VARIABILITY OF PRESSURE-FLOW ANALYSIS PARAMETERS IN REPEATED CYSTOMETRY IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

PETER F. W. M. ROSIER, JEAN J. M. C. H. DE LA ROSETTE, EVERT L. KOLDEWIJN, FRANS M. J. DEBRUYNE AND HESSEL WIJKSTRA

From the Department of Urology, University Hospital Nijmegen, Nijmegen, The Netherlands

ABSTRACT

Urodynamic investigation becomes increasingly important in the diagnosis of bladder outflow obstruction in patients with benign prostatic hyperplasia. To date, different methods for evaluation of the pressure-flow relationship and quantification of the grade of obstruction are available. Models for pressure-flow analysis are briefly explained.

The variability of the parameters is investigated by evaluation of 75 patients in whom 2 sequential voidings during urodynamic investigation were analyzed. The results showed that in 87% of these patients individual flow differences of first and second voidings were less than 2 ml per second. Individual detrusor pressure at maximum flow differences were less than 15 cm. water in 80% of these patients, while in 80% the intra-individual variation of the pressure-flow results was less than 15 cm. water for the minimal voiding pressure parameters (minimal urethral opening detrusor pressure and urethral resistance factor). For the pressure-flow parameter that defines the theoretical urethral lumen during voiding, the variation was less than 1.5 mm.2 in 84% of the patients. Patients with larger intra-individual differences are discussed. We concluded that the observed, aforementioned differences can be regarded as an indication of normal intra-individual variability of voiding during urodynamic investigation. This intra-individual variability, however, seldom leads to a change in the clinical grade of bladder outflow obstruction. We conclude that investigators involved in therapeutic trials of benign prostatic hyperplasia must be aware of this intra-individual variability of micturition, since this variability is greater than the refined scale of the pressure-flow analysis models.

KEY WORDS: urodynamics, prostatic hypertrophy, prostatic diseases

Urodynamic investigation is the gold standard to quantify the grade of bladder outlet obstruction in elderly men with voiding symptoms.1,2 Precise grading of obstruction is becoming increasingly important in the evaluation and comparison of new therapeutic options in the treatment of benign prostatic hyperplasia (BPH).3,4 Furthermore, stratification of therapeutic options based on the individual grade of obstruction may become available.

Symptoms, prostate size, free uroflowmetry parameters and the amount of post-void residual urine are associated with obstructive voiding but the correlation with the grade of obstruction is weak.5-7 Only by means of pressure-flow analysis can a precise quantification of the grade of obstruction be achieved.1,4 It is not yet established whether a precise grading of obstruction is always clinically relevant but, for investigational purposes, it is mandatory to perform an accurate evaluation of the voiding and to report (changes in) grade of obstruction on a continuous scale.4 To our knowledge the physiological variability of the resulting parameters has not been described to date, which makes clinical but also basic research with these parameters difficult to evaluate. We studied the variability in sequential voidings of patients with BPH. The differences between 2 voidings were compared on a clinical scale, the linearized passive urethral resistance relation, of which it has been stated that the classes represent clinically relevant groups.8 The aforementioned increased clinical importance of quantification of obstruction in BPH patients makes it useful to introduce some pressure-flow analysis parameters.

Pressure-flow analysis parameters. The pressure-flow relationship during voiding can be analyzed on an X-Y graph of subtracted bladder pressure and synchronous flow, that is a pressure-flow graph. The pressure is projected on the Y-axis and flow on the X-axis.10 The pressure-flow graph near the Y-axis (fig. 1, A), indicating a high pressure and generating a low flow, is the result of more obstructive voiding than the graph near the X-axis (fig. 1, B) which shows a lower subtracted bladder pressure in relation to a higher flow. Visual evaluation of a pressure-flow graph allows a rough estimation of the grade of obstruction but, for objective and quantitative definition of the pressure-flow relationship, more exact analysis methods are available. Based on the concept of distensible and collapsible tube hydrodynamics, it was shown that a traditional resistance parameter, such as maximum subtracted bladder pressure divided by flow squared, was misleading.11 Such a parameter does not take in account the balance between detrusor function and bladder outlet throughout the entire voiding cycle and disregards the collapsible aspect of the urethra.11,12 The parameters resulting from 2 different pressure-flow analysis methods, both based on the distensible and collapsible tube hydrodynamics concept, will be explained. A third method of pressure-flow analysis, additionally providing an estimation of urethral elasticity13 and known as the 3-parameter model, is not included in this article.

