1985

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[MEDICAL INSTRUMENTATION 19(1), 27-33, 1985]

ABSTRACT

The feasibility of combining local heat treatment with whole- body hypothermia in an effort to improve therapeutic gain was assessed. Superficial, non perfused phantom tumors were fashioned in eight anesthetized mongrel dogs by transplantation of the spleen from the abdomen to a subcutaneous site on the hind limb. After pretreatment of the animal with the vasodilator hydralazine (0.5 mg/kg, IV) to enhance normal tissue perfusion, the spleen implant was heated with a 2450-MHz microwave diathermy apparatus, first with the animal's core body temperature in the normal range (39°C) and then after the animal had been packed in ice to reduce core temperature to 30°C. Applied power density and temperatures in both the phantom tumor and underlying muscle tissue were recorded during brief interruptions of diathermy until steady-state temperatures had been achieved. Under normothermic conditions with time-averaged applied power of 0.038 W/ml to phantom tumor and 0.014 W/ml to underlying muscle, tumor temperature rose to 45.9 ± l.8°C, while muscle temperature remained at 40.5 ± 0.7°C. During whole-body hypothermia applied power could be increased to 0.114 W/ml in phantom tumor and to 0.025 W/ml in muscle. Muscle temperature rose only to 33.8 ± l.6°C, while that of the nonperfused phantom tumor rose to 53.6 ± 4.3°C with systemic hypothermia. These results are in agreement with predictions based on the bioheat transfer equation, i.e., heat extraction from well-perfused normal tissues is greatly augmented by cooling of the arterial blood, allowing greater power input to the tumor-bearing region, higher tumor temperatures, and enhanced therapeutic gain during local heat treatments of poorly perfused tumor nodules.

Key words: cancer, heat therapy, hyperthermia, therapeutic advantage, tumor, safety

Supported in part by Research Career Development Award HL-00587 from the National Heart, Lung, and Blood Institute, U.S. Public Health Service (C.F.B.), and by PHS grant CA-32691 from the National Cancer Institute.

INTRODUCTION

During local heat therapy for cancer, power is applied to the tumor-bearing region by microwaves, radiofrequency current, or high-intensity ultrasound. The goal of such therapy is to elevate tumor temperature to cytotoxic levels, while avoiding thermal damage to surrounding normal tissues. In addition to technological methods for focusing applied power within the tumor [1], there are physiologic methods for accentuating selective temperature elevations in tumor tissue during local heating by manipulation of blood flow. In particular, vasodilator drugs can selectively increase blood perfusion of normal tissues in hamsters, rats, and dogs without increasing blood flow in any of several transplanted tumor types. The augmented perfusion of normal tissues allows greater power input to the treatment region and, in turn, higher steady-state temperatures in the tumor, without elevation of normal tissue temperatures to damaging levels [2. 3]. These effects can be quite dramatic for larger tumor masses, as has been shown both theoretically by solution of the bioheat transfer equation [2, 4] and experimentally by Voorhees and Babbs [3]. In those experiments, after administration of a vasodilator drug, hydralazine, blood perfusion of normal muscle rose approximately three-fold, while blood perfusion of the tumor dropped more than four-fold. In turn, central tumor temperature rose from 39°C to 48°C, a level 9.5°C greater than that of the underlying muscle. Those experiments show that selective heating of tumor tissue to cytotoxic levels is possible when a difference in local blood flow exists and that therapeutically useful perfusion differences can be created with vasoactive drugs.

In theory, such perfusion-related temperature differences between tumor tissue and normal tissue during local heating can be further exaggerated by reduction of arterial blood temperature, because tissue cooling by blood perfusion depends on both local blood flow and the prevailing difference between tissue temperature, T, and arterial blood temperature, T_a [5,6]. In particular, the temperature difference, $T - T_a$, between heated tissue and arterial blood multiplies the effects of perfusion on heat transfer.

Accordingly, we performed the following series of in vivo experiments to determine, in a tumor model, whether whole-body hypothermia in conjunction with the administration of vasodilators can permit lethal temperature elevations sufficient to destroy a neoplasm in a single treatment session, while safe temperatures are maintained in surrounding normal tissue. For this initial study we chose a tumor model system in which blood flow is known to be zero, yet in which histologic and cellular structure is similar to that of many neoplasms.

