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Abstract

Human intracranial tumours were treated using local heat therapy produced by surgically implanted catheters containing local resistive heating elements. Changes in local tumor blood flow were assessed indirectly from an algorithm based on the bioheat transfer equation. The algorithm used the ratio of catheter power to catheter temperature rise to estimate regional blood perfusion. Local heat therapy produced consistent reductions in local apparent perfusion. Changes in apparent regional perfusion occurred in intriguing patterns that gave clues to possible vascular events of therapeutic significance.

Key words: Bioheat transfer equation, Conductive heating Interstitial hyperthermia, Tumour blood flow

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1 Introduction

In conductive interstitial hyperthermia, heat sources are implanted into the treated tissue. Heat is transferred to the tissue from the heat sources by thermal conduction and blood convection. Heating sources that have been used for conductive interstitial hyperthermia include inductively heated ferromagnetic seeds (STAUFFER *et al.* 1984), tubes perfused with hot water (PRIOR *et al.,* 1988), and catheters containing wire-wound, electrically resistive heaters (BAUMANN and ZUMWALT, 1989).

Conductive interstitial hyperthermia using electrically resistive catheters is currently being used to treat human patients with intracranial tumours (MARCHOSKY *et al.,* 1990). In these patients, general anaesthesia is induced and then an array of catheters is implanted through twist-drill holes in the skull with the aid of a template. Catheters are arranged in repeating equilateral triangles with 1.5 cm spacing between adjacent catheters (Fig. 1). The procedure is done in the CT suite to allow confirmation of catheter placement. Typically, repeated treatments are administered, in which heat is applied for 3 h of continuous therapy followed by a 1 h rest period, until a total of 72 h of hyperthermia have been accrued. The total 72 h treatment is called a cycle of therapy.

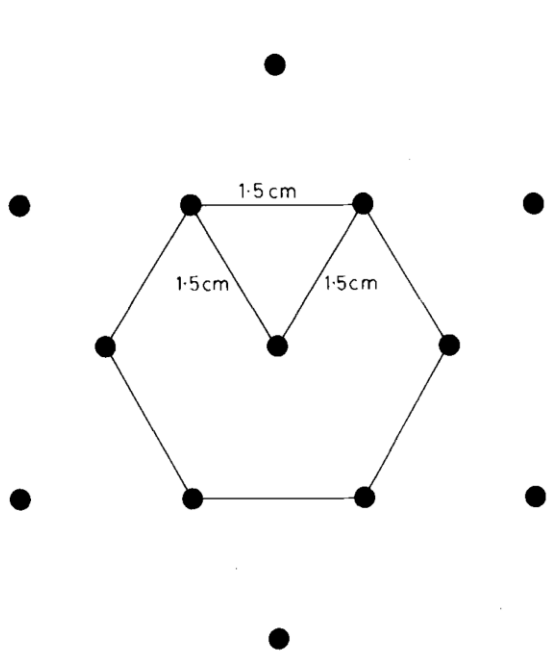

Fig. 1. *Sketch showing the implantation geometry in cross-section for catheters used in conductive interstitial hyperthermia therapy.*

Blood perfusion has been shown to be an important factor governing the success of hyperthermia treatment. HILL *et al.* (1989), for example, demonstrated that treatments of hot water baths and radiofrequency currents on slow-growing carcinomas in mice gave significant growth delays only when there was 60 per cent decrease in blood perfusion. Vascular destruction within a tumour causing hypoxia is known to potentiate the effects of heat (SONG *et al.,* 1980). BABBS *et al.* (1990a) have shown histological evidence of vascular stasis during conductive interstitial hyperthermia in canine liver.

In the present study, vascular alterations in human intracranial tumours during one complete cycle of therapy were indirectly assessed by evaluating the changes in regional blood perfusion. Regional blood perfusion, defined as the perfusion in the region near a catheter, was estimated from an algorithm developed using a computer model based on the bioheat transfer equation. The algorithm used the ratio of catheter power to catheter temperature rise to estimate regional perfusion. Changes in apparent regional perfusion occurred in intriguing patterns that gave clues to possible vascular events of therapeutic significance.

