1991

Effective Estimation and Computer Control of Minimum Tumour Temperature During Conductive Interstitial Hyperthermia

J A. DeFord

Charles F. Babbs
Purdue University, babbs@purdue.edu

U H. Patel

M W. Bleyer

J A. Marchosky

See next page for additional authors

Effective Estimation and Computer Control of Minimum Tumour Temperature During Conductive Interstitial Hyperthermia

J.A. DeFord †, C.F. Babbs †, U.H. Patel †,

M.W. Bleyer *, J.A. Marchosky ‡, C.J. Moran §

† Hillenbrand Biomedical Engineering Center
Purdue University
West Lafayette, IN 47907 (USA)

* Cook Incorporated
925 South Curry Pike
Bloomington, IN, 47401 (USA)

‡ Neurosurgical Associates
224 South Woods Mill Road
Chesterfield, MO 63017 (USA)

§ Radiological Associates
3015 North Ballas Road
St. Louis, MO 63131 (USA)

Address for correspondence:

John A. DeFord, Ph.D.
Hillenbrand Biomedical Engineering Center
Potter Building
Purdue University
West Lafayette, IN 47907
(317) 494-2995
FAX (317) 494-0811

Running Head: Minimum Temperature Control

Supported by Grant CA-38144 from the National Cancer Institute, U.S. Public Health Service, Bethesda, Maryland.

International Journal of Hyperthermia ›

Volume 7, 1991 - Issue 3 pp. 441-453

ABSTRACT

The goal of heat therapy in the treatment of malignant disease is to raise the temperature of all neoplastic tissue to a cytotoxic temperature for a predetermined period of time. This seemingly simple task has proved difficult in-vivo, in part because of non-uniform power absorption and in part because of nonhomogeneous and time varying tumour blood flow. We have addressed this difficulty first by utilizing the conceptually simple technique of conductive interstitial hyperthermia, in which the tumour is warmed by multiple, electrically heated catheters, and second by implementing on-line control of minimum tumour temperatures near each catheter, estimated on the basis of the steady-state ratio of catheter power to catheter temperature rise. This report presents an analysis of the accuracy, precision, and stability of the on-line minimum temperature estimation/control technique for 22 patients who received 31 separate courses of conductive interstitial hyperthermia for the treatment of malignant brain tumours, and in whom temperature was monitored independently by 12 to 16 independent sensors per patient. In all patients, the technique was found to accurately and precisely estimate and control the local minimum temperatures. Comparison of measured and estimated temperatures revealed a mean difference of $0.0 \pm 0.4\ ^{o}C$ for those sensors within 1.0 mm of the expected location for minimum temperatures. This technique, therefore, offers an attractive method for controlling hyperthermia therapy -- even in the presence of time varying local blood flow.

Key Words (not in title): algorithm, blood flow, heat therapy, glioma, glioblastoma, minimum temperature, intracranial tumour, perfusion

1.0 Introduction

Hyperthermia has gained notoriety as a possible fourth modality for the treatment of malignant tumours. Initially many institutions reported encouraging results in patients for whom conventional therapies of surgery, radiation, or chemotherapy had failed (Crile 1962, LeVeen et al. 1976, LeVeen et al. 1980, Storm et al. 1979, U et al. 1980). However, as shown in a recent, large multi-centre study (Perez et al. 1988), failure of hyperthermia therapy can often occur because of imprecise knowledge and control of tumour temperature distributions, with the likely frequent occurrence of under-treated cold spots. Because the minimum tumour temperature during hyperthermia therapy is known to be one of the most important predictors of therapeutic success (Cetas et al. 1980, Dewhirst et al. 1984), the control of minimum intratumoral temperatures and the elimination of cold spots has become a major technological challenge.

In the general case, knowledge of temperature distributions on-line is fundamentally limited by the number of implanted temperature sensors, since the actual minimum temperature can readily occur at an unmeasured site. However, in certain special cases for which the temperature distribution assumes a predictable, well-behaved shape, the estimation of minimum temperature from limited data samples becomes a tractable problem. The most obvious such case is that of uniform, whole body hyperthermia (Thrall et al. 1989), during which blood circulation imposes a uniform, flat temperature distribution throughout tissues a few millimeters from the skin surface. A somewhat more complex case involving local hyperthermia, which we have extensively

investigated (DeFord et al. 1990a, DeFord et al. 1990b), occurs when heat transfer to the tissue is accomplished by implanted, needle-like hot sources, such as ferromagnetic seed (Oleson and Cetas 1982, Partington et al. 1989), hot water perfused catheters (Meredith et al. 1990), or electrically heated catheters (Marchosky et al. 1990). Among these, the use of electrically heated catheters is especially amenable to computer based data acquisition, temperature estimation, and control, which are the subject of this report.

The currently available computer controlled, hot catheter system employs arrays of 2.2 mm diameter, interstitially implanted catheters. To date, this system has been used almost exclusively to treat intracranial tumours in man (Marchosky et al. 1990). The catheters, containing electrically resistive heating elements, surrounded by sterile insulating sheaths, are implanted directly via twist drill holes in the skull by a neurosurgeon with the aid of a template to specify geometry. The catheters are implanted such that each is equidistant from its six nearest neighbors, forming a pattern of equilateral triangles. In the current clinical implementation, the catheters are implanted with a 15 mm spacing (Figure 1). The lengths of heating elements within the catheters are matched approximately to the dimensions of the tumour, thus limiting the heating of adjacent normal tissue. When electric current (DC) is applied, each catheter is heated and in turn warms neighboring tissue by thermal conduction and blood convection. No current passes through the tissue. The steady-state temperature distributions assume a regular, peak-and-valley configuration, in which the height of each thermal peak corresponds to the catheter temperature, and the depth of the surrounding thermal valleys is determined by blood flow (Babbs et al. 1990). An idealized

temperature distribution appears as shown in Figure 2.

When the catheters are implanted in arrays, having interior and exterior elements, the valleys near interior probes are isolated from one another by thermal ridges that prevent conductive heat transfer from one valley to another (Figure 2). As a result, heat flowing "down" from adjacent peaks accumulates in each valley and, as modeled by the bio-heat transfer equation, is carried away only by blood perfusion. As a result, the steady-state minimum temperature of the interior valleys is determined solely by the balance between conduction from surrounding hot sources and blood perfusion. This simplified scheme of heat transfer in conductive interstitial hyperthermia makes the estimation of minimum temperatures a tractable problem.

In recent publications (DeFord et al. 1990a, DeFord et al. 1990b, Babbs et al. 1990, Patel et al. 1990), we have described the theoretical basis for minimum temperature estimation and control during conductive interstitial hyperthermia. In brief, the essential features of the peak-and-valley temperature profile between implanted heating elements may be described by a dimensionless parameter called "droop". Droop is defined as:

$$\text{droop} = \frac{T_{\text{catheter}} - T_{\text{minimum}}}{T_{\text{catheter}} - T_{\text{arterial}}} \tag{1}$$

and represents the relative fall in tissue temperature from the thermal peaks to the thermal valleys between hot sources. A rearrangement of equation (1) in the form,

$$T_{\text{minimum}} = T_{\text{catheter}} - \text{droop}(T_{\text{catheter}} - T_{\text{arterial}}) , \tag{2}$$

provides an expression for local minimum tissue temperature in terms of catheter

temperature, arterial blood temperature, and droop. The key idea of our temperature control strategy is that droop can be estimated from the ratio of steady-state catheter power to steady-state catheter temperature elevation. When blood flow is high, droop is large, and a greater power is required to maintain an interior catheter at a given elevated temperature. Under these conditions, conductive heat loss from the catheter surface is great, because steep thermal gradients develop (Figure 2). The physics are especially predictable for domains around interior catheters, which are thermally insulated from each other and from surrounding normal tissues. Plotting droop versus catheter power divided by catheter temperature rise provides a polynomial relationship for droop as a function of temperature and power. Droop, and in turn minimum temperature, are therefore simple functions of catheter temperature and power (Figure 3), both of which may be clinically monitored on-line.