MATERIALS AND METHODS

Specifically, we sought to measure temperature differences between a nonperfused spleen implant and underlying normal muscle tissues during local microwave therapy. Eight anesthetized dogs were pretreated with the vasodilator hydralazine (0.5 mg/kg, IV), to maximize perfusion of normal tissues [3]. Local microwave diathermy of the phantom tumors was administered, first with each animal's core body temperature at 38.7 ± 0.8°C and then with temperature maintained at 30.3 ± l.4°C.

Tumor Models

Autotransplanted sections of spleen with known zero perfusion were used as tumor models. The spleen of the experimental animal was exposed by midline laparotomy. Excess blood was expressed from the spleen into the venous system by injection of 1 to 5 ml of dilute (l:20,000) epinephrine into the splenic artery. This procedure reduced the spleen to a firm mass of tissue with a "fish flesh" consistency. Splenectomy was then performed, hemostasis secured, and the abdomen closed in layers with continuous silk sutures. The spleen was trimmed to form a discoid approximately 5 to 8 cm in diameter and 0.7 to 1.7 cm thick that was inserted into a subcutaneous pocket on the left hind limb of the experimental animal (fig. 1), and the wound was closed tightly with sutures. This preparation provided an easily created tumor model that was certain to have poor blood flow compared with surrounding normal tissues and that was likely to have other thermal properties similar to those of actual tumors.

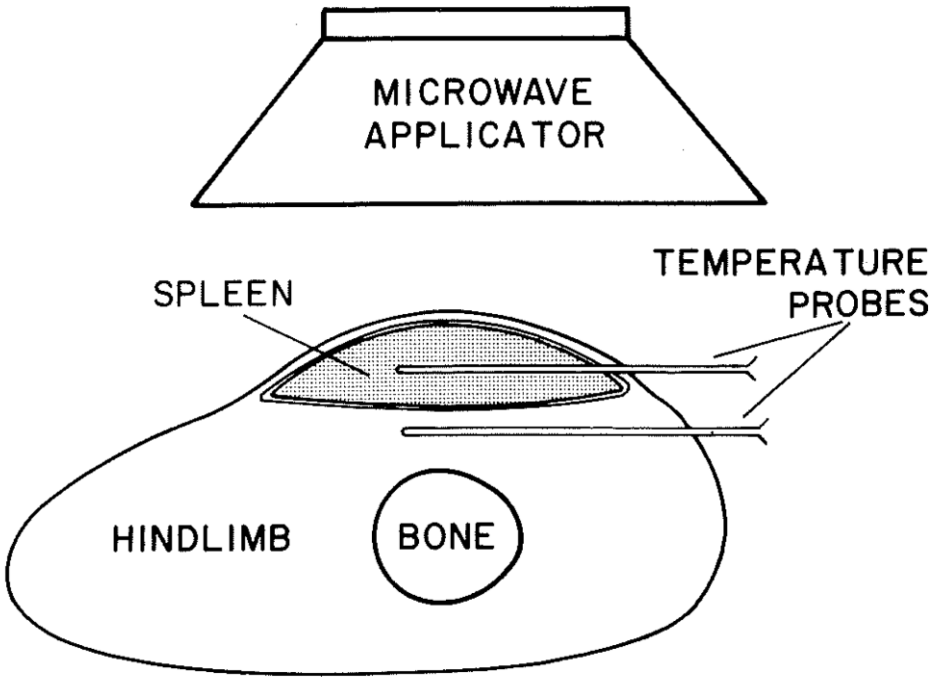

Figure 1 Arrangement of dog hind limb, spleen tumor model, and microwave applicator.