2 Methods

2.1 Computer model for conductive interstitial hyperthermia

A computer model was developed to describe the conductive heating of tissue from which data were obtained to develop a perfusion estimation algorithm. In brief, the volume of tissue modeled was a cylindrical volume having the heating element of the catheter located at the centre of the cylinder (Fig. 2) with other catheters surrounding the cylinder. To simulate the thermal effects of the surrounding heating elements, the outer wall of the modeled cylinder was adiabatic. The radius of the cylinder was found by finding the average distance of the adiabatic boundary from an interior catheter in a validated two-dimensional Cartesian co-ordinate model as described by PATEL *et al.* (1991). The cylindrical model was 'one dimensional' in the sense that heat conduction occurred radially only, away from the catheter. For simplicity longitudinal heat conduction (along the length of the catheter) was not modeled.

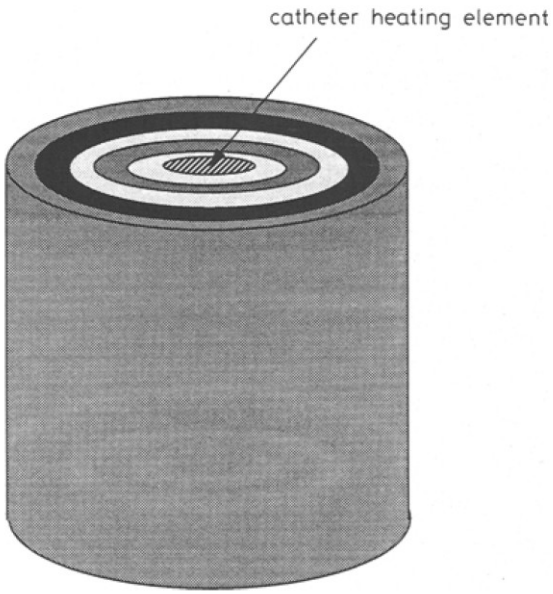

Fig. 2. *Sketch showing the modeled cylindrical volume of tissue. The cylinder radius was 0.8 cm and contained 210 control volumes.*

Although physically longitudinal heat conduction does occur, a region of minimal longitudinal heat conduction exists in a slice of tissue at the level of the centre of the catheter heating element, equidistant from the heating element tips (midplane level). The validity of this assumption is illustrated in Fig. 3, which shows a plot of temperature profiles produced from computer simulations using the one-dimensional model (solid line) and a two-dimensional cylindrical-co-ordinate model (broken line) that allowed for longitudinal heat conduction (PATEL *et al.,* 1991). For the two-dimensional model the temperature profile is shown for the midplane level. Note that the one-dimensional temperature profile is only 0.5 ^{o}C greater than the two-dimensional midplane level temperature profile. If longitudinal heat conduction was significant at the midplane level, the difference in the two temperature profiles would be much greater.

The steady-state heat transfer in the cylindrical volume was evaluated by computational formulae based on the bioheat transfer equation described by PENNES (1948) for a small volume of tissue or a control volume. In the present model, each control volume was a tiny ring of tissue having a width of 0.0037cm. This model contained 210 control volumes. The computational formulae were solved using the tri-diagonal matrix algorithm described by PATANKAR (1980). This algorithm provided an implicit method of solving the bioheat equations for a one dimensional case. Thermal properties for tissue, blood and the catheter were found in the literature or experimentally (PATEL *et al.,* 1991). The computer simulations allowed for catheter power and blood perfusion to be easily changed from a control file. A series of simulations were run for catheter power levels from 0.05 to 0.4 W/cm and tissue perfusions from 0.001 to 2.2ml/min/lg. The output of the simulations was a temperature profile of the cylindrical volume, from which catheter temperature was obtained.

2.2 *Perfusion estimation algorithm*

Although conductive heat transfer is generally a major contributor to energy balance in local hyperthermia therapy, making it difficult to accurately estimate blood flow from thermal data (ROEMER, 1990), the physical simplicity of conductive interstitial techniques makes the thermal estimation of perfusion a viable approach in selected regions of treated tissue. In particular, for interior catheters in the implanted array, conductive heat transfer is sufficiently well behaved to permit estimation from thermal data of both minimum temperature (DEFORD *et al.,* 1990; BABBS *et al.,* 1990b; 1989) and regional blood perfusion for central regions of the tumour.