Utilizing the bio-heat transfer equation of Pennes (1948) to model tissue heat transfer, we characterized the droop for catheters in an implanted array in terms of the clinically measurable variables of heating catheter power and heating catheter internal temperature. These simulations allowed on-line local minimum temperature estimation from (2), in which droop is inferred from catheter power and temperature and the other variables are directly measured. Development of a feedback control scheme (DeFord et al. 1990b) was then coupled with the droop-based minimum temperature estimation equation to provide on-line control of hyperthermia treatments. The control system adjusts power on-line to each catheter heating element, based upon the difference between the estimate of local minimum temperature and the desired minimum

temperature, using a standard proportional-integral (PI) control law (El-Hawary 1984). The presented estimation-control system was installed at Missouri Baptist Medical Center and St. Luke's West Hospital in St. Louis, Missouri, USA, in February of 1989 to allow assessment of its stability, accuracy, and precision during actual patient treatments. This paper presents a comparison of estimated and measured intratumoral temperatures for the first 31 human patient treatments in which conductive interstitial hyperthermia with closed-loop feedback control was employed.

2.0 Methods

2.1 Patients

The 22 patients received 31 treatments with conductive interstitial hyperthermia between February 1989 and February 1990. There were 14 men, ages 40 to 75, and 8 women, ages 39 to 64. The tissue diagnoses at the time of hyperthermia therapy included 18 glioblastoma multiformes, 3 astrocytomas with anaplastic features, and 1 metastatic lesion. One patient was treated on three separate occasions, 7 patients were treated on two separate occasions, and the remaining 14 patients were treated once. Each patient treatment cycle consisted of a separate hospital admission and implantation of the tumour volume. Catheters were explanted at the end of each treatment cycle (Marchosky et al. 1990). Therefore, 31 patient treatments were accrued and included in the present study. All patients were treated at Missouri Baptist Medical Center or Saint Luke's West Hospital, with approval from their respective Institutional Review Boards and under an investigational device exemption from the U.S. Food and Drug Administration.

Two patient groups were studied. The first consisted of 15 patients with local tumour recurrence, and the second consisted of 7 patients with primary disease. Patient selection criteria for the recurrent tumour group included an age of greater than 15 years and a Karnofsky neurologic function score (Karnofsky and Burchenal 1949) of at least 40 on a scale of 100. All patients with recurrent disease had conventional therapy prior to hyperthermia treatment, consisting of either surgery, radiation, brachytherapy, chemotherapy, or some combination thereof. Hyperthermia treatments were initiated in these patients because other treatments failed to control the tumours. Patient selection criteria for the primary disease group included an age of greater than 15 years and a Karnofsky score of at least 70. Hyperthermia was given as the only treatment for the 15 patients with recurrent disease, while concomitant hyperthermia plus radiation was given for 5 patients with primary disease. The remaining 2 patients with primary disease received hyperthermia plus chemotherapy. All patient data were pooled in the estimation/control analysis.

2.2 Hyperthermia Therapy

Each patient received hyperthermia therapy according to a treatment protocol that consisted of one to three separate hospital admissions for multiple hyperthermia fractions. Subsequent treatments were prescribed if the tumour continued to show contrast enhancement on computed tomographic (CT) scans. Each complete treatment cycle (hospital admission) consisted of delivery of hyperthermia 3 hours out of every 4, repeated 6 times per day until 72 hours of hyperthermia were delivered. The number of

hyperthermia catheters implanted varied with tumour size. Thus, each patient treatment was tailored to the tumour volume and location. The number of implanted heating catheters ranged from 6 to 22 with a mean value of 13. The mean tumour volume (defined as zone of contrast enhancement on CT) was 84.9 cm^3 and the mean tumour diameter was 5.2 cm.

2.3 Thermometry

In order to assess the accuracy, precision, and stability of the minimum temperature estimation and control technique, small diameter temperature sensing catheters (OD 1.2 mm) were implanted between the heat generating catheters, as shown in Figure 4, to gather independent comparison data. Each of the temperature sensing catheters contained four thermistors spaced in one centimeter increments along the catheter length, thus, allowing a sampling of temperatures along the axis of the implantation. Four temperature sensing catheters were implanted in each patient, thereby allowing simultaneous thermometry at 16 discrete sites during treatment. Typically two thermometry catheters were implanted in central tumour locations and two thermometry catheters were implanted in the tumour periphery. The temperatures measured by these independent thermistor probes along the central tumour axis, in the steady state, were used as comparison values for assessing the accuracy, precision, and general stability of the estimation/control algorithm. Only thermometry points along the central tumour axis were compared to the estimated temperatures.

2.4 Patient Data Acquisition

After implantation, each patient was awakened and transferred to the neurosurgical intensive care unit for recovery and subsequent treatment. After a complete neurological assessment, treatment parameters were entered into the resident computer of the hyperthermia delivery system (VH8500 Hyperthermia Treatment System, manufactured by Cook, Inc., Bloomington, Indiana, USA). Prescribed treatment parameters included the location and heating section element length of each heating catheter, the desired local minimum tumour temperature, safety limits (e.g. maximum tissue temperature), the number of treatment fractions, and the duration of each fraction. After preparing the patient for treatment, the implanted catheters were connected to the hyperthermia generator and treatment commenced. During the course of treatment, the power delivered to each heating catheter, heating catheter temperatures, and sensing catheter temperatures were continuously monitored and stored on magnetic disk every 3 to 5 seconds for later data analysis.

2.5 On-line Temperature Estimation and Control

The power delivered to individual heating catheters was adjusted under feedback control, in which the estimate of minimum tissue temperature (2) served as the feedback parameter. The PI controller altered delivered catheter power to maintain the estimated minimum temperature equal to the minimum temperature setpoint selected by the physician. Local minimum temperatures were estimated as follows. Heating catheter power and temperature were scanned every 3 to 5 seconds and updated estimates of all

local minimum temperatures (near each heating catheter) were computed using the polynomial expression droop = $-827.5\sigma^2 + 72.9\sigma - 0.006$ (Figure 3), where σ is heating catheter power divided by the heating catheter temperature rise, in conjunction with expression (2). That is, an updated estimate of the local minimum temperature near each heating catheter was determined and compared to the prescribed temperature value. If the estimate was below the prescription value, power was increased (under the PI control law) to that heating element to further heat the tumour, conversely, if the estimate of minimum temperature was above the prescription value, power was decreased to that heating element. For example, given a measured catheter temperature of 50 °C, arterial (or core body) temperature of 37 °C, and delivered catheter power of 0.15 Watts/cm, droop is estimated as 0.725, and $T_{minimum}$ is estimated as 40.6 °C. Utilizing this technique and PI feedback control previously described (DeFord et al. 1990b), the power delivered to each heating catheter is adjusted to achieve an estimated $T_{minimum}$ equal to the prescribed minimum temperature setpoint. In this manner, local minimum temperature is controlled near each implanted heating catheter.

