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Development of Feedback Microwave Thermotherapy in Symptomatic Benign Prostatic Hyperplasia.

Schelin, Sonny

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LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Effects of Intraprostatic and Periprostatic Injections of Mepivacaine Epinephrine on Intraprostatic Blood Flow during Transurethral Microwave Thermotherapy: Correlation with [¹⁵O]H₂O-PET

SONNY SCHELIN, M.D.,¹ ANDERS CLAEZON, M.D.,² ANDERS SUNDIN, M.D.,²
and LENNART WAGRELL, M.D.²

ABSTRACT

Background and Purpose: Experiences with the ProstaLund Feedback Treatment® (PLFT®) with the CoreTherm® device and results from a previous positron emission tomography (PET) study suggest that the intraprostatic blood flow increases considerably during treatment in response to heat exposure. Early results with intraprostatic injection of mepivacaine epinephrine prior to PLFT have indicated greater patient comfort during treatment and shorter treatment time secondary to lower intraprostatic blood flow. In this pilot study, the effect of intraprostatic injection of mepivacaine epinephrine on intraprostatic blood flow before and during PLFT was evaluated by PET using [¹⁵O]H₂O.

Patients and Methods: In four patients scheduled for PLFT, a baseline value of the intraprostatic blood flow was established using [¹⁵O]H₂O-PET. Thereafter, intraprostatic injections of mepivacaine epinephrine were given using a prototype of the Schelin Catheter™. In two of the patients, PET was performed immediately after the mepivacaine epinephrine injections and 10 and 24 minutes after the start of PLFT. To reduce the risk of wash-out of the drug, the next two patients were examined 7 and 17 minutes after the start of PLFT but not in connection with the anesthetic injection.

Results: In patients 1 and 2, mepivacaine epinephrine decreased the prostatic blood flow. During PLFT, there was a slight increase in blood flow in patient 1 and a more pronounced increase in patient 2. In patient 3, the blood flow during treatment was almost unchanged, while it decreased in patient 4.

Conclusions: Intraprostatic injection of mepivacaine epinephrine may reduce, or even eliminate, the increase in blood flow that is usually seen during PLFT. The vague effect seen in patients 1 and 2 may be explained by wash-out of the drug.

INTRODUCTION

SEVERAL NEW MINIMALLY INVASIVE TECHNIQUES for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) have been introduced during the last 15 years. The aim of all these methods is to destroy the hyperplastic prostate tissue that causes the symptoms by means of heat. So far, transurethral microwave thermotherapy (TUMT) has shown the most promising results and is now used worldwide.¹⁻³

ProstaLund Feedback Treatment® (PLFT®) with the CoreTherm® device (ProstaLund, Lund, Sweden) is a further method for TUMT, with clinical outcomes similar to those of transurethral resection (TURP) in terms of symptomatic as well as objective improvement.⁴ In a randomized multicenter study comparing PLFT with TURP, no statistically significant differences in subjective measures (quality of life and International Prostate Symptom Score [IPSS]), objective signs (Q_{max}), or urodynamics were seen 12 months after treatment.⁵ Some advantages of PLFT are that the intraprostatic temperature, intrapro-

¹Kalmar County Hospital, Kalmar, Sweden.

²Uppsala University Hospital, Uppsala, Sweden.

static blood-flow index, and online cell-kill calculations are displayed during treatment.^{6,7} A good correlation between the calculated intraprostatic blood-flow index and calculations based on [¹⁵O]H₂O-PET was found by Wagrell and associates.⁸ The operator adjusts the microwave power to achieve therapeutic temperatures in the prostate tissue for a certain amount of time. This is essential in order to produce the desired degree of tissue necrosis. However, in some cases, therapeutic temperatures are never reached, resulting in suboptimal treatment outcomes.

Intraprostatic blood flow has been recognized as a key factor influencing the intraprostatic temperature during TUMT.^{9,10} In order to protect the prostatic gland, the intraprostatic blood flow often rises, so the supplied heat is transported away from the tissue, which prevents therapeutic intraprostatic temperatures from being reached. However, according to our experience, variations between patients are extensive, as calculated by the device.

