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ABSTRACT

Normal arterioles, in contrast to the abnormal microvasculature of many solid tumors, provide a target for selective drug action that can enhance local heat treatment of the tumors. Measurements of tissue blood flow with radioactive microspheres and estimates of changes in blood flow with thermal clearance methods revealed that vasodilator drugs either decreased or did not alter blood flow in hamster melanoma, rat hepatoma, and canine transmissible venereal tumor, while increasing perfusion in adjacent normal tissues 2 to 4-fold. Solutions of the bio-heat transfer equation, which take into account such selective effects of vasodilators on blood flow in normal tissues, clearly demonstrate improved selective heating for spheroidal tumors over 2 cm in diameter. In the presence of vasodilator drug effect, steady-state center tumor temperatures of 45-50°C can be achieved by increased power input, while surrounding normal tissues remain below 42°C.

Key words: blood flow, cancer, heat, hyperthermia, therapeutic ratio, treatment

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INTRODUCTION

Heat therapy for cancer is a promising adjunct or alternative to radiation and chemotherapy [l-6]. During local heat therapy, as opposed to whole-body hyperthermia, core body temperature remains close to normal, and so the circulation of blood tends to cool the heated region. The ability to produce selective local temperature elevations in solid tumors in vivo is related to differences in vascularization and blood flow between tumor tissues and normal tissues [6-9].

The principal difference between the microcirculation of solid tumors and that of normal tissues is the abundance of sinusoidal capillary beds in solid tumors. These capillary sinusoids are broader, longer, and separated by larger intercapillary distances than normal capillaries [10-16]. These vessels penetrate neoplastic tissues in response to a chemical tumor angiogenesis factor (TAF) liberated by tumor cells [17]. TAF appears to stimulate the growth of such capillaries but not to stimulate the development of capillary sprouts into well differentiated, larger-caliber arterioles. Consequently, the density of arteries and arterioles in tumor tissues is abnormally small in relation to the venous vasculature [15, 16, 18]. The arterial vessels nourishing a tumor exhibit little vasomotion [19] and seem to be maximally dilated during tumor growth [16, 20].

If solid tumors are nourished by maximally dilated vessels feeding capillary sinusoids with poorly developed smooth muscle walls, then it is likely that the tumor vascular bed offers a relatively fixed resistance to blood flow. We reasoned, therefore, as have LeVeen et al. [3], that vasoactive drugs, which affect normal vascular smooth muscle, might be employed to change the ratio of tumor to normal tissue perfusion. This concept is presented by means of the electrical analogy in Fig. 1. In the figure the variable resistor (R_1) denotes normally reactive arterioles and the fixed resistor (R_2) denotes tumor vessels. The series resistance (R_s) denotes the normal arterioles which branch to feed both tumor and normal vessels. If a pump (the heart) feeds the parallel normal and tumor tissue beds, dilation of the normal vessels will create an effective arteriovenous shunt around the tumor. Flow to normal tissue will increase and flow to the tumor will tend to decrease. During local heat therapy, such changes in the distribution of blood flow would enhance cooling of normal tissues and simultaneously reduce cooling of the tumor. Consequently, more power can be applied to the tumor-bearing region, causing greater temperature elevations in the tumor, while surrounding normal tissues remain at a safe temperature.

Accordingly, we wondered if it is reasonable, on the basis of known physics, that blood flow changes caused by vasodilators might be exploited to enhance therapeutic temperature differences between tumor and adjacent normal tissues during local heat therapy. To answer this question we first studied the effects of vasodilators on the ratio of normal perfusion to tumor perfusion in three species of animals bearing different tumor types. Then we used computer programs to solve the bio-heat transfer equation for temperature distributions in and around spherical tumor models as a function of blood flow. Such computations provide pictures of complete temperature distributions in space, which are difficult to appreciate from the few values of temperature at specific points that can be obtained experimentally. Moreover, computer models allow easy study of the effects of tumor size and the distribution of blood flow in order to suggest the most fruitful circumstances for future animal and clinical trials.

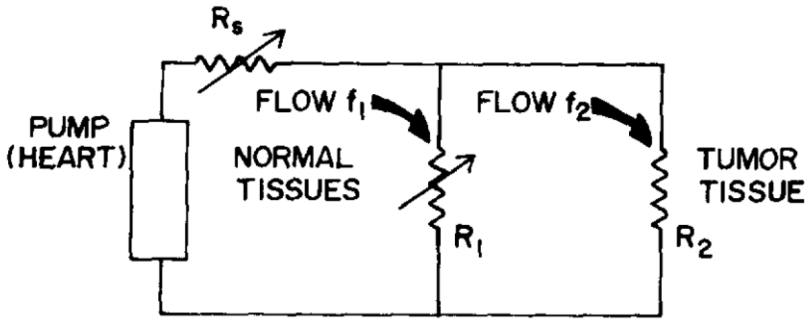

Fig. 1. Electrical analogy of tumor vs. normal blood flow. Arrows indicate variable resistances subject to drug action.