2.6 Patient Data Analysis

In the present study, the estimated minimum temperatures were compared with the independently measured temperatures to assess the effectiveness of the foregoing control strategy. Since the heating catheters were implanted with a nominal 15 mm separation (Figure 1), one would expect intratumoral temperature minima to occur in the central regions between heating elements. The centre of the equilateral triangle with 15 mm

sides, formed by the cross-sectional profiles of each triplet of catheters, occurs about 8.7 mm from each vertex (Figure 1). It was these central regions that were the targets for implantation of independent thermistor catheters. However, in practice, of course, the implanted thermistors could not be precisely positioned at the exact central points where minimum temperatures were likely to occur. Thus, in order to accurately compare the temperatures measured by the independent thermistor probes with the temperatures estimated by the minimum temperature algorithm, it was important to establish the locations of the measured temperature points with respect to the surrounding heating catheters. Toward this end, sequential, coronal section CT scans 3mm thick were obtained. Using a GE 9800 CT scanner and its resident computer, intercatheter distances were calculated in the following manner: [1] sequential coronal CT scans were viewed to determine the location of the thermistor probes (Figure 5), [2] a central tumour cross section was selected through a temperature sensor using the CT scan computer, as denoted by the dashed line in Figure 5, [3] the dashed line was placed approximately orthogonal to the heating catheter axis, [4] a sagittal reconstruction of that implantation cross section was computed, using the CT system software, as seen in Figure 5, thus allowing a view of the implantation geometry in cross section, and finally, [5] the CT system software was again utilized to determine the distance between each temperature sensor and its surrounding heating catheters by placing one cross hair over the heating catheter and another cross hair over the temperature sensor and computing the linear distance (Figure 6). This technique allowed an accurate and precise method for ascertaining the actual implantation geometry.

Using the implantation geometry reconstructed via CT, we simply plotted the temperature difference between the measured and estimated temperatures ($T_{measured} - T_{estimated}$) versus the distance between each temperature sensor and the nearest heating catheter. This criterion was utilized, since it was expected that the nearest heating catheter would exhibit a dominant effect on the local temperature, given the character of the temperature distributions illustrated in Figure 2. We used only those independent temperature sensors that were within ± 1 cm of the tumour midplane as determined from CT reconstruction. Because the minimum temperature setpoints selected by the physician at time of treatment varied from 41 °C to 43 °C, we analyzed the difference, $T_{measured} - T_{estimated}$, to compare data from all patients. Sixty-two separate comparisons were performed and a plot of the temperature difference versus anatomical distance to nearest heating catheter was obtained.

3.0 Results

Figure 7 illustrates the results of 31 patient treatments performed with closed-loop feedback control. With the clinically used 15 mm catheter spacing, we expected the minimum temperature to occur about 8.7 mm from the heating element. This location is denoted in Figure 7 as point P. The cross hairs through point P divide the plot into four quadrants. If temperature estimation and control are accurate, one would expect that all data points to the left of point P in Figure 7, closer to the nearest heating catheter, would lie above the zero difference ($T_{measured} = T_{estimated}$) line under conditions of closed loop feedback control, in which $T_{estimated} = T_{target}$, the desired setpoint. That is, ideally

measured temperature should be greater than or equal to the estimated temperature for all points within 8.7 mm of a heated catheter. Only if the distance to the nearest heating catheter were greater than 8.7 mm (i.e. to the right of point P in Figure 7) would measured temperatures be below the estimated temperature, owing to nonideal clinical placement of catheters. This effect did occur to some extent.

Notice that all data points in Figure 7 fall into the two anticipated quadrants, with no data points in the remaining two quadrants. The mean estimation error for the 13 sensors within 1.0 mm of point P was 0.0 °C with a standard deviation of 0.4 °C. However, one may also note that the data points are scattered throughout the two quadrants. This scatter is to be expected since variations in blood flow will alter the thermal profiles between heating catheters. In particular, for the case of very low blood flows, tumour temperatures would be expected to fall very little between heated catheters; whereas high blood flows would cause steep thermal gradients to appear between heated catheters. Figure 8 presents the temperature profiles expected for representative high and low blood flow conditions, determined using the bio-heat transfer equation (DeFord et al. 1990a,b). Notice that for a high blood flow of 50 ml/min/100 gm the thermal profile approaches point P with a steep slope; while for a low blood flow of 5 ml/min/100 gm the slope of the temperature profile is nearly zero.

To evaluate blood flow effects in the present clinical data, we retrospectively divided the data from Figure 7 into 2 groups -- a low power set (less than 0.2 W/cm of heating element length) and a high power set (greater than 0.2 W/cm of heating element length).

In the context of conductive interstitial hyperthermia, high steady-state power implies higher local blood flow and low steady-state lower local blood flow. The mean temperature difference for all points between 0 and 8.7 mm from the nearest heated catheter was 1.88 °C ± 1.3 °C for catheters requiring high power, versus 0.65 °C ± 0.9 °C for the catheters requiring low power. This difference in measured temperatures is in the expected direction and is congruent with the anticipated effects of variable tumour blood flow.

Since closed loop control was employed in each patient treatment, we could also analyze the stability of the control system. Stability of performance defined as smooth, non-oscillatory power delivery and smooth, non-oscillatory estimated and measured temperatures was maintained in all patient treatments. No evidence of instability (defined here as oscillations growing in amplitude) was found during any of the over 700 individual treatment fractions analyzed (31 patient treatments with 24 fractions per treatment for a total of 31*24 = 744 treatment fractions).

4.0 Discussion

The results of this study, to our knowledge, provide the first reported evidence of accurate and precise estimation and feedback control of local minimum temperatures during local hyperthermia treatment in human patients. The conceptual simplicity of conductive interstitial hyperthermia and the similarity of local temperature distributions near each heated catheter allow a single temperature estimation algorithm to be applied to all implanted catheters. The ability to estimate local tissue temperatures from

clinically obtainable data makes the on-line, closed loop control of hyperthermia treatments possible. With the conductive interstitial technique, it is possible to estimate local minimum tumour temperatures near each heated catheter using a simple polynomial function for a given implantation geometry constructed from off-line solutions of the bio-heat transfer equation, in terms of the droop parameter. Changes in local perfusion rates alter the catheter power/temperature relationship, thereby altering droop and the estimate of local minimum temperature. Therefore, the estimation of local minimum temperatures based upon the droop parameter allow on-line compensation for blood flow variations. Incorporation of expression (2) into hyperthermia treatment systems provides an on-line estimation technique that requires very little computation time and obviates the need for solving the complete bio-heat transfer equation on-line (a task still beyond the capabilities of today's super-computers).

The minimum temperature estimation technique employed in this study was originally designed to predict local minimum temperatures in central tumour regions only, and we initially expected greater deviations in measured and estimated temperatures near the tumour periphery than were actually observed. In retrospect, it is clear that an intrinsic self-compensation occurs to a large extent in estimated temperatures from peripheral catheters. The reason is as follows. Since there is a greater conductive heat loss at the tumour edge, the measured ratio of catheter power to catheter temperature rise is increased at the periphery, thereby mimicking to some extent the response of an increase in local blood perfusion. As a result, greater power is delivered to the peripheral catheters under feedback control, compensating in part for conductive

heat loss to adjacent normal tissue. Parenthetically, an alternative technique of employing catheters with multiple, independently controllable heating elements would allow even greater compensation at the tumour periphery. Design of such catheters has been described elsewhere (Patel et al. 1990), but they are not presently in clinical use.