Computer simulations have revealed a fundamental relationship for interior catheters showing that the power required to keep a catheter at a given temperature is governed almost exclusively by perfusion, ω. In this geometric configuration the adiabatic boundaries created by hot sources minimise conductive heat loss to the periphery, and tissue cooling is dominated by blood perfusion. When blood perfusion to is plotted against the ratio of catheter power dissipation to temperature rise σ, the relationship in Fig. 4a is obtained. This relationship is nearly linear when ω is divided by σ and plotted as a function of ω (Fig. 4b), upon which second-order regression analysis yields the following equation:

$$\frac{\omega}{\sigma} = 8{\cdot}82 + 57{\cdot}6\omega - 3{\cdot}84\omega^2 \qquad (1)$$

Solving for ω gives the following quadratic estimation equation for regional perfusion near interior catheters with a 1.5 cm inter-catheter spacing:

$$\omega = \frac{57{\cdot}6\sigma - 1 + (3453\sigma^2 - 115{\cdot}2\sigma + 1)^{1/2}}{7{\cdot}68\sigma} \quad , \qquad (2)$$

where ω is perfusion in ml/min/g, and σ is the ratio of catheter power per cm of catheter length to catheter temperature rise above arterial or core body temperature, expressed in W/cm/^{o}C.

Using eqn. 2, which was obtained from computer simulations, we were able to estimate regional perfusion near each interior catheter from clinically available data during the course of therapy. Eqn. 2's range of validity is $0 < \sigma < 0.025$ W/cm/^{o}C. When σ is greater than 0.025 W/cm/^{o}C, second-order effects dominate the function, thus producing inaccurate estimates of ω.

Fig. 5 shows a plot of predicted values of ω against σ in the range of validity. Clinically, catheter power and catheter temperature rise, the values required to calculate σ, can be measured with minimal error. The accuracy to which catheter temperature can be measured is $\pm 0.1\ ^{o}C$, and the accuracy to which heating element voltage can be measured is $\pm$ 0.015V. Catheter power is then calculated by squaring the measured voltage and dividing by heating element resistance. This perfusion estimation equation allowed for moment-to-moment comparison of relative regional perfusion with other interior catheters and at other instants in time.

2.3 *Data acquisition and analysis*

The computer system driving the hyperthermia generator provided automated recording of pertinent information on magnetic tape (DEFORD *et al.,* 1989), including catheter powers, catheter temperatures and temperatures at independent sensors located within the tumour. Catheter temperature was recorded from a thermistor located in the catheter next to the heating element. From CT scans, catheters that were located in the interior of the tumour and had other catheters surrounding them were identified.

For the interior catheters, data from every alternate treatment were obtained and catheter power (W/cm), catheter temperature and core body temperature were recorded during periods of steady-state temperature elevation, in which both catheter power and catheter temperature were constant. Regional perfusion was then estimated using eqn. 2. Data from a total of 36 interior catheters were evaluated in the analysis from seven cycles of therapy in six patients. The patient population comprised four males and two females having a mean age of 57 years ranging from 40 to 75 years. Five patients had glioblastoma multiforme, the other an astrocytoma with anaplastic features. Catheter powers varied from 0.001 to 0.4 W/cm. Catheter temperatures varied from 42 to 60 ^{o}C. For each complete cycle of therapy, a plot of estimated regional perfusion against treatment number within that cycle was constructed for each interior catheter. Additionally, for all cycles, the perfusion estimates from the first treatment and the last treatment of a cycle were pooled, and histograms were plotted showing the variation in perfusion estimates for the patient population.

Retrospectively, perfusion changes from the first treatment to the last treatment for all interior catheters were classified as 'major' or 'moderate', based on the amount of perfusion change. A 'major' decrease in perfusion was defined as a decrease greater than 0.4 ml/min/g, and a 'moderate' decrease was defined as perfusion less than 0.5 but greater than 0.25 ml/min/g.