It was thus hypothesized that the probability of reaching therapeutic temperatures would increase if the rise in intraprostatic blood flow could be counteracted. Early results with intraprostatic injections of mepivacaine epinephrine prior to PLFT indicate a pronounced reduction of the intraprostatic blood flow, as calculated by the ProstaLund device. In addition, treatment time was reduced by about 50%, and the energy consumption was reduced to about one third that required by a reference group, yet the clinical outcome was similar.¹¹ In the present study, the intraprostatic blood flow during PLFT after intraprostatic injections of mepivacaine epinephrine was assessed using PET with [¹⁵O]H₂O.¹²

PATIENTS AND METHODS

The PET was performed at different times during PLFT. The results of a study group that received intraprostatic injections of mepivacaine epinephrine prior to PLFT were compared with the results from a reference group that did not receive mepivacaine.

Microwave thermotherapy using PLFT

Microwave treatment was given using PLFT as previously described.^{5,11} During the procedure, the intraprostatic temper-

ature is measured continuously using a sensor that is inserted into the left prostatic lobe via the treatment catheter. On the basis of information about the intraprostatic temperature¹³ and Penne's bioheat model,¹⁴ the device calculates the amount of tissue necrosis online throughout the treatment session. The treatment is stopped manually when adequate tissue necrosis has been obtained.

Patient characteristics

Because we expected a considerable effect of the mepivacaine epinephrine injections, only a few patients were considered to be needed to detect a difference from the reference group. The reference group constituted of three patients, while four patients were enrolled in the mepivacaine epinephrine group. All patients had clinical BPH and were scheduled for PLFT. Demographic data (age, prostate size as determined by transrectal ultrasonography [TRUS] [B&K Medical 3535], IPSS, bother score, and maximal flow rate) are shown in Table 1. Statistical tests with Student's *t*-test for normally distributed data and Mann-Whitney U Test for non-normally distributed data showed the groups not to be significantly different at baseline for the variable of prostate size ($P = 0.2246$ and 0.2888 , respectively). Furthermore, tests of homogeneity of variances of the two groups for this variable by Levene's test ($P = 0.1160$) and the Brown and Forsythe test ($P = 0.1564$) showed nonsignificance. Hence, the groups were not statistically different for this variable, and variances were not statistically different regarding homogeneity.

One of the patients in the mepivacaine group had undergone TURP 6 years earlier, but no cavity or other indication of this procedure was seen with TRUS. None of the other patients had previously been treated with surgery for BPH. On one patient in each study group, sextant biopsies were performed to rule out prostate cancer.

Anesthesia: Reference group

All three patients were given 400 mg of norfloxacin orally and 10 mg of oxybutynin hydrochloride intravesically prior to the treatment. Patient 2 needed additional analgesics during the treatment.

TABLE 1. DEMOGRAPHIC DATA

	Age (years)	Prostate size (cc)	IPSS	Bother score	Q_{max} (mL/sec)
Reference group					
Patient 1	75	47	28	5	11.8
Patient 2	63	35	20	3	7.8
Patient 3	72	60	23	4	2.0
Mean	70	47	24	4	7.2
Mepivacaine group					
Patient 1	64	58	20	4	8.5
Patient 2	68	46	34	6	7.5
Patient 3	70	98	18	4	5.6
Patient 4	63	162	19	4	6.8
Mean	66	91	23	4.5	7.1

Anesthesia: Mepivacaine epinephrine group

All patients were given 50 mg of diclofenac sodium rectally and 400 mg of norfloxacin orally before treatment. Prostatic local anesthesia (2×20 mL of 0.5% and 10 mL of 1% mepivacaine epinephrine) was administered with a prototype of the Schelin Catheter™ (ProstaLund), which was CE marked in 2002. The catheter was anchored at the bladder neck by means of a balloon at its tip. A cannula was guided through a separate channel inside the catheter and protruded at the level of the prostate. The injections were made at three positions: 10 mL of the 0.5% solution each in the 4 o'clock and 8 o'clock positions and 10 mL of the 1% preparation in the 12 o'clock position. Patients 1, 2, and 4 received 2 mg of midazolam intravenously prior to local anesthesia. Patients 1 and 2 were given an additional dose of 2 mg of midazolam IV during treatment. Patient 3 did not request any sedating medication. During treatment, patient 2 received 2 mg of morphine intravenously.