Since all comparisons of measured and estimated temperatures were found to behave as expected, we have some assurance that the temperatures we did not measure were also near the desired temperatures predicted by the bio-heat equation and that the temperature distributions were similar in shape to the theoretical distribution in Figure 2. In turn, we have some assurance that, in the case of the conductive interstitial hyperthermia of human brain tumours, cold spots can be eliminated by active computer control. A secondary advantage of this technique may be to reduce the number of implanted temperature sensing catheters required to monitor intratumoral temperatures, thereby limiting the possibility of patient trauma and reducing the treatment cost. The practicality of closed-loop temperature estimation and control for conductive interstitial hyperthermia therapy of intracranial tumours may soon lead to the development of similar techniques for the treatment of tumours outside the skull.

Acknowledgement

The authors thank Dr. Neal Fearnot and Colleen Tennyson for their technical assistance in the conduct of this research and in the preparation of the manuscript.

REFERENCES

Babbs, C.F., Fearnot, N.E., Marchosky, J.A., Moran, C.J., Jones, J.T., and Plantenga, T.D., in press "Theoretical basis of controlling minimal tumor temperature during interstitial conductive heat therapy", *IEEE Transactions in Biomedical Engineering*.

Cetas, T.C., Conner, W.G., and Manning, M.R., 1980, "Monitoring of Tissue Temperature during Hyperthermia", *Annals of New York Academy of Science,* Vol. 335, pp. 281-297, 404-407.

DeFord, J.A., Babbs, C.F., Patel, U.H., Fearnot, N.E., Marchosky, J.A., and Moran, C.J., (a) 1990, "Accuracy and Precision of Computer Simulated Tissue Temperatures in Individual Human Intracranial Tumors Treated with Interstitial Hyperthermia", *International Journal of Hyperthermia,* Vol. 6, No. 4, pp. 755-770.

DeFord, J.A., Babbs, C.F., Patel, U.H., Fearnot, N.E., Marchosky, J.A., and Moran, C.J., (b) in press "Design and Evaluation of Closed-Loop Feedback Control of Minimum Temperatures in Human Intracranial Tumours Treated with Interstitial Hyperthermia", *Medical & Biological Engineering & Computing*.

Dewhirst, M.W., Sim, D.A., Sapareto, S., and Connor, W.G., 1984, "Importance of minimum tumor temperature in determining early and long term responses of spontaneous canine and feline tumors to heat and radiation", *Cancer Research,* 44 pp. 43-50.

El-Hawary, M.E., (1984), "Control System Engineering", *Reston Publishing Company, Inc.*

Karnofsky, D.A., Burchenal, J.H., (1949), "The clinical evaluation of chemotherapeutic agents in cancer", Evaluation of chemotherapeutic agents, *Columbia University Press,* C.M. Macleod (ed), pp 199-205.

LeVeen, H.H., Wapnick, S., Piccone, V., Falk, G., and Ahmed, N., 1976, "Tumor eradication by radio-frequency therapy: Response in 21 patients", *Journal of American Medical Association,* 235(20), pp. 2198-2220.

LeVeen, H.H., Ahmed, N., Piccone, V.A., Shugaar, S., and Falk, G., 1980, "Radio-frequency therapy: clinical experience", *Annals of the New York Academy of Sciences,* 335 pp. 362-371.

Marchosky, J.A., Moran, C.J., Fearnot, N.E., and Babbs, C.F., 1990, "A technique for hyperthermia catheter implantation and therapy in the brain", *Journal of Neurosurgery, 72 (6).*

Meredith, R., Brezovich, I., Weppelmann, B., Kim, R., Spencer, S., Peters, G., Hicks, J., Franklin, L., Glisson, W., and Salter, M., (1990), "A clinical trail of interstitial thermo-radiotherapy with perfusion heating", presented paper at the Tenth annual meeting of the North American Hyperthermia Group, abstract Cza-5.

Oleson, J.R., and Cetas, T.C., 1982, "Clinical Hyperthermia with RF Currents", Physical Aspects of Hyperthermia, *American Institute of Physics, Inc., New York, New York,*

G Nussbaum (ed), pp. 280-305.

Partington, B.P., Steeves, R.A., Su, S.L., Paliwal, B.R., Dubielzig, R.R., Wilson, J.W., and Brezovich, I.A., (1989), "Temperature distributions, microangiographic and histopathologic correlations in normal tissue heated with ferromagnetic needles", *International Journal of Hyperthermia,* Vol. 5, No. 3, 319-327.

Patel, U.H., DeFord, J.A., and Babbs, C.F., in press "Computer Aided Design and Evaluation of Novel Catheters for Conductive Interstitial Hyperthermia", *Medical & Biological Engineering & Computing.*

Pennes, H.H., 1948, "Analysis of Tissue and Arterial Blood Temperatures in Resting Forearm", *Journal of Applied Physiology,* 1, pp. 93-122.

Perez, C.A., Emami, B.N., Kuske, R.R., Hornback, N.B., Pajak, T.J., and Kasdorf, P., 1988, "Irradiation and Hyperthermia in the Treatment of Recurrent Carcinoma of the Breast and Chest Wall: MIR and RTOG Experience", *Radiation Oncology Center Scientific Report, St. Louis, Missouri,* C. Povilat (ed.), Mallinckrodt Institute of Radiology, Washington University Medical Center (publishers).

Storm, F.K., Harrison, W.H., Elliott, R.S., and Morton, D.L., 1979, "Normal tissue and solid tumor effects of hyperthermia in animal models and clinical trials", *Cancer Research,* 39(6) pp. 2245-2250.

Thrall, D.E., Page, R.L., Dewhirst, M.W., Macy, D.W., McLeod, D.A., Scott, R.J., Allen, S., and Gillette, E.L., (1989), "Whole body hyperthermia in dogs using a radiant

heating device: effect of surface cooling on temperature uniformity", *International Journal of Hyperthermia,* Vol.5, No.2, 137-143.

U, Raymond, Noell, K.T., Woodward, K.T., Worde, B.T., Fishburn, R.I., and Miller, L.S., (1980), "Microwave-induced local hyperthermia in combination with radiation of human malignant tumors", *Cancer,* Vol. 45, No. 4, pp 638-646.

Figure Legends

Figure 1: Catheter implantation geometry as seen in cross section. Catheters are implanted in staggered rows with the aid of a template. Each triplet of heated catheters forms an equilateral triangle with 15 mm intercatheter spacing. Heated catheters are 2.2 mm in diameter.

Figure 2: Idealized temperature distribution during interstitial hyperthermia computed from the bio-heat equation (Babbs et al. 1990). The temperature peaks occur at each heated catheter while cooler temperature valleys develop in the centre of each triplet. Zero represents the level of baseline arterial (or core body) temperature.

Figure 3: Droop as a polynomial function of delivered heated catheter steady-state power per unit length and internal heated catheter temperature. Performing a second order least-squares regression allows a parameterization for droop.

Figure 4: Nominal location of independent temperature-sensing (thermistor) catheters between heated catheters. Each thermometry catheter is implanted in the region between heated catheters to monitor local temperatures, at sites where temperature minima are likely to occur. Thermometry catheters contained 4 separate thermistors spaced 1 cm apart, 2 extending above and 2 extending below the midplane of the tumour sketched here.

Figure 5: Coronal CT scans were taken along the axis of implantation to verify the location of heated and thermometry catheters. A reconstruction plane (cross-section) was selected through a thermometry point in the central tumour, denoted by the dashed line.

