

Thermoregulation in the canine prostate during transurethral microwave hyperthermia, part I: temperature response

L. X. XU†*, L. ZHU† and K. R. HOLMES‡

†Dept. of Applied Sciences, The College of Staten Island, The City University of New York

‡Dept. of Veterinary Biosciences, The University of Illinois at Urbana-Champaign

(Received 17 February 1997; revised 20 August 1997; accepted 26 August 1997)

In this research, experiments were performed to study thermoregulation in the canine prostate during microwave hyperthermia. The transurethral thermal therapy (T3) system provided by Urologix, Inc. was used to impose microwave heating in the canine prostate. Five types of temperature responses to different microwave power levels as time varies, including both damped and sustained oscillatory temperature responses, have been observed. Decreases in prostatic tissue temperature during the microwave heating are believed to be caused by the increase in local blood flow stimulated by tissue temperature elevations. In this study, the characteristic temperatures and time associated with each response. This work will help to provide a better understanding of how tissue temperature is regulated within the canine prostate during transurethral microwave hyperthermia. Results of the present study offer an experimental foundation for a more detailed theoretical analysis on the temperature distribution based on the power input and local blood perfusion.

Key words: Thermoregulation, microwave hyperthermia, temperature, canine prostate

1. Introduction

The concept of physiological thermoregulation followed naturally from Blagden's discovery in 1774 (Lomax 1979) that body temperature remained fairly constant in spite of exposure to extremely dry heat. Sufficient anatomical and physiological evidence has been produced to point to the preoptic-anterior hypothalamus as a major site of body temperature regulation by the sympathetic nervous system (Lomax 1979). The central nervous system (CNS), as the regulator of animal heat, controls not only vasoconstriction or vasodilation but also a corresponding local decrease or increase in metabolism. The cutaneous thermoreceptors are involved in conscious temperature sensations as well as in connection with behavioural and physiological thermoregulatory responses.

Ever since local hyperthermia was used as therapeutic modality to selectively cause irreversible damage to malignant cells while sparing normal cells, it has been desirable to know how local tissue temperature regulates blood flow in response to the heating, and how the local control system functions in addition to the CNS, especially when the treated subject is anaesthetized (Sekins *et al.* 1984, Roehrborn *et*

*To whom correspondence should be addressed at School of Mechanical Engineering, Purdue University, 1288 Mechanical Engineering Building, West Lafayette, IN 47907-1288, USA.

al. 1992, Devonec *et al.* 1993). Compared to the CNS control which either alters the cardiac output or redistributes blood flow within the whole body, the local control seems to be directly exerted through localized vasoconstriction and vasodilation in arterioles. When these vessels are stimulated to be constricted, the down stream resistance increases to result in a decrease in the up stream blood flow, and when the arterioles dilate, the vascular resistance decreases and the blood flow increases. Changes in blood flow in turn alter the local tissue temperature due to the convective effect of the flowing blood. The resulting tissue temperature may change the smooth muscle function which would lead to vasodilation or constriction. Therefore, although it is now well recognized that the thermoregulation in biological systems represents a multiple input system, from a local point view, the integrated effect is to change blood flow with respect to temperature. If this relationship can be quantified experimentally, then how local temperature responds to the heating power can be predicted during hyperthermia treatment.

In the present research, thermoregulation in the canine prostate during microwave hyperthermia has been studied. The transurethral thermal therapy (T3) system provided by Urologix, Inc. (Minnesota MN.) was used to impose microwave heating in the canine prostate. Various types of temperature responses to different power levels as time varies have been observed. The characteristic temperatures and time associated with each response, and causes of different temperature responses are discussed. Relationships between blood perfusion, microwave power, and local tissue temperature have been investigated.

2. Materials and methods

Fourteen male mongrel dogs (over four years old) weighing 21.9 ± 3.1 kg, were used in our blood perfusion studies. The dogs were anaesthetized 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 (see figure 1). A fibre optic thermosensor built inside the catheter monitored the prostatic urethral wall temperature during microwave treatment. Throughout each experiment, the EKG and blood pressure of the dog were constantly monitored using a Gilson Physiography and the computer assisted data acquisition system, respectively.