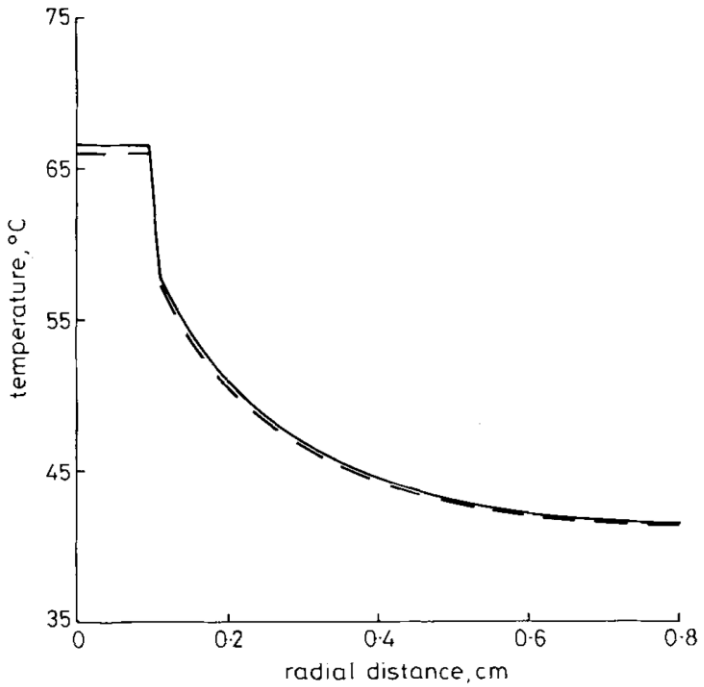

Fig. 3. *Plot of radial temperature profiles produced from a one-dimensional cylinder model without longitudinal heat conduction (----------) and a two-dimensional cylinder model with longitudinal heat conduction (- - -) . For both simulations, catheter power was 0.4 W/cm and tissue perfusion was 0.5 ml/min/g. The radial resolution for both simulations was 210 control volumes in an 0.8 cm radius cylinder. The height of the control volumes in the two-dimensional model was 0.04 cm.*

3 Results

Figs. 6a and 6b each show a plot of perfusion estimate against treatment number for interior catheters over the course of one complete cycle of therapy in two different patients. Fig. 6a demonstrates an initial significant fall in estimated perfusion at four out of five locations over the first five treatments before settling down to a relatively stable level. A significant fall in estimated perfusion at one location is also demonstrated between treatments 17 and 19. The other reductions in perfusion indicated are much smaller and not completely irreversible.

Fig. 6b shows initial significant drops in estimated perfusion in two out the six locations. For the total patient population studied, major decreases in estimated regional perfusion were observed near 11 out of 36 catheters. Moderate decreases were observed near two out of 36 catheters. No major or moderate decreases in estimated perfusion were found near any of the other 23 catheters. Noteworthy increases in estimated perfusion did not occur.

The histogram including all catheters in all patients during the first treatment (Fig. 7a) includes 20 initial regional perfusion estimates less than 0.4ml/min/g and 10 greater than l ml/min/g. The

corresponding histogram from the last treatment (Fig. 7b) includes 25 regional perfusion estimates less than 0.4 ml/min/g and only 1 greater than 1 ml/min/g. Evidently, the regions of relatively high estimated perfusion tended to drop out during a complete cycle of therapy. The time domain plots, such as Fig. 6a, indicated that these events occurred relatively suddenly, somewhat unpredictably, and at discrete sites within the tumour.

