Whole-Body Hyperthermia Induction Techniques

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Abstract
Currently, there are three techniques used for delivery of whole-body hyperthermia. The simplest of these is direct contact between skin and some surrounding fluid. The surrounding fluid can be either water, wax, air, or other fluid medium; heat is transferred from the surrounding fluid to the body surface. Vessels in the skin surface transfer heat to the perfusing blood, which uniformly distributes it throughout the body.

The second technique uses irradiation of the body surface with nonionizing radiation to deliver heat to the first few cm from the surface. This heat can be picked up by local blood perfusion and distributed throughout the body. One advantage of this method is that heat is deposited at the surface and temperature increases at the surface are lower.

The third technique is extracorporeal perfusion which allows most promising method for delivery of whole-body hyperthermia. This allows for greater control of central temperature via rapid change in temperature of blood passing through the external heat exchanger. The increased ability to control temperature resulting from this advanced instrumentation allows accurate delivery of whole-body hyperthermia. This permits comparison studies of therapeutic effectiveness.

Introduction
When discussing mechanisms for induction of whole-body hyperthermia, one must remember the fever therapy performed by Coley (6) in 1893. He induced fever in cancer patients by administering erysipelas bacteria. These pyrogens induced high fevers with resultant tumor effects, and his was the first report of whole-body hyperthermia. It is the intent here to describe new techniques which use currently available technology for the delivery of whole-body hyperthermia.

Most likely, there is no difference between the heat generated by bacterial infections or medical instruments. The benefit of using external means for delivery of whole-body hyperthermia is the increased degree of control of central or core body temperature within the patient. This control is critically important for comparing treatment protocols to determine maximum effectiveness.

Currently, there are 3 types of technology for the delivery of whole-body hyperthermia: (a) direct skin contact; (b) externally applied power absorption; and (c) extracorporeal perfusion. Each of these methods has specific advantages and will be discussed below.

Heating Techniques

Contact Methods
Of all methods used for whole-body hyperthermia, the easiest are direct-contact techniques. These use contact between the skin (or relatively accessible internal organs such as the lungs) with a heated surrounding fluid. This heated fluid can be water, melted wax, air, etc. The rate of body temperature rise is dependent upon several parameters, some being adjustable from the outside.

The transfer of heat from surrounding fluid through the body is a complex process involving a number of intermediate steps including conductive processes between the fluid and the body surface. Heat transfer also occurs by convection at this interface. Finally, heat transfers from the body surface through the body by conduction through tissue, but in large part it is distributed by heated circulating blood. Each of these heat transfers may be described by a series of mathematical relationships.

The rate-limiting step in this heat transfer is convection at the body surface. Using the Lorenz equation (16), heat flux during natural convection across the interface is equal to:

\[ q = \frac{0.548 (\rho g \beta C_p k^2) \left( T_s - T_c \right)^{0.2}}{\mu L} \]

where \( q \) is heat flux, \( A \) is surface area, \( \rho \) is fluid density, \( g \) is gravitational acceleration, \( \beta \) is fluid coefficient of thermal expansion, \( C_p \) is fluid heat capacity, \( k \) is fluid thermal conductivity, \( \mu \) is fluid viscosity, \( L \) is significant length, \( T_s \) is body surface temperature, and \( T_c \) is fluid temperature. This relationship holds for natural convective processes. If a fluid is forcibly passed over the body surface, the heat transfer occurring across the interface is substantially increased.

This increase is due to the increased value of the convective heat transfer coefficient. This coefficient depends upon the geometry of the material surface, in this case, the tissue; therefore, there is no single equation which governs heat transfer. The equations which describe heat transfer are derived from a series of dimensionless constants used in fluid analysis including Reynolds number, the Nusselt number, the Grashof number, and the Prandtl number.

The 3 methods clinically used for heating patients by direct skin contact include: (a) hot wax baths; (b) heated water blankets surrounding the patient; and (c) a space suit.

Hot Wax Bath. This method for delivering whole-body hyperthermia was pioneered by Pettigrew et al. (13) (Chart 1). In their system, a low-melting-point (43 to 46°) paraffin wax was used with the surrounding fluid acting as a large thermal reservoir. The heat transfer occurring within this system was complex because of the establishment of thermal zones between the patient's skin surface and surrounding liquid wax. Pettigrew et al. (13) reported that, when the liquid wax in the reservoir was heated to only 50°C, the wax directly in contact with the cooler...
patient was solidified, and acted as an insulating material from the higher-temperature molten wax in the bath. Heat transfer was then complicated because of increased number of thermal interfaces between molten wax and body surface. There was convective heat transfer from the molten wax to the solid wax following Equation A for heat transfer under natural convection (assuming no forced wax flow). Heat was subsequently conducted through the layer of solid wax and was governed by the following:

