

The value of home urodiagnostics in the assessment of men with lower urinary tract symptoms

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As man draws near the common goal

Can anything be sadder

Than he who, master of his soul

Is servant to his bladder?

Anon

Abstract

A third of all men experience unpleasant lower urinary tract symptoms (LUTS) such as a poor stream and being unable to postpone urination, usually later in life. Two important investigations for these men are: a one-off clinic-based measurement of urine flow rate, and the patient's hand written record of volumes passed over the course of several days.

Well acknowledged deficiencies in these tests have spurred research into home-based alternatives. 'Home urodiagnostic' devices have been developed that obtain multiple measurements of flow rate and an electronic voiding diary. However, little conclusive evidence exists as to their clinical utility. The aim of this thesis is to investigate the value of home urodiagnostics in the assessment of men with LUTS.

First, the improvement in clinical performance of an average rather than single flow rate measurement is calculated based upon the theory of combining variance, predicting benefit for thousands of men per year. Next, finding existing devices deficient, the characteristics and technical performance of a novel device are presented. Despite its low cost, it is found to meet the required standard.

In a study of conventional versus home urodiagnostics in men with LUTS, the latter is better tolerated, less likely to fail and gave more reliable measurement of flow rate. A study in which home urodiagnostics was performed before and after prostate surgery reveals large variation in the response of flow rate to surgery. Subtle changes within an individual are demonstrable.

Finally, home urodiagnostics is piloted within primary care, where the resulting data suggests benefit from a change in the management strategy of over a third of patients studied.

In conclusion, home urodiagnostics shows promise for improving the assessment of men with LUTS. The next step is to evaluate the effect on patient reported outcomes in a large scale trial.

Abbreviations

Abbreviation	Definition
A	Cross sectional area
α	Level of significance
ADC	Analog-to-digital conversion
AG	Abrams-Griffiths (nomogram)
AUC	Area under an ROC curve
BNI	Bladder neck incision
BOO	Bladder outlet obstruction
BOR	Bladder output relation
BPE	Benign prostatic enlargement
BPH	Benign prostatic hyperplasia
BPO	Benign prostatic obstruction
CNS	Central nervous system
DHT	Dihydrotestosterone
DO	Detrusor overactivity
DRE	Digital rectal examination
DU	Detrusor underactivity
FCZ	Flow controlling zone
FVC	Frequency-volume chart
GP	General practitioner
GPwSI	GP with a Special Interest
HOLEP	Holmium laser enucleation of the prostate
Hz	Hertz
ICS	International Continence Society
IPSS	International Prostate Symptom Score
IQR	Interquartile range

Abbreviation	Definition
κ	Cohen's kappa
KTP	Potassium titanyl phosphate
L	Length
LED	Light-emitting diode
LIN-PURR	Linear passive urethral resistance relation
LUT	Lower urinary tract
LUTS	Lower urinary tract symptoms
μ	Mean
MHRA	Medicines and Healthcare Products Regulatory Agency
n	Number of measurements
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NP	Nocturnal polyuria
p	Probability of observed result
p	Pressure
P	Power
p_{abd}	Abdominal pressure
PAG	Periaqueductal grey
$p_{cuff.int}$	Cuff interruption pressure
p_{det}	Detrusor pressure
$p_{det.iso}$	Isovolumetric detrusor pressure
$p_{det.Qmax}$	Detrusor pressure at the moment of Q_{max}
PFS	Pressure-flow studies
PMC	Pontine micturition centre
PSA	Prostate specific antigen
p_{uo}	Urethral opening pressure
p_{ves}	Intravesical pressure

Abbreviation	Definition
PVR	Post void residual
Q	Flow rate
Q^*	Potential maximum flow rate
Q_{ave}	Average flow rate
Q_{max}	Maximum flow rate
QoL	Quality of life
R	Resistance
r^2	Coefficient of determination
ρ	Density
ρ	Spearman's rank correlation coefficient
RCT	Randomised control trial
ROC	Receiver operating characteristic
σ	Conductivity
σ	Standard deviation
SD	Standard deviation
t_{flow}	Flow time
$t_{Q_{max}}$	Time to Q_{max}
TRUS	Transrectal ultrasound scan
TUIP	Transurethral incision of the prostate
TURIS	Transurethral resection in saline
TURP	Transurethral resection of the prostate
$t_{voiding}$	Voiding time
UTI	Urinary tract infection
URR	Urethral resistance relation
v	Velocity
V	Voltage
V_{void}	Voided volume

Achievements

Publications

Papers

Bray A, Griffiths C, Drinnan M, Pickard R. Methods and value of home uroflowmetry in the assessment of men with lower urinary tract symptoms: A literature review. *Neurourology and Urodynamics*, 31(1): p7-12, 2012.

PubMed ID [22038511](#)

Summary A review of current evidence regarding the technology and value of multiple and home urodiagnostics. Previously reported methods were assessed against ICS recommendations for uroflowmetry and the results of several studies investigating variability of flow parameters, such as maximum flow rate, were presented.

Abstracts

Bray A, Robson W, Griffiths C, Harding C, Pickard R, Drinnan M. No improvement in home flow rates in a quarter of men undergoing transurethral resection of the prostate (TURP). *Neurourology and Urodynamics*, 32(6): p888-889, 2013.

<http://www.ics.org/Abstracts/Publish/180/000261.pdf>

Summary 17 men used a portable home flowmeter for one week prior to, and at least four months following, transurethral resection of the prostate. Four patients did not experience an increase in flow rate following surgery; the possible reasons for this are discussed. Home uroflowmetry is a sensitive tool for investigating treatment-induced changes in voiding parameters.

Bray A, Griffiths C, Pickard R, Harding C, Drinnan M. Do primary care practitioners comply with NICE guidelines? *Journal of the British Association of Urological Surgeons*, 111(S3): p60, 2013.

<http://onlinelibrary.wiley.com/doi/10.1111/bju.12137/pdf>

Summary 87 patients in attendance at local prostate assessment centres were surveyed regarding their evaluation in primary care prior to referral. This demonstrated large variation in the management of men with LUTS in primary care; several of the investigations recommended by NICE guidelines were only carried out in a small percentage of cases.

Bray A, Griffiths C, Pickard R, Drinnan M. Can we use the Wii to measure wee? *Neurourology and Urodynamics*, 31(6): p931-932, 2012.

<http://www.icsoffice.org/Abstracts/Publish/134/000155.pdf>

Summary An investigation of whether the Wii Balance Board can be implemented as a home flowmeter by measuring the decreasing weight of the body during voiding. A surprisingly accurate volume measurement can be obtained, but noise on the signal prevents interpretation of maximum flow rate.

Bray A, Griffiths C, Pickard R, Drinnan M. Patient opinion of three methods of recording voiding habits at home. *Neurourology and Urodynamics*, 30(6): p1138-1139, 2011.

<http://www.icsoffice.org/Abstracts/Publish/106/000245.pdf>

Summary 20 male participants carried out three methods of recording voiding habits at home (electronic home flowmeter, Uflow Meter[®] and conventional frequency-volume chart) and gave questionnaire feedback.

Bray A, Caffarel J, Whitaker M, Robson W, Drinnan M, Pickard, R, Griffiths C. Multiple home uroflowmetry - a better outcome measure? *Neurourology and Urodynamics*, 29(6): p827-829, 2010.

<http://www.icsoffice.org/Abstracts/Publish/105/000017.pdf>

Summary 18 patients with suspected bladder outlet obstruction used a low-cost home flowmeter for one week before and one week after a course of medication, and also performed a single clinic flow test before and after the medication. There was no agreement between home and clinic assessment of the effect of medication on flow rate, demonstrating the weakness of single clinic measurements as the objective indication of treatment outcome.

Prizes

Newcastle University Faculty of Medical Science triennial postgraduate public speaking prize, May 2013.

As part of Newcastle University's INSIGHTS public lecture series, three young researchers describe their quests at the cutting-edge of science and how their findings may underpin the medical interventions of tomorrow.

Newcastle University event page <http://www.ncl.ac.uk/events/public-lectures/item.php?three-tales-from-the-biomedical-frontier1>

Grant awards

A Portable, Low Cost, Electronic Urine Flowmeter to Assess Lower Urinary Tract Symptoms (LUTS), March 2010.

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Conference proceedings

Bray A, Griffiths C, Harding C, Pickard R, Drinnan M. Home uroflowmetry for assessment of men with LUTS. 43rd annual meeting of the International Continence Society, August 2013, Barcelona, Spain.

<http://www.ics.org/Abstracts/Publish/180/000525.pdf>

Summary 59 men were recruited to use a home flowmeter for one week, complete a manual frequency-volume chart and attend a clinic urine flow test. Home uroflowmetry was superior in terms of test success rate (100 % versus 90 %), test-retest reliability, and patient preference (87 % versus 13 %).

Bray A, Caffarel J, Whitaker M, Robson W, Drinnan M, Pickard R, Griffiths C. IPSS: does it relate to an objective score derived from multiple home flow data? 39th annual meeting of the International Continence Society, August 2009, San Francisco, USA.

<http://www.icsoffice.org/Abstracts/Publish/47/000397.pdf>

Summary 18 men treated with medication for suspected bladder outlet obstruction completed a symptom scoring questionnaire before and after medication. They also used an electronic home flowmeter before and after treatment, from which objective equivalents of certain symptom scores were derived. No agreement was found between subjective and objective symptom change following medication.

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Chapter 1

Introduction

A third of all men experience the onset of lower urinary tract symptoms (LUTS) in the autumn of their life. At a conservative estimate, this amounts to 100,000 new cases each year in the UK, and several million worldwide. At best, LUTS hamper enjoyment of one's retirement; at worst they progress to serious and even life-threatening conditions.

Measurement of urine flow rate (uroflowmetry) requires men to attend a clinic in order to pass urine into a flowmeter. It is a simple, non-invasive test that helps to establish the cause of LUTS and select appropriate treatment. Commonly, uroflowmetry, usually including measurement of post void residual, is the only objective assessment of lower urinary tract function made prior to surgery.

Although this measurement is valuable, the circumstances surrounding the test are far from ideal. Owing to closely scheduled appointments and the requirement to arrive with a full bladder, missed measurements - and missed toilets - are not uncommon. In addition, the artificial environment of the flow clinic may yield results that are unrepresentative of the patient's true voiding. Further, we know that an individual's flow rate varies, and this potentially important information cannot be captured.

Meanwhile, these men are also required to complete a frequency-volume chart at home for several days. This involves buying, or appropriating from the kitchen cupboard, a measuring container suitable for receiving urine. Each volume passed, day and night, must be recorded on a printed chart. Compiling this information requires motivation, dexterity and sustained effort, and so inevitably the quality of the result varies.

What if these men were provided with the means to record all of this information, in the comfort of their own home, and without the requirement to write anything down? This has the potential to provide more detailed and representative information on which to base clinical decisions, whilst improving patient experience.

To this end, the departments of Regional Medical Physics and Urology within Newcastle upon Tyne Hospitals NHS Foundation Trust have collaborated to develop such a means: the PeePod, a portable, electronic home flowmeter and volume diary.

1.1 Aims and objectives

The aim of this thesis is to investigate the clinical value of ‘home urodiagnostics’ (to coin a phrase) using the PeePod in the assessment of men with LUTS. Specifically, it aims to measure the effect of home urodiagnostic data on diagnosis and assessment of treatment outcome in these men.

Following a summary of the relevant background in Chapters 2 and 3, this aim will be addressed by the following objectives:

1. To evaluate current evidence regarding methods and value of home urodiagnostics by reviewing the literature (Chapter 4).

2. To calculate the improvement in clinical accuracy that could be achieved by averaging multiple measurements of flow rate in an individual (Chapter 5).
3. To compare home urodiagnostics to conventional assessment in terms of patient preference, test success rate, test-retest reliability and diagnostic consistency and confidence (Chapter 7).
4. To measure the sensitivity to change of home urodiagnostic data to surgical treatment for LUTS (Chapter 8).
5. To test the feasibility and utility of home urodiagnostics in a primary care setting (Chapter 9).

Finally, the conclusions drawn throughout will be summarised in Chapter 10.

My role in the work described in this thesis, with supervision from Michael Drinnan, Robert Pickard and, prior to his retirement, Clive Griffiths, was as follows:

- Study design.
- Development of study documentation.
- Application for relevant approvals (ethical, R&D, MHRA, UKCRN Portfolio, Caldicott).
- Identification, recruitment and consent of study participants.
- Data collection.
- Data analysis.
- Interpretation of results.
- Reporting and dissemination.

All Methods sections constitute my own work. The contributions of others are described where relevant.

Chapter 2

Anatomy and physiology of the male lower urinary tract

2.1 Introduction

The human urinary system consists of the kidneys, ureters, bladder, urethra and urinary sphincters. The former two elements are referred to as the upper urinary tract, and the latter three, the lower urinary tract (LUT, Figure 2.1). The kidneys have several critical functions including removal of waste products and regulation of hydration and blood pressure. The LUT is concerned with internal storage of urine and its subsequent elimination by voluntary and socially appropriate voiding.

This chapter details the anatomy and function of the LUT, followed by a description of its nervous control, and concludes with discussion of its mechanical properties.

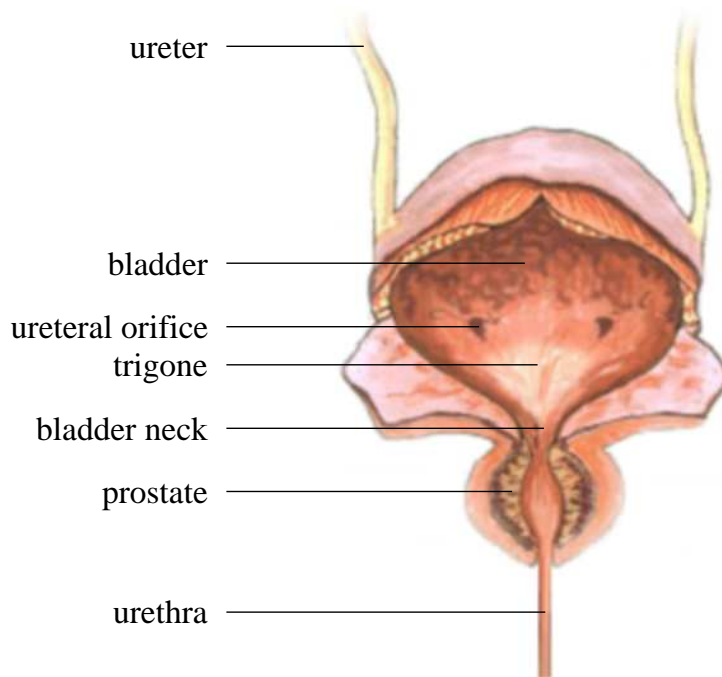


Figure 2.1 *Coronal schematic section of the adult male lower urinary tract.*

2.2 Anatomy

2.2.1 Bladder

The urinary bladder is a hollow, muscular organ responsible for storage and subsequent voiding of urine. Urine is produced by the kidneys at a rate of approximately 1 or $2 \text{ ml}\cdot\text{min}^{-1}$ (although this rate depends upon several factors such as fluid intake and temperature), and transported to the bladder by the ureters via intermittent peristalsis.

The bladder wall is capable of folding in order to reduce the volume within to only a few millilitres. On filling, once the volume reaches around 100 ml , it unfurls to assume a roughly spherical shape with a radius of up to approximately 5 cm (Griffiths, 1980). The healthy bladder is highly compliant; its volume can increase to several hundred millilitres with little or no increase in pressure (Small, 2013).

The bladder wall comprises three layers (although poorly distinguished) of smooth muscle, referred to collectively as the detrusor (Figure 2.2). The muscle cells run in different directions, the outer layers being mostly longitudinal and the inner layer being mostly circular (Gray, 1989). The resulting muscle fibre ‘mesh’ gives a uniform wall tension during bladder contraction.

A triangular zone known as the trigone, formed by the two ureteral orifices and the internal urethral orifice, has an additional inner layer of muscle to that of the detrusor. Any specialised function of the trigone is uncertain; it is hypothesised to contract during filling, widening the ureteral orifices, and then relax with the onset of voiding to direct urine into the urethra (Roosen et al., 2009).

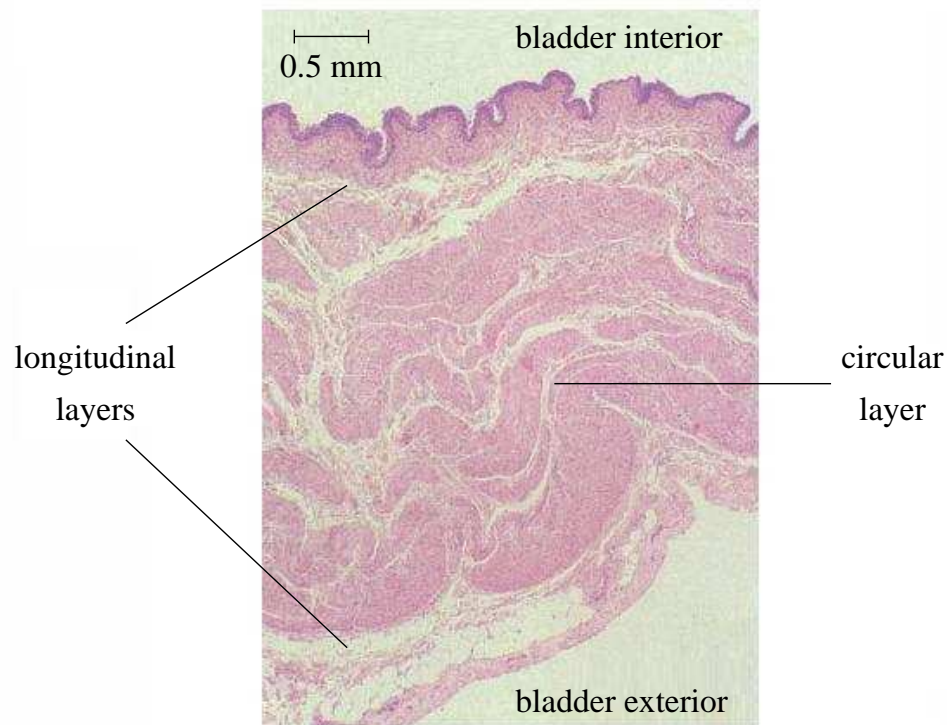


Figure 2.2 *Microscopic cross section of the bladder wall (magnification $\times 18$) (University of Iowa Hospitals and Clinics, 2013).*

2.2.2 Urethra

The male urethra is a flexible tube of around 20 cm in length through which urine is voided from the body via the external meatus at the end of the penis. In its relaxed state, the urethra curves upwards and forwards below the prostate and then downwards and forwards at the point where the penis joins the body. Proximal to distal, it consists of the following regions (Figure 2.3):

- Pre-prostatic, between the internal urethral orifice and prostate. Here the smooth, circular muscle of the bladder neck thickens; there is debate as to whether this forms an inner sphincter which aids continence under autonomous control.
- Prostatic, where the urethra passes through the prostate. This section contains ducts through which the constituents of ejaculate enter the urethra.
- Membranous, a narrow region surrounded by two layers of muscle: one smooth, longitudinal layer and an outer circular layer. The latter, the external sphincter, is made of striated, skeletal muscle and is therefore voluntarily controlled, allowing men to postpone and interrupt urination.
- Spongiose, the long and, when flaccid, fairly passive region of the urethra surrounded by erectile tissue.

To maintain continence during the storage phase, the urethra resides in a collapsed state due to sustained contraction of its smooth muscle, its walls sealed by a viscid secretion (Griffiths, 1980). The pressure profile of the urethra varies along its length due to the differences in composition described above. The point at which the pressure is highest constitutes the flow controlling zone (FCZ). As discussed later in Section 2.4.1, the urethra is thought to remain closed until the urethral closure pressure at the FCZ is exceeded to allow voiding, at which point it opens

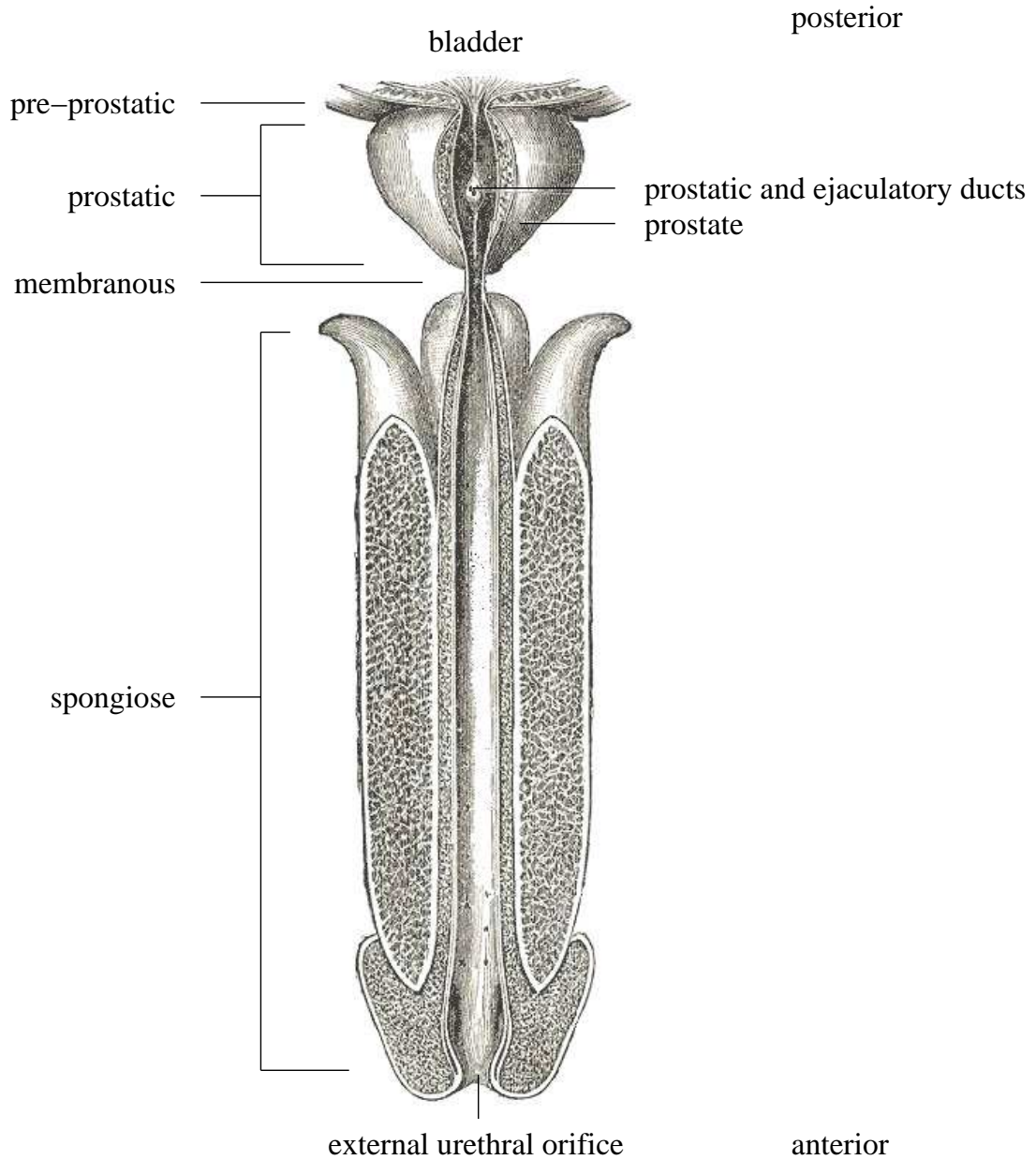


Figure 2.3 *Anatomical schematic of a coronal section of the male urethra (Gray, 1989).*

to a diameter of several millimetres. The FCZ is usually in the region of the prostatic urethra and bladder neck, although abnormalities resulting from disease or injury may result in higher pressures elsewhere.

2.2.3 Prostate

The prostate gland is responsible for production and secretion of a substance that combines with sperm from the testes to produce seminal fluid. It is positioned directly below the bladder, encircling the urethra (Figure 2.4). Therefore, although not part of the urinary system per se, the prostate when enlarged can have a considerable effect on the mechanism of the LUT.

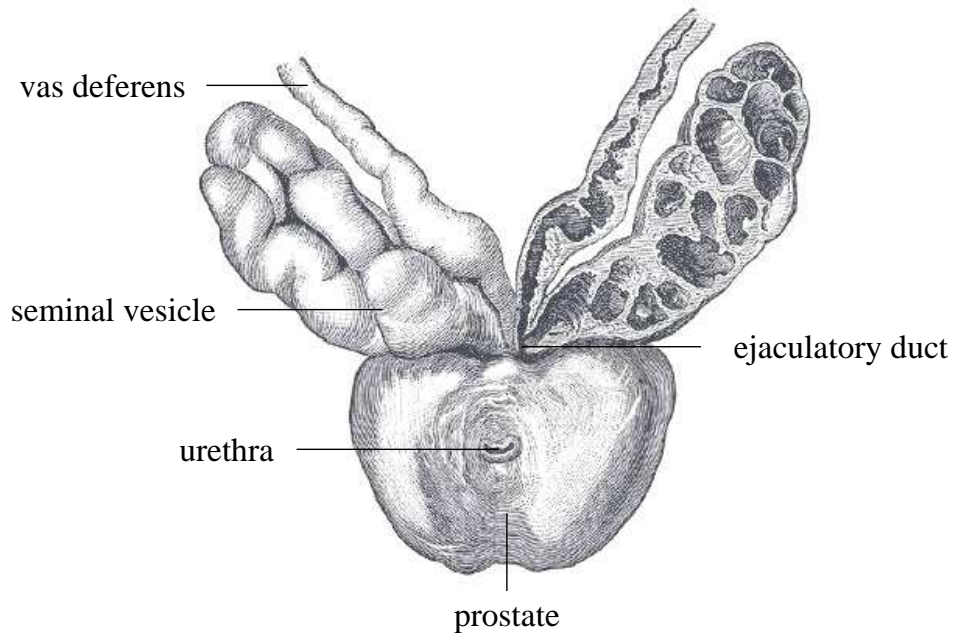


Figure 2.4 *Anatomical schematic of a transverse section of the prostate gland (Gray, 1989).*

2.3 Control

The majority of the visceral organs are regulated entirely below the level of consciousness through spinal and brain stem reflexes. The urinary and defecatory systems are therefore unusual in that an extent of conscious control from the cerebrum is learned during childhood. The LUT is governed by complex interaction between the central, autonomic (subconscious) and somatic (conscious) nervous systems.

The autonomic nervous system is divided into two branches: sympathetic and parasympathetic. Differentiation between the two is given by the chemical neurotransmitter released at the at the neuroeffector junction (sympathetic: noradrenaline, parasympathetic: acetylcholine) and in general the two branches have the opposite effect on a given organ or system. The somatic system also involves the release of acetylcholine at the neuroeffector junction (Griffiths, 1980).

These chemical neurotransmitters couple with receptors on the surface of the muscles cells of the bladder wall, bladder neck and urethra. The consequence of this coupling may be inhibitory, resulting in muscle relaxation, or excitory, resulting in muscle contraction through reduction or elevation, respectively, of intracellular calcium levels.

Although there is much debate regarding the neural control of the human LUT, with animal trials providing the majority of evidence, the following sections attempt to summarise current opinion.

2.3.1 Storage

Both sensory and motor nerve activity take place during the storage phase. At first, this activity is controlled by subconscious reflexes within the brain stem.

Sympathetic efferent activity within the hypogastric nerve inhibits the detrusor and activates the smooth muscle within the bladder neck and urethra. Thus, the detrusor is relaxed and the bladder neck and urethra are contracted, promoting internal urinary storage. The pudendal nerve excites the skeletal muscle of the external urethral sphincter and it too remains contracted. Meanwhile, parasympathetic efferent nerve pathways, the role of which is described below, are relatively inactive.

As the bladder fills, the sensory afferent components of the pelvic (parasympathetic) and hypogastric (sympathetic) nerves are responsible for informing the central nervous system (CNS) as to the fullness of the bladder via receptors in the bladder wall sensitive to distension. Sensory information from the bladder neck and urethra is carried in the pudendal and hypogastric nerves. As a result of these feedback loops, the electrical activity within the external sphincter increases with increasing bladder volume and raised abdominal pressure, resulting in strengthened contraction (de Groat, 2006).

The pontine micturition centre (PMC) is an area of the pons within the brain stem associated with regulation of storage and voiding. Input to the PMC is controlled by a region of the brain called the periaqueductal grey (PAG), which is thought to co-ordinate sensory information from the LUT with messages from areas of the brain responsible for conscious control. When a critical level of bladder distension is reached, parasympathetic activity within the LUT is triggered and the brain becomes aware of the desire to void. At this stage, the prefrontal cortex is capable of suppressing excitatory signals that would otherwise result in bladder contraction and therefore incontinence (Fowler et al., 2008).

2.3.2 Voiding

With the conscious decision to empty the bladder, the LUT switches: active becomes inactive, excited becomes inhibited, contracted becomes relaxed.

Excitation of the PMC, once this is permitted by higher centres of the brain, triggers the onset of voiding. Initially, sympathetic signals to the external urethral sphincter are inhibited and the muscle becomes relaxed. This is soon followed by parasympathetic activity via the pelvic nerve which results in contraction of the detrusor, relaxation of the outlet, and the flow of urine. Once the bladder is empty, the system switches back to the storage mechanisms described previously.

These neural control concepts are illustrated in Figure 2.5.

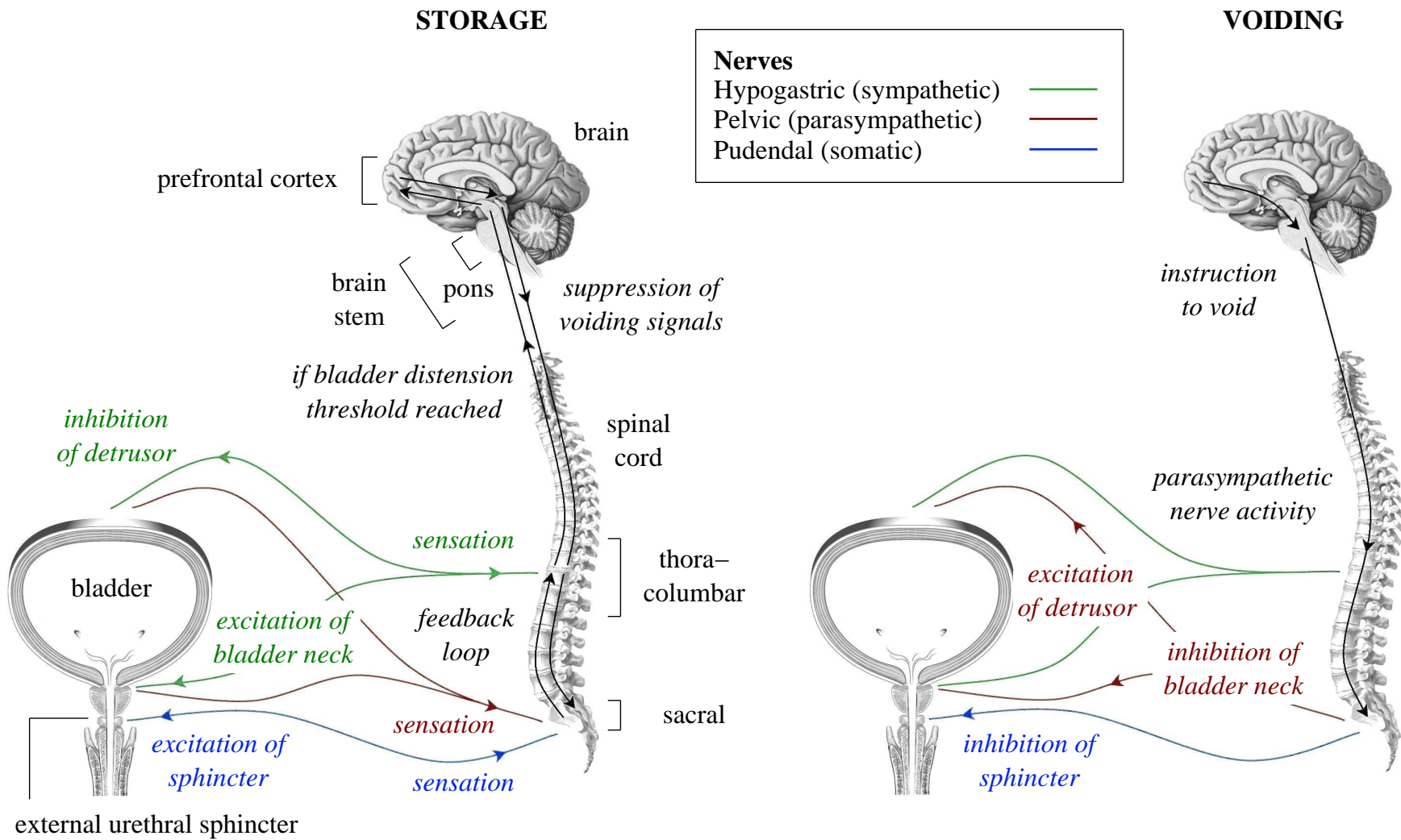


Figure 2.5 Illustration of the neural control of the lower urinary tract during storage (left) and voiding (right).

2.4 The mechanics of voiding

The following chapter describes the diseases that can interfere with the normal working order of the LUT. The most common affect the mechanical properties of the system, characterised by changes in the observed pressures and flow rates. Models of the LUT, described below, enable us to relate these clinical measurements to the underlying mechanisms in order to aid diagnosis and guide effective treatment.

2.4.1 Urethral resistance relation

In the simplest case, the bladder outlet can be modelled as a rigid opening through which fluid flows as a result of a driving pressure. The following form of Bernoulli's principle applies:*

$$p = \frac{\rho v^2}{2} \quad \Rightarrow \quad v = \sqrt{\frac{2p}{\rho}} \quad (2.1)$$

Where:

p = driving pressure

ρ = fluid density $\approx 1,000 \text{ kg}\cdot\text{m}^{-3}$ for urine

v = fluid velocity

Combining this with Equation 2.2 for volumetric flow rate in order to eliminate velocity results in Equation 2.3, describing how pressure dictates flow rate through a rigid opening; a higher pressure yields a higher flow rate.

* Any effects due to gravity, fluid viscosity or turbulence are small compared to the influence of driving pressure and are therefore ignored (Schäfer, 1990).

$$Q = vA \quad (2.2)$$

$$Q = A\sqrt{\frac{2p}{\rho}} \quad (2.3)$$

Where:

Q = volumetric flow rate

A = cross-sectional area of outlet

The bladder outlet, however, is not rigid but elastic. Consequently, even when the bladder outlet and sphincter are relaxed, the urethra remains closed until subject to a certain opening pressure, p_{uo} , which is the detrusor pressure at which flow begins. The equation must therefore be modified taking this elasticity into account as in Equation 2.4[†], which is a statement of the urethral resistance relation (URR) (Schäfer, 1985), illustrated in Figure 2.6.

$$Q = A\sqrt{2(p - p_{uo})} \quad \Rightarrow \quad p = p_{uo} + \frac{Q^2}{2A^2} \quad (2.4)$$

The URR defines the relationship between pressure and flow rate arising from the passive bladder outlet, which is dependent only upon opening pressure and cross-sectional area. However, the bladder outlet is only half of the story; the function of the detrusor muscle that generates the opening pressure and drives the flow of urine must also be taken into consideration.

[†] Density, ρ , has disappeared from this equation on the condition that $\rho \approx 1 \text{ g}\cdot\text{cm}^{-3}$, requiring the following units: Q in $\text{cm}^3\cdot\text{s}^{-1}$, A in cm^2 and p in $\text{g}\cdot\text{cm}^{-1}\cdot\text{s}^{-2}$.

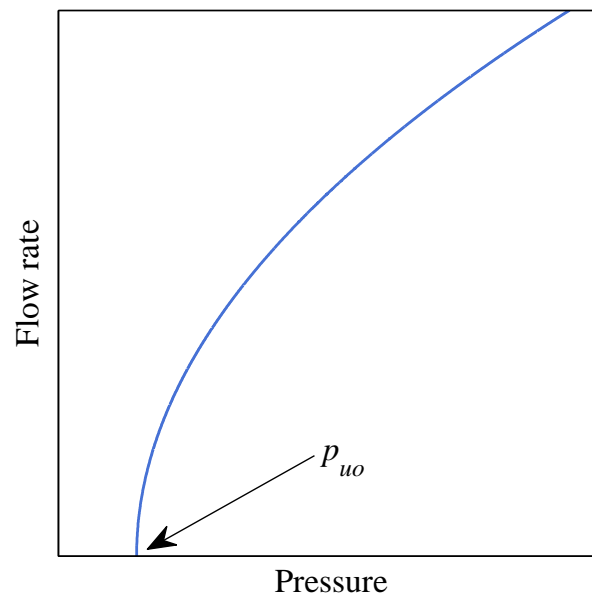


Figure 2.6 *The urethral resistance relation (URR) describing the relationship between pressure and flow rate arising from the passive bladder outlet (Schäfer, 1985). In accordance with Schäfer's convention, pressure is plotted on the horizontal axis and flow rate on the vertical axis.*

2.4.2 Bladder output relation

The Hill muscle model describes the relationship between the tension within a muscle strip and its speed of shortening (Hill, 1938). In the context of the detrusor, pressure can be derived from tension, and flow rate from speed of muscle fibre shortening. The model was therefore adapted to describe the relation between detrusor pressure and urine flow rate during voiding: the bladder output relation (BOR) (Griffiths, 1980). The BOR is given in Equation 2.5 and illustrated in Figure 2.7. Contrary to the URR, it indicates that pressure and flow are inversely related. This follows from the fact that there is a limit to the power output of the detrusor, power being the product of pressure and flow rate (Equation 2.6).

$$\left(\frac{p_{det}}{p_{det.iso}} + \frac{1}{4} \right) (4Q + Q^*) = \frac{5}{4} Q^* \quad (2.5)$$

Where:

p_{det} = detrusor pressure

$p_{det.iso}$ = isovolumetric detrusor pressure

Q = flow rate

Q^* = potential maximum flow rate

$$P = pQ \quad (2.6)$$

Where:

P = power

p = pressure

Q = flow rate

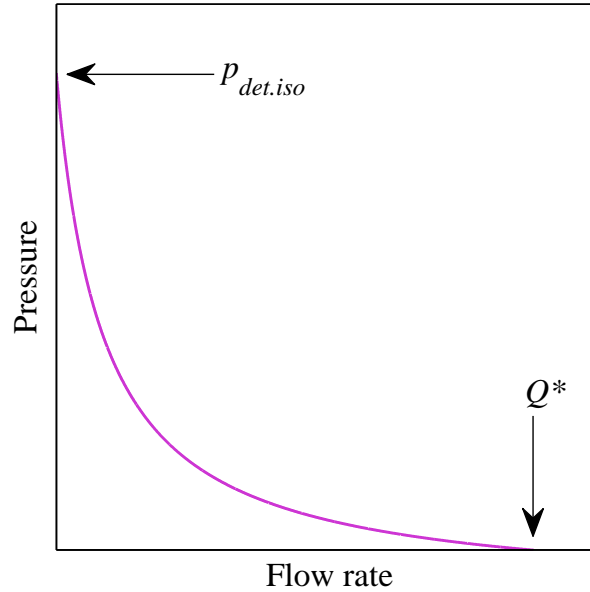


Figure 2.7 *The bladder output relation (BOR) describing the relation between detrusor pressure and urine flow rate during voiding (Griffiths, 1980).*

Determination of the URR and BOR in an individual would allow calculation of detrusor strength and outlet conditions, which would be of great clinical value. However, the volume dependency of $p_{det.iso}$ and Q^* causes the BOR to change throughout the course of a void. Outlet conditions also vary, partly due to sphincteric muscle activity and partly due to slow, viscoelastic relaxation of the outlet. The reciprocal nature of the BOR and URR, along with these constantly changing conditions, make the relationships very difficult to establish.