Several thermistor bead probes of different lengths were placed at various locations and depths within the prostatic tissue. Figure 2 shows that each probe consists of one or two small (0.5 mm in diameter) thermistor beads situated at the end or near the middle of a glass fibre reinforced, epoxy shaft. The diameter of the finished probe is typically 0.3 mm, and the length can vary as desired. Probes are structurally strong and because the end can be sharpened to a point, they are capable of piercing most tissues with very minimal trauma. These probes serve two purposes: thermal pulse delivery and local temperature measurement. Blood perfusion rate and tissue thermal conductivity were measured using the Thermal Pulse Decay (TPD) technique based on a comparison of the measured with the model simulated temperature decay following a heating pulse (Arkin *et al.* 1986, Wideman *et al.* 1992). It considers a tissue sphere which is small enough to assume uniform blood perfusion rate and thermal properties, but sufficiently large to simulate the bead as a point source that

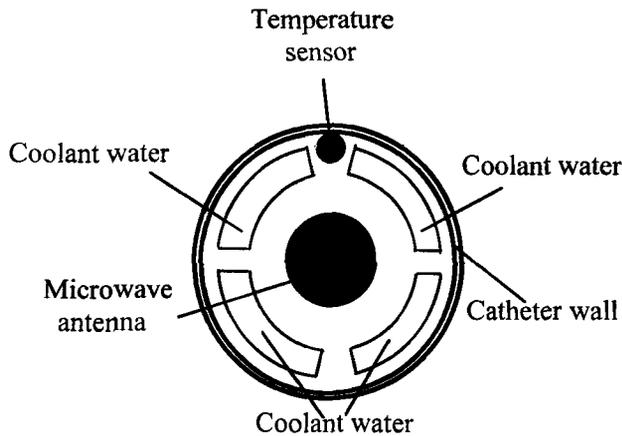


Figure 1. Cross-sectional view of the transurethral thermal therapy (T3) catheter (Urologix, Inc.)

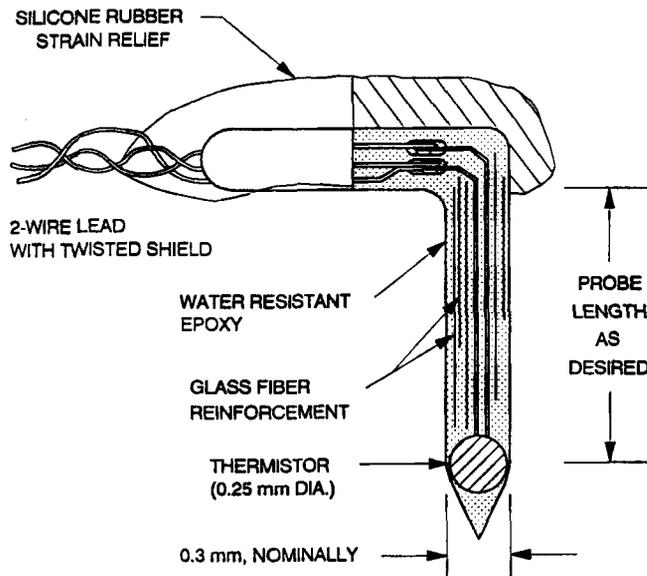


Figure 2. Sketch of a thermistor bead probe.

inserts heat into the centre of the tissue sphere for a given period of time. For the limiting case of an infinitesimally small probe with a short heating pulse, the transient temperature decay is predicted using a solution of the Pennes bioheat transfer equation (Pennes 1948). The values of the tissue thermal conductivity and local blood perfusion rate in the equation are adjusted simultaneously to fit the measurements (Arkin *et al.* 1986).

Two fibre optic thermosensors (Luxtron Corp., Santa Clara, CA) were placed between the prostate, and rectum and the abdominal wall, respectively. The laparotomy incision was closed for the blood perfusion studies to avoid external cooling of the prostate and bladder area. Initial interstitial prostate and urethral wall

temperatures were measured to determine baseline temperatures. For each local perfusion and conductivity measurement, a heating pulse (3 s) was delivered and subsequent temperature decay was measured by the thermistor bead probe. The sampling time plus 3 s of pulse heating totalled 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 for ten times at all probe locations, resulting in a total measuring period of 30 min. Following the baseline measurements, the microwave power was turned on and increased from 5W, then to 10W, and the finally 15W. At each level, temperature rise was recorded at various locations within the prostate for another 30 min. The rectal, prostatic urethral wall and boundary temperatures were continuously monitored via a resistive thermal device (RTD) and fibre optic thermosensors throughout the experiment.

