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Optimizing transurethral microwave thermotherapy: a model for studying power, blood flow, temperature variations and tissue destruction

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Objective To examine the role of microwave power and blood flow on temperature variations and tissue destruction in the prostate, using a theoretical model of transurethral microwave thermotherapy (TUMT), and thus compare fixed-energy TUMT with no intraprostatic temperature monitoring (constant microwave power applied over a fixed period) with 'feedback' TUMT in which the microwave power is adjusted according to the monitored intraprostatic temperature.

Materials and methods The temperature distribution in the prostate was modelled for a typical TUMT catheter at various blood flow rates. The volume of tissue destroyed was simultaneously calculated from cell survival data after thermal exposure. The calculated quantity of tissue destroyed at the different microwave power levels and blood flow rates was used to describe qualitatively the simulated treatments.

Results Treatment monitoring and consistency were better during feedback TUMT than fixed-energy TUMT, in that the former compensated for variations in blood flow rate. The modelled values agreed with observations during real TUMT.

Conclusions Blood flow rate is a key factor in the outcome of TUMT. Only by measuring intraprostatic temperature is it possible to compensate for the large variations in prostatic blood flow and obtain consistent treatment results. Repeated interruptions prompted by high rectal temperatures should be minimized and preferably avoided, as the quantity of tissue destroyed is then greatly reduced, and in extreme cases the treatment is totally ineffective.

Keywords Transurethral microwave thermotherapy (TUMT), prostate, power, blood flow, coagulation, destruction, feedback

Introduction

Transurethral microwave thermotherapy (TUMT) is a new treatment for BPH, having the advantages of simplicity, minimal side-effects, low cost and the potential to deliver the treatment in the out-patient department. The most common TUMT treatment protocols generally alleviate symptoms and improve maximum urinary flow rate. In recent years, high-energy protocols have been developed which have further improved the results; high-energy TUMT now provides a similar outcome to that from TURP for symptom alleviation, urinary flow rate and bladder pressure [1,2]. However, the reported clinical results are very variable [3]. Several methodological issues have not been completely resolved, e.g. how factors such as temperature, microwave power, the cooling effect of blood flow, treatment duration and interruptions during treatment affect the result. Only understanding how these factors interact will enable an optimal treatment strategy to be formulated.

The tissue temperature during TUMT is mainly determined by three processes, i.e. the generation of heat through absorption of microwave energy, the dispersion of heat by conduction in the tissue and the loss of heat through blood flow. The first factor is specific to the treatment catheter being used, the second depends on tissue composition and the third depends on the patient, and is unknown. The relationship is given by the heat equation described by Pennes [4].

Studies have shown that blood perfusion greatly affects tissue temperature during thermotherapy [5–8]; blood flow transports heat from the treated area, lowering the temperature. The prostatic blood flow in untreated patients with BPH was 10.8–24.2 mL/min per 100 g [9]; in that study, there were only six patients, so individual variations may be greater. Blood perfusion may also change during the course of treatment; blood flow in muscular tissue increased by up to nine times at

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temperatures of up to 45°C. Above this temperature, blood flow decreases again because vascular damage is induced [10–12]. In TUMT, a doubling of blood flow has been reported [13]. As the blood flow in individual patients is thus unknown, it follows that the intraprostatic temperature during the treatment cannot be determined by anything less than direct measurement [1,14].

Standard treatment with TUMT is usually carried out with a constant microwave power over a pre-set time; e.g. a common protocol is 60 W for 60 min [15,16]. With standard TUMT, measuring the temperature in the treatment catheter and in the rectum is the most important tool to control the treatment. If the temperature in either location becomes too high, the treatment is temporarily interrupted. However, long or frequent interruption of microwave emissions causes the prostate to cool and this may adversely affect the final results [17]. In standard TUMT the true prostatic temperature is not monitored; this omission means that the treatment is essentially 'blind', as it is not known how hot the prostate becomes.