The models have, however, given us a better understanding of measurements of pressure and flow made in the clinic. The BOR tells us that a high detrusor pressure is not necessarily synonymous with a strong bladder muscle and may instead be the response of a normal or weak bladder to high outlet resistance. Importantly, they have allowed identification of pressure-flow combinations that are suggestive of certain diseases. This can be seen by comparing Figure 2.8, which shows the superimposition of the URR and BOR, with pressure-flow nomograms discussed in Chapter 3 (Figure 3.11, page 40).

The subject of this thesis is largely uroflowmetry, the measurement of urine flow rate with respect to time, which does not include direct measurement of detrusor pressure. It is, nevertheless, important to discuss uroflowmetry in the context of the function of the LUT, and this may allow speculation regarding the mechanisms behind observed flow information.

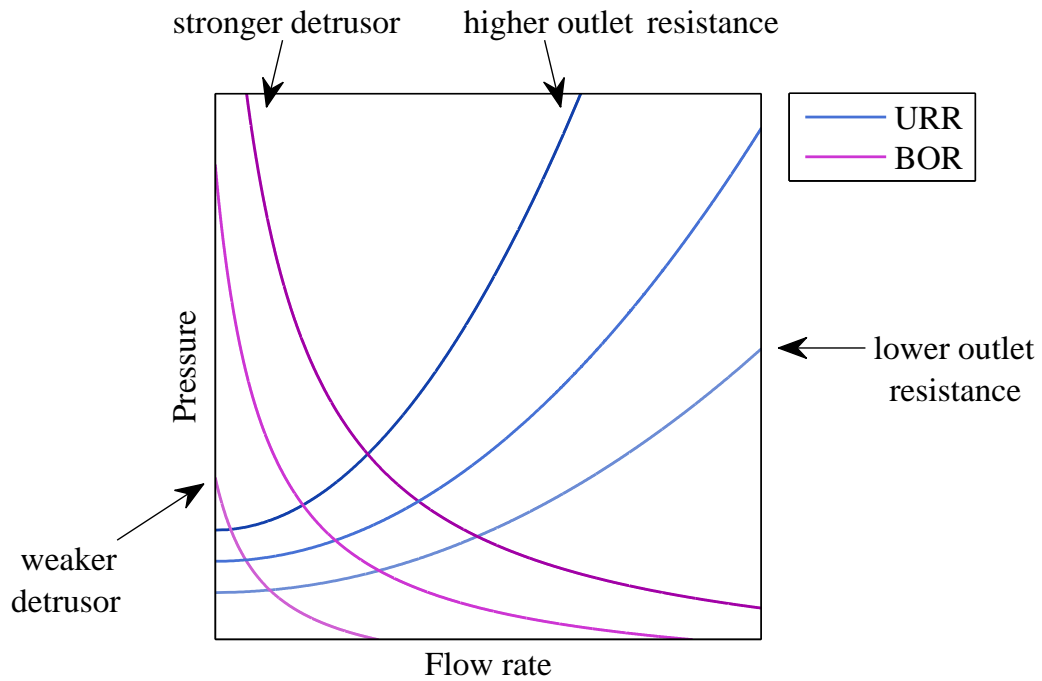


Figure 2.8 Superimposition of the URR and BOR, showing how the plots are shifted for higher or lower outlet resistance, and a stronger or weaker detrusor.

Chapter 3

Lower urinary tract symptoms: clinical background

3.1 Introduction

Chapter 2 described the form and function of the healthy male LUT. Sadly, as with many parts of the anatomy, age brings about change and deterioration of the LUT, often manifesting as lower urinary tract symptoms (LUTS, Table 3.1).

LUTS may be categorised into storage symptoms, such as difficulty postponing urination (urgency), voiding symptoms, such as a weak stream, and, according to some, post micturition symptoms, such as a sensation of not having emptied the bladder. This chapter describes the diseases associated with LUTS, the assessments carried out in order to diagnose their cause, and ways in which they may be treated.

Storage symptoms experienced during the storage phase	
Frequency	Voiding more often by day.
Nocturia	Having to wake at night one or more times to void.
Urgency	A sudden compelling desire to void which is difficult to defer.
Urinary incontinence	Any involuntary leakage of urine.

Voiding symptoms experienced during the voiding phase	
Slow stream	Reduced urine flow.
Spitting or spraying	Spitting or spraying of the urine stream.
Intermittency	Urine flow which stops and starts, on one or more occasions, during micturition.
Hesitancy	Difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine.
Straining	Muscular effort used to initiate, maintain or improve the urinary stream.
Terminal dribble	A prolonged final part of micturition, when the flow has slowed to a trickle / dribble.

Post micturition symptoms experienced immediately after micturition	
Incomplete emptying	A feeling of not having emptied the bladder after passing urine.
Post micturition dribble	Involuntary loss of urine immediately after voiding has finished.

Table 3.1 *Lower urinary tract symptoms as defined by the Standardisation Subcommittee of the International Continence Society (Abrams et al., 2002).*

3.2 Causes of lower urinary tract symptoms

3.2.1 Relating to the outlet

The most common cause of male LUTS is bladder outlet change due to benign enlargement of the prostate gland (BPE). Owing to the position of the prostate in relation to the urethra, histological changes within the prostate can interfere with the function of the LUT.

Benign prostatic hyperplasia (BPH), an increase in the number of prostatic cells, is closely related to the ageing process, present in the prostates of 50 % of men aged 51 to 60 years (Berry et al., 1984). The mechanism of BPH remains uncertain, but it is believed to occur with hormonal changes within the prostate. Early development of the gland depends upon the androgen dihydrotestosterone (DHT) which is derived from testosterone in the presence of the 5α reductase enzyme (Gormley et al., 1992). Levels of DHT within the prostate appear to increase with age, prompting a second growth spurt later in life. Figure 3.1 shows BPH in a sectioned prostate.

In approximately half of those with BPH, the prostate gland grows in size (BPE). The normal adult prostate is often described as walnut-sized; the enlarged prostate may be compared to anything up to that of a grapefruit*.

In approximately half of those with BPE, growth of the prostate into the urethra results in benign prostatic obstruction (BPO) (de la Rosette et al., 1998). Consequently, the detrusor pressure required to open the urethra is elevated and less bladder energy is available to generate flow, hence flow rate decreases and bladder emptying may be impaired.

* My personal favourite: “*His prostate was as large as a Newtown pippin.*” (Jones, 1897).

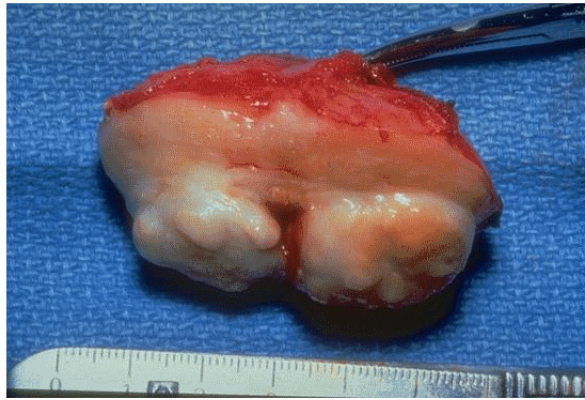


Figure 3.1 *A sectioned prostate showing two masses of BPH (University of Washington, Department of Pathology, 2010).*

Bladder outlet obstruction (BOO) is an umbrella term for obstruction of the bladder outlet, including BPO, characterised by increased detrusor pressure and reduced urine flow rate (Abrams et al., 2002). Strictures (a narrowing of the urethra due to scar tissue) and other such changes to the outlet resulting from injury, disease or congenital malformation may also cause obstruction (Griffiths, 1980). In this thesis, the term ‘obstruction’ generally refers to that of the bladder by the enlarged prostate.

3.2.2 Relating to the detrusor

Detrusor underactivity (DU) An underactive detrusor has poor contractile strength, or cannot sustain contraction for a sufficient period of time to complete bladder emptying (Abrams et al., 2002). Symptoms of DU can appear similar to those of BOO, in particular a weak urine stream. As with BPH, reduction in detrusor contractility accompanies the ageing process, but does not always induce symptoms. DU may be secondary to conditions such as diabetes or BOO, or neurological in cause (van Koevinge et al., 2011).

Detrusor overactivity (DO) Overactivity of the detrusor (not in fact the opposite of DU) is characterised by involuntary detrusor contractions that occur during the filling phase (Abrams et al., 2002). Frequency and sensations of urgency are often associated with DO, which may also lead to incontinence. The cause of DO is poorly understood; it is classified either as neurogenic, when the patient is known to have a relevant neurological condition, or otherwise idiopathic (Abrams et al., 2002).

3.2.3 Further causes of LUTS

Neurological As described in Section 2.3 (page 10), control of the LUT involves complex interaction between various parts of the CNS and peripheral nervous system, leaving it susceptible to interference from neurological disease or spinal injury. Patients with neurological LUT dysfunction may be unable to void at will or, conversely, may lack control over bladder emptying.

Behavioural The origin of LUTS may be behavioural rather than pathological. Over-consumption of fluids, particularly those with a diuretic effect, such as alcohol, may induce storage symptoms. Apparent frequency may in fact be ‘opportune’ voiding.

Urinary tract infections Symptoms of urinary tract infection (UTI) include haematuria (blood in the urine), dysuria (painful urination) and frequency.

Prostatitis Inflammation of the prostate, causing dysuria and frequent urination, is usually suspected in a man with a tender prostate gland.

Cancer Cancers of the prostate or bladder occasionally present as voiding or storage symptoms, respectively.

3.3 Investigation of the lower urinary tract

Clearly, each symptom has a number of possible origins, and each disease a number of possible symptoms. This many-to-many relationship makes it impossible to identify the cause of LUTS based upon symptoms alone. Therefore, within health services across the world, a considerable amount of resource is dedicated to investigations of the LUT. This section describes those investigations, beginning with uroflowmetry and voiding diaries, and continuing in approximate order of relevance to this thesis.

3.3.1 Uroflowmetry

The voiding phase can be quantified by asking the patient to pass urine into a flowmeter, giving measurements of flow rate (Q) as a function of time and voided volume (V_{void}). Uroflowmetry is a simple, informative and, therefore, popular investigation. At a conservative estimate, around 100,000 tests take place within the UK each year. This section focuses upon the patient experience and the characteristics and utility of the measurement.

Patient experience A typical day in our flow clinic will see up to 20 appointments scheduled at 15 minute intervals. The appointment letter requests that patients attend with a full bladder. Whilst feasible for some, the very nature of LUTS makes this a frightening prospect for others. These men sit in the waiting room and drink water until the desire to void arrives. Once it does, they are given an explanation of the test and left alone in the measurement room to pass urine. If the volume of urine passed is deemed insufficient, as discussed below, they return to the waiting room and refill their bladder for another attempt.

Not all men find the test difficult or unpleasant. There are those who arrive at the allotted time, ready to void, and are homeward bound within a few minutes. However, matters often do not go according to plan. Episodes of incontinence in the waiting room, sickness due to a stomach full of cold water, and ‘bashful bladder’ preventing any measurement being obtained; I have witnessed all of these during a relatively short spell in the flow clinic.

Parameters A multitude of parameters can be derived from a urine flow study; those most commonly reported are illustrated in Figure 3.2. In order to describe flow rate by a single parameter, either the maximum (Q_{max}) or average (Q_{ave}) is chosen. Q_{max} has been found to have higher diagnostic accuracy for obstruction and is therefore the recommended and more commonly reported parameter (Schäfer et al., 2002; Oelke et al., 2007).

The main application of Q_{max} is to determine the probability that a man is obstructed, but caution should be exercised. Firstly, a low flow rate alone cannot distinguish between an obstructed outlet and a hypocontractile detrusor. Secondly, the variability of Q_{max} within and between individuals results in an overlap, too, between obstructed and unobstructed men. This can be seen from Figure 3.3, which illustrates data from a large study of men with LUTS and shows the typical distributions of Q_{max} in obstructed and unobstructed populations. What can be said is that a man with a low flow rate is more likely to be obstructed than one without, and more likely to have obstruction than a weak detrusor, to such an extent to make Q_{max} a clinically valuable measurement.

Intra- and inter-subject variability of Q_{max} is an important theme throughout this thesis. The clinical effect of taking an average value from multiple measurements in each individual will be examined in detail in Chapter 5.

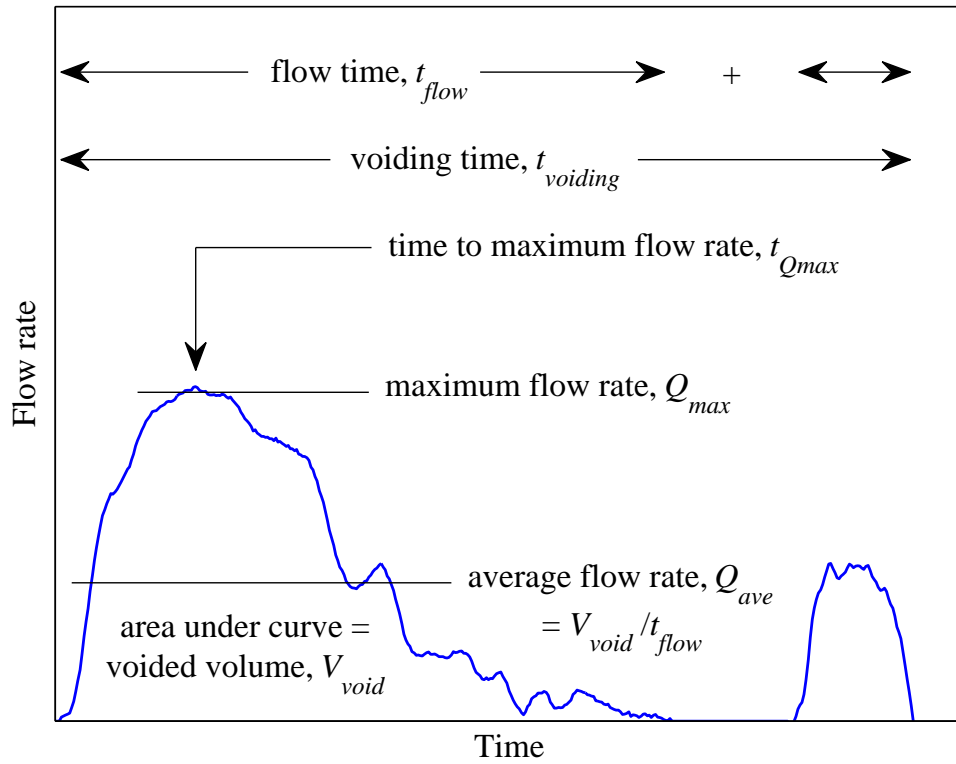


Figure 3.2 An annotated urine flow curve showing derivation of the following parameters: t_{flow} , $t_{voiding}$, t_{Qmax} , Q_{max} , Q_{ave} and V_{void} .

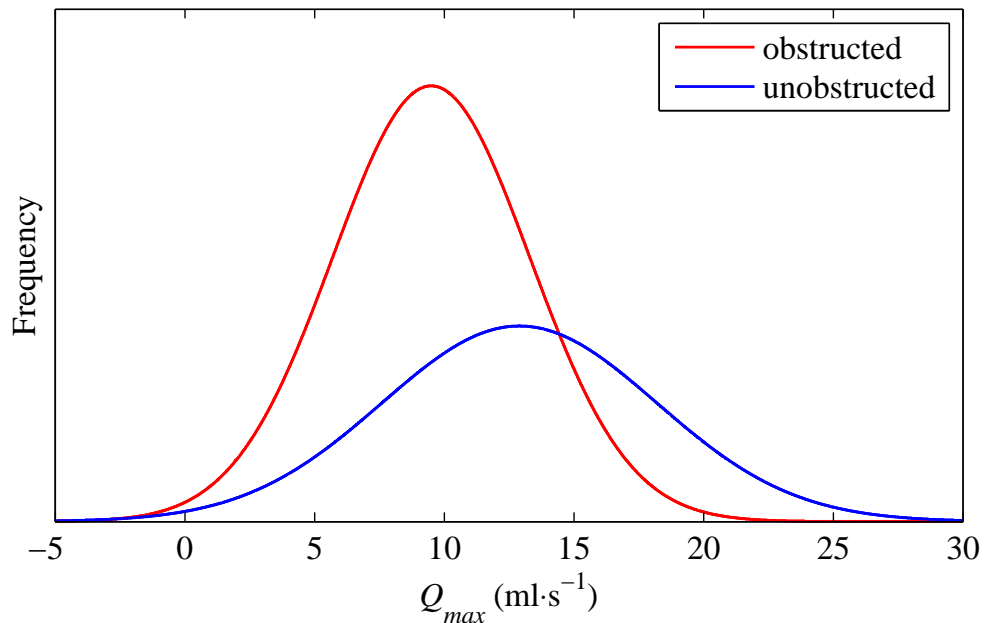


Figure 3.3 *The distributions of Q_{max} in obstructed and unobstructed populations as measured in a study of 871 men with LUTS (Rosier et al., 1996).*

There is no consensus regarding a threshold below which Q_{max} is abnormal. Commonly examined values are 10 and 15 $\text{ml}\cdot\text{s}^{-1}$. A study of 165 men with LUTS found 10 $\text{ml}\cdot\text{s}^{-1}$ to have sensitivity and specificity of 71 %, whereas 15 $\text{ml}\cdot\text{s}^{-1}$ had 95 % sensitivity and 35 % specificity (Reynard et al., 1996); these results are in keeping with similar studies (Poulsen et al., 1994; van Venrooij et al., 1995; Homma et al., 1998; Reynard et al., 1998; Oelke et al., 2007).

Volume-flow rate nomograms Intra-subject variability of Q_{max} can be explained to an extent by variation in bladder volume. As a muscle is stretched, the force that the muscle can exert once stimulated increases (Hill, 1938). Past an optimal level of distention, thought for the bladder to be 400 to 500 ml on average, the muscle becomes overstretched and the potential force decreases again. This effect is illustrated in Figure 3.4, which shows three flow recordings provided by a healthy subject.

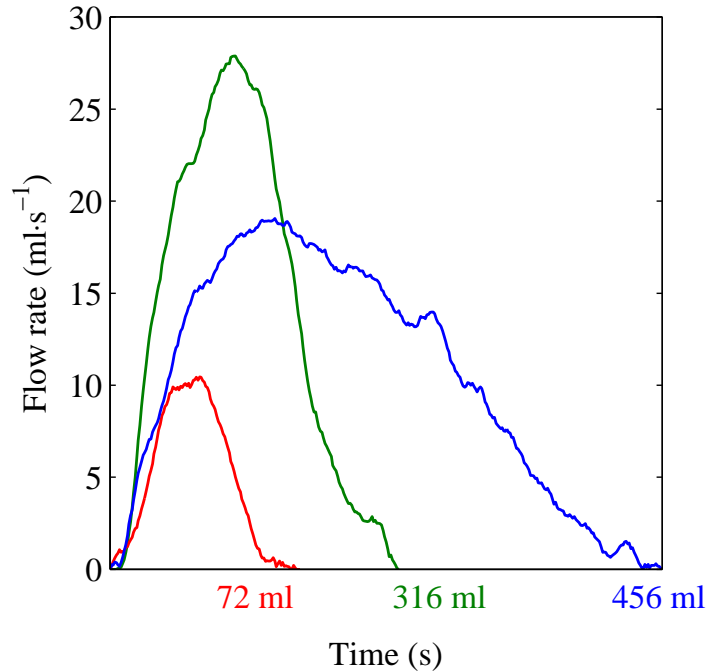


Figure 3.4 *Three flow recordings from a healthy subject, showing the dependency of maximum flow rate on bladder volume.*

In an attempt to account for this dependency of maximum flow rate upon bladder volume, Q_{max} can be evaluated in the context of volume information rather than alone. The Siroky nomogram is based upon 300 measurements from 80 asymptomatic men (Siroky et al., 1979). Maximum flow rate was plotted against bladder volume for each void with a line of best fit and confidence intervals according to what appears to be a quadratic relationship. This allows maximum flow rate to be classified as normal or, if it falls below the 2 standard deviation line, abnormally low (Figure 3.5, grey shaded area). The nomogram was subsequently validated in a second group of men undergoing disobstructive surgery; 98 % of pre-surgery measurements fell into the abnormal area and all post-surgery values into the normal area (Siroky et al., 1980).

The Bristol and Liverpool nomograms are similar concepts but derived instead with voided volume in the place of bladder volume (Kadow et al., 1985; Haylen et al., 1989). If the bladder does not empty completely, these two measurements

are not equivalent. Therefore, although the performance of the detrusor is better predicted by its starting volume, it is more appropriate to apply a nomogram based upon voided volume if only this measurement is known.

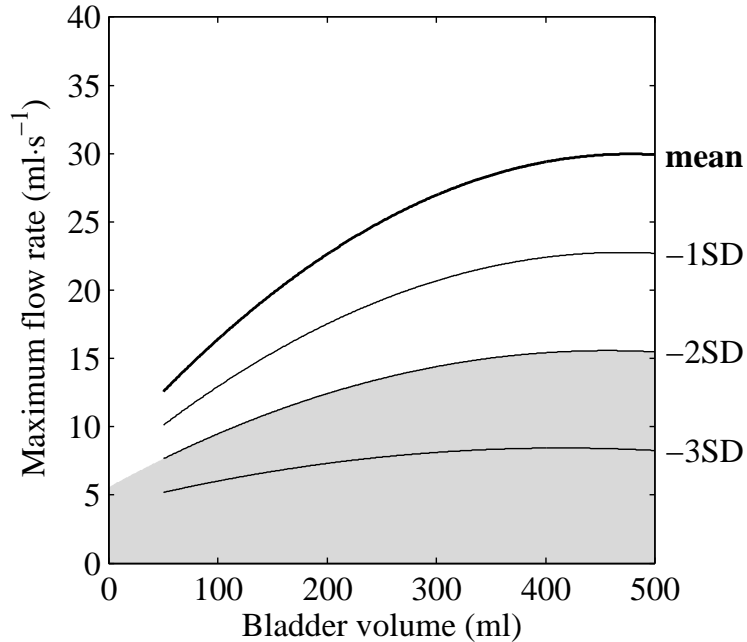


Figure 3.5 *The Siroky nomogram for maximum flow rate in men (Siroky et al., 1979). Flow rates of voids which fall into the grey shaded area below the $-2SD$ line are deemed to be abnormally low.*

Given that a low volume does not stretch the bladder to generate its optimum level of force, urological guidelines recommend that in order to obtain a representative flow rate measurement, the voided volume should be at least 150 ml (de la Rosette et al., 2001; National Institute for Health and Clinical Excellence, 2010). This may require repeat tests during one appointment, or multiple visits to the urology clinic.

Plotting a single $[V_{void}, Q_{max}]$ point can establish whether flow rate is low for a given volume. However, as shown later in this thesis, men with LUT dysfunction often do not exhibit the relationship between V_{void} and Q_{max} that is assumed, potentially invalidating this interpretation. More value may lie in establishing

whether a patient's voiding follows this 'normal' pattern, although in order to do so multiple measurements would be required.

Flow curves It is not only the parameters that are calculated from a urine flow study that are of clinical value, but also the shape of the curve (Abrams, 2006). A variety of shapes have become associated with different pathophysiologies; as illustrated in Figure 3.6.

In particular, flow patterns resulting from diseases of the outlet have been discussed. Figure 3.7 shows the effect of constrictive (stricture) and compressive (BPO) obstruction types on the urethral resistance relation (see Section 2.4.1, page 14). In the case of constrictive obstruction, there is no additional external compression of the urethra and voiding begins at a normal opening pressure. However, the much increased resistance to flow down the narrowed urethra alters the relationship between pressure and flow rate, resulting in less variation in flow rate and a flattened flow curve (Figure 3.6C).

In the case of compressive obstruction, compression of the urethra by the enlarged prostate requires a higher pressure to open the urethra and begin voiding. The relationship between pressure and flow rate is similar to that of a normal outlet, albeit shifted towards higher pressure. Thus, the compressive curve rises in a normal fashion, but with lower amplitude (Figure 3.6E) (Schäfer et al., 2002).

Equipment Most modern flowmeters are based upon either weight transducer or spinning disc technology. Weight transducer flowmeters weigh the volume of urine as it fills a container. This is converted to volume using a scaling factor and then to flow rate by differentiation with respect to time (Equation 3.1).

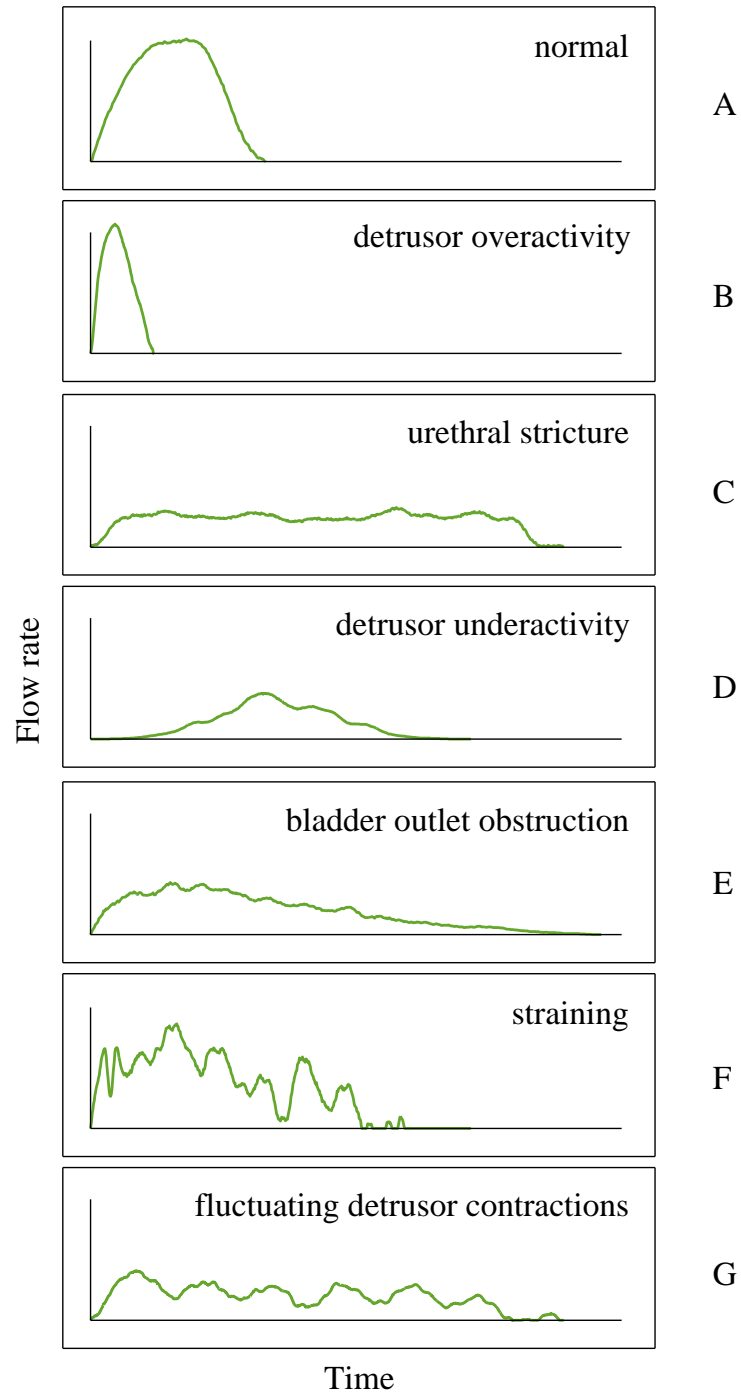


Figure 3.6 Flow curves associated with particular urological diagnoses (Abrams, 2006): (A) Normal bell-shaped curve, (B) supranormal flow which may be associated with detrusor overactivity, (C) the long, flat flow of a urethral stricture, (D) low flow rate and a delayed peak, thought to reflect detrusor underactivity, (E) the long, declining flow of bladder outlet obstruction, (F) relatively rapid fluctuations due to straining of the abdominal muscles, and (G) slower undulations reflecting fluctuating detrusor contraction, most commonly seen in patients with neurological conditions.

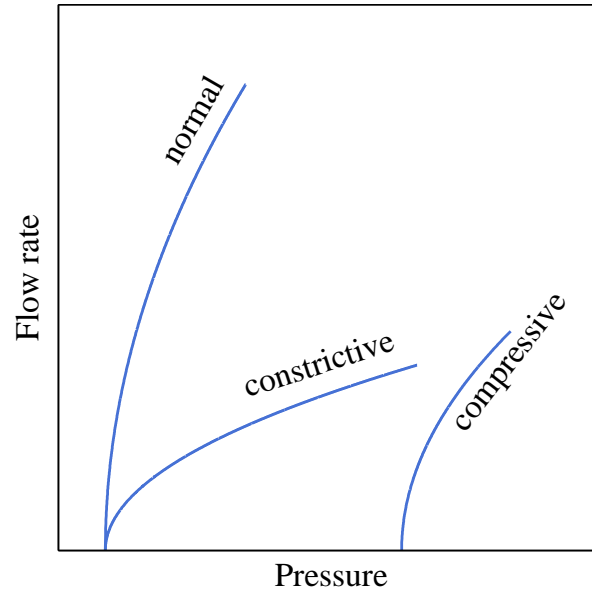


Figure 3.7 *The effect on the urethral resistance relation of constrictive and compressive obstruction types (Schäfer, 1990).*

A spinning disc flowmeter directs urine onto a motor-driven disc. Given that the urine tends to slow the rotation of the disc, the power supplied to the motor must vary to maintain a constant speed. This power is converted to flow rate using a scaling factor and then volume is calculated by integration with respect to time (Equation 3.2).

$$Q = \frac{dV}{dt} \quad (3.1)$$

$$V = \int Q dt \quad (3.2)$$

Where:

Q = volumetric flow rate

V = volume

t = time

By measuring flow rate directly, spinning discs avoid the amplification of noise by differentiation that occurs with weight transducer devices. However, given that urine comes into contact with moving parts, they are more difficult to clean and maintain.

3.3.2 Voiding diaries

A voiding diary complements the urine flow study by obtaining information about the storage phase. Patients are provided with a pre-printed chart on which to record their voiding habits over the course of several days. These range from the simplest form where only the times of voids are noted, to more involved bladder diaries which may require details of leaks, urgency and fluid intake. The most common for men with LUTS is a frequency-volume chart (FVC) where voided volumes are recorded against the appropriate hour.

Very frequent urination, nocturia, consistently low volumes, polyuria ($>40 \text{ ml}\cdot\text{kg}^{-1}$ body mass passed over 24 hours) and nocturnal polyuria (nocturnal volume $>33 \%$ of 24 hour volume) are all signs of abnormality (Abrams et al., 2002; van Kerrebroeck et al., 2002).

The length of the monitoring period ranges from 3 to 14 days, although there is evidence to suggest that longer diaries may cause ‘fatigue’ or even ‘despair’ (Tincello et al., 2007), resulting in poor compliance. As can be seen from Figure 3.8, the quality of these charts varies; some men neglect to complete them altogether.

	DAY 1	DAY 2	DAY 3	DAY 4
Time	Volume	Volume	Volume	Volume
6.00 am				
7.00 am	225	250	300	250
8.00 am		150		150
9.00 am	125 100	50	100	
10.00 am		100 150	100	150
11.00 am	50	100		75
NOON	100	75	150	100
1.00 pm	100	75		150
2.00 pm		100	175	
3.00 pm	200	150	100	
4.00 pm	50 100	250		75
5.00 pm		75	150	200
6.00 pm	200		200	100
7.00 pm		100 100	125	150
8.00 pm	100	150	200	50
9.00 pm		100		
10.00 pm	150	125	150	150
11.00 pm	100		50	100
MIDNIGHT			250	200
1.00 am			300	300
2.00 am	200			
3.00 am		250	200	400
4.00 am	300			
5.00 am		200		150

Total Volume passed 2200 2550 2550 2750

	DAY 1	DAY 2	DAY 3	DAY 4
Time	Volume	Volume	Volume	Volume
6.00 am		600 113 ml	860 227 ml	1260 340 ml
7.00 am	300 85.2 ml			
8.00 am				
9.00 am		35 99.4 ml	640 170 ml	
10.00 am				
11.00 am		300 85.2 ml		
NOON	700 71 ml			
1.00 pm	25		760 198 ml	900 255 ml
2.00 pm	300 85.2 ml			
3.00 pm			580 142 ml	
4.00 pm				
5.00 pm		700 98.8 ml	460 113 ml	
6.00 pm	300 85.2 ml			
7.00 pm				
8.00 pm				
9.00 pm				
10.00 pm		600 98.8 ml		
11.00 pm	200 56.8 ml		900 255 ml	
MIDNIGHT		460 113 ml		
1.00 am				
2.00 am				
3.00 am				
4.00 am				
5.00 am				

Figure 3.8 Two examples of patient-completed frequency-volume charts demonstrating their variable quality.

3.3.3 Post void residual (PVR)

A flow test may be followed by a scan to estimate the residual urine inside the bladder after voiding is apparently complete. Once the bladder has been scanned by an ultrasound probe, associated software calculates the volume within. The bladder is usually assumed to be spherical, resulting in errors to the order of $\pm 15\%$. Scans occasionally detect abnormalities of the bladder such as diverticula, where high intravesical pressures cause formation of pouches in the bladder lining (Figure 3.9). A less common technique for determination of PVR is by catheterisation.

Someone with normal LUT function may have a PVR of up to approximately 50 ml. A patient who leaves in excess of 1,000 ml in their bladder is considered to be in chronic urinary retention (National Institute for Health and Clinical Excellence, 2010).

It is thought that as voiding in the presence of obstruction demands more energy, the energy available for voiding is depleted before the bladder is emptied (Schäfer, 1990). In the case of the underactive detrusor, the same phenomenon results from the fact that less energy is available initially. Therefore, whilst a large PVR is abnormal, the measurement cannot distinguish between the two conditions. Whilst the same is true for Q_{max} , PVR has been found to have considerably lower diagnostic accuracy for obstruction (Oelke et al., 2007) and is therefore regarded as a less useful measurement.

3.3.4 Symptom scores

Patients may be asked to complete a symptoms questionnaire, commonly the International Prostate Symptom Score (IPSS, Figure 3.10). This involves scoring how often they experience various symptoms, ranging from 0 (*Not at all*) to 5

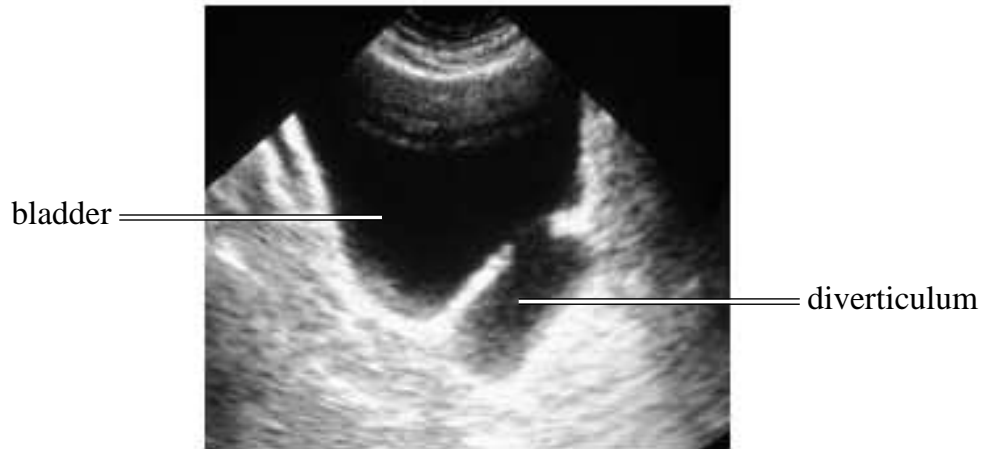


Figure 3.9 A bladder diverticulum revealed on an ultrasound bladder scan (Manski, 2013).

(*Almost always*) and rating quality of life (QoL), ranging from 0 (*Delighted*) to 6 (*Terrible*). Symptom scores correlate very poorly with specific conditions and objective assessment of disease and are therefore of little diagnostic worth (Rosier et al., 1996; de la Rosette et al., 1998). Rather, their value lies in being able to categorise baseline severity and bother, and track the improvement or decline in a patient's symptoms over time or following treatment. Change in symptom score is often the primary patient-reported outcome measure for clinical trials involving men with LUTS.

3.3.5 Urodynamics

The gold standard test for investigating the function of the LUT is urodynamics. This test measures the pressure generated by the detrusor muscle during storage and then during voiding when the data can be related to the recorded urine flow rate. The term pressure-flow studies (PFS) refers to the voiding phase of urodynamics.

