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Perfusion and thermal field during hyperthermia. Experimental measurements and modelling in recurrent breast cancer

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Abstract. Recurrences of malignant tumours in the chest wall are proposed as a valuable model of tissue mainly perfused by small size vessels (the so-called 'phase III' vessels). Invasive thermal measurements have been performed on two patients affected by cutaneous metastasis of malignant tumours during hyperthermic sessions. Thermal probes were inserted into catheters implanted into the tissue at different depths. In one of the catheters a probe connected with laser-Doppler equipment was inserted to assess blood perfusion in the tumour periphery. The perfusion was monitored throughout the sessions, and a noticeable temporal variability was observed. The effect of the perfusion on the thermal map in the tissue was evaluated locally and the 'effective conductivity' of the perfused tissue was estimated by means of the numerical integration of the 'bio-heat' equation.

The tumour temperature, at the site where the perfusion probe is located, can be predicted by the numerical model provided two free parameters, α and β, are evaluated with a fitting procedure. α is related to the effective conductivity and β to the SAR term of the bio-heat equation. The model aimed at estimating the 'effective conductivity' K_{eff} of the perfused tissue, and average values of K_{eff} of 0.27 ± 0.03 W m^{-1} °C^{-1} in Patient 1 and of 0.665 ± 0.005 W m^{-1} °C^{-1} in Patient 2 were obtained throughout the treatment.

However, when the average temperature in a larger tumour volume is to be predicted but only a single, 'local' measurement of the perfusion is available and is assumed to be representative for the whole region, the model results are far less satisfactory. This is probably due to the fact that changes of blood perfusion throughout hyperthermic sessions occur to different extents within the tumour volume, and the differences in perfusion cannot be ignored.

The above result suggests that, in addition to the 'temperature map', also a 'perfusion map' within the heated volume should be monitored routinely throughout hyperthermic sessions.

1. Introduction

Previous investigations stressed the importance of accounting for the perfusion in 'provisional thermometry' protocols. The therapeutic effectiveness of hyperthermia is related to the temperature level reached in the tumour and to its uniformity (Vaupel and Kallinowsky 1987). Both aspects are critically affected by blood perfusion. Lagendijk *et al* (1988), for instance, showed that in advanced breast carcinoma, about 10 times as much

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power as in a non-perfused phantom was needed to maintain therapeutic temperatures during hyperthermic sessions.

Let us define the 'thermal equilibrium length' as the distance needed to observe a complete thermal equilibrium between the fluid in the vessel and the surrounding tissue. Depending on the ratio between their physical length and their thermal equilibrium length, vessels are sometimes divided in 'phase I' (ratio much larger than 1), 'phase II' (ratio about 1) and 'phase III' (ratio much smaller than 1) (Lagendijk and Mooibroek 1986).

The thermal effects of perfusion are known to be related both to the size (or the 'phase'), of the vessels (Lagendijk and Mooibroek 1986) and to the vascular damage caused by previous radiotherapy and hyperthermia treatments (Lyng *et al* 1991b). On this basis, it is mandatory to restrict the field of investigation to a well defined type of tumour and to pay attention to clinical history. Recurrences of malignant tumours in the chest wall, pretreated by radiotherapy (RT) and/or surgery, will be the target of our study.

The chest wall is the most frequent site of recurrences of breast carcinoma; only 50% of patients with chest wall recurrences develop distant metastasis within two years (Bedwinek *et al* 1981). Radiation therapy may induce a complete remission (CR) in about 50% of local recurrences (Bedwinek *et al* 1984). When the local recurrence is macroscopically manifest not only are radiation doses exceeding 60 Gy required for tumour eradication, but also local control is generally difficult to achieve. Some studies have shown that external hyperthermia (HT) in combination with low doses of RT is able to markedly improve the CR rate in recurrences in the chest wall. The isodose thermal enhancement ratio (TER), computed as the ratio between the percentage of CR after RT + HT and the percentage of CR after RT alone, is between 1.22 and 2.36 (Vernon 1997, Overgaard 1989, Gabriele *et al* 1996).

Improved thermal sensitivity is probably due to the poor perfusion of recurrent tumours after RT and surgery, which both damage small and intermediate vessels. The latter modality, in particular, destroys larger vessels ('phase I' vessels). In our opinion, the healthy tissue of the breast is also poorly vascularized after heavy pretreatment. Heat is therefore likely to be effective since it counteracts the lowering of radiation sensitivity observed as the blood supply is impaired (Hahn 1982, Storm 1983).

