THE PREDICTION OF CLINICAL OUTCOME FROM TRANSURETHRAL MICROWAVE THERMOTHERAPY BY PRESSURE-FLOW ANALYSIS: A EUROPEAN MULTICENTER STUDY

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ABSTRACT

A total of 100 patients treated with a single session of microwave thermotherapy at 4 European centers was stratified according to 2 different types of obstruction (constrictive and compressive) and compared to clinical outcome at 6 months. Patients had a Madsen-Iversen score of 8 or more, maximum flow rate of 15 ml. per second or less and residual urine volume of 300 ml. or less at entry. The change in Madsen-Iversen score was the same in the 2 groups. Maximum flow rate increased from 8.71 ± 2.62 to 14.78 ± 4.04 ml. per second in the constrictive group, and from 8.54 ± 2.26 to 10.41 ± 4.52 in the compressive group (p ≤0.0001). Residual urine decreased from 96.00 ± 72.85 to 40.34 ± 56.33 ml. in the constrictive group and from 109.86 ± 67.09 to 84.65 ± 81.45 ml. in the compressive group (p ≤0.0001). Success, as defined by an increase of 50% or more in maximum flow rate and Madsen-Iversen score, was noted in 68% of the constrictive but only 15% of the compressive groups (p ≤0.0001 chi-square test for trend). Selection by pressure-flow criteria for patients being considered for thermotherapy should improve the overall clinical results.

KEY WORDS: prostate hypertrophy, thermotherapy, urodynamics

Transurethral microwave thermotherapy is a minimally invasive treatment for benign prostatic obstruction.1-3 Therapeutic levels of heating are obtained deep inside the prostatic lateral lobes while preserving the urethral mucosa by application of 1.296 MHz. microwave radiation from a transurethral antenna simultaneously cooled by circulating fluid within the applicator. It is presumed that clinical benefit is achieved by a small decrease in adenoma volume and the destruction of certain specific cell types that have some role in the development of bladder outflow obstruction. A significant decrease in benign prostatic hyperplasia (BPH) related symptoms, and an increase in maximum and average flow rates have been found in phase II studies worldwide.1-4 The clinical improvement has been shown not to be due to a placebo effect or to be the result of the associated urethral instrumentation in randomized trials of transurethral microwave thermotherapy against sham therapy.5,6 However, the criteria currently used for inclusion do not prevent a high variability in terms of clinical response to microwave thermotherapy so that treatment outcome is difficult to forecast in the individual patient.

The heterogeneity of symptoms and objective parameters in patients with BPH is well known.7 Even more confusing is the differing patterns of obstruction as shown by pressure-flow studies.8,9 Invasive urodynamic studies have been used to investigate the pathophysiology of benign prostatic disease and to evaluate clinical outcome of various treatment modalities but contradictory data exist as to the possibility of predicting the outcome of treatment by voiding urodynamic studies.10-12 Plotting the pressure and flow values obtained during voiding urodynamic studies produces a hysteresis curve that describes the unique urethral resistance relationship of voiding for an individual.8 To simplify the complex hysteresis plot only the second part of the curve (from maximal flow to the end of micturition) is considered and described by an approximated parabolic curve, which is known as the passive urethral resistance relation.9 To avoid the need for digital data processing the hysteresis plot can be approximated by a linear approach.13 The slope of the linear passive urethral resistance relation is calculated by the formula (detrusor pressure at maximum flow − minimum detrusor pressure during flow)/maximum flow rate. The various combinations of slope and minimum detrusor pressure during flow provide the specific types of obstruction characterizing difficulty in opening the urethra (compressive obstruction) and decreasing elasticity of the urethra (constrictive obstruction).9,14,15 Patients with symptomatic BPH always have both elements although one or the other will predominate.16 In a previous series detrusor pressures required during voiding were slightly decreased by transurethral microwave thermotherapy but simple indicators of urethral resistance were decreased.17,18 More complex analysis of the passive urethral resistance shows that there is a decrease in slope but not of the “footpoint” (minimum detrusor pressure during flow) of the pressure-flow curve.19,20 No single simple parameter from the urodynamic study has been shown to predict the outcome of treatment. Preliminary analysis of our group suggested a correlation between urodynamic criteria at entry and clinical outcome of transurethral microwave thermotherapy.21 Therefore, a retrospective analysis was planned on 100 patients undergoing transurethral microwave thermotherapy for BPH at 4 European centers to evaluate any predictive parameters that might identify the patients who respond best to microwave thermotherapy.