$$q = \frac{kA}{L} (T_1 - T_2)$$

where \(q\) is heat transfer from the molten wax to the solid wax, \(k\) is thermal conductivity of the solid wax, \(A\) is surface area, \(L\) is thickness of the solid wax, \(T_1\) is temperature at the outside surface of the solid wax, and \(T_2\) is temperature at the inside surface of the solid wax. Heat is conducted to the body surface, and transfer through the patient's skin is governed by Equation B with appropriate values for skin thermal conductivity and thickness. The transfer is further complicated since the wax is neither liquid nor solid, but passes through a transition from molten to solid phase.

Heated Water Blankets Surrounding the Patient. The use of a heated water blanket for delivery of whole-body hyperthermia has proven successful at a number of institutions. Barlogie et al. (1) and Larkin et al. (11) have used this system for treatment of patients with disseminated disease (Chart 2). They used 2 Blanketrol (Cincinnati Sub-Zero, Inc., Cincinnati, OH) water blankets sealed together to prevent heat loss. The physical principles which govern the deposition of heat within the patient are similar to those described for hot wax baths. Heat from water inside the blanket is transferred by forced convection to the internal surface of the blanket. By conduction, heat passes through the blanket to its surface. From the blanket surface, heat transfer occurs by conduction between points of direct contact between patient and blanket, or by convection via surrounding heated air. Equations which govern transfer of heat from blanket to patient represent a summation of these 2 mechanisms. Because heat transfer occurs by conductive processes at points of contact between the patient and surrounding blanket, Herman et al. (9) suggested pressure points (i.e., points of close contact between patient and blanket) be carefully padded. This padding increases thermal resistance between blanket and skin, thereby decreasing the heat flow between these surfaces. One advantage of the heated blanket treatment (compared to the hot wax treatment) is that temperatures of the circulating heated water in the blanket are easily and rapidly controlled. Because of this increased control, patient temperature is easier to regulate. Herman et al. (9) reported that, in a series of 6 patients, they maintained core temperatures at 42° while skin temperature was maintained just below 43°. Among complications they reported were second-degree cutaneous burns in 4 of the 6 patients treated. These burns occurred over pressure points at heel and buttock.

When using these techniques, it should be anticipated that these pressure areas will be subjected to increased temperature because of decreased thermal resistance. Therefore, these areas should be carefully padded with a material to increase the thermal resistance, thereby lowering local temperature.

There are numerous blanket systems that can be used for whole-body hyperthermia. Corry et al. (7) also used a Blanketrol water blanket system for whole-body hyperthermia. In this system, he placed the patient between 2 water blankets and sealed them to prevent heat loss. Herman et al. (9) used a Duotherm pad (American Hospital Supply Corp., Michigan Park, IL) and placed the patient between 2 water blankets taped together. The blankets were attached to a modified K-Thermia Water Circulating Reservoir (Model RK-600, Gorman-Rupp Industries, Bellevue, OH) capable of heating water to 50° and cooling water to 40°. Cole et al. (5) also reported the use of the K-Thermia Water Circulating Reservoir for hyperthermia. They also placed patients between 2 blankets. The additional control these systems offer compared to the hot wax bath can be further augmented by increasing the water flow rates through the blankets. With a high flow rate through the blanket, temperature control can be rapid, permitting more accurate control of core temperature.

Space Suit. The space suit approach used by Bull et al. (4) was an extension of the hot water blanket system (Chart 3). The
Whole-Body Hyperthermia Instrumentation

**Externally Applied Power Absorption Methods**

The externally applied whole-body heating methods use non-ionizing electromagnetic radiation for delivery of heat to the body. The body must be within a closed or semiclosed system. Pomp (14) has described the Seiman’s Hyperthermia Cabinet (Selmedic, Inc., Greensburg, PA) which houses a 450-mHz microwave antenna capable of delivering 200 watts of power. This antenna was placed on top of the cabinet and irradiated the patient contained within the cabinet. Additionally, the patient can be placed on a platform under which is contained an induction coil driven at radio frequencies, allowing for heating from below. Temperatures of 40 to 42° are reached within 30 min and, by keeping the temperature of the air within the hyperthermia cabinet between 53 to 60°, patient core temperature is easily controllable.

A second technique which can deliver absorbed power to the skin surface, and subsequently increase core temperature, in an IR chamber was described by Heckel (8) in 1975. The patient is placed within a closed system under a series of IR lamps. These lamps emanate photons which can penetrate the skin to a depth of 1 to 2 mm and subsequently transfer heat to the patient’s core via mechanisms discussed above. Heckel was able to achieve body temperatures of approximately 40°.