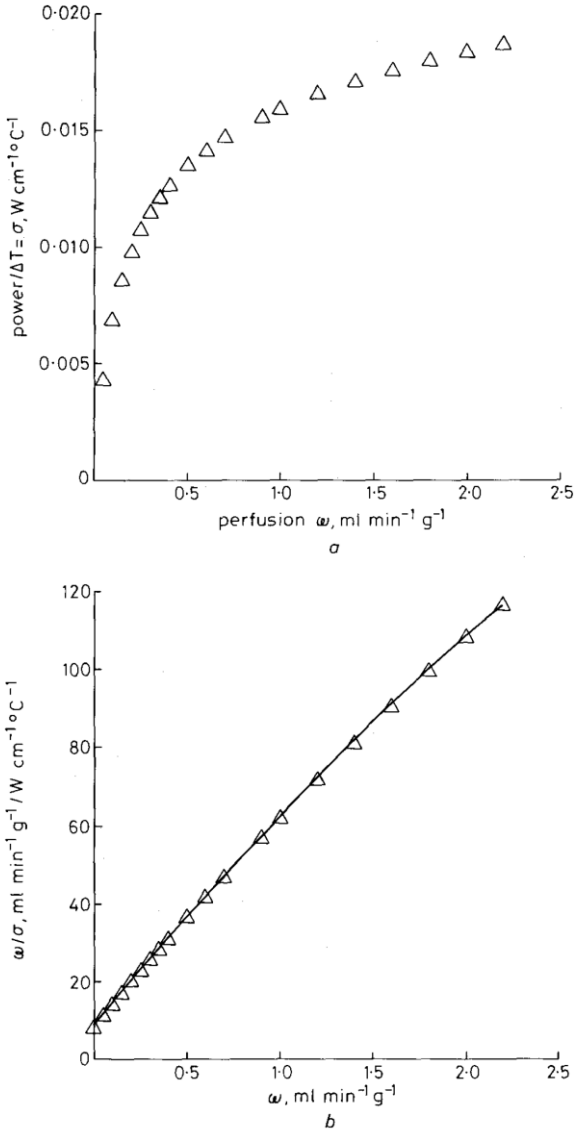

Fig. 4. *(a) The ratio of catheter power to catheter temperature rise σ (W/cm/°C) plotted as function of perfusion co (ml/min/g). ω ranges from 0.001 to 2.2 ml/min/g. (b) Partially rectified curve obtained when ω is divided by σ and plotted against ω. Data for both functions were generated from computer simulations that used a tridiagonal matrix algorithm to solve the bioheat transfer equation (PATANKAR, 1980).*

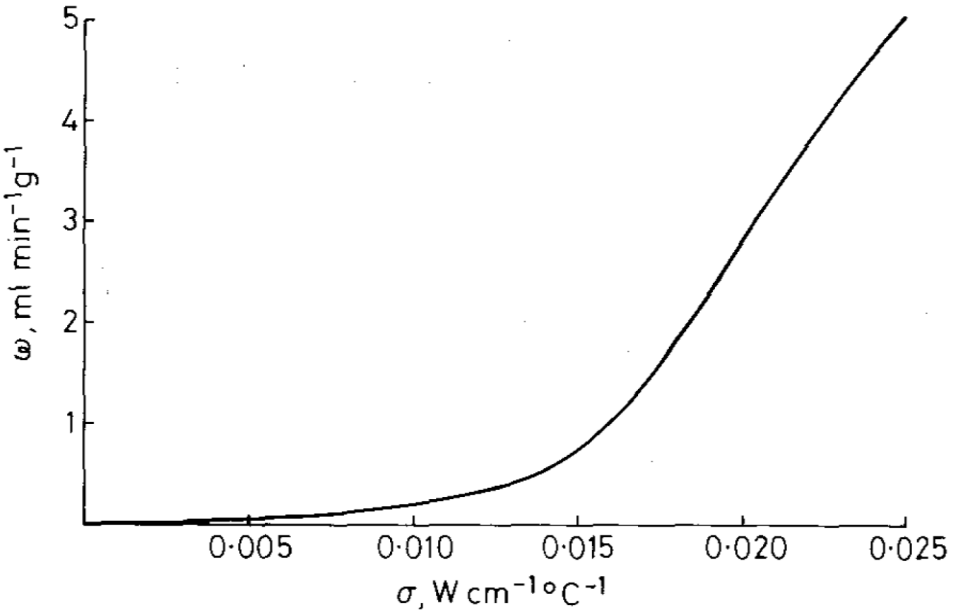

Fig. 5. *Plot showing perfusion estimates ω for σ ranging from 0.001 to 0.025 W/cm/^{o}C.*