MATERIALS AND METHODS

Data from 100 patients treated at 4 European centers were collected. Each center submitted data from consecutive patients in whom a pressure-flow study was included in the pretreatment assessment and for whom complete followup data were available at 6 months. All patients were screened, treated and followed according to a common protocol. Inclusion criteria consisted of candidates for transurethral resection of the prostate, patient age 45 years or older, bilobar

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prostatic hypertrophy, anesthesia risk group 1 to 3 according to the American Society of Anesthesiology, symptoms of prostatism for more than 3 months, Madsen-Iversen score of 8 or more, peak flow rate of 15 ml. per second or less and residual urine volume of 300 ml. or less. Patients were excluded if they had carcinoma of the prostate, bladder neoplasm, a neurological disorder that may affect bladder function, disorders of hemostasis, total hip replacements or other pelvic metallic implant, diabetic neuropathy, a cardiac pacemaker, bladder stones, a history of prostatic surgery or rectal surgery other than hemorrhoidectomy, chronic renal failure due to BPH, urethral stricture, evidence of urinary tract infection or a prostate shorter than 35 mm. in longitudinal diameter. Baseline evaluation consisted of patient history, including Madsen-Iversen symptom score, physical examination, hematology and blood chemistry studies (including prostate specific antigen), urinalysis, urinary tract imaging, prostate ultrasonography, flexible cystoscopy, free average prostate specific antigen), urinalysis, urinary tract imaging, prostate ultrasonography, flexible cystoscopy, free average and peak flow rates (corrected for artifacts during a 2-second period), residual urine (measured by suprapubic sonography) and pressure-flow study. Urodynamic investigations were performed according to International Continence Society guidelines, although there were minor differences in equipment and technique used at each site.

Treatment was done on an ambulatory basis without use of anesthesia. The operating software for this series of patients provided a 60-minute treatment with a maximum power output of 60 watts and a total possible power deposition of 197 kj. The treatment has been described in more detail previously. In this series the C10 catheter (with the microwave applicator located 10 mm. below the Foley balloon) was used in all patients. For the purposes of defining clinical outcome 6-month followup data were analyzed for changes in symptom score evaluation, uroflowmetry and residual urine.

Hard copies of the pressure-flow tracings were analyzed in a blind fashion by 2 separate investigators. A 1-second delay was used to calculate the detrusor pressure at various points of the flow curve. For each patient the parameters derived were minimum detrusor pressure during flow and detrusor pressure at maximum flow. Artifactual data in pressure and flow measurements were corrected when required (see figure). The 2 tracings from each individual patient were compared and, in the absence of gross technical artifacts, the lowest detrusor pressure regimen was considered to be more representative of mechanical BPH obstruction (the obstructive condition). For each patient the linear passive urethral resistance relation was calculated.

The relative proportions of success and failure of microwave thermotherapy were evaluated by percentage improve-
ment in objective and subjective parameters. The number and percentages of patients improving by 75% or more, 50% or more, or 25% or less were analyzed. The hypothesis of significant differences between parameters before and after transurethral microwave thermotherapy was tested by nonparametric means. Differences between baseline or posttreatment values in constrictive and compressive groups were evaluated by nonparametric tests. The relationship between subjective/objective parameters and clinical outcome was evaluated by Spearman's correlation coefficient. Significance of the increasing proportion of therapy success in the constrictive versus compressive groups was tested by the chi-square test for trend. Statistical analysis was done by computer.

RESULTS

The overall clinical results in terms of Madsen-Iversen symptom score, peak and average flow rates, voided volume and residual urine at 6 months are summarized in table 1. Analysis of symptoms by Madsen-Iversen symptom score showed a mean decrease of 61.8% after treatment. Peak and average flow rates increased by 35.0% and 28.3%, respectively. Evaluation of the residual urine showed a mean decrease of 32.16%. All changes were highly statistically significant. No significant variation in voided volume occurred after treatment. Stratification of patients according to single subjective and objective parameters (peak and average flow rates, voided volume, residual urine, minimum urethral opening pressure, maximum flow rate during pressure-flow study and slope) did not show any strong correlation with clinical outcome using Spearman's correlation coefficients.

Two groups of patients were identified by a 2-parameter discriminant factor (minimum urethral opening pressure and slope), defining predominantly constrictive (defined by a 5 cm. water or less and a slope of 2.5 or more) or compressive obstruction (defined by a minimum urethral opening pressure of 45 cm. water or more and/or a slope value of less than 2.5), otherwise comparable before treatment but having a significantly different outcome (table 2). Madsen-Iversen score was similarly altered in each group, although there was a trend toward a slightly greater improvement in patients with constrictive obstruction. Significantly greater changes in peak and average flow rates were noted in the constrictive obstruction group. Voided volume remained unchanged for each group but residual urine was significantly less after treatment in the constrictive group.