Previous investigations (Acker *et al* 1990) have shown that monitoring the blood perfusion in human tumours during hyperthermic treatments, by means of a laser-Doppler apparatus, is a reliable and sensitive method to obtain information regarding the tumour response to heat. Since patients are already submitted to catheter implantation in order to monitor the temperature in different tumour sites, insertion of a perfusion probe does not cause further discomfort. It has also been shown (Madon 1993) that no mutual disturbances between the electrical signals generated by the nearby probes of temperature and perfusion occur during the treatment.

The effect of blood perfusion on the temperature field has already been studied with mathematical techniques. The first approach (Pennes 1948), is based on the hypothesis that blood enters any (infinitesimally) small block of tissue at artery temperature and leaves the block at local tissue temperature. This is a poor approximation of the very complex phenomenon of the approaching of thermal equilibrium in tissue. Large vessels of known geometry have a dramatic influence on the temperature of the surrounding tissue, it is, however, possible to predict their cooling effects by mathematical modeling (Crezee and Lagendijk 1990, 1992).

The thermal influence of small vessels is described by an 'effective conductivity', much larger than that pertaining to the unperfused tissue. This approach is based on the hypothesis that small arteries and veins are almost parallel and the flow direction is

antiparallel, or countercurrent, so that their heating and cooling effects are counterbalanced. The contribution of these 'countercurrent pairs' has been summarized by Weinbaum and Jiji (1985) by means of an 'effective conductivity' linearly dependent on the tissue perfusion. Mixed models have been proposed, in which the perfusion is taken into consideration with both a 'Pennes' term and an 'effective conductivity' (Charny *et al* 1990, Crezee *et al* 1994).

The aim of the present study is to test whether the thermal effect of hyperthermia in a tissue mainly perfused by 'phase III' vessels can be described by means of an effective conductivity, and to estimate its value.

2. Materials and methods

2.1. Measurements on patients, tissue geometry and position of the probes

The investigated tissue was the chest wall region in two patients affected by cutaneous metastasis of malignant tumours; the patients had been previously operated for primary tumours and treated with post-operative radiation therapy.

The size of the lesion of Patient 1 was 5×5 cm^2, and its depth, estimated by ultrasound, was 1.8 cm (minimum 1.1 cm, maximum 2.5 cm). Concomitant radiation therapy was done by electrons with a Linac (13 MeV, effective field 88×84 mm^2 on the chest wall); the radiation total dose was 30 Gy in 15 fractions in 29 days.

The size of the lesion of Patient 2 was 5.7×5.5 cm^2, and its depth, estimated by ultrasound, was 1.2 cm (minimum 0.9 cm, maximum 1.4 cm). Concomitant radiation therapy was done by electrons with a Linac (6 MeV, effective field 186×156 mm^2 on the chest wall); the radiation total dose was 46 Gy in 23 fractions in 40 days.

Prior to the hyperthermic treatment, three catheters were inserted in the treated region at about 1 cm depth to contain the temperature and perfusion probes. The catheters were approximately 1 cm distant from each other (see figure 1). Ultrasonic (and CT) imaging of the region showed that arteries and veins lay well below (about 4 cm) the fat tissue, i.e. out of the region actually heated during the treatment.

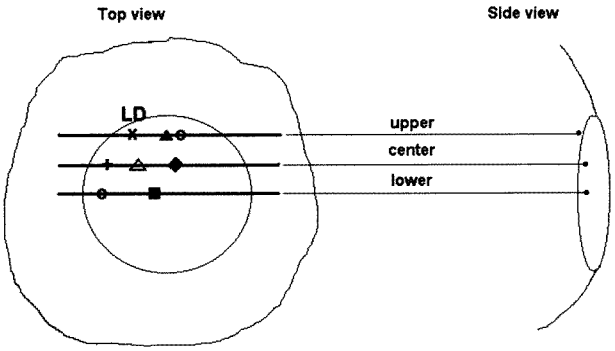

Figure 1. Scheme of the position of the thermal and perfusion probes on the patients' chest walls. Probes positions are indicated by the same symbols used in figure 3(*a*) for the corresponding temperatures.

Both patients underwent 6 HT sessions, twice a week, immediately after RT (about 5 min) during the first 3 weeks of treatment, but perfusion was monitored only in three sessions for Patient 1 and two sessions for Patient 2.

The temperature probes (one multipoint (3) probe and 4 monopoint probes in Patient 1, one multipoint (4) and 2 monopoint probes in Patient 2) and the perfusion probe were inserted in the catheters. The temperature probes were connected to a multichannel thermometric system with a fibreoptics thermometer (model 3000 fluoroptic thermometry system, Luxtron, Canada). Temperatures were affected by an error of $\pm 0.5\,^{\circ}$C. One of the temperature probes was selected as the 'controller' for the delivered power: when the measured temperature was different from the selected treatment temperature, a feed-back control loop was activated to regulate the temperature.