THEORETICAL CONSIDERATIONS AND COMPUTATIONAL METHODS

During local hyperthermia therapy, heat is deposited in the tissue by the tissue's own metabolism and to a much greater extent by the external energy source. Heat leaves the tissue as a result of thermal diffusion (conduction) and as a result of tissue perfusion with arterial blood, which remains approximately at core body temperature. Classically, this heat balance in tissue is described by the bio-heat transfer equations [8, 21-23], which serves as the basis for our theoretical computations.

The bio-heat equation

Consider a small volume of tissue which is being heated by an external energy source. This 'control volume' is small enough that its thermal properties are uniform. The conservation of energy requirement may be written as

$$k\nabla^2 T - \omega c_b (T - T_a) + q_m + P = \rho c \frac{dT}{dt},$$

where

k = local thermal conductivity (W/cm-^{o}C),

T = tissue temperature (^{o}C),

ω = blood perfusion (g/sec-cm^3),

c_b = blood specific heat (J/g-^{o}C),

T_a = arterial temperature (^oC),

q_m = metabolic heat generation (W/cm^3),

P = absorbed power density (W/cm^3),

c = tissue specific ($J/g\text{-}^oC$), and

ρ = tissue density (g/cm^3).

Considering the terms from left to right, the first represents the net heat transfer out of the control volume by conduction, the flow of heat by molecular action due to a thermal gradient. The second term represents heat loss due to blood perfusion, assuming that blood in the smaller vessels comes into thermal equilibrium with surrounding tissues. (Chen and Holmes [22] have scrutinized this assumption and found it to be essentially valid for tissues that are not close to very large blood vessels.) The third and fourth terms represent heat gain due to exothermic metabolism, q_m , and power input from an external source P. In the local heat therapy of tumors, P is much greater than q_m . The right-hand term represents the change in internal energy of the tissue when its temperature changes with time. Under steady-state conditions, in which temperature is constant ($dT/dt = 0$), this last term is zero, so that the heat loss from conduction and blood perfusion exactly balances heat gain from metabolic and external sources. If heat gain exceeds heat loss, however, the right-hand term, $\rho c(dT/dt)$, describes the rate of tissue temperature rise.

Numerical methods

The simplest clinically realistic solution of the bio-heat equation, which has been studied by others [21], describes a spherical tumor surrounded by a single type of normal tissue (Fig. 2). The bio-heat equation for this one-dimensional, spherical system has the form

$$\frac{1}{r^2}\frac{d}{dr}\left[r^2\frac{dT}{dr}\right]+\omega(r)\frac{c_b}{k}\left(T_a-T\right)+\frac{P(r)}{k}=0$$

for steady-state conditions and uniform thermal conductivity. The variable, r, indicates radial distance from the center of the tumor. Blood perfusion $\omega(r)$ and power absorption P(r) are specified functions of r. In the model of Fig. 2, a spherical tumor of radius r is treated by local heat therapy. Power is deposited from an external source to a radial distance r_{Rx} greater than the radius of the tumor. A large shell of unheated normal tissue extends to radius R_0, beyond which the temperature will no longer change. The metabolic heat generation q_m is either considered to be negligible or included in the term P(r).

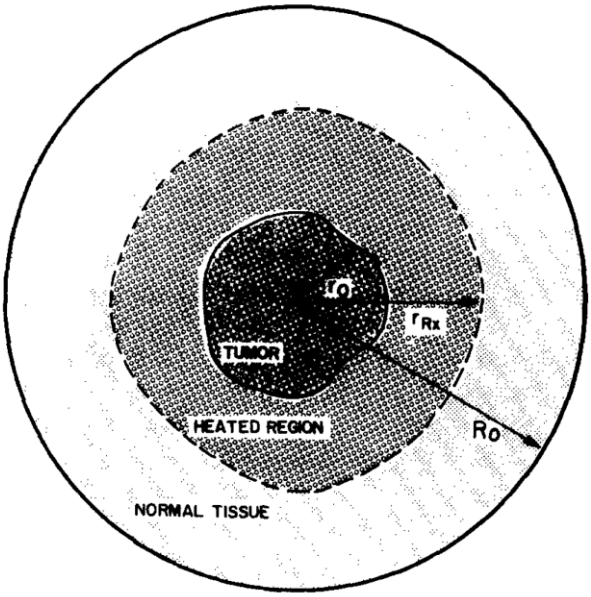

Fig. 2. Sketch of spherical tumor model used in computations.

