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# Why is Transurethral Microwave Thermotherapy (TUMT) Positively Effective?

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Between 1992 and 1994, 157 patients with benign prostatic hyperplasia were treated with transurethral microwave thermotherapy (TUMT). In evaluating the efficacy of TUMT with the International Prostate Symptom Score (I-PSS) in 121 patients, 18 (15%) showed excellent and 42 (35%) showed good response. In evaluation of QOL, the result was 43 patients (33%) excellent and 42 patients (35%) good response. In objective evaluation of uroflow in 93 patients, 12 (13%) showed excellent and 13 (14%) showed good response. The prostatic volume did not show a significant decrease after treatment. In terms of overall improvement, according to the criteria proposed at the 2nd International Consultation on BPH, the treatment was considered effective in 53 of 108 patients (48%). Histological examination of the prostate enucleated from a patient 7 months after TUMT revealed degenerative changes of nerve fibres on S-100 protein immunohistochemical staining, which were more extensive than those in smooth muscle cells on HE staining. In *in vitro* tests the isometric contraction force of the rabbit prostatic tissue was measured after exposure to different temperatures, ranging from 37 to 50 °C. No significant change was observed up to 45 °C vs. 37 °C. After exposure to 48 °C, the nerve mediated contractions became completely depressed, although phenylephrine or KCl induced contractions were only partially suppressed. After exposure to 50 °C, no contraction was induced by any type of stimuli. In conclusion, it is suggested that good symptomatic improvement after TUMT results from both neural and muscular damage to the prostate. As TUMT is not aiming at a relief of anatomical obstruction, 50 °C is thought to be a sufficient thermal condition to cause an irreversible damage to prostatic tissue, which will provide a relief from functional obstruction and urethral instability.

## Introduction

The worldwide application of TURP was considered an advance in the treatment of benign prostatic hyperplasia (BPH), but recently less invasive and higher QOL therapeutic strategies have been sought. Transurethral microwave thermotherapy is a newly developed method with the potential to satisfy these increased requirements [1, 2]. In this therapy, prostatic tissue is heated to 45 °C or higher using microwaves. Details of the physiological mechanism by which this treatment is effective, however, remain unknown. In this study, firstly we

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investigated the clinical outcome of TUMT applied to 157 patients with BPH. Secondly, we tried to find the *in vitro* effect of heat exposure on rabbit prostatic tissue. The results of these studies will provide the future prospects for this therapy.

## Clinical study

### *Patients and methods*

The subjects were 157 patients with benign prostatic hyperplasia (BPH) aged between 51 and 93 years (average 70) treated with TUMT during the period from July 1992 to September 1994. Evaluations with the I-PSS symptom score, QOL and uroflow (MFR) were made before and again 6 months after treatment. Effectiveness was evaluated with a set of criteria proposed at the 2nd International Consultation on BPH [3]. The volume of the internal prostate gland was also measured with transrectal ultrasonography before and after treatment.

Histological examinations with S-100 protein immunohistochemical staining and HE staining were performed on the specimens obtained from the patient who underwent enucleation of the prostate for poor response to TUMT 7 months earlier.

The equipment used was PROSTATRON, manufactured by the French company Technomed Medical System. The prostate was heated with 1,296 MHz microwaves, with a maximum power of 50 watts [4]. The treatment was performed in a single session lasting one hour on an outpatient basis.

