Hyperthermia Induction with Thermally Self-regulated Ferromagnetic Implants[1]

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We have developed a self-regulating thermoseed for interstitial hyperthermia treatment of tumors. The seeds are made of a 70.4% nickel-29.6% copper alloy, and they have a Curie point at 50°C. When exposed to an oscillating magnetic field (90 kHz, 50 Oersted amplitude), these seeds show a sharp drop in the rate of heat production at temperatures above the Curie point. In a simulated treatment of a small visceral mass that had negligible blood flow, the tissue temperature stabilized at the Curie point of the alloy with good temperature homogeneity throughout the volume heated by an array of thermoseeds.

Index terms: Hyperthermia • Therapeutic radiology, interstitial and intracavitary

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THE production of localized hyperthermia for tumor treatment has been hindered by a number of physical and biologic factors, including heterogeneous temperature distribution (1) and the inability of current techniques to selectively heat many smaller visceral masses (2, 3). A variety of interstitial techniques has been proposed to overcome some of these limitations. Most of these methods have depended on heating by electrical currents flowing within the tissues (4–6). Recently several workers have proposed implanting ferromagnetic materials into a tumor mass (7, 8). When placed in an appropriate oscillating magnetic field, such implants become heated through eddy currents flowing within the implant (7) or through hysteresis losses (8). A substantial advantage offered by these ferromagnetic methods is that the implants do not have to be connected to an external power source.

In an effort to obtain better control of tumor temperature, we have developed self-regulating thermoseeds based on the principle proposed by Burton *et al.* (9). These thermoseeds demonstrate a rapid drop in their rate of heat production, *i.e.*, the number of calories generated per second by each implant, at a predetermined temperature (Curie point). This temperature is dependent on the composition of the alloy from which the thermoseeds are made. Theoretical studies suggest that thermoseeds with a Curie point at the therapeutic temperature may improve temperature homogeneity in situations where there is irregular implant geometry or variable thermal properties of the target tissues (10). We investigated the possibility of using self-regulating thermoseeds in clinical hyperthermia by studying temperature distributions in a simulated treatment situation.

Materials and Methods

Thermoseeds: The alloy was made by melting a mixture of 70.4% nickel and 29.6% copper in an induction furnace under argon atmosphere. The resultant alloy was fashioned into a 0.9 mm diameter wire that was cut into 5.5 cm lengths and annealed at 1,100°C for 36 hours. Such an alloy has a Curie point of 50°C at a magnetic field amplitude of 50 Oersted (10).

Magnetic fields: For all experiments a laboratory-built induction coil was used. The coil was 45 cm long, and had an oval cross section (42 × 48 cm). At a frequency of 90 kHz it produced a magnetic field of amplitudes up to 3.98×10^3 A·m^{-1} (= 50 Oersted).

Thermometry: Commercially available copper-constantan thermocouples sheathed with polytetrafluorethylene and an electronic thermometer were used for all temperature measurement. The magnetic field was briefly turned off for each measurement.

Measurement of rate of heat production: A laboratory-built calorimeter was used to measure the rate of heat production of thermoseeds directly. An array of seven seeds was placed inside a thin-walled plastic tube filled with water. A thermocouple was inserted into the tube, and the whole then embedded in a block of polystyrene foam. The resultant calorimeter was then exposed to a magnetic field of 3.98×10^3 A·m^{-1} at 90 kHz, and the rate of heat production was determined from the temperature rise and the heat capacity of the calorimeter.

Results

Figure 1 displays the rate of heat production of our thermoseeds at a variety of clinically relevant temperatures. Up to about 40°C heat production was quite constant, at about 450 mW/cm. As the temperature increased beyond 45°C the rate of heat production dropped rapidly. This is in agreement with the rapid loss of ferromagnetism as the Curie point is approached.