Positron emission tomography image acquisition

For the reference group, a baseline value of intraprostatic blood flow was established using PET before the start of treatment and at 6 to 8 minutes, 21 to 22 minutes, 35 to 41 minutes, and 53 to 57 minutes into treatment. A baseline intraprostatic blood flow was established also for the four patients in the mepivacaine group. Thereafter, the intraprostatic injections were given. In patients 1 and 2, another baseline value was established after the injections but before the treatment started. In those patients, PET was performed 10 and 24 minutes after the start of treatment. To reduce wash-out of the drug, no second baseline was established for patient 3 and 4; PET examinations were made 7 and 17 minutes after start of treatment for these patients.

The patients were placed supine, and the prostatic region was positioned within the 15-cm axial field of view of the PET camera (ECAT HR+ PET scanner; Siemens) by means of a laser beam. The PET scanner provided 63 2.5-mm slices with a res-

olution of about 5.5 mm. A transmission scan was first generated by an external rotating ^{68}Ge rod to correct the resulting emission scans for attenuation. Following rapid delivery of an intravenous bolus of 1 GBq of ^{15}O H_2O , a 6-minute dynamic scanning sequence was started to allow blood-flow measurements. In each examination, data were collected during 29 time-frames which were prolonged during scanning and consisted of 18×5 , 2×5 , 2×15 , and 7×30 seconds.

Image reconstruction and interpretation

Dynamic images were reconstructed in a 128×128 matrix to permit a quantitative estimate of the radioactivity concentration. The images were reconstructed using filtered backprojection and were corrected for attenuation and scattered radiation. For each study, the radioactivity concentration in the prostate was plotted over time in order to determine the plateau phase of ^{15}O H_2O . On the basis of these time-activity curves, images obtained 0.5 to 6 minutes after ^{15}O H_2O injection were summed to create an average image. These average images were recalculated to provide images of standardized uptake values (SUV) whereby the radioactivity concentration (Bq/cc) was divided by the injected dose (GBq) per gram of body weight. Thus, given a density of 1.0 g/mL, this recalculation provides an estimate of the tracer accumulation related to a presumed even radioactivity distribution in the body as a whole, which corresponds to an SUV of 1.0.

In these images, for each patient, the largest axial area of the prostate was delineated as a region of interest (denoted ROIp) according to a standardized procedure, outlining an isocontour half-way between the area of the highest activity in the prostate and its immediate surroundings. For optimal correlation between studies, this delineation was performed on the PET study in which the radioactivity concentration in the prostate was highest. A second ROI was drawn on the last PET examination to outline the central low radioactivity region, if any, surrounding the treatment catheter (ROIc). A third ROI outlining

TABLE 2. TREATMENT TIME, MEAN POWER, NET ENERGY USED, AND INTRAPROSTATIC TEMPERATURE DEVELOPMENT

	<i>Treatment time (min)</i>	<i>Mean power (W)</i>	<i>Net energy (kJ)</i>	<i>Energy/prostate volume (kJ/cc)</i>	<i>Intraprostatic temperature (°C)</i>
Ref. 1	63	59.3	186.5	4.0	50 after 30 min; max 61.5
Ref. 2	61	70	220.6	6.3	50 after 43 min; max 52
Ref. 3	59	71.4	262.6	4.4	Max 49 at end of treatment
Mean	61	70	223	4.9	N/A
ME 1	30	45.9	80	1.4	50 after 10 min; max 60
ME 2	44	55.4	143	3.1	50 after 30 min; max 66.7
ME 3	23	32.7	45	0.5	50 after 5 min; max 61.1
ME 4	40	46.7	110	0.7	50 after 6 min; max 66.6
Mean	34	45.2	94.5	1.4	N/A

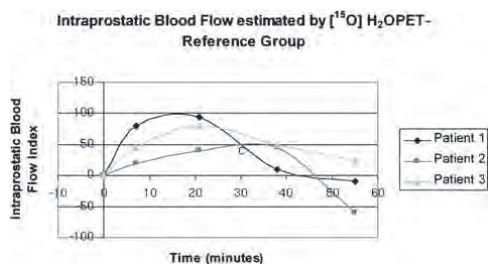


FIG. 1. Intraprostatic blood flow estimated by $[^{15}\text{O}]\text{H}_2\text{O}$ -PET for reference group.

the remaining doughnut-shaped prostatic area was denoted ROI_d. These three ROIs were transferred to all PET examinations of this patient, and the SUVs for all ROIs were recorded to estimate the blood flow in the various prostatic regions.

