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## WHOLE BODY HYPERTHERMIA RESEARCH

### 1. BACKGROUND

ENTHERMICS MEDICAL SYSTEMS has designed and built a Whole Body Hyperthermia radiant heat device capable of efficiently transferring energy to a human subject by the simultaneous delivery of radiative and convective heat. The purpose of this WBH device was to induce hyperthermia in a human subject within a reasonable amount of time without inducing harmful effects - surface burns being the most guarded. In simple terms, the WBH radiant heat device consists of a cylindrical heating chamber contained within a generally rectangular housing, a patient stretcher that can slide completely in and out of the heating chamber, and a special computerized thermometry system to measure critical body temperatures and store the treatment data.

The biological basis for the effective use of a radiant heat device for inducing hyperthermia in patients is firmly grounded in physiological concepts<sup>1</sup>, namely, “if evaporative losses are controlled, a major determinant in the heat balance between a human and the environment is radiant energy”. The dominant heat loss mechanism in a human subject is the evaporation of perspiration, and it can be controlled by maintaining the patient in a water-saturated air space. Normally the skin temperature is higher than the surroundings and a net loss of heat occurs. However, if the structure surrounding a patient is held at a higher temperature – and its emissivity approaches that of a black body – a substantial net gain of heat can be realized. The external induction of heat produces physiological changes – additional heat is generated through metabolism. This internal heat generation is a strong function of temperature (ranging from 84 Watts at 37°C to 162 Watts at 41.8°C), and is a critical factor in establishing an elevated thermal balance.

During the period of heating from a normal core temperature to 41.8°C, it is important that the water vapor in the air surrounding the patient (in the chamber) be maintained near saturation to minimize evaporative heat losses. In fact, the essential feature of the radiant WBH device is the ability to specifically control radiant heat exchange as a supplement to the metabolic heat production while minimizing evaporative losses. This net energy gain absorbed by the body results in an efficient – yet controlled – elevation of core temperature.