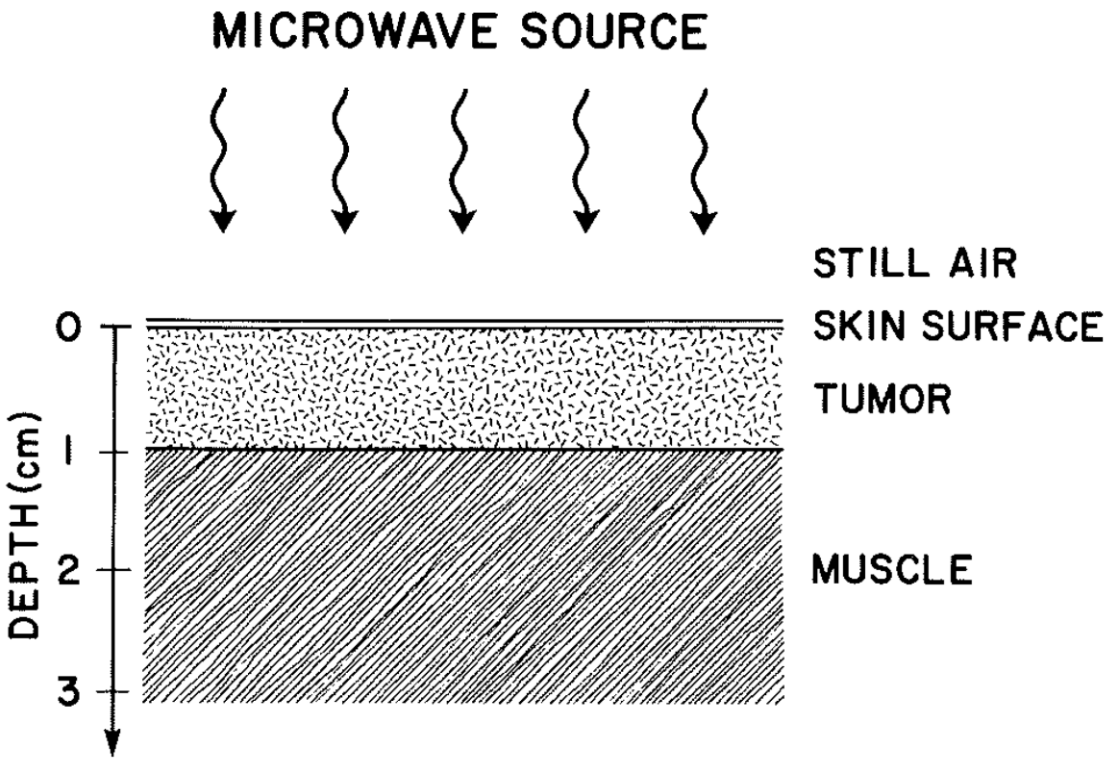

Figure 2 One-dimensional computer model of a superficial tumor.

Heating Apparatus

Local heating was accomplished by a Burdick Model MW/200 microwave diathermy apparatus incorporating a 12 x 18-cm dihedral angle applicator and operating at 2450 MHz (fig. 1). The applicator was placed 2 cm from the phantom tumor surface, with a wooden block 2 cm thick used to gauge the distance, and angled such that incident radiation was approximately normal to the skin surface. The wooden block was gently removed prior to heating, leaving a 2-cm air gap.

Thermometry

Yellow Springs Instruments (YSI) 500 series hypodermic thermistor probes were used to measure tissue temperatures during interruption of the microwave diathermy. Probe resistance values were converted to temperature by an electronic driver that provided a digital readout of temperature to the nearest 0.1°C. This system, in turn, was calibrated against a mercury thermometer traceable to the United States National Bureau of Standards.

Temperature distributions in phantom tumor and underlying normal tissues were sampled by inserting the YSI probes intermittently into preplaced plastic 1-mm microprobes (fig. l) during interruption of the microwave diathermy. This intermittent thermometry technique was chosen to avoid field-probe interactions, particularly self-heating of the probes [7]. An attempt was made to place the microprobes parallel to each other and separated by a distance of 1 cm, such that the interface between the phantom tumor and normal tissue would be approximately halfway between the probes. (The exact placement of the catheters was subsequently confirmed at postmortem examination.) The rise time for the entire thermometry system, with hypodermic thermistors surrounded by plastic cannulas, was 3.7 seconds.

Estimates of the spatial average temperature in the central portion of the phantom tumor and in underlying muscle approximately 0.6 cm from the tumor edge were made by averaging discrete measurements made at three points, 0.5 cm apart, within each microprobe by withdrawing the probe in 0.5-cm increments after the readings had stabilized. Recording of three discrete temperature values in the same cannula by this method required about 20 seconds. The core body temperature of the animal was measured by a YSI probe of larger caliber placed in the esophagus at the level of the point of maximal cardiac impulse palpated on the left chest.

Measurement of Applied Power Density

From the bioheat transfer equation [4, 5] it is easy to show that, beginning with a steady-state condition in which temperature is constant with time, if the applied power density is suddenly changed, the slope of the temperature-time curve, dT/dt, extrapolated back to the time at which power was suddenly changed, is related to the change in applied power, ΔP, by the following expression:

$$\Delta P = \rho c \frac{dT}{dt}, \text{ where}$$

ΔP = the change in applied power (W/cm^3),
ρ = the tissue density (g/cm^3),
c = the tissue-specific heat ($J/g\text{-}^oC$), and
dT/dt = the slope of the temperature-time curve (°C/second).