The laser-Doppler probe was inserted in a peripheral catheter. The volume of tissue investigated was about 0.5 mm^3. The probe was connected with an He–Ne laser-Doppler apparatus (Periflux PF3 laser Doppler perfusion monitor, Perimed, Sweden). Perfusion was measured by the apparatus as the product of the number of red blood cells within the measuring volume times their mean velocity, and was given in arbitrary units, in a scale between 0 and 120.

A bolus was inserted between the patient's skin and the applicator, both to improve the impedance matching and to keep the skin temperature comfortable.

2.2. Applicator characteristics, heating apparatus and procedure

Two different loaded waveguide applicators, operating at 433 MHz and 915 MHz, were used for Patient 1 and Patient 2 respectively. Their characteristics are given in table 1.

Table 1. Applicator characteristics.

	Patient 1	Patient 2
Applicator		
Frequency (MHz)	433	915
External dimensions (cm^2)	11.7×7.8	15×15
Maximum delivered power (W)	150	200
ESHO parameters (Hand *et al* 1989)		
Penetration depth (cm)	4.9	1.9
Effective field size (cm^2)	5×4.5	11×11
Isodose 100% (cm^2)	1×1	8.5×8.5

The hyperthermic system (SAPIC SVC3/A, Alenia, Italy) (Audone *et al* 1985, Ogno *et al* 1987) controlled the power delivery to the patient (maximum 200 W), the bolus temperature (35–37 °C) and flow rate, the thermometric device as well as the monitoring and recording of temperature and power data. Once the rate of heating, the stationary heating temperature (about 43 °C) and the duration of the treatment (about 30 min) were selected, the protocol was automatically performed by the system.

2.3. Model: main hypothesis

Considering the power delivered to the patient throughout each hyperthermia session and the blood perfusion measured in one point of the lesion, we aimed at predicting a map of the temperature levels in the tumour region and to compare that with the measured temperature data. This was done by numerical integration of the so-called 'bio-heat equation', originally

proposed by Pennes (1948)

$$\rho c \frac{\partial T}{\partial t} = K \Delta T + \mathrm{SAR} + M + B \tag{1}$$

where T is the local temperature, Δ the Laplace operator, ρ, c and K are the tissue density, specific heat and heat conductivity respectively, SAR is the specific absorption rate, M is the metabolic heat production (we will disregard the latter in what follows). The term (Pennes perfusion term)

$$B = w_b c_b (T - T_{\mathrm{art}}) \tag{2}$$

where w_b and c_b are the volumetric rate of perfusion and blood specific heat, and T_{art} is the temperature of the arterial blood (normally assumed to be 37 °C), accounts for blood perfusion.

Our main hypotheses are the following:

(i) The specific absorption rate SAR is known to vary in time with the power delivered by the hyperthermic system (corrected for the reflected power) and in space depending on the applicator characteristics. We assumed a heuristic expression proposed by Olmi (1990) and Andreuccetti *et al* (1991), suitable for the radiative applicators in homogeneous tissues and based on the hypothesis that the absorption is described by a linear term in the exponent in the z-direction and a quadratic term in the x- and y-directions:

$$\mathrm{SAR}(x, y, z, t) = \beta \exp[-ax^2 - by^2 - c(z - z_0)] P(t) \tag{3}$$

where $P(t)$ is the delivered power corrected for the reflected fraction. For computing requirements, the power was filtered with a moving average algorithm (MATLAB, USA) on 10 min intervals. a, b and c are related to the ESHO parameters 'effective field size' EFS_x and EFS_y and to the penetration depth PD (Hand *et al* 1989) of the applicator (Olmi 1990), and to the constant z_0, according to the following equations:

$$a = \frac{4 \ln 2}{\mathrm{EFS}_x^2} (\mathrm{m}^{-2}) \qquad b = \frac{4 \ln 2}{\mathrm{EFS}_y^2} (\mathrm{m}^{-2}) \qquad c = \frac{\ln 2}{\mathrm{PD} - 10^{-2} z_0} (\mathrm{m}^{-1}). \tag{4}$$

(See table 2.) β is actually a free parameter, whose value can be determined by a fitting procedure.

Table 2. Numerical values used in the model.