Analysis of clinical outcome by highly selective criteria that include a percentage improvement in Madsen-Iversen symptom score and peak flow rate resulted in a large proportion of successful cases in the constrictive group and in a significant percentage of failures in the compressive group (table 3). Stratification of patients treated at each of the 4 sites for type of obstruction and outcome after transurethral microwave thermotherapy produces comparable results (data not shown), suggesting that the use of slightly different techniques and equipment for the pressure-flow study did not affect the reliability of the test.

DISCUSSION

The great variety of therapies currently available for symptomatic BPH demands that the physician must make a choice for treatment in each individual patient. Previously, almost every patient with the combination of prostatic symptoms, demonstrable benign prostatic enlargement and low urinary flow rates could be treated by transurethral resection of the prostate with a high expectation of success. Sophisticated investigation for treatment selection was not required. However, the alternative treatments currently available do not
TABLE 1. Parameters of BPH severity before and after microwave thermotherapy

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Baseline*</th>
<th>6 Mos.*</th>
<th>Difference*</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madsen-Iversen score</td>
<td>100</td>
<td>14.18 ± 3.75</td>
<td>5.45 ± 4.85</td>
<td>-8.75 ± 0.55</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Maximum flow rate (ml/sec.)</td>
<td>100</td>
<td>8.59 ± 2.36</td>
<td>11.6 ± 4.79</td>
<td>3.07 ± 0.45</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Av. flow rate (ml/sec.)</td>
<td>100</td>
<td>4.69 ± 1.47</td>
<td>5.90 ± 2.33</td>
<td>1.30 ± 0.26</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Voided vol. (ml.)</td>
<td>100</td>
<td>247.34 ± 95.27</td>
<td>202.65 ± 98.81</td>
<td>5.21 ± 11.4</td>
<td>≤0.6498</td>
</tr>
<tr>
<td>Residual urine (ml.)</td>
<td>100</td>
<td>105.84 ± 95.73</td>
<td>71.80 ± 77.43</td>
<td>-24.04 ± 8.98</td>
<td>≤0.0002</td>
</tr>
</tbody>
</table>

* Mean plus or minus standard deviation.
† Wilcoxon matched-pairs signed rank test.

Total No. pts. | 29 | 71 | 100

% Increase in Madsen-Iversen score and maximum flow rate:
- 75 or more | 12 (41.38) | 5 (7.04) | 17
- 50 or more | 19 (66.62) | 11 (15.49) | 30
- Less than 50 | 10 (34.48) | 60 (84.50) | 70
- 25 or less | 5 (17.24) | 50 (70.42) | 55

% Increase in maximum flow rate (ml/sec.):
- 3 or more | 25 (86.2) | 6 (8.4) | 31
- Less than 3 | 4 (13.8) | 65 (91.6) | 89

Chi-square test for trend, p ≤0.001. Categories are not mutually exclusive.

TABLE 2. Symptoms and signs of BPH severity evaluated at baseline and 6 months after microwave thermotherapy

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Baseline</th>
<th>6 Mos.</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in Madsen-Iversen symptom score</td>
<td>4.72 ± 1.55</td>
<td>5.21 ± 2.06</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Increase in maximum flow rate (ml/sec.)</td>
<td>8.55 ± 4.62</td>
<td>4.72 ± 1.55</td>
<td>≤0.0004</td>
</tr>
<tr>
<td>Voided volume (ml.)</td>
<td>244.38 ± 96.34</td>
<td>297.21 ± 98.81</td>
<td>Not significant</td>
</tr>
<tr>
<td>Residual urine (ml.)</td>
<td>105.84 ± 95.73</td>
<td>71.80 ± 77.43</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

† Wilcoxon rank sum W test.

TABLE 3. Relative proportions of success and failure in constrictive and compressive groups

<table>
<thead>
<tr>
<th>Increase</th>
<th>No. of Obstruction (%)</th>
<th>Total No.</th>
<th>Constrictive</th>
<th>Compressive</th>
</tr>
</thead>
</table>
| % Increase in Madsen-Iversen score and maximum flow rate:
- 75 or more | 12 (41.38) | 5 (7.04) | 17
- 50 or more | 19 (66.62) | 11 (15.49) | 30
- Less than 50 | 10 (34.48) | 60 (84.50) | 70
- 25 or less | 5 (17.24) | 50 (70.42) | 55

Chi-square test for trend, p ≤0.001. Categories are not mutually exclusive.