Robins et al. in 1983 reported on a radiant heat device for the delivery of whole-body hyperthermia (15). In contrast to incan-

descent bulbs for the production of radiative heat, Robins used a heated chamber of approximately 0.9 meter in diameter and 2 meters long. The wall was formed of 1.22-mm-thick copper and was sealed on one end by a disc of similar material. The wall was heated with an electric heating cable wrapped uniformly circumferentially around the exterior. The patients were inserted into the chamber while lying on a stretcher mounted on rails on the inside. The chamber wall was heated to 70°, and radiant energy from the surface of the chamber was absorbed by the patient. Air temperature increased only marginally, and core temperatures of 41.8° were reached within 80 to 90 min in pigs used in experimental studies. Preliminary human work with this device demonstrated that human core temperatures of 41.8° were achievable within approximately 60 min (0.08°/min), while skin temperatures reached a maximum temperature of 42°. Core temperature control was achieved by moving the patient in and out of the chamber while on the stretcher, thereby radiating heat to a smaller body surface. One specific advantage with this technique was that air temperature surrounding the patient was lower than achievable with other techniques, because the body surface absorbs more radiant heat than surrounding air.

Whole-body hyperthermia has also been delivered with a 433-mHz diathermy unit. Hornback et al. (10) have reported the use of 8 to 10 433-MHz diathermy antennae placed in a series of concentric rings about the patient to increase core temperature. Each antenna was capable of producing 150 to 180 watts, and with an array of 10 antennae, power of up to 1800 watts was delivered. The device was a semiclosed system, since the head and feet of the patient were located outside the ring, with only the trunk of the patient within the ring. The patient was covered with an absorbant material, to absorb perspiration.

Hornback et al. (10) reported core temperatures up to 41.5° with this system. An advantage of this system is that power is deposited over a depth of 2 to 3 cm. Heat is picked up by local perfusion and carried away to increase core temperature. This situation differs from those of direct contact wherein surface temperature is the maximum temperature achieved and the heat is conducted inward from that point. Temperature regulation can be achieved by adjusting the number of amplifiers which are operational. Since as many as 10 antennae can function at one time, the number can be adjusted as temperature increases to bring measured core temperature to the desired value.

**Extracorporeally Induced Hyperthermia**

Three investigators have reported the use of an extracorporeal hyperthermia system (2, 3, 12). This system was developed by Parks et al. (12) and heats blood which is passed through a high-flow arterial-venous shunt between femoral artery and vein (Chart 4). The shunt may be left in place for a long period of time and is capable of handling blood flows up to 1.2 to 2.1 liters/min. Blood is passed from the femoral artery through a pump and into a heat exchanger which is capable of heating blood to temperatures up to 49°. This system can increase temperatures to 41.5 to 42° within 30 to 90 min.

The advantage of this system is rapid control of temperature of externally heated blood. This increased control arises because the blood is heated by passage through the heat exchanger, and the core temperature increase does not depend upon the heat flow through skin. Additionally, because the pump is capable of a high throughput, rapid changes of temperature are achievable.

**Chart 3. Schematic of "space suit" for whole-body hyperthermia.**

**Chart 4. Schematic of arterial-venous shunt.**
There is little "dead time" between adjustment of heated blood temperature on the output side of the heat exchanger and the observation of the core temperature change. This "dead time" is partly responsible for the inherent difficulty in controlling core temperature with the other whole-body hyperthermia systems. An additional advantage of this system is the ease in which successive hyperthermia treatments can be delivered to the patient. The shunt between the femoral artery and vein is made from Dacron, and multiple treatments can be performed due to the ease of connecting the shunt to the heat exchanger. The major disadvantage to this system is the necessity to perform a "cut down" for each procedure to connect the heat exchanger to the shunt. This invasive procedure has the obvious risk of infection resulting from each treatment.

Summary

The major consideration in therapeutic hyperthermia is ability to control heat deposition patterns and resulting temperature increases. With whole-body hyperthermia, this takes on added significance because of potentially serious effects of overheating. Therefore, techniques which allow for more rapid and efficient temperature control should present major advantages over other techniques.

Within the scope of this review, extracorporeal perfusion promises the greatest potential for rapid and accurate temperature control. Heat transfer with other methods depends upon a number of rate-limiting heat transfer interfaces that add substantially to the control response time of the system. It appears that the disadvantages realized with extracorporeal perfusion are small compared to the advantage of increased ability to control core temperature. While certain diseases may lend themselves to heat treatment with other techniques (perhaps because of need to increase skin surface temperature above that of the core), in most situations, extracorporeal perfusion promises most accurate control of whole-body hyperthermia.

References

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