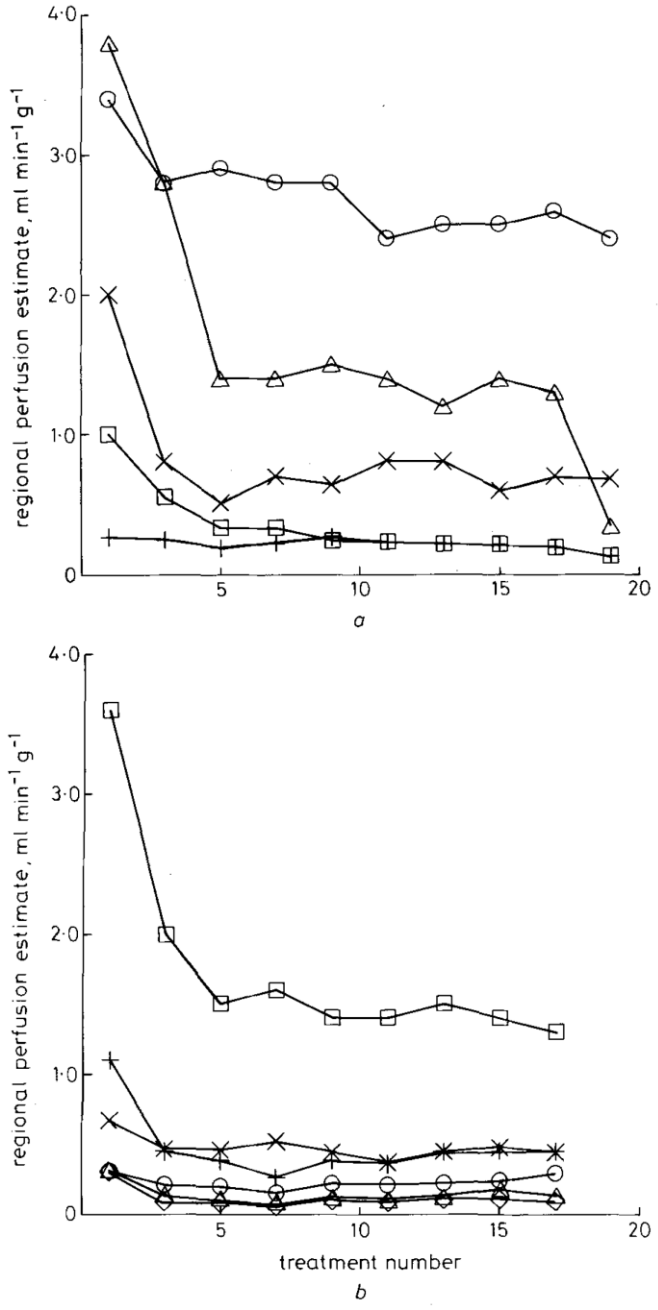

Fig. 6. *(a) Plot showing effect of conductive interstitial hyperthermia on regional perfusion during the course of a treatment cycle in a 75-year-old male patient with a glioblastoma multiforme. The tumour was located in the right temporal region of the brain. Each symbol represents a perfusion estimated near a different interior catheter within the same tumour. (b) Plot showing change in regional perfusion during the course of a treatment cycle in a 55-year-old male patient with an astrocytoma with anaplastic features. The tumour was located in the right parietal-temporal region of the brain.*