To solve the bio-heat equation for steady-state temperature profiles in and around the tumor, we implemented a finite-difference routine with a mesh size of 200 nodes, using standard computation techniques [24]. The functions $\omega(r)$ and $P(r)$ were represented by twenty-five discrete levels. The remaining thermophysical properties required in the solution (c_b and k) were taken, for convenience, to have values corresponding to water (k = 0.6 W/m-^{o}C, c_b = 4179 J/kg-^{o}C). In any specific numerical solution of the bio-heat equation one must also specify the size (radius) of the tumor, the blood flow in and around the tumor, and the radius of the treated region. In addition, one must specify the presumed effect of vasodilator drugs on the distribution of blood flow. These considerations led us to animal studies of the influence of vasodilator drugs on the pattern of blood flow in several experimental tumor models.

EXPERIMENTAL METHODS

Estimation of vasodilator effects on perfusion from temperature-time curves

In addition to providing a basis for calculation of temperature profiles in and around a heated tumor, the bio-heat equation provides a rationale for estimating the effects of vasoactive drugs on blood flow. Consider an experiment in which one records tumor and normal tissue temperatures continuously during or after local heating, while a rapidly-acting vasodilator drug is injected. From the bio-heat equation for steady-state conditions with a prescribed perfusion, there will be no change in tissue temperature with time. However, if the perfusion rate is suddenly changed, the tissue temperature will change with time according to the expression

$$-\Delta\omega c_b\left[T-T_a\right]=\rho c\Delta\left[\frac{dT}{dt}\right],$$

where $\Delta\omega$ is the drug-induced change in perfusion. Hence it is possible to estimate $\Delta\omega$ as

$$\Delta\omega=-\frac{\rho c\Delta\left[\frac{dT}{dt}\right]}{c_b\left[T-T_a\right]}$$

from the change in the slope of the temperature- time curve $\Delta[dT/dt]$ produced by injection of the rapidly-acting drug. This expression is based upon the assumption that the conduction and heat deposition terms of the bio-heat equation are not immediately changed by drug injection and that the observed slope change is entirely due to the drug effects upon perfusion.

In the present studies, we recorded tumor and normal tissue temperatures continuously after a brief period of radiofrequency (RF) heating. Using this technique we studied two of the three tumor models to be described subsequently: a transplantable melanoma in Golden Syrian hamsters and the much larger transplantable transmissible venereal tumor in mongrel dogs. The rapidly-acting vasodilators included intravenous sodium nitroprusside in the hamsters and acetylcholine chloride infused into the femoral artery nourishing the tumor bearing hind limbs of the dogs. We then estimated the drug-induced change in perfusion, $\Delta\omega$, from the slope changes of tissue temperature-time curves for tumor and for adjacent muscle tissue, taking specific heat and density values as those of water and taking core (esophageal) temperature as a measure of arterial blood temperature. These data provided one estimate of the relative effect of the vasodilators on perfusion in tumor tissues as compared to normal tissues.

Microsphere technique for estimation of local blood flow

In another series of experiments, we used the tracer microsphere technique to provide a second, independent measure of the effects of vasodilators on the distribution of perfusion between tumor and normal tissues. The use of microspheres to measure tumor blood flow is reasonably well established [7, 25-27]. In this study, radioactively labeled polystyrene microspheres, 15 μm in diameter, containing one of four different gamma-emitting labels, were employed, according to the method of Heymann et al. [28]. To measure regional blood flow in peripheral tissues, a well-mixed suspension of microspheres was injected rapidly into the left ventricle of an anesthetized, tumor-bearing dog or rat. In the dogs, a commercial pigtail catheter with multiple side-holes (Cook, Inc., Bloomington, Indiana, U.S.A.) was placed in the left ventricle via the right common carotid artery for injection of microspheres.

In the rats, a PE 50 polyethylene catheter was placed into the left ventricle via the right common carotid artery for injection of microspheres. The catheter used in the rats had a closed end and six side-holes to promote good mixing of the microspheres with blood. A ‘surrogate organ’ reference blood sample was collected from the femoral artery (in rats) or the brachial artery (in

dogs) at a measured, constant flow rate, starting before the microspheres were injected and continuing until well after their entrapment in systemic vascular beds.

