# Blood Perfusion Measurements in the Canine Prostate During Transurethral Hyperthermia

LISA X. XU, [a] LIANG ZHU, [b] AND KENNETH R. HOLMES [c]

[a] *School of Mechanical Engineering, Purdue University, West Lafayette, IN 47907-1288, USA*

[b] *Department of Mechanical Engineering, University of Maryland at Baltimore, MD 21250, USA*

[c] *Department of Veterinary Biosciences, The University of Illinois at Urbana-Champaign Champaign, IL 61801, USA*

**ABSTRACT: Using a thermal pulse decay technique, blood perfusion rates were measured within different regions in the canine prostate under normal and hyperthermic conditions induced either by the microwave or the radio frequency heating. Results indicate that, under the normal condition, the periurethral region is most highly perfused with an average rate of 0.60±0.25ml/min/gm (n=4) while the perfusion rate is 0.34±0.22ml/min/gm (n=10) in parenchyma. An approximately 3.5 fold increase in perfusion from the respective baselines was observed in both regions when the local tissue temperature was raised to 41.5°C by the microwave heating. Another 0.5 fold increase was found in parenchyma after the tissue was further heated to 43.1°C at which oscillatory behaviors in tissue temperature have been observed. To further study the cause of these oscillatory behaviors, the instantaneous blood perfusion response to changes in local tissue temperature was investigated using the radio frequency heating. It has been revealed that blood flow acts as a feedback of local tissue temperature in a closed control system. The thermally stimulated blood perfusion increase appeared to be a function of tissue temperature and its temporal gradient. Results from this study have shown experimental evidences of local thermo-regulation in the prostate during hyperthermia.**

[a] Address for correspondence: School of Mechanical Engineering, 1288 Mechanical Engineering Building, Purdue University, West Lafayette, IN 47907-1288, USA. Phone: 765-494-6637; Fax: 765-494-0539; E-mail: lxu@ecn.purdue.edu

## INTRODUCTION

Benign prostatic hyperplasia (BPH) is a serious disease that generally occurs in elderly men. Most of these individuals are in the high surgical risk group. As an alternative to surgery, one of the recently developed therapeutic modalities is the local hyperthermia induced either by the microwave or the radio frequency (RF) heating.[1-10] Histologically, prostatic hyperplasia develops spontaneously in both the dog and human. Since the natural history of this condition in the dog is remarkedly similar to that in the human,[11] the dog has been widely used in experimental studies to examine the effectiveness of the microwave or the RF hyperthermia for BPH.

Recent studies on the transurethral-applied local hyperthermia in the canine and human prostate have revealed significant effects of natural thermoregulation on the therapeutical results. 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.[12-14] In the present study, using a thermal pulse decay (TPD) technique,[15] blood perfusion rates were measured in different regions within the canine prostate during transurethral heating. Relationships of the blood perfusion, power deposition, and tissue temperature were observed and analyzed.

## METHODS

The blood perfusion rate and tissue thermal conductivity were measured simultaneously in the canine prostate using the TPD technique. [15] This 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. A solution of the Pennes bio-heat transfer equation [16] is used to construct the theoretical model which relates 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 sphere center for a given time ($t_p$ ). In the model, densities and heat capacities of the blood and tissue are assumed equal, and the initial and boundary conditions are:

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

A heat pulse is deposited locally into the tissue through a very small thermistor bead probe of 0.3mm dia. as:

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

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 from the Pennes equation as:

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

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

For the limiting case of an infinitesimally small probe with an infinitesimally short heating pulse, the solution of Eqn.1 for the interval of temperature decay takes the form:

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

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

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 Eqn.2. The tissue conductivity and blood perfusion rate can then be simultaneously calculated by fitting the predicted to the measured temperature decay.

During the microwave hyperthermia, fourteen male mongrel dogs (wt. 21.9 ± 3.1 kg) over four years old were used for blood perfusion studies. 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. Within the catheter, a microwave antenna is located approximately in the center and chilled water at a given temperature flows between the antenna and the inner catheter wall. A fiber optic thermosensor built inside of the catheter monitored the prostatic urethral wall temperature throughout each experiment.