Recently a modified treatment technique was proposed, 'feedback' TUMT, in which the intraprostatic temperature is measured with a thin probe inserted into the prostatic tissue. The operator can then monitor the intraprostatic temperature during treatment and can control the microwave power accordingly [1]. Thus, one aim of the present report was to determine whether it is possible to optimize TUMT and ensure that the results of treatment are predictable and independent of blood flow. To examine how the different variables affect the destruction of prostatic tissue, we developed a theoretical TUMT model. The model can be used to calculate the temperature in the prostate during TUMT treatment and hence calculate the quantity of tissue destroyed. Previous theoretical studies have been reported for transrectal microwave treatment [18] and thermotherapy of canine prostates [19]. The present model provided an opportunity to study; (i) the effect of microwave power and blood flow on temperature variation and tissue destruction in the prostate; (ii) a comparison of standard fixed-energy TUMT and feedback TUMT; (iii) how the duration of treatment affects the quantity of tissue destroyed; and (iv) how temporary interruptions prompted by high rectal temperatures affect the treatment.

Materials and methods

Three situations were simulated for different blood flow rates in the range 10–60 mL/min per 100 g prostate: (i) Standard fixed-energy TUMT with a treatment protocol of 60 W. The temperature distribution and quantity of tissue destroyed were calculated after treatment periods of 15, 30, 45 and 60 min. (ii) Feedback TUMT; similar calculations were obtained with the microwave power adjusted to achieve a constant temperature at a reference point within the prostate. (iii) Standard TUMT in which the microwave emission was interrupted regularly to simulate the response to excessive rectal temperature. The interruptions lasted for 10–200 s and were repeated every 5 min during the whole treatment period of 60 min. The quantity of tissue destroyed was used to assess the effect of the interruption.

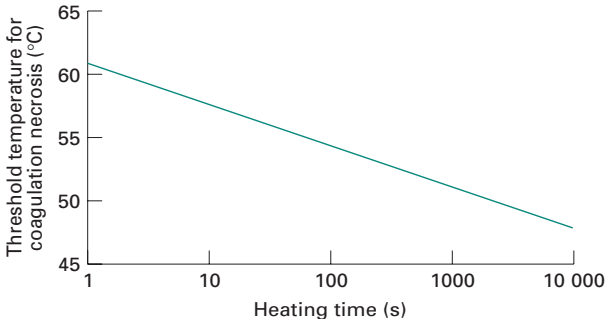

Fig. 1. The temperature required for coagulation as a function of heating duration.

The temperature distribution in the prostate was calculated from the heat equation for a medium-sized TUMT catheter (ProstaLund ProSitex Precision, Lund Instruments AB, Sweden) [20]. The thermal properties of the prostate gland were calculated from its water content [21], which was assumed to be 80%. Knowing the temperature distribution in space and time, the tissue destruction induced by therapy was simultaneously calculated from the cell damage caused by thermal exposure [22], as described mathematically by the Arrhenius equation [23]. The relationship between temperature and time for achieving thermally induced coagulation is given in Fig. 1.

The calculated volume of tissue destroyed at different microwave powers and blood flow rates was used to describe the simulated treatments quantitively. This approach was used and verified previously to model heat treatment with laser, but has not been applied to TUMT [24,25].

Results

Figure 2 shows the calculated temperature distributions for standard fixed energy TUMT (Fig. 2**a**) and for feedback TUMT (Fig. 2**b**) for different blood flow rates of 10–60 mL/min per 100 g. With standard TUMT and a constant 60 W, the calculated temperature at a reference point 8 mm into the prostate was 46.3–67.7°C, depending on the blood flow rate. With feedback TUMT, the temperature was maintained at 53.5°C at the reference point while the power was 35–104 W. The