If, for convenience, the tissue-specific heat and density used are those of water,

$$\Delta P = 4.2 \frac{dT}{dt} \ W/cm^3 .$$

In the present study we used this method to estimate power density in two ways. First, tap water models at room temperature were studied according to the method described in the Appendix. Second, in animal experiments, applied power was determined from the temperature elevations after 60-second periods of heating in each spleen implant and in underlying normal muscle prior to sustained microwave heating. Interrupted heating was then begun to achieve a thermal steady state. Because sustained heating was interrupted briefly from time to time for temperature

measurements, the time-averaged power density at steady state was computed by multiplying the initially measured power density by the duty cycle of heating (i.e., fraction of on-time).

Experimental Protocol

Anesthesia was induced with thiopental sodium and maintained with methoxyflurane, nitrous oxide, and oxygen inhalation. Each dog was placed in dorsal recumbency on a V-shaped animal board. A rubber mat through which either warmed (40°C) or chilled (2°C) water could be circulated was placed under the animal. The animal was monitored electrocardiographically (lead II), and a catheter was placed in a brachial artery to record arterial blood pressure with a strain-gauge transducer and stripchart recorder. Laparotomy, splenectomy, and autotransplantation of the spleen segment to the left hind limb were then performed. All animals received hydralazine (0.5 mg/kg, IV) 15 minutes prior to heating of the spleen implants. The effects of this single dose on arterial blood pressure persisted for the duration of the experiment, except in one animal, to which a booster dose was given.

Local temperature responses to microwave diathermy were measured, first with core temperature maintained at 39°C and then after reduction of core temperature to 30°C by surface cooling. Heating was thus continued for at least 35 minutes, or until tissue temperatures had become stable. During the normothermic phase of the experiment core temperature was maintained as close to 39°C as possible by circulating warm water through the mat. The diathermy apparatus was set to deliver 50 percent of maximal power. Power was then applied during successive intervals lasting 1 to 2 minutes, between which temperatures were measured and recorded, with the aim of bringing normal tissue to a safe, steady-state level of hyperthermia (40°C). By varying the lengths of the off-times between heating periods, the time-averaged applied power could be titrated to maintain the measured normal tissue temperature as close to 40°C as possible. During this normothermic phase of the study, the duty cycle of heating at steady state averaged 40 per cent.

Diathermy was then discontinued, and systemic hypothermia was induced by placing ice bags over the thorax and abdomen and circulating 2°C water through the rubber mat under the animal. This surface cooling technique produced a reduction in systemic (esophageal) temperature of approximately 1 °C/10 minutes and required about 90 minutes. When esophageal temperature had reached 30°C, response to diathermy was again monitored. During this hypothermic phase the diathermy unit was set to deliver 100 per cent of maximal power, and after measurement of applied power density, diathermy was applied for intervals of 3 to 5 minutes, between which temperatures were measured. Since the time required to measure temperature in both tumor and muscle remained less than 1 minute, the effective duty cycle of heating could be increased to 61 percent. As before, the achievement of steady-state tissue temperatures was monitored for at least 45 minutes. This longer time required to achieve steady state is consistent with the greater tissue temperature changes generated during the hypothermic phase.

Postmortem Examination

After completion of the hypothermic phase the animal was killed by intravenous injection of saturated KCl solution, and postmortem examination of the tumor bed was performed. The

position and separation of the cannula tracts were determined by serial sectioning of the phantom tumor with a sharp knife.

Data Analysis

First, for each time of measurement, the three discrete observations of temperature in the phantom tumor and in the underlying normal tissue were averaged. The resultant values were plotted as a function of time during the normothermic or hypothermic phase for each animal. To combine data from all animals, temperature values were obtained at 5-minute intervals along these curves by linear interpolation. The interpolated temperatures at these times were then averaged to provide composite heating curves for the population of eight dogs. Finally, the steady-state temperatures in phantom tumor and muscle were determined as the average of the last three measured temperature values during a diathermy treatment period. Of particular interest was the difference in steady-state temperature between tumor and muscle tissue during systemic hypothermia as compared with systemic normothermia.