Following the conclusion of the microwave treatment session, the dog was euthanized by injection of a commercial barbiturate euthanasia agent, Sleepaway (Fort Dodge Laboratories, Inc. Fort Dodge, IA). The prostate was removed from the body, and its volume and weight was measured. The average size of the prostate was 23.6 ± 8.8 ml, and the weight was 23.7 ± 6.8 g, indicating that the prostatic tissue density is close to that of water. The probe locations were verified by gross dissection of the prostate.

3. Results

Microwave thermal treatment achieved temperature elevations at the prostatic and periprostatic tissue sites in all fourteen dogs. The maximum tissue temperature was 45.4°C , measured at approximately 5 mm radially from the antenna, which is consistent with that found in the human prostate under microwave heating using the same T3 system (Larson and Collin 1995). Throughout the treatment, due to the convective effect from the water (20°C) running within the catheter, maximum urethral wall temperatures ranged from 30.0 to 35.9°C . The rectal temperatures observed were from 26.2 to 39.1°C .

Figure 3 shows typical temperature measurements at selected prostatic tissue sites as well as at the urethral wall and prostatic boundaries during microwave heating session. The interstitial prostate temperatures were measured by the thermistor bead probes, while the prostate boundary and urethral wall temperatures were recorded by the Luxtron fibre optical thermosensors. When the 5W microwave heating was turned on, the prostatic tissue temperatures started increasing at different rates depending on the geometrical locations of probes with respect to the microwave antenna. Approximately 6 min later, temperatures became stable for all the probe locations. A similar pattern of temperature rise was found during the 10W heating except that the time to reach the new steady state temperature was longer. However, when microwave power was increased to 15W, an oscillatory behaviour was observed in temperature transients although the rise-time is about the same as that for the 10W level.

Different forms of temperature responses observed during microwave heating are shown in figure 4. As defined in (Roemer *et al.* 1985), they vary from type I response: temperatures rise monotonically with time to elevated steady-state values at low power levels (typically seen at the 5W and 10W levels of heating), to type V response: a series of self-sustaining oscillations in temperature at a high power level (15W). Table 1 summarizes the experimental results categorized according to the type of temperature response. It gives the number of each response observed, the power level

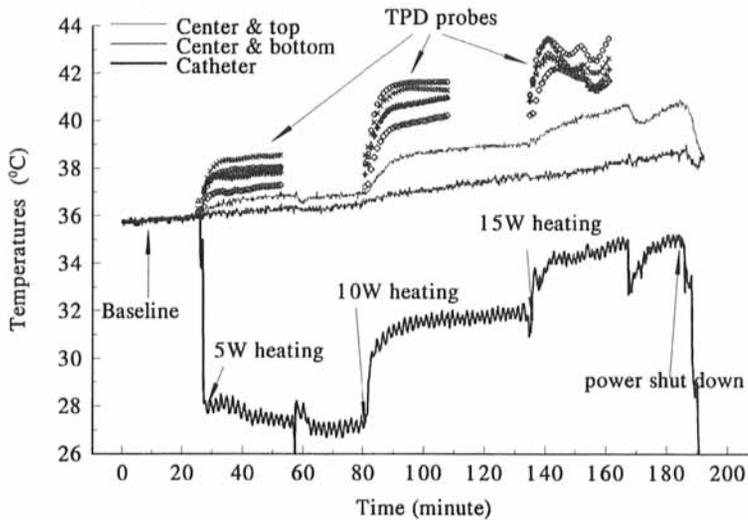


Figure 3. Temperature responses to the microwave heating (W) at various probe locations in the canine prostate during transurethral hyperthermia treatment. B.C. = Boundary Condition.

as well as the characteristic temperatures (T_c , T_{ss} and ΔT_1) and the rise-time (t_r) associated with it. T_c is the critical temperature at which tissue temperature starts to decrease, and ΔT_1 is the magnitude of the first temperature drop. T_{ss} is the steady state temperature associated with type I to IV response. t_r is the rise-time during which tissue temperature increased a factor of 67% of the first peak in all five types of the responses. Δt is the approximate period of temperature oscillations associated with types IV and V response.

