



Mathematical Modeling and Uroflow-Based Nomograms in Voiding Dysfunction Evaluation: Ready for Prime Time?

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Abstract

Purpose of Review In this review, we will describe the interest and role of mathematical modeling and uroflow-based nomograms in voiding dysfunction evaluation.

Recent Findings Due to the time-consuming character of implementation and use, mathematical models are now used to build “numerized nomograms.” These have the advantage over nomograms to allow the study of systems with more than two parameters. While at early stages, assessment of bladder outlet obstruction using nomograms has been initiated in men, and recently, an interesting nomogram has been developed in women.

Summary Mathematical modeling and uroflow-based nomograms in voiding dysfunction evaluation are an interesting field of research. Models need time, accuracy, and perseverance. Nomograms and numerized nomograms are easier to use. The number of proposed nomograms is growing. Today, the lack of external validation limits their use.

Keywords Voiding dysfunction · Evaluation · Uroflow · Mathematical modeling · Nomograms

Introduction

Evaluation of voiding dysfunction remains an important goal for urologists. They aim to scale the severity of any dysfunction. To do this easily, measurable quantities must be brought together. Information must be obtained quickly and accurately, and should inform the clinician about the most appropriate management. This raises several challenges. To relate a number to measurable quantities, it is necessary to know in advance which quantities must be measured and to have a quantitative description (mathematical) of the dysfunction. Each dysfunction can be thought of an intricate system; its description is an accurate mathematical model. This involves mathematical concepts and language, but enough of a schematic to

remain manipulable and flexible giving it the ability to account for the whole family of phenomena within that condition.

The aims of mathematical modeling are to define the measures which are needed to study phenomena which are difficult to investigate during urodynamic studies and to allow less invasive urodynamics. The use of most models requires a computer and, despite the improvement of the processors, can be time consuming to calculate. Another requirement for effective models is to ensure that the results can be presented in a timely manner to be used by the practitioner. This contradiction was solved by using nomograms and more recently by using “numerized nomograms.” René Descartes showed in 1637 [1], that any equation $f(x, y) = 0$ could be associated with a curve in the plane (x, y) which name was abacus. The nineteenth-century engineers used this discovery for practical purposes. A nomogram (this word soon replaced the word “abacus”) is a graphic tool which, starting from two measured parameters, gives instantaneously on a simple graphical presentation the value of a characteristic parameter of occurrence of a clinical event. But at the end of the twentieth century, the handheld dethroned the slide rule and the concept of nomogram was generalized. A “numerized nomogram” is a simple software for such device; it allows to obtain on a handheld the results of a model whose resolution requires a large computer

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and to look at problems with more than two measured parameters. In this article, two topics will be considered with the target of evaluation of voiding dysfunction: first mathematical modeling, second uroflow-based nomograms.

Mathematical Modeling in Voiding Dysfunction

To consider an application for evaluation of voiding dysfunction, we must have a mathematical model of micturition. Therefore, partial models (urethra, sphincters, or bladder) will not be discussed.

In the particular case of a micturition model, the basic description relates to a healthy subject (male or female) under normal conditions who will be referred to as a standard subject. Then, each abnormality of the system (pathological or not) is described as a disturbance of the standard state, i.e., as a deviation of some elements from the standard description.

The model is a set of equations. By solving these equations, it is possible to predict the measured quantities (flow rate, bladder pressure) from the initial bladder volume and the presumed condition of the patient.

But the practitioner has to deduce the patient's condition from the measured quantities. The solution of this new problem involves additional mathematical developments. So, to be acceptable, a model must have four elements:

- 1- description of the standard case
- 2- description of the abnormalities
- 3- method for solving the direct problem
- 4- method for solving the reverse problem

Why Use Mathematical Models?

Very often, during an experiment, “big” phenomena mask the smaller ones. Suppose that a model gives an account of these big phenomena, the experience-computation comparison will reveal undetectable differences at first reading. These gaps play the role of complementary experimental results which, in turn, must be modeled.

Thus, the refinement of models accompanies the development of knowledge. This procedure requires 5% inspiration and 95% perseverance.

Many models of micturition [2–7], often interesting, were published but were not validated in clinical settings.

Only VBN (knowledge model) [6] and PUMA (empirical model) [7] were applied to clinical urodynamics. Other models have remained theoretical studies.