Comparison with Theoretical Calculations

To compare measured temperature differences with those that would be expected on the basis of the fundamental physics of heat transfer, we solved the bioheat transfer equation for the particular geometry of a slab of tumor tissue underlain by a much thicker slab of muscle tissue and irradiated from above by a microwave generator (fig. 2). To solve the bioheat equation for the one-dimensional model, a finite difference routine with a mesh size of 500 nodes was implemented using standard computational techniques [8, 9]. The values for absorbed power were assumed to decay linearly with depth into the tissue and were scaled to reflect the time-averaged, steady-state power deposition measured in the experiment. A linear, rather than exponential, function relating absorbed power density to depth was chosen on the basis of measurements made with the particular antenna used in these experiments, as described in the Appendix. Values for muscle blood flow in the presence of hydralazine were taken from published studies [3]; for the purposes of these computations, it was assumed that these values do not change as arterial blood temperature is reduced.

RESULTS

Figure 3 shows temperature-time profiles in phantom tumor and underlying muscle tissue during microwave heating in a representative animal during normothermia (left) and systemic hypothermia to 30°C (right). Figure 4 shows mean temperature-time curves (± 1 SD) for the population of eight animals derived from interpolated values at 5-minute intervals. Much higher steady-state temperature differences between phantom tumor and underlying normal tissue were obtained when arterial blood temperature was reduced to 29°C. The mean tumor-muscle differences averaged 5.4°C for normothermic and 19.8°C for hypothermic conditions. The corresponding temperature gradients (temperature difference/probe separation) were 4.9 ± 2.3°C/cm for normothermia and 18.9 ± 5.6°C/cm for hypothermia.

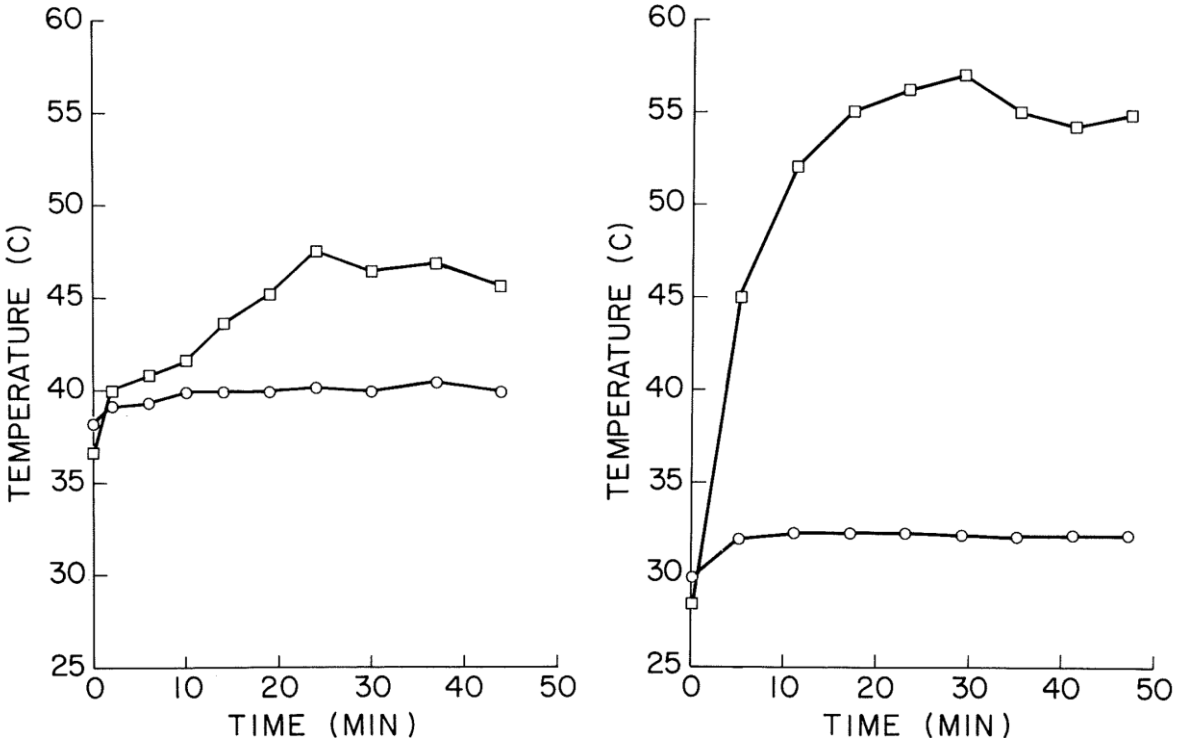

Figure 3 Temperature-time curves for a representative animal during heating: left, systemic normothermia (39°C); right, systemic hypothermia (30°C). Squares represent temperatures in tumor; circles, temperatures in underlying muscle.