Fat tissue parameters:	
$\rho = 940$ kg m^{-3}	
$c = 2500$ J kg^{-1} °C^{-1}	
$K = 0.2$ W m^{-1} °C^{-1}	
Model parameter values:	
$l_x = 5$ cm, $l_y = 3$ cm, $l_z = 5$ cm	
$\mathrm{RAP}_x = \mathrm{RAP}_y = \mathrm{RAP}_z = 1.5$	
$N_x = 47$, $N_y = 23$, $N_z = 24$	
$DT = 1$ s	
Applicator parameters (Olmi 1990, Andreuccetti *et al* 1991):	
433 MHz loaded waveguide:	$a = 640$ m^{-2}, $b = 1111$ m^{-2}, $c = 16$ m^{-1}, $z_0 = 0.004$ m
915 MHz loaded waveguide:	$a = 229$ m^{-2}, $b = 12323$ m^{-2}, $c = 46$ m^{-1}, $z_0 = 0.004$ m

(ii) It is thought that both the fat tissue and the tumour are perfused mainly by the microvascular network ('phase III' vessels). We will assume, according to Weinbaum and Jiji (1985), that the thermal effect is summarized by the introduction in the bio-heat equation of an effective conductivity larger than that pertaining to the same 'unperfused' tissue:

$$K_{\text{eff}}(t) = K(1 + \alpha w_b(t)). \tag{5}$$

Since perfusion changes in time, the effective conductivity can also vary. K_{eff} and K are the 'effective' and 'non perfused' conductivities respectively, α is a constant dependent on the vessels dimension and density and w_b is the volumetric rate of perfusion. In our model α is a free parameter to be estimated by fitting procedures. In this model the Pennes term B is disregarded.

2.4. Numerical solution of the bioheat equation

In order to solve the bioheat equation numerically, an implicit Crank–Nicolson method has been selected to assure numerical stability (Hoffmann 1992). The equation is solved on a 3D grid of dimensions $l_x \times l_y \times l_z$, which is a spatial domain comparable with the one heated by the applicator. Since we assumed boundary conditions of Dirichlet type with fixed temperature equal to 37 °C, however, we had to be sure that the boundaries of our test volume remained at that temperature throughout all the hyperthermic sessions. For this reason, we defined the parameters RAP_x, RAP_y and RAP_z as multiplicative factors to test the actual boundary temperature and to increase the volume dimension when appropriate.

The spatial steps of integration, and therefore the number of grid points N_x, N_y and N_z in the directions x, y and z respectively, and the temporal step DT, were selected in such a way that further refinement would not change the temperature values predicted by the model (parameter analysis) by more than 1%. A scheme of the grid and the points where the predicted temperatures are computed is given in figure 2.

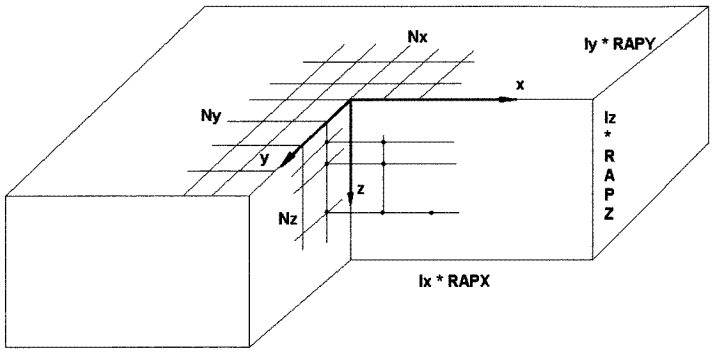

Figure 2. Scheme of the simulated heated volume.

As already stated, the model has two free parameters to be adjusted: α and β. α is related to the conductivity, and is expected to affect the temperature level mainly during stationary heating, while β is related to SAR, and is therefore expected to influence the predicted temperature mainly in the warming up phase. It is therefore logical to assume that an unambiguous combination of α and β values could fit the data.

Since the perfusion has been measured at one point, we assume that the experimental values are representative of the perfusion only at that point, i.e. at the position of the perfusion probe. Therefore each time we compare the experimental temperature measured

at the probe nearest to the perfusion measuring point, $T_{\mathrm{sper}}(t)$, with the one computed by the model in the same point, $T_{\mathrm{pred}}(t)$. The parameters α and β are adjusted in order to minimize the chi-squared function, defined as

$$\chi^2 = \sum_{t=nDT} (T_{\mathrm{sper}}(t) - T_{\mathrm{pred}}(t))^2 / T_{\mathrm{pred}}(t). \tag{6}$$

In addition, we have taken the perfusion measured by the perfusion probe as representative for the whole volume. The above algorithm has also been evaluated in this case, and compared with previous results. Now $T_{\mathrm{sper}}(t)$ has become the average value of the experimental temperatures within the heated volume and $T_{\mathrm{pred}}(t)$ the one computed by the model within the same volume.

3. Results

Three treatments have been carried out on Patient 1 and two on Patient 2, according to the procedure described in section 2. Figure 3 shows the measured temperatures (*a*), powers (*b*) and blood perfusion rate (in arbitrary units) (*c*) in one 'exemplary' treatment.