Studies using PUMA mainly aimed to assess the correlation with other methods of quantification of urethral obstruction (ICS nomogram, Schäfer diagram, URA) [7], to define

values of urodynamic parameters characterizing obstruction in women [8] or to explore poor detrusor contractility [7]. No data on PUMA have been published since 2003.

Studies using VBN model are still in progress, although the direct use of the model is difficult in intricate cases and time consuming. Modeling allowed the study of phenomena difficult to access during urodynamic tests: relaxation of the prostate, coupling of bladder and bladder neck contraction [9]. Analysis of successive voidings of a patient whose status does not evolve allows to highlight that a number of voidings that might appear abnormal are solely due to poor nervous control (break of detrusor excitation, incomplete relaxation of the striated sphincter) and therefore have nothing pathological.

Evaluation of chemical treatments for prostate enlargement (Alfuzosin, Tadenan) [10, 11] and of surgery for urinary incontinence in women (Gynemesh-TVT-O) [12] were made possible by the analysis of uroflowmetries.

The model makes it possible in benign prostatic enlargement (BPE) patients to quantitatively evaluate the variation of the state parameters (reduction or disappearance of the obstruction after TURP, etc.) and to show that the improvement remains stable [13].

Due to the time required for the modeled analyzes, these analyses are devoted to intricate cases or investigation of a poorly known condition in a large population. Their results are used to build nomograms.

Uroflow-Based Nomograms in Voiding Dysfunction

In the evaluation of voiding dysfunction based on nomograms, a milestone was reached with the work of Abrams and Griffiths [14] who published in 1979 a founding study carrying out the first satisfactory simple nomogram for diagnosing of bladder outlet obstruction (BOO) in male patients. As BOO is a common cause of voiding dysfunction in men and, while less common, in women, the main studies that have resulted in the creation of nomograms have focused on that clinical condition.

Uroflow-Based Nomograms in Voiding Dysfunction from Invasive Investigation

Men

Abrams–Griffiths' nomogram was built in the plane (Q_{\max} , $p_{\det.Q_{\max}}$) from invasive pressure-flow studies and consists of three zones: obstructed, equivocal, and unobstructed [14]. Later [15], the nomogram has been modified by assigning an Abrams–Griffiths number ($AG = p_{\det.Q_{\max}} - 2 * Q_{\max}$) to each set of pressure-flow data (obstructed if $AG > 40$, equivocal if $20 \leq AG \leq 40$, and unobstructed if $AG < 20$). Even later, AG

number was renamed bladder outlet obstruction index (BOOI) and the provisional ICS nomogram published [16].

This nomogram is now recommended for the diagnosis of BOO. AG number can also be used to evaluate the outcomes of therapies (pharmacological treatments, surgery, etc.)

Evaluation of BOO cannot be dissociated from evaluation of detrusor contractility. In 1990, Schafer proposed a modified PURR [17]: linear PURR. The linear PURR nomogram grades the severity of obstruction: 0–1 no obstruction, 2 mild obstruction, 3 to 6 moderate to severe obstruction.

From Schafer's contractility groups, a bladder contractility index (BCI) and an associated nomogram were proposed [18]. Contractility is divided in strong, normal, and weak. BOOI and BCI nomograms were combined for categorization of patients into nine zones [19].

Note that since its initial definition (graphical tool starting from two measured parameters), the word nomogram has evolved, and often refers to a graphical tool.

Women

In women, the causes of obstruction vary greatly from anatomic to functional. Some cut-off values combining flow rate and detrusor pressure at Q_{\max} have been proposed [20, 21]. Three nomograms have been described for classification of BOO in women.

In 2000, Blaivas and Groutz created a nomogram (BG nomogram) using free Q_{\max} and $p_{\det\max}$ which is four-zone nomogram [22]. The choice of these parameters was the adverse effect of the transurethral catheter. They conclude that the nomogram makes it possible to differentiate between obstructed and unobstructed women and between various degrees of obstruction and say that they believe the nomogram may also serve as an instrument to assess treatment outcomes. Virsen et al. found [23] that the BG nomogram showed a significant association with the videourodynamic data and that it is a sensitive method for the diagnosis of obstruction. However, authors who tested the BG nomogram (Virsen et al. [23] Akikwala et al. [24], Massolt et al. [25], and Solomon et al. [26]) concluded that it overestimates the prevalence of obstruction and underestimates the severity of BOO [E 25].