Systemic blood cooling allowed safe application of much greater microwave power. The time-averaged power density at steady state was 0.040 ± 0.13 W/ml for tumor tissue and 0.014 ± 0.005 W/ml for muscle tissue during normothermia, compared with 0.114 ± 0.049 W/ml for tumor tissue and 0.025 ± 0.028 W/ml for muscle tissue during the hypothermic phase. These values measured in vivo agreed well with those measured in tap water models with similar power settings: 0.04 W/ml at the tumor probe depth and 0.02 W/ml at the muscle probe depth for the normothermic power setting; 0.12 W/ml at tumor probe depth and 0.06 W/ml at muscle probe depth for the hypothermic power setting. Ventricular fibrillation did not occur during systemic hypothermia in any animal. Neither profound hypotension nor profound bradycardia (table 1) was observed.

TABLE 1. Mean Blood Pressure (mm Hg) During Microwave Diathermy after Hydralazine Pretreatment (0.5 mg/kg, IV) in Eight Dogs

Normothermia (39°C)	Hypothermia (29°C)
60–110	58–76
82–98	95–100
46–66	85–95
91–102	85–100
60–70	78–86
60–64	39–60
60–70	60–75
77–85	50–70

The observed results are substantially in agreement with theoretical solutions of the bioheat equation for a slab of tumor underlain by a much thicker slab of muscle tissue with similar blood flow and power levels. The smooth curves shown in figure 5 represent the expected steady-state temperature-depth profiles derived from the bioheat equation for the values of power applied in this experiment, with the assumption that blood f1ow was zero in the phantom tumor and 60 ml/minute/100 g in the underlying muscle tissue. Tumor thickness in this simulation was 1.2 cm (mean measured thickness). No attempt was made to optimize tumor edge temperature by adjusting applied power. The results for the mathematical model (solid curves in fig. 5) are substantially in agreement with the experiment results. The dramatic improvement in temperature differentials associated with systemic cooling and increased power density is thus largely explained on the basis of heat transfer by conduction and perfusion, as embodied in the bioheat equation. The dashed line in figure 5 represents the calculated temperature distribution that would have been obtained with the same applied power, but with less arterial blood cooling than that used in the experimental model, in order to optimize tumor edge temperature.