After the experiment the animal was killed and samples of tumor and normal tissues were excised and weighed. Radioactivity (counts/min) in the tissue samples and the 'surrogate organ' blood samples was measured by a Beckman 8000 gamma-spectrophotometer. Total flow (cardiac output) was calculated from the measured activity (counts/min) according to the relationship:

$$\frac{\text{total flow}}{\text{counts/min injected}} = \frac{\text{surrogate organ flow}}{\text{surrogate organ counts/min}} .$$

Regional blood flows to the tumor and normal tissue samples were calculated according to the relationship:

$$\frac{\text{tissue flow}}{\text{tissue counts/min}} = \frac{\text{surrogate organ flow}}{\text{surrogate organ counts/min}} .$$

Animal preparations

To gain some appreciation for the generality of vasodilator effects, we studied three different vasodilators in three different transplantable tumor models.

Hamster melanoma. Subcutaneous nodules of a transplantable melanoma [29] were grown in the hind limbs of 93 to 104-g outbred Golden Syrian hamsters of either sex (obtained from Harlan Sprague Dawley, Inc., Madison, Wisconsin, U.S.A.), and tumors weighing 1.8-4.7 g were heated with 500 kHz radiofrequency current via gel pad electrodes (Fig. 3). This moderately slow growing melanotic melanoma was obtained from the American Type Culture Collection (Rockville, Maryland, U.S.A.). Tumor cells were grown at 37°C in McCoy's 5A medium (Gibco Co., Grand Island, New York, U.S.A.), supplemented with penicillin (100 units/ml), streptomycin (0.1 mg/ml) and fetal calf serum (20% v/v). The cells were maintained in monolayer cultures in 75-cm^2 plastic flasks. Hamsters were injected subcutaneously in the right rear leg with 1 x 10^6 melanoma cells suspended in 0.05 ml of the previously described medium. Tumors of adequate size developed within 20 days.

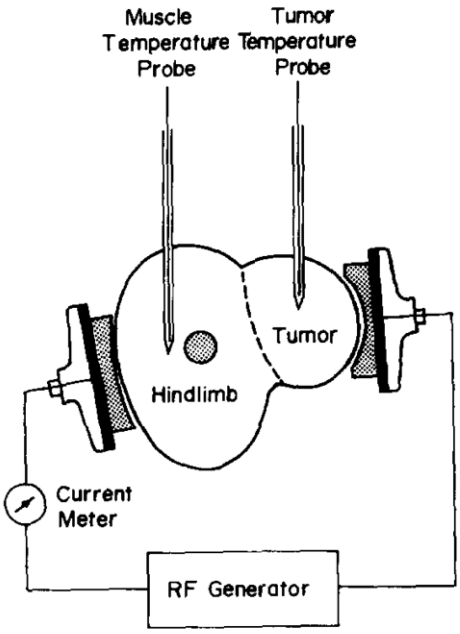

Fig. 3. Temperature probes in hamster leg heated with gel pad electrodes.

After induction of anesthesia with sodium pentobarbital (30 mg/kg, i.p.), hollow glass microprobes, 1 mm in external diameter, were advanced into the center of the tumor nodule and into underlying skeletal muscle of the limb at right angles to the current field lines (Fig. 3). Thermistor probes could then be advanced into the microprobes to measure tissue temperatures, which were graphically displayed on a stripchart recorder. The jugular vein of the hamster was exposed to permit injection of sodium nitroprusside (1 mg/kg), a potent, direct acting vasodilator, or saline vehicle (0.1 ml) as a control.

With this animal preparation we obtained artifact-free records of tumor and muscle tissue temperatures during periods of 500 kHz RF heating and could observe the transient effects of bolus injections of nitroprusside. The changes in effective perfusion, seen for several minutes after drug injection, were calculated from the drug-induced slope changes of the temperature-time curves, as previously described.

Rat hepatomas. Studies using radioactive microspheres were conducted in two types of transplantable rat hepatoma. The two types of tumor differed greatly in their vasculatures as seen under the light microscope. The first, which we called the 'hard' tumor, contained infrequent discrete, thin-walled capillaries. The second, which we called the 'soft' tumor, contained abundant wide sinusoidal spaces, filled with blood. Both tumor types diverged from a hepatoma which first appeared in a rat being fed the carcinogen FAA (N-2- fluorenylacetamide) [30]. To transplant these tumors into the recipient Harlan Fischer rats, a tumor was excised from a donor

rat and minced into 1 mm^3 pieces. Two to four pieces were then implanted subcutaneously into the left thigh using a trocar needle. A growing period of two to three weeks was required.

Thirty-four male Harlan Fischer rats with body weights ranging from 150 to 250 g, with 4.3 to 21.9 g tumor nodules on the left leg, were used for this study, 12 bearing the hard tumor and 22 bearing the soft tumor. The animals were first anesthetized with ketamine (0.2 g/kg i.m.). Radioactive microspheres were used to determine the blood flow in tumor and surrounding normal tissues. Two groups of rats were studied: rats given the vasodilator hydralazine, 0.5 mg/kg i.v., and rats given 0.2 ml of 0.9% saline vehicle as a control.

