

## Thermoregulation in the canine prostate during transurethral microwave hyperthermia, part II: blood flow response

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Recent studies on transurethral-applied local hyperthermia in both the canine and human prostate have revealed significant effects of natural thermoregulation on the therapeutical results in the prostate. Using a thermal clearance method, blood perfusion rates were measured within different regions in the canine prostate under normal and hyperthermic conditions. It has been found that the canine-prostatic blood perfusion is strongly linked to the geometrical location within the gland, the local tissue temperature, and the imposed thermal dosage. Results from this research are expected to provide a better understanding of the thermoregulatory behaviour in the canine prostate, and thus lay an important foundation for predicting tissue temperature in the human prostate during transurethral microwave hyperthermia.

*Key words:* Thermoregulation, perfusion, microwave hyperthermia, canine prostate

### 1. Introduction

Benign prostatic hyperplasia (BPH) is a serious disease that generally occurs in elderly men. These individuals are also at a high surgical risk. As an alternative to surgery, one of the most recently developed therapeutic modalities of treatment for BPH is transurethral microwave hyperthermia (Magin *et al.* 1980, Sapozink *et al.* 1990, Strohmaier *et al.* 1990, Carter *et al.* 1991, Bdesha *et al.* 1993, Belot and Chive 1993, Blute *et al.* 1993, de la Rossette *et al.* 1993, Devonec *et al.* 1993, Galatioto 1993, Homma and Aso 1993, Laduc *et al.* 1993, Marteinsson and Due 1993, Nissenkorn and Meshorer 1993, Van Cauwelaert 1993, Wong *et al.* 1993, Mulvin 1994, Larson and Collins 1995). Prostatic hyperplasia develops spontaneously in both dog and human. Since the natural history of this condition in the dog is remarkably similar to that in the human, the dog has been widely used in experimental studies to examine the effectiveness of microwave hyperthermia for BPH. It has been long recognized that a major factor which affects tissue temperature elevation and heterogeneity during hyperthermia is the augmentation of blood flow concomitant with the heating (Sekins *et al.* 1984). In the present study, local blood perfusion rate within the canine prostate during transurethral microwave heating was measured using the thermal pulse decay (TPD) technique (Arkin *et al.* 1986).

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Relationships between the blood perfusion, microwave deposition, and tissue temperature have been obtained and analysed.

## 2. Methods

The blood perfusion rate and tissue thermal conductivity were measured simultaneously in the canine prostate during microwave treatment using the thermal pulse decay (TPD) technique. The technique is based on a comparison of the measured with the model simulated temperature decay following a heating pulse delivered by a thermistor bead probe (Arkin *et al.* 1986, 1987). A solution of the Pennes bioheat transfer equation (Pennes 1948) is used to construct the theoretical model which relates the local blood perfusion to the temperature decay. It considers a tissue sphere which is small enough to assume uniform blood perfusion rate ( $\omega$ ; ml/s/ml) and thermal properties within it, but sufficiently large to simulate the bead as a point source that inserts heat into the centre of the sphere for a given time ( $t_p$ ) (Arkin *et al.* 1986). Densities and heat capacities of the blood and tissue are assumed equal, and the initial and boundary conditions are:

$$T(r, t = 0) = T_{ss}(r); \quad T(r = \infty, t) = 0$$

A heat pulse is deposited locally into the tissue through a very small thermistor bead probe as:

$$q_p(r) = P \cdot \delta(0) \text{ for } t \leq t_p; \quad q_p(r) = 0 \text{ for } t > t_p$$

where  $P$  is the deposited power, and  $\delta(0)$  is the Dirac delta function. The transient temperature elevation  $\theta = T - T_{ss}$  can thus be calculated using the following equation:

$$\frac{\partial \theta}{\partial t} = \alpha \cdot \nabla^2 \theta - \omega \theta + \frac{1}{\rho c} q_p \quad (1)$$

$$\theta(r, t = 0) = 0; \quad \theta(r = \infty, t) = 0$$

For the limiting case of an infinitesimally small probe with an infinitesimally short heating pulse, the solution of equation 1 for the interval of temperature decay takes the form (Arkin *et al.* 1986):

$$\theta = \lambda_2 \cdot \int_0^{t_p} (t-s)^{-1.5} \cdot e^{-\omega(t-s)} \cdot e^{-r^2/[4\lambda_1(t-s)]} ds \quad (2)$$

$$\lambda_1 = P(\rho c)^{0.5}/8\pi^{1.5}; \quad \lambda_2 = \alpha/k^{1.5}/t_p^{0.5}$$

Due to the fact that the bead diameter is nearly zero compared to the large measuring tissue volume, the temperature of the tissue adjacent to the thermistor bead surface is approximately predicted using  $r = 0.0$  in equation 2. The tissue conductivity and blood perfusion rate are then calculated simultaneously by fitting the predicted to the measured temperature decay (Arkin *et al.* 1986, 1987a).