The perfusion baseline was different for each patient and for successive sessions in the same patient, but in all the sessions the measured perfusion changed in a similar way during the treatments. When the power was switched on the temperature started to rise, and in reaction the perfusion started to rise as well, with a delay which was different depending on the session. Table 3 summarizes the perfusion data for all the sessions. When the temperature changed notably during the treatments, the perfusion showed oscillations which were almost synchronized with those in the temperature.

Table 3. Increase of perfusion throughout treatment.

	Patient 1			Patient 2	
	Treat. 1	Treat. 2	Treat. 3	Treat. 1	Treat. 2
Time after power on (min)	13 ± 1	6 ± 1	6 ± 1	22 ± 1	7 ± 1
% increase (with respect to baseline)	667 ± 60	49 ± 17	156 ± 44	286 ± 33	104 ± 46

At first we defined the model parameter values. The results of the parameter analysis are given in table 2. Then, for all the sessions, the comparison between experimental and predicted temperatures during the stationary heating phase was performed in order to adjust model parameters. The estimated values of α and β were retained when the chi-squared value was statistically acceptable ($p < 0.05$). There was greater agreement between measured and estimated temperatures when a single temperature probe (near the perfusion one), instead of its averaged value in the heated volume was considered.

Figure 4(*a*) shows both the measured temperature and that estimated by the model at the perfusion probe location throughout one exemplary session. The dotted curve was the local temperature value predicted by the model in the absence of perfusion ($K_{\mathrm{eff}}(t)$ was replaced by the constant value of K pertaining to the fat tissue). Figure 4(*b*) shows the comparison between the experimental temperature averaged on the heated volume, and the temperatures predicted in the same volume. Provided the perfusion $w_b(t)$ is replaced in equation (5) by its average value throughout the treatment, the corresponding value of K_{eff} is assumed to represent the average effective conductivity throughout the pertaining session. The relevant values are given in table 4.