Canine transmissible venereal tumor. The well known effects of tumor size on tumor blood flow [7, 11, 31] and preliminary results of computer modeling showing the effects of tumor size upon temperature distribution [8] led us to investigate a larger animal model. The transmissible venereal tumor (TVT) is a naturally occurring neoplasm of the penis and vagina in dogs. Transmission from animal to animal occurs during coitus. The biology and mechanism of transmission of TVT in dogs have been previously reported by several investigators [32-36]. Tumors can be seeded in experimental animals by hypodermic injection of TVT cell suspensions and will grow rapidly in locations where they would not often occur in nature.

We initiated TVTs in the subcutaneous tissue of the hind limbs in 10 dogs, using the technique of Epstein and Bennett [35] and Cohen [33]. After a growing period of 40-80 days, anesthesia was induced with thiopental sodium (~10 mg/kg) and maintained with methoxyfluorane, nitrous oxide and oxygen inhalation. In 3 dogs intra-arterial acetylcholine, which has a rapid onset of action, was infused via a catheter in the abdominal aorta at 100 mg/kg/min to produce local vasodilation in the tumor-bearing hind limb. In the remaining 7 dogs intravenous hydralazine (0.5 mg/kg) was given as a single bolus and blood flow determined 20 min later, when effects of the drug on blood pressure had stabilized.

Local heating of the tumor-bearing limb on one side was accomplished with the use of a pair of Helmholtz coils of radius 8 cm and a Bircher electrosurgery/diathermy generator operating at 13.56 MHz. Heating was done during intermittent 1 to 3 minute periods, between which temperatures of the tumor and of underlying normal muscle were recorded using Yellow Springs Instruments thermistor probes, calibrated against a mercury thermometer traceable to the U.S. National Bureau of Standards. In the 3 dogs given acetylcholine, changes in tumor and normal tissue perfusion caused by the drug were estimated from the slope changes of the temperature-time curves. In the 7 animals given hydralazine, tissue perfusion was estimated using the microsphere technique.

RESULTS

Vasodilator effects on blood flow

Tables 1A and 1B present effects of vasodilators upon tumor and normal tissue perfusion. Table 1A presents changes in blood perfusion caused by drug treatment; Table 1B presents absolute values of blood perfusion before and after drug treatment. By either measure, blood perfusion in normal tissues increased after vasodilator injection, and blood perfusion of tumor tissue either remained the same (in hamster melanoma and in rat heapatoma) or decreased (in dog venereal tumors).

Table 1A. Vasodilator influence on blood flow determined from analysis of temperature-time curves

Species	Tumor model	No. of trials/ animals	Drug and dose	Drug-induced change in blood flow (ml/min/g) ± S.E.M.	
				Tumor	Normal muscle
Hamster	melanoma	14/7	0.9% saline (control)	0.00 ± 0.01	0.00 ± 0.01
Hamster	melanoma	13/7	Na nitro prusside 1 mg/kg i.v.	0.00 ± 0.02	+ 0.08 ± 0.03
Dog	TVT	6/3	Acetyl-choline, 0.1 mg/min i.a.	0.00 ± 0.04	+ 0.49 ± 0.13

Table 1B. Influence of hydralazine (0.5 mg/kg iv.) on blood flow determined using radioactive microspheres

Species	Tumor model	No. of trials/ animals	Blood flow (ml/min/g) ± S.E.M. Tumor Control	Tumor Drug	Normal tissue* Control	Normal tissue* Drug
Rat	'hard' hepatoma	12/12	0.19 ± 0.04	0.14 ± 0.02	0.29 ± 0.02	0.48 ± 0.06
Rat	'soft' hepatoma	22/22	0.08 ± 0.03	0.06 ± 0.02	0.30 ± 0.05	0.41 ± 0.04
Dog	TVT	28/7	0.29 ± 0.14	0.03 ± 0.02	0.14 ± 0.04	0.80 ± 0.17

*Cardiac output per gram of body weight in rats; regional blood flow per gram of underlying muscle in dogs.

The results obtained with two different and independent techniques are substantially in agreement and yield a similar picture of the blood flow redistribution caused by vasodilator drugs. All three vasodilator drugs selectively improved blood flow to normal tissues. Typically, it appears that without vasodilator effect, both tumor and normal tissue perfusion in anesthetized animals lie in the neighborhood of 0.2 ml/min/g. After treatment with vasodilators normal tissue perfusion increased about 2 to 4-fold, while tumor flow either remained the same or decreased. These data allowed us to proceed to estimate the effects of vasodilator treatment upon tumor temperature profiles using the bio-heat equation.