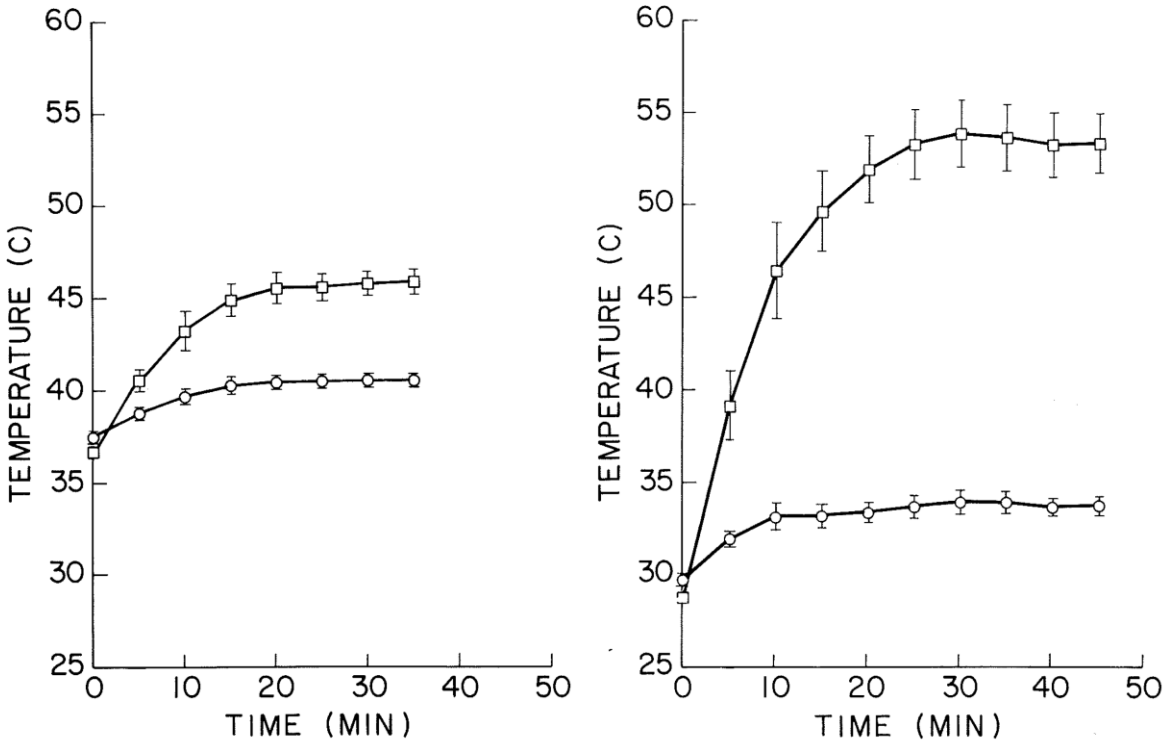

Figure 4. Mean temperature-time curves for the population of eight animals during heating: left, systemic normothermia (39°C); right, systemic hypothermia (30°C). Squares represent temperatures in tumor; circles, temperatures in underlying muscle; error bars, ± 1 SD.

DISCUSSION

This study demonstrates that reduced arterial blood temperature, in conjunction with enhanced normal tissue perfusion, can substantially improve temperature differentials between superficially located, poorly perfused tumors and underlying normal tissues during local heat treatments. With combination therapy, including systemic hypothermia and local hyperthermia (SH/LH), a majority of the nonperfused tumor tissue can be brought to clearly cytotoxic temperatures (>43°C), while normal tissues remain within a clearly safe temperature range (<37^{o}C). Such enhanced temperature differences represent significant improvements in therapeutic gain over conventional hyperthermia therapy. By means of this therapeutic gain, either power levels or blood temperature can be adjusted to bring tumor edge temperatures to satisfactory, therapeutic levels.

Typically, 42°C is considered the ideal tumor edge temperature; this corresponds to the maximal "safe" temperature for normal tissue. An ideal therapeutic temperature distribution can be thought of as one in which all intratumoral temperatures are greater than 42°C and all normal

tissue temperatures are less than 42°C. Once it becomes possible to obtain large temperature differences between tumor and normal tissue, fine tuning of temperature distributions becomes possible. For example, in figure 5 (dashed curve) a therapeutic temperature distribution with all intratumoral temperatures greater than 42°C is simulated with the same power levels used in our experiment by increasing arterial blood temperature slightly. A similarly improved temperature distribution could be obtained by increasing total applied power until edge temperature rose to 42°C. (The former approach may be necessary with the currently available commercial diathermy apparatuses, which have limited power output.)