Prior to beginning the study, manometer catheters are inserted into the patient's bladder (urethrally) and rectum, to measure intravesical pressure (p_{ves}) and

International Prostate Symptom Score (IPSS)

Over the past month, how often have you experienced...	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost Always	Your score
Incomplete emptying	0	1	2	3	4	5	
Frequency	0	1	2	3	4	5	
Intermittency	0	1	2	3	4	5	
Urgency	0	1	2	3	4	5	
Weak stream	0	1	2	3	4	5	
Straining	0	1	2	3	4	5	

Nocturia	None	1 time	2 times	3 times	4 times	5 times or more	Your score
Over the past month, how many times did you most typically get up to urinate from the time you went to bed to the time you got up?	0	1	2	3	4	5	

Total IPSS score	
-------------------------	--

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel?	0	1	2	3	4	5	6

Total score: 0 – 7 mildly symptomatic; 8 – 19 moderately symptomatic; 20 – 35 severely symptomatic.

Figure 3.10 *The International Prostate Symptom Score questionnaire began life as the AUA-7 (Barry et al., 1992). The eighth question regarding quality of life was added later.*

abdominal pressure (p_{abd}), respectively. p_{abd} is subtracted from p_{ves} to determine the pressure generated by the detrusor muscle (p_{det}). The urethral catheter has a second lumen through which the bladder is filled with room-temperature saline. During filling, bladder sensations are documented with respect to the observed pressures. The patient is then asked to pass urine into a flowmeter whereby flow rate (Q) and V_{void} are measured. A contrast agent may be included with the filling fluid to allow X-ray imaging of the LUT.

A number of diseases of the LUT, such as BOO, DO and DU, are defined according to observations made during urodynamic studies (Abrams et al., 2002). Particular effort has gone into applying urodynamics to classification of obstruction, the result being pressure-flow nomograms. Three of these are shown in Figure 3.11 and described below.

The Abrams-Griffiths (AG) nomogram (Figure 3.11A) is based upon urodynamic data from 117 men with suspected BOO. First, p_{det} versus Q was plotted for each void. Those with mean gradient below $2 \text{ cmH}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$ and with final $p_{det} \leq 40 \text{ cmH}_2\text{O}$ were classified as unobstructed, and the remainder as obstructed. Q_{max} was then plotted against $p_{det.Qmax}$ (the detrusor pressure at the point of maximum flow) for each void. The boundaries of the nomogram are those that separated obstructed and unobstructed patients, with an equivocal region where classifications overlapped (Abrams and Griffiths, 1979).

The International Continence Society (ICS) nomogram (Figure 3.11B) is a simplification of the AG nomogram, with the low pressure, low flow region reclassified from equivocal to unobstructed. This allows categorisation according to AG number ($p_{det.Qmax} - 2Q_{max}$) with <20 , 20 to 40 and >40 corresponding to unobstructed, equivocal and obstructed, respectively (Griffiths et al., 1997).

Figure 3.11C shows the linear passive urethral resistance relation (LIN-PURR) nomogram. In addition to obstruction classification, this grades the extent of

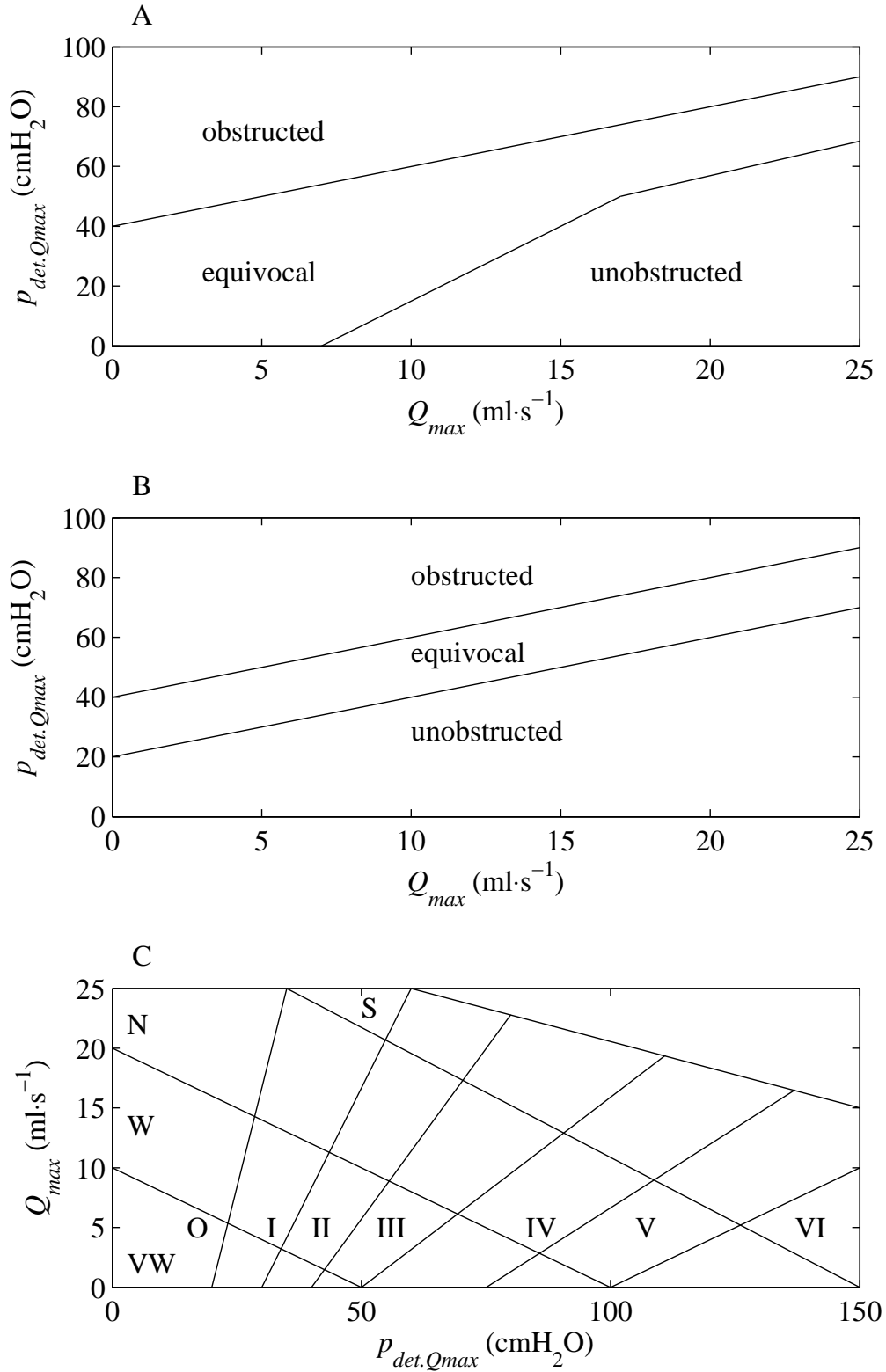


Figure 3.11 Three pressure-flow nomograms: (A) Abrams-Griffiths, (B) ICS and (C) LIN-PURR.

the obstruction (0 = unobstructed, I = mildly obstructed, II to VI = obstructed with increasing severity) and also the strength of the detrusor (ST = strong, N = normal, W = weak, VW = very weak). A straight line is drawn between $[p_{det.Qmax}, Q_{max}]$ and $[p_{uo}, 0]$, the gradient and position of which provides the classifications (Schäfer, 1990). The nomogram is a linearisation of the BOR and URR, as can be seen by comparison with Figure 2.8 (page 19). The axes are inverted with respect to the above two nomograms; its grade II obstruction zone corresponds approximately to the equivocal region of the ICS nomogram.

3.3.6 Non-invasive pressure-flow measurements

The ability to measure bladder pressure non-invasively would be highly advantageous, reducing morbidity and discomfort associated with invasive procedures and increasing efficiency. This is the motivation behind the development of non-invasive pressure-flow systems over the past 15 years. Examples include Pel's condom catheter (Pel and van Mastrigt, 1999), and the penile cuff device, described below.

The penile cuff machine (CT3000, Mediplus Ltd), developed in this department, works upon the same principle as measurement of systolic blood pressure by occlusion of blood vessels. A pneumatic cuff is positioned around the penis and the patient asked to pass urine. Once the flow of urine is detected by a flowmeter, the cuff inflates until the point where flow ceases. This cuff interruption pressure, $p_{cuff.int}$, is a measure of bladder pressure under isovolumetric conditions (Griffiths et al., 2002).

Through a combination of theory and experimentation, the ICS nomogram was adapted for use with $p_{cuff.int}$ in place of $p_{det.Qmax}$. The line separating obstructed and equivocal was raised by 40 cmH₂O to account for abdominal pressure plus the height difference between bladder and cuff, and its slope increased by $2Q_{max}$ to

account for the increase in detrusor pressure under isovolumetric rather than flow conditions. The line separating unobstructed and equivocal was removed, and a line at $Q_{max} = 10 \text{ ml}\cdot\text{s}^{-1}$ inserted to improve predictive performance (Griffiths et al., 2005).

3.3.7 Digital rectal examination (DRE)

The prostate is positioned slightly anterior to the rectum and so a digital rectal examination can be performed to assess its size, symmetry, firmness and tenderness. BPO is more likely to result from a large prostate, malignancy can cause hard, irregular nodules, whereas a tender gland may indicate prostatitis.

3.3.8 Prostate specific antigen (PSA)

PSA is an enzyme secreted by the prostate gland, a small amount of which diffuses into the blood stream and is measured by a blood test. Malignant changes within the prostate result in a larger concentration of PSA in the blood. However, the same is true for benign conditions such as BPH and prostatitis; PSA therefore has low specificity for diagnosing cancer. PSA levels are also elevated by infection, retention and catheterisation and so values obtained under these circumstances should be rechecked at an appropriate time. A rapid increase in PSA level, even if it remains within the normal range, is also suspect. Following an abnormal result, patients may be expedited to specialist assessment for further, more specific tests such as a transrectal ultrasound scan of the prostate (TRUS) or biopsy. A study of over 2,000 healthy men established the age-specific normal reference PSA ranges displayed in Table 3.2 (Oesterling et al., 1993).

Age range (years)	PSA range (ng·ml ⁻¹)
40 - 49	0 - 2.5
50 - 59	0 - 3.5
60 - 69	0 - 4.5
70 - 79	0 - 6.5

Table 3.2 Age-specific reference PSA ranges derived from a study of over 2,000 healthy men (Oesterling et al., 1993).

3.3.9 Further investigations

Urinalysis Urinalysis tests a mid-stream sample of urine for the presence of various substances, such as blood and protein, and measures pH and specific gravity. The results may be suggestive of infection, renal disease, malignancy, diabetes, or stones of the kidney or bladder.

Pad tests For patients suffering from incontinence, a pad can be worn for a specific period of time, or during a particular activity, and then weighed in order to quantify urine leakage.

Serum creatinine The blood can be tested in order to measure the concentration of creatinine, a waste product filtered out by the kidneys. A high level may indicate impaired renal function.

Cystoscopy The appearance of the lower urinary tract can be investigated by passing an endoscope through the urethra and into the bladder.

3.3.10 Evidence

There is very little evidence, particularly of high level and quality, regarding the value of performing the investigations just described in men with LUTS. Guideline recommendations regarding which tests should be offered in which care settings are often based upon expert opinion alone; the lowest level of clinical evidence (Figure 3.12). This applies even to the ‘gold standard’ urodynamics, prompting the National Institute for Health Research in 2012 to launch a commissioned Health Technology Assessment call to answer the following research question:

“In men with lower urinary tract symptoms, does the addition of multichannel cystometry change management and improve patient outcomes?”

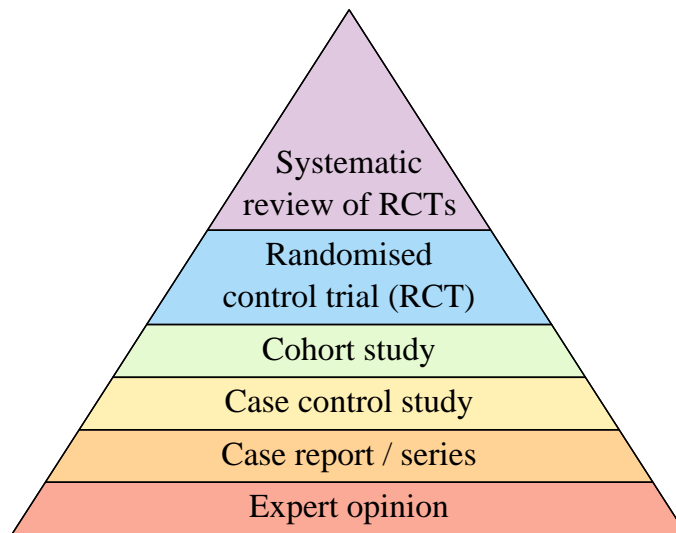


Figure 3.12 *The hierarchy of evidence (Guyatt et al., 1995).*

3.4 Treatment

Once the probable cause of LUTS has been established, treatment options fall into the categories of conservative, medical and surgical. Broadly speaking these categories correspond to mildly, moderately and severely symptomatic, respectively. The IPSS questionnaire is one way in which symptom severity is defined (Figure 3.10).

3.4.1 Conservative management

Men with mild symptoms may be satisfied to receive fluid intake and lifestyle advice and undergo watchful waiting, where their condition is monitored over time. Measures such as these are less effective in reducing symptoms than medical and surgical treatments. Nevertheless, a net reduction in symptom scores is observed in men assigned to watchful waiting (Wasson et al., 1995).

Other conservative measures include training of the pelvic floor muscles and bladder to increase muscle strength and suppress urge, containment products such as pads and penile clamps, and intermittent or permanent catheterisation.

3.4.2 Medical therapy

Men with suspected BOO and moderate symptoms are often treated with medication, most commonly alpha-adrenergic-antagonists (α -blockers). As discussed in Section 2.3 (page 10), the noradrenaline neurotransmitter interacts with receptors within the smooth muscle of the LUT to maintain contraction, and therefore assists in maintaining continence, during the storage phase. As the name suggests, α -blockers block these receptors, resulting in relaxation of the bladder neck and prostate and therefore lower outlet resistance. α -blockers have been found consistently to decrease IPSS score by around 8 points and increase Q_{max} by 2

to $3 \text{ ml}\cdot\text{s}^{-1}$ on average across a cohort (National Institute for Health and Clinical Excellence, 2010).

Men found to have a large prostate on DRE or TRUS, or with high PSA, may be prescribed 5α -reductase inhibitors. Section 3.2.1 described how growth of the prostate involves conversion of testosterone to DHT, requiring the presence of the 5α reductase enzyme. 5α -reductase inhibitors decrease the amount of 5α reductase within the prostate, resulting in a lower level of DHT. This halts growth and eventually results in shrinkage of the gland to the order of 20 % over 6 months.

The above medications may also be prescribed to unobstructed men with detrusor underactivity so that the weakened detrusor faces less resistance to flow.

An overactive bladder may be treated medically with antimuscarinics, which suppress the activity of the parasympathetic nervous system responsible for instigating detrusor contraction (see Section 2.3, page 10). A muscarinic agonist may be used to treat underactivity by the opposite mechanism, although there is little evidence of benefit.

Other medical options include desmopressin to reduce urine production, or an afternoon diuretic to encourage evening, rather than nighttime, voiding for men suffering from nocturia. Combined medical therapy includes an α -blocker plus 5α -reductase inhibitor, and an α -blocker plus antimuscarinic.

3.4.3 Surgery

For men with severe voiding symptoms, or more serious consequences of obstruction, several types of surgery are available to remove the obstructive prostate in part or, rarely, in its entirety. These disobstructive surgeries, of which there are approximately 30,000 performed each year in the UK (Abrams, 1994), are the subject of Chapter 8.

Surgical options to combat storage symptoms include augmentation cystoplasty to increase bladder capacity, myectomy or intravesical botulinum toxin injection to decrease muscle activity, and sacral nerve stimulation to inhibit the bladder (National Institute for Health and Clinical Excellence, 2010).

3.5 Conclusion

LUTS, previously termed ‘prostatism’, were once thought as the name suggests to be synonymous with disease of the prostate. In 1994, Abrams published a plea to abolish this presumptive term in order that fewer men be treated without sufficient diagnostic work-up. In fact, a third of men with LUTS are not obstructed (Abrams and Feneley, 1978) and will experience poorer outcome from treatment as such.

Storage symptoms such as frequency, urgency and nocturia are far more bothersome than a weak urine stream, probably owing to the resulting social disruption. This suggests that we ought to focus upon treating the bladder. However, animal studies have shown the obstructed bladder to become ischemic and hypertrophied, reducing the energy supply to the muscle and altering its viscoelastic properties (Levin et al., 1990). Consequently, it becomes ‘weak’ (DU) and ‘twitchy’ (DO), with overactivity found to occur in 50 % of men with BOO (National Institute for Health and Clinical Excellence, 2010). There is also evidence to suggest that by treating the outlet, the bladder will revert towards its original function (van Venrooij et al., 2002; de Nunzio et al., 2003). Therefore, the first question to the urologist’s mind is often: *Obstructed or not?*

In men with suspected obstruction, invasive investigation is generally reserved for cases in which surgery poses a particular risk, such as very elderly patients, or younger men wishing to retain sexual function. Therefore, diagnosis is usually based upon a series of non-invasive investigations. Uroflowmetry is often the only objective assessment of LUT function made prior to surgical intervention.

The primary aim of urodynamic investigation is to reproduce the patient's symptoms (Abrams, 2006), requiring the circumstances of the tests to be as 'normal' as possible. How many men *normally* pass urine with someone waiting behind the door, having filled their bladder as quickly as possible and then held on until they were called? Men often complain of a variable flow rate, perhaps depending on time of day, but this cannot be described by a single measurement.

These issues led naturally to the conclusion that urine flow studies may be better placed in patients' homes, and that the supplementary information available from multiple measurements may be clinically valuable. Recent research interest in the subject has therefore been high; a number of different techniques and devices have been reported. The following chapter presents a review of the literature regarding methods and value home urodiagnostics.

Chapter 4

Methods and value of home urodiagnostics in the assessment of men with lower urinary tract symptoms: A literature review

4.1 Introduction

The aim of this chapter is to review the literature regarding techniques and devices used for home urodiagnostics, to discuss their value as alternatives to clinic-based assessment, and to identify gaps in the evidence. The ability to record multiple flows in an individual is perceived as a key advantage of home urodiagnostics. Thus, where relevant to the clinical value of multiple home measurements, literature describing clinic-based studies of multiple flow measurements is also included.

4.2 Methods

A search of PubMed and Embase was conducted for the period January 1988 to September 2013 using keywords ‘home uroflowmetry’, ‘multiple uroflowmetry’, ‘uroflowmeter’, ‘electronic voiding diary’ or ‘automated voiding diary’, and focussed subject headings ‘uroflowmetry’ or ‘urine flow rate’. Reference lists from retrieved articles were examined and additional papers checked for relevance. Proceedings of the annual meetings of the ICS* since 2008 were searched. Relevant guidelines were obtained from the UK NHS Evidence repository†. Papers were deemed eligible if they described original studies of the use of home uroflowmetry in adult men or the use of multiple clinic-based readings in an individual. Eligible literature was retrieved and further checked for relevance. The results of this systematic search are shown in Figure 4.1.

4.3 Results

4.3.1 Home uroflowmetry techniques

Timing methods The simplest method is to time a void of given volume, such as the first 100 ml (Hansen and Zdanowski, 1997; Folkestad and Spangberg, 2004), or measure V_{void} over a given time (Bloom et al., 1985; Schwartz et al., 1998). The measured parameter, which must be documented manually, is an average flow rate over the timed period rather than Q_{max} .

Timed flow rates correlate moderately with Q_{max} , suggesting their value as a home screening tool. However, the practicality of the test is questionable, particularly if the stream must be stopped or redirected after 100 ml. Further, the requirement

* www.icsoffice.org

† www.evidence.nhs.uk

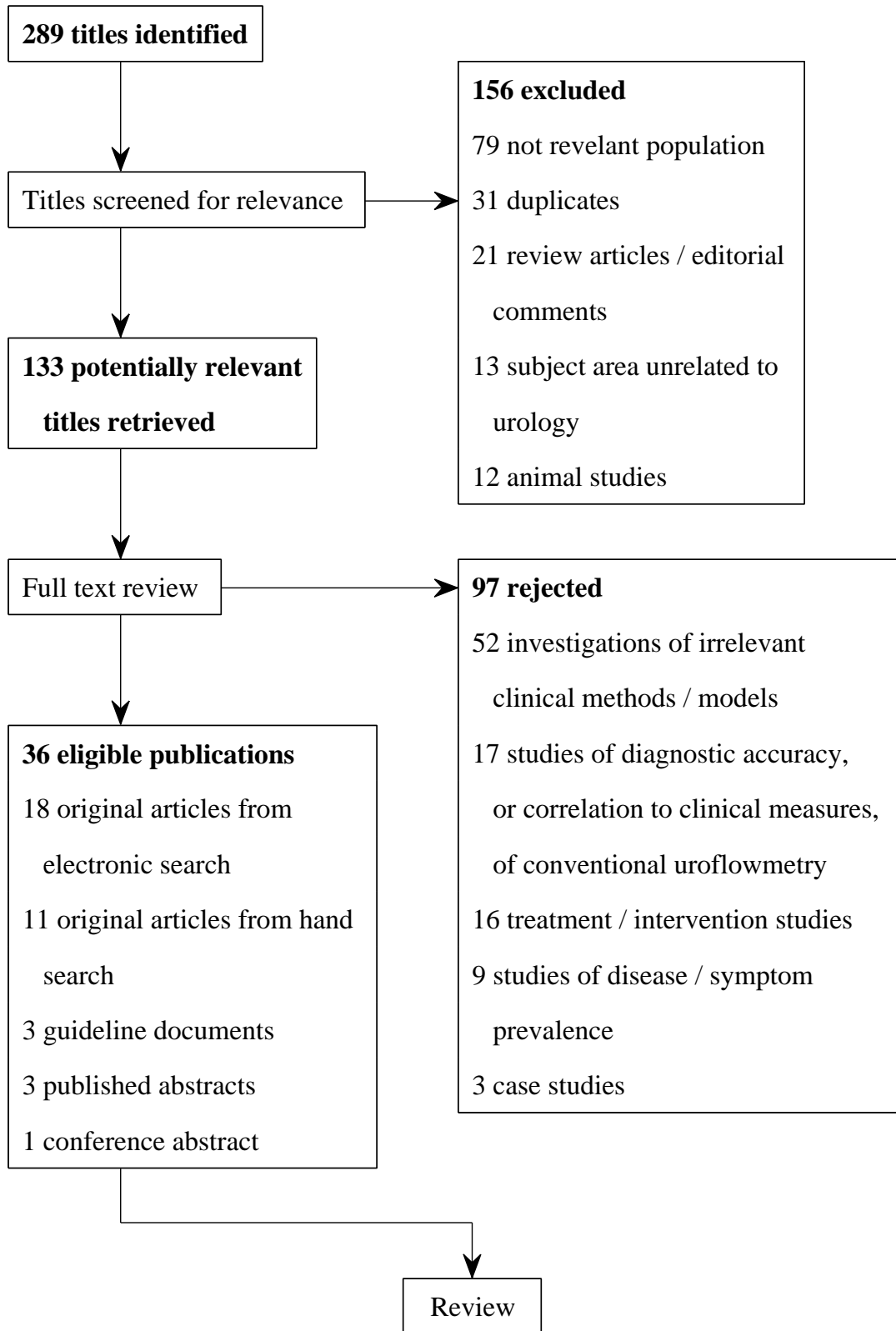


Figure 4.1 *Flow chart of selection process for reviewed literature.*

to begin timing “*when the stream has reached full strength*” or “*from the distinct feeling of relief*” (Bloom et al., 1985) is certain to introduce an element of subjectivity.

Funnel devices An estimate for Q_{max} can be obtained using hand-held funnel devices. The user voids into the funnel and urine flows out through a suitably restricted aperture into a measuring container.

When flow from the funnel, determined by the size of the aperture and the height of fluid above it, equals the patient’s flow rate into the device, the level of urine inside the funnel remains constant. When outflow exceeds inflow, the level falls; when inflow exceeds outflow, the level rises. Thus the maximum level to which urine rises during a void gives an indication for Q_{max} . The measurement is documented by writing the value along with V_{void} on a chart.

Basic designs reported by Smith (1965; Figure 4.2A) and more recently Currie (1998; Figure 4.2B) were calibrated to a single Q_{max} threshold. If urine did not rise to the threshold level the test was deemed positive, indicating an abnormally low Q_{max} . The next development was to incorporate multiple calibrated levels into the device in order to categorise Q_{max} into ranges. The device reported by Pel and van Mastrigt (2002) categorised Q_{max} into one of seven ranges using a funnel with multiple apertures (Figure 4.2C). The Uflow Meter[®] (MDTi, Wolverhampton, UK) comprised a funnel of progressively narrow chambers with the aperture and diameters calibrated to indicate three ranges for Q_{max} : $<10 \text{ ml}\cdot\text{s}^{-1}$, $10 \text{ to } 15 \text{ ml}\cdot\text{s}^{-1}$ and $>15 \text{ ml}\cdot\text{s}^{-1}$ (Figure 4.2D). When evaluated in 46 men with LUTS, results from the Uflow Meter showed reasonable agreement with clinic uroflowmetry (Kappa = 0.61), but 11 % of participants found the device difficult to use due either to obesity or the requirement to void whilst observing the level of urine (Pridgeon et al., 2007).

The Peakometer, first reported by Drach and Binard (1976), incorporated a calibrated indicator strip that was stained by urine as it rose in the chamber and hence recorded Q_{max} automatically, although V_{void} was still documented manually following visual inspection of the level of fluid in the container (Drach and Binard, 1976; Ball, 1982; Colstrup et al., 1983; Figure 4.2E). The more recent CaptiFlow™ is identical in concept to the Peakometer (Lucas, 2009).

Electronic devices Electronic flowmeters based upon similar technology to standard clinic-based instruments have also been evaluated in the home. Those reported in the literature include the handheld P-flow meter (de la Rosette et al., 1996; Witjes et al., 1997; Sonke et al., 1999, 2002; Figure 4.2F), the Da Capo™, a weight transducer clinic flowmeter adapted for home use (Jørgensen et al., 1998; Porru et al., 2005; Figure 4.2G), the PUF2000 (Boci et al., 1999) and the Home UroData system (Golomb et al., 1992). These devices obtain an automated frequency-volume chart along with measurements of the full flow trace and voided volume for multiple voids, without the need for the user to document results manually. Little need be said about their technical capabilities in comparison to in-clinic flowmeters; they are essentially the same equipment operated in a different setting.

Electronic voiding diaries Only one study was found describing the use of an electronic voiding diary in adult men, which included only three male participants (Quinn et al., 2003). There was deemed to be insufficient evidence to allow discussion.

4.3.2 Reported benefits of home uroflowmetry

Describing variability Many studies have analysed multiple flow measurements from an individual, obtained in the home or clinic, in order to investigate

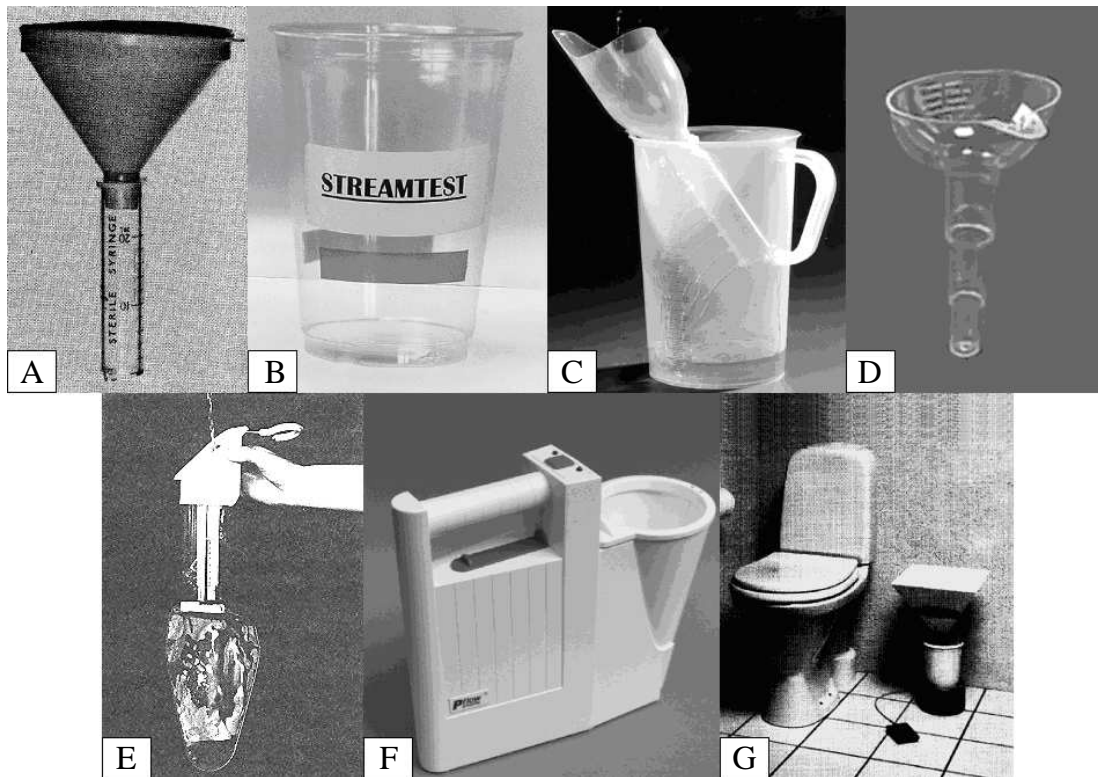


Figure 4.2 Seven home uroflowmeters described in the literature: (A) Smith's device (Smith, 1965), (B) Streamtest cup (Currie, 1998), (C) PEL device (Pel and van Mastrigt, 2002), (D) Uflow Meter[®] (Caffarel et al., 2007; Pridgeon et al., 2007), (E) Peakometer (Drach and Binard, 1976; Ball, 1982; Colstrup et al., 1983), (F) P-flow (de la Rosette et al., 1996; Witjes et al., 1997; Sonke et al., 1999, 2002) and (G) Da Capo (Jørgensen et al., 1998; Porru et al., 2005).

variability of flow parameters. Section 3.3.1 (page 29) described the Siroky nomogram which quantified the relationship between flow rate and voided volume in a cohort of asymptomatic men (Figure 3.5). Sonke et al. (2002) analysed the relationship between Q_{max} and V_{void} by collecting multiple home flows from 208 men with LUTS and found it to differ considerably between individuals; 28 % having an inverse relationship. They also reported that unobstructed patients had steeper regression lines than obstructed patients, although this was not quantified.

Golomb et al. (1992) measured the variability of home uroflowmetry in patients with LUTS. In their study group, uroflowmetric parameters varied more in men with BPE than in healthy controls. Witjes et al. (1997) compared circadian changes at home in men with varying grades of BOO according to LIN-PURR evaluation. Significant differences in Q_{max} and V_{void} between groups with differing grades of obstruction were seen according to time of day. V_{void} was higher, and Q_{max} lower, during the night, the difference in Q_{max} being larger for men with more severe obstruction. Porru et al. (2005) also found significant circadian differences in multiple measurements of Q_{max} at home in 107 patients with LUTS. Systematic variability in Q_{max} has also been found in the clinic with voiding position (such as sitting versus standing, the latter yielding a higher flow rate) (Yamanishi et al., 1999) and even season and temperature (Watanabe et al., 2007).

One way to determine the likely spread of flow rates measured in practice for an individual is to calculate the intra-subject standard deviation (SD) of multiple readings. Home studies have found the intra-subject SD of multiple measurements of Q_{max} in an individual to range between 0.5 and 6.0 ml·s⁻¹ (Matzkin et al., 1993; Boci et al., 1999). This implies that for a patient with a moderate intra-subject SD of 2.5 ml·s⁻¹, Q_{max} may vary by up to 10 ml·s⁻¹ (95 % confidence interval) between voids due to random fluctuation alone (Sonke et al., 1999).

Caffarel et al. (2007) recruited 22 volunteers to perform two clinic flows and record home flows for two weeks using the Uflow Meter. Bland-Altman analysis showed considerable variation between the two clinic readings (mean difference = $2.5 \text{ ml}\cdot\text{s}^{-1}$) whereas comparison of average Q_{max} from two series of multiple home flow recordings made during successive weeks showed little variation (mean difference = $-0.2 \text{ ml}\cdot\text{s}^{-1}$).

Meier et al. (1994) recruited 100 men with micturition disorders to record multiple home flows and thus calculated the number of measurements required to reliably detect a given difference in average Q_{max} . For example, it was found that approximately 50 measurements before and after an intervention were needed to be certain of a difference of $2 \text{ ml}\cdot\text{s}^{-1}$ within an individual. The same group went on to show that for clinical trials with Q_{max} as an outcome measure, sample sizes could be reduced considerably by recording multiple voids from each individual before and after the intervention (Meier et al., 1995).

Increasing diagnostic accuracy Boci et al. (1999) analysed multiple home flows and pressure-flow studies from 24 patients with symptomatic BPE. Mean home Q_{max} was compared to obstruction grade according to the LIN-PURR nomogram (see Figure 3.11C, page 40). Although no unobstructed patient had a mean home Q_{max} below $10 \text{ ml}\cdot\text{s}^{-1}$ and no obstructed patient was above $14 \text{ ml}\cdot\text{s}^{-1}$, the interval 10 to $14 \text{ ml}\cdot\text{s}^{-1}$ contained mixed diagnoses. Just 46 % (11/24) of patients were classified correctly using mean Q_{max} alone.

Reynard et al. (1996) recruited 165 patients to perform four consecutive clinic flows, each having previously undergone PFS with obstruction diagnosed according to the Abrams-Griffiths nomogram (see Figure 3.11A, page 40). The diagnostic accuracy of the highest Q_{max} recorded from one, two, three and four voids was compared for different cut-off values. If Q_{max} of any void was above the chosen threshold, the patient was classed as unobstructed. In order to achieve good

specificity (94 %) whilst retaining moderate sensitivity (39 %), it was concluded that the highest reading from three flows and a threshold of $<10 \text{ ml}\cdot\text{s}^{-1}$ provided a valuable improvement over a single reading to diagnose obstruction. Recently, these data were re-analysed by Caffarel et al. (2009) using the area under the receiver operating characteristic (ROC) curve for one to four voids. No difference in diagnostic accuracy was found between Q_{max} from one void and the maximum of up to four voids. This can be seen from Figure 4.3, which shows the ROC curves for the four test protocols examined by Reynard et al. The area under each smoothed curve is between 75 and 77 %, indicating similar diagnostic power; in fact their confidence intervals are almost identical (Caffarel et al., 2009).

Combating psychological effects Several studies have reported the phenomenon of an increase in Q_{max} readings from successive clinic-recorded voids (Carter et al., 1991; Feneley et al., 1996; Reynard et al., 1996; Jepsen et al., 1998). This is thought to reflect an effect whereby patients become accustomed to the test environment. In the clinic-based study reported by Feneley et al. (1996), 147 patients voided twice on two separate clinic visits. The average reading from the second void was statistically higher than the first on both visits, with a difference of approximately $0.5 \text{ ml}\cdot\text{s}^{-1}$. A larger effect was observed by Reynard et al. (1996) where the mean Q_{max} of one to four clinic voids in 165 men with LUTS rose progressively from 10.2 to $14.9 \text{ ml}\cdot\text{s}^{-1}$, the differences apparently not predicted by voided volume. In contrast, Sonke et al. (1999) found no evidence of this effect in home recordings from a sample of 212 men with LUTS.

Investigating symptoms Matzkin et al. (1996) compared frequency, intermittency, weak flow and nocturia symptom scores with equivalent measures derived from home uroflowmetry recordings over 24 hours in 42 men with LUTS and found that only nocturia data correlated. Porru et al. (2005) found a significant

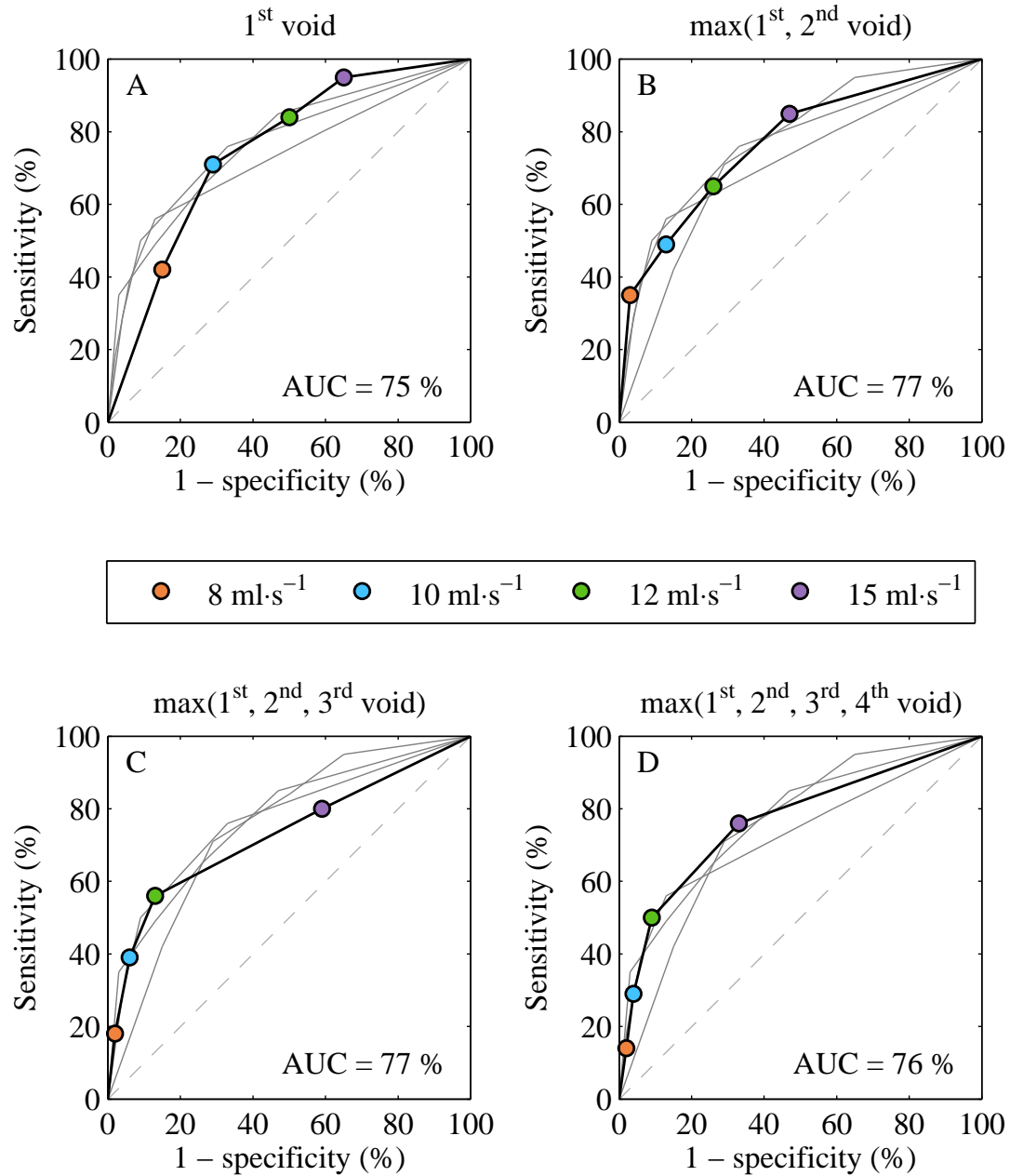


Figure 4.3 ROC curves showing diagnostic accuracy for BOO of the four clinic test protocols examined by Reynard et al. (1996): (A) Q_{max} from a single clinic void, (B) maximum Q_{max} from two clinic voids, (C) maximum Q_{max} from three clinic voids and (D) maximum Q_{max} from four clinic voids. For each plot, the other three are underlaid in grey to demonstrate the similarity in diagnostic power, indicated by the area under the curve.

correlation between the frequency symptom score and frequency derived from multiple home flow data in 107 men with LUTS.