Method 1 is called the passive urethral resistance relation analysis.14 With this analysis, a quadratic curve, the passive urethral resistance relation curve, is fitted to the lowest pressure part of the pressure-flow graph, which is normally the phase of voiding subsequent to maximum flow. Maximum flow with corresponding subtracted bladder pressure normally represents the first moment of maximal distension and is seen as the top of the subtracted bladder pressure-flow
Fig. 1. A, pressure-flow graph shows obstructed voiding with high pressure ($P_{\text{detr}}$) and low flow. B, less obstructed voiding. Flow is higher with lower subtracted bladder pressure.

The passive urethral resistance relation parameter of minimal urethral opening detrusor pressure during voiding is observed at the end of voiding. Minimal urethral opening detrusor pressure is the minimal subtracted bladder pressure that makes flow possible.

Minimal urethral opening detrusor pressure must not be confused with the (detrusor) opening pressure at the onset of measured flow. At the start of voiding the balance between neurogenic and myogenic (bladder, urethra and pelvic floor) activity is too unstable to be reliable for analysis of bladder outlet obstruction. When the passive urethral resistance relation curve is fitted, the theoretical area of the urethra is computed from the “slope” of the curve to the pressure axis. A steep curve with a small angle to the pressure axis (thus a small theoretical urethral area) reflects a narrow urethral cross-sectional area. Patients with obstruction usually have a theoretical urethral area of less than plus or minus 2.5 mm.$^2$, while those without prostatic obstruction frequently have a theoretical urethral area of more than plus or minus 5 mm.$^2$ (fig. 3). However, patients can have obstruction despite a large theoretical urethral area.$^{16}$

The second method of pressure-flow analysis results in a resistance factor. In a group of patients examined by pressure-flow analysis, the investigators found a statistical correlation of theoretical urethral area and minimal urethral opening detrusor pressure in those with BPH and infravesical outlet obstruction.$^{17}$ This correlation was used to decrease both parameters to 1 resistance factor, which was named the urethral resistance factor. Based on the average shape of the passive urethral resistance relation in BPH patients, the urethral resistance factor quantifies obstruction by computing a preset curve, with a fixed minimal urethral opening detrusor pressure-to-theoretical urethral area ratio, through subtracted bladder pressure at maximum flow. Figure 3 shows both graphs of figure 1, fitted with a passive urethral resistance relation and a urethral resistance factor curve.

**PATIENTS AND METHODS**

From November 1992 to April 1993, 91 patients (mean age 63.6 years, range 42 to 83) underwent 2 filling and voiding sessions during a single urodynamic investigation. Of these patients 8 could not produce any flow during 1 of the 2 intended voidings (6 times during the first attempt): in 7 the transurethral (pressure recording) catheter slipped out (5 times during the initial voiding) and 1 lost the rectal catheter during both voidings. The remaining 75 investigations were used for this analysis. To cover all grades of obstruction, we included a mixed group of 62 untreated BPH patients (3 of whom were investigated again after 6 months of expectant
RESULTS

Mean first sensation, strong desire, and end filling volume and pressure did not show significant differences between the 2 investigations (table 1). Individual differences in voided volumes were slight. Of all patients only 5 (7%) exceeded a difference of 100 ml. in voided volume. In 53 patients (71%) the difference in both voided volumes was less than 50 ml.