### *Results*

The number of subjects available for evaluation were 121 for I-PSS, 121 for QOL and 93 for uroflow. I-PSS and QOL evaluations showed good or better responses in 50% and 68%, respectively, while uroflow showed good or better responses in 27% (Table 1). Nevertheless, the mean uroflow improved sig-

Table 1
Evaluation of clinical responses on symptom, QOL and uroflow

| Parameter | Response | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Excellent | | Good | | Fair | | None | |
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| Symptom (I-PSS) | 18 | (15) | 42 | (35) | 30 | (25) | 31 | (25) |
| QOL (I-PSS) | 40 | (33) | 42 | (35) | 22 | (18) | 17 | (14) |
| Uroflow (MFR) | 12 | (13) | 13 | (14) | 24 | (26) | 44 | (47) |

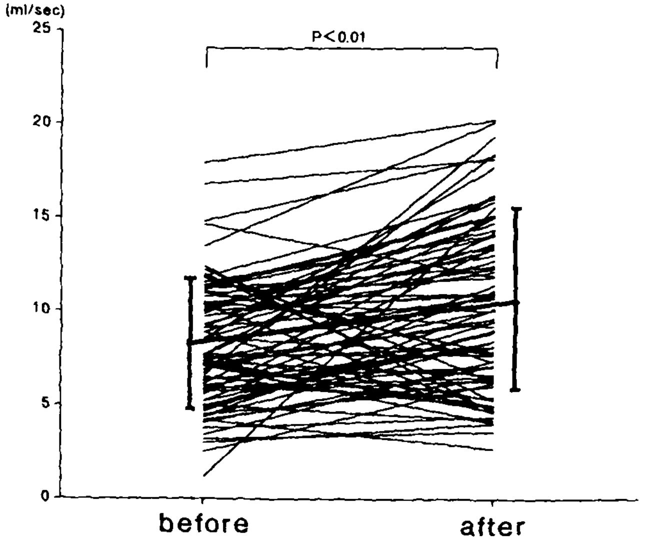


Fig. 1. Changes in maximum flow rate before and 6 months after TUMT

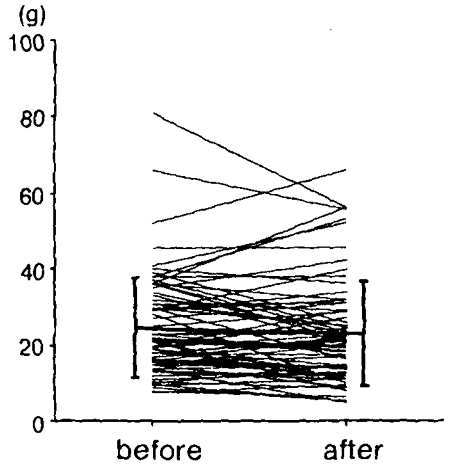


Fig. 2. Changes in estimated weight of prostatic adenoma by transrectal ultrasonography before and after TUMT

nificantly after treatment (Fig. 1). The average volume of the internal prostate gland was 27.0 g before and 24.3 g after treatment, showing no significant change (Fig. 2). In terms of overall effectiveness, the treatment was considered effective in 52 (48%) of 108 patients (Table 2).

In the specimen obtained from the patient 7 months after TUMT, macroscopic changes were localized within 2 cm or so from the urethra (Fig. 3). At lower magnification of the HE-stained specimens on the urethral side, necrosis and inflammation were prominent. High magnification pictures obtained from the deeper portion to the urethra showed atrophy or rupture of the cell body, dark staining of the nucleus, and reduction of the number of nuclei of the smooth muscle cells, without any pathological change in the epithelium

Table 2
Overall responses

| | No. | (%) |
|---|---|---|
| Effective | 52 | (48) |
| Excellent | 17 | (16) |
| Good | 35 | (32) |
| Not effective | 56 | (52) |
| Fair | 22 | (20) |
| None | 34 | (31) |