Improving patient experience Boci et al. (1999) reported a questionnaire study in which 20 of 25 patients considered home uroflowmetry using an electronic device to be simpler and more acceptable than clinic uroflowmetry. Several studies reported that participants found home flow devices easy to use, but neither quantitative data nor the method used to establish this were presented (de la Rosette et al., 1996; Currie, 1998; Jørgensen et al., 1998; Pel and van Mastrigt, 2002; Caffarel et al., 2007; Pridgeon et al., 2007).

4.4 Discussion

4.4.1 Techniques and devices: Good Urodynamic Practice?

For a frame of reference against which to judge reported techniques and devices, the 2002 ICS standardisation report, *Good Urodynamic Practices: Uroflowmetry, Filling Cystometry, and Pressure-Flow Studies*, was used (Schäfer et al., 2002). According to this document, the requirements for uroflowmetry include: adequate privacy, a normal desire to void and repeated and representative measurements. The variables measured should include a graphical plot of flow rate against time for the whole void, Q_{max} rounded to the nearest $1 \text{ ml}\cdot\text{s}^{-1}$, and V_{void} and PVR to the nearest 10 ml.

Simple timing methods may hold appeal as they require no specialist equipment, although interpretation of Q_{ave} is hampered by the lack of validated diagnostic thresholds. Use of standard Q_{max} thresholds is possible which would tend to improve sensitivity, for example for diagnosis of BOO, at the expense of reduced specificity.

Several simple, low-cost home flow instruments that provide a measure of Q_{max} have been reported, at least one of which was commercially available at the time of writing. It has been demonstrated that the large potential error in a single measurement from these devices is counteracted by the effect of averaging repeated measurements (Caffarel et al., 2007). Combining Q_{ave} from a timed void with Q_{max} from a funnel device may provide information regarding the shape of the flow curve to take this low technology concept further. These attributes suggest that such methods may be valuable where low technology solutions are preferred, for example remote or underdeveloped areas.

Electronic measurement has undoubted advantages in terms of precision and data management and interpretation. The resulting data include the plot of flow rate against time, which may aid the assessment and with which clinicians are familiar. The main barrier to increased home use of electronic devices is cost, with currently available options retailing at approximately £2,500 (€3,000, \$4,000). At this level, it is unlikely to be financially viable to use electronic equipment for routine home use due to capital investment and servicing requirements.

One disadvantage of home uroflowmetry is the lack of a measurement of PVR, which is part of the ICS recommendation. However, as discussed in Section 3.3.3 (page 36), the value of PVR is uncertain, with low diagnostic accuracy compared to Q_{max} (Oelke et al., 2007). It may be envisaged that an abnormal result from home uroflowmetry would lead to a subsequent clinic visit, where if necessary a stand-alone measurement of PVR could be obtained after normal, private voiding.

Table 4.1 summarises the above discussion, showing the performance of both clinic uroflowmetry and methods reported for home uroflowmetry against ICS recommendations (Schäfer et al., 2002).

	Clinic uroflowmetry	Timing methods	Simple funnels	Disposable funnels	Electronic devices
Measurement of Q_{max} : 0-50 to 1 ml·s ⁻¹	✓	Q_{ave} measured and documented manually	Q_{max} categorised and documented manually	✓	✓
Measurement of V_{void} : 0-1,000 to 10 ml	✓	Documented manually	Documented manually	Up to 600 ml, documented manually	✓
Measurement of flow curve	✓	×	×	×	✓
Measurement of PVR to 10 ml	✓	×	×	×	×
Adequate privacy	×	✓	✓	✓	✓
Normal desire to void	×	✓	✓	✓	✓
Representative measurement	?	✓	✓	✓	✓
Repeated measurements	×	✓	✓	✓	✓
Automated analysis verified by inspection	✓	×	×	×	Yes, but may be time consuming

Table 4.1 *The performance of clinic uroflowmetry and methods for home uroflowmetry against ICS recommendations (Schäfer et al., 2002).*

4.4.2 The value of home uroflowmetry

Describing variability in flow rate to improve diagnostic accuracy A number of studies were found that investigated both inter- and intra-subject variability of Q_{max} recorded using home uroflowmetry. The low reliability of a single clinic flow measurement was often cited as the motivation for such studies. What is the implication of this, and do the findings have any practical importance? By averaging multiple measurements of Q_{max} in an individual the influence of extreme values, either outliers or unrepresentative flows, is reduced. Statistically, this ought to improve sensitivity and specificity for diagnosis of BOO, but the evidence to support this statistical prediction is lacking. One small study showed that just 46 % of the men assessed could be classified as minimally obstructed (mean $Q_{max} >14 \text{ ml}\cdot\text{s}^{-1}$) or clearly obstructed (mean $Q_{max} <10 \text{ ml}\cdot\text{s}^{-1}$). The remaining 54 % could not be classified correctly using mean Q_{max} alone (Boci et al., 1999).

Reynard et al. (1996) concluded that the maximum Q_{max} of three clinic flow measurements provides a valuable improvement in diagnostic power over a single measurement. However, improvement in sensitivity could equally, and more conveniently, be achieved by applying a lower threshold for abnormality to a single measurement of Q_{max} (Caffarel et al., 2009). The observation of an increase in Q_{max} readings from successive clinic voids indicates that a single flow recording tends to underestimate an individual's true Q_{max} , thereby reducing its specificity. Again, this can be corrected without making multiple measurements by adjusting the threshold for abnormality, unless the effect is found to differ between obstructed and unobstructed patients.

The experimental use of home uroflowmetry has revealed interesting differences between obstructed and unobstructed populations. These include circadian variability and the relationship between Q_{max} and V_{void} ; the reasons for the

observed differences are not clear. Further research into this area may allow specification of thresholds for such parameters that best separate populations with different conditions, and hence aid diagnosis.

Describing variability in flow rate to assess treatment outcome Home uroflowmetry studies have shown that Q_{max} varies typically by up to $10 \text{ ml}\cdot\text{s}^{-1}$ in an individual (Sonke et al., 1999). Q_{max} is the most common objective indication of the need for treatment for BOO and of treatment outcome in an individual. Yet, the typical increase in flow rate of $2 \text{ ml}\cdot\text{s}^{-1}$ from medical treatment in particular is smaller than this variation. Conducting follow-up clinic measurements under the same conditions as those performed initially (such as time of day and voiding position) may go some way towards reducing variation but is unlikely to be practical.

Measurement of multiple flows in an individual reduces the error in mean Q_{max} by the square root of the number of measurements. This will result in greater certainty in determining whether a treatment effect has occurred or alternatively whether the clinical condition has become worse. Further, use of average Q_{max} from multiple flows as an outcome measure would reduce the required sample size, and therefore possibly cost and duration, for clinical trials (Meier et al., 1995). These areas will be examined in more detail, and the effects quantified, in Chapter 5.

This advantage of multiple home uroflowmetry raises a key question: How many flow recordings should be obtained? The answer will depend upon the situation and the desired level of accuracy for average Q_{max} (Sonke et al., 1999). For example, in a trial of medical treatment where we anticipate an improvement of $2 \text{ ml}\cdot\text{s}^{-1}$ in Q_{max} , we may wish to reduce the standard error of a patient's average Q_{max} to $0.5 \text{ ml}\cdot\text{s}^{-1}$ or lower. Assuming the highest reported intra-subject SD of $6 \text{ ml}\cdot\text{s}^{-1}$ (Boci et al., 1999), this would require 144 measurements or more.

In contrast, for a man complaining of LUTS with $Q_{max} > 25 \text{ ml}\cdot\text{s}^{-1}$ on a single void, repeated measurements are unlikely to much increase the certainty that he is unobstructed.

Investigating symptoms Symptom scores have been compared to home uroflowmetry data, resulting in the conclusion that men are poor at quantifying symptoms (Matzkin et al., 1996). Whilst this is an interesting observation, it has little value given that the purpose of measuring symptoms is to obtain a patient's subjective view of their condition.

Improving patient experience Patient opinion regarding new practices and changes to clinical care is likely to become increasingly important. An example of this trend in the UK is the NHS *Choose and Book* system[‡] where patients select the location for their first outpatient appointment, generating income for the chosen department. Some evidence was found, although predominantly anecdotal, that men preferred home over clinic uroflowmetry. Perceived benefits of electronic voiding diaries over hand-written diaries, such as reduced burden and improved compliance, have yet to be confirmed.

[‡] www.chooseandbook.nhs.uk.

4.5 Conclusion

The findings of this chapter illustrate the gulf between low-cost methods of obtaining average or peak flow measurements, and precise, expensive devices with the capabilities of clinic flowmeters. Simple methods and devices may be suitable as screening tests or for long-term self-monitoring, or further on in the patient pathway where attendance at a specialised clinic is not convenient or possible. However, they are not ideal for diagnostic use since they fall short of ICS recommendations for uroflowmetry.

In contrast, electronic devices clearly score highly in terms of their adherence to ‘good practice’ for uroflowmetry. However, the cost of such equipment is currently too high for routine home use. An ideal device to replace clinic-based uroflowmetry would combine reliable and continuous measurement of flow rate throughout each void and concise data presentation, at a cost that could be absorbed into current tariffs for assessment of men with LUTS.

The statistical benefit of averaging multiple measurements of Q_{max} , made feasible by home uroflowmetry, should translate to improved diagnostic accuracy and assessment of treatment outcome. This hypothesis will be tested in the following chapter.

Chapter 5

The clinical benefit of an average maximum flow rate

5.1 Introduction

The literature reviewed in the previous chapter revealed that the practice of recording several measurements of flow in each individual, and applying a threshold to the resulting maximum Q_{max} , provided no improvement in diagnostic power over a single measurement. One study reported that mean Q_{max} derived from multiple measurements in an individual also produced no improvement (de la Rosette et al., 1996). Yet, quite the opposite conclusion was drawn: that averaging multiple measurements of Q_{max} should translate to improved diagnostic accuracy and assessment of treatment outcome. This statement seems unfounded, perhaps even contrary to the evidence. Upon what is it based? The answer lies within this chapter.

5.2 Single versus multiple measurements

Investigation of symptoms often involves measuring a physiological parameter and categorising the result as normal or abnormal, usually by comparison to a threshold. These parameters often exhibit appreciable within-subject variability, examples being blood pressure, heart rate and of course urine flow rate.

The use of solitary measurements of variable parameters made in the clinic raises two issues. Firstly, what are the implications of cases where this one-off measurement is an outlier? Secondly, there may be an effect by which measurements obtained in an artificial environment are in fact unrepresentative of the patient's true condition; they are drawn from a different distribution.

We are therefore in the midst of a shift away from diagnoses based upon one-off clinical measurements and towards closer-to-home monitoring to obtain multiple readings under more natural circumstances. An example of this trend is the 2011 NICE clinical guideline concerning the management of hypertension in adults (National Institute for Health and Clinical Excellence, 2011). The most radical distinction between it and its 2006 predecessor is the strong recommendation that hypertension observed in the clinic be investigated by ambulatory or home blood pressure monitoring. This is acknowledgement in part of the intra-subject variability of these measurements, and in part of anxiety-induced elevation of blood pressure which occurs in the clinic, termed 'white coat hypertension'. This is beginning to sound familiar.

The volume of data resulting from ambulatory and home monitoring techniques raises its own issue. In order to apply a threshold and test diagnostic accuracy, we must reduce these data, from which an almost unlimited number of parameters may be derived, to a single value.

Commonly, multiple measurement are averaged to give a mean value, such is the treatment of multiple blood pressure measurements allowing comparison to the threshold separating normo-tensive and hyper-tensive subjects. As discussed in the previous chapter, the allure of a mean compared to a single value is that it varies far less: by a factor of \sqrt{n} , where n is the number of measurements averaged. Crucially, this means that when examining distributions of means rather than single values, there is a narrowing of the distribution and subsequently less overlap between individuals and between groups of individuals.

By modelling Q_{max} according to descriptive statistics reported in the literature, the present chapter aims to quantify this effect in relation to men with LUTS. Thus, the improvement in clinical performance to be achieved by averaging multiple measurements in an individual is predicted.

5.3 Sensitivity, specificity, ROC curves and accuracy

The performance of a clinical test is often described by its sensitivity (the proportion of positives correctly classified) and specificity (the proportion of negatives correctly classified). These measures can be difficult to interpret because they vary from 0 to 100 %, in opposite directions, as the threshold separating test positives and test negatives is varied.

An ROC curve, a plot of sensitivity versus [1-specificity], usually for multiple thresholds, allows visualisation of how sensitivity and specificity vary with respect to each other. A smoothed line is drawn through the points, allowing calculation of the area under the curve (AUC), a threshold-independent measure of the discriminatory power of the test. An AUC of 100 % signifies a perfect test*,

* An AUC below 50 % can be increased to (100–AUC) % by reversing the classifications, so that those classified as positives become negatives, and vice versa. Therefore, the worst possible AUC is 50 %.

of 0 % a test that always classifies incorrectly and of 50 % a test equivalent to classification at random.

The AUC reflects the probability that the measured parameter will be lower (if test positives are classed as those below the thresholds) or higher (if test positives are classed as those above the thresholds) for a randomly chosen positive than for a randomly chosen negative. In practice, a threshold must be chosen and applied. If prevalence is known, accuracy may be calculated from sensitivity and specificity for a given threshold according to Equation 5.1[†]. Accuracy is also defined more intuitively by Equation 5.2.

$$accuracy = (sensitivity \times prevalence) + [specificity \times (1 - prevalence)] \quad (5.1)$$

$$accuracy = \frac{true\ positives + true\ negatives}{total} \quad (5.2)$$

5.4 Theory versus practice

There are two methods by which sensitivity and specificity, and thus the AUC and accuracy, may be calculated.

The first is to measure the parameter under test in a study cohort and compare the results to the gold standard. Of course, the resolution of the resulting ROC is limited by the sample size; the larger the sample, the more it approaches the true ROC, as illustrated in Figure 5.1. This method requires the value of the test parameter to be known for every individual; for Q_{max} , this has not previously been reported in a study of sufficient size to allow robust calculations.

[†] Sensitivity, specificity, accuracy, AUC and prevalence may be expressed as percentages or as proportions from 0 to 1; percentages are used throughout this chapter except for Equation 5.1.

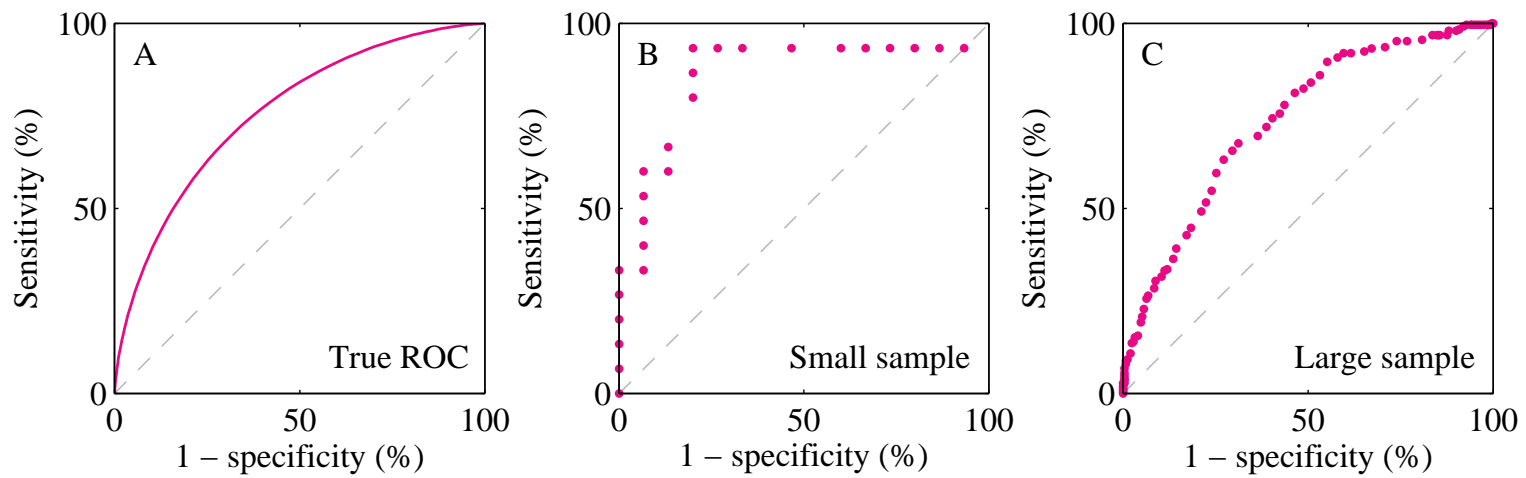


Figure 5.1 *The effect of small (B) and large (C) sample sizes on estimation of the true ROC curve (A) for a test parameter.*

Alternatively, with knowledge of the distributions of the test parameter in the positive and negative populations, as determined by the gold standard, ROC curves may be calculated theoretically. At each threshold, sensitivity is the integral of the positives' distribution below the threshold as a proportion of the integral of the whole distribution. Specificity is the integral of the negatives' distribution above the threshold as a proportion of the integral of the whole distribution. These calculations are shown in Equations 5.3 (sensitivity) and 5.4 (specificity) and Figure 5.2 for normal distributions, which are assumed throughout this chapter, but the theory holds true for any kind of distribution.

$$\int_{-\infty}^{thresh} \exp \left\{ -\frac{(TP - \mu_{pos})^2}{2\sigma_{pos}^2} \right\} / \int_{-\infty}^{+\infty} \exp \left\{ -\frac{(TP - \mu_{pos})^2}{2\sigma_{pos}^2} \right\} \quad (5.3)$$

$$\int_{thresh}^{+\infty} \exp \left\{ -\frac{(TP - \mu_{pos})^2}{2\sigma_{pos}^2} \right\} / \int_{-\infty}^{\infty} \exp \left\{ -\frac{(TP - \mu_{pos})^2}{2\sigma_{pos}^2} \right\} \quad (5.4)$$

Where:

thresh = the threshold at which sensitivity and specificity are evaluated

TP = the range of values across which the frequency of the test parameter $\neq 0$

μ_{pos} , μ_{neg} = the mean of the test parameter in the positive and negative populations

σ_{pos} , σ_{neg} = the standard deviation of the test parameter in the positive and negative populations

In this case, the limiting factor for the accuracy of the results is the size of the sample from which the summary statistic were calculated. Being that only a mean and standard deviation for positive and negative populations are required, this information is likely to be widely available from the literature. However, for Q_{max} , only the characteristics of single values have been reported. In order to complete the theory, distributions of mean Q_{max} must also be determined. This requires consideration of multiple sources of variance and their combined effect.

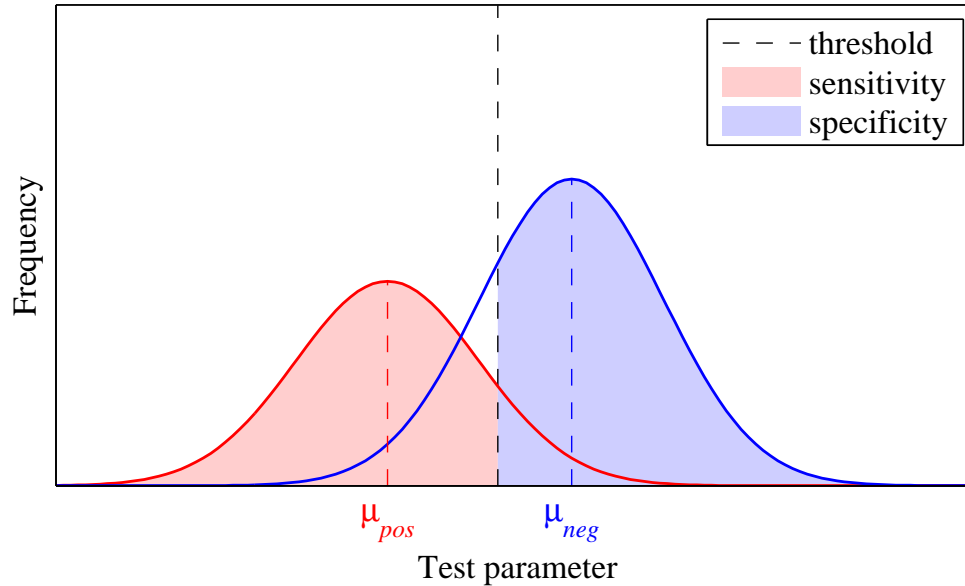


Figure 5.2 *Theoretical calculation of sensitivity and specificity from distributions of positives and negatives. Sensitivity (true positives) is the red shaded region as a proportion of the area under the red curve, and specificity (true negatives) is the blue shaded region as a proportion of the area under the blue curve. In this illustration, prevalence is 40 % (the area under the red curve is two thirds that of the blue curve), the distributions have the same standard deviation, and the test parameter is lower in positives than negatives.*

5.5 Combining variance

Let's begin by imagining that we measure a test parameter once in a group of subjects. The parameter varies between subjects with standard deviation $\sigma_{BETWEEN}$, but does not vary within subjects; one subject always produces the same value. The distribution of values is shown in Figure 5.3A; its variance (σ^2) is simply equal to the between subject variance (Equation 5.5).

$$\sigma_{TOTAL}^2 = \sigma_{BETWEEN}^2 \quad (5.5)$$

Next we introduce within subject variability, with standard deviation σ_{WITHIN} , and remeasure the parameter once per subject. The spread of the resulting distribution increases according to Equation 5.6 (Figure 5.3B).

$$\sigma_{TOTAL}^2 = \sigma_{BETWEEN}^2 + \sigma_{WITHIN}^2 \quad (5.6)$$

Finally, we measure the parameter n times in each subject and take the mean value. Mean values vary less than single values by a factor of \sqrt{n} and so the term involving σ_{WITHIN} is reduced accordingly (Equation 5.7). With a sufficiently large number of measurements per subject, we can essentially eliminate the effect of intra-subject variability; as n increases, σ_{TOTAL} approaches $\sigma_{BETWEEN}$ (Figure 5.3C).

$$\sigma_{TOTAL}^2 = \sigma_{BETWEEN}^2 + \left(\frac{\sigma_{WITHIN}}{\sqrt{n}} \right)^2 \quad (5.7)$$

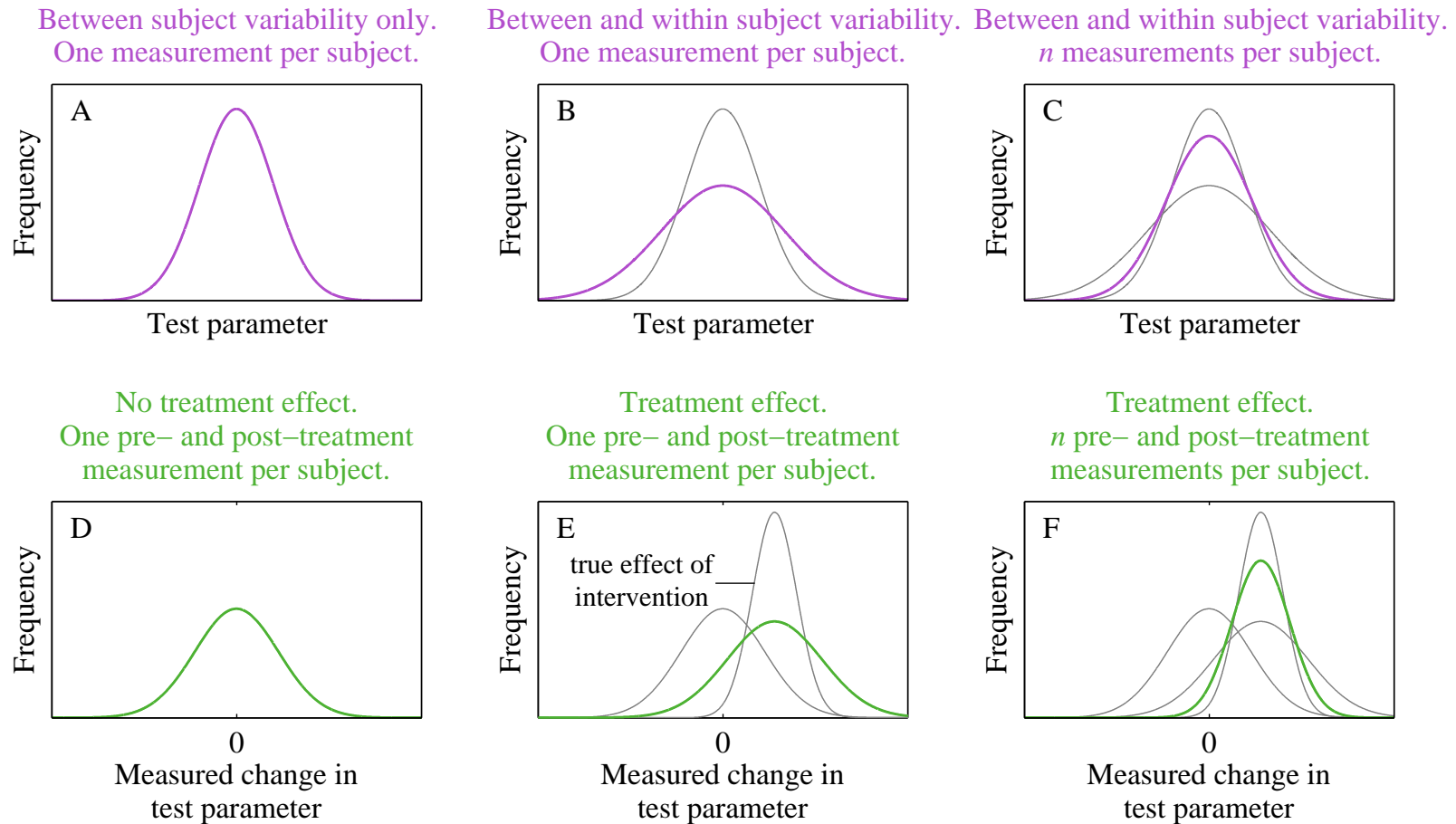


Figure 5.3 An illustration of the effect of combining multiple sources of variance on measurement of a test parameters (A to C) and the measured change in a test parameters following an intervention (D to F).

In a second scenario, we measure a test parameter before and after an intervention. This time, we are not interested in distributions of the test parameter itself, but rather the distributions of the measured change in the parameter following the intervention. As we have a paired situation, between-subject variance disappears from the calculations.

If we begin by assuming that the intervention has no effect, we need only consider within subject variance (Equation 5.8). The term appears twice because we are comparing two measurements in each subject. The distribution of measured changes is shown in Figure 5.3D.

$$\begin{aligned}\sigma_{TOTAL}^2 &= \sigma_{WITHIN}^2 + \sigma_{WITHIN}^2 \\ \Rightarrow \sigma_{TOTAL}^2 &= 2\sigma_{WITHIN}^2\end{aligned}\tag{5.8}$$

If the intervention does alter the value of the test parameter, there is an additional contribution from the variance of the intervention effect across the subjects (Equation 5.9, Figure 5.3E).

$$\begin{aligned}\sigma_{TOTAL}^2 &= \sigma_{WITHIN}^2 + \sigma_{WITHIN}^2 + \sigma_{INTERVENTION}^2 \\ \Rightarrow \sigma_{TOTAL}^2 &= 2\sigma_{WITHIN}^2 + \sigma_{INTERVENTION}^2\end{aligned}\tag{5.9}$$

Finally, if we take the mean value of the difference between n pre- and post-intervention measurements in each subject, the σ_{WITHIN} term is reduced (Equation 5.10, Figure 5.3F). Again, with sufficiently large n , the total variance tends to that of the intervention effect.

$$\begin{aligned}\sigma_{TOTAL}^2 &= \left(\frac{\sigma_{WITHIN}}{\sqrt{n}}\right)^2 + \left(\frac{\sigma_{WITHIN}}{\sqrt{n}}\right)^2 + \sigma_{INTERVENTION}^2 \\ \Rightarrow \sigma_{TOTAL}^2 &= \frac{2\sigma_{WITHIN}^2}{n} + \sigma_{INTERVENTION}^2\end{aligned}\tag{5.10}$$

These are the concepts that underpin calculations of the benefit of mean Q_{max} in the remainder of this chapter.

5.6 Diagnostic accuracy for obstruction

As discussed in Section 3.3.1 (page 28), the accuracy of single values of Q_{max} to diagnose BOO has been reported in numerous studies. This section aims to determine the improvement in diagnostic accuracy achievable by averaging multiple measurements in an individual.

5.6.1 Methods

Calculations were based upon a predictive model built using the parameters and assumptions listed on the following page, derived from a report of 871 men with LUTS (Rosier et al., 1996), and a small home uroflowmetry study in which details of Q_{max} were presented for each patient (Boci et al., 1999).

Throughout the literature, Q_{max} in a symptomatic population has repeatedly been described using parametric statistics (Golomb et al., 1992; Meier et al., 1994, 1995; van Venrooij et al., 1995; de la Rosette et al., 1996; Reynard et al., 1996; Witjes et al., 1997; Homma et al., 1998; Reynard et al., 1998; Boci et al., 1999; Sonke et al., 1999). One exception was found that did not provide details of the observed distribution (Oelke et al., 2007). Although information regarding the characteristics of Q_{max} in an individual is scarce, one study provided the mean and standard deviation of Q_{max} for each participant (Boci et al., 1999). Therefore, for these analyses Q_{max} was modelled as normally distributed at both population and individual level.

- The prevalence of obstruction in the study population is 62 % (Rosier et al., 1996).
- Individuals' Q_{max} are normally distributed around their mean with standard deviation (SD) $3 \text{ ml}\cdot\text{s}^{-1}$ (pooled from Boci et al., 1999).
- Single values of Q_{max} in the obstructed population are normally distributed with mean [SD] $9.3 [3.8] \text{ ml}\cdot\text{s}^{-1}$ (Rosier et al., 1996).
- Single values of Q_{max} in the unobstructed population are normally distributed with mean [SD] $12.9 [5.3] \text{ ml}\cdot\text{s}^{-1}$ (Rosier et al., 1996).
- For consideration of multiple voids, the mean of 40 voids is calculated (this is based upon 10 voids per day (Boci et al., 1999) for 4 days, the standard length of a frequency-volume chart).

This information enabled distributions for single values of Q_{max} in the obstructed (positive) and unobstructed (negative) populations to be created.

Those for the mean of 40 values of Q_{max} required further consideration. Their SDs may be calculated from Equation 5.7: we know σ_{WITHIN} ($3 \text{ ml}\cdot\text{s}^{-1}$) and n (40), but $\sigma_{BETWEEN}$ is missing. However, applying Equation 5.6 to single values of Q_{max} , we know σ_{WITHIN} ($3 \text{ ml}\cdot\text{s}^{-1}$) and σ_{TOTAL} (obstructed: $3.8 \text{ ml}\cdot\text{s}^{-1}$, unobstructed: $5.3 \text{ ml}\cdot\text{s}^{-1}$), allowing calculation of $\sigma_{BETWEEN}$ for use in Equation 5.7. The means are the same as those for single values.

The above calculations are based upon the assumption that single values of Q_{max} recorded in the clinic always reflect normal voiding. Finally, as this may not always be the case, simulations were performed in which a proportion of these values were set to be unrepresentative. MATLAB software (MathWorks, Natick, USA)

was used to generate single and multiple values of Q_{max} for 100,000[‡] ‘patients’ as pseudorandom numbers drawn from the normal distributions described previously. However, for 10 % of cases, the single value of Q_{max} was instead drawn from a uniform distribution on the interval 0 to 30 ml·s⁻¹[§], the effect being that 10 % of these voids were unrepresentative (outside two standard deviations above or below the mean) rather than the expected 5 %. Sensitivity and specificity were then determined by counting the number of obstructed / unobstructed patients for whom (mean) Q_{max} was below / above a range of thresholds.

5.6.2 Results

The distributions of single Q_{max} and the mean of 40 values of Q_{max} for obstructed and unobstructed patients is shown in Figure 5.4. For mean Q_{max} calculated from 40 voids, the effect on the population distributions is a decrease in spread according to Equation 5.7. The effect of intra-subject variability has almost been eliminated, leaving a total SD just marginally above the between subject SD (obstructed patients: 2.38 ml·s⁻¹ versus 2.33 ml·s⁻¹, unobstructed patients: 4.39 ml·s⁻¹ versus 4.37 ml·s⁻¹).

Once the four distributions were known, ROCs were calculated as described in Section 5.4. These are shown in Figure 5.5. By averaging 40 measurements, there is an improvement in the AUC of 5 %, from 70 to 75 %.

Here, the AUC reflects the probability that (mean) Q_{max} will be lower for a randomly chosen obstructed patient than for a randomly chosen unobstructed patient. Commonly examined thresholds of 10 and 15 ml·s⁻¹ are marked on both curves on Figure 5.5. Table 5.1 compares diagnostic accuracy at these two

[‡] An estimate for the number of men with LUTS who undergo a urine flow test in the UK each year.

[§] The approximate range for Q_{max} resulting from the above distributions.

thresholds for the two protocols, calculated using sensitivities, specificities and prevalence according to Equation 5.1.

Following simulations in which 10 % of single values of Q_{max} were drawn from a uniform rather than normal distribution, the AUC for single voids fell from 70 to 67 %, and the accuracies at 10 and 15 $\text{ml}\cdot\text{s}^{-1}$ fell from 61 to 60 % and 70 to 68 %, respectively. The simulated ROCs are shown in Figure 5.6, and the simulated statistics in Table 5.2.

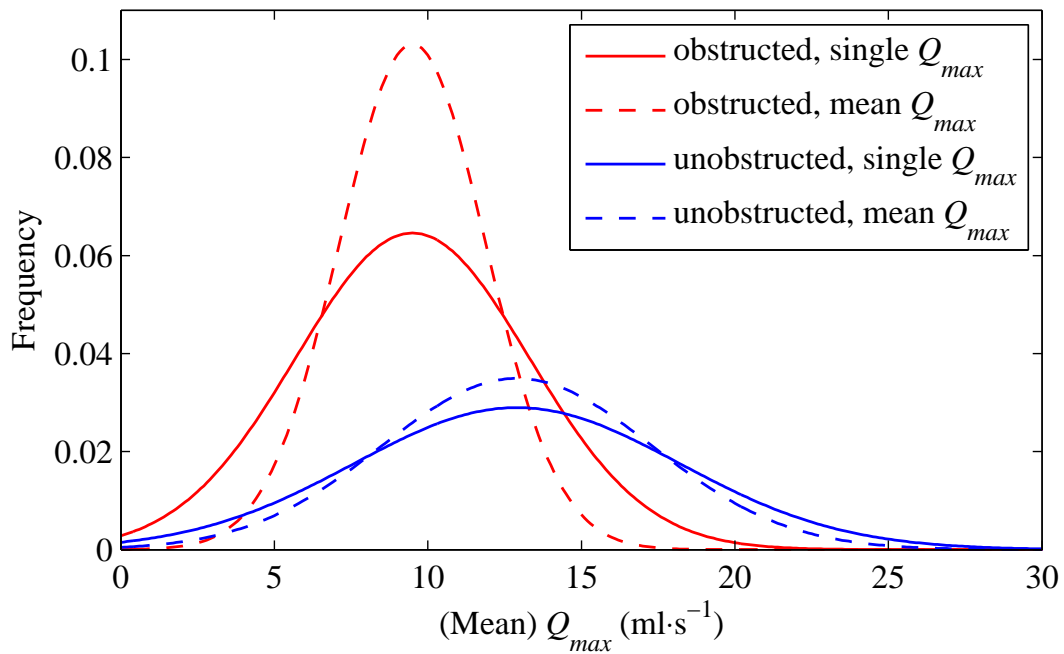


Figure 5.4 The distributions of single values of Q_{max} in the obstructed (red) and unobstructed (blue) populations (solid lines) from Rosier et al. (1996), and how these are affected by instead measuring the mean of 40 voids in each individual (dashed lines).