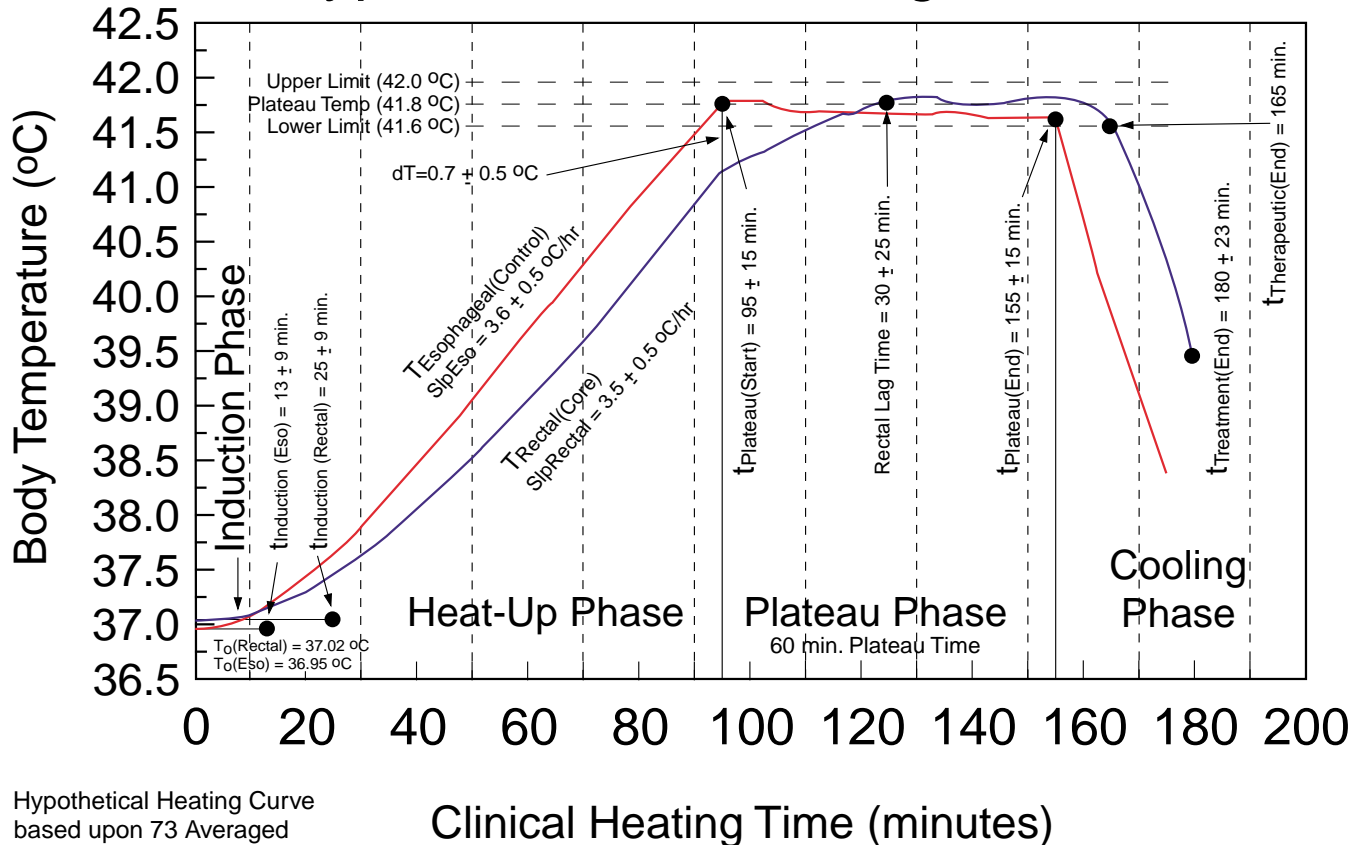
Physiologically at temperatures above 41.5°C there exists a state where the human organism loses its thermoregulatory capacity, and thus cannot overcome the increase in metabolic heat. Once this threshold is reached, cooling is slow even if heating is stopped. It is this point which is utilized in maintaining an elevated body temperature (>41.5°C) without the use of external heat, simply by minimizing heat losses. Since little or no external heat is required to keep the patient at the ‘plateau’ (or ‘target’) temperature, the patient can be removed from the heating chamber and receive concurrent chemotherapy *outside* the device. It has been found that patients can maintain this elevated thermal state for prolonged periods of time by simply wrapping them in plastic sheets and blankets to minimize evaporative heat losses. This state of thermal balance during drug delivery results in *lower* skin temperatures (than core), and many of the typical toxicities associated with older WBH techniques are consequently reduced. This illustrates the ‘*magic*’ of whole body hyperthermia with the radiant ENTHERMICS WBH device – a thermally balanced patient at therapeutic temperature, conveniently outside of the device for drug delivery, and with low skin temperatures. Patients treated with the radiant WBH device also require only sedation, not general anesthesia as with other systemic heating techniques (although general anesthesia can be employed).

The ENTHERMICS WBH radiant heat device employs a high emissivity cylindrical chamber surface at  $\sim 65^{\circ}\text{C}$  which radiates heat through a water-saturated environment to the surface of the patient generating skin temperatures of  $\sim 43^{\circ}\text{C}$  ( $46^{\circ}\text{C}$  in the air above the skin surface) resulting in a desired target core temperature of  $41.8^{\circ}\text{C}$  after approximately 95 minutes of applied heat. These operating conditions have been determined such that pain, patient burns, erythema, sympathetic stimulation and vasodilatation are controlled and minimized. Clinical studies have demonstrated a very typical heating curve exists, and that it is *extremely* reproducible treatment-to-treatment, and patient-to-patient, unlike other types of hyperthermia. The relatively slow heating rates produce lower skin temperatures, maximize blood flow to the organs, minimize the typical temperature gradients which have been shown to exist between various organs<sup>1,2</sup> during heating, and minimize typical WBH toxicities. Whole body hyperthermia produces negligible temperature gradients as compared to those registered during local or regional hyperthermia treatments<sup>3</sup>. The measured heating time (*e.g.*, time to heat a patient from  $37.0$  to  $41.8^{\circ}\text{C}$ ) using the ENTHERMICS device is 95 minutes (*i.e.*, averaged as  $0.05$  degrees/min.)<sup>4</sup>.

Unlike other clinical hyperthermia systems, the ENTHERMICS system uses five (5) *non-invasive* temperature probes to monitor the WBH treatment. The probes are placed in the esophagus, rectum, and three (3) places on the skin (axilla, chest, and thigh). The temperature probes are connected to the special ENTHERMICS computerized thermometry system. The esophageal probe is used as the control probe since it has been established as representative of the pulmonary artery temperature<sup>5</sup>. The rectal probe is also used as an indicator of the core temperature, and has been positively correlated with the bladder temperature<sup>6</sup>. Three (3) separate skin probes are used to monitor the axilla, chest, and thigh temperatures to guard against skin burns. It has been demonstrated that these five (5) non-invasive, strategically located temperature probes are sufficient to ensure a safe and effective treatment.