Computed effects of vasodilators on temperature profiles

Considering published work of others describing tumor blood flow [20, 31, 37, 38] and our own observations of the redistribution of tumor blood flow by vasoactive drugs, we chose as a starting point the following specific conditions for modeling steady-state temperature profiles before and after administration of vasodilator drugs. Tumor radius: 5, 10, 20 or 40 mm. Power deposition: uniform in intensity and extending from the center of the tumor to twice the radius of the tumor. Initial tumor flow: equal to normal tissue flow, 0.2 ml/min/g. Drug effect: 2 x or 4x increase in normal tissue flow with no change in tumor flow and an abrupt, linear transition to normal tissue flow in the outer shell of the tumor. We evaluated the bio-heat equation for these conditions to determine the probable effect of vasodilators on the temperature distributions in and around tumors of various sizes during local heat therapy. Then we studied the influence of alternative assumptions for a 20 mm radius tumor, including (a) reduced blood flow within the tumor itself caused by vasodilators, in addition to increased flow in normal tissue, and (b) the existence of a hyperperfused outer shell in the tumor. In all of these computations the value of uniform power input was adjusted--as one would hope to do in practice-to keep the normal tissue at the edge of the tumor at a 'safe' temperature, which we took to be 42 °C.

Calculated temperature profiles and tumor size

Figures 4 A-D show temperature profiles computed from the bio-heat equation for 5, 10, 20 and 40-mm radius tumors. Tumor blood flow is always 0.20 ml/min/g. The solid curves represent control conditions in which blood flow in surrounding normal tissue is also 0.20 ml/min/g. The dashed and dotted lines represent two plausible levels of vasodilator effect, in which normal tissue perfusion is twice or four times tumor perfusion (0.40 or 0.80 ml/min/g). Central tumor temperatures approaching 10°C greater than core temperature and over 5°C greater than surrounding normal tissue can be achieved in this tumor model during typical vasodilator action.

Clearly, tumor temperature increases as a function of the tumor radius when blood flow is greater in normal tissue than in tumor tissue. This result is easily understood. Heat is deposited uniformly in the tumor volume (proportional to r^3), but under conditions of relatively low tumor blood flow a significant amount of 'heat leaves by conduction through the tumor surface (proportional to r^2). Hence the ratio of heat input to heat output, which determines tumor temperature, tends to increase as a function of r^3/r^2, and it follows that the effectiveness of vasodilator-enhanced heat treatment will be greater for larger tumors than for smaller ones.

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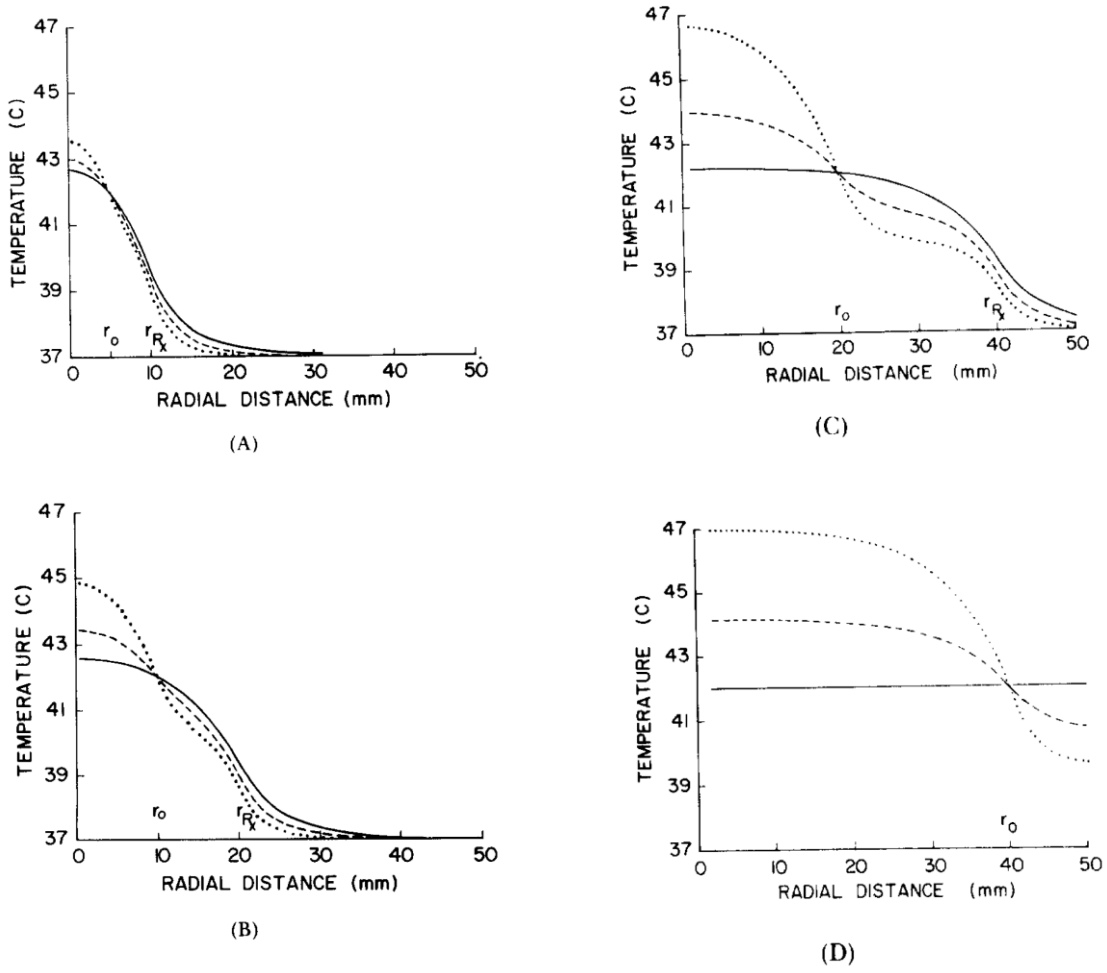