In 2014, Dybowki et al. proposed a “pressure-flow nomogram” for a specific group of women with sign or symptoms of bladder outlet obstruction but without anatomical obstruction [27]. In fact, their proposal is straight line described by the equation $p_{\det Q_{\max}} = 1.5 \times Q_{\max} + 10$ which is a boundary between unobstructed (below) and obstructed (above). The new cut-off can be considered a screening test which efficiently excludes obstruction among women with low Q_{\max} in a pressure-flow study.

In 2018, Solomon et al. developed a nomogram based on radiographic evidence of increased urethral resistance for the

diagnosis of BOO in women. They proposed a female BOO index (BOOIf) defined by $BOOIf = P_{\det, Q_{\max}} - 2.2 \times Q_{\max}$ to stratify the degree of obstruction (< 0 no obstruction, > 5 likely obstructed and > 18 obstructed almost certain [26]). As numerous indices or nomograms, nomogram does not allow for the diagnosis of BOO in presence of detrusor underactivity. In addition, it is not validated externally.

The aims of these last two studies were very different: the first [27] wanted to exclude BOO while the second [26] was trying to stratify BOO. Note that no study has evaluated the ability of nomograms to predict the outcomes of treatments aiming to relieve BOO.

Uroflow-Based Nomograms in Voiding Dysfunction from Non-Invasive Investigation in Men

Semi-invasive method and non-invasive techniques have been developed for men in order to minimize the invasive nature of urodynamics.

Comiter et al. proposed a nomogram from a semi-invasive method the penile urethral compression and release (PCR): combination of Q_{\max} from an uroflowmetry and isometric pressure (P_{iso}) recorded during isometric detrusor contraction at strong desire to void during cystometry [28]. This is a four quadrants nomogram with threshold values of $Q_{\max} = 12$ mL/s and $P_{\text{iso}} = 100$ cm H₂O because a combination of Q_{\max} and P_{iso} was found better than either parameter alone to predict obstruction [28].

Non-invasive techniques involve the non-invasive measurement of isovolumetric bladder pressure combined with a free uroflow to diagnose obstruction.

The first is the cuff-uroflow method described by McRae [29]. This method has been used by Salinas et al. [30] to propose a nomogram divided into three areas (obstructed, indeterminate, and not obstructed) linking $P_{\text{cuff,op}}$ with $Q_{\text{cuff,op}}$ [30].

In the second technique, an external condom catheter is used to interrupt flow distal to the urethral meatus. A pressure transducer is located between the penis and the point of occlusion along the catheter. The method, first described by Schafer [31] was developed by the team of Rotterdam [32, 33]. Recently, van Mastrigt et al. proposed a new three-zone nomogram to improve the diagnosis of BOO using condom catheter measurements [34]. However, this method has limitations including adverse events [35], some discomfort and scant data available [36].

The third technique is the penile cuff test (PCT). The method involves interruption of flow by inflation of a penile cuff; cuff pressure at flow interruption correlates closely with isovolumetric bladder pressure [37]. A four-zone nomogram is drawn in the plane (Q_{\max} - cuff interruption pressure) upper right and lower left quadrants are uncertainty zones, upper left obstructive zone and lower right unobstructed zone [37]. ICS

nomogram is modified as follows: first, the slope of the obstruction line takes into account abdominal pressure, cuff height, and increase to isovolumetric pressure during interruption, and second, a Q_{\max} less than 10 mL/s alone as a predictor of obstruction [37].

Studies from the Newcastle team [38] and from other teams have concluded that PCT is a good alternative to PFS for diagnosing BOO [39, 40•, 41•].

The UroCuff test (another name for a PCT) uses the Newcastle nomogram, and is also found accurate in predicting BOO when compared to conventional invasive pressure flow studies in men with LUTS [42•].

From Micturition Model to Nomograms

Due to the time required for direct use of the modeled analyzes, the VBN mathematical model of micturition has been used to carry out nomograms.

Men

From Invasive Investigation

Experiment shows that quantification of outflow obstruction and detrusor contraction needs not only the knowledge of one parameter, as it was believed initially, but of two parameters (Q_{\max} and $p_{\det, Q_{\max}}$) as shown by AG and BCI. Then, nomograms can be built.