The temperatures seen in a regular WBH radiant heat treatment are referred to as the *Typical Heating Curve*<sup>4</sup>. This typical heating curve (or profile) represents the average experience, and demonstrates the various distinct phases of the treatments, and the temperatures encountered. The esophageal temperature should be  $\leq 0.5^{\circ}\text{C}$  of the rectal temperature at the start of the treatment (this is also a check of the proper placement of the esophageal probe). The patient is inserted into the prewarmed heating chamber, the chamber is 'sealed', and the treatment begins. The patient is now physiologically interacting with the specialized environment in what is termed the *Induction Phase*. In this phase the patient's senses are evaluating the situation and the patient is absorbing heat; the skin temperatures begin to rise, but the core temperature initially does not. Then the patient's core temperature does begin to rise, almost linearly, as the patient absorbs heat and the metabolic rate begins to double; this is termed the *Heat-Up Phase*. (Technically, the Heat-Up Phase starts, and the Induction Phase ends, when the *instantaneous* clinical heating slope is 80% of the *averaged* clinical heating slope.) At the 'plateau' (or 'target') temperature (as measured by the esophageal probe) of  $41.8 \pm 0.2^{\circ}\text{C}$ , the patient is *removed* from the chamber and the *Heat-Up Phase* ends. The patient (still on the special stretcher integral to the WBH device) is wrapped in insulating plastic sheets and blankets, and this starts the *Plateau Phase*. From the beginning of the treatment the control probe is always the esophageal probe because this probe is most correlated with core blood temperature, and is the most sensitive to changes in temperature. The rectal probe temperature always *lags* the esophageal probe temperature, and does not catch up until about halfway through the Plateau Phase. The relationship between the two probes is always the same, so this is very important in the monitoring of the patient. The average time to reach the Plateau Phase has been established at  $95 \pm 15$  minutes, and the average hourly *Clinical Heating Rate* during the Heat-Up Phase is  $3.6 \pm 0.5^{\circ}\text{C}$  (or approximately  $.06^{\circ}\text{C}$  per minute). The length of the Plateau Phase (or *Time-at-Target*) is determined by the particular clinical protocol in use, but it is most often an hour. The chemotherapy is administered during the Plateau Phase, again according to the particular protocol. The *Cooling Phase* follows the timed Plateau Phase, and is initiated by simply removing the insulating wraps from the patient. The end of the Cooling Phase is marked by a rectal temperature of  $39.5^{\circ}\text{C}$ , and takes about 25 minutes to reach. An average WBH radiant heat treatment lasts  $180 \pm 23$  minutes.

# Typical Clinical Heating Curve\*



\* Hypothetical Heating Curve based upon 73 Averaged Clinical Responses Reported in ENT-ITPN-9812-1.

Clinical Heating Time (minutes)

## 2. PAST CLINICAL EXPERIENCE

Since beginning the clinical investigation into the validity of using WBH as a concomitant modality to chemotherapy, Phase I Clinical Trials have been carried out at various sites by various investigators. For brevity, we will only discuss the largest past contributor to the ENTHERMICS experience, namely, The University of Wisconsin Medical Center at Madison, Dr. H. I. Robins – Principal Investigator. This work was conducted under the sponsorship of ENTHERMICS under an Investigational Device Exemption using FDA-approved protocols. This section summarizes some of the clinical experience.

Both *in vitro* and *in vivo* data demonstrate that carboplatin and moderate hyperthermia administered simultaneously are synergistically cytotoxic. A University of Texas Health Science Center laboratory studied tumor cells in mice and found that malignancies which were minimally responsive to heat alone *and* resistant to carboplatin alone exhibited a marked synergistic response when heat and carboplatin were *combined*. The normal tissue toxicity caused from carboplatin is only minimally enhanced by heat, but the tumor cytotoxicity is markedly enhanced, therefore, indicating a definite increase in the therapeutic ratio<sup>7,8</sup>.