Figure 6: Sagittal reconstruction of several coronal scans, performed to allow a view of the tumour implantation site in cross section (top) utilizing the GE 9800 CT scanner software. Distance measurements were then performed by placing cross-hair cursors on heated and thermometry catheters and requesting calculation of the linear distance between the cross-hairs via the CT scanner-computer.

Figure 7: Comparison of the difference between measured and estimated temperatures as a function of the distance to the nearest heated catheter in-vivo demonstrates the ability of the estimation/control system to control minimum tissue temperatures. Point P indicates anatomic site where minimum temperature is expected, given ideal catheter spacing (inset). Horizontal line at 0.0 indicates target minimum temperature.

Figure 8: Influence of blood flow upon tissue temperature profile near minimum temperature point, P. Curves are theoretical data computed from the bio-heat equation. The higher the blood flow, the steeper the slope of the temperature profile between catheters and central minimum temperature points.

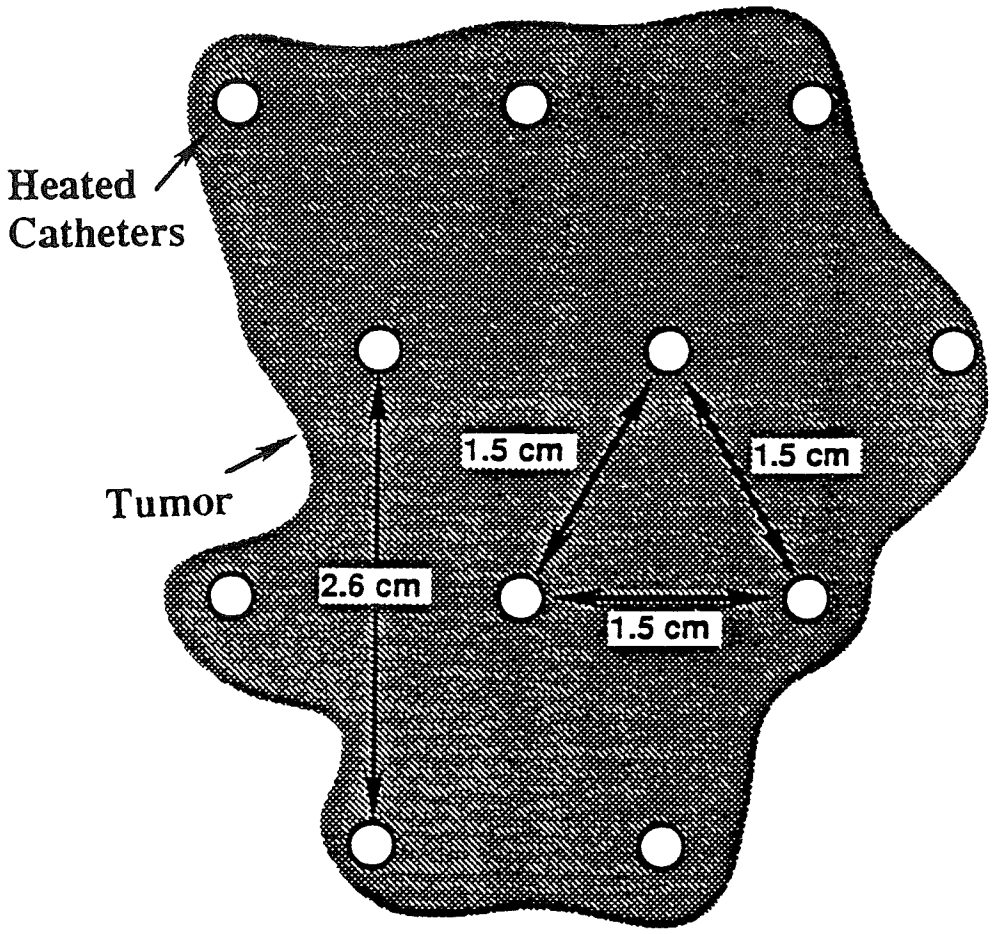
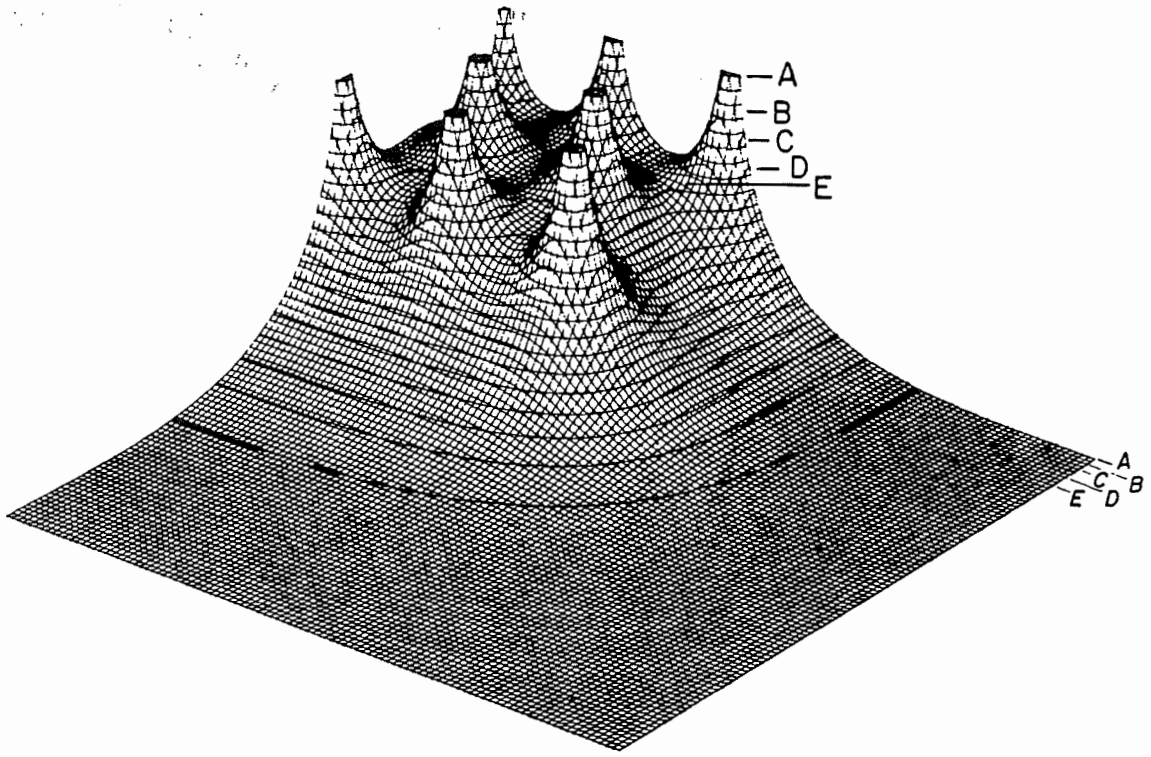


Fig. 1.