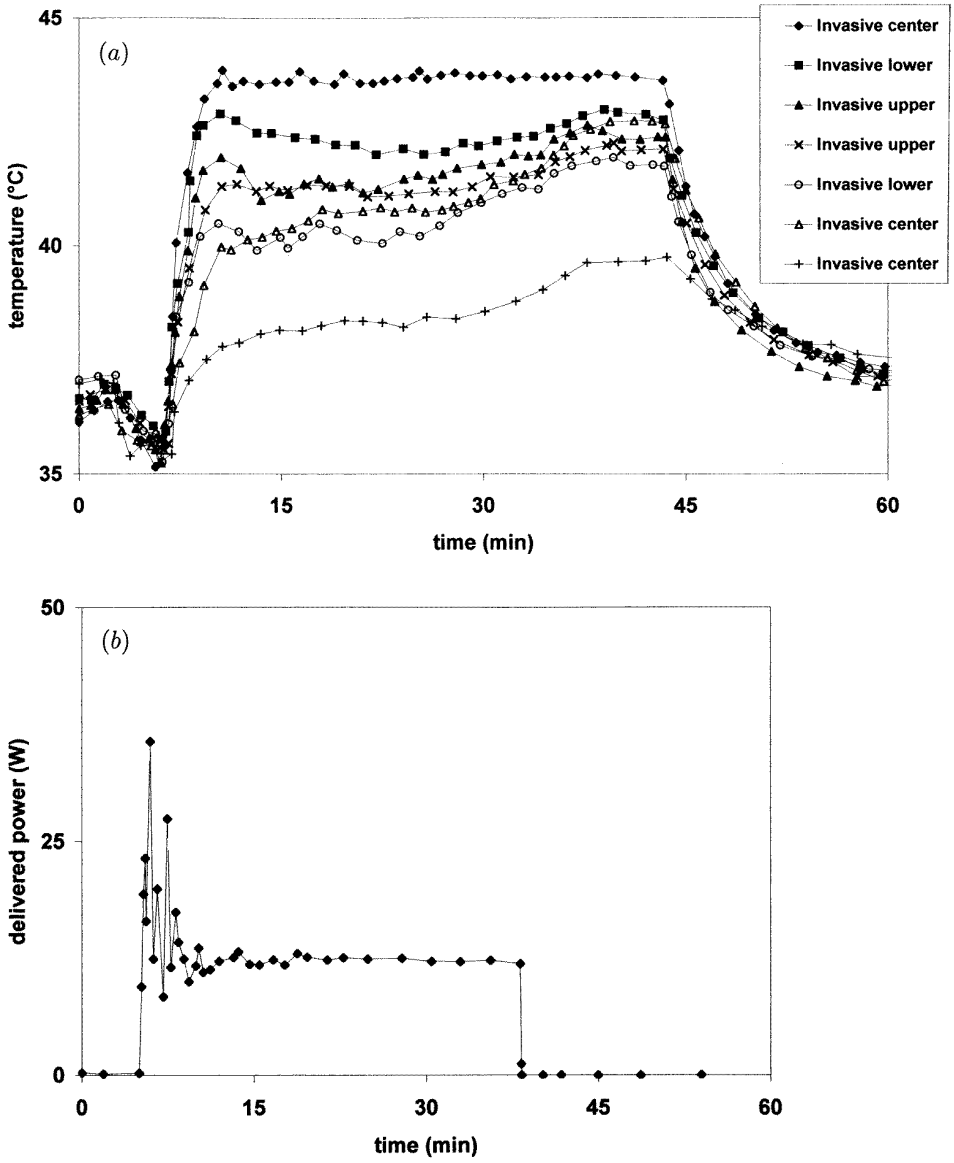

Figure 3. Temperatures (*a*), delivered power (*b*) and perfusion (*c*) measured in one exemplary session.

Finally, figure 5 shows the comparison between the measured temperatures and those predicted by the model at the site of the perfusion probe for all the sessions. We define the ratio

$$\Delta = \frac{T_{\text{pred}} - T}{\text{SD}} \tag{7}$$

SD being the error affecting T (equal to $\pm 0.5\,^{\circ}\text{C}$). During the stationary heating Δ is normally in the range between ± 1 (i.e. the discrepancy between the actual temperature and

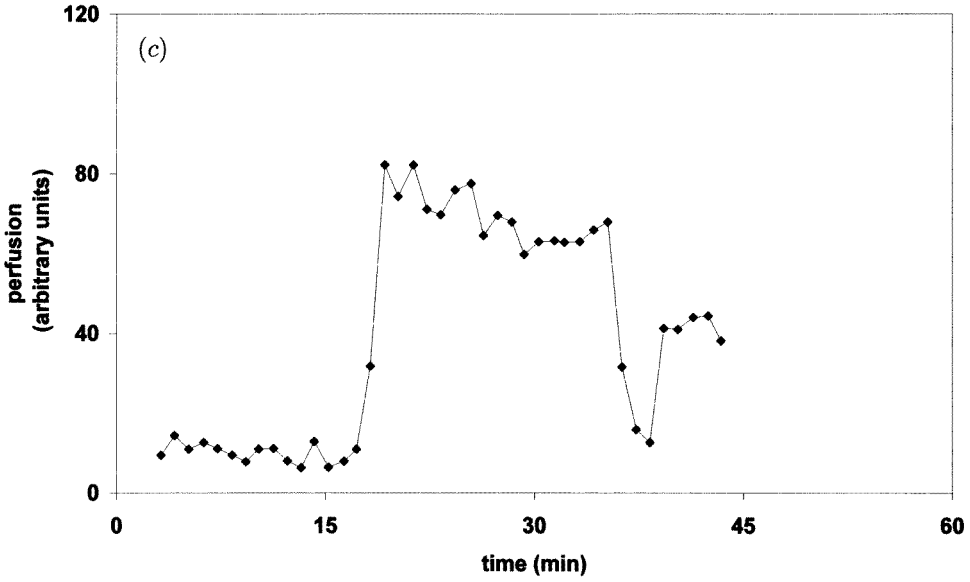

Figure 3. (Continued)

Table 4. Effective conductivity values evaluated by the model.

	Estimated K_{eff} (W m^{-1} °C^{-1})
Patient 1	
Treat. 1	0.24
Treat. 2	0.29
Treat. 3	0.29
Patient 2	
Treat. 1	0.67
Treat. 2	0.66

the predicted one is less than 1 °C), while in the warming-up phase it is included between ±3, with the exception of two sessions where, because of patient discomfort, the power was manually corrected and an additional warming-up phase occurred during the treatment.

4. Discussion

The present study is based on the direct measurement of the local perfusion in the tumour periphery throughout five hyperthermic sessions. Numerical integration of the bio-heat equation is performed. Blood perfusion entering equation (1) was monitored, and not derived on the basis of the recorded temperature, as in Lagendijk *et al* (1988) and Lyng *et al* (1991a).