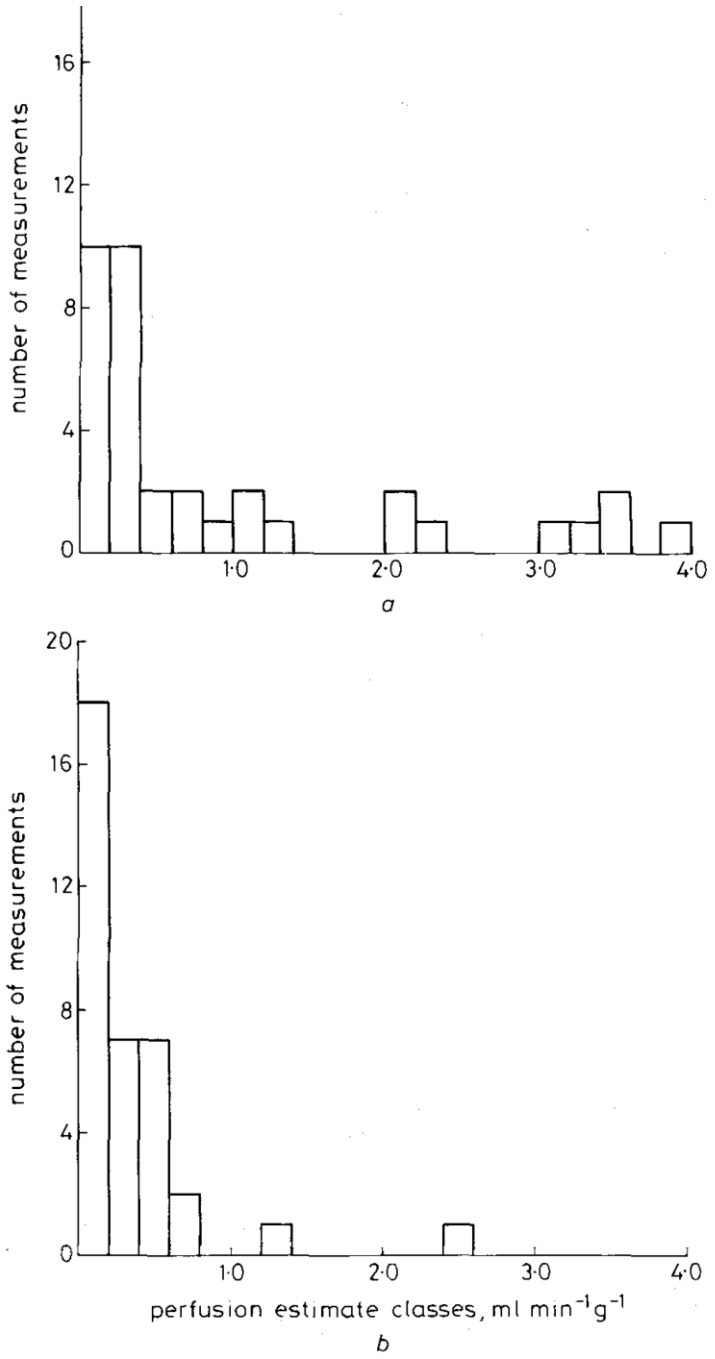

Fig. 7. (a) Upper histogram shows distribution of regional perfusion estimates during the first treatment of the cycle from all interior catheters (n = 36) in the patient population. (b) Lower histogram shows distribution of regional perfusion estimates during the last treatment of the cycle.

4 Discussion

The initial heterogeneity in blood flow shown by the histograms for all tumours (Fig. 7a) and by the initial perfusion estimates in Figs. 6a and 6b for a single tumour are consistent with results obtained by ACKER *et al.* (1990). The forgoing data also indicate that successive treatments of conductive interstitial hyperthermia in human intracranial tumours may cause irreversible, quantum decreases in local blood perfusion near particular interior catheters.

Although perfusion estimates were intended primarily as relative indicators, their absolute values are noteworthy. High values greater than 1.0 ml/min/g are rare in tumours (PETERSON, 1979), and were found for a minority of catheter domains. These high values cannot be explained by conductive heat loss in the longitudinal dimension (parallel to the axis of the catheters) because in many cases the high values changed abruptly with time, and simple conductive error in the thermally obtained perfusion estimates would not do so. Interestingly, only catheters which had an initial perfusion estimate greater than 1.0 ml/min/g had a 'major' decrease in perfusion over the course of a cycle. These quantitative features of the distribution of perfusion estimates support the interpretation that thermally significant blood vessels, transferring heat away from the tumour, were responsible for the initial high estimates.

During a cycle of therapy, there appeared to be a succession of discrete, irreversible shifts from high to low perfusion values as a result of treatment. Because the affected tissue regions were interior regions, not border regions, it is difficult to imagine irreversible changes in conductive heat transfer that could account for the observed changes. Rather, we suspect that coagulation of thermally significant vessels was responsible for the irreversible decreases in apparent perfusion that were observed. Importantly, as there were no instances in which regional perfusion increased significantly, it is unlikely that regional blood flow was shunted from one interior region of the tumour to another. This mechanism of thrombosis and/or vascular stasis may be especially likely to occur with conductive techniques, because of the sleeve-like high-temperature zones surrounding the heated segments of each catheter. It may also be abetted in some cases by long-duration therapy, lasting 72 h, as opposed to shorter duration therapy of l h or less (Fig. 6a, triangles),

The methodology employed in the present study provides a useful monitor of the biological response to conductive interstitial hyperthermia, even though the estimates obtained are not direct measures of blood flow. In particular, the estimation equation was derived from a computer model that assumed blood flow was omni-directional, and that longitudinal heat conduction (along the length of the catheter) and power loss through the catheter tips was negligible. Clinically, longitudinal heat conduction is minimal at the midplane of the tumour and omni-directional blood flow is approximated in most, but not all, cases relevant to clinical hyperthermia (CHEN and HOLMES, 1980). In the present study, catheter temperatures were recorded near the midplane level of the tumour, but there was no compensation for longitudinal power loss through the catheter tips. Therefore, overestimates of true perfusion are obtained. However, this method does seem to provide an approximate indicator of regional perfusion that tracks changes in true perfusion with time. Moreover, we cannot imagine any plausible

mechanisms by which the minor errors, inevitably introduced by necessary simplifying assumptions, would produce the type or magnitude of time-varying changes that we observed.

Despite limitations introduced by simplifying assumptions, we suggest that in many cases the analysis of regional perfusion estimates online may provide useful insights into tumour biology during routine hyperthermia therapy in patients. For the conceptually simple geometry of the interior domains in conductive interstitial hyperthermia, quantum shifts in effective perfusion are revealed in the time domain, which give clues to underlying vascular events *in vivo*.

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