4. Discussion

The results of temperature response observed in the canine prostate during microwave heating session suggest that, either a second order self-regulatory system has been turned on when local temperature is raised to certain level or there is a time lag between the local blood perfusion response to tissue temperature. Although the details of the physiological and biochemical bases for this behaviour are unknown, the integrated effect from the increase of blood perfusion, local tissue temperature, and temperature gradients which are associated with the heating power level, could play an important role here.

In a type I response, temperature increases monotonically until it reaches its steady-state (figure 4), in which the local energy absorption is balanced by the conduction and convection due to temperature gradients and blood perfusion, respectively. This kind of response is possible when there is only a moderate timely change in blood perfusion. In our experiment, most of the temperature responses observed during the 5 and 10W heating were type I responses. The type II response with an over-shoot can also be caused by an increase in blood perfusion with a short time lag. The over-damped responses were previously observed in the canine muscle under the microwave heating by other investigators (Sekins *et al.* 1984, Roemer *et al.* 1985).

A third type response has been observed only under the 10W heating. The data showed that after tissue temperature rose to certain point (39.6 °C), it started to drop for about 0.2 °C and then increased again at a slower rate until its steady state. The

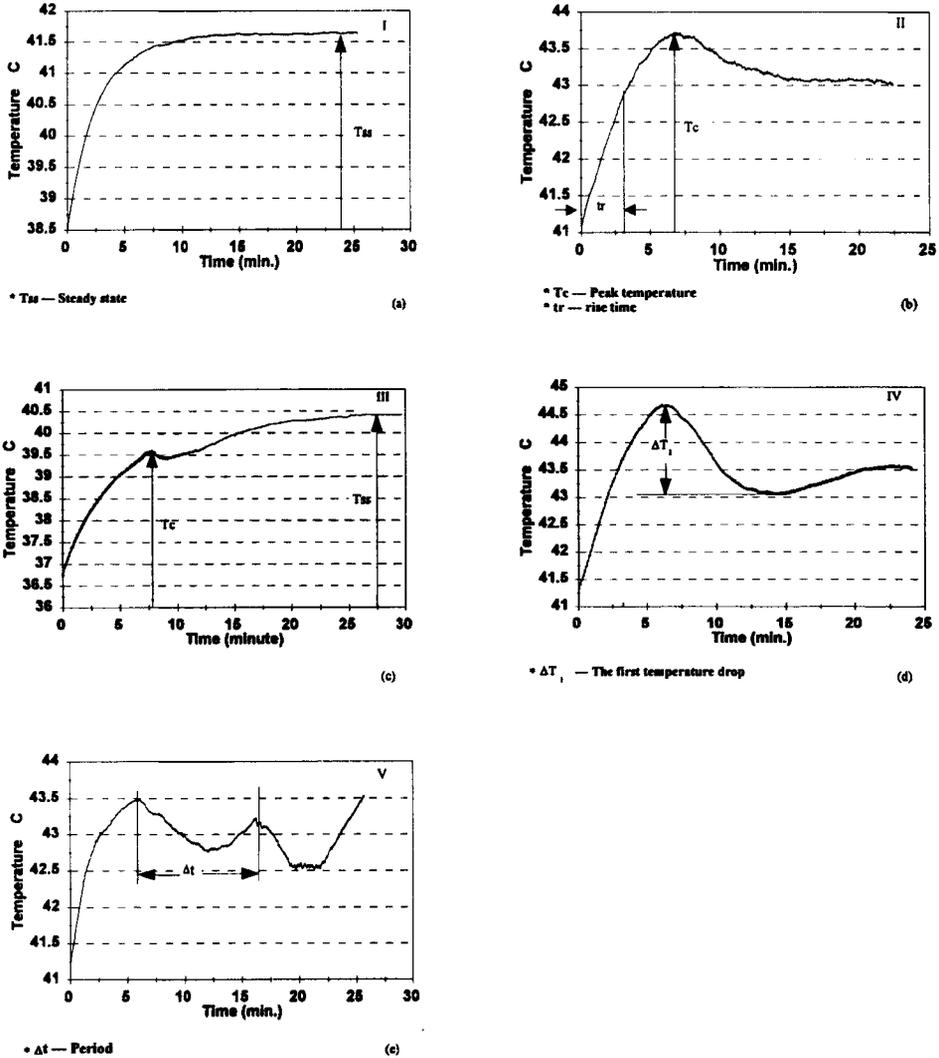


Figure 4. Five different types of tissue temperature response to the microwave heating observed in the canine prostate during transurethral hyperthermia treatment.

fact that the temporal temperature gradient changed from a negative to positive value, may suggest that the initial perfusion response was not strong enough to stabilize the tissue temperature. It therefore continued to increase until the local absorbed thermal energy was balanced by a larger increase in perfusion later.