A
B
C
D
E
A
C
B
E
D

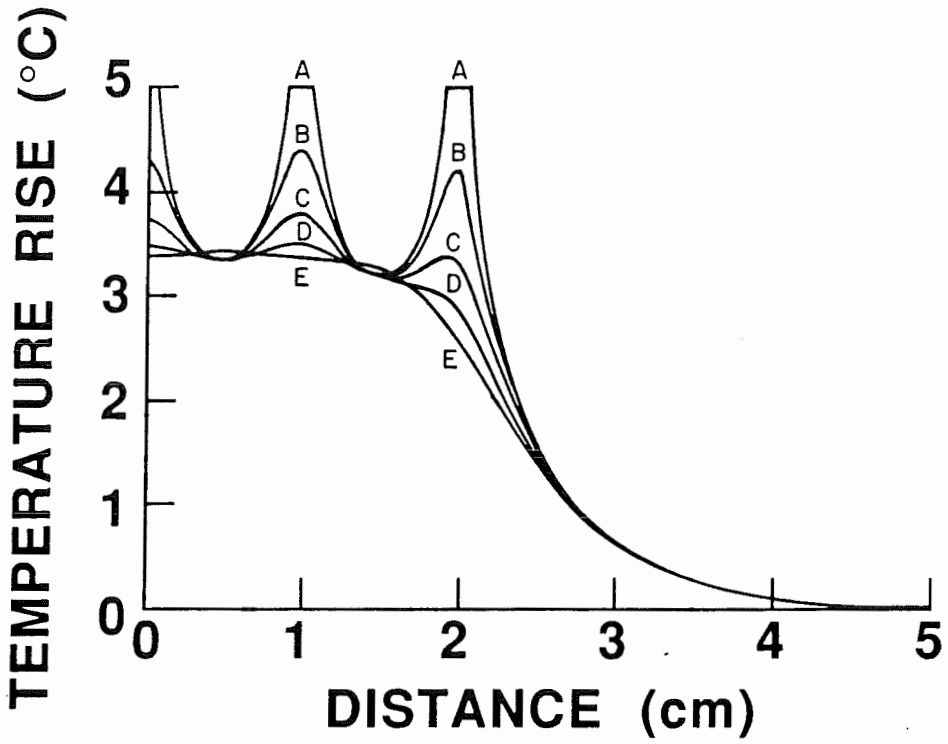

TEMPERATURE RISE (°C)
0
1
2
3
4
5
A
B
C
D
E
A
B
C
D
E
0
1
2
3
4
5
DISTANCE (cm)

Fig. 2

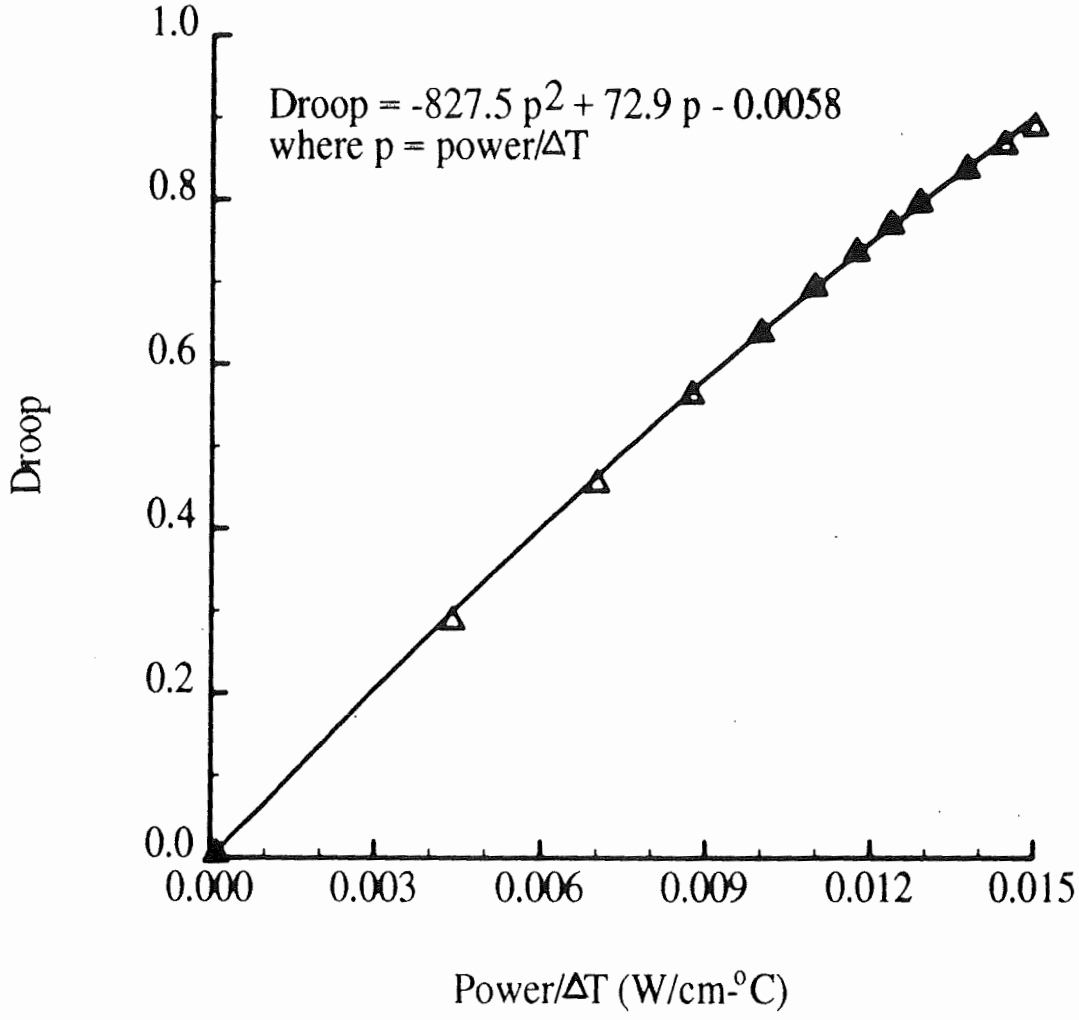

Droop = -827.5 p2 + 72.9 p - 0.0058
where p = power/ΔT
Droop
1.0
0.8
0.6
0.4
0.2
0.0
0.000
0.003
0.006
0.009
0.012
0.015
Power/ΔT (W/cm-°C)