Table 2 shows the mean differences in the pressure and flow parameters. Group mean maximum flow rates for both voidings were 7.4 ml. per second and 7.6 ml. per second, respectively. The percentages of patients with a higher or a lower result during the second voiding are shown. A total of 40 patients (53%) had a higher secondary maximum flow rate. The difference in mean maximum flow did not reach statistical significance but a significant number of patients (36%) voided with a lower subtracted bladder pressure at maximum flow rate the second time.

When theoretical urethral area and urethral resistance factor were regarded, a statistically significant number of patients had improved voiding the second time. In 49 patients (65%) theoretical urethral area was larger and in (not the same) 49 urethral resistance factor was lower during the second voiding. Table 3 shows the mean individual absolute differences, that is the positive difference resulting from the subtraction of both voidings. The mean absolute difference in maximum flow rate between 2 voidings was 1.2 ± 1.4 ml. per second (standard deviation). Values of extreme and large

<table>
<thead>
<tr>
<th>Table 1. Parameters of filling phase in 75 studies</th>
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<tr>
<td><strong>Parameter</strong></td>
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<tr>
<td><strong>First sensation of filling</strong></td>
</tr>
<tr>
<td>Subtracted bladder pressure (cm. water) Vol. (ml.)</td>
</tr>
<tr>
<td>Subtracted bladder pressure (cm. water) Vol. (ml.)</td>
</tr>
<tr>
<td>Strong desire to void:</td>
</tr>
<tr>
<td>Subtracted bladder pressure (cm. water) Vol. (ml.)</td>
</tr>
<tr>
<td>End of filling (capacity):</td>
</tr>
<tr>
<td>Subtracted bladder pressure (cm. water) Vol. (ml.)</td>
</tr>
<tr>
<td>Vol. (ml.)</td>
</tr>
<tr>
<td>Residual urine (ml.)</td>
</tr>
<tr>
<td>Voided volume (ml.)</td>
</tr>
<tr>
<td>Residual urine (ml.)</td>
</tr>
</tbody>
</table>

*a Wilcoxon test on differences of first and second fillings.
differences are shown in this table, as well as the number of patients exceeding these differences. In 10 patients (13%) the difference in maximum flow rate between both voidings was more than 2.0 ml. per second and in 7 the second flow was better (fig. 4).

In 2 patients we observed large differences in maximum flow rate and subtracted bladder pressure at maximum flow rate. One of these patients had a large secondary detrusor pressure increase and 1 had significant instability in the filling phase and imperative voiding during the initial cystometry study. Five patients with large urethral resistance factor differences had large differences in subtracted bladder pressure maximum flow rate (4) or maximum flow rate (1). In 5 patients minimal urethral opening detrusor pressure and urethral resistance factor values showed large differences. Large theoretical urethral area differences were related to large maximum flow rate differences in 50% of 12 patients.

Fitting of the passive urethral resistance relation or urethral resistance factor curve of 1 or 2 investigations was hampered in 15 patients by the occurrence of a secondary detrusor pressure increase just before the end of voiding or because of excessive straining, especially at the end of voiding. When we performed the statistical analysis without these patients the (mean) results remained unchanged. Exclusion of 9 patients with a maximum flow rate of more than 13 ml. per second also did not influence the mean results as mentioned in the tables. For 12 patients this was not the first urodynamic investigation and their exclusion did not influence the overall results.

Analysis of the pressure-flow relationship on the clinical nomogram showed that 32% of the cases could be classified as (nearly) not obstructed, 48% as moderately obstructed and 20% as severely obstructed. Of the 10 patients with large maximum flow rate differences 60% were classified as with obstruction (fig. 4). A better secondary voiding was noted in 63% of the patients. For a small group of 12 patients this was the second urodynamic investigation. On average, these patients did not show the tendency to improve the second voiding.