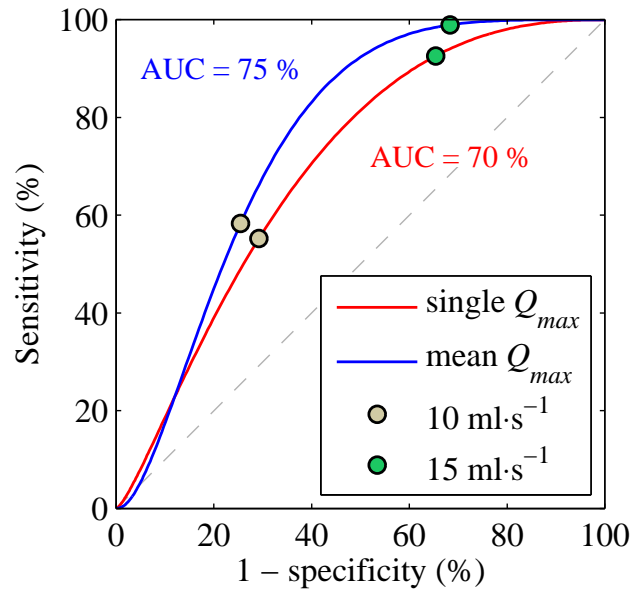


Figure 5.5 Calculated ROC curves illustrating the power of single values (red) and the mean of 40 values (blue) of Q_{max} to diagnose obstruction. Thresholds of 10 and 15 $\text{ml}\cdot\text{s}^{-1}$ are marked on both curves. Note that the curves cross over at the bottom left hand corner of the plot. Because the distributions of single values of Q_{max} are more spread, up to a certain threshold a larger proportion of this distribution for obstructed men falls below the threshold, resulting in better sensitivity. The same effect gives single values better specificity at high thresholds. The benefit of averaging multiple measurements in each individual occurs where distributions of obstructed and unobstructed patients overlap.

Threshold	10 $\text{ml}\cdot\text{s}^{-1}$		15 $\text{ml}\cdot\text{s}^{-1}$	
Protocol	Single	Mean	Single	Mean
Sensitivity	55 %	58 %	93 %	99 %
Specificity	70 %	75 %	35 %	32 %
Accuracy	61 %	65 %	70 %	73 %

Table 5.1 Calculated sensitivities, specificities and accuracies of single values and the mean of 40 values of Q_{max} to diagnose obstruction at 10 and 15 $\text{ml}\cdot\text{s}^{-1}$.

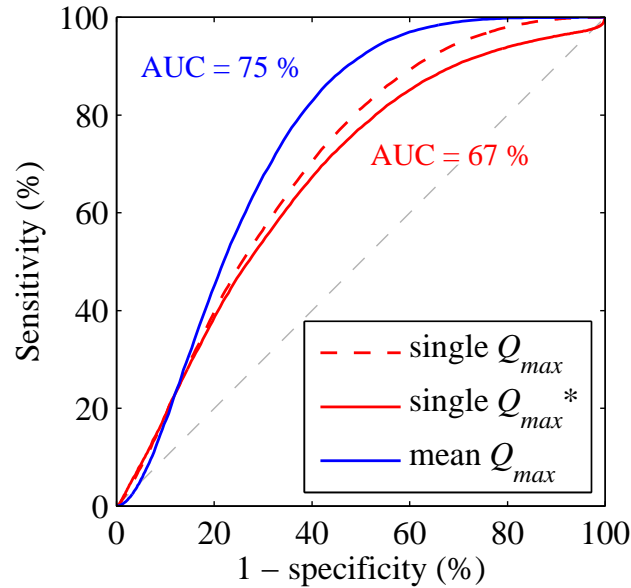


Figure 5.6 Simulated ROC curves illustrating the power of single values (red) and the mean of 40 values (blue) of Q_{max} to diagnose obstruction. The dashed red line is derived from a simulation in which all single values of Q_{max} are drawn from the normal distributions described previously. The solid red line (*) is derived from a simulation in which 10 % of single values of Q_{max} are instead drawn from a uniform distribution on the interval 0 to $30 \text{ ml}\cdot\text{s}^{-1}$.

Threshold	$10 \text{ ml}\cdot\text{s}^{-1}$			$15 \text{ ml}\cdot\text{s}^{-1}$		
Protocol	Single	Single*	Mean	Single	Single*	Mean
Sensitivity	55 %	53 %	58 %	93 %	88 %	99 %
Specificity	70 %	69 %	75 %	35 %	36 %	32 %
Accuracy	61 %	60 %	65 %	70 %	68 %	73 %

Table 5.2 Simulated sensitivities, specificities and accuracies of single values, single values of which 10 % are drawn from a uniform distribution (*), and the mean of 40 values of Q_{max} to diagnose obstruction at 10 and $15 \text{ ml}\cdot\text{s}^{-1}$. For those with equivalent calculated values in Table 5.1, all are equal.

5.7 Measurement of treatment outcome

5.7.1 Methods

Similar calculations may be carried out in order to compare the ability of single and the mean of multiple values of Q_{max} to assess treatment outcome, based upon the following model:

- Let us imagine that we treat our obstructed patients from Section 5.6 with an α -blocker. All patients therefore begin with distributions according to the obstructed population described therein.
- Half of the patients do not respond to treatment: their distributions remain unchanged (Norg et al., 2006).
- The other half do respond to treatment: their true mean Q_{max} increases. These improvements are normally distributed with mean $2 \text{ ml}\cdot\text{s}^{-1}$ (Djavan et al., 2004) and SD $0.5 \text{ ml}\cdot\text{s}^{-1}$ (ensuring all changes are positive).
- Thus the prevalence = 50 %.
- Again, Q_{max} in each individual is normally distributed about their mean with SD $3 \text{ ml}\cdot\text{s}^{-1}$ (Boci et al., 1999).
- For consideration of multiple voids, the mean of 40 voids is calculated both before and after treatment.

In this scenario, ‘positives’ are defined as those who experience an improvement in mean Q_{max} following medication, and ‘negatives’ as those who do not.

Again, simulations were performed to investigate the effect of unrepresentative voiding in the clinic. 62,000 sets of pre- and post-medication single and multiple values of Q_{max} were generated as pseudorandom numbers drawn from the normal

distributions described above. However, for 10 % of cases, the single value of Q_{max} was instead drawn from a uniform distribution on the interval 0 to 30 ml·s⁻¹.

5.7.2 Results

The pre- and post-medication distributions of single Q_{max} for responders and non-responders are illustrated in Figure 5.7A and Figure 5.7B, respectively, and for mean Q_{max} , Figure 5.7C and Figure 5.7D, respectively. Pre-medication and non-responder distributions are centred around 9.3 ml·s⁻¹, and responder distributions around 11.3 ml·s⁻¹. For the non-responders these distributions have SDs as described in Section 5.6: 3.8 ml·s⁻¹ for single values and 2.4 ml·s⁻¹ for mean values. For responders, the SDs are slightly larger as a result of the spread of the effect of medication: 3.83 ml·s⁻¹ for single values and 2.43 ml·s⁻¹ for mean values[¶].

Sensitivity and specificity can be applied in a slightly unconventional context to measure the performance of both single and mean values of Q_{max} to assess outcome. In order to do so, we need to consider the distributions of the difference between one pre- and one post-medication measurement of (mean) Q_{max} .

For the non-responders, the distribution is centred around 0 ml·s⁻¹ and for the responders around 2 ml·s⁻¹. The SDs may be calculated using the concepts presented in Equations 5.8 to 5.10^{||}. For non-responders, the variance equals twice the intra-subject variance. For responders, the variance of the medication effect is added to this. For mean Q_{max} , the intra-subject SD is reduced by a factor of $\sqrt{40}$. The resulting distributions are shown in Figure 5.8.

[¶] $\sqrt{3.8^2 + 0.5^2} = 3.83$ and $\sqrt{2.38^2 + 0.5^2} = 2.43$.

^{||} Single values: 4.3 ml·s⁻¹ for responders and 4.2 ml·s⁻¹ for non-responders. Mean values: 0.8 ml·s⁻¹ for responders and 0.7 ml·s⁻¹ for non-responders.

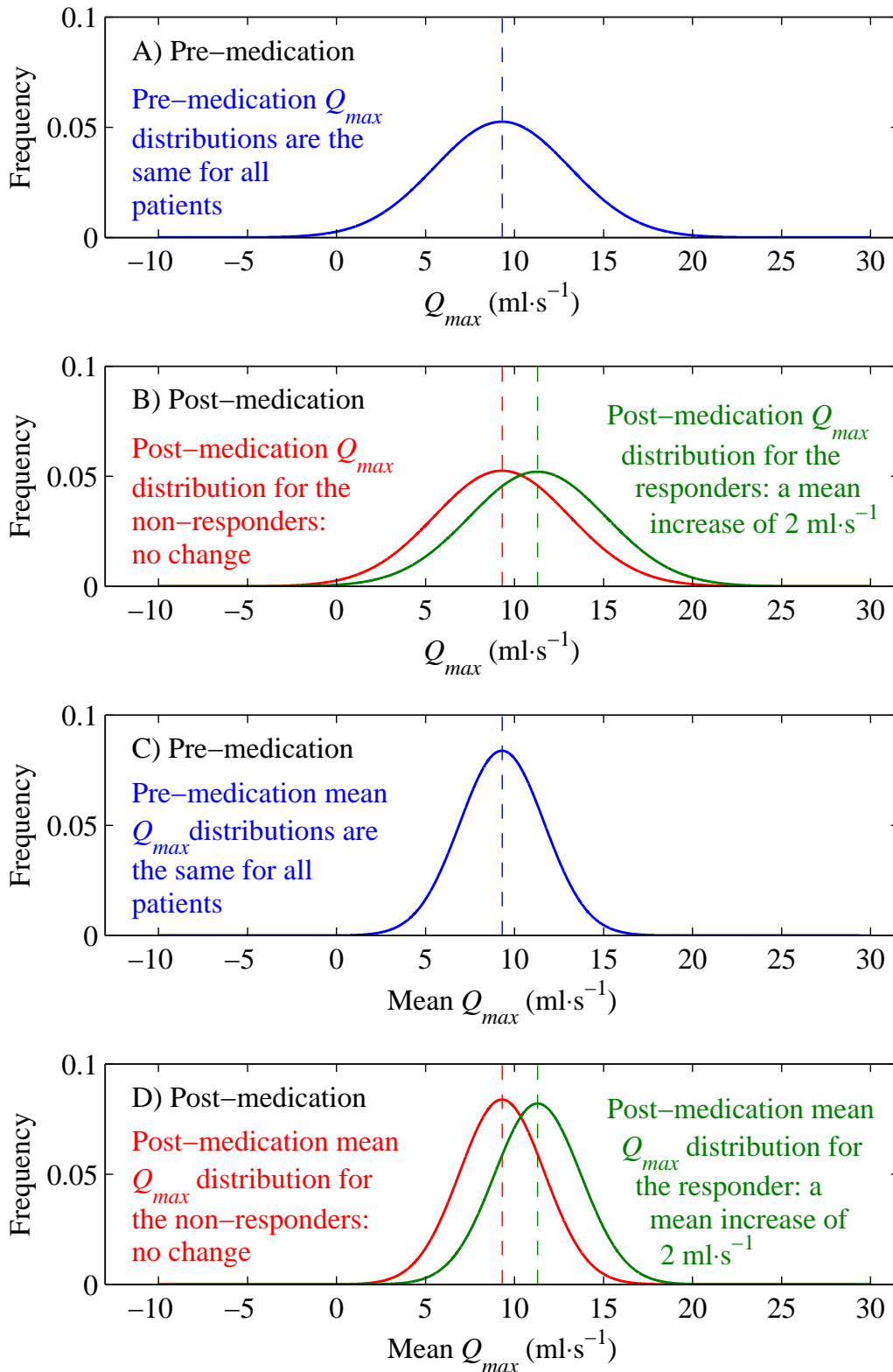


Figure 5.7 (A) The pre-medication distribution of single values of Q_{max} . (B) The post-medication distributions of single values of Q_{max} for responders (green) and non-responders (red). (C) The pre-medication distribution of the mean of 40 values of Q_{max} . (D) The post-medication distributions of the mean of 40 values of Q_{max} for responders (green) and non-responders (red).

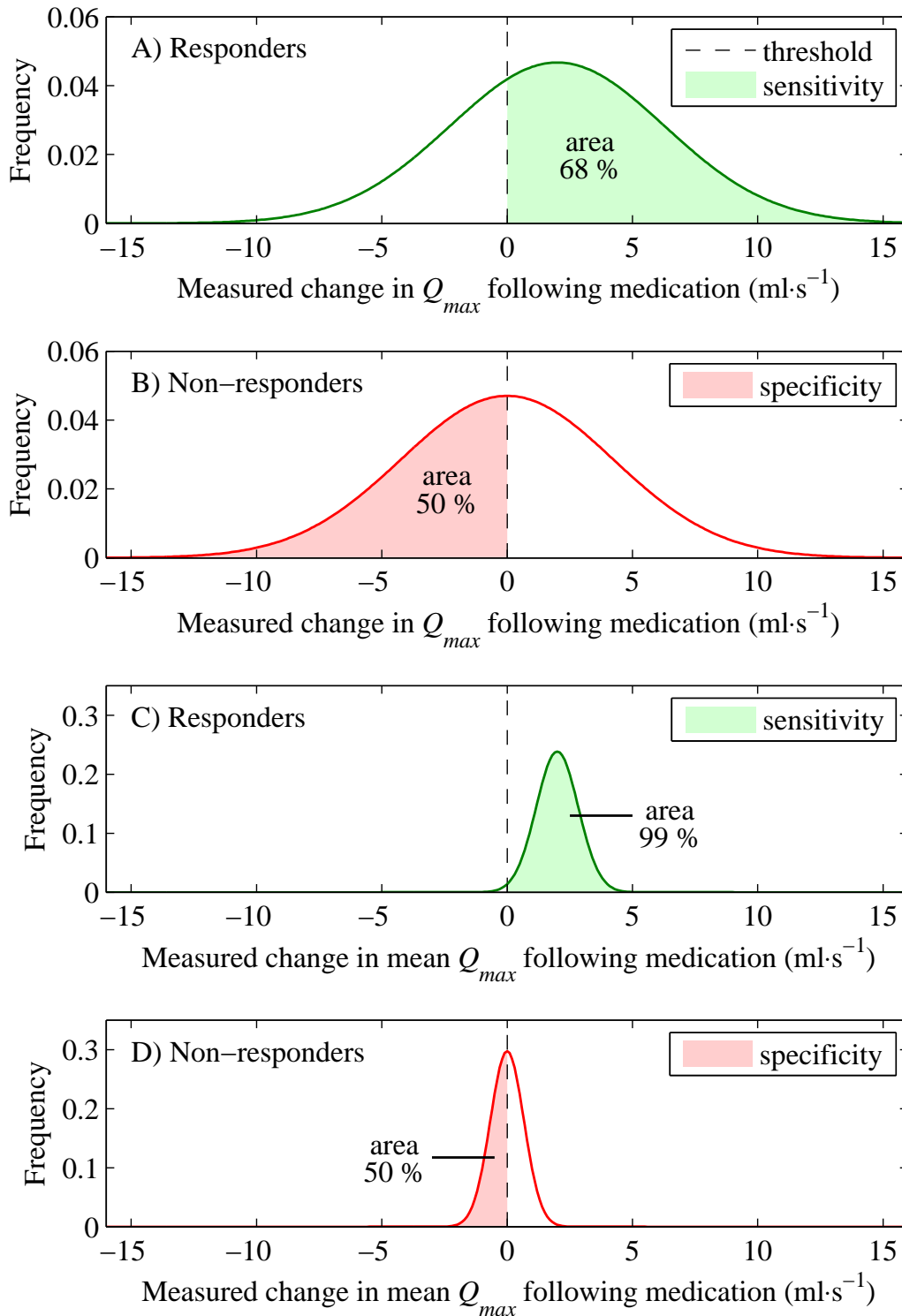


Figure 5.8 (A) The distribution of measured change in single values of Q_{max} for responders. (B) The distribution of measured change in single values of Q_{max} for non-responders. (C) The distribution of measured change in the mean of 40 values of Q_{max} for responders. (D) The distribution of measured change in the mean of 40 values of Q_{max} for non-responders. Green and red shading illustrate calculation of sensitivity and specificity for a threshold of $0 \text{ ml}\cdot\text{s}^{-1}$. Note that plots (A) and (B) have a smaller vertical-axis limit than plots (C) and (D).

Pragmatically, we may consider Q_{max} to have improved following medication if it is any higher than pre-medication Q_{max} , which equates to a threshold of $0 \text{ ml}\cdot\text{s}^{-1}$. Sensitivity is then the probability for the responders of measuring a difference in Q_{max} above $0 \text{ ml}\cdot\text{s}^{-1}$, and specificity is the probability for the non-responders of measuring a difference below $0 \text{ ml}\cdot\text{s}^{-1}$. Figure 5.8 also illustrates the derivation of sensitivity and specificity for a threshold of $0 \text{ ml}\cdot\text{s}^{-1}$.

These distributions enabled construction of ROCs as described in Section 5.4 (Figure 5.8). Single voids have an AUC of 63 %, whereas the means of 40 measurements have an almost perfect AUC of 97 %.

Here, the AUCs reflect the probability that (mean) Q_{max} will be measured to increase more for a randomly chosen responder than for a randomly chosen non-responder. Thresholds of 0, 1 and 2 $\text{ml}\cdot\text{s}^{-1}$ are marked on both curves in Figure 5.9.

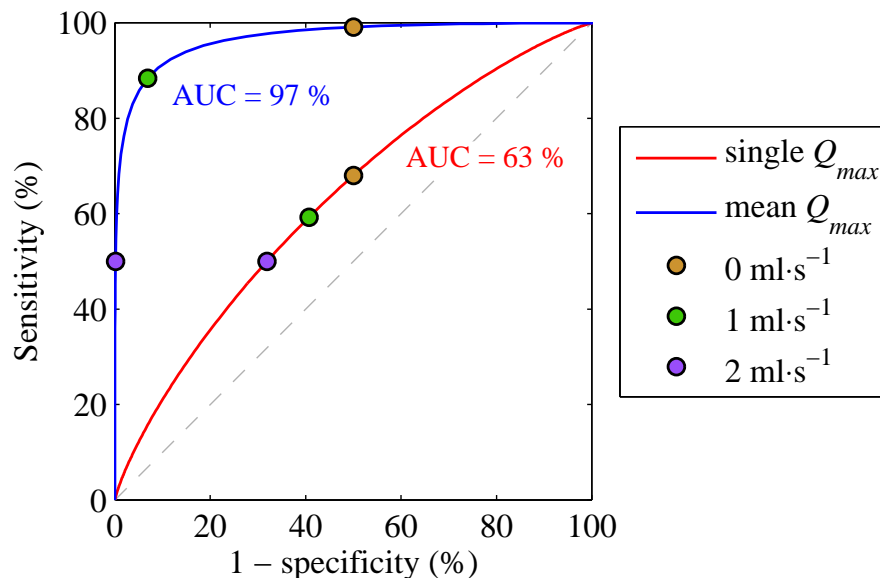


Figure 5.9 Calculated ROC curves illustrating the power of single values (red) and the mean of 40 values (blue) of Q_{max} to assess treatment outcome. Thresholds of 0, 1 and 2 $\text{ml}\cdot\text{s}^{-1}$ are marked on both curves.

Table 5.3 compares the treatment assessment accuracy for the two protocols at these three thresholds. The best accuracy, 91 %, is achieved by applying a threshold of $1 \text{ ml}\cdot\text{s}^{-1}$ to mean Q_{max} .

Threshold	$0 \text{ ml}\cdot\text{s}^{-1}$		$1 \text{ ml}\cdot\text{s}^{-1}$		$2 \text{ ml}\cdot\text{s}^{-1}$	
Protocol	Single	Mean	Single	Mean	Single	Mean
Sensitivity	68 %	99 %	59 %	88 %	50 %	50 %
Specificity	50 %	50 %	59 %	93 %	68 %	100 %
Accuracy	59 %	75 %	59 %	91 %	59 %	75 %

Table 5.3 *Calculated sensitivities, specificities and accuracies of single values and the mean of 40 values of Q_{max} to assess treatment outcome at thresholds of 0, 1 and $2 \text{ ml}\cdot\text{s}^{-1}$.*

Following simulations in which 10 % of single values of Q_{max} were drawn from a uniform rather than normal distribution, the AUC for single voids fell from 63 to 60 %, and the accuracies at 0, 1 and $2 \text{ ml}\cdot\text{s}^{-1}$ fell from 59 to 57 %, 59 to 58 %, and 59 to 57 %, respectively. The simulated ROCs are shown in Figure 5.10, and the simulated statistics in Table 5.4.

5.8 Discussion

As discussed in Chapter 3, the main limitation of Q_{max} is its performance in distinguishing between obstructed and unobstructed men. The area below any threshold applied to Q_{max} encompasses a proportion of the obstructed population plus a lesser proportion of the unobstructed population**. These proportions are slightly altered for the mean Q_{max} protocol, giving an increase in diagnostic accuracy of at least 3 %.

** Unless extremely high, in which case all men will fall below the threshold.

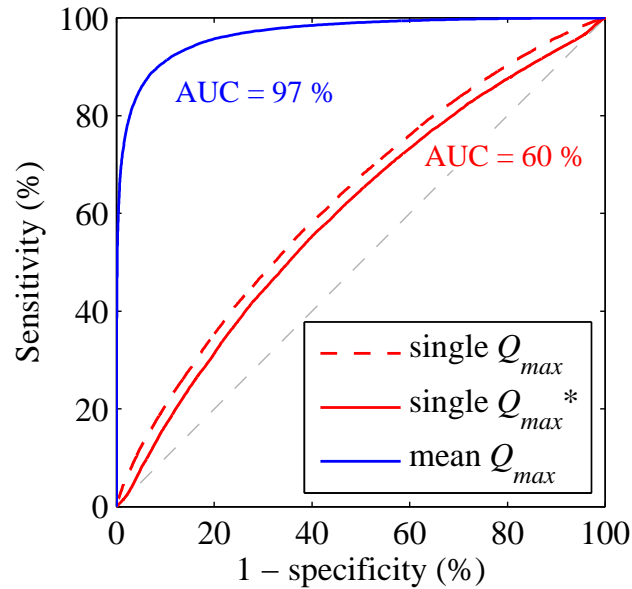


Figure 5.10 Simulated ROC curves illustrating the power of single values (red) and the mean of 40 values (blue) of Q_{max} to assess treatment outcome. The dashed red line is derived from a simulation in which all single values of Q_{max} are drawn from the normal distributions described previously. The solid red line (*) is derived from a simulation in which 10 % of single values of Q_{max} are instead drawn from a uniform distribution on the interval 0 to 30 $\text{ml}\cdot\text{s}^{-1}$.

Threshold	0 ml·s ⁻¹			1 ml·s ⁻¹			2 ml·s ⁻¹		
Protocol	Single	Single*	Mean	Single	Single*	Mean	Single	Single*	Mean
Sensitivity	68 %	65 %	99 %	59 %	57 %	88 %	50 %	49 %	50 %
Specificity	50 %	50 %	50 %	59 %	58 %	93 %	68 %	66 %	100 %
Accuracy	59 %	57 %	75 %	59 %	58 %	91 %	59 %	57 %	75 %

Table 5.4 *Simulated sensitivities, specificities and accuracies of single values, single values of which 10 % are drawn from a uniform distribution (*), and the mean of 40 values of Q_{max} to assess treatment outcome at thresholds of 0, 1 and 2 ml·s⁻¹. For those with equivalent calculated values in Table 5.3, all are equal.*

Given this relatively modest effect, it is no surprise that small studies involving a few tens of men have failed to detect an improvement. De la Rosette et al. (1996) concluded that grade of obstruction in their cohort of 67 agreed no better with results from home uroflowmetry than with those from the clinic. However, they did not acknowledge that the study lacked the power to detect a small difference. The improvement predicted here would require a sample of over 1,000 men to detect with 80 % power. Yet, the prevalence of male LUTS is such that this would benefit thousands of men in the UK each year.

Far more apparent is the advantage of using mean Q_{max} to assess the effect of treatment on flow rate. Uroflowmetry is commonly performed as follow-up for treatment of suspected BOO, and this is in accordance with the recommendation of the European Association of Urology (Oelke et al., 2011). The change in Q_{max} measured following an intervention is the main, usually only, objective indication of treatment response.

Due to intra-subject variability of Q_{max} often being higher than medication-induced benefit, the conventional single void method of assessing the response of flow rate to medication achieves at best 59 % accuracy: little better than guesswork. Far higher accuracy of up to 91 % may be achieved by averaging multiple flows before and after treatment. In fact, this is just one of several aspects of treatment assessment that could benefit from this practice.

Secondly, we can associate the measured change in Q_{max} with a confidence interval for each man by performing a statistical comparison of mean Q_{max} before and after treatment. Therefore, we can express the uncertainty surrounding the outcome in an individual. The same calculation for single values of Q_{max} would require use of an estimated SD, running the risk of type I and II errors if the assumed value was different to the man's true SD.

Thirdly, the use of mean Q_{max} considerably reduces the effect of regression to the mean that may occur during treatment trials. How often does a treatment trial for suspected or diagnosed BOO enforce inclusion criteria upon IPSS and Q_{max} , and then remeasure these parameters as outcomes? The subsequent observation of improvement may be attributed to regression to the mean rather than any treatment effect. This is a well acknowledged phenomenon, demonstrated by Prescott and Garraway (1995) to occur when measuring Q_{max} .

By way of demonstration, let us imagine that we screen a sample of our obstructed cohort from Section 5.6 and treat only those who have Q_{max} below $12 \text{ ml}\cdot\text{s}^{-1}$ based on a single measurement. Of 1,000 men screened, 600 fulfill this criterion and receive treatment, but the treatment has no effect and flow rates remain unchanged. Q_{max} is remeasured following treatment and a paired t-test measures a net improvement in Q_{max} of $1 \text{ ml}\cdot\text{s}^{-1}$, with associated p-value 5×10^{-6} . The reason is clear from Figures 5.11A and 5.11B. Two identical distributions are being compared, only the former has an artificially imposed upper limit and the latter does not.

If instead we screen and treat based upon mean Q_{max} from 40 measurements, we are comparing Figures 5.11C and 5.11D. This time, a paired t-test will correctly measure no difference. At sufficiently large sample sizes, or with fewer measurements per man, the effect is still present to a small extent, but considerably reduced.

Finally, averaging multiple values of Q_{max} in an individual enables a reduction in the sample size of clinical trials for which Q_{max} is an outcome measure. The larger the number of voids averaged per man, the closer the distribution of measured improvements converges to the true distribution; the effect of treatment minus the ‘noise’ of intra-subject variability. This is apparent from Equation 5.10.

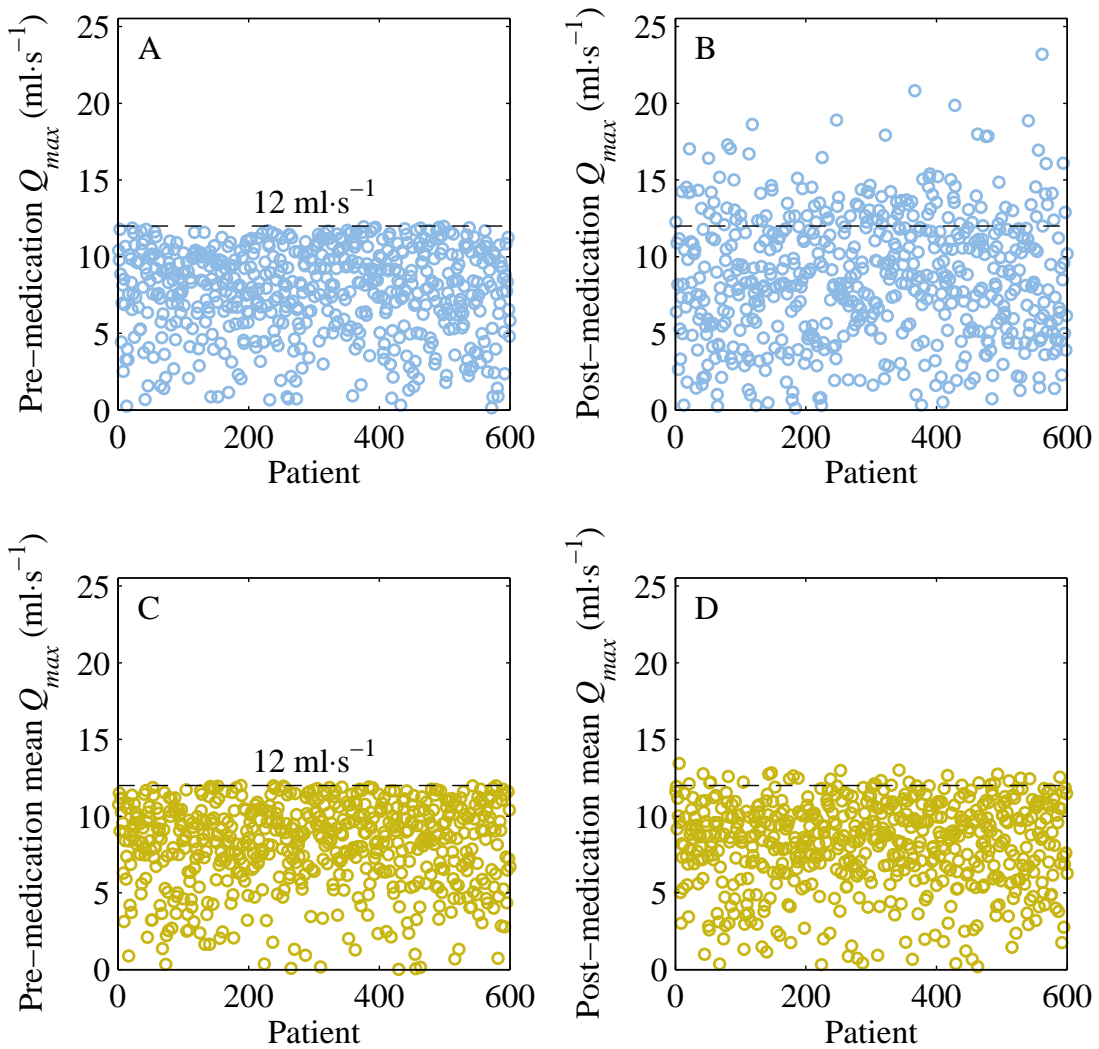


Figure 5.11 An illustration of regression to the mean when using a single value of Q_{max} to select those to treat and the reduction in this effect when instead using the mean of 40 measurements per individual. (A) Simulated values for single measurements of Q_{max} in 600 patients selected for treatment from 1,000 based upon a criterion of $Q_{max} < 12 \text{ ml}\cdot\text{s}^{-1}$, (B) simulated values for a second single measurement of Q_{max} in these patients, (C) simulated values for measurements of mean Q_{max} in patients instead selected based upon a criterion of mean Q_{max} from 40 measurements $< 12 \text{ ml}\cdot\text{s}^{-1}$ and (D) simulated values for a second mean Q_{max} from 40 measurements in these patients.

Figure 5.12 shows the sample size required to detect a given difference with a given power versus the number of measurements averaged. A marked decrease is observed from one to ten voids: a reduction of over 80 % in the required sample size. Ten voids would therefore appear to represent a good balance between cost of, and benefit from, multiple uroflowmetry for the purpose of reducing the sample size for clinical trials.

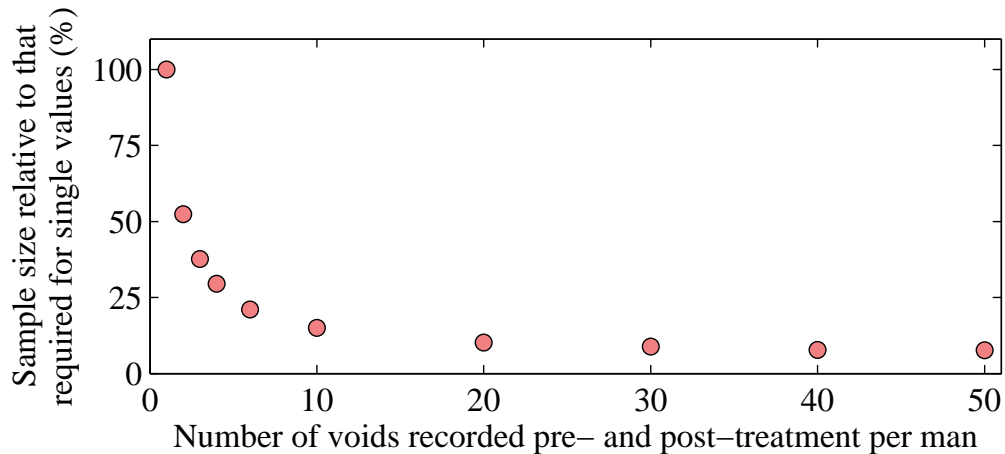


Figure 5.12 *The number of pre- and post-treatment measurements of Q_{max} averaged per man versus the sample size required to detect a given difference in mean Q_{max} with given power. Values are expressed as a percentage of the sample size required if only one measurement is made per man.*

5.9 Conclusion

As Q_{max} is a well established clinical parameter, an obvious first step is to extract from multiple home uroflowmetry a mean Q_{max} : the clinician's familiar friend in a slightly different guise. Both diagnostic accuracy and, particularly, assessment of treatment outcome would benefit from using a mean rather than single value of Q_{max} . The extent of this benefit has been predicted by models founded upon descriptive statistics from the literature.

The results, whilst suggesting that thousands of men per year may benefit from more accurate clinical decision making, are perhaps not quite enough of a sensation to move uroflowmetry from the clinic into the home just yet.

Mean Q_{max} is not the only parameter available from multiple measurements of flow made in the home. There is a wealth of uncharted information that may provide new insight into lower urinary tract function. However, how can we investigate this further without an appropriately designed device?

Chapter 6

The PeePod

6.1 Introduction

It is apparent from the literature reviewed in Chapter 4 that a variety of home flowmeters have been developed for both research and commerce since the 1960s. It is also clear that the clinical performance of Q_{max} could be improved in terms of diagnostic accuracy, and even more so for evaluation of treatment outcome, by averaging multiple measurements in an individual. Despite this, home uroflowmetry has not been incorporated into common clinical practice, and this can be attributed to a number of factors. First and foremost is the absence of sufficiently powered, high quality studies demonstrating in a clinical setting the benefit of home uroflowmetry over conventional methods. But there is also the matter of the technology itself; none of the devices identified in Chapter 4 fulfill the recommendations of the ICS at a sufficiently low cost to allow widespread use. Indeed, if such an instrument did emerge, attempts to fill the evidence gap may not be far behind.

It is this factor that the Regional Medical Physics and Urology departments within Newcastle upon Tyne Hospitals NHS Foundation Trust sought to address some years ago. Prior to my joining the department, a prototype device based upon a very economic capacitive measurement technique was developed, led by Jennifer Caffarel. This work laid the foundations for development of a second generation device, selected for funding by the Wellcome Trust's Technology Transfer Translation Award in 2010. This chapter describes the characteristics and technical performance of that device: the PeePod.

The PeePod was developed by Michael Drinnan (research, general development and software), Mike Whitaker (research, general development, electronics, firmware and maintenance software), Clive Griffiths (research and general development), Rob Beckwith (3D mechanical computer aided design model) and me (research, general development and reporting algorithms). Robert Pickard provided clinical insight to guide the development.

The intellectual property associated with the PeePod, namely a patent application and trademark registration, is described in Appendix A1, page 237. Prior to patient use, the device was registered with the Medicines and Healthcare Products Regulatory Agency (MHRA) (see Appendix A2, page 239).

6.2 Scope and specification

To inform the development of the device, we began by producing a scope and specification, based upon guideline recommendations (Schäfer et al., 2002) and consideration of what could be achieved at low-cost.

6.2.1 Scope

The PeePod is an electronic urine flowmeter and voiding diary designed for operation by patients in their homes. It is intended to fill the technology gap, being simple and low-cost to allow widespread single-patient use, but sufficiently sophisticated to obtain precise data that can replace conventional flow rate testing and frequency-volume charts. It must be simple to operate, self contained and portable, and battery-powered. The data obtained are to include the date, time, duration and continuous volume and flow rate measurements for multiple voids. The device must connect to a PC for the purpose of data download, followed by simple and concise presentation of results via bespoke software.

6.2.2 Specification

The specification is described in Table 6.1 overleaf.

	Range	Resolution		Accuracy	
		Reporting	Plotting	Required	Desirable
Volume	0 - 1,000 ml	10 ml	2 ml	$\pm 5\%$ (± 50 ml in 1,000 ml)*	$\pm 0.5\%$ (± 5 ml in 1,000 ml)
Flow rate	0 - 50 ml·s ⁻¹	1 ml·s ⁻¹	0.1 ml·s ⁻¹	$\pm 5\%$ (± 2.5 ml·s ⁻¹ in 50 ml·s ⁻¹)	$\pm 1\%$ (± 0.5 ml·s ⁻¹ in 50 ml·s ⁻¹)
Void duration	-	1 s	-	$\pm 4\%$ (± 5 s in 2 mins)	$\pm 1\%$ (± 1.2 s in 2 mins)
Time of void	-	1 min	-	$\pm 0.1\%$ (± 25 mins in 2 weeks)	$\pm 0.025\%$ (± 5 mins in 2 weeks)
		Required	Desirable		
Memory capacity	Up to 50 voids	Up to 100 voids			
Battery life	Up to 1 week	Up to 2 weeks			

* Here, \pm denotes the maximum permissible error.

Table 6.1 *The initial specification for the PeePod describing measurement range, resolution and accuracy.*

6.3 Measurement technique

The PeePod employs weight transducer technology. It is in essence a pair of weighing scales, measuring the downward force due to gravity of urine inside a container. A base unit houses electronics and a load beam: an aluminium bar with a cutout around which four strain gauges are positioned (Figure 6.1A). The cutout ensures that when force is applied, deformation occurs at the narrowest, and therefore weakest, parts of the beam where the strain gauges are located. The strain gauges are constructed of an arrangement of metal foil so that deformation changes their resistance according to Equation 6.1.

$$R = \frac{L}{A\sigma} \quad (6.1)$$

Where:

R = resistance

L = length of foil

A = cross-sectional area of foil

σ = conductivity of foil

They are arranged in a Wheatstone bridge configuration, which is illustrated in Figure 6.1C. The output voltage is given by Equation 6.2.

$$V = V_s \left(\frac{R_2}{R_1 + R_2} - \frac{R_3}{R_3 + R_4} \right) \quad (6.2)$$

Where:

V = measured voltage

V_s = supply voltage

R_1, R_2, R_3, R_4 = strain gauge resistances

When no force is applied, all four resistances are equal and so the output voltage is zero. When force is applied to the load beam, the resistance of the strain gauges under tension, $R1$ and $R3$, increases, and that of those under compression, $R2$ and $R4$, decreases. The electrical output is therefore proportional to the applied force. The volume of urine inside the container is in turn proportional to the force and so can be determined simply by application of a conversion factor. Flow rate is then derived from volume via differentiation in software.