Fourteen male mongrel dogs (over four years old) weighing  $21.9 \pm 3.1$  kg, were used in our blood perfusion studies. The dogs were anesthetized using Na-pentobarbital, i.v. (30 mg/kg). The bladder and prostate were exposed through a midventral abdominal incision. A small cut was made in the bladder wall to allow insertion of the transurethral thermal therapy (T3) catheter (Urologix, Inc. MN) into the prostatic urethra. A microwave antenna is located approximately in the centre of the

catheter and the chilled water at a given temperature flows between the antenna and the inner catheter wall. A fibre optic thermosensor built inside of the catheter monitors the prostatic urethral wall temperature during microwave treatment.

Several thermistor bead probes of different lengths were placed at various locations and depths within the prostatic tissue. These probes serve two purposes: thermal pulse delivery and local temperature measurement. The abdominal incision was then closed and covered with plastic wrap to avoid evaporative cooling from the viscera. The EKG and blood pressure of the dog were constantly monitored throughout each experiment using Gilson Physiography and the computer assisted data acquisition system, respectively.

Blood perfusion rate and tissue thermal conductivity were measured using the above mentioned TPD technique. At the baseline (prior to the microwave heating), heating pulses were delivered and subsequent tissue temperature decays were measured by the thermistor bead probes inserted into the prostate. The sampling time plus 3 s of pulse heating was about 23 s, followed by an interval of 157 s to allow the surrounding tissue to return to thermal equilibrium before the next pulse heating and measurement. This was repeated 10 times at all probe locations, resulting in a total measuring period of 30 min. The microwave heating was then turned on. After heating the prostate at the 5W level for about 30 min, 10 more perfusion measurements were performed over another 30-min period while the heating was maintained at the 5W level. A similar procedure was followed to obtain blood perfusion rates when microwave power increased to 10W, and then to 15W. At the end of each experiment and while still under anaesthesia, the animal was euthanized by injection of a commercial barbiturate solution (Sleepaway; Fort Dodge Laboratories, Inc. Fort Dodge, IA). The prostate was removed from the body and dissected to establish the locations of the TPD probes, which were localized to one of the three different prostatic regions: periurethral (inner 35%), parenchymal (middle 60%) and capsular (outer 5%); as shown in figure 1.

Data are shown as mean  $\pm$  standard deviation (SD). Differences among the mean values were determined by one-way repeated measures ANOVA using SYSTAT software. The *post hoc* comparisons between any two levels were performed by the modified student *t*-test (Wallenstein *et al.* 1980).

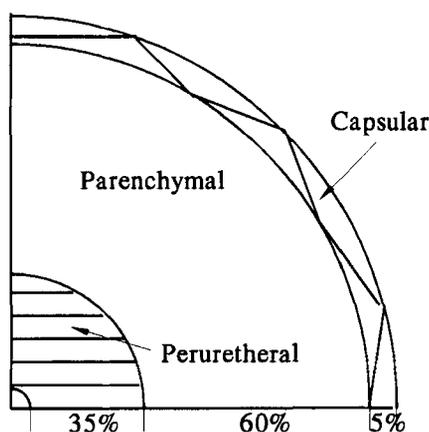


Figure 1. Three different regions in the canine prostate.

### 3. Results

A two-parameter least-square residual fit was first performed for all thermal pulse decay measurements at different probe locations within the 14 prostates used in our study. There was no significant statistical difference in thermal conductivity among these three regions; average value =  $0.493 \pm 0.018 \text{ W/}^\circ\text{C} \cdot \text{m}$  ( $n = 89$ ). This value was then used to perform a one-parameter curve fit for the TPD measurements to obtain the average blood perfusion rate at each probe location.

Figure 2 shows blood perfusion rates in different prostatic regions under the 5, 10 and 15W microwave heating respectively. At baseline conditions, the periurethral tissue was the most highly perfused region with an average value of  $0.603 \pm 0.251 \text{ ml/min/gm}$  ( $n = 4$ ), which was significantly different from both observed in the parenchymal ( $0.339 \pm 0.208 \text{ ml/min/gm}$ ;  $n = 10$ ) and capsular region ( $0.352 \pm 0.269 \text{ ml/min/gm}$ ;  $n = 5$ ). There was no significant difference in perfusion between the parenchymal and capsular regions. In figure 3, the measurements made in these two regions have been combined. The average perfusion changed from  $0.368 \pm 0.219 \text{ ml/min/gm}$  (baseline) to  $1.352 \pm 0.621 \text{ ml/min/gm}$  (10W), and  $1.481 \pm 0.439 \text{ ml/min/gm}$  (15W).