Fig 3

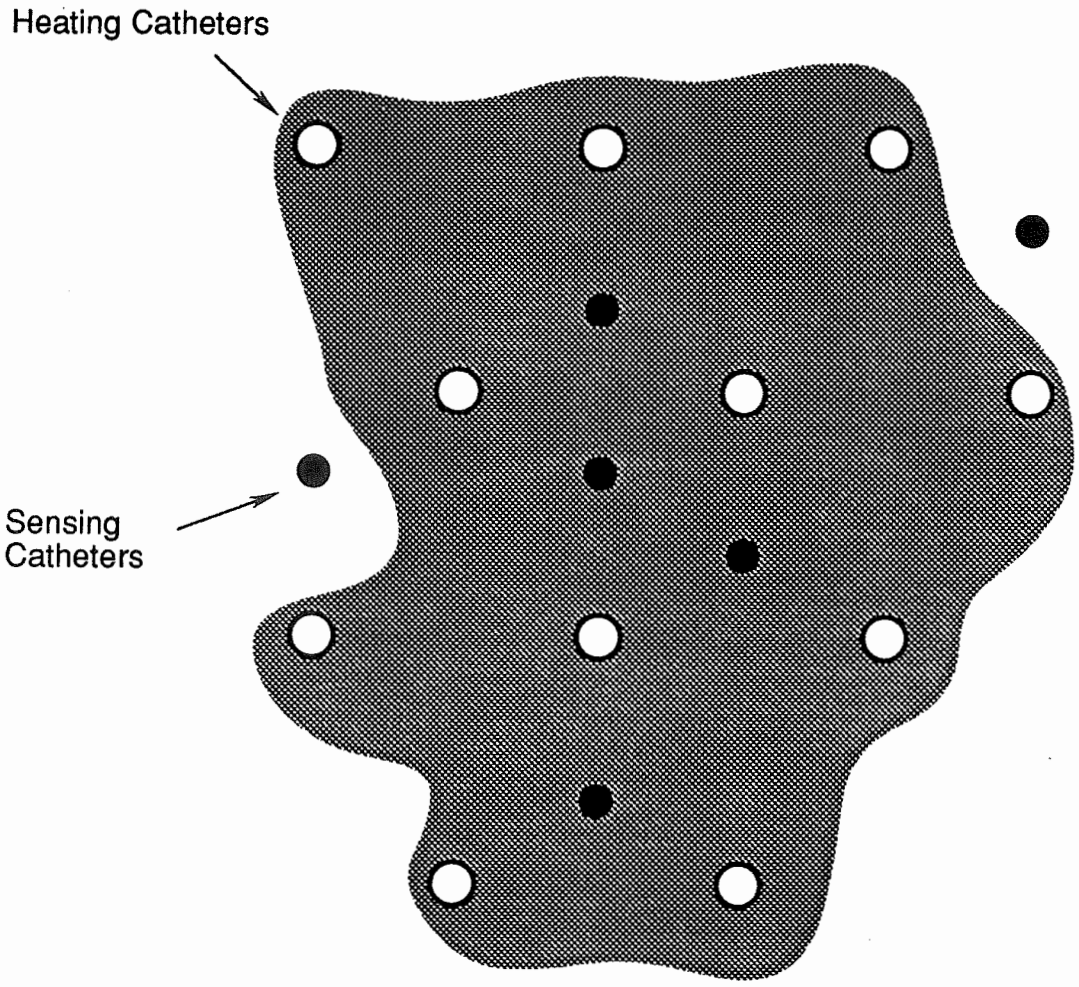


Fig 4

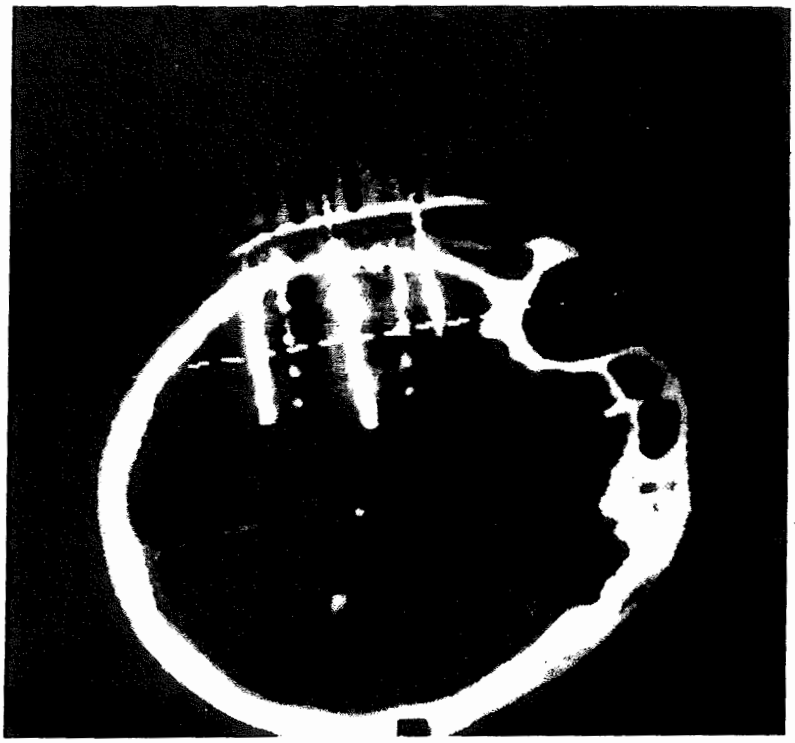


Fig 5

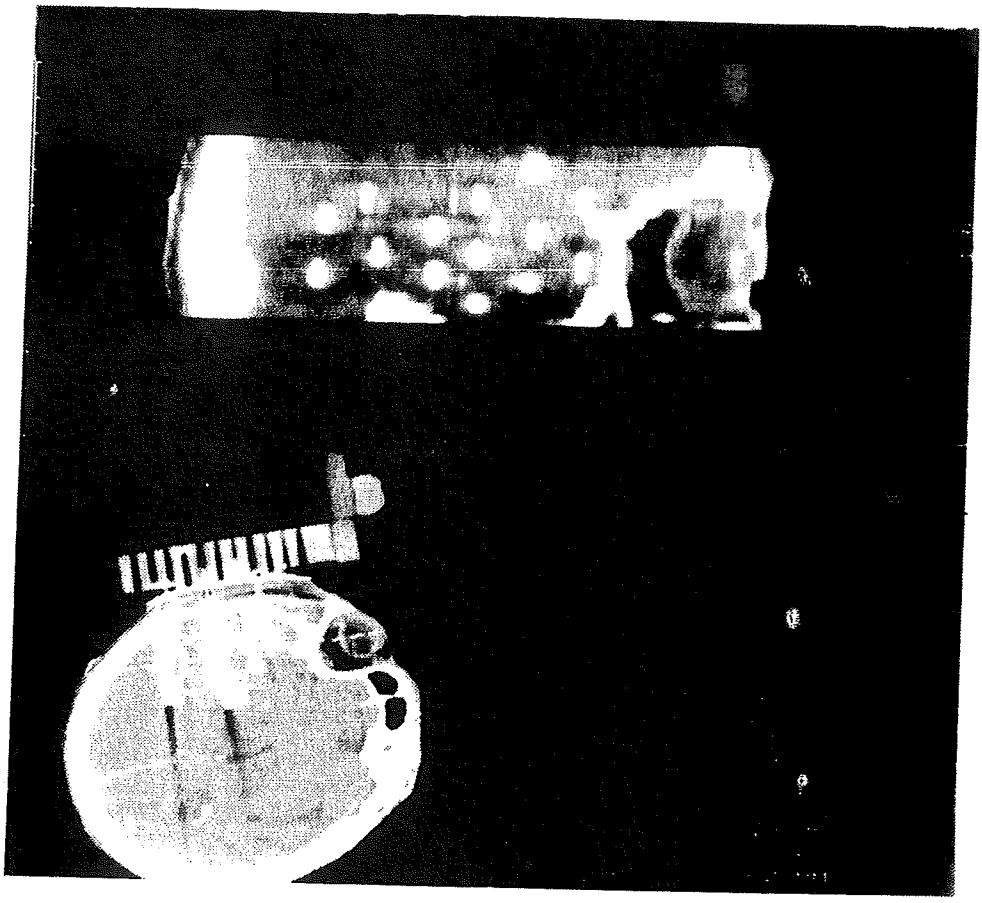


Fig 6

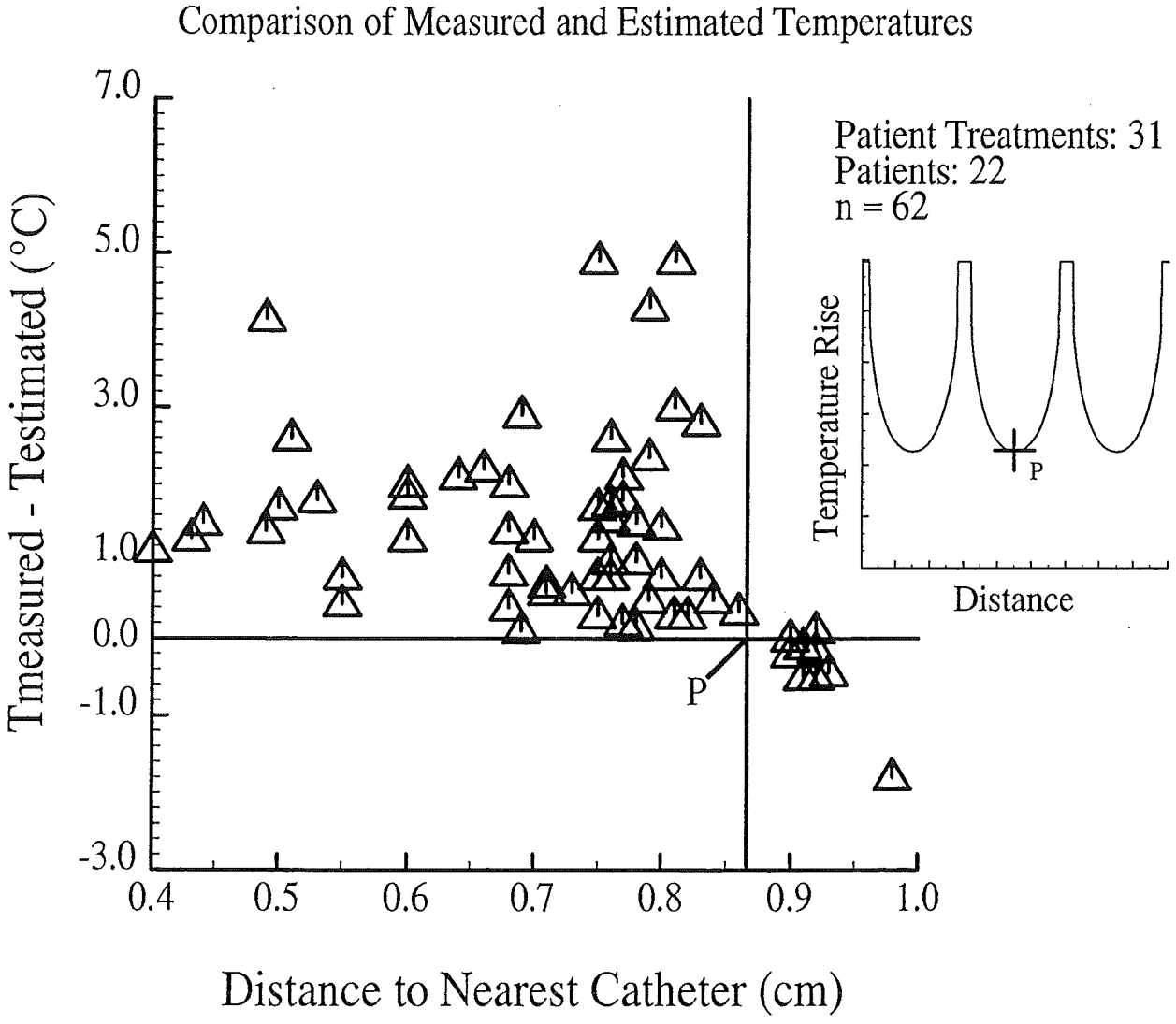

Comparison of Measured and Estimated Temperatures
Tmeasured - Testimated (°C)
7.0
5.0
3.0
1.0
0.0
-1.0
-3.0
0.4
0.5
0.6
0.7
0.8
0.9
1.0
P
Distance to Nearest Catheter (cm)