Perfusion is measured by a single probe, investigating about 0.5 mm^3 of tissue. Since the probe was in the tumour periphery, it is difficult to say whether the investigated tissue is tumour or healthy tissue in all the treatments considered. Previous literature would predict a different response of the perfusion to heating, since in normal tissue blood flow is expected

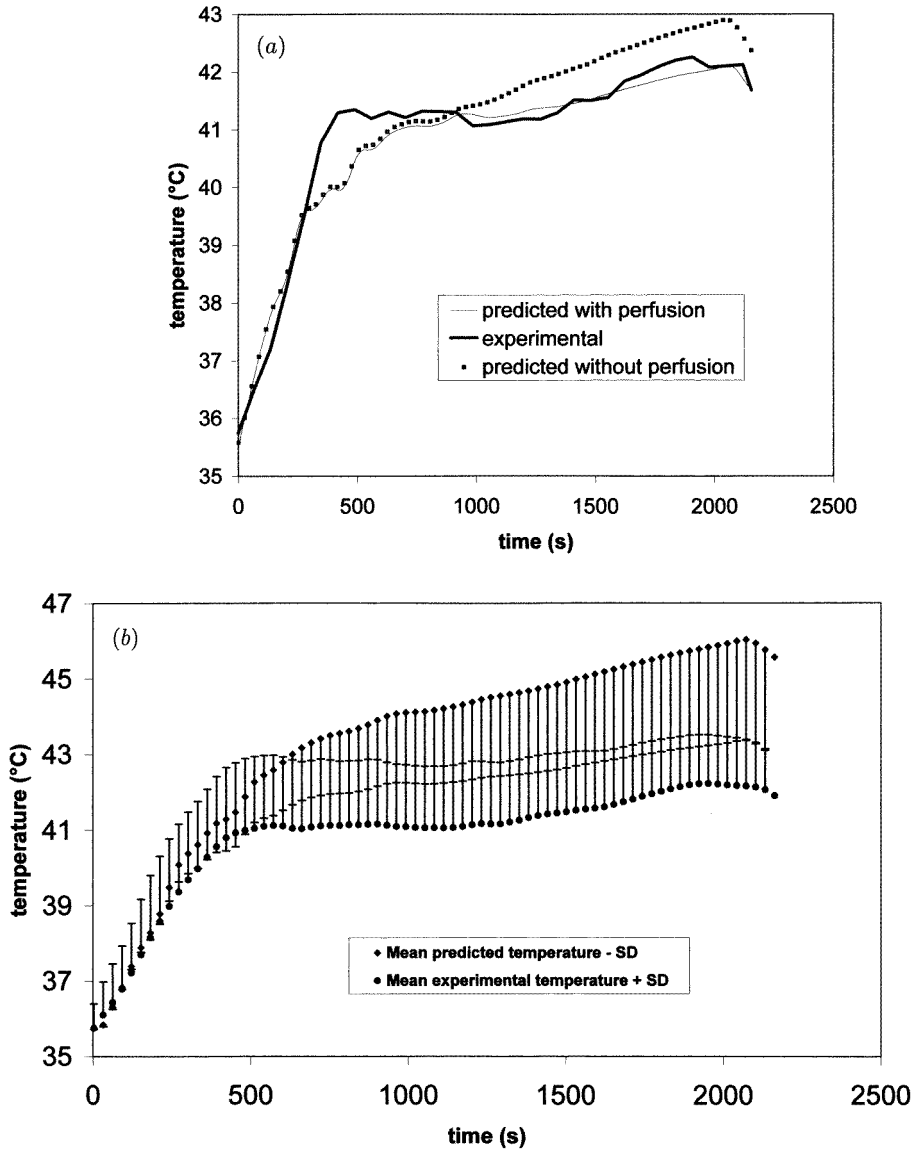

Figure 4. (*a*) The experimental temperature at the perfusion probe position (thick full curve) is compared with the predicted one in the presence (thin full curve) or in the absence (dotted curve) of perfusion. (*b*) Comparison between the measured (mean ±SD, full circles) and predicted (mean ±SD, full diamonds) temperature within the heated volume.

to increase with temperature, while in the tumour it has been observed to increase, decrease or not to change at all (Emami and Song 1984).

Although both the host tissue (mainly fat) and the tumour (concomitantly irradiated) are poorly vascularized, the region is still well perfused, and a local response to the increase in temperature is always present.

Baseline perfusion values were different between patients and hyperthermic sessions in the same patient, but there are similar patterns throughout the heating sessions. In all