Figure 4 reports a comparison of perfusion measurements at different power levels in each of the three regions. Compared to the baseline, no significant increase in perfusion was observed in any of the three regions at the 5W level of heating. Most of our observations were made in the parenchymal region, where blood perfusion increased significantly from  $0.339 \pm 0.208 \text{ ml/min/ml}$  (baseline) to  $1.162 \pm 0.454 \text{ ml/min/ml}$  (10W), and  $1.514 \pm 0.459 \text{ ml/min/ml}$  (15W). A 3.3-fold increase in perfusion

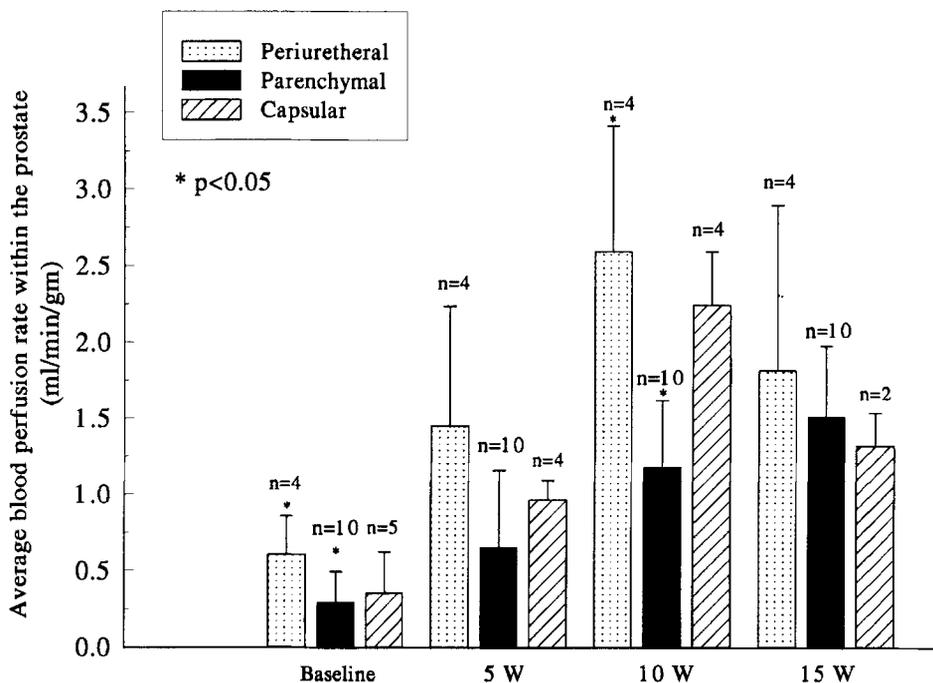


Figure 2. Blood perfusion rates measured in different prostatic regions at different microwave power levels.

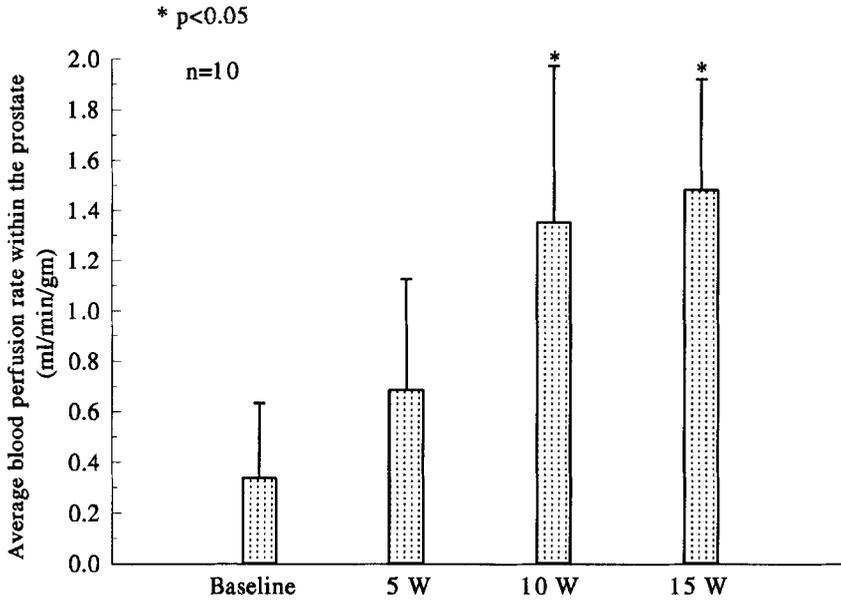


Figure 3. Blood perfusion rates measured in the parenchymal and capsular regions at different microwave power levels.