Thermistor bead probes of different lengths were placed at various locations 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. Prior to the experiment, the interaction of the thermistor probe with either the microwave or the RF radiation was examined by observing the temperature discontinuities when the radiation power was interrupted. The temperature discontinuity was found to be less than 0.2°C, which indicated nonsignificant interactions. At the baseline (prior to the microwave radiation), heating pulses were delivered to the prostatic tissue and subsequent temperature decays were measured by the thermistor bead probes. The pre- and post-sampling time plus 3 sec. of pulse heating was about 23 sec., followed by an interval of 157 sec. to allow the surrounding tissue to return to thermal equilibrium before the next pulse heating and measurement. This was repeated for ten 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. when tissue temperature was stable, ten 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 after microwave power increased to 10W, and then to 15W. At the end of each experiment and while still under anesthesia, 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%),

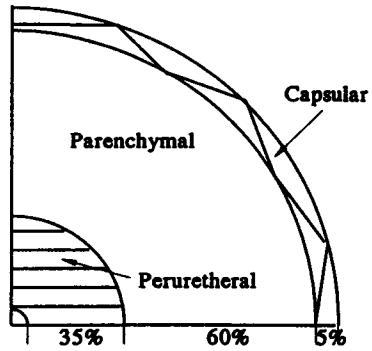


**FIGURE 1.** Three different regions in the canine prostate.

parenchymal (middle 60%), and capsular (outer 5%), as shown in FIGURE 1.

To study the instantaneous blood perfusion response to the local tissue temperature increase, the RF heating was applied to the canine prostate using the EESY-100 RF Prostatic Hyperthermia System (Yuanshui Industrial Com. PRC). The use of the RF heating was intended in this part of the study to ensure a broad uniformly heated tissue region for examination of the blood perfusion response. Nine male mongrel dogs (wt. 21.9 ± 3.1 kg) over four years old were used. In each experiment, the baseline blood perfusion was measured prior to the RF heating following the same procedure as mentioned above. The tissue was then heated for 25 min. at the 5W level before the power was increased to 10W and then to 15W, each for 25 min., during which perfusion measurements were made with an interval of about 3 min. A thermocouple built inside the RF catheter was used to monitor the urethral wall temperature throughout the entire experiment.

Experimental data are shown as mean ± 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. [17]

## RESULTS AND DISCUSSION

### *Microwave Heating*

A two-parameter least-square residual fit was first performed for all thermal pulse decay measurements within the fourteen prostates used in the first part of this study. There was no significant statistical difference in thermal conductivity found in three different regions of the prostate. The average value of $0.49 \pm 0.02 W/°C \cdot m$ (n=89) 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.

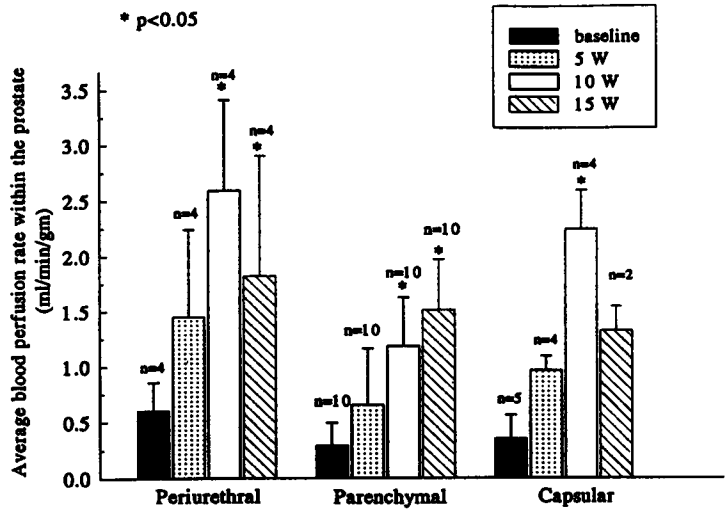


**FIGURE 2.** Blood perfusion rates in different regions within the canine prostate during transurethral microwave heating.