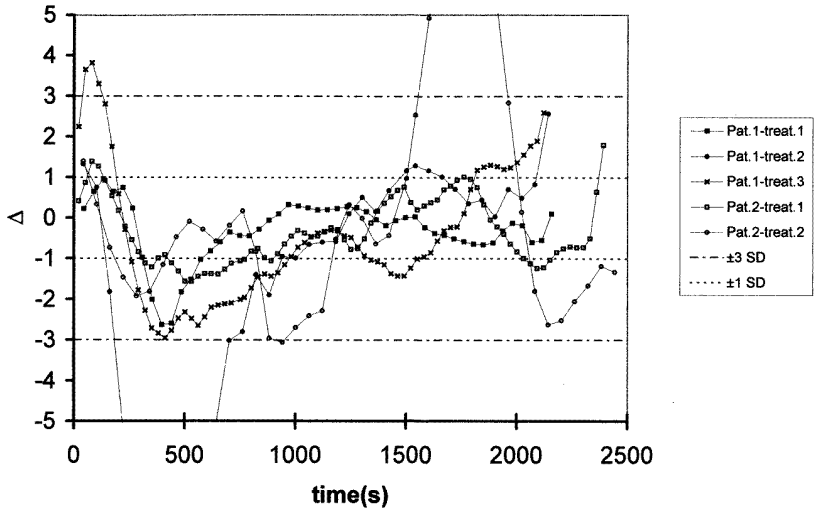

Figure 5. Δ (defined as in equation (7)) throughout all the sessions. Symbols are given in the legend.

treatments the blood perfusion increased some time after the beginning of the hyperthermic session, with oscillations which reflected those measured in the temperatures and in the delivered power. A difference has been observed in the delayed increase of the blood perfusion after the delivered power was switched on between the first treatment, in which the delay is normally longer, and the others (see table 3). This result complies with the hypothesis that a vasodilatatory response is still elicited by the increase in temperature in the tumoural tissue, and the response may occur more rapidly when repeatedly evoked.

According to previous observations (Acker *et al* 1990), differences were observed in the level of the perfusion in the tumour periphery between the first and the following sessions, which could be speculated to be the effect of the previous treatments. However, in the above mentioned paper, this difference is shown to occur after four sessions, not only two as in our case.

A further conclusion is suggested by the fact that a better agreement is found between experimental and predicted temperature when the perfusion is considered as a 'local' parameter, and not as an averaged value within the heated volume.

Due to the small volume detected by the probe, measurements of perfusion done with a laser-Doppler apparatus are able to describe in detail the time variation of perfusion throughout a hyperthermic session, but only in a small area. This means that, together with the thermal map, we would actually need also a 'perfusion map', since the local value of perfusion can be very different within a few cm^3!

As far as the model is concerned, the following points are of interest:

(i) The parameter evaluation was carried out during the stationary heating phase, where the agreement between experimental and predicted temperatures is more accurate than during the warming up phase (see figure 5). This is probably due to the fact that the heating phase is mainly influenced by the pattern of the delivered power. Before reaching the steady state, however, the values of $P(t)$ show irregularities which prevent numerical integration of equation (1). Instead of using the original data, therefore, we filtered the delivered power, and this can explain the mismatch between the temperatures in that part of the hyperthermic

session. Another possible explanation is that the rate of increase of the temperature is critically related to SAR, which is probably not well simulated by our assumptions.

(ii) Our model disregarded the 'Pennes term' since Weinbaum and Jiji (1985) showed that its contribution is negligible in tissues perfused by the microcirculatory network. Since during the heating phase blood perfusion is generally small, as well as the difference between local and arterial temperature, we presume, however, that no substantial improvements can be expected by adding the Pennes term in the bio-heat equation (2). If we account for perfusion by estimating an 'effective heat conductivity' (obtained by adjusting a free parameter in equation (5)), the agreement between experimental and simulated temperature in the steady state is acceptable.

(iii) Comparing the experimental temperature measured very near to the perfusion probe with that predicted by numerical integration of the bio-heat equation in the absence of perfusion (figure 4), it is apparent that perfusion is effective in reducing (by about 1 °C) the temperature that would otherwise be measured in the region. The difference in temperature is clearly related to the difference between K_{eff} and K, which, in our cases, was not very marked for Patient 1, but is about a factor 3.3 for Patient 2 (see table 3). The former is a confirmation of the conclusion already proposed by Lagendijk *et al* (1988) based on the comparison between the temperatures reached in the chest wall and in a simulation phantom.

(iv) The evaluated values of the effective conductivity K_{eff} are markedly different for the two patients and do not vary during subsequent sessions. The difference between patients could be related to the different depth and extension of the lesions or perhaps to the different applicators used. This may have caused the different temperatures reached in the tissue. We can speculate, for instance, that in Patient 1 K_{eff} has been estimated deep in the tumour, while in Patient 2 the estimated value refers to the superficial layers, which are normally better perfused.

In conclusion our study suggests that, in clinical applications of provisional thermometry, together with the local influence on the tissue temperature of phase I and phase II vessels, the role of phase III vessels on the global temperature has to be accounted for as well. Moreover, when the tissue is mainly perfused by phase III vessels, as in recurrent cancer lesions on the chest wall, perfusion can notably affect the therapeutic temperature, and its variability in time and in space within the heated volume should be monitored.

More definitive conclusion will be inferred if a larger number of lesions with the same histologic diagnosis and in the same anatomical site are investigated.

Acknowledgments

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