We implanted an array of thermoseeds in a ligated dog kidney to simulate treatment of a small visceral mass with negligible blood flow. A total of 14 needles was implanted into the kidney, arranged parallel to each other about 1 cm apart. The laparotomy incision was then closed, and the dog was placed into the induction coil so that the needles were at the center of the coil and parallel to the axis of the magnetic field. Radiofrequency power was then applied, producing a 90 kHz, 3.98×10^3 A·m^{-1} (= 50 Oersted) amplitude magnetic field. The time course of heating, recorded by a thermocouple in the center of the kidney, is shown in Figure 2. The temperature stabilized at 50°C, coinciding with the loss of ferromagnetism and heat production as the Curie point is reached (Fig. 1).

When thermal equilibrium was reached, a temperature profile of the kidney was recorded by slowly withdrawing a thermocouple through the tissue. Temperature within the kidney fluctuated by no more than ±10% (Fig. 3). During treatment there was no increase in systemic temperature, as measured by thermocouples in the liver and subcutaneous tissues.

Discussion

These data demonstrate that nickel-copper thermoseeds can be used to produce localized heating of a visceral mass with negligible blood flow. The temperature stabilizes at the Curie point of the alloy and is relatively uniform within the implanted volume. Thus our *in vivo* observation agrees closely with the theoretical projections (10) for models with very low blood flow. Burton *et al.* (9) felt it unlikely that a nickel-copper alloy would be useful for the production of thermal lesions. We are pleased that our results suggest the opposite. The raw materials for these thermoseeds are inexpensive, readily available, and easily worked. The heat production characteristics and sharpness of the magnetic/non-magnetic transition of this alloy are also favorable for clinical application. Some concern may be raised over the biocompatibility of these seeds. We are currently investigating a variety of metallic and non-metallic coatings that are compatible and do not perturb the magnetic properties of the implants. We feel however that self-regulating thermo-

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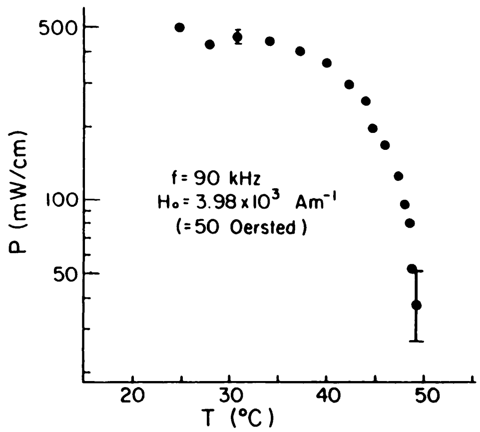
Figures 1-3



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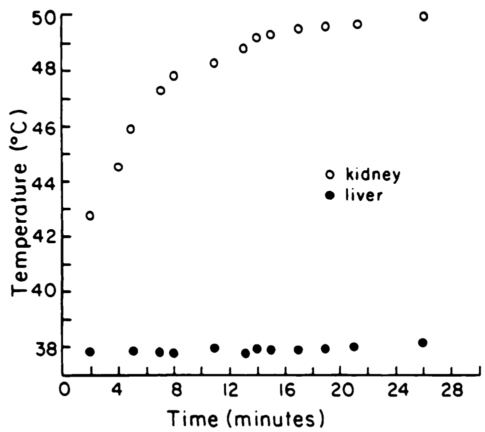

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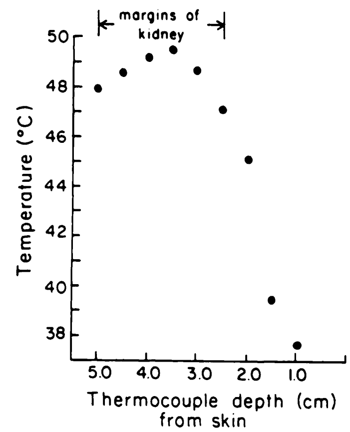

3.

1. Rate of heat production, expressed in mW per cm thermoseed, as a function of temperature. Error bars were estimated from the accuracy and resolution of the thermometer (±0.1°C) and from the heat losses of the calorimeter (0.15°C/min at 49°C). The relatively large error at the higher temperatures occurs because the rate of heat production approximates the rate of heat loss.

2. Time course of heating. Thermoseeds were implanted in the kidney but not in the liver.

3. Temperature profile through kidney and subcutaneous tissue.

seeds such as these offer many advantages for production of localized hyperthermia and should be widely investigated.

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