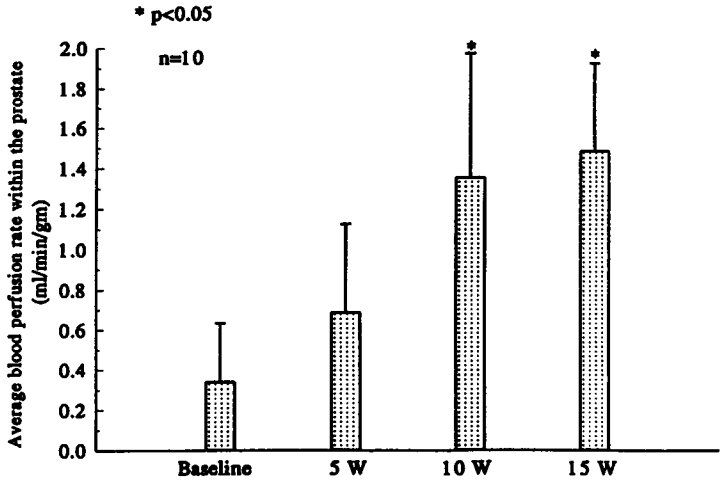


**FIGURE 3.** Blood perfusion rates in the parenchymal and capsular regions within the canine prostate during transurethral microwave heating.

FIGURE 2 shows blood perfusion rates measured in different prostatic regions under the 5W, 10W and 15W microwave heating, respectively. At the baseline, the periurethral was the most highly perfused region and the average perfusion rate was 0.60±0.25 ml/min/gm (n=4). This is significantly different from the perfusion observed in the parenchymal (0.34±0.21 ml/min/gm; n=10) and capsular region (0.35±0.27 ml/min/gm; n=5). Since the blood perfusion rate appears insignificantly different in the parenchymal and capsular regions, measurements made in these two regions have been combined and presented in FIGURE 3. The average perfusion changed from 0.34±0.22 ml/min/gm (baseline) to 1.35±0.62 ml/min/gm (10W), and 1.48±0.44 ml/min/gm (15W). An approximately 3.5 fold increase in perfusion occurred in both periurethral and parenchymal regions when local tissue temperature was stable at 41.5°C under the 10W heating. Another 0.5 fold increase was observed in parenchyma after the tissue was further heated to 43.1°C under the 15W heating. In reference to the baseline, no significant increase in perfusion was observed in any of the three regions after being heated at the 5W level for 30-60 minutes. This could be due to the fact that the change in tissue temperature is not large enough to stimulate any increase in blood perfusion.[18]

In general, the present baseline perfusion falls within the range of 0.20 - 0.79 ml/min/gm, the measured average perfusion rate throughout the entire canine prostate via different techniques from previous studies.[1,19,20] The use of the TPD technique in this study has enabled us to examine blood perfusion in different regions within the prostate. 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 in the prostate gland, the periurethral region is supplied by the artery of the urethral bulb while the parenchyma is perfused by radial tributaries from the subcapsular artery passing along the capsule septa toward the urethra.[21] Therefore, the baseline and the response of blood perfusion to the microwave heating would likely be different in these two regions.

### *RF Heating*

FIGURE 4 shows a set of the tissue temperature (solid lines) and corresponding perfusion (symbols) responses to the RF heating in the canine prostate. As revealed earlier, there was no significant increase in perfusion observed in the prostate under the 5W microwave heating. Blood perfusion response to the RF heating was therefore observed only at the 10W and 15W level. Unlike the microwave catheter which has a cooling system to protect the urethral wall, in the RF heating, the maximum temperature occurs at the urethral wall inside the prostate. When the 5W heating was turned on, this temperature increased and became stable after approximately 2 min. At the 10W or 15W heating level, it increased first and then decreased before it gradually reached a stable value. As seen in FIGURE 4, a similar pattern but with much smaller magnitudes, can be found in the interstitial temperature increment measured at 1mm radially from the urethral wall. In the same location, instantaneous blood perfusion rates were measured. FIGURE 4 also illustrates a close relationship between the change in blood perfusion and local tissue temperature. At the 10W level, blood perfusion increased with the tissue temperature until it reached its maximum of approximately 3ml/gm/min. Then, it started decreasing with tissue temperature. Once the temperature became more stable after the tissue was heated for about 15 min., the perfusion increased again until a relatively