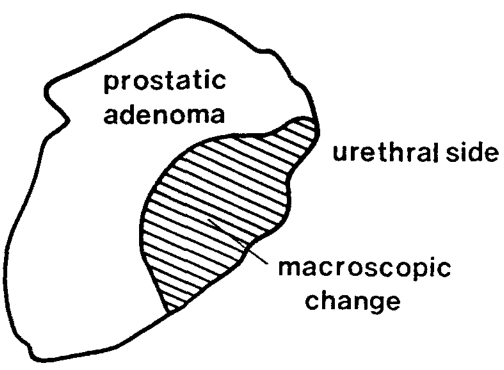


Fig. 3. Macroscopic picture of prostatic adenoma extirpated 7 months after TUMT

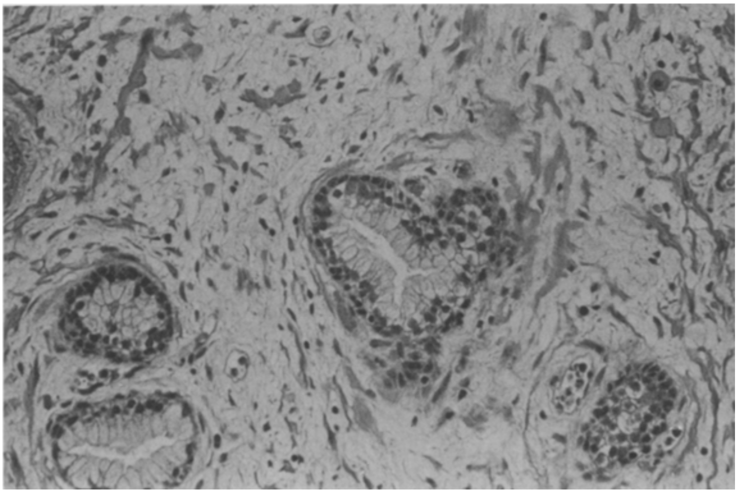

Fig. 4. Microscopic picture of prostatic adenoma
7 months after TUMT. HE, ×200

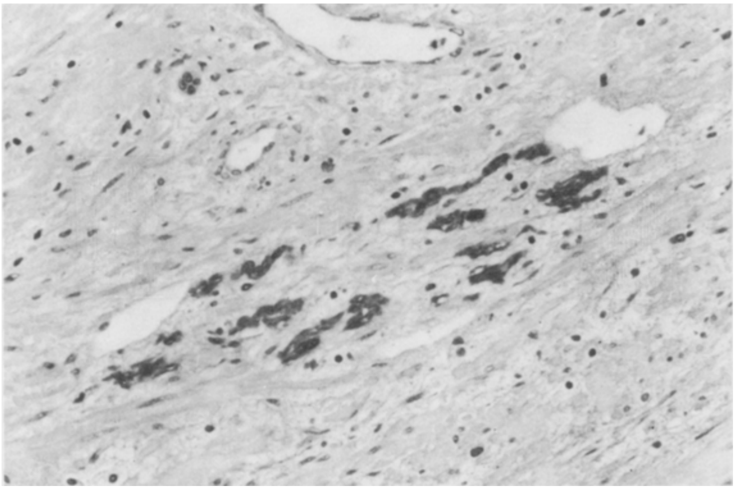

Fig. 5. S-100 protein immunostained nerve fibres
after TUMT. HE, ×400

(Fig. 4). Changes in nerve fibres were also checked in the same specimens, using the S-100 protein immunohistochemical staining. The distribution of nerve fibres was found to be the highest underneath the urethral mucosa, gradually becoming less in the outer phases. Figure 5 is a high magnification picture obtained at about 3 cm from the urethra. Vacuolization and cystic degeneration of the nerve fibres were observed. These changes were not found in the outer phases, though they were observed in a wider area than those of muscular damage on HE-stained preparation.

## In vitro study

### *Materials and methods*

Prostatic tissues isolated from male rabbits were cut into strips in the longitudinal direction. The strips were suspended in a Magnus tube filled with Krebs solution and the isometric contraction force evoked by three types of stimulation was measured; transmural electrical field stimulation (EFS), addition of phenylephrine (0.1 mM), and addition of KCl (90 mM). Following the experiment at incubation temperature of 37 °C, the strip was exposed to high temperature (42, 45, 48 or 50 °C) for 30 minutes and reincubated at 37 °C for 30 minutes. Then the contraction force was determined again to calculate an inhibitory effect (%) of heat exposure to the control (37 °C). The specimens were also examined histologically after each experiment.