**DISCUSSION**

We discuss the variability of pressure-flow relationship parameters in sequential voiding during urodynamic investigation of a group of BPH patients. Analysis of this variability provides insight into the clinical relevance of observed or reported differences. When the therapeutic choice is limited to surgery or watchful waiting, the value of an “obstructed or not” diagnosis is recognized. The clinical nomogram, with 7 classes of obstruction, is more detailed than an obstructed or not diagnosis. Pressure-flow analysis can provide a continuous scale of obstruction and, therefore, it is even more refined.

We compared the intra-individual variability of the results on a continuous scale with the classes of the clinical nomogram. We found that the individual differences in 2 sequential voidings were greater than 1 class of this nomogram in less than 20% of the patients. Large differences were mainly found in the patients without infravesical obstruction or with severe obstruction. In these classes there is a less differentiated choice of treatment than in the moderately obstructed classes so that the observed larger differences were of lesser clinical relevance.

Severe unstable contractions in the filling phase influenced voiding, sometimes resulting in large maximum flow rate differences. Some indications about variability of voiding may be found in the literature. In a home (free) uroflowmetry study, the variability of maximum flow rate in repeated voidings is reported to have a standard deviation of 5.7 ml per second in a group of BPH patients with a mean maximum flow rate of 9.3 ml. per second. As in our study, the reported variability of maximum flow rate was larger in the nonobstruction group (mean 21.2 ± 7.3 ml. per second).

Two recent intervention studies showed group mean changes of subtracted bladder pressure at maximum flow rate of −3 cm. water (27 patients, urodynamic investigation with a single voiding) and −5 cm. water (17 patients, repeated voiding during urodynamic investigation), respectively, after use of placebo for 24 weeks. The group mean change in the 5a-reductase treated group from the first study was −40 cm. water. In the leuprolide treated patients (the second study) the mean change was −13.7 cm. water. Mean improvement in symptom score in both treated groups compared to placebo was not significant. The articles do not discuss the limits of the individual differences in these patients but it could be interesting to compare the urodynamic results of symptomatic responders with symptomatic nonresponders. The group mean results of the second study, however, may have reflected the effect of normal variability in the majority of the patients.

In our study the mean of the individual differences of the observed minimal voiding pressure (minimal urethral opening detrusor pressure) and the estimated minimal voiding pressure (urethral resistance factor) was less than 10 cm. water (table 2, 36.6 and 44.2 cm. water, respectively). This

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**Table 2. Mean results of pressure-flow analysis of sequential cystometry in 75 studies**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Wilcoxon p Value</th>
<th>% Second Voiding</th>
</tr>
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<tbody>
<tr>
<td>Maximum flow (ml/sec.)</td>
<td>7.36 ± 3.83</td>
<td>0.1450</td>
<td>53.3 45.3</td>
</tr>
<tr>
<td>Maximum flow with corresponding subtracted bladder pressure (cm. water)</td>
<td>74.4 ± 29.7</td>
<td>0.0810</td>
<td>62.6 56.0*</td>
</tr>
<tr>
<td>Minimal urethral opening pressure (cm. water)</td>
<td>36.6 ± 13.2</td>
<td>0.0039</td>
<td>44.0 56.0</td>
</tr>
<tr>
<td>Theoretical urethral area (mm.³)</td>
<td>3.07 ± 1.97</td>
<td>0.0039</td>
<td>34.0 65.3*</td>
</tr>
<tr>
<td>Urethral resistance factor (cm. water)</td>
<td>44.2 ± 19.8</td>
<td>0.0036</td>
<td>34.0 65.3*</td>
</tr>
</tbody>
</table>

* Significant difference.