RESULTS

The mean treatment time for the reference group was 61 minutes compared with 34 minutes for the patients in the mepivacaine group (Table 2). For the patients in the reference group, an average microwave power of 70 W was used, while a mean of only 45 W was necessary for the mepivacaine patients. There was also a pronounced difference in the net energy used, 223 kJ for the reference group compared with 94.5 kJ for the mepivacaine group.

Reference group

Within the reference group, the blood-flow pattern during treatment was similar but at differing levels (Fig. 1). Typically, the blood flow increased rapidly and dramatically, 40% to 100%, within the first 25 to 30 minutes of the start of treatment. It then decreased almost to, or below, the baseline value by the end of the treatment. The treatment time was about 60 minutes in all cases.

Patient 1. After 27 minutes, the intraprostatic blood flow had increased by 40% compared with baseline, and it stayed at this level for about 15 minutes. At the end of the treatment, the blood flow had decreased to 60% of the baseline value.

Patient 2. The second patient had a pronounced increase in intraprostatic blood flow. After 14 minutes, the blood flow had

TABLE 3. INTRAPROSTATIC BLOOD FLOW INDEX (%) FOR PATIENTS RECEIVING MEPIVACAIN EPINEPHRINE

Patient	2 nd baseline	Time 1 (min)	Time 2 (min)
1	-63	+22 (10)	+25 (24)
2	-31	+94 (10)	+100 (24)
3	N/A	+21 (7)	-2 (17)
4	N/A	-73 (7)	-34 (17)

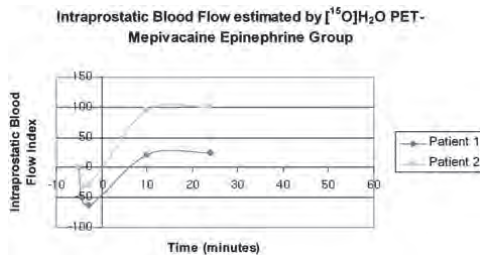


FIG. 2. Intraprostatic blood flow estimated by $[^{15}\text{O}]\text{H}_2\text{O}$ -PET for patients 1 and 2 in mepivacaine epinephrine group.

increased by 80%, and 28 minutes into the treatment, the increase was 100% compared with the baseline value. At the end of treatment, the blood flow was slightly below baseline.

Patient 3. The increase in intraprostatic blood flow was 40% after 13 minutes and 80% after 26 minutes. Contrary to the findings in the other patients, the blood flow did not decrease below the baseline value at the end of treatment; after 60 minutes, the blood flow was still 30% above baseline.

Patients receiving mepivacaine epinephrine

The situation was different in the patients who received intraprostatic injections of mepivacaine epinephrine (Table 3). In patients 1 and 2, the blood flow decreased after administration of mepivacaine. During treatment, there was a slight increase in blood flow in patient 1 and a more pronounced increase for patient 2. In patient 3, the blood flow during treatment was around the baseline value, while it decreased in patient 4. The treatment time ranged from 23 and 44 minutes.

Patient 1. The intraprostatic blood flow decreased about 60% after the intraprostatic injection of mepivacaine. At 10 and 24 minutes into treatment, the blood flow was slightly above baseline (about 20%) (Fig. 2).

Patient 2. The second patient also had a decrease in intraprostatic blood flow after the mepivacaine injection, although it was not as pronounced as in patient 1. During treatment, the intraprostatic blood flow was considerably higher (about 100%) than at baseline at both times (10 and 24 minutes) (Fig. 2).