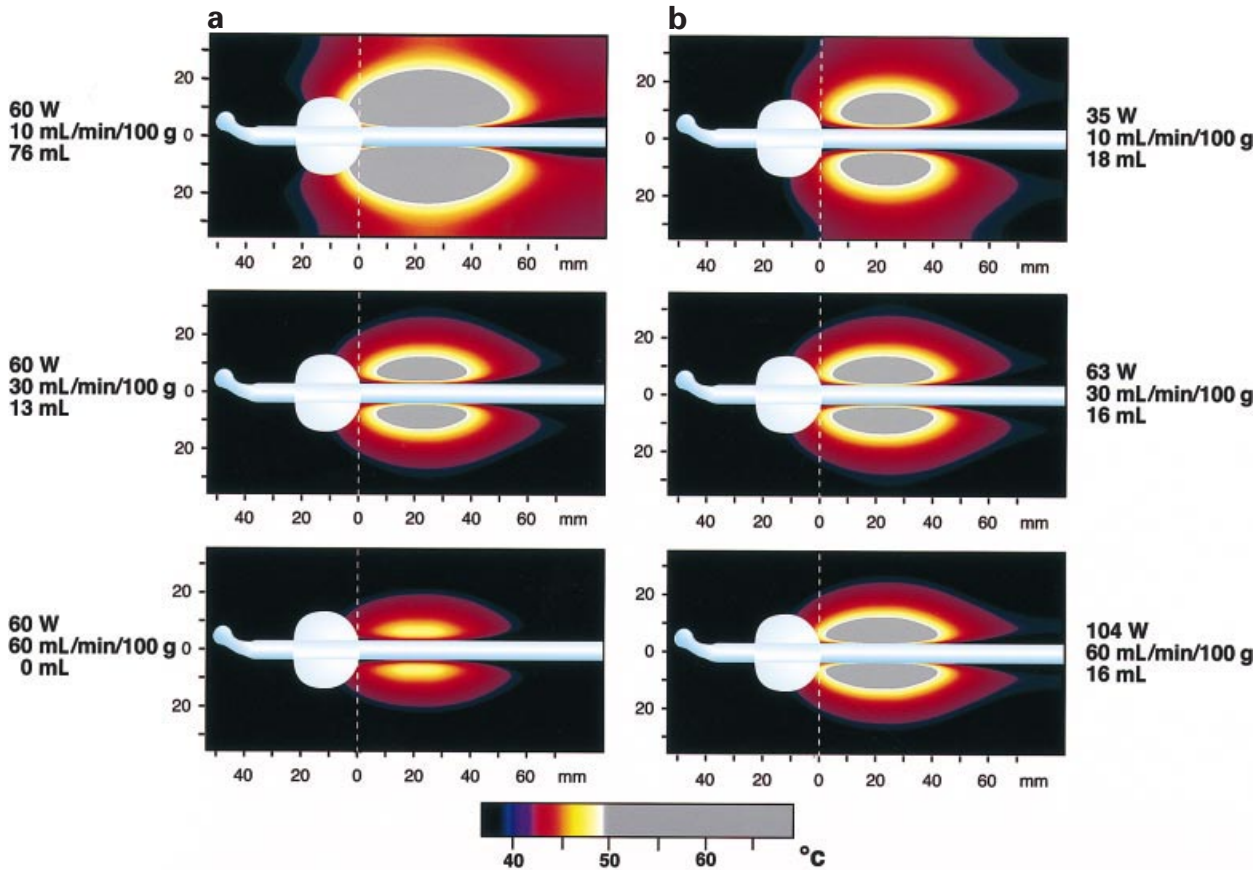

Fig. 2. The temperature distribution in the prostate after 60 min calculated for **a** standard TUMT at 60 W microwave power and **b** feedback TUMT with a variable microwave power of 35–104 W for blood flow from 10 to 60 mL/min per 100 g. Microwave power, blood flow and quantity of tissue destroyed are shown for each diagram. The tissue in the grey areas was destroyed.

diagrams in Fig. 2 are colour-coded, with grey representing destroyed tissue, white the highest temperature of intact tissue, with the other colours in a linearly descending scale. A drawing of the catheter is included in the diagrams to facilitate orientation; the balloon base corresponds to the bladder neck in a patient.