Type IV and V responses observed at the 15W heating could be also due to blood perfusion changes but with much longer time lag. Considering that the higher power level usually causes a steeper temperature gradient within the prostate, these damped or self-sustaining oscillations in temperature could be closely related to the local temperature gradient as well. In Roemer *et al.*'s experimental study of temperature responses in the canine thigh during microwave heating, higher order responses were also observed at superficial hotter locations (Roemer *et al.* 1985). A more detailed

Table 1. Summary of the characteristic temperatures (T_c , T_{ss} and ΔT_1) and the rise-time (t_r) associated with different types of tissue temperature response to the microwave heating in the canine prostate during hyperthermia treatment.

Type	Number of observations				$T_c(^{\circ}\text{C})$			$T_{ss}(^{\circ}\text{C})$			$\Delta T_1(^{\circ}\text{C})$			$t_r(\text{min.})^*$			$\Delta t(\text{min})$
	Total	5W	10W	15W	Average	Min	Max	Average	Min	Max	Average	Min	Max	5W	10W	15W	
I	57	23	27	7	N/A	N/A	N/A	38.2	35.0	41.2	N/A	N/A	N/A	3.8	4.7	5.4	N/A
II	19	13	0	6	38.89	34.8	44.0	38.0	34.0	42.8	0.8	0.2	2.0	2.3	N/A	3.9	N/A
III	6	0	6	0	39.6	38.9	41.4	41.5	41.2	41.8	0.2	0.1	0.2	N/A	3.6	N/A	N/A
IV	18	0	0	18	42.6	40.3	45.0	41.8	39.5	44.2	1.7	0.3	2.1	N/A	N/A	3.2	~ 28.0
V	6	0	0	6	43.5	42.3	45.5	N/A	N/A	N/A	1.7	0.8	2.0	N/A	N/A	4.2	~ 7.5

quantitative analysis will be performed in the near future to explore the individual effects of these factors on temperature response, especially to explain the theoretical basis of the difference between type II and III and type IV and V from a heat transfer point of view.

One of the most interesting responses to local heating found in the prostatic tissue is an increase in blood perfusion, which plays an important role in local tissue thermo-regulation. This response to hyperthermia, if sufficient, can result in a decrease, a steady state, or oscillations in tissue temperature, which has been observed by many investigators (Sekins *et al.* 1984, Song 1984, Roemer *et al.* 1985, Roehrborn *et al.* 1992, Devonec *et al.* 1993, Larson and Collins, 1995, Zhu *et al.* 1995, Xu *et al.* 1996). This behaviour is generally attributed to the local thermally induced vasodilation. From our observation, there seems to be a critical tissue temperature which simulates an initial increase in local blood perfusion which in turn reduces the tissue temperature. Data presented in table 1, suggest that the average value of this critical temperature varies from 38.7°C to 43.5°C, and is associated with different types of temperature responses. In skeletal muscle (Sekins *et al.* 1984, Roemer *et al.* 1985), the initial measured blood flow response was also characterized by a 'critical temperature' behaviour such that rapid increases in blood flow occur when the tissue temperature exceeds 42°C. To further analyse blood perfusion as the primary physiological variable for tissue cooling, we expect to study the canine prostatic blood perfusion rate under both normal and hyperthermic conditions to provide a starting point for a non-linear theory for local thermo-modulatory responses.