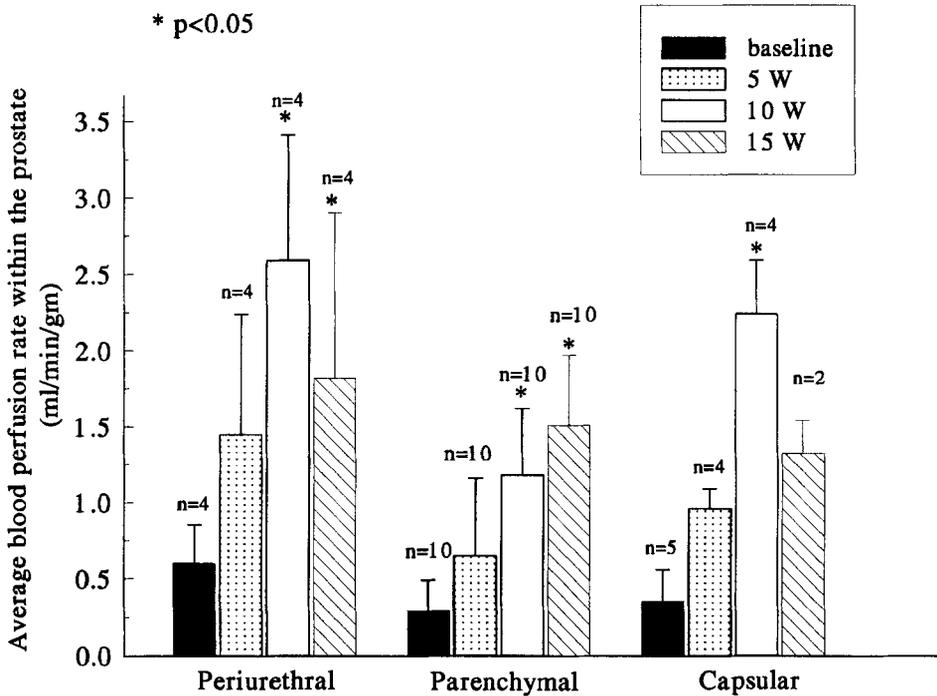


Figure 4. Blood perfusion rates measured at different microwave power levels in different prostatic regions.

was observed in the periurethral region at the 10W level while there is a 5.4-fold increase in the capsular region. However, only about 2-fold increase was found in these two regions at the 15W level.

#### 4. Discussion

The TPD technique used in this study to measure blood perfusion introduces a small thermal disturbance and then examines the temperature decay in a stable temperature field. The measured blood perfusion was actually a steady state value, which could be related to not only temperature but also local energy balance, i.e. the integrated effect from EM power deposition and the temperature gradient. Figure 5 depicts a linear relationship between the steady state blood perfusion and tissue temperature. This blood perfusion is expected to be lower than its initial increase which was stimulated by an instantaneous increase in local tissue temperature.

Blood perfusion increased significantly in the canine prostate tissue when exposed to 30 min of the 10 and 15W microwave heating. Additionally, the periurethral perfusion was significantly higher than that in the parenchymal region at the baseline and 10W microwave heating level. This could be partially attributed to the fact that the periurethral region of the prostate gland is supplied by the artery of the urethral bulb, whereas radial tributaries from the subcapsular artery pass along the capsule septa toward the urethra to supply the parenchymal region (Hodson 1968). Therefore, the baseline and the response of blood perfusion to microwave heating could be different in these two regions.