Figure 3 shows the quantity of tissue destroyed for the two treatment regimens at different blood flow rates. With standard TUMT, 0–76 mL of tissue was destroyed, while feedback TUMT destroyed a nearly constant quantity of ≈16 mL.

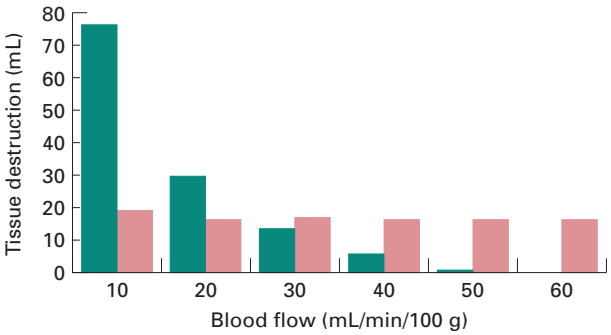

Fig. 3. The quantity of tissue destroyed in standard (green) and feedback (red) TUMT. The set temperature for feedback TUMT was 53.5°C at a tissue depth of 8 mm.

The monitoring probe in feedback TUMT measures the tissue temperature, but this is not solely proportional to the quantity of tissue destroyed, as the treatment time is also a calculation variable (cf. Fig. 1). Thus it is important to know whether there is an optimal location for the monitoring probe where a specific temperature represents a certain quantity of destroyed tissue, regardless of the blood flow rate. If the monitoring probe is placed too close to the cooled treatment catheter, the temperature reading will be affected by cooling, especially at low blood flow rates. Conversely, the monitoring probe should not be placed further into the prostate adenoma than the effective range of the microwaves. Figure 4 shows that there is an optimal position for the monitoring probe. At a depth of 8–8.5 mm, a given temperature will destroy the same quantity of tissue, regardless of blood flow rate. Such precise placement of the monitoring probe would not be practically possible and a good

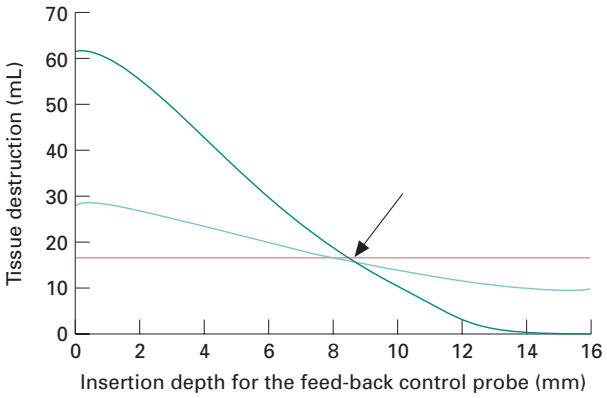

Fig. 4. The monitoring probe should be inserted 8–8.5 mm (arrow) into the prostate, calculated from the catheter wall, if the quantity of tissue destroyed is not to be influenced by the blood flow rate. If TUMT treatment is controlled by the temperature on the exterior of the catheter (insertion depth = 0), the quantity of tissue destroyed will fluctuate substantially as a function of the blood flow rate. Flow rates: Dark green, 10 mL/min per 100 g; light green, 30 mL/min per 100 g; red, 60 mL/min per 100 g.

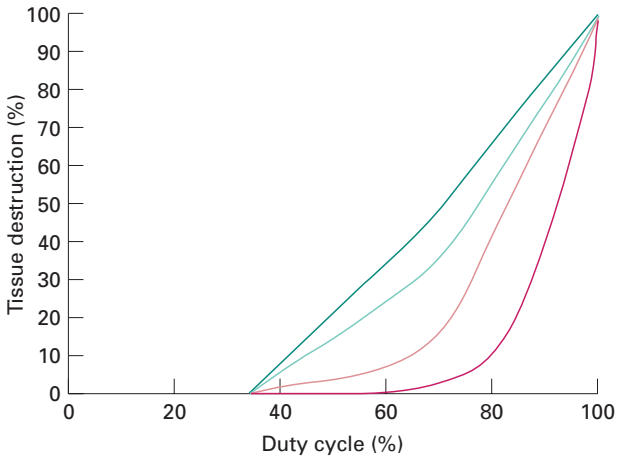

Fig. 6. The effect of intermittent interruptions to microwave emissions. The duty cycle is the total time that microwaves are applied divided by the treatment time, i.e. a duty cycle of 100% corresponds to no interruptions at all (dark green, 10 mL/min per 100 g; light green, 20 mL/min per 100 g; light red, 30 mL/min per 100 g; dark red, 40 mL/min per 100 g).