Patient Treatments: 31
Patients: 22
n = 62
Temperature Rise
P
Distance

Fig 7

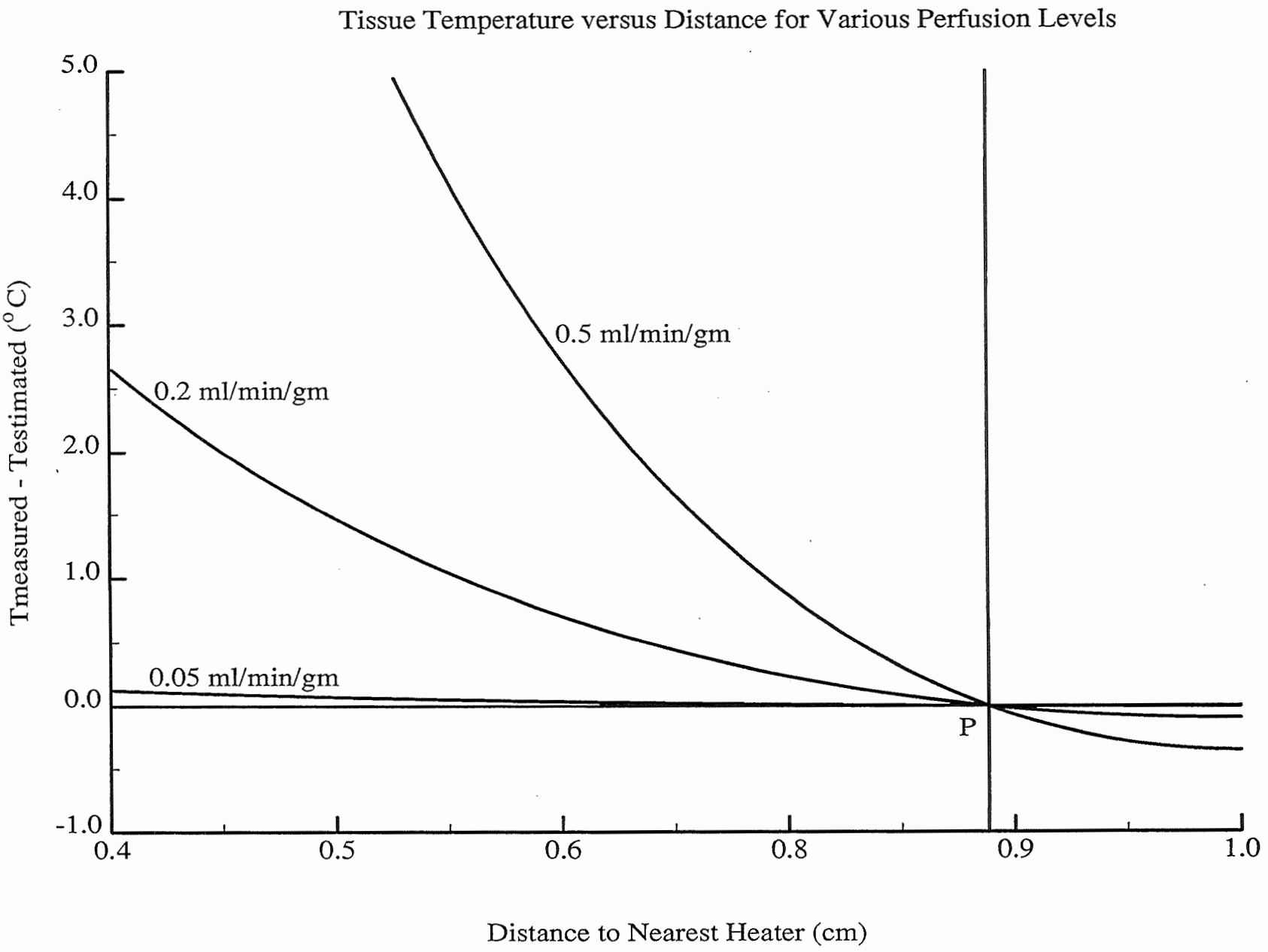

Tissue Temperature versus Distance for Various Perfusion Levels
Tmeasured - Testimated (°C)
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
0.4
0.5
0.6
0.8
0.9
1.0
0.5 ml/min/gm
0.2 ml/min/gm
0.05 ml/min/gm
P
Distance to Nearest Heater (cm)

Fig. 8