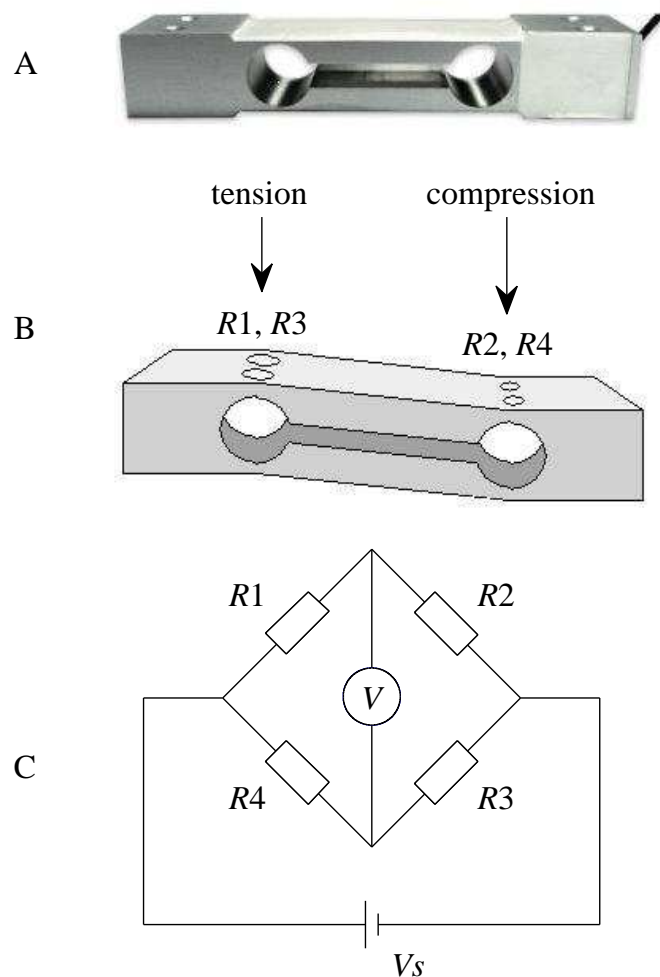


Figure 6.1 (A) An aluminium load beam. (B) An exaggerated illustration of the effect of load on four strain gauges with resistances $R1$ to $R4$: two experience tension and two experience compression. (C) An electronics block diagram showing the configuration of four strain gauges with resistances $R1$ to $R4$ in a Wheatstone bridge, with supply voltage V_s and output voltage V .

6.4 Design and operation

The PeePod consists of two components: a measurement base unit, or ‘pod’, and a jug for collection of urine (Figure 6.3). All that is required of the patient is to place the jug on top of the pod, void into the jug, and then dispose of the urine. To ensure simplicity of operation, the PeePod is devoid of buttons, switches and displays. A light-emitting diode (LED) indicator communicates the current status of the device to the user, as illustrated in Figure 6.2.

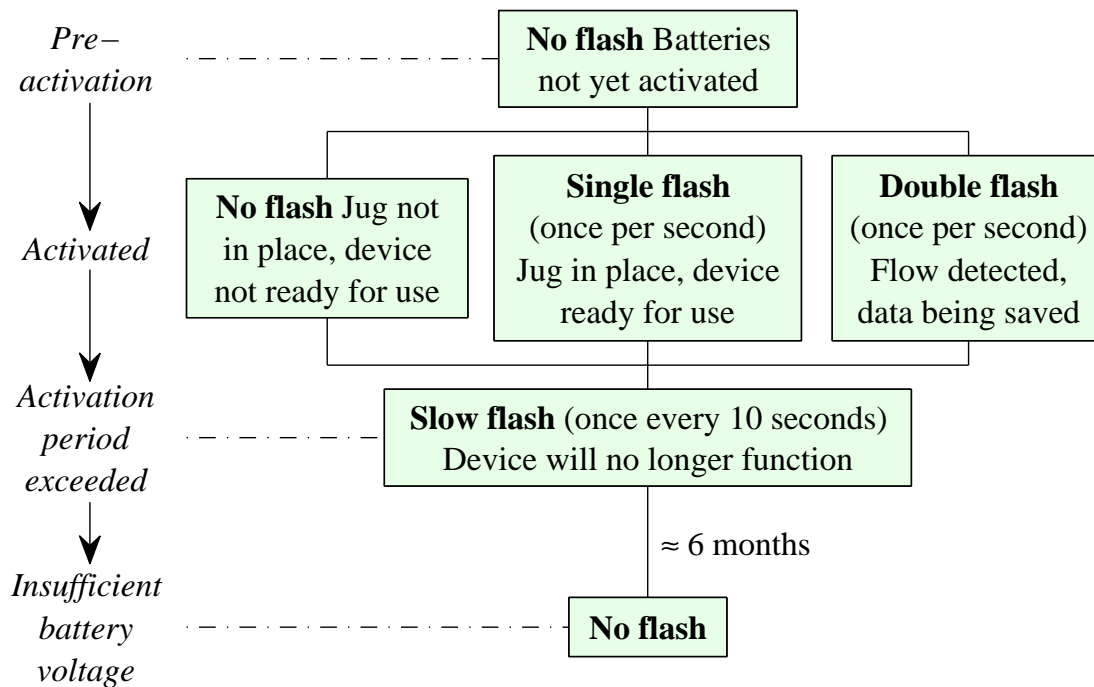


Figure 6.2 *The various states assumed by the PeePod, and how these are conveyed by the LED indicator. Once the activation period has been exceeded, the device enters a state of hibernation, lasting approximately 6 months. Following this, flow rate and volume data are retained but void dates and times are lost.*



Figure 6.3 *The PeePod with the collecting jug positioned on top of the pod, and the pod alone showing user instruction label. A green LED indicates the state of the device to the user according to Figure 6.2.*

6.5 Hardware and firmware

For a conventional clinic flowmeter, a base unit typically containing a load beam and analogue amplifier connects to a separate system including data-logger, power, and control firmware. For the PeePod, all of this functionality is incorporated into the pod. It has inbuilt power, memory and control in the form of two AA batteries, memory chip, and microcontroller, respectively. It connects to a PC via USB for the purpose of calibration and data download, which are performed by bespoke pieces of software. Once the batteries have been activated by removal of an isolation tab, the PeePod functions for a period of time dictated by the firmware, set at present to be two weeks. The memory capacity of the PeePod is 0.5 megabytes which equates to around 33,000 seconds' worth of data, amounting to over 500 voids with an average duration of 1 minute. In a low power state, the device continually monitors activity in order to implement a flow-detection algorithm that rejects movement and handling artefacts and saves only valid voiding data to memory. A quartz crystal, with claimed accuracy $\pm 0.003\%$ (± 36 s in 2 weeks), maintains timing information.

6.5.1 Sample rate

Due to the resonant frequency of this crystal and the firmware involved, accuracy of timing information depends upon the sample rate being a power of two. Given that the recommended sample rate is 10 Hz (Schäfer et al., 2002), the neighbouring possibilities are 8 and 16 Hz. The contractions and relaxations of the detrusor muscle responsible for changes in urine flow rate are relatively slow and can therefore be reliably represented by sample rates upwards of 0.2 Hz (Gammie et al., 2014). However, in order to reproduce artefacts such as abdominal straining and (in the case of weight transducer flowmeters) knocking, a higher rate is required.

The guideline also recommends that flow data are filtered using a sliding average with a duration of 2 seconds. The low-pass tendency of this filter attenuates high frequencies such that there is very little difference between signals recorded at 8 and 16 Hz. This is illustrated in Figure 6.4, which shows four flow traces recorded at 16 Hz and subsequently displayed at 8 and 4 Hz by discarding samples. Even at 4 Hz the effect of downsampling on the shape of the curves and interpretation of Q_{max} is negligible.

The design of the PeePod is a compromise between function, performance and cost. A sample rate of 16 Hz rather than 8 Hz would double the required memory and at least double the power consumption. On balance, a sample rate of 8 Hz was chosen rather than the recommended 10 Hz.

6.6 Maintenance software

Maintenance software developed by Mike Whitaker allows calibration and testing of the PeePod both prior to and following patient use. Calibration is performed by programming the analog-to-digital conversion (ADC) values corresponding to 0 and 1,000 g into the device's memory, after which gain is checked by applying a 500 g mass. The measurement limit is tested to ensure a saturation point beyond 1,000 ml plus the jug weight, and the flow rate measurement verified using a constant flow device (Griffiths et al., 1983). Following the patient study, data may be saved as a *.csv* or *.xml* file.

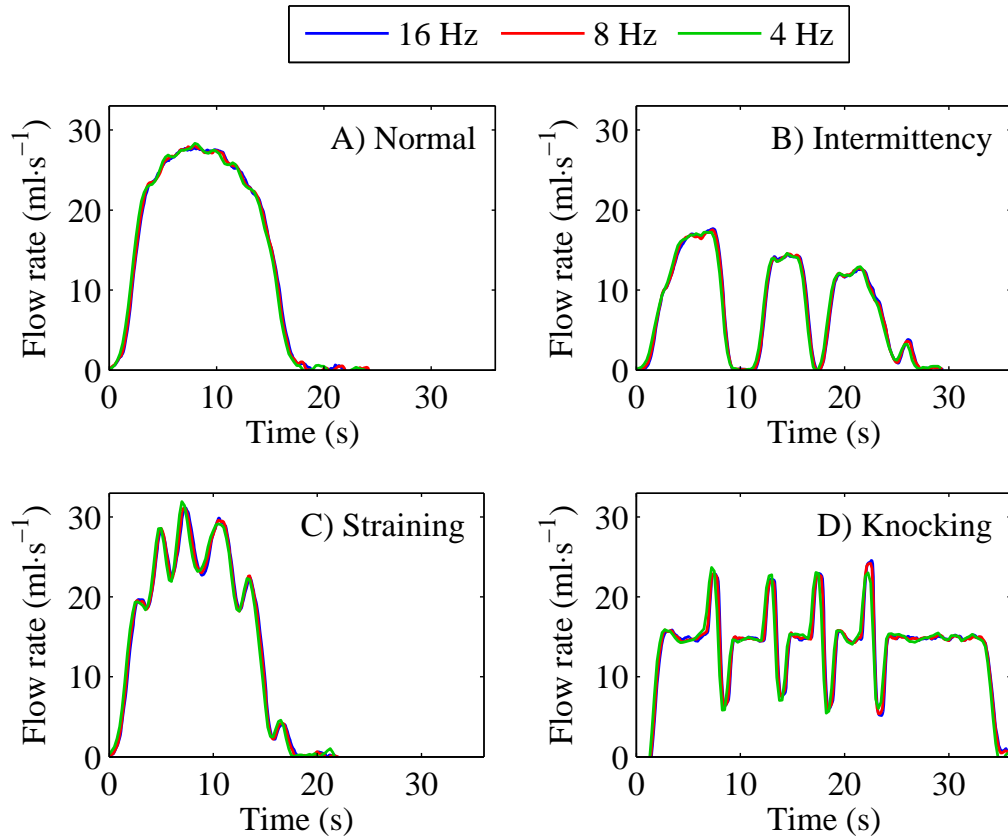


Figure 6.4 Four flow traces recorded at 16 Hz and downsampled to 8 and 4 Hz. A healthy subject was asked to (A) void normally, (B) void intermittently by contracting their external urethral sphincter, and (C) strain their abdominal muscles intermittently. (D) shows a trace from a constant flow device (described later in Section 6.9.1) interspersed with knocking artefacts. The effect of downsampling on the shape of the curves and interpretation of Q_{max} is negligible.

6.7 Reporting

For the purpose of the studies described in the following chapters, the *.csv* data were loaded into MATLAB in order to produce a clinical report. This report, illustrated in Figures 6.5 and 6.6, comprises the following (calculations are described later):

- A ‘supertrace’ on which all flow traces are superimposed, with the ‘median scored’ trace highlighted (Figure 6.5).
- An electronic frequency-volume chart with daily totals (Figure 6.5).
- Summary statistics (Figure 6.6).
- A plot of Q_{max} versus V_{void} for each void, with median Q_{max} versus median V_{void} highlighted. The Siroky nomogram for maximum flow rate in men is underlaid, with indication of normality accordingly (Figure 6.6)[†].
- A series of individual flow traces marked with Q_{max} (Figure 6.6).

6.7.1 Calculations

Flow rate Volume data extracted from the PeePod are converted to the flow information displayed in the report by two point differentiation, multiplication by the sample rate, and convolution with a two second triangle window. The maximum point, reported as Q_{max} , is detected following further application of a two second median filter so that sharp spikes such as knocking artefacts are ignored. This signal processing is illustrated in Figure 6.7.

[†] In retrospect, given the issues discussed under Section 3.3.1, from page 29, it would have been more appropriate to use a nomogram based upon voided rather than bladder volume. This will be corrected for future data analyses and presentation.

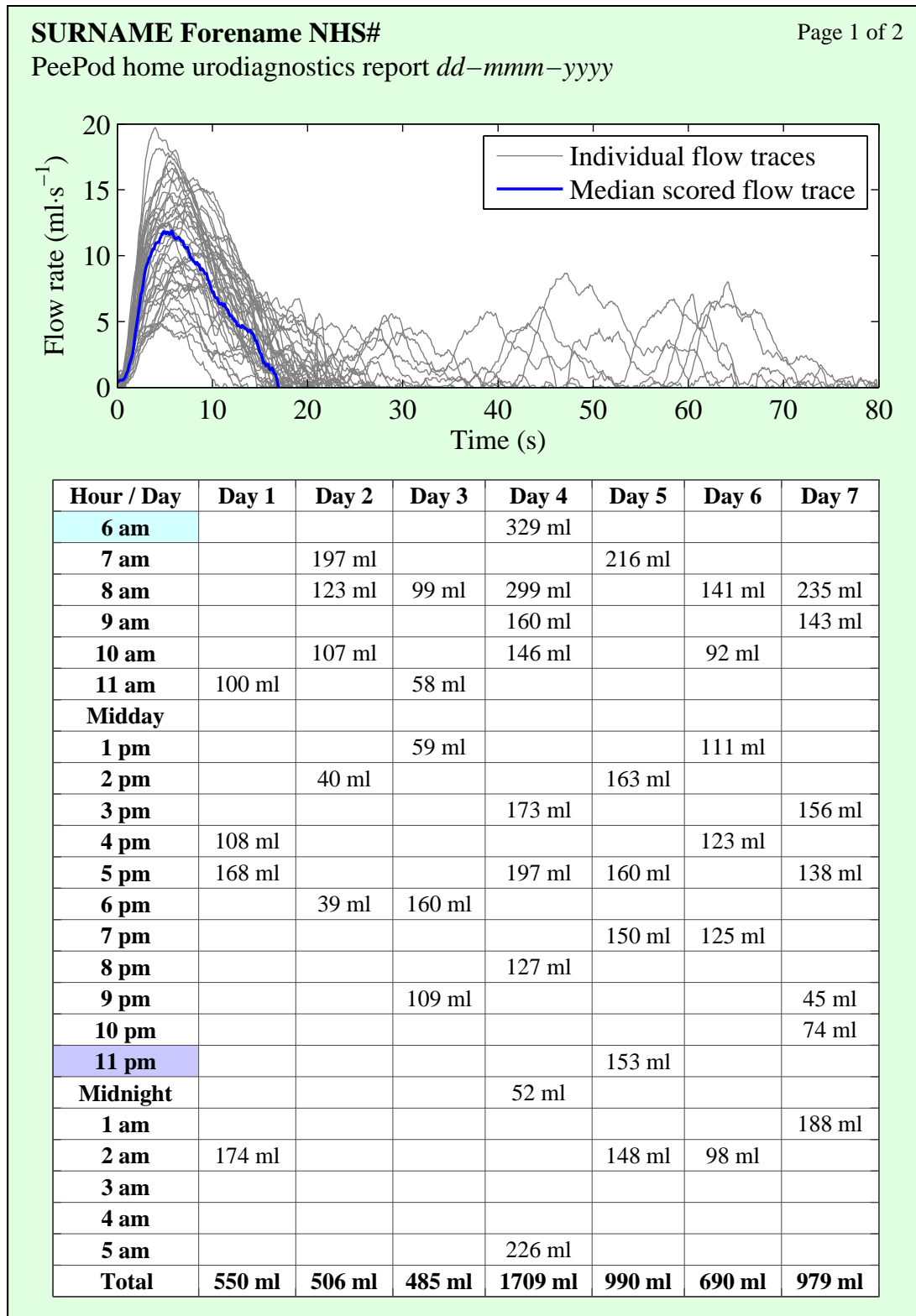


Figure 6.5 Page 1 of the PeePod report with a supertrace, showing individual flow traces with the median scored trace highlighted, and electronic frequency-volume chart with daily totals. Light and dark blue shading at 6 am and 11 pm denote the start of the daytime and nighttime periods, respectively. Days with low 24-hour V_{void} may be due to insufficient fluid intake, or periods of poor device compliance.

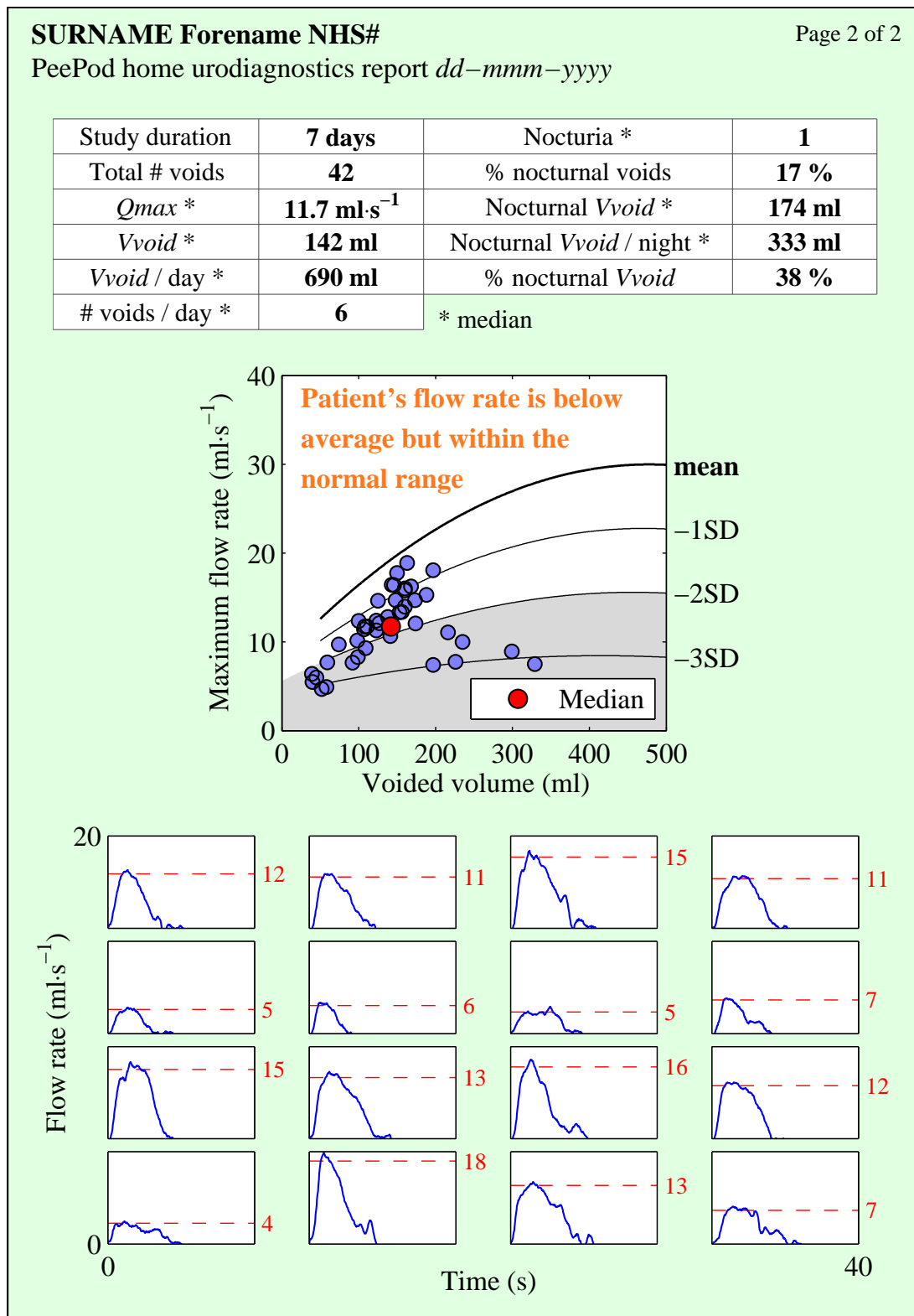


Figure 6.6 Page 2 of the PeePod report with summary statistics, V_{void} plotted against Q_{max} for each void and for median values, with an indication of normality according to the Siroky nomogram, which is underlaid, and a series of individual flow traces with Q_{max} marked for each. The six voids with abnormally low Q_{max} at larger volumes may reflect high bladder volume and therefore large post void residual.

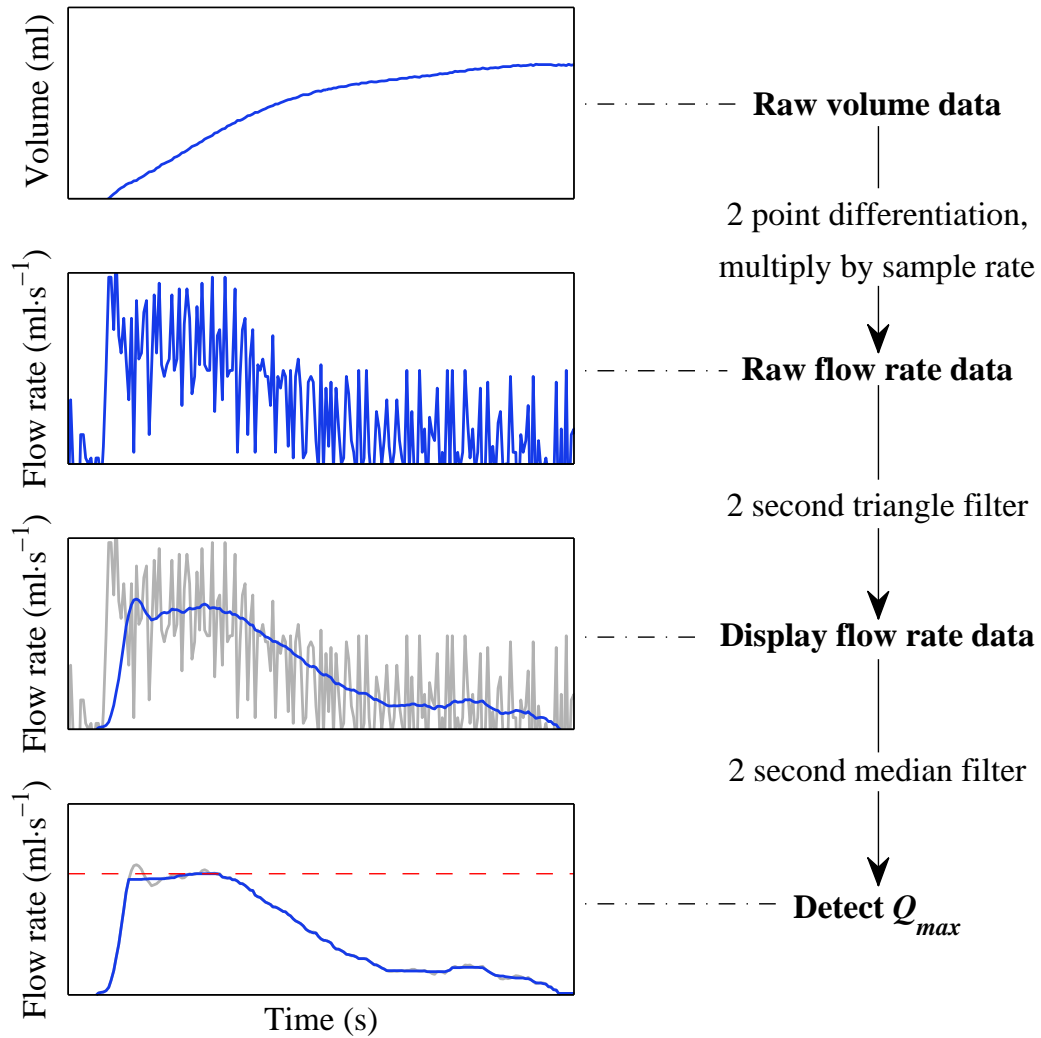
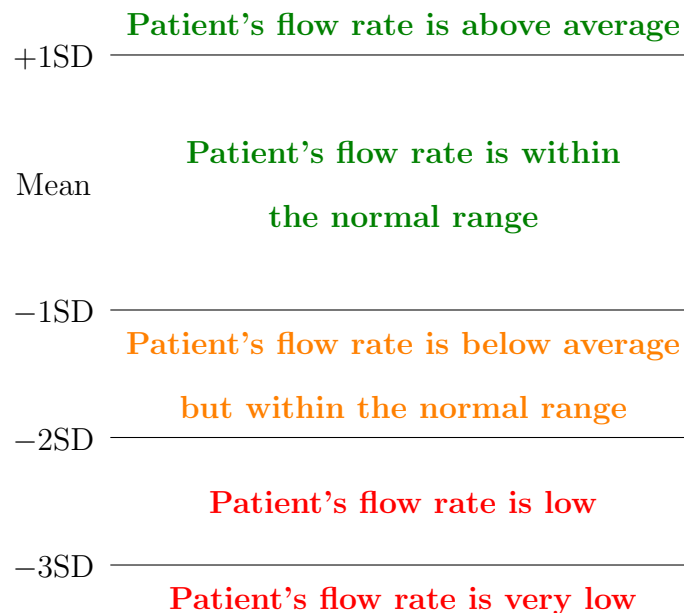


Figure 6.7 An illustration of the signal processing which converts volume measurements as recorded by the PeePod to reported flow rate information.

Median scored flow trace The flow trace highlighted on the supertrace is selected as follows: All traces are aligned at time zero. At each sample, the trace closest to the median value of all traces at that sample receives a point. The median scored trace is that which receives the most points. This has various advantages over a simple mean or median calculation, as illustrated in Figure 6.8.

Summary statistics To reduce the influence of extreme values, medians were chosen over means as the more appropriate representation of central tendency. This is because the number of voids recorded may be small, and the duration in days certainly will be. Table 6.2 describes calculation of the summary statistics shown in Figure 6.6, other than those which are self-explanatory. Guidance was taken from standardisation of terminology reports published by the ICS (Abrams et al., 2002; van Kerrebroeck et al., 2002).

Indication of normality for voiding parameters The point [median V_{void} , median Q_{max}] is classified according to the Siroky nomogram (see Figure 3.5, page 30), and the classification displayed, as follows:



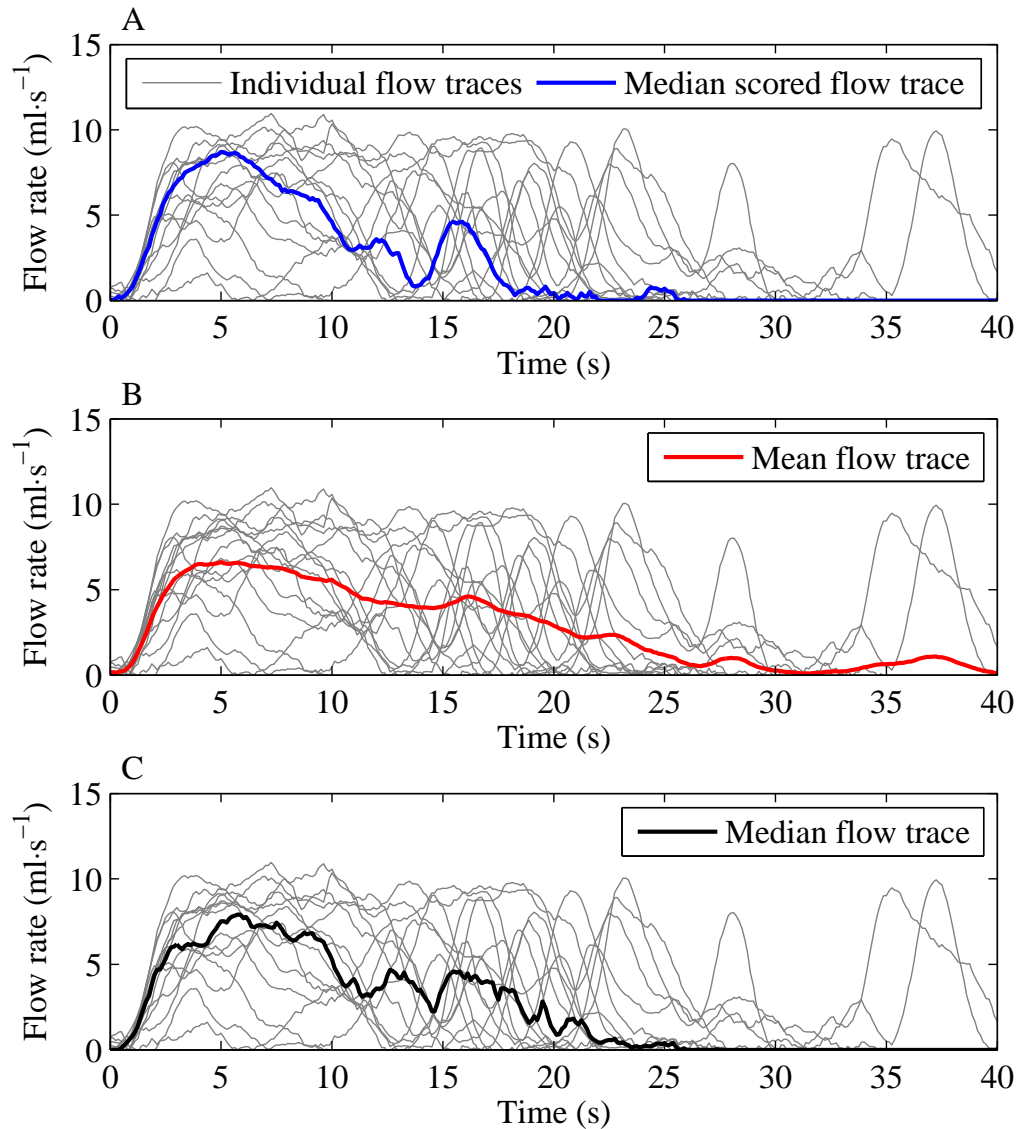


Figure 6.8 Three alternatives for displaying the average flow trace: (A) Median scored trace. (B) The result of taking the mean measurement is an oversmoothed trace, which may mask intermittency. Due to the staggered void end points, it tends to have a long decreasing tail with the appearance of terminal dribble, even if individual voids do not exhibit this characteristic. (C) The median flow trace suffers a similar problem to a lesser extent, and jumps from trace to trace, giving an unphysiological appearance. This patient appears to be straining towards the end of some voids, perhaps to improve bladder emptying.

Statistic	Calculation
Median V_{void} / day	V_{void} is totalled per 24 hour period (6 am to 6 am) and the median value reported.
Median # voids / day	The number of voids are totalled per 24 hour period and the median value reported.
Median nocturia	The number of voids are totalled per night (11 pm to 6 am) and the median value reported.
% nocturnal voids	The number of voids during nighttime hours as a percentage of the total number of voids.
Median nocturnal V_{void}	The median volume of all voids during the night (including the first void of the following morning if before 10 am).
Median nocturnal V_{void} / night	V_{void} is totalled per night (including the first void of the following morning if before 10 am) and the median value reported.
% nocturnal V_{void}	The total volume of all voids during the night (including the first void of the following morning if before 10 am) as a percentage of the total volume of all voids.

Table 6.2 Calculation of summary statistics included in the PeePod report. Guidance was taken from ICS standardisation of terminology reports (Abrams et al., 2002; van Kerrebroeck et al., 2002).

6.8 Software

A second piece of software (the PeePortal) was subsequently created by Michael Drinnan, combining data download, analysis and reporting, and including the following functionality (Figure 6.9):

- A second-level valid flow algorithm is applied, which may hide obviously artefactual recordings from the user altogether (such as those due to the device being handled or transported), and suggest that others may be invalid by marking them with a red cross.
- For each void, the start point, end point, and Q_{max} are determined automatically, but may be corrected by the user if necessary.
- Voids may be flagged as invalid in order to exclude them from all analyses, and marked as day or night to allow calculation of nocturia and nocturnal voided volume.
- The electronic voiding diary allows exclusion of whole days from per-day calculations, although individual voids are still included for average Q_{max} and V_{void} . This may be appropriate in order to exclude a period of apparently poor compliance.

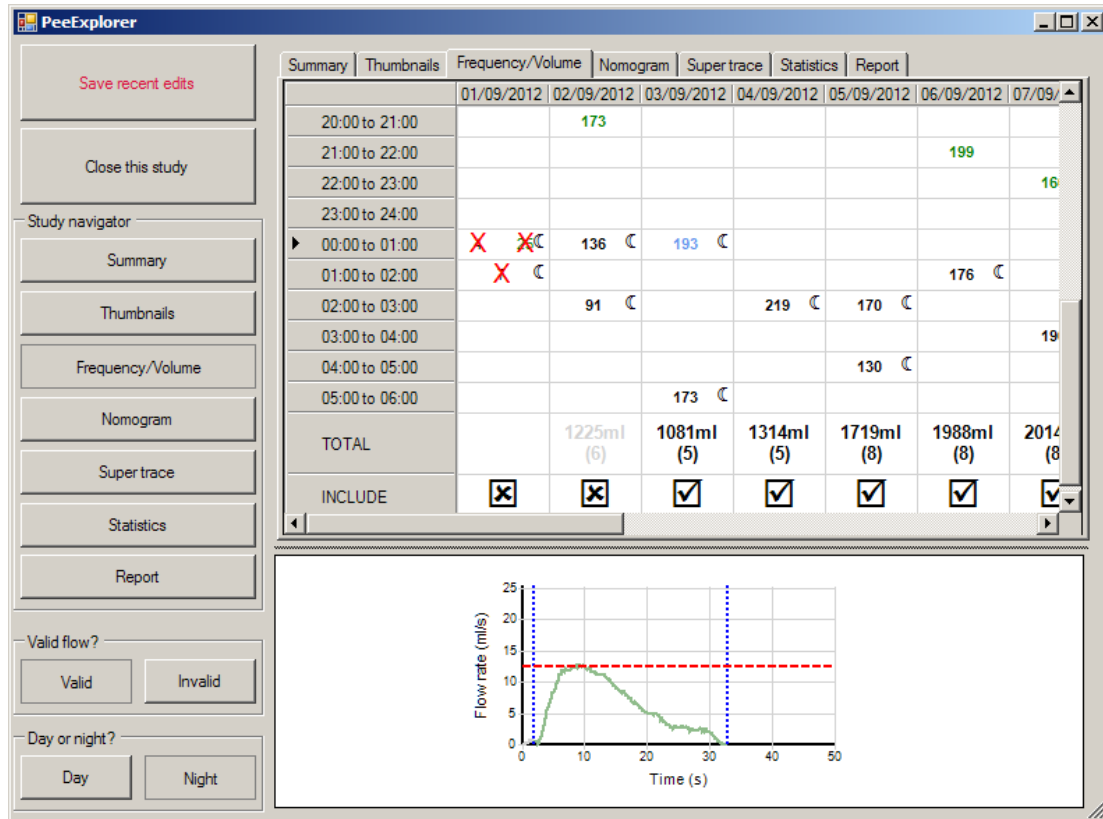


Figure 6.9 A screenshot from the PeePortal showing the frequency-volume chart tab. Green text denotes daytime voids, black text with moon symbol denotes nocturnal voids, and red crosses denote voids marked as invalid. Days marked with a tick are included in calculation of per-day statistics, whereas those marked with a cross are not. The selected void, shown in blue, is displayed in the lower panel to allow correction of start time, end time and Q_{max} by dragging the blue and red dashed bars.

6.9 Technical performance

This section aims to test the most crucial aspects of the PeePod's measuring function: the accuracy of its volume and flow rate measurements.

For calibration purposes, a linear relationship is assumed between the force applied to the PeePod and its electrical output and so any non-linearity will result in errors. The performance of the load beam is not the only factor; the beam is mounted into plastic housing and any force that serves to deform the plastic and prevent force being transmitted to the beam will affect the linearity of the measurement.

In addition, patients are asked to place the PeePod on a flat surface at a convenient height before use, and as it happens the closed toilet seat is usually ideal. For those with combined toilet/shower rooms, devices may be exposed to, and required to function accurately at, high humidity.

Finally, unlike a conventional flowmeter which resides in the relative safety of the hospital clinic, the portable nature of the PeePod leaves it susceptible to being dropped, sat on, etc, which may inflict damage to the load beam or plastic housing. Such damage may affect the PeePod's calibration, resulting in voiding information being reported incorrectly.

These effects, which may compromise the PeePod's accuracy, are examined below.

6.9.1 Methods

Linearity 10 PeePods were tested in order to investigate the linearity of the volume measurement. 26×50 g masses were loaded onto each device one by one, and the ADC values recorded at each point (providing 27 measurements per

device)^{‡§}. Residuals were calculated between the linear relationship connecting ADC values corresponding to 0 and 1,000 g and the actual ADC values recorded for each load[¶]. In addition, in order to evaluate the linearity at high humidity, one device was tested as described above, following which it was placed in a bathroom whilst a hot shower was run for 10 minutes, and then retested.

Calibration errors following use Chapters 7, 8 and 9 will describe studies of the PeePod in clinical practice, totalling approximately 100 datasets. Here, these data are used to present shifts in the device’s calibration during use. Each time a PeePod was prepared for patient use, a calibration procedure was performed. As described earlier, this involved programming the ADC values corresponding to 0 g and 1,000 g into the PeePod’s memory using custom-built calibration software. The values were then rechecked when a device was returned. Both gain and zero calibrations were examined. The zero error was simply the post-use reading in ml with no load applied. The gain error was defined as follows:

$$error_{gain} = ml_{1,000} - ml_0 - 1,000 \quad (6.3)$$

Where:

$error_{gain}$ = gain error (ml)

$ml_{1,000}$ = the post-use reading in ml with 1,000 g applied

ml_0 = the post-use reading in ml with no load applied

[‡] Errors associated with decreasing mass are not presented because the measurement of interest is always that of increasing weight.