This work helps to provide a good understanding of how blood flow changes and then tissue temperatures are related within the canine prostate during transurethral microwave hyperthermia. Because the dog and man are the only common mammals in which benign prostatic hyperplasia (BPH) develops spontaneously and the natural history of this condition in the dog is remarkably similar to that in the human (Coffey and Walsh 1990), the dog has been used widely in experimental studies attempting to induce the disease and examine the effectiveness of microwave hyperthermia treatment for BPH, which is a common disease among elderly man. As the average of the US population grows older over the next several decades, the incidence of this disease can be expected to increase. The use of microwave heating for hyperthermic treatment of BPH is a novel approach to the problem desired by high surgical risk patients. To improve treatment efficacy, any increase in the thermal dose can only be achieved through a better knowledge and more accurate predictions on the tissue temperature rise resulted from both the natural (blood flow) and man-imposed (thermal dose) thermoregulation processes.

Acknowledgement

This research was supported in part by NIH 5 R29 CA67970-01. Authors wish to thank Urologix, Inc. for providing the transurethral thermal therapy system and technical assistance for this research. Many thanks also go to Mr David Y. Yuan for his great assistance during this experimental study.

References

- ARKIN, H., HOLMES, K. R., CHEN, M. M., and BOTTJE, W. G., 1986, Thermal pulse decay method for simultaneous measurement of local thermal conductivity and blood perfusion: a theoretical analysis. *ASME Transactions*, **108**, 208–214.

- COFFEY, D. S., and WALSH, P. C., 1990, Clinical and experimental studies of benign prostatic hyperplasia. *Urological Clinics in North America*, **17**, 461.
- DEVONEC, M., BERGER, N., FENDLER, J. P., JOUBERT, P., NASSER, M., and PERRIN, P., 1993, Thermoregulation during transurethral microwave thermotherapy: experimental and clinical fundamentals. *European Urology*, **23** (suppl.): 63–67.
- LARSON, T. R., and COLLINS, J. M., 1995, Increase prostatic blood flow in response to microwave thermal treatment: preliminary findings in two patients with benign prostatic hyperplasia. *Urology*, **46**(4), 584–590.
- LOMAX, E., 1979, Historical development of concepts in thermoregulation. *Body Temperature: Regulation, Drug Effects and Therapeutic Implications*, E. Lomax and E. Schonbaum, eds (New York: Marcel Dekker).
- PENNES, H. H., 1948, Analysis of tissue and arterial blood temperatures in resting forearm. *Journal of Applied Physiology*, **1**, 93–122.
- ROEMER, R. B., OLESON, J. R., and CETAS, T. C., 1985, Oscillatory temperature response to constant power applied to canine muscle. *American Journal of Physiology*, **249**, R153–R158.
- ROEHRBORN, C. G., KRONGGRAD, A., and MCCONNELL, J. D., 1992, Temperature mapping in the canine prostate during transurethrally-applied local microwave hyperthermia. *The Prostate*, **20**, 97–104.
- SEKINS, K. M., LEHMANN, J. F., ESSELMAN, P., DUNDORE, D., EMERY, A. F., DELATEUR, B. J., and NELP, W. B., 1984, Local muscle blood flow and temperature responses to 915 MHz diathermy as simultaneously measured and numerical predicted. *Archives in Physical Medicine and Rehabilitation*, **65**, 1–7.
- SONG, C. W., 1984, Effect of local hyperthermia on blood flow and microenvironment: a review. *Cancer Research*, **44** (suppl.), 4721s–4730s.
- WIDEMAN JR., R. F., GLAHN, R. P., BOTTJE, W. G., and HOLMES, K. R., 1992, Use of a thermal pulse decay system to access avian renal blood flow during reduced renal arterial perfusion pressure. *American Journal of Physiology*, **262**, R90–R98.
- XU, L. X., ZHU, L., YUAN, D. Y., and HOLMES, K. R., 1996, Thermoregulation in the canine prostate during hyperthermia. *Annals of Biomedical Engineering*, **24** (suppl. 1), s-20.
- ZHU, L., LEMONS, D. E., and WEINBAUM, S., 1995, A new approach for predicting the enhancement in the effective conductivity of perfused muscle tissue due to hyperthermia. *Annals of Biomedical Engineering*, **23**, 1–12.

Nomenclature

- T tissue temperature, °C
- ΔT magnitude of the first drop in tissue temperature responding to hyperthermia
- t time, s
- Δt period of the temperature oscillation in response to hyperthermia
- l first temperature drop
- c critical temperature
- r rise-time
- ss steady state