Elasticity of the bladder neck and prostatic urethra, and the needed opening pressure are the 2 major factors that affect voiding in men with BPH. Two specific types of obstruction, according to the grade and type of urethral resistance (relative weight of urethral disorders), have been described by Schäfer.9 Compressive obstruction is characterized by difficulty in opening the urethra during voiding. After urinary flow is initiated a maximum rate can be reached with little pressure increase. Therefore, the pressure-flow study is characterized by a high minimum urethral opening pressure value and low slope value of less than 2.5. Constrictive obstruction (the archetype being a urethral stricture) is characterized by decreased elasticity at the level of the prostatic urethra. Urinary flow can be induced with a low pressure but a significant increase in detrusor pressure is observed during the passage from minimal to maximal urinary flow rate. The pressure-flow study is, therefore, characterized by a fairly normal minimum urethral opening pressure value and a high slope of 2.5 or more. BPH patients are always characterized by the presence of both types of obstruction but in some the constrictive obstruction may be predominant.16

In our study patients were divided into 2 groups having either predominantly constrictive (29, or 29%) or compressive (71, or 71%) obstruction. It was impossible to distinguish between these 2 groups by the simple evaluation of symptoms, uroflowmetry or ultrasound assessment. After transurethral microwave thermotherapy symptoms as graded by the Madsen-Iversen scoring system were equally improved in both groups. However, the results of treatment in both groups were significantly different in terms of the achieved urinary flow rates and decrease in residual urine. In the patients with predominantly constrictive obstruction the
mean increase in peak flow rate was 69% as opposed to 22% for those with mainly compressive obstruction. The mean peak flow rate achieved was 14.7 ml per second, which is not too dissimilar to many series on transurethral resection of the prostate.26 Similar changes were noted for the average flow rate with no difference in the voided volume, indicating an overall shorter flow time. Residual volume in the constrictive group was significantly more improved and decreased to a mean of 40 ml, which is also close to normal for men of this age.

Response rates to new treatments for symptomatic BPH have recently been proposed in an article by Holtgrewe outlining the regulatory affairs process for devices being submitted to the Food and Drug Administration.23 Graded categories of response using greater than 75%, 50% and less than 25% change in symptoms and/or flow rate have been suggested. In this study the proportion of patients with a successful outcome as defined by an improvement of more than 75% in flow rate and symptom score is 41% for the constrictive group and only 7% for the compressive group. In the former group 65% of the patients had greater than a 50% response in both parameters. In terms of patients with a poor response, 70% with compressive obstruction had less than a 25% change in either or both categories. To facilitate comparison with success data in recent studies on BPH, patients with an increase in peak flow rate of 3 ml per second or more were evaluated.26 Of these patients 86% were from the constrictive group and 91% of those who failed to obtain an increase of this magnitude were from the compressive group. The division of patients into predominantly constrictive and compressive obstruction groups enables selection of those who will have a successful outcome.

It is important to note that the determination of the type of obstruction in an individual patient need not be particularly onerous or costly, nor need it be done with complex equipment. There was no evidence of variability in the accuracy of the test among sites. In particular, it is of note that calculation of the minimum urethral opening pressure and the relative slope was based on differential pressure values (that is, the numerator of the slope formula is given by detrusor pressure at maximum flow rate — minimum urethral opening pressure). Differential pressure values are less dependent on the technique used for recording the pressure-flow relationship than are absolute values. The investigation of voiding pressure studies may be considerably simplified to obtain the data used in our analysis, and additionally there is no need for a sophisticated computer analysis program to calculate the values of the linear passive urethral resistance relation for allocating patients to constrictive or compressive categories. In our experience this type of analysis may be done at any urodynamic laboratory when pressure-flow tracings are evaluated for report with no significant increase in urologist work load.

CONCLUSIONS

To date pressure-flow studies have been used as a research tool to investigate the effect of different treatment modalities on BPH. The results of our analysis support the decision of the American Urological Association to include pressure-flow study in the evaluation process of any new treatment.23 In the future, as different clinical syndromes are recognized in patients with BPH, pressure-flow studies are likely to have a major role in decision making between therapeutic alternatives with different impacts on the disease. Our results strongly suggest that transurethral microwave thermotherapy should be offered to BPH patients with obstruction of the constrictive type, with transurethral resection of the prostate reserved for those with compressive bladder outlet obstruction. There have been suggestions in the literature that patients who do not fare well after transurethral resection of the prostate have the noncompressive type of obstruction.10 Although this concept remains to be tested fully, the intriguing prospect of using urodynamic studies to select patients for in situ heating and transurethral resection of the prostate with improvement in the results of both treatments is raised.

REFERENCES