Clinical studies have shown that WBH is associated with the temporary regression of metastatic colon cancer, and initial studies of WBH combined with carboplatin have shown a therapeutic index as high as 3.5<sup>9,10,11,12</sup>. The results of a Phase I trial using carboplatin combined with WBH delivered at 41.8°C was first reported by H. I. Robins at the University of Wisconsin at Madison. Dr. Robins reported that treatments involving the delivery of standard doses of carboplatin combined with WBH were well tolerated by the patients. Evaluation of this data and quantification of related toxicities suggest that a carboplatin dosage level of 400 mg/m<sup>2</sup> provides the optimum balance between safety and efficacy<sup>13</sup>.

Robins<sup>14</sup> reviewed the experience at the University of Wisconsin using WBH delivered using the ENTHERMICS radiant heat device for Phase I toxicity studies. The author reported that this WBH system provided several advantages (over other WBH techniques): “a) decreased morbidity; b) elimination of general anesthesia and endotracheal intubation; c) improved patient comfort; and d) favorable cost-benefit considerations”. Robins reported no significant alteration of pulmonary artery pressures during WBH. Cardio-respiratory changes included increased cutaneous blood flow and volume, sympathetic vasoconstriction of the splanchnic muscle and renal circulation, and an increase in sympathetic output to the heart resulting in increased heart rate and contractility. Peripheral vascular resistance and mean arterial blood pressure decreased. Robins stated that circulatory and respiratory stresses in cancer patients who are treated with WBH are significant. Electrolyte, biochemical changes and hormonal changes have been noted after WBH. Hourly urine output falls significantly. No significant hepatic toxicity was observed. Hematological changes were observed. An increase in stress hormones was recorded during WBH. There was no evidence of peripheral neuropathy observed. Transverse myelitis was observed in four patients treated who had received previous spinal irradiation. Gastrointestinal toxicity included nausea, vomiting and diarrhea. Robins concluded from the results of a Phase I study that “the ENTHERMICS Radiant Heating System provides a safe and effective method of inducing WBH which is suitable for combined modality therapy.” He stated that (at that time) over 450 WBH treatments had been delivered without clinically significant toxicity.

In a biological review of WBH, Robins *et al.*<sup>15</sup> observed that many of the toxicities associated with WBH are related to the methodology used, and that minimal WBH toxicities appear achievable<sup>16</sup> by applying the optimal one. In the past, whole body hyperthermia has been induced by a variety of techniques including bacterial toxin, hot wax, hot water, hot air, extracorporeal blood heating, and a water suit; general anesthesia was usually required, and toxicities were common. The typical toxicities associated with WBH are protracted nausea and vomiting, protracted diarrhea, confusion, pulmonary edema, myocardial infarction, hepatitis, seizures, arrhythmias, disseminated intravascular electrolyte abnormalities, strokes, peripheral neuropathy, pressure sores, and burns.

Robins *et al.*<sup>17,18</sup> reported the results of a Phase I trial using carboplatin and WBH to treat 30 patients with cancer refractory to conventional therapy. Comparison data of the average WBC and platelet nadirs for carboplatin alone and carboplatin combined with WBH demonstrated no enhancing effect from the WBH. Toxicities included nausea and/or vomiting and myelosuppression, which were within acceptable limits, allowing dose escalation to 575 mg/m<sup>2</sup>. Three (3) patients treated at this level experienced Grade 4 myelosuppression with no associated bleeding or infection. No renal toxicity was observed. Only slight effects of WBH on the pharmacokinetics and renal excretion of platinum were observed. Results included a minor response in a lung cancer, a CR (complete response) in a gastrointestinal cancer, a PR (partial response) in a pancreatic cancer, a PR in a small bowel cancer, and a CR in an ovarian cancer. An additional three (3) patients experienced clinical improvement following treatment. Side effects were minimal and the tachyarrhythmias observed in some WBH studies were not observed in these trials. The authors stated that, “We conclude that carboplatin with WBH is well tolerated even at conventional carboplatin doses. Clinical results are consistent with preclinical predictions of an increased therapeutic index for this combination, which encourages future clinical studies.”

Robins *et al.*<sup>5,10,11</sup> reported protocol-specific results of a Phase I study using WBH delivered with the ENTHERMICS WBH radiant heat device to treat twelve (12) patients. The researchers noted that pain relief or a sense of well being was observed in three (3) patients. They reported increased B-endorphin levels in patients. The researchers concluded that the ENTHERMICS device was safe and effective and *appropriate for use in a multi-modality treatment scheme for various systemic cancers*. Overall, a total of 105 human subjects received a total of 681 whole body hyperthermia treatment sessions at the University of Wisconsin at Madison.

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