compromise might be to place the monitoring probe at a depth of 8–10 mm in the tissue. Then 11–18 mL of tissue will be destroyed at the set temperature of 53.5°C for prostate blood flow rates of 10–60 mL/min per 100 g. Compared with standard TUMT, in which 0–76 mL of tissue is destroyed for a similar range of blood flow rates, this is a considerable improvement. Both standard and feedback TUMT show the same pattern in the speed at which the tissue is destroyed (Fig. 5); 50–80% of the tissue is destroyed during the first 30 min of treatment and after 45 min, this proportion increases to 78–94%.

Figure 6 shows the results of simulating interruptions during TUMT; short interruptions ($\leqslant$10 s) have little effect on the quantity of tissue destroyed, whereas longer interruptions ($\geqslant$1 min) destroy significantly less. When the duration of interruption and power application are equal (50% duty cycle) the quantity of tissue destroyed is barely 20% of the corresponding value for a continuous treatment.

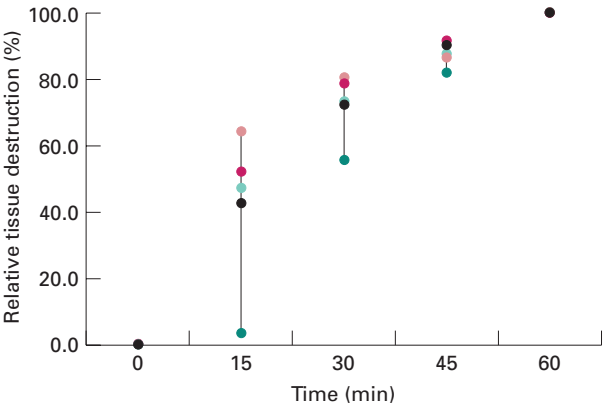

Fig. 5. The quantity of tissue destroyed increases with treatment duration for different blood flow rates between 10 and 60 mL/min/100 g for both feedback TUMT (dark green, 10 mL/min per 100 g; light green, 30 mL/min per 100 g; light red, 60 mL/min per 100 g,) and standard TUMT (dark red, 10 mL/min per 100 g; black, 30 mL/min per 100 g). All the tissue is destroyed after 60 min.

Discussion

The temperature distribution and quantity of tissue destroyed during standard fixed-energy TUMT are heavily dependent on blood flow rate in the prostate; when the flow rate is low, fixed-energy TUMT causes comprehensive tissue destruction, but none is destroyed at all where the blood flow is >40 mL/min per 100 g. Hence, there is a risk that patients with low or high blood flow rates will be over- or under-treated when using fixed-energy TUMT. If instead the temperature of the prostate is measured at a depth of 8–10 mm and the power adjusted accordingly, compensation can be made for blood flow rate and a consistent treatment administered. To compensate for a sixfold increase in blood flow rate the power has to be increased threefold, highlighting the major impact of blood flow rate on TUMT. Locating the monitoring probe on the exterior of the catheter (depth = 0) is practically simple but unfortunately, according to Fig. 4, it is a poor strategy, as the quantity of tissue destroyed will then be largely determined by blood flow rate. In a recent study [10], there was no correlation between the intraprostatic temperature and the temperatures on the catheter surface or in the rectum.

Occasionally, the microwave power is controlled from the temperature in the catheter [26], but this provides no greater benefit than no monitoring at all.