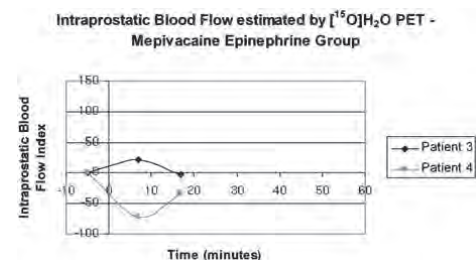


FIG. 3. Intraprostatic blood flow estimated by $[^{15}\text{O}]\text{H}_2\text{O}$ -PET for patients 3 and 4 in mepivacaine epinephrine group.

Patient 3. Initially (7 minutes), the intraprostatic blood flow in this patient was slightly above the baseline, 21%. It decreased to about the baseline values later during the treatment (17 minutes) (Fig. 3).

Patient 4. The intraprostatic blood flow was considerably below the baseline value in this patient when both PET scans were made. After 7 minutes, the blood flow was more than 70% below the baseline and at 17 minutes more than 30% below (Fig. 3).

DISCUSSION

The outcome of TUMT has improved as a result of the development of the technique from low-energy devices to the high-energy devices that are used today.^{1,3} In our clinic, PLFT has been a first-line option for the treatment of medium to severe BPH since 1996, with good results. During PLFT, the variations in intraprostatic blood flow between patients are generally extensive. Also, a twofold increase for the same patient during treatment is regularly experienced. This pronounced increase regularly starts about 6 to 8 minutes into the treatment session and lasts for 30 to 40 minutes, after which, the blood flow successively decreases and the intraprostatic temperature rises.

These observations are confirmed by the blood-flow measurements using PET with [¹⁵O]H₂O in the patients in the reference group in this study. The decrease that follows the initial rise in intraprostatic blood flow is probably related to the development of edema and microthrombosis as a result of heat-induced tissue damage. However, we have also observed that in approximately 15% of patients, the blood flow, as calculated by the device, increases to a level that prevents therapeutic temperatures from being established during the session, leading to suboptimal outcomes.

When injections of mepivacaine epinephrine were given prior to PLFT, the blood flow pattern was different for three of the four patients examined. The exception was patient 2, in whom the drug could not be properly administered for technical reasons, which may explain why the blood-flow pattern coincided with that of the reference group. The other three patients had a low to intermediate intraprostatic blood flow at the start of treatment. The increase in blood flow usually seen after 6 to 8 minutes was eliminated, and the temperature instead increased rapidly to therapeutic values. After 5 to 10 minutes, temperatures >50°C were achieved, whereas this required more than 30 minutes in the reference group. The tissue necrosis started after 8 to 12 minutes compared with 35 to 45 minutes without mepivacaine epinephrine injections. Also, treatment time, energy consumption, and mean power were significantly lower than in the reference group. The difference between the study groups is further emphasized when considering the energy used for ablation of each gram of the prostate: 4.9 kJ/g for the reference group compared with 1.4 kJ/g for the mepivacaine group.

According to previous experience,¹¹ the intraprostatic blood flow was reduced more than 50% as calculated by the PLFT software in 15 consecutive patients who were given mepivacaine prior to PLFT compared with a reference group of 35 pa-

tients treated with PLFT without mepivacaine. Also, the results of this study suggest that intraprostatic injections of mepivacaine epinephrine lead to a decrease in the intraprostatic blood flow during microwave thermotherapy.

CONCLUSION

The results of this study further support the hypothesis that intraprostatic injection of mepivacaine epinephrine causes a reduction of intraprostatic blood flow during PLFT. On the basis of these results and observations of improved patient comfort, intraprostatic injections of mepivacaine epinephrine prior to PLFT are now routine in our clinic. A fully astringent effect of intraprostatic injections of mepivacaine seems to remain for 15 to 20 minutes, after which it declines. It is therefore important that the treatment start as soon as possible after the injections. This idea is supported by the higher prostatic blood flow seen during treatment in the two patients in whom the start of PLFT was delayed by the PET examination.

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Address reprint requests to:

Sonny Schelin

Skeppsbrogatan 47

SE-392 31 Kalmar, Sweden

E-mail: sonny.schelin@telia.com