### *Results*

Neither of these stimuli produced differences in the contraction force compared to the control after heat exposure up to 45 °C. But after heat exposure to 48 °C, the mean contraction force evoked by EFS was almost completely depressed (94%), while that by phenylephrine and KCl was only partially depressed (34% and 10%, respectively). Once the tissue was exposed to 50 °C, no contractile response was induced by any type of stimuli (Fig. 6). The HE-stained specimens revealed no clear morphological changes in the prostatic smooth muscles up to 45 °C. After exposure to 48 °C or higher, however, atrophy of the smooth muscle cells, deep staining of the cytoplasm, atrophy of the nuclei, and expansion of intercellular spaces were observed (Fig. 7). These findings were very similar to those of a clinical subject after TUMT.

## Discussion

Both conventional TURP and newly developed VLAP (visual laser ablation of the prostate) are volume reducing type therapies, which release anatomical occlusion by resection or ablation of the adenoma [4, 5]. Unlike such treatments, TUMT did not show any reduction in prostatic volume [6]. Therefore, the new approach examined in this study exhibited its effectiveness via a mechanism different from that explicated in the above mentioned TURP and VLAP. The results obtained from the isometric contraction study revealed that nerve fibres are more heat sensitive than smooth muscles and such damages are irreversible when heated above 48 °C. It seems that the effectiveness of TUMT

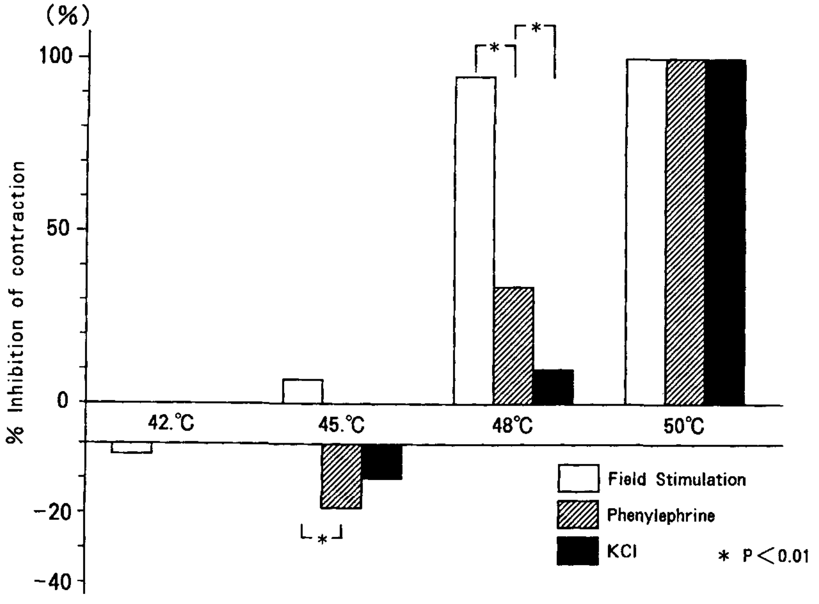


Fig. 6. Inhibitory effect of thermal exposure on contraction force of rabbit prostatic tissue elicited by transmural stimulation, addition of KCl and phenylephrine at each temperature