Fig. 4. Temperature profiles computed from the bio-heat equation for: A, 5; B, 10; C, 20; and D, 40-mm radius tumors surrounded by homogeneous normal tissue. r_0 is the tumor radius; r_{Rx} is the treatment radius. Tumor perfusion is always 0.20 ml/min/g. In A power input was 0.17412. 0.22622 and 0.31102 W/ml for blood flows of 0.20, 0.40 and 0.80 ml/min/g in surrounding normal tissue. In B power input was 0.09564, 0.13564 and 0.20188 W/ml for blood flows of 0.20, 0.40 and 0.80 ml/min/g in surrounding normal tissue. In C power input was 0.07358, 0.10857 and 0.16035 W/ml for blood flows of 0.20, 0.40 and 0.80 ml/min/g in surrounding normal tissue. In D power input was 0.06981, 0.10027 and 0.14062 W/ml for blood flows of 0.20. 0.40 and 0.80 ml/min/g in surrounding normal tissue.

Variation of blood flow

The effect is similar for other plausible combinations of tumor flow and vasodilator-enhanced normal tissue flow presented in Table 2. The table gives predicted center temperatures during vasodilator enhanced local heat therapy for various flow conditions. Also presented are the temperature gradients at the edge of the tumors, which are measures of the selectivity of heat therapy. Whenever tumor flow is relatively low compared to flow in normal tissues, there can be greater power input to the treated region without excessive temperature elevation in normal tissues. As a result, the tumor temperature rises toward cytotoxic levels, and steep temperature gradients in the neighborhood of –0.5 ^{o}C/mm radial distance can be established at the tumor edge.

Table 2. Calculated center tumor temperatures during vasodilator enhanced local heat therapy for various flow conditions

20-mm radius tumor flow (ml/min/g)	Normal tissue flow (ml/min/g)	Center tumor temperature (°C)	Gradient at tumor edge (°C/mm)
0.20	0.40	44.0	−0.275
	0.80	46.6	−0.633
0.10	0.20	43.7	−0.203
	0.40	45.8	−0.444
	0.80	48.8	−0.796
0.05	0.10	43.4	−0.157
	0.20	44.8	−0.309
	0.40	47.1	−0.546
	0.80	50.4	−0.851

Power adjusted to maintain tumor edge at 42°C.

Spatial profile of perfusion

The existence of a hyperfused outer shell has been described in at least some tumor types [14, 17, 39] and may be evident as a hypervascularized surface of many solid tumors at surgery. Figure 5 presents perfusion and steady-state temperature profiles during local heat therapy in a 20-mm radius tumor model with an underperfused core and a hyperperfused outer shell. Curve A represents the base conditions and curve B represents the hypothetical effect of a vasodilator that increases flow in the outer shell of the tumor as well as in adjacent normal tissue. Contrary, perhaps, to intuition, the presence of a relatively well-perfused tumor shell permits greater power input to the tumor core and higher overall tumor temperatures while the tumor edge is maintained at 42°C.