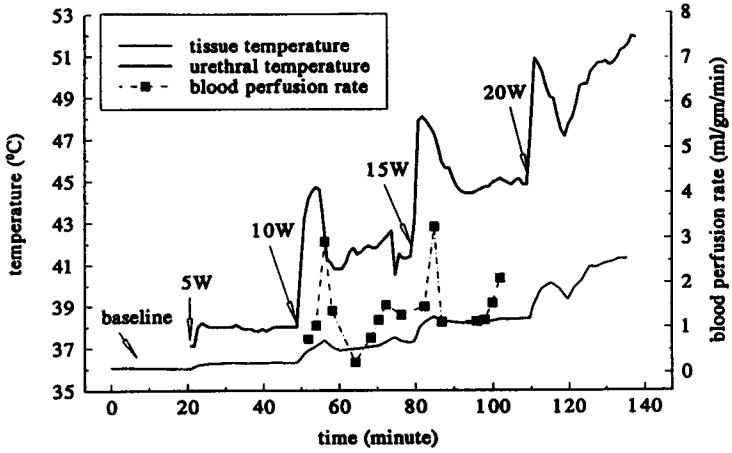


**FIGURE 4.** Blood perfusion and local tissue temperatures in the canine prostate during transurethral RF heating.

constant value of approximately 1.5ml/gm/min was reached. A similar cycle of change in perfusion was found at the 15W level. However, a higher stable value could be predicted by observing the trend of perfusion increase at the end of the heating. This agrees with the results presented above for the microwave heating.

Two interesting phenomena should be noted here. First, the oscillatory temperature behavior seems to be coupled with an oscillatory change in blood perfusion. Within each cycle, the change in perfusion appears to be closely related to not only the tissue temperature but also the temporal temperature gradient. Second, the maximal perfusion and interstitial temperature occurred almost at the same moment which was several minutes behind the time when the maximal urethral wall temperature was reached. Since both the urethral wall and interstitial temperatures are regulated by the blood perfusion which can be viewed as a feedback of local tissue temperature in a closed control system with different time delays, it is not difficult to see why the former is more oscillatory than the later.

It is well known that general anesthesia suppresses the CNS controlled thermoregulatory system. Considering that dogs were anesthetized using pentobarbital sodium during each experiment, the anesthetic effect on the blood flow response is expected. The thermoregulatory controlling factors which influenced the blood flow response to the heating are mainly limited to local in this study. Because the small arteries and arterioles are well endowed with smooth muscle, they provide most of the resistance to flow in the vascular system. An increase in blood flow can be attributed to dilation of arterioles beyond their basal level induced by local extrinsic stimulation. As studied in previous research,[12] in normal tissue, several factors may contribute to the flow increase, among which are vasoactive compounds, such as bradykinin release in the heated tissue. In addition, the heat-induced increase in local metabolic rate increases the

oxygen consumption in tissues and decreases the tissue $pO_2$. A decrease in $pO_2$ in smooth muscle of blood vessels and in parenchymal cells causes vasodilation and opening more capillaries which results in an increased blood flow. After its initial increase, at a certain critical temperature and heating time, a decrease in flow is often observed. It has been hypothesized that an increase in intravascular pressure within the microcirculation due to increased blood viscosity causes decreased flow through the microcirculation. Increase in viscosity is mainly attributed to the increased permeability of vessel walls to plasma.

## CONCLUSION

In this study, a close relationship of blood perfusion to local tissue temperature and its temporal gradient has been observed. It seems that all the above mentioned physiological factors which influence the change of blood flow are most likely stimulated by the thermal field rather than the nonthermal effects from the electromagnetic fields as suggested by Sekins et al.[13] and Roemer et al.[14] Results from this study will not only help to improve the efficacy of hyperthermia treatment, but more importantly to provide a better understanding of thermoregulation in biological systems during hyperthermia.

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## NOMENCLATURE

$k$ tissue termal conductivity, $W / °C \cdot m$
$P$ pulse heating power, $W/m^3$
$q$ volumetric heat, $W/m^3$
$r$ radial distance, m
$T$ tissue temperature, °C
$t$ time, s

***Greek***

$\alpha$ tissue thermal diffusivity, $m^2/s$
$\theta$ transient tissue temperature elevation, °C
$\omega$ blood perfusion rate, ml/s/ml

***Subscript***

$p$ heating pulse
$ss$ steady state