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**Table 3. Mean individual absolute differences of urodynamic results, number of patients with statistically extreme differences, number of patients with clinically large differences and number of patients with small differences**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Difference ± SD</th>
<th>Extreme Differences</th>
<th>Large Differences</th>
<th>Very Small Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum flow (ml/sec.)</td>
<td>1.2 ± 1.4 ± 2.8</td>
<td>More than 2.0</td>
<td>More than 2.0</td>
<td>Lose than 1.0 4.650</td>
</tr>
<tr>
<td>Maximum flow with corresponding subtracted bladder pressure (cm. water)</td>
<td>15.2 ± 13.3 ± 27.9</td>
<td>More than 15.0</td>
<td>15 (20.0)</td>
<td>Less than 5.0 29.385</td>
</tr>
<tr>
<td>Minimal urethral opening pressure (cm. water)</td>
<td>9.0 ± 8.0 ± 34.0</td>
<td>More than 15.0</td>
<td>14 (18.6)</td>
<td>Less than 5.0 28 (37.3)</td>
</tr>
<tr>
<td>Theoretical urethral area (mm.³)</td>
<td>0.80 ± 0.88 ± 2.3</td>
<td>More than 2.3</td>
<td>7 (9.3)</td>
<td>Less than 0.5 39 (52.0)</td>
</tr>
<tr>
<td>Urethral resistance factor (cm. water)</td>
<td>5.8 ± 6.2 ± 15.0</td>
<td>More than 15.0</td>
<td>5 (6.6)</td>
<td>Less than 5.0 46 (61.3)</td>
</tr>
</tbody>
</table>

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In our study the mean of the individual differences of the observed minimal voiding pressure (minimal urethral opening detrusor pressure) and the estimated minimal voiding pressure (urethral resistance factor) was less than 10 cm. water (table 2, 36.6 and 44.2 cm. water, respectively). This
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Fig. 4. Individual differences in maximum flow ($Q_{\text{max}}$) between both voidings. There is negative difference, that is second flow is better. Individual differences are grouped according to obstruction classes of 0—not obstructed to 6—very obstructed. PURR, passive urethral resistance relation.

finding indicates that the difference in both methods of assessing minimal urethral opening pressure is not large and, in fact, seldom clinically relevant. The individual difference in the results of both analysis methods (passive urethral resistance resolution or urethral resistance factor) is related to maximum flow rate differences. When the cross-sectional area (theoretical urethral area) is small and/or the maximum flow rate is low (less than 10) the urethral resistance factor number is greater than the minimal urethral opening detrusor pressure value and when maximum flow rate is greater than 10 ml. per second, especially in the case of high pressure, high flow obstruction, the urethral resistance factor value is lower than that for minimal urethral opening detrusor pressure. When an individual maximum flow rate difference of less than 2 ml. per second is regarded as slight, the reproducibility of this parameter is fair in 87% of the patients. The 12 patients who underwent an earlier examination did not show significant mean improvement in the second voiding. The question arises whether the observed tendency for improvement during the second voiding in the entire group could be due to the fact that the patients became more familiar with the given situation.

Although this study strictly concentrated on quantification of the variability, it is possible to speculate about the reason for this variability. The magnitude of the differences in the parameters of most patients is slight and could be related to pelvic floor activity during micturition. However, it can also be possible that slight changes in the bladder contraction or in internal sphincter relaxation are responsible for the differences. We report differences in immediate repetition of micturition. Recently, we completed a study that showed similar results of variability for 6 months.

In patients with large pressure or flow differences no tendency towards positive or negative differences was noted. The observed tendency towards improved flow during the second voiding is of little clinical importance since the differences are slight. However, when urodynamics are used to evaluate interventions (such as pharmacotherapy) it seems better to prevent bias from this effect, and perform investigations with repeated voidings and/or inclusion of a placebo group.

Our results indirectly show that mean differences between therapy groups or placebo treatment must be regarded critically when the reported differences are slight and possibly within the limits of physiological variability. This finding is in accordance with an earlier observation in which individual changes after pharmacotherapy were studied in a "meta-analysis" and compared with the nomogram classes.