The present model gives realistic values for the quantity of tissue destroyed. In a former clinical study comprising 30 patients, we showed that the mean diminution in volume with feedback TUMT was 14 mL [1]. This correlates well with the present calculations (Fig. 4) in which 16 mL of tissue was destroyed during feedback TUMT. It was also shown [1] that there is no direct relationship between temperature in the prostate and a given microwave power; some patients required 45 W while others needed up to 90 W of power to reach the desired intraprostatic temperature. These findings also support the present calculations, i.e. the temperature is determined by the combination of microwave power and blood flow. By applying the data in [1] to the present model, the blood flow reported in [1] would seem to have been 13–45 mL/min per 100 g, consistent with the values reported by Song [12].

TUMT treatments are usually performed over 60 min; the reasons for choosing this duration are historical and arise from the experience gained during the 1980s, when thermotherapy was being developed from hyperthermia treatment of cancer [27]. The present results (Fig. 5) can be interpreted as showing that the duration of TUMT treatments could be reduced from 1 h to 45 min, without particularly impairing the treatment effect. From the patients' perspective, a shorter treatment should be welcome.

Temporary interruptions of treatment arising from excessive rectal temperatures are well-known [5]; allowing the tissue to cool during the interruption prevents the accumulation of effective cell destruction. In a randomized study in which standard TUMT was compared with TURP [7] there was no objective improvement after TUMT, but the authors mention that the power was often interrupted because the rectal temperature was excessive. The mean power applied in that study was reduced from 216 to 81 kJ as a result of these interruptions, corresponding to a mean power of only 23 W. From the present model, short interruptions of $\approx$10 s do not markedly affect the quantity of tissue destroyed, but if the interruptions exceed the duration of applied power, the treatment is probably valueless. We will discuss various methods and strategies for avoiding high rectal temperatures in a future report.

It has been suggested previously that the stromal : epidermal tissue ratio might be a prognostic factor in TUMT which could explain the wide variation in reported treatment results [28]. No conclusive results have yet been presented to support this view. Instead, we propose that the 'prognostic factor' is blood flow rate. If, as with standard fixed-energy TUMT, the cooling effect of blood flow is not considered, it is reasonable that the treatment results will show the wide variations reported.

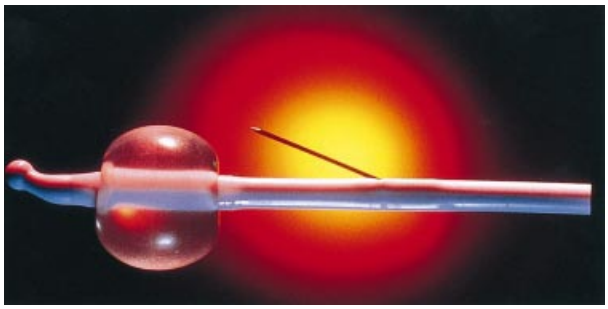

Fig. 7. Example of a ProSitex Precision TUMT catheter (ProstaLund) with an integral temperature probe that protrudes from the catheter into the prostate. The temperature probe contains many temperature transducers to map the temperature distribution in the prostate along the probe.

Given that tissue destruction is the decisive factor in the effectiveness of thermotherapy, it follows that TUMT should not be performed with a fixed-energy protocol. Instead, the prostate temperature should be measured and the microwave power adjusted to maintain the desired intraprostatic temperature and degree of tissue destruction. By using a modified treatment catheter, from which a monitoring probe can be inserted into the prostate, it is practically possible to achieve this; Fig. 7 shows an example of such a treatment catheter.

In clinical practice, microwave power must sometimes be reduced because the patient is in pain or the rectal temperature is too high. The treatment duration should then preferably be increased to compensate for the subsequently lower tissue destruction. If the treatment computer repeatedly calculates the amount of tissue destruction during treatment, based on the intraprostatic temperature, and presents it in a suitable format, then TUMT treatment could be controlled precisely. Both the microwave power and treatment time could then be varied for each patient. It remains for other studies to confirm that treatment in patients will follow the course calculated in the present theoretical model.

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