Previous studies (Andersson *et al.* 1967, Hirai 1992, Nau *et al.* 1996) have shown that the baseline blood perfusion rate in the canine prostate varies in the range of 0.20–0.79 ml/min/gm. Results from our study fall within this range. Nau *et al.* (1996) observed a 4.5-fold increase in perfusion during 1 min of a 40W laser prostatectomy and the perfusion was 3.1× the baseline 20 min after the procedure. In contrast, Hirai (1992) found that blood perfusion increased linearly by only 0.2-fold when the prostatic tissue temperature was raised to 45°C by a 100W external RF heating

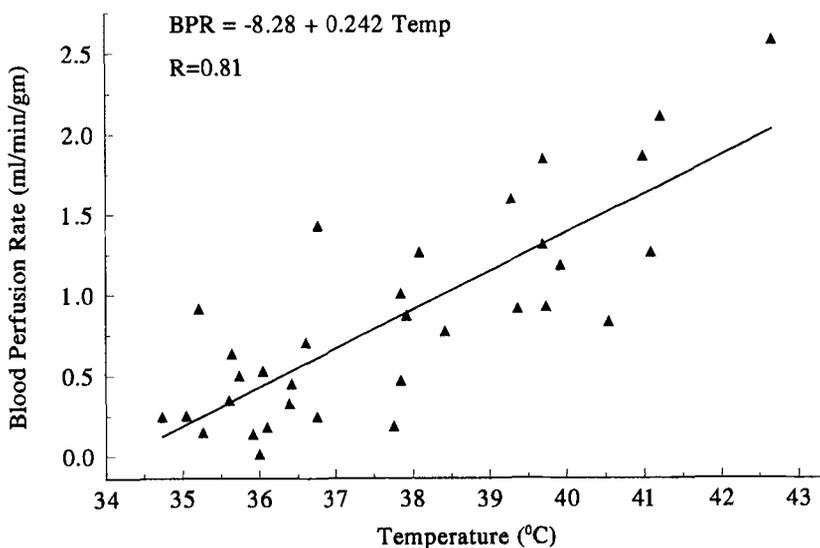


Figure 5. Blood perfusion rates measured with respect to the local tissue temperature.

for 15 min. Although the exact cause of this low increment is not clear, the external RF heating tends to be more uniform and global instead of local which is also dependent on the configuration of the RF heating apparatus. In the present study, after microwave heating of prostate for about 60 min at 5 and 10W respectively, a 5.4-fold increase from the baseline perfusion was found during the 15W heating period. However, there is no significant increase in perfusion in any of the three regions of the canine prostate during the 5W heating. This may be partially due to the fact that the maximum tissue temperature was 38.2°C during this heating, which is lower than the minimum critical temperature stimulating an increase in blood perfusion as given in (Xu *et al.* 1996). A more detailed analysis on the local temperature distribution within the canine prostate during microwave heating and its correlation with blood perfusion will be investigated in the near future.

General anesthesia suppresses the CNS controlled thermoregulatory system (Heller and Glotzbach 1985). Considering that anaesthetized dogs were used in this experimental study, only local thermoregulatory controlling factors are expected to be dominant. Because the small arteries and arterioles are well endowed with smooth muscle, they provide most of the resistance to flow in the vascular system. Dilation of arterioles beyond their basal level may be induced by local extrinsic stimulation. That is during the microwave hyperthermia, it seems likely that elevated temperature along with local metabolite accumulation or lowered pH would contribute to dilate arterioles and thus to increase local blood perfusion. Sekins *et al.* (1984) and Roemer *et al.* (1985) suggested that the blood flow response in diathermy is probably due exclusively to a thermal or thermally related set of stimuli but not to the non-thermal effects from the electromagnetic (EM) fields. Although the initial blood perfusion increase triggered by the instantaneous local tissue temperature could not be measured by the TPD technique, the effect of this increase to reduce the tissue temperature has been observed by Xu *et al.* (1996).

In this study, the relationships between the steady state blood perfusion, the power deposition, and tissue temperature have been reported in the canine prostate under transurethral microwave hyperthermia. Thermoregulatory behaviours have been observed and analysed which will help provide a better understanding of the physiological response to hyperthermia within the prostate gland. Based on the results reported here, a theoretical analysis will be performed to directly relate tissue temperature to the local blood perfusion and the microwave power deposition. This theoretical modelling will allow one to predict the temperature distribution in the human prostate during hyperthermia and thus to increase the effectiveness and safety of the treatment.

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### Nomenclature

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| k        | tissue thermal conductivity, $W/^\circ C \cdot m$  |
| P        | pulse heating power, $W/m^3$                       |
| q        | volumetric heat, $W/m^3$                           |
| r        | radial distance, m                                 |
| T        | tissue temperature, $^\circ C$                     |
| t        | time, s  |
| $\alpha$ | tissue thermal diffusivity, $m^2/s$                |
| $\theta$ | transient tissue temperature elevation, $^\circ C$ |
| $\omega$ | blood perfusion rate, ml/s/ml                      |
| p        | heating pulse                                      |
| ss       | steady state                                       |