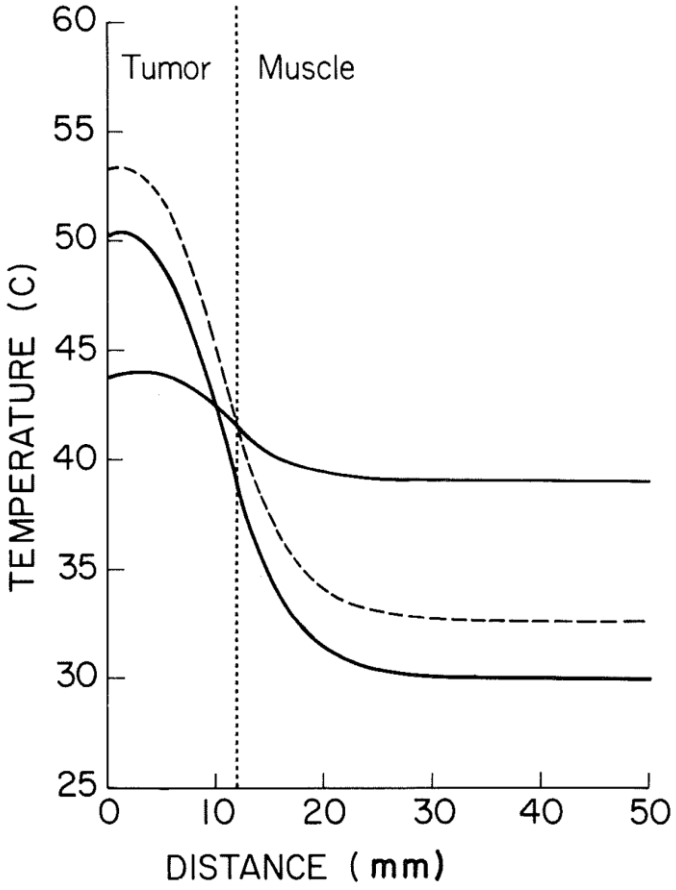

Figure 5. Simulation of experimental results with the bioheat equation for the geometry shown in figure 2. Curves represent calculated temperature distributions within and beneath a nonperfused, superficial tumor, 1.2 cm thick. Shallow solid curve, normothermic arterial blood; steep solid curve, hypothermic arterial blood; dashed curve, adjustment of arterial blood temperature necessary to bring tumor edge temperature to 42°C. Model parameters were similar to those of the animal experiment. Normal tissue perfusion is 0.60 ml/minute/g. Power density, P (W/ml), is computed as a function of depth, d (cm), according to the expression $P = 0.051 - 0.022d$ for conditions of normothermia and $P = 0.153 - 0.068d$ for conditions of hypothermia. Therapeutic gain, related to the slope of the temperature-depth curves at the tumor edge, is greatly improved by increased power density and systemic hypothermia.

The mechanism for the enhancement of therapeutic gain during SH/LH therapy is related to the fact that overheating of normal tissues sets a practical limit on the power that can be applied during treatment of any specific patient. Heat extraction by blood perfusion is related to the difference between local tissue and arterial blood temperatures. During systemic hypothermia, local tissues can be raised to higher temperature levels relative to the arterial blood, without reaching an absolute temperature likely to produce normal tissue damage. Accordingly, heat extraction from well-perfused normal tissues is more efficient, while heat extraction from poorly perfused tumor tissue is relatively less enhanced. This physical process was predicted for spherical tumor models by Oleson et al. [10] in a previous publication and is predicted as well for the bilayered slab geometry (fig. 5).

Clinically, Hahn and Kim [11] heated superficial tumor masses that they believed to have reduced blood flow. The temperature elevations that they measured in normothermic patients using an inductive heating apparatus (roughly 42°C in tumor and 40.5°C in underlying muscle) were not unlike those achieved in our phantom tumor models in normothermic animals. Additionally, Song et al. [12] and von Ardenne and Kruger [13] showed that greatly decreased perfusion of transplanted carcinomas in the rat may occur during the first 24 hours after an initial heat treatment as a result of microvascular stasis. A similar decrease in tumor perfusion may be produced with pretreatment by vasodilator drugs [3].

Therefore, we believe that a clinical analog to the present experiment can be created in humans, especially during the second and successive heat treatments of superficial tumor nodules or after pretreatment with such vasodilator drugs as hydralazine. Since it is well known that patients tolerate systemic hypothermia during cardiovascular surgery and other procedures, it is not clinically inconceivable that, for patients with superficial tumor masses that are refractory to conventional therapy, combination SH/LH treatment similar to that described in this paper may offer a practical and effective alternative.

The authors thank Ralph C. Richardson for helpful suggestions and Susan D. Merritt and Teresa M. Skojac for technical assistance.

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APPENDIX

To measure the specific absorption rate (SAR) of microwave power independently as a function of depth in an irradiated aqueous medium, such as tissue, we performed experiments with a cylindrical beaker of tap water based on the following rationale. For a cylinder of water of cross-sectional area A and depth h, if microwave radiation is applied from one end of the cylinder, the total absorbed power in volume, V = Ah, is

$$P_T(h) = \int_0^h SAR \cdot A dx .$$

In turn,

$$SAR = \frac{1}{A} \cdot \frac{dP_T}{dh} .$$

It is easy to perform an experiment in which P_T is measured for various depths, h, by placing the microwave applicator a fixed distance (2 cm) under a glass beaker of water at room temperature. The water is irradiated from below for a short interval, Δt; the water is stirred, and the temperature rise, ΔT, is measured immediately. Because the water begins at room temperature and ΔT is small, thermal losses to the environment are negligible. P_T is then calculated as

$$P_T = 4.2V \frac{\Delta T}{\Delta t} .$$

The process is repeated with different depths of fresh water at room temperature, until a curve of P_T versus depth is created. The slope of this curve, determined graphically and divided by A, is the desired function of SAR versus depth. Such measurements of the SAR-depth integral require the simplest phantom possible. They avoid the complications of thermal diffusion and convection within a phantom and the uncertainty as to location of temperature probes that are associated with direct measurements of SAR. They also provide a spatial average value of SAR over an area, A, corresponding in size to the treatment area--the desired result in the present studies.