CONCLUSION

From a clinical and diagnostic viewpoint, the variability of urodynamic investigation with pressure-flow analysis is slight. An approximate analysis, on a scale with pressure classes of approximately 15 cm. water and flow classes of approximately 2 ml. per second probably has sufficient reliability to establish a clinically relevant diagnosis of bladder outflow obstruction. Such a scale is relatively insensitive to the effect of normal variability. In the majority of our patients the clinical diagnosis could be established with analysis of the initial voiding and remained unchanged after the second voiding despite the fact that the latter was somewhat better in 65% of the patients. Individual (clinically relevant) differences are probably greater than 10 to 15 cm. water for the voiding pressure parameters and greater than 2 ml. per second for maximum flow. Patients with high grade bladder outlet obstruction, nonobstructed patients and those with severe detrusor overactivity in the filling phase showed the largest intra-individual variability of voiding. For fundamental research, or for the evaluation of new therapeutic modalities (for example pharmacotherapy), it seems mandatory to analyze at least 2 voidings during each investigation to rule out (patho)physiological variability.

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EDITORIAL COMMENT

For reasons that elude my own sense of logic, the urological community seems much more at ease criticizing its members for small points of disagreement than banding together to recognize simple truths, and so it is with the diagnosis of bladder outlet obstruction. Virtually all experts in voiding dynamics agree that the detrusor pressure-flow relationship defines urethral obstruction. However, in clinical practice and in most reports, the terms BPH and prostatic obstruction are used synonymously. They are not synonymous but it is far easier for the clinician to evaluate the prostate with the finger than with sophisticated urodynamic tests.

BPH is a pathological diagnosis and bladder outlet obstruction is a urodynamic diagnosis. While all experts agree that the pressure-flow relationship defines obstruction, they may disagree on the actual numbers that define obstruction. The "nonurodynamics" use this disagreement to their own advantage and claim that "even the experts don't agree," and revert to the index finger to make the diagnosis.

In the introduction to this article the authors state that "urodynamic investigation is the gold standard to quantify the grade of bladder outlet obstruction." I agree. This simple fact must be universally recognized by the urological community. Pressure-flow relationships, not the size or feel of the prostate, define prostatic obstruction. A high detrusor pressure and low flow document obstruction, while a low flow and low pressure document impaired detrusor contractility.

The authors continue, "it is not yet established whether a precise grading of obstruction is always clinically relevant, but for investigational purposes it is mandatory to perform an accurate evaluation of the voiding and to report (changes in) grade of obstruction on a continuous scale." This is the essence of clinical research. One must be able to quantify an objective measurement before and after therapy to determine the degree of change, and to determine the clinical relevance of defining obstruction in the first place. I do not know whether the presence or degree of obstruction correlates with symptoms of prostatism or the responses to different therapies but I do know how to find out, that is make the measurements and compute the correlations.

To do credible outcomes research in BPH, one need not only make the measurements, one must evaluate the end point in relation to the starting point. A patient who ends with a flow of 12 ml per second may be considered to have a successful result if he started with a flow of 11. This is straightforward for uroflow rates that are described by a single number but complicated mathematical formulas and computer analysis.

Rosier et al document the intra-individual variability in 2 methods of expressing objective parameters of outflow obstruction. As they correctly note, their results are important in 2 respects. From a clinical standpoint, urodynamic studies are clinically relevant and reproducible, which means that the clinical diagnosis of obstruction or not remains the same after 2 urodynamic studies. I already knew that but I believe it merits emphasis. Also, the urodynamic results are not that reproducible, which means that there are differences in urodynamic results from 1 study to another, which are not clinically relevant but, nevertheless, are different. These differences can provide a subset of patients to confound clinical trials. For example, in 13% of the patients there was a more than 2 ml per second difference between the maximum flow of voidings 1 and 2. In many clinical trials, 1 ml per second was the cutoff of efficacy with respect to uroflowmetry. We must consider these factors when we evaluate the results of clinical research.

Jerry G. Blaivas
Department of Surgery/Urology
New York Hospital-Cornell Medical Center
New York, New York