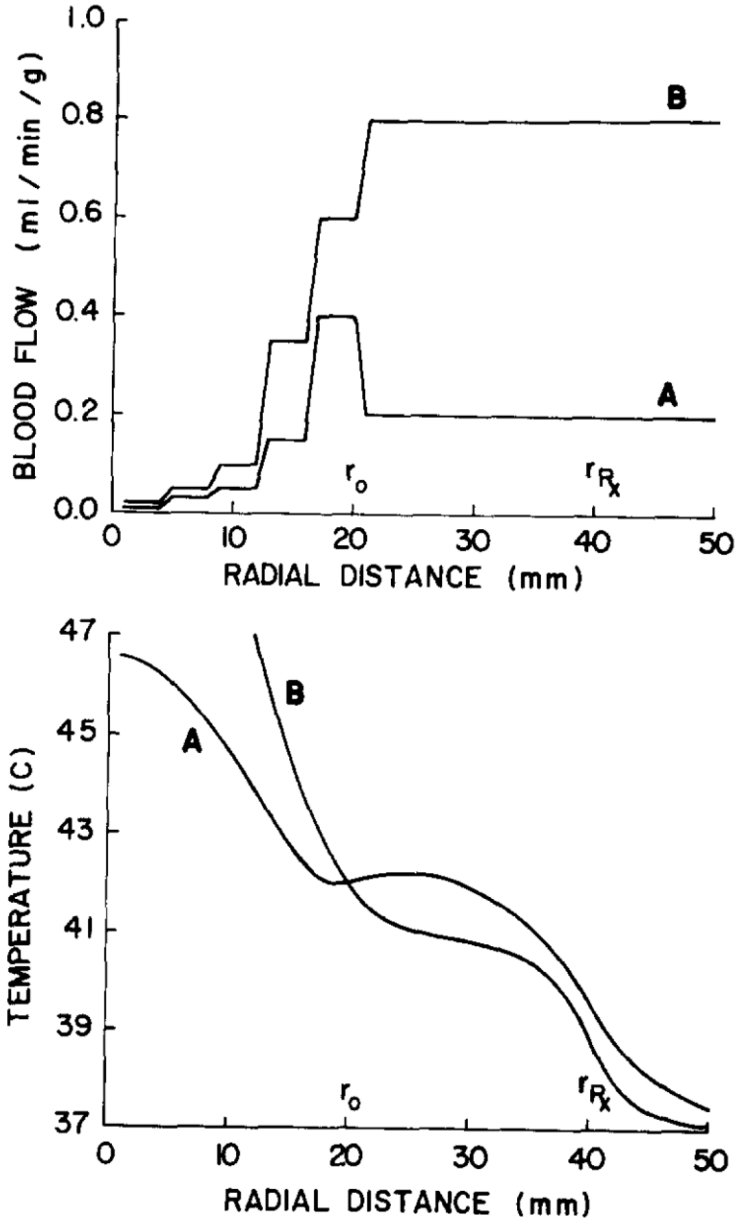

Fig. 5. Perfusion and temperature profiles in a 40-mm diameter tumor model with various transition patterns between tumor and normal tissue blood flow.

DISCUSSION

Vasodilators have profound effects upon the distribution of blood flow between tumor and adjacent normal tissues. Dilation of normal arterioles improves blood flow in normal tissues and may shunt blood away from the tumor. According to the physical laws of heat transfer, such perfusion effects can greatly enhance the temperature difference between the tumor and adjacent normal tissues during local hyperthermia therapy. Our experimental studies involving three species, three tumor types and three different vasodilators show that such drugs can increase regional blood flow in normal tissues to several times that in tumor tissue, making possible steady-state intratumor temperatures of over 45°C while temperatures in surrounding normal tissues remain near 40°C. Temperature elevations of this magnitude are sufficient to produce tumor necrosis in a single treatment session lasting less than 1 hr [40, 41]. This influence of vasodilators upon the calculated temperature distributions is especially pronounced for larger tumor masses.

Clinically, Jonsson and associates [42] studied the effects of intra-arterial prostaglandin E_1, a potent vasodilator, as an adjuvant to angiography of tumors of the extremities in 10 patients. Except in one case, involving a hemangioma, the arteriographic visualization of tumor vessels and delineation of the extent of disease were worse after the use of prostaglandin E_1, while visualization of small normal muscular arteries improved. Evidently, prostaglandin increased blood flow in normal tissues relative to the tumor in a manner similar to the action of vasodilators reported in the present paper. In principle, such vascular effects are capable of increasing the therapeutic ratio (tumor temperature rise/normal tissue temperature rise) several fold to the point where a large proportion of the tumor tissue can be selectively destroyed by local hyperthermia therapy.

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