But experiments show also that the quantification of contractility needs the measurement of three parameters (Q_{\max} , $p_{\det, Q_{\max}}$ and initial bladder volume). A 3D nomogram would not be of practical use. Thus, a numerized nomogram had to be written. It gives instantaneously detrusor contractility and urethral obstruction from the three measured parameters.

The same method can be applied to problems requiring more than three parameters. Thus, comparison of dynamic differences between free uroflow (FF) and intubated flow (IF) as assessed with VBN can only be done by numerized nomograms implying five parameters. From a sequence of tests including one FF followed by one PF, numerized nomogram gives: from PF detrusor contractility and apparent obstruction (AG). Then, from backward computation using the detrusor contractility (unchanged between the two tests), we obtain from the FF a “ $p_{\det, Q_{\max, FF}}$ ” and a corrected AG (corr-AG) number. When $Q_{\max, FF} > 1.5 \times Q_{\max, IF}$, 53.5% of patients were found less obstructed with corr-AG while no patient was found more obstructed [43••].

The same method can be used to evaluate the obstruction change after pharmacological treatment or TURP in men with benign prostatic obstruction.

From Only Free Uroflows

The D index derived from free uroflows has been developed to assist in the management of BPE patients [44••]. Correlation of D (in cmH_2O) and AG number is as follow $D < 18.5$ unobstructed, $18.5 \leq D \leq 32.5$ equivocal, $D > 32.5$ obstructed. Nomograms were built in the plane (initial bladder volume- Q_{\max}) and in the plane (voided volume- Q_{\max}) using the VBN mathematical micturition model [6]. These non-invasive methods are usable by general practitioners and could make easier watchful waiting and follow-up of BPE patients.

Women

The VBN model of micturition allowed construction of two main nomograms to evaluate detrusor contractility and urethral obstruction in women from a pressure-flow study. Algebraic fitting of the curves was performed, which led to an economy of equipment and of time needed for evaluation of these two mechanical parameters. In order to be tested, the nomogram has been applied to populations of non-neurological women referred for evaluation of lower urinary tract dysfunction [45•].

Discussion

Modeling provides extremely accurate results from accurate measurements. Although, in some cases (e.g., astronomy), experimental data are extremely accurate, in other cases (e.g., urodynamics) experimental data are not very accurate.

Mathematical modeling makes it possible to separate the description of past observations (the setting in equation) and a large number of specific observations (the introduction of data) and the resolution of this system of equations (whereas the two phases are confounded in direct reasoning).

If the accuracy of the mathematical models is not debatable, there are very strict conditions for their use which requires great precision and care. Moreover, they are time-consuming.

The structure of a model of micturition is very broad and must cover all the possible voiding dysfunctions. But both instrumental and computational practical constraints lead the clinicians to choose the phenomenon to be studied.

Building a model of micturition requires a multidisciplinary team: physician, physicist, mathematician, etc.

So, because of its complexity, a mathematical model is difficult to use by another team than the inventing team. That condition largely explains that models are rarely used in daily practice.

The purpose of nomograms is very different from that of models. The nomogram applies to a single dysfunction and is

used to characterize that dysfunction. The main proposed nomograms address bladder outlet obstruction.

In some clinical conditions (e.g., outlet obstruction due to benign prostatic enlargement), useful information can be drawn from two parameters (e.g., Q_{\max} and $p_{\det, Q_{\max}}$). Building the nomogram requires that these two parameters are measured in a large population of men suspected of BOO. The nomogram that is built from these data is immediately usable in daily practice.

In other cases, the result depends on three parameters or more (e.g., when detrusor contractility contributes to the analyzed phenomenon). The value of these parameters can then be displayed as a “numerized nomogram” immediately usable by the practitioner. The method can be extrapolated to analyze tests repeated over time for instance to follow-up patients under pharmacological treatments or post-operatively.

Conclusion

Mathematical modeling and uroflow-based nomograms in voiding dysfunction evaluation are an interesting field of research. Mathematical modeling remains scarcely used because of constraints like the size and skills of required teams and of the time required to achieve reliable analysis of any urodynamic curves.

Nomograms are easier to use. They will be perhaps ready for prime time if they are externally validated. Today, for evaluation of BOO in men, until the nomogram developed by the Newcastle team meets this requirement, the provisional ICS nomogram is the only one to fulfill this condition.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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