-body hyperthermia was consistent with the tachypnea. The significant drop in PaO2 (mean, 177 torr) was not consistent with a tachypneic state. This drop in PaO2 may be explained by either the development of pulmonary shunting (16), increased oxygen demand due to temperature (8, 25), increased oxygen demand associated with a tachypneic state (23), a diffusion barrier such as pulmonary edema (10), or a combination of these mechanisms. Pulmonary edema has been reported as a complication of whole-body hyperthermia in humans (15).

The initial low arterial pH was attributed to the slow spontaneous breathing and hypercarbia associated with a nonventilated, anesthetized animal during probe placement. During hyperthermia, tachypnea developed, producing a respiratory alkalosis (arterial pH, 7.42) similar to that reported by Bull et al. (4) in human patients. Despite the alkalotic arterial blood pH, the dogs developed a metabolic acidosis, as indicated by the large calculated anion gaps. Metabolic acidosis has been previously reported in humans undergoing whole-body hyperthermia (25), and in dogs it was due to measured elevated serum lactate levels (8).

The leukocytosis observed 24 h following whole-body hyperthermia was characterized by a neutrophilia, lymphocytosis, and monocytosis. Although leukocytosis has been previously reported following whole-body hyperthermia in humans and dogs (4, 5), it has been characterized primarily as a neutrophilia with a lymphopenia. The effects of whole-body hyperthermia on hematopoietic precursor cells have been studied in vitro in humans and in mice (2, 27). Our present in vivo study of canine hematopoietic precursor demonstrated only mild inhibition of cell proliferation following hyperemia at temperatures of 42°C. This was expected since the in vivo studies suggest that significant inhibition of hematopoietic cell proliferation does not occur below a temperature of 43.5°C.

In this investigation, the observed decreases in serum phosphorus and potassium levels during heating were similar to those described in humans during whole-body hyperthermia (1, 3, 15). Urinary loss of these electrolytes remained unchanged, suggesting that these electrolyte changes were due to the development of respiratory alkalosis. However, some human patients maintained normal arterial pH with hypophosphatemia, suggesting that intracellular shifts of serum phosphorus occurred as a direct response to whole-body hyperthermia (12, 18). Increased urinary loss of sodium chloride and calcium was attributed to the saline diuresis produced by fluid administration. Decreases in serum calcium have been previously reported during whole-body hyperthermia in humans (4). In this study, however, the drop in serum calcium levels was observed prior to heating in the anesthetized dogs, and appeared to be associated with a concurrent drop in total protein.

Dogs undergoing whole-body hyperthermia in the temperature and humidity chamber appeared to manifest many of the same physiological behaviors as humans and other species with other methods of whole-body hyperthermia. These included transient lethargy and diarrhea, tachypnea, tachycardia, hypophosphatemia, hypokalemia, metabolic acidosis, and respiratory alkalosis. Physiological mechanisms associated with the significant inhibition to temperatures of 42°C. This is the first in vivo hematopoietic precursor cell study to be done with whole-body hyperthermia indicating resistance to temperatures of 42°C.

Additionally, we have treated 2 dogs with chest metastases for a total of six 1-h treatment sessions. Physiological data obtained were similar to those observed in the beagles. Tumor response to whole-body hyperthermia included decreased growth rate and cavitation, and the latter resulted in spontaneous pneumothorax and death in one of the dogs.

A normal 25-kg adult Yucatan pig was heated and monitored using the same method described for the dogs. The physiological responses of the pig were similar to those of the dog, except for the tachypnea and tachycardia, which were less severe. The dog appears to be a good model to study the temperature and humidity chamber as a preclinical evaluation of this method of whole-body hyperthermia or treatment of disseminated disease in humans.
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REFERENCES


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