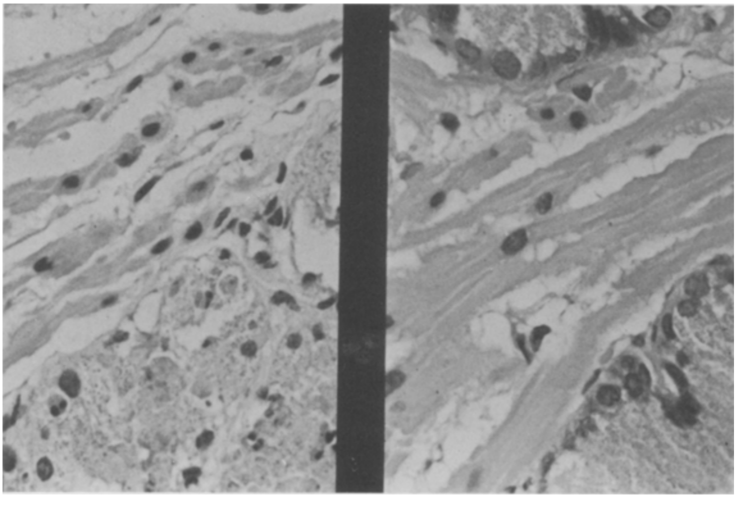

Fig. 7. Microscopic picture of rabbit prostatic tissue after thermal exposure to 45 °C (left) and to 48 °C (right). HE, ×400

results from reducing outflow obstruction by suppressing autonomic contraction of the prostatic smooth muscle, or by blocking the sympathetic system innervating the prostatic urethra. Moreover, the clinical histological study revealed that the neural damage was present in wider extent than the muscular damage [7]. The urethral afferent nerves, which mainly run underneath the urethral mucosa, are thought to be suffered from thermal damage as well as efferent sympathetic nerves. If the local heating of the prostate produces blockage of the urethral afferent, it is presumed that the anaesthesia-like effect of TUMT suppresses involuntary contraction of the bladder, leading to relieve irritative symptoms in BPH [8, 9]. In conclusion, we think TUMT is not a volume reducing treatment but mimics long acting pharmacological treatment behaving like alpha-blockers, smooth muscle relaxants and local anaesthetics.

## References

1. Yershalmi, A., Fishelovitz, Y., Singer, D., Reiner, I., Arielly, J., Abramovici, Y., Catsenison, R., Levy, E., Shani, A.: Localized deep microwave hyperthermia in the treatment of poor operative risk patients with benign prostatic hyperplasia. *J. Urol., 133,* 873 (1985).
2. Blute, M. L., Tomera, L. M., Hellerstein, D. F., McKiel, C. F., Benign, J. B., Sankey, N. E.: Transurethral microwave thermotherapy for management of benign prostatic hyperplasia: Result of the United States prostatoron cooperative study. *J. Urol., 150,* 1591 (1993).
3. Cookett, A. T., Aso, Y., Denis, L., Khoury, S.: Recommendations of the International Consultation on Benign Prostatic Hyperplasia (BPH). Paris, June 1991.
4. Kabalin, J. N.: Prostatectomy performed with a right angle firing neodymium:YAG laser fiber at 40 watts power setting. *J. Urol., 150,* 95 (1993).
5. Norris, J. P., Noris, D. M., Lee, R. D., Rueenstein, M. A.: Visual laser ablation of the prostate: Clinical experience in 108 patients. *J. Urol., 150,* 1612 (1993).
6. Ogden, C. W., Reddy, P., Johnson, H., Ramsay, J. W. A., Cater, S. S. T. C.: Sham versus transurethral microwave thermotherapy in patients with symptoms of benign prostatic bladder outflow obstruction. *Lancet, 341,* 14 (1993).
7. Perachino, M., Boozzo, W., Puppo, P., Vitali, A., Ardoino, S., Ferro, M. A.: Does transurethral thermotherapy induce a long-term alpha blockade? An immunohistochemical study. *Eur. Urol., 23,* 299 (1993).
8. Chalfin, S. A., Bradly, W. E.: The etiology of detrusor hyperreflexia in patients with infravesical obstruction. *J. Urol., 127,* 938 (1982).
9. Yokoyama, O., Nagano, K., Kawaguchi, K., Ueki, O., Ohkawa, M.: The influence of prostatic urethral anesthesia on overactive detrusor in patients with benign prostatic hyperplasia. *J. Urol., 151,* 1554 (1994).