[§] The PeePod is required to measure up to 1,000 ml plus the weight of a collecting vessel, hence a limit of $26 \times 50 \text{ g} = 1,300 \text{ g}$ was chosen.

[¶] Consequently, there will be no errors measured at 0 g or 1,000 g, and a spurious reading at either or both of these calibration points will result in large errors across the measurement range. Whilst this is not a true indication of the PeePod’s inherent linearity, it does reflect use of the device in practice.

Where large errors were observed, the raw data were examined in an attempt to determine the point at which the change occurred. This often gave an indication of the cause, and also allowed subsequent data to be excluded from the patient's results.

Propagation of errors into flow rate Errors associated with the flow rate measurement are a combination of errors due to non-linearity and those due to shifting calibration. Therefore, the above data allowed calculation of the propagation of volume errors into flow rate.

For each of the 10 devices tested for linearity, the resulting volume measurements were combined with the largest observed gain error following use. In other words, each volume measurement was altered to add the effect of the worst gain error on top of the effect of non-linearity. Flow rate measurements for each device were then simulated by linear interpolation between these volume measurements to achieve a flow rate of $50 \text{ ml}\cdot\text{s}^{-1}$, followed by differentiation. This represents the worst case in terms of error maximisation for the following reasons:

1. Errors simulated in this way are proportional to the chosen flow rate, and are expressed as the percentage of full scale ($50 \text{ ml}\cdot\text{s}^{-1}$). Errors are therefore maximised if the simulated flow rate is chosen to be $50 \text{ ml}\cdot\text{s}^{-1}$. The PeePod will rarely be required to measure flow rates in excess of $50 \text{ ml}\cdot\text{s}^{-1}$ in clinical practice.
2. As mentioned previously, prior to presentation for analysis, flow data should be smoothed by a sliding average filter, which serves to reduce the errors. Therefore, errors following application of a filter will also be presented.
3. The largest gain error may be an outlier.

The above method was chosen over that of testing the flow rate measurement using a constant flow device. It is not a trivial matter to generate a constant flow rate with high accuracy. Figure 6.10 shows an example trace from one such device (Griffiths et al., 1983)^{||}, which deviates by up to $2.7 \text{ ml}\cdot\text{s}^{-1}$ (18 %) from the intended constant flow rate of $15 \text{ ml}\cdot\text{s}^{-1}$.

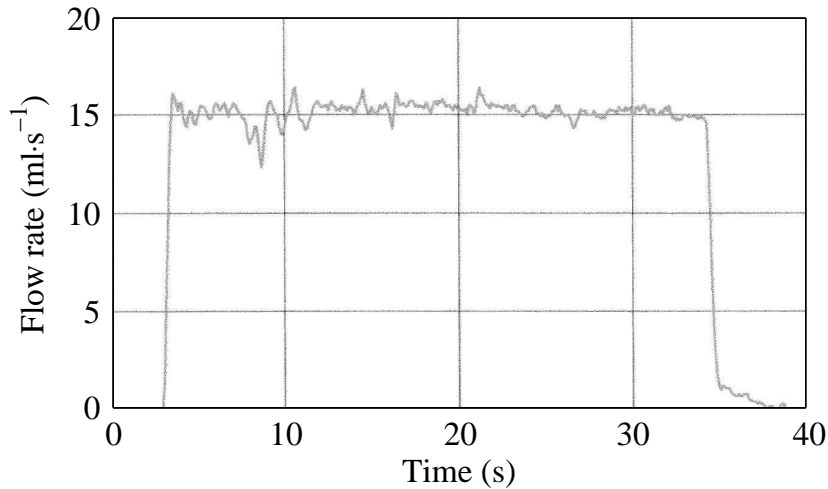


Figure 6.10 *The flow rate produced by a constant flow device (Griffiths et al., 1983) showing deviation of up to $2.7 \text{ ml}\cdot\text{s}^{-1}$ (18 %) of the intended rate of $15 \text{ ml}\cdot\text{s}^{-1}$.*

6.9.2 Results

Linearity Figure 6.11 shows individual histograms of the residuals for each device tested; in general they are approximately normally distributed. Figure 6.12 shows the histogram of residuals for the 10 devices combined; all are comfortably within $\pm 5\%$ of full scale (1,000 ml). The maximum error was 2.2 ml (0.2 % of full scale). All errors combined had mean [SD] -0.09 [0.7] ml.

^{||} The device comprises a milk bottle, rubber bung, short metal tube and longer rubber tube. The rubber tube vents to atmosphere at the top of the metal pouring tube of length h . Therefore, flow rate, $Q = A\sqrt{2gh}$, remains constant.

Figure 6.13 shows deviation from linearity for the load test at (A) 53 % humidity** and (B) following exposure to 99 % humidity, with humidity as measured by a digital hygrometer. The errors do not appear to be exacerbated by high humidity; they are in fact slightly, although not significantly, smaller ($p = 0.2$, absolute unpaired errors compared using Mann Whitney U).

Calibration errors following use A total of 105 full calibration datasets were available for investigation of change in calibration during use. Histograms showing all gain and zero errors are displayed in Figures 6.14A and 6.14B, respectively.

All gain errors were within ± 10 ml (± 1 %), with the exception of one device returned with an error of -29 ml (2.9 %). On investigation, the electrical wiring inside this device was found to make contact with the lid, causing reduced gain by a reduction in the force transferred to the load beam. All gain errors combined had mean [SD] -0.5 [4.0] ml.

95 % of zero errors were within ± 100 ml, with the remaining 5 % ranging from 129 to 811 ml. Raw data revealed that larger shifts coincided with excessive force applied to device. All zero errors combined had mean [SD] 18 [104] ml.

The PeePod's zero calibration is far less crucial than its gain. The volume for each void is calculated by subtracting the volume at the start of the void, rather than the value programmed as zero, from that at the end. Therefore, the reported volume and flow rate measurements depend only upon the gain. The sole requirement is that there are sufficient ADC units above the zero for measurement of the jug weight plus 1,000 ml of urine, and in practice usually far less.

** Normal room humidity on the day of the test.

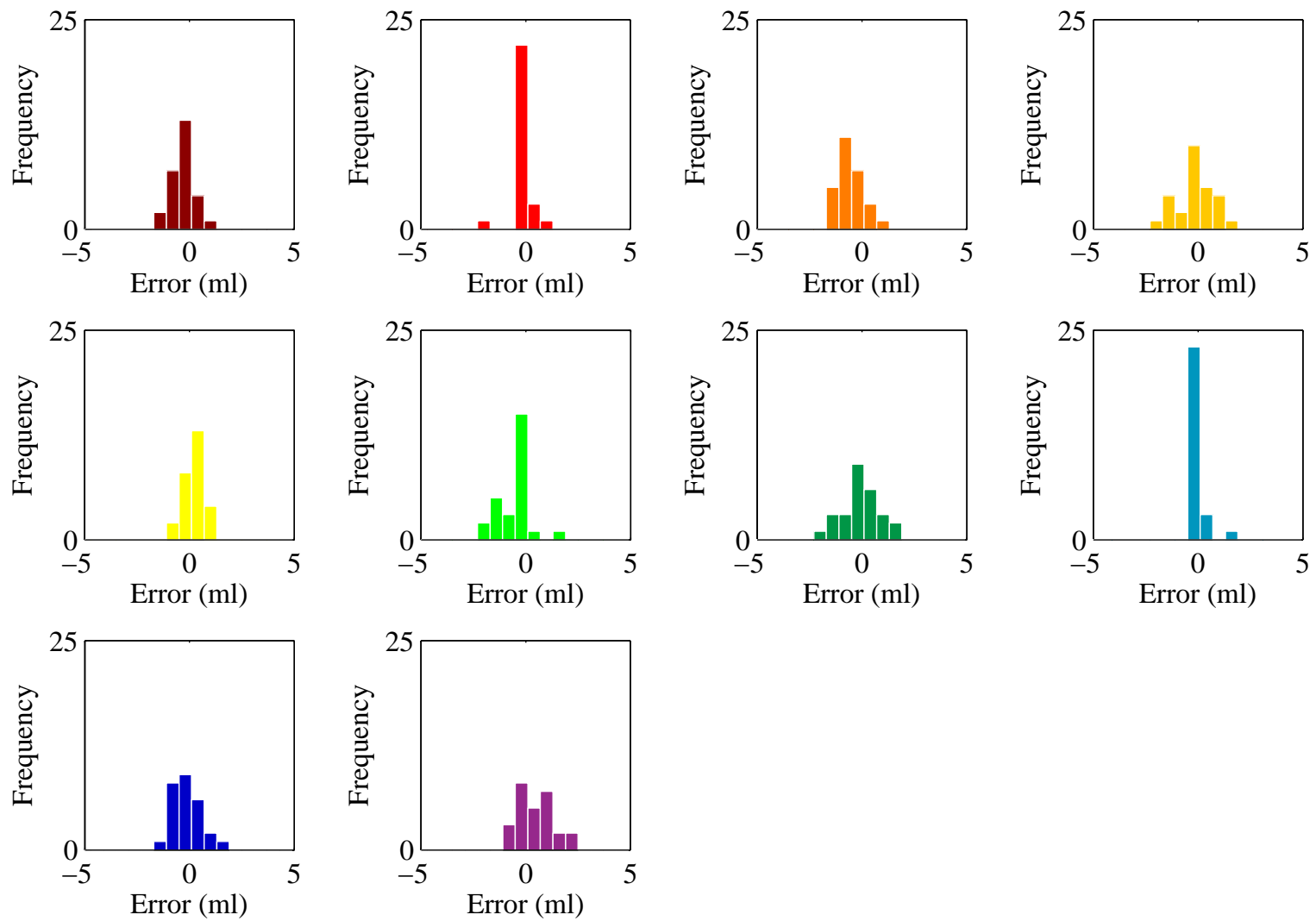


Figure 6.11 Histograms showing deviation from linearity for 10 devices tested by applying increasing load.

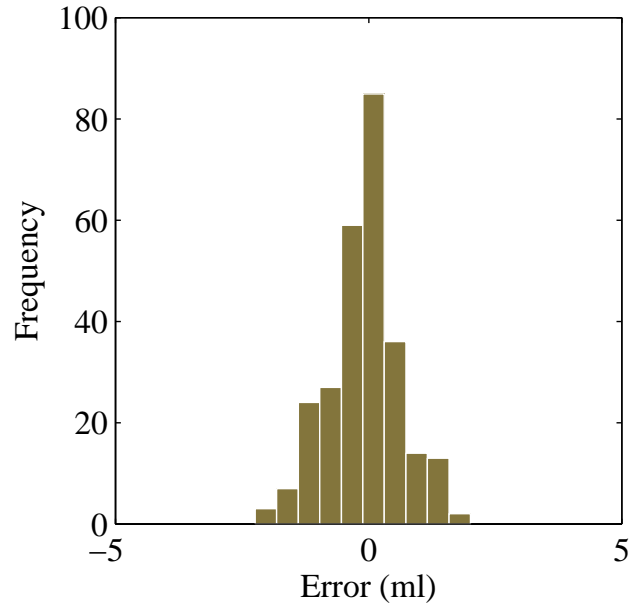


Figure 6.12 Histograms showing deviation from linearity for the combined results from 10 devices tested by applying increasing load.

Propagation of errors into flow rate The worst gain error was an extreme outlier, as shown in Figure 6.14A. Nevertheless, this error was combined with the volume linearity measurements in order to calculate the propagation of these two sources of error into flow rate. That is, all volume measurements became 97.1 % of their original value. Flow rate measurements were then simulated as described earlier. Figure 6.15A shows the simulated flow rate measurements superimposed over the intended flow rate of $50 \text{ ml}\cdot\text{s}^{-1}$, (B) the same plot with a focussed vertical scale and (C) the results following application of a 2 second triangle filter.

Prior to filtering, the maximum error was $3.5 \text{ ml}\cdot\text{s}^{-1}$ (7 %) and following filtering was $2.8 \text{ ml}\cdot\text{s}^{-1}$ (5.6 %). The ± 5 % limit was exceeded at two points as shown in Figure 6.15C. For all other combinations of the remaining 104 gain errors and 10 devices tested for linearity (1040 measurements), all errors were within the recommended ± 5 % relative to full scale (within $\pm 2.5 \text{ ml}\cdot\text{s}^{-1}$ of $50 \text{ ml}\cdot\text{s}^{-1}$).

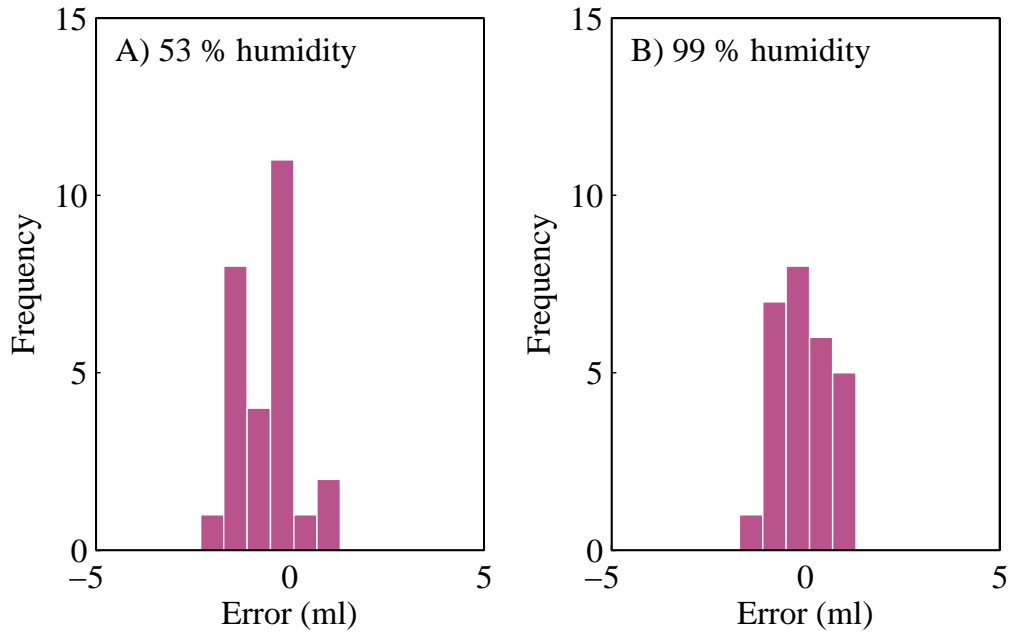


Figure 6.13 Histograms showing deviation from linearity for one device tested by applying increasing load at (A) 53 % humidity and (B) 99 % humidity.

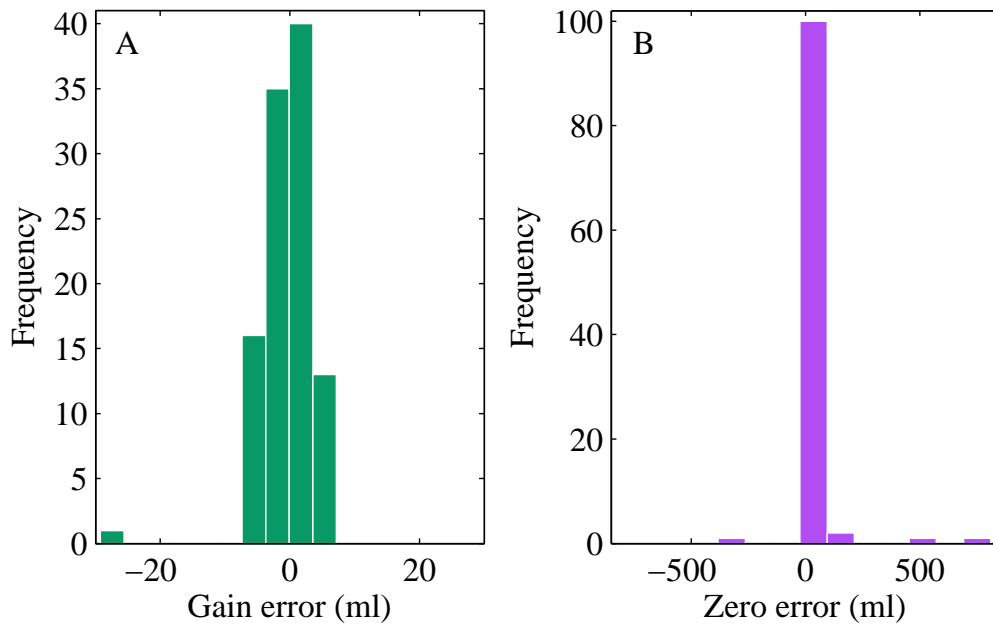


Figure 6.14 Histograms showing the change in (A) gain and (B) zero calibration from pre- to post-use for 105 devices.

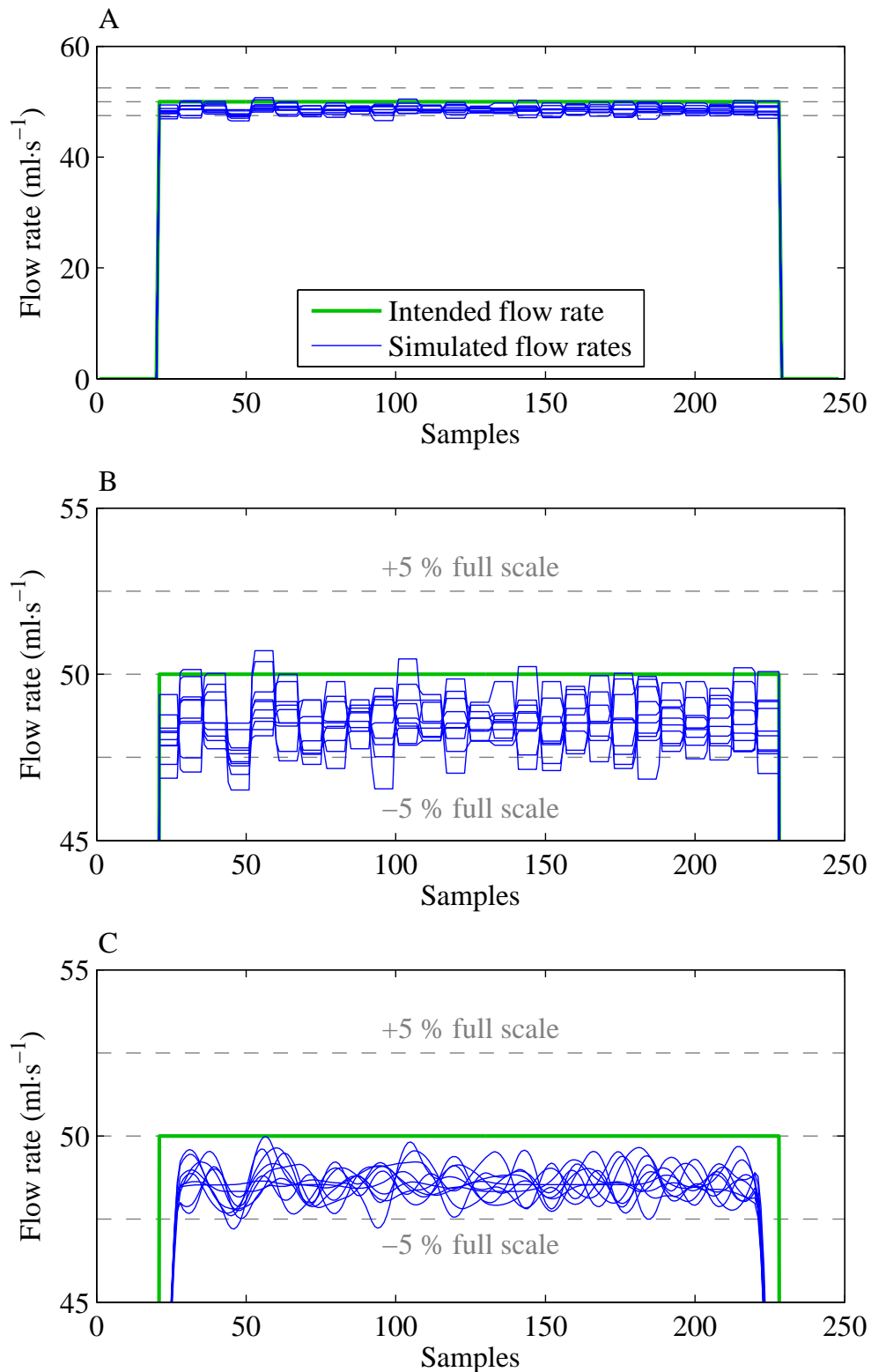


Figure 6.15 (A) Flow rates simulated from linear interpolation of volume linearity measurements plus gain errors (blue) superimposed over the intended flow rate of $50 \text{ ml}\cdot\text{s}^{-1}$ (green). (B) The same plot with focussed vertical scale. (C) The result following application of a 2 second triangle filter. Dashed grey lines show $50 \text{ ml}\cdot\text{s}^{-1} \pm 5 \%$. The traces are zero padded at the beginning and end.

6.9.3 Discussion

Potential sources of error were identified and a limited amount of testing carried out to assess the accuracy of the PeePod's volume and flow rate measuring functions. With the exception of one extreme case, the reason for which was identified, both volume and flow rate were reported to within the required accuracies as stated in the initial specification. The gain calibration, upon which volume and flow rate calculations are based, appears to be extremely resilient to damage during use.

Testing has identified measures that will further improve the PeePod's reliability, listed below. Therefore, the errors presented here represent the worst case.

- A more accurate manufacturing processes (steel rather than silicone tooling to improve tolerances).
- More secure mounting of the load beam into the plastic housing.
- Improved mechanical end stops to reduce the risk of the load beam exceeding its damage limit.
- Increased clearance around the load beam and improved securing of wires to reduce the risk of fouling.
- More robust packaging to reduce damage in transit.

Systematic, larger-scale testing of the device will form part of the CE marking process. This should verify the results reported here and the accuracy that ought to result from the hardware responsible for maintaining and calculating timing information.

6.10 Conclusion

Having identified a gap in the evidence, and a gap in the technology, we have developed a novel instrument: a low-cost electronic home flowmeter and voiding diary. Our primary aim was to create a device which is simple and intuitive to use for both patients and clinicians alike.

Despite its low cost and portable nature, the PeePod performs extremely well. It reports both volume and flow rate with accuracies within those expected of conventional clinic flowmeters carrying hefty price tags.

With this confirmation that the PeePod is fit for purpose, reliable and robust, the next step is to investigate the performance of the device within a clinical setting to determine the benefit for men with LUTS.

Chapter 7

Home versus conventional urodiagnostics in the assessment of men with lower urinary tract symptoms

7.1 Introduction

Before embarking upon a large scale trial, such as that comparing patient reported outcomes, a new clinical tool such as the PeePod should undergo preliminary validation. This should include verification of robustness, accuracy and reliability, and acceptability to both patients and clinicians.

A number of these issues were addressed in the previous chapter, which showed that the technical performance of the device was to the required standard. Despite the existence of a large amount of relevant literature, summarised in Chapter 4, several other of these questions, more general to home urodiagnostics, remain unanswered.

Patient opinion and preference has yet to be investigated robustly. Of the reviewed literature, a number of studies reported that home urodiagnostic devices were easy to use, but no further details were provided (de la Rosette et al., 1996; Currie, 1998; Jørgensen et al., 1998; Pel and van Mastrigt, 2002; Caffarel et al., 2007; Pridgeon et al., 2007). Only Boci et al. (1999) reported the use of a questionnaire. 25 patients were asked, perhaps slightly leadingly: *Is home uroflowmetry simpler and more acceptable than free [clinic] uroflowmetry?*, to which 80 % responded that it was.

Test-retest reliability of flow rate has been reported for a simple categorical funnel flowmeter, the Uflow Meter (Caffarel et al., 2007), but not for more precise electronic devices. In a diagnostic context, an average Q_{max} has been examined in isolation, but the remaining novel information available from home urodiagnostics has not been taken into consideration. Test success rates have not been formally measured.

The aim of this chapter is therefore to assess home urodiagnostics using the PeePod by comparison to conventional assessment, comprising clinic uroflowmetry and manual frequency-volume chart, in the following areas:

- Patient opinion.
- Test-retest reliability of flow rate.
- Test success rate.
- Diagnostic consistency and confidence.

7.2 Methods

This section describes the methodology relating to study design and recruitment. For continuity, methods of data analysis are described later alongside the results.

7.2.1 Study design

Two sample size calculations were conducted using Minitab software (Minitab Inc, Pennsylvania, USA) prior to beginning the study:

Patient opinion The primary outcome measure was patients' preference towards either conventional or home urodiagnostic assessment. Applying a power calculation with 80 % power, a null hypothesis that neither method is preferred (50 %), and the preferred method requiring at least 70 % (deemed to be the smallest clinically significant majority), gave a sample size of 47 patients. This was increased to 60, allowing an attrition rate of approximately 20 %.

Test-retest reliability For assessment of test-retest reliability, paired t-tests, or non-parametric equivalent, of the absolute difference between the first and second sets of measurements were planned. Applying a power calculation with 80 % power to detect a difference of $1.5 \text{ ml}\cdot\text{s}^{-1}$ between repeatability of clinic Q_{max} and average home Q_{max} (an estimate based upon pilot data from the capacitive prototype device mentioned previously), gave a sample size of 16 patients.

7.2.2 Recruitment

Ethical approval for the study was obtained from Newcastle & North Tyneside 1 Research Ethics Committee, covered by application 10/H0906/10 Assessment of home uroflowmetry: Amendment 3 (08/06/2011) which received favourable opinion on 15th July 2011 (see Appendix A3, page 241 onwards).

All men attending the urine flow clinic at the Freeman Hospital were eligible for inclusion into the study, with the following exclusion criteria:

- Inability to understand written or verbal instructions or give informed consent to participate in the study.
- Inability to void in a standing position, or preference towards voiding in a position other than standing.
- Presence of an indwelling urinary catheter.
- Inability to operate the PeePod, for example, poor hand function.

Patients were approached and, if willing, recruited on arrival at the Urology clinic for their urine flow study appointment. Those who agreed to take part:

- Carried out a urine flow test and completed a manual frequency-volume chart for four days. These tests formed part of their routine assessment for LUTS.
- Used the PeePod at home for one week. Patients were given a brief explanation of the device during consent and provided with an instruction sheet (see Appendix A4, page 246).
- Completed a questionnaire to provide feedback about their experience of the clinic test, frequency-volume chart, and PeePod (see Appendix A5, Section A5.1, page 247 onwards).

The first half of patients recruited were also asked to return to perform a second clinic urine flow test after using the PeePod at home.

7.3 Analyses and results

60 men were recruited into the study between January and July 2012. One man dropped out before using the PeePod due to ill health, leaving 59 sets of data available for analysis. The median age of the remaining 59 men was 67 years (range 45 to 89 years) at the time of entry into the study.

Voiding parameters were found in a high proportion of individuals to be non-Gaussian (37 % of Q_{max} distributions and 59 % of V_{void} distributions, according to the Anderson-Darling test). Volumes tended to be skewed towards lower values, whilst around half of patients' Q_{max} distributions were variably skewed in either direction. Therefore, non-parametric statistics are used to describe and analyse the data from this point onwards.

Figure 7.1 shows the single clinic measurement versus median home voiding parameters. Median home Q_{max} was significantly higher than Q_{max} in the clinic (11.9 versus 11 ml·s⁻¹, $p = 0.02$, Wilcoxon signed rank test), and median home V_{void} significantly lower (198 versus 242 ml, $p = 0.001$).

Figure 7.2 shows Q_{max} versus V_{void} at home and in the clinic for two interesting cases, where despite clinic V_{void} and Q_{max} being within the range of normal voiding at home, the combination of the two did not conform to the usual pattern.

Figures 7.3 and 7.4 show all maximum flow rates and voided volumes recorded at home and in the clinic.

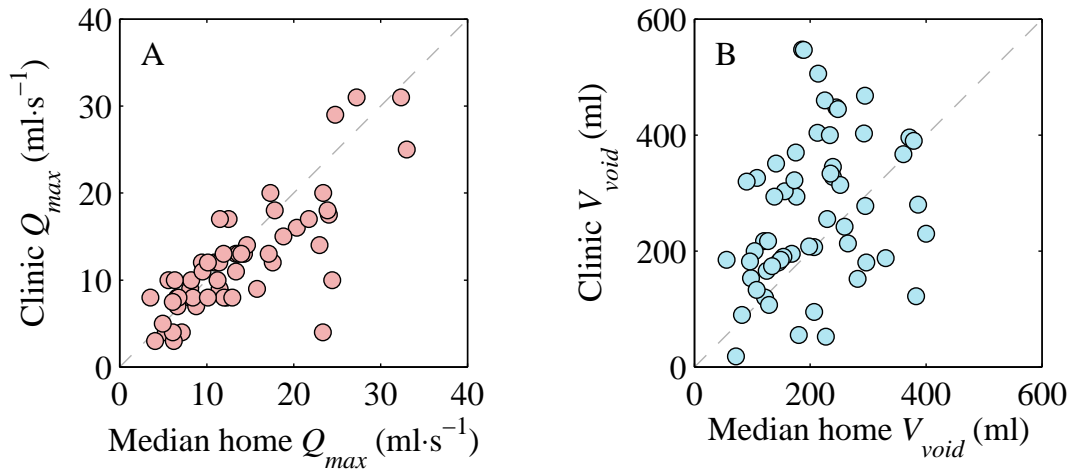


Figure 7.1 (A) Clinic Q_{max} versus median home Q_{max} , and (B) clinic V_{void} versus median home V_{void} . Dotted lines represent identity.

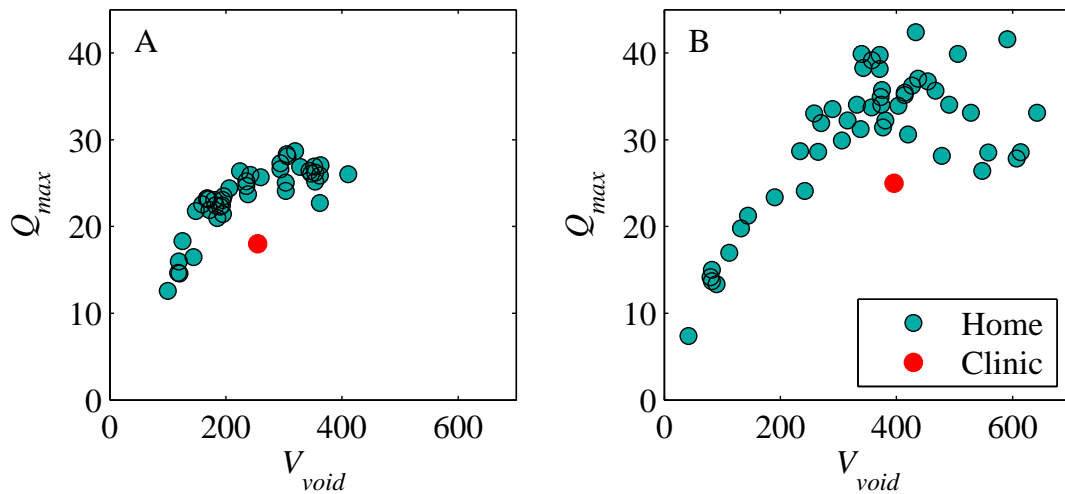


Figure 7.2 Q_{max} versus V_{void} at home (green) and in the clinic (red) for two patients: (A) patient 53 from Figures 7.3 and 7.4 and (B) patient 59. Despite clinic V_{void} and Q_{max} being within the range of normal voiding at home, the combination of the two does not conform to the usual pattern.

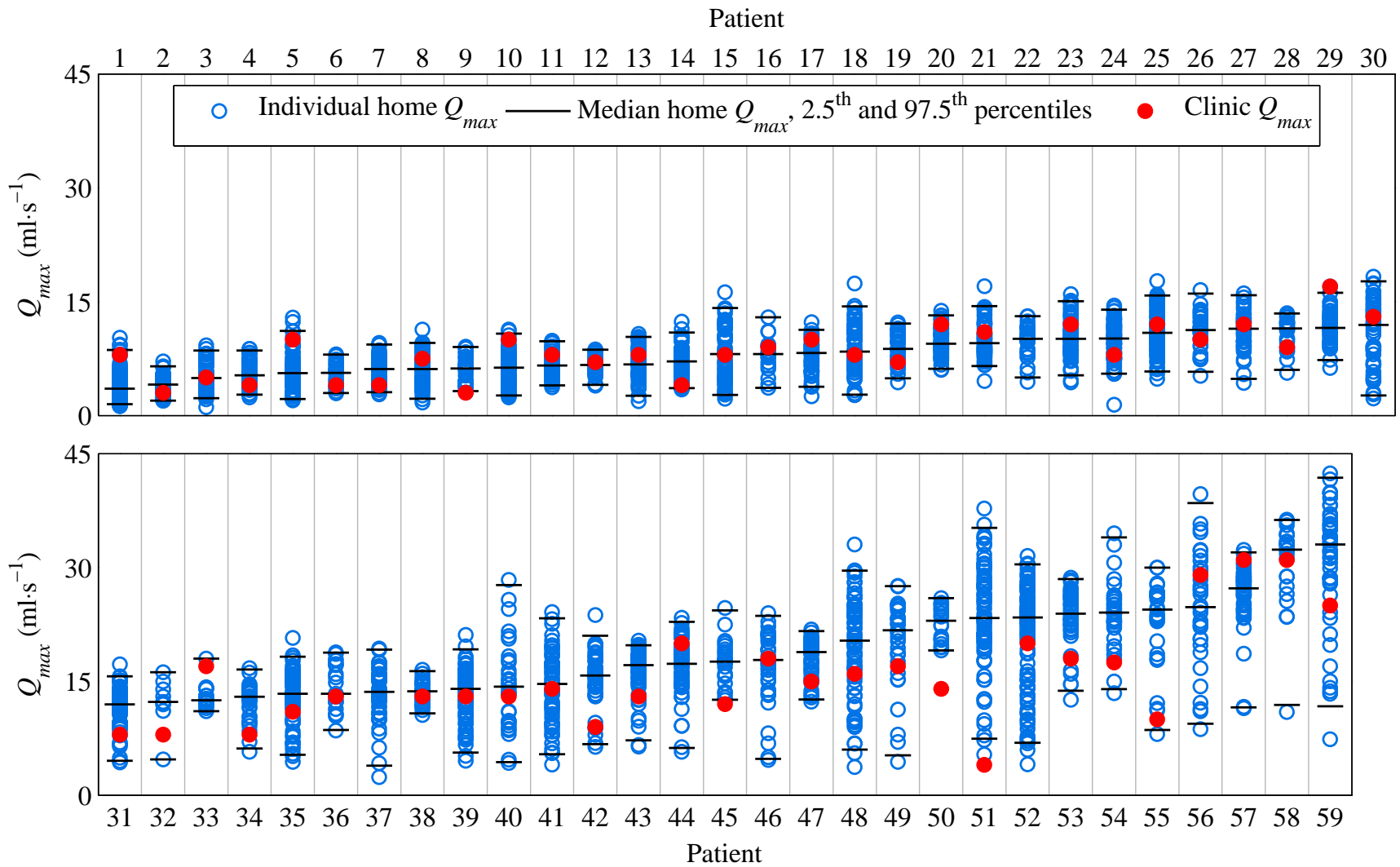


Figure 7.3 All maximum flow rates recorded at home (blue) and in the clinic (red). Black bars show median home Q_{max} and 2.5th and 97.5th percentiles. Patients are ordered by increasing median home Q_{max} . As discussed later, two patients (22 and 37) were unable to void in the clinic, hence no clinic void is marked.

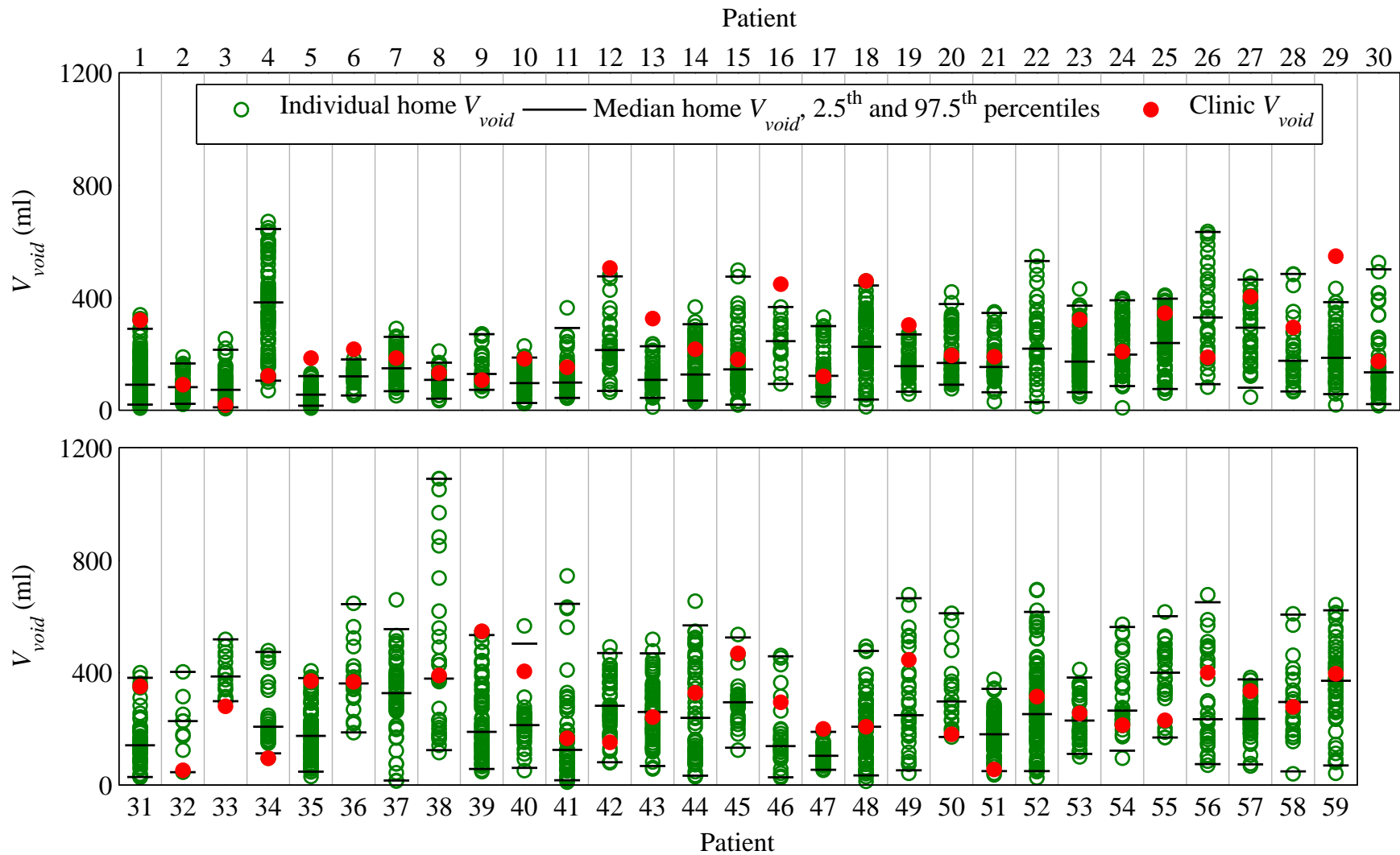


Figure 7.4 All voided volumes recorded at home (green) and in the clinic (red). Black bars show median home V_{void} and 2.5th and 97.5th percentiles. Patients are ordered by increasing median home Q_{max} , corresponding with those in Figure 7.3. As discussed later, two patients (22 and 37) were unable to void in the clinic, hence no clinic void is marked.

Overall, volumes recorded on manual and electronic frequency-volume charts were no different ($p = 0.2$, Wilcoxon sign rank test), although when each individual's volumes were compared, five (9 %) were significantly larger at home and 11 (20 %) were significantly smaller at home ($p < 0.05$, Mann-Whitney U); the remaining 39 (71 %) were no different.

The median number of volumes recorded per day on the manual charts was eight, and on the electronic was seven (calculated by dividing the number of voids recorded by the number of days elapsed between the first and last); these were significantly different ($p = 0.02$, Wilcoxon signed rank test). In addition, half of participants who completed a manual FVC included at least one 'tick', denoting a void whose volume could not be measured. Across these 27 patients, the median number of ticks per day was 0.8. Including ticks, the median number of voids recorded per day on the manual charts across all patients was nine.

7.3.1 Patient opinion

Patients were asked to complete a questionnaire in order to provide feedback regarding home and conventional assessment. Questions 1 and 2 below were presented as visual scales and were repeated for the three investigations: clinic flow test, frequency-volume chart, and PeePod:

1. Please rate the burden of [investigation]. (0 = *Not at all burdensome* and 10 = *Very burdensome*).
2. In the future, if you required investigation for urinary symptoms, how willing would you be to carry out [investigation]? (0 = *Not at all willing* and 10 = *Very willing*).
3. In the future, if you required investigation for urinary symptoms, which would you prefer? *Hospital flow test and frequency-volume chart / PeePod*

Free text areas were also provided for justification of these responses.

The results are shown in Tables 7.1 and 7.2 and Figure 7.5. Patients found the clinic flow test the most burdensome and the PeePod the least; all comparisons were statistically significant ($p < 0.05$, Wilcoxon sign rank test). Patients were most willing to repeat the PeePod and least the clinic flow test. Only the comparison between these two investigations was significant for this question ($p = 0.001$, Wilcoxon sign rank test).

Test	Mean score	Median score	p-value (Wilcoxon)	
PeePod	0.98	0	←	←
			0.001	
FVC	2.18	1	←	←
			0.007	
Urine flow test	3.25	2.5	←	←

Table 7.1 Patient feedback regarding the burden of using the PeePod, completing a manual frequency-volume chart and attending a clinic flow test. Arrows indicate the two investigations being compared.

Test	Mean score	Median score	p-value (Wilcoxon)	
PeePod	9.21	10	←	←
			0.085	
FVC	8.49	10	←	←
			0.052	
Urine flow test	7.52	10	←	←

Table 7.2 Patient feedback regarding their willingness to repeat using the PeePod, completing a manual frequency-volume chart and attending a clinic flow test. Arrows indicate the two investigations being compared.

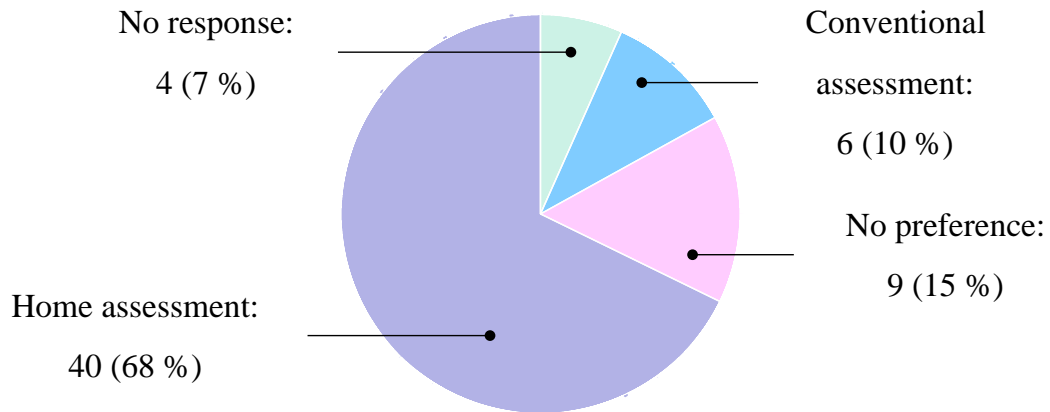


Figure 7.5 *Patient preference towards the mode of urodiagnostic assessment.*

Regarding Question 3, of 46 men who expressed a preference for one mode of investigation over the other, 40 (87 %) chose home assessment and six (13 %) chose conventional assessment ($p = 3 \times 10^{-7}$, one sample binomial test). Where men justified their choice, the most common reasons for choosing home assessment were convenience (18 instances), more private and natural voiding (8), to save time or money or avoid travel (4) and the absence of paperwork (3). Comments included the following*:

“I find it difficult to hold my water and need to urinate the moment I feel the need.”

“[I have] never been able to produce samples on demand.”

“I find attending hospital for a flow clinic causes some form of psychological problem, I want to go but the environment doesn't feel right.”

* Redaction key: [] = word(s) inserted or replaced for clarity.

Reasons for choosing conventional assessment included the notion that the resulting data were of higher quality (2), to receive feedback from staff (1) and to obtain a measurement post void residual (1). Comments included the following:

“[I’m] not sure how much information you get from the PeePod!”

“[The hospital flow test] gives a more exact record.”

7.3.2 Test-retest reliability

The estimated sample size required for these analyses was 16. A second man withdrew from the study after using the PeePod but prior to his repeat clinic flow test, also due to health issues. This left 28 sets of data available for analysis. Figure 7.6 shows Bland-Altman plots for home and conventional measurement of Q_{max} and Figure 7.7 shows all maximum flow rates recorded at home and in the clinic for patients in whom test-retest reliability of flow rate was assessed.

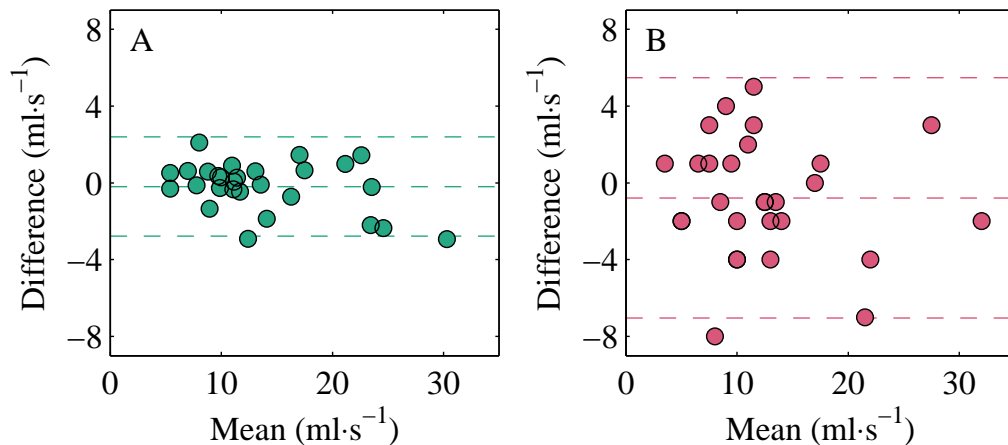


Figure 7.6 Bland-Altman plots showing test-retest reliability for (A) median home Q_{max} and (B) clinic Q_{max} . Dashed lines denote the mean difference plus and minus two standard deviations.

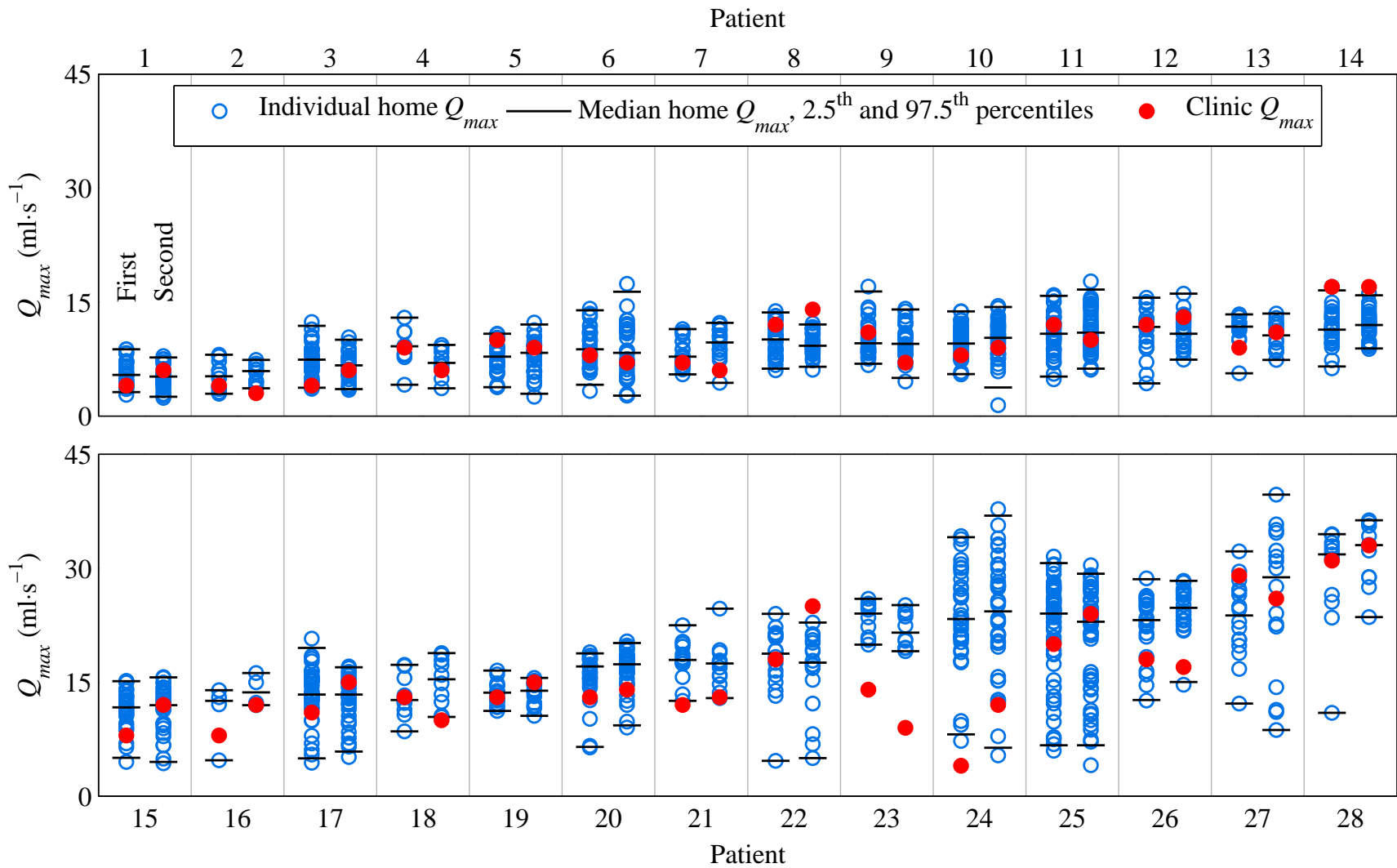


Figure 7.7 All maximum flow rates recorded at home (blue) and in the clinic (red) for 28 patients in whom test-retest reliability of flow rate was assessed. First clinic measurements and the first half of home measurements are shown on the left, and second sets on the right, as indicated for patient 1. Black bars show median home Q_{max} and 2.5th and 97.5th percentiles. Patients are ordered by increasing median home Q_{max} .

Repeatability of clinic flow data was assessed by comparison of Q_{max} from the first clinic flow test to that from the second. Repeatability of home flow data was assessed by comparison of median Q_{max} from the first half of home measurements to that from the second half[†]. These absolute paired differences were compared using Wilcoxon signed rank test. The mean difference at home was $1.0 \text{ ml}\cdot\text{s}^{-1}$ and in the clinic was $2.6 \text{ ml}\cdot\text{s}^{-1}$ ($p = 5 \times 10^{-4}$).

No learning effect was observed either in the clinic or at home for Q_{max} . That is, when the first measurement of Q_{max} in the clinic was compared to second, and the median of the first half of home measurements of Q_{max} compared to that of the second half, neither were significantly different ($p > 0.05$, Wilcoxon signed rank test). The same was true for V_{void} .

Q_{max} is often considered in relation to the following thresholds: $<10 \text{ ml}\cdot\text{s}^{-1}$, abnormal, 10 to $15 \text{ ml}\cdot\text{s}^{-1}$, equivocal and $>15 \text{ ml}\cdot\text{s}^{-1}$, normal. Based upon these thresholds, Table 7.3 compares the clinical indication from the first test protocol to that from the second for both home and conventional data.

7.3.3 Test success rate

All patients successfully recorded home voiding data using the PeePod.

Two patients were unable to void in the clinic due to ‘bashful bladder’ and four others failed to complete a manual frequency-volume chart. Therefore, a total of six patients (10 %) did not provide a complete set of results for the clinic-based assessment. This difference in success rate was statistically significant ($p = 0.03$, McNemar’s test).

[†] Where an odd number of voids were recorded, the last value was discarded.

		Home assessment (second half)			
		Abnormal	Equivocal	Normal	
$\kappa = 0.84$					
Home assessment (first half)	Abnormal	8	1	0	9
	Equivocal	1	8	1	10
	Normal	0	0	9	9
		9	9	10	28

		Clinic assessment (second)			
		Abnormal	Equivocal	Normal	
$\kappa = 0.61$					
Clinic assessment (first)	Abnormal	7	4	0	11
	Equivocal	3	8	0	11
	Normal	0	0	6	6
		10	12	6	28

Table 7.3 Contingency tables showing the agreement between first and second test protocols regarding the clinical interpretation of Q_{max} and median Q_{max} . Kappa values represent agreement according to Cohen's kappa.

There was, however, large variation in the amount of data recorded using the PeePod, as shown in Figure 7.8. One patient recorded just nine voids, although the same individual failed to complete a manual frequency-volume chart, and voided in the clinic on both occasions with a voided volume below 150 ml.

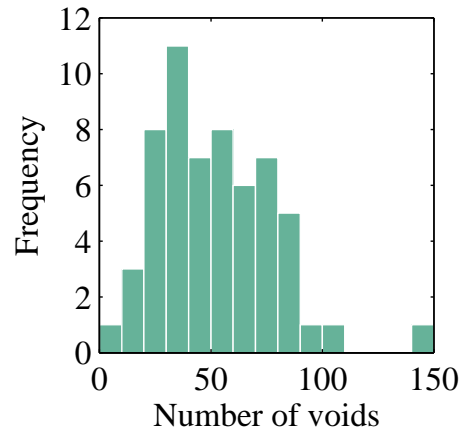


Figure 7.8 *Histogram of the number of voids recorded using the PeePod.*

Nine patients voided in the clinic with a volume less than 150 ml, which is generally deemed to be insufficient for reliable interpretation of flow rate (de la Rosette et al., 2001; National Institute for Health and Clinical Excellence, 2010). One of these patients voided at home with all 100 voided volumes below 150 ml (patient 5, Figures 7.3 and 7.4). For one third of patients (19/59), over half of their voided volumes at home were below 150 ml. Figure 7.9 shows a histogram of all voided volumes recorded at home.

7.3.4 Diagnostic consistency and confidence

For each patient, two reports were constructed. One contained conventional data (single clinic flow trace with Q_{max} , V_{void} and PVR, Siroky nomogram with indication of normality, and manual frequency-volume chart) and the other contained home urodiagnostic data (up to 16 flow traces, electronic frequency-volume chart, median flow trace with summary statistics, and Siroky nomogram

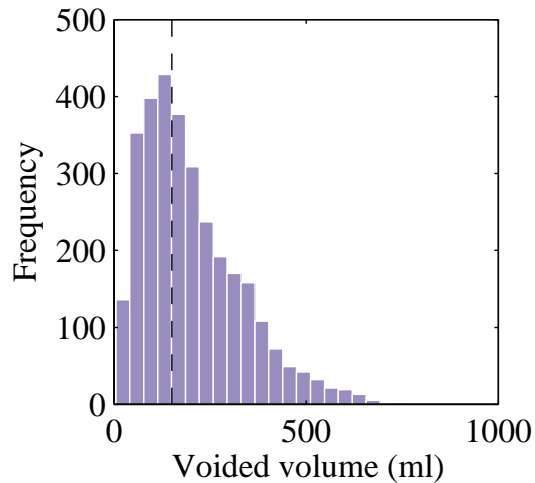


Figure 7.9 Histogram of all voided volumes recorded at home. The dashed line marks 150 ml, below which flow rate in the clinic is deemed to be unrepresentative.

with indication of normality for median V_{void} versus median Q_{max}^{\ddagger}). The reports were anonymised using a cipher, ordered at random and compiled into a booklet. Four consultant urologists from the Freeman Hospital with no prior involvement in the project answered the following questions in relation to each report[§]:

1. Based upon this report, please make a suggested diagnosis (tick one):

- Normal
- Bladder outlet obstruction
- Detrusor underactivity
- Detrusor overactivity
- Other (please state)

[‡] As in Chapter 6, Figures 6.5 and 6.6.

[§] The intention had been to ask all raters to score all patient reports. However, a time and motion study revealed that a booklet containing half of the data (29 patients and thus 58 reports) took 2 hours and 48 minutes to complete! Therefore, raters were instead given packs containing paired data for half of the patients. Those included in each pack were overlapped such that each report was rated twice, allowing assessment of inter-rater agreement. One patient was excluded as his clinic flow trace was missing from his notes; fortuitously this left an even number of patients.

2. Please rate your confidence in this diagnosis (tick one):

- Very confident
- Quite confident
- Not very confident
- Not at all confident

Intra- and inter-rater agreement Intra-rater agreement between home and clinic diagnosis for each patient was fairly poor, being either 13 or 14 out of 29 for all four raters. These results are shown in Table 7.4.

There was no statistical difference between diagnostic inter-rater agreement at home where 36/58 (62 %) diagnoses agreed ($\kappa = 0.42$, Cohen's kappa), and in the clinic where 35/58 (60 %) diagnoses agreed ($\kappa = 0.4$) ($p = 1$, McNemar's test).

Confidence and adjusted confidence Raters were more confident with their diagnoses based upon home data than conventional data ($p = 0.006$, Wilcoxon signed rank test). The mean confidence score for home was 2.0 compared to 1.8 in the clinic (where 0 = *Not at all confident* and 3 = *Very confident*).

Regarding inter-rater agreement, an 'adjusted confidence' score was calculated to reflect the relationship between confidence and concord, according to the system illustrated in Table 7.5.

The mean adjusted confidence score for home data was 3.0 out of 16 (had all diagnoses agreed and all ratings been *Very confident*) and for conventional data was 2.2 ($p = 0.6$, Wilcoxon sign rank test).

		Diagnosis based upon conventional data								
		Normal	BOO	DU	DO	Stricture	Polyuria	NP		Unsure
Diagnosis based upon home data	Normal	10	8	0	3	0	1	0	0	22
	BOO	6	38	9	6	1	0	0	1	61
	DU	0	8	3	1	0	0	1	1	14
	DO	6	7	0	1	0	0	0	2	16
	Stricture	0	0	0	0	1	0	0	0	1
	Polyuria	0	1	0	0	0	0	0	0	1
	NP	0	0	0	0	0	0	1	0	1
	Unsure	0	0	0	0	0	0	0	0	0
		22	62	12	11	2	1	2	4	116

Table 7.4 Intra-rater agreement between diagnoses based upon home urodiagnostic and conventional data. Green shading denotes agreement, red shading denotes disagreement. Each patient was rated twice, providing 116 comparisons.

		Second diagnosis			
		Very confident	Quite confident	Not very confident	Not at all confident
First diagnosis	Very confident	± 16	± 12	± 8	± 4
	Quite confident	± 12	± 9	± 6	± 3
	Not very confident	± 8	± 6	± 4	± 2
	Not at all confident	± 4	± 3	± 2	± 1

Table 7.5 *Adjusted confidence scores used to weight the consistency of diagnoses based upon home and conventional data. Matching diagnoses were allocated the positive score, and conflicting diagnoses the negative score.*

7.4 Discussion

The discovery that Q_{max} was not normally distributed in around half of the patients in this study introduces a potential source of error into the calculations performed in Chapter 5. However, a perfect model incorporating multiple distributions would be complicated and would require many patients to be studied to represent these distributions accurately. This would negate the benefit of modelling rather than performing a large study of diagnostic accuracy. Chapter 5 presented a simple method of approximating the clinical benefit of averaging Q_{max} in an individual.

7.4.1 Comparison of home and conventional data

Figure 7.3 reveals that the majority of patients voided in the clinic with flow rates within the 95 % confidence limits of their voiding at home. Just five patients

voided with Q_{max} outside this range[¶] (one higher, four lower), and 13 patients for V_{void} (11 higher, two lower)^{||}. Although, using results from two participants as an example, illustrated in Figure 7.2, voiding parameters within these confidence intervals did not always constitute representative voiding.

Ten patients (17 %) voided in the clinic with a volume higher than any volume at home. Given the circumstances surrounding a clinic flow test, quickly filling the bladder with fluid and often having to wait for the flowmeter once full, this isn't surprising. Whilst this didn't necessarily cause flow rates to be unrepresentative, it is probably not a particularly pleasant experience for the patient.

Overall, voided volumes recorded in the clinic were significantly higher than the median value of those obtained at home, and flow rates significantly lower. The clinician should consider this trend for interpretation of clinic Q_{max} and regard the measurement as being more sensitive to abnormality than specific to normality. From Figure 7.3, this statistic appears to be due to a number of men with high home flow rates producing a lower rate in the clinic, sometimes associated with low voided volumes (patients 50, 51 and 55), and sometimes with high (patients 6, 45 and 47). In general, patients with lower home flow rates tended to over-perform in the clinic, whereas those with higher home flow rates tended to under-perform. Among the top row of Figure 7.3, 57 % voided in the clinic with Q_{max} above the median at home and among the bottom row, this was just 21 %. This tendency reduces diagnostic certainty in terms of separating those with low and high flow rates, reducing the discriminatory power of clinic Q_{max} .

Conversely, de la Rosette et al. (1996) found in a study of similar size that clinic Q_{max} was slightly, although not significantly, higher than the mean value at home.

[¶] Thus 9 % (5/57) were unrepresentative, close to the 10 % resulting from simulations in Chapter 5.

^{||} By the definition of 95 % confidence limits, 5 % (three patients) would be expected to fall outside these limits.

However, most patients recorded fewer than ten voids, perhaps insufficient to obtain a stable average. In this study the median number of voids recorded per patient was 49 (range 9 to 146).

When manual and electronic voiding diaries were compared, manual diaries contained on average one additional volume per day. This should be borne in mind for interpretation of electronic diaries. It is perhaps due to the template nature of a manual chart being a visual reminder that a particular space on a particular day should be filled. (Anecdotally, one gentleman arrived at his flow appointment apologising for the incomplete nature of his chart; he had not been able to void *every* hour.) Further, electronic diaries such as the PeePod do not allow for the placing of a tick to signify an unquantified void, amounting on average to one void per day.

7.4.2 Test re-test reliability

Figure 7.6 illustrates the superior repeatability of median home Q_{max} versus clinic Q_{max} . Absolute differences between first and second repeats were significantly higher for clinic flow data. This result is to be expected due to the narrowing of confidence intervals surrounding an average value calculated from multiple measurements. Although, looking at Figure 7.6, the confidence intervals for home measurements are not as narrow compared to those of clinic measurements as may be anticipated. The reason may lie in Figure 7.7: for many patients, often despite large variability of Q_{max} at home, clinic voids are close together. This is interesting and perhaps stems from the particular conditions of voiding in the clinic: on his two clinic visits, each man probably voided before leaving the house, arrived and drank a particular amount of water, possibly even attended at the same time of day. These repeatable circumstances are resulting in repeatable, although not necessarily representative, clinic voiding. The same may be true for

home urodiagnostic data, given the difference between voiding into a flowmeter and into a toilet, but the circumstances are far closer to ‘normal’.

Of particular interest is the clinical implication of repeatability of flow rate: whether repeated measurements affect the interpretation of flow rate. Based upon thresholds for normality commonly applied to Q_{max} , 25/28 (89 %) of first and second tests agreed for home data, whereas for clinic data this was 21/28 (75 %). This difference was not statistically significant ($p = 0.3$, McNemar’s test).

7.4.3 Patient opinion

A common theme amongst men who expressed a preference towards home assessment was convenience, or more particularly, avoidance of the inconvenience of long drives, lengthy waiting times and expensive car parking associated with a hospital visit. Amongst these important but non-clinical issues were a small number of poignant statements regarding negative experiences of the flow clinic.

A small percentage of participants favoured conventional assessment. Two were dubious about the PeePod’s technical capabilities, perhaps due to the simple nature of its appearance and operation.

Overall, preference towards home rather than conventional assessment was indisputable, verified by significantly lower burden scores and more willingness to repeat the investigation in the future.

7.4.4 Test success rate

Despite only brief instruction and the requirement to use the device unsupervised at home, all patients successfully recorded voiding data using the PeePod. The success rate for conventional assessment was 90 %. Whilst this may appear high, a failure rate of 10 % would be regarded as poor for a simple, non-invasive diagnostic

test such as uroflowmetry. This amounts to 10,000 failed tests of an estimated 100,000 in the UK each year, many of which will require a repeat appointment, costly for both the patient and the NHS.

Due to the dependency of flow rate upon volume, urological guidelines recommend that for a clinic flow test to be considered valid, the voided volume should be at least 150 ml. Otherwise, the test should be repeated until a valid volume is achieved. 15 % of clinic tests would have been deemed as failures for not meeting this criterion. The importance of the volume produced in the clinic is that it is representative of normal voiding. With one third of patients usually voiding less than 150 ml at home, clearly lower volume voiding often is representative. Figure 7.9 is of course weighted towards patients who voided many times with low volumes, but gives an idea of the proportion of true voids that would be rejected in the clinic: over 40 %. Reynard et al. (1998) found that 25 % of around 900 men voided less than 150 ml in the clinic.

A flow test should be evaluated in the context of the patient's voiding diary (Schäfer et al., 2002). Perhaps recommendations should place more emphasis upon this method of validation rather than application of a blanket threshold to V_{void} . The important question is: what is the aim of a clinic flow test? Is it to make a measurement which is representative of the patient's true voiding, or is it to measure the patient's flow rate capabilities under circumstances that are not necessarily normal? It is professed to be to reproduce the patient's symptomatic complaints (Abrams, 2006), surely more akin to the former.

7.4.5 Diagnostic consistency and confidence

Finally, diagnostic consistency and confidence were examined. Inter-rater diagnostic consistency was compared for home urodiagnostic and conventional data and no difference found. A scoring system was devised to penalise conflicting

yet confident diagnoses and reward confident consensus. This system was based upon the notion that a patient who is diagnosed confidently yet incorrectly may receive ineffective treatment, whereas he who is diagnosed correctly with confidence would be managed appropriately in a timely fashion. Again, no difference was found. These results are perhaps another manifestation of the repeatability of clinic data resulting from repeatable circumstances, discussed previously.

The missing piece of this puzzle is each patient's true condition, or more pragmatically, the condition which when treated would bring him the most benefit. The assumption that the condition that both raters agree on is the correct one is not necessarily valid. Further, there could be no accounting for comorbidities. Commonly, *BOO* and *DU* (17 cases) or *BOO* and *DO* (13) were diagnosed based upon the same report; conditions well known to coexist. The same applied to *BOO* and *Normal* (14) and *DO* and *Normal* (9). Both *BOO* and *DO* are progressive diseases, rather than simply present or not; these cases may represent borderline clinical significance.

An attempt was made to review each patient's notes and determine a true urodynamic diagnosis. However, invasive pressure-flow measurements were reported in only a small minority of cases. Considering instead treatment outcome, the vast majority of treatment episodes were for *BOO*, the outcomes of which were often undocumented.

What can be concluded is that the clinicians were more confident in their diagnoses based upon home urodiagnostic data. This is despite the lack of measurement of post void residual measurement and despite the unfamiliar nature of the novel data. This elevated confidence, which may simply stem from a larger volume of data available for review, could at least promote benefit from the 'doctor as a drug' placebo effect.

Further, in four cases, the rater felt too uncertain to make a diagnosis based upon conventional data, whereas no PeePod reports went undiagnosed. This suggests that patients assessed at home are less likely to require further investigation.

7.5 Conclusion

Home-based assessment using the PeePod was much better tolerated, less likely to fail and gave more reliable measurement of Q_{max} than a standard combination of clinic-based uroflowmetry and manual FVC.

The study was not powered to detect differences in diagnostic consistency or the reliability of clinical indication of Q_{max} and indeed none were found. However, the results could be used to power larger follow-on studies.

The following chapter describes a study of home urodiagnostics in a more specific group of patients: men who have reached the stage where their LUTS require surgical intervention.

Chapter 8

Sensitivity to change following disobstructive bladder outlet surgery

8.1 Introduction

Chapter 7 examined the potential impact of PeePod data on the diagnosis of men with LUTS. As discussed previously, the second important application of flow and volume information is evaluation of the effect of treatments, particularly medical and surgical relief of bladder outlet obstruction.

The most common form of surgery for men with LUTS, in fact one of the most prevalent operations for older men, is endoscopic resection of the bladder outlet (Health and Social Care Information Centre, 2012). This procedure is usually performed for men with suspected or proven obstruction in order to reduce outlet resistance and allow a return to efficient voiding. An instrument containing a camera and a means of removing tissue (either an electrically heated wire or a laser) is passed into the urethra and used to widen the narrowed prostatic or bladder neck region, assumed to be the flow controlling zone.

Figure 8.1 illustrates the most frequently performed type of outlet surgery: transurethral resection of the prostate (TURP). Being well established and having a large evidence base, TURP remains the gold standard. However, newer procedures, particularly laser-based, with fewer risks and shorter recovery time may supersede TURP as set-up costs fall and expertise becomes more widespread. Table 8.1 gives a description of the disobstructive surgeries relevant to this chapter.

Approximately 30,000 of these procedures are performed in the UK each year, and over a million worldwide (Jensen et al., 1996; National Institute for Health and Clinical Excellence, 2010). Recently, NICE has highlighted the importance of being able to predict the outcome of TURP. Overall failure rates (failure being defined as a lack of sufficient symptomatic improvement) are between 25 and 30 % (National Institute for Health and Clinical Excellence, 2010), and up to 20 % even in those who are urodynamically obstructed (Homma, 2001). With each elective procedure costing in the region of £2,000 to £3,000 (Department of Health, 2012), improving the discriminatory power of the diagnostic work-up to predict outcome from surgery could save the NHS up to £30 million per year.

Given that many recordings are obtained in each individual, home urodiagnostics is extremely sensitive to change in storage and, particularly, voiding parameters. Hypothetically, patients undergoing these surgeries are obstructed to begin with and, subsequently, completely unobstructed. Thus, the parameters which are most sensitive to change ought to be those which best separate obstructed and unobstructed populations. The aim of this chapter is therefore to measure the sensitivity to change of home urodiagnostics in men undergoing disobstructive procedures and to present for the first time the nature of these data before and after surgery on an individual level.

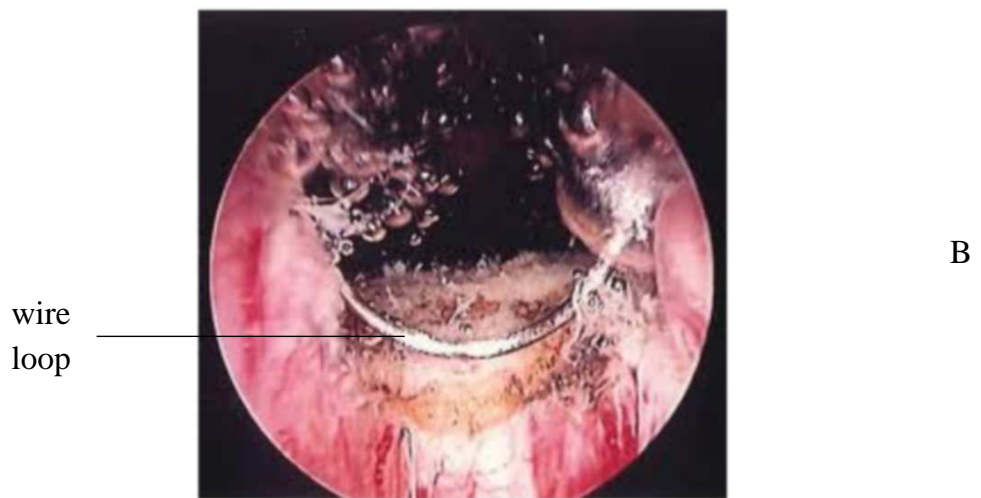
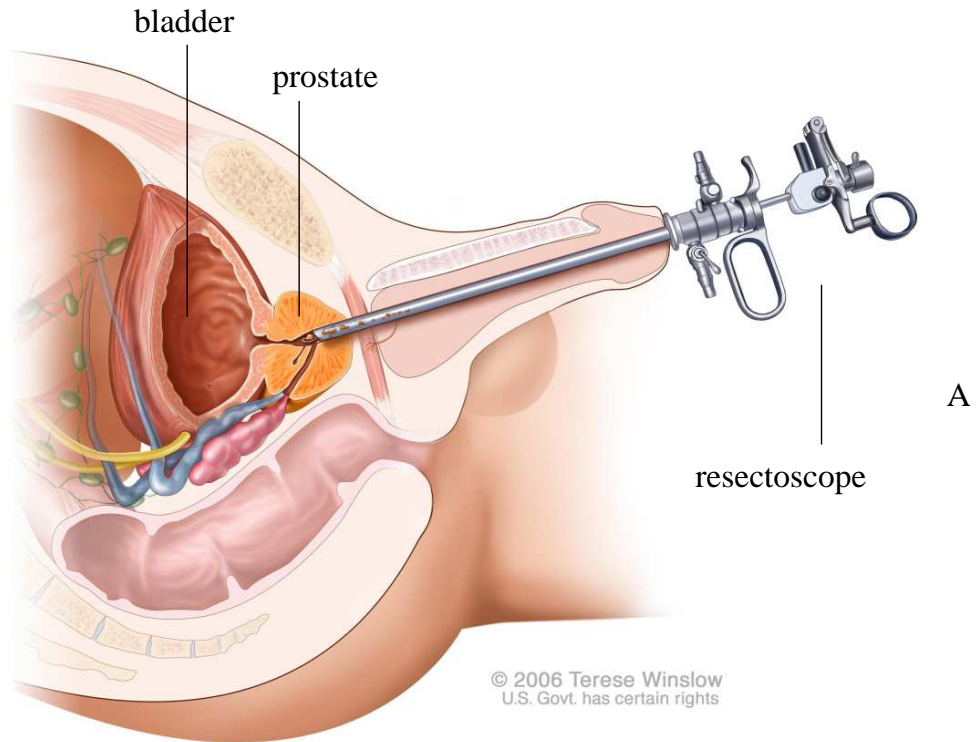


Figure 8.1 (A) An illustration of transurethral resection of the prostate surgery (Terese Winslow, 2006). (B) The surgeon's view: an image from the resectoscope during surgery (Nottingham Urology Group, 2013).

Type of surgery	Description
TURP	<i>Transurethral resection of the prostate.</i> A resectoscope (cystoscope and electrically heated wire loop) is passed into the urethra where prostate tissue is resected by electrocauterisation. A non-conducting glycine solution is used for irrigation; in a small percentage of cases, excess absorption may lead to water intoxication (hyponatremia).
TURIS	<i>Transurethral resection in saline.</i> Similar to TURP, although this technique permits the use of isotonic saline for irrigation. This reduces the risk of hyponatremia, allowing for longer procedures; TURIS is therefore more appropriate for men with larger prostates.
HOLEP	<i>Holmium laser enucleation of the prostate.</i> Prostate tissue is resected, and blood vessels coagulated, by a holmium laser. Again, the irrigation fluid is saline. HOLEP is advised for men taking anticoagulants due to reduced bleeding.
KTP laser prostatectomy	<i>Potassium titanyl phosphate laser prostatectomy.</i> Prostate tissue is vapourised by a KTP laser. Tissue cannot be collected for pathological examination to detect prostate cancer as is routine practice for the above procedures.
BNI or TUIP	<i>Bladder neck incision or transurethral incision of the prostate.</i> For men found to have a minimally enlarged prostate, an incision is made in one or both sides of the bladder neck or the prostate. Resection may be carried out by electrocauterisation or a laser. A BNI may also be necessary to treat scarring of the bladder neck which occasionally results from one of the above surgeries.

Table 8.1 *A description of the five types of disobstructive surgery performed for patients recruited into this study.*

8.2 Methods

8.2.1 Study design

In conceiving this study, initial consideration was given to powering for predictive performance. That is, attempting to measure the difference between home urodiagnostics and conventional assessment in predicting which men would experience good, and which would experience poor, surgical outcome. This methodology has been used by our group in the past in order to assess the predictive value of non-invasive bladder pressure measurements obtained using the ‘cuff-machine’ (CT3000) (Harding et al., 2007).

Homma (2001) modelled surgical success rates based upon estimates for prevalence of obstruction, success rates of surgery in the obstructed and unobstructed populations, and accuracies of various diagnostic protocols. He predicted an improvement of 9 % (from 81 to 90 %) in outcome from TURP in the scenario where all men undergo invasive PFS, and then only those diagnosed as obstructed are operated upon, versus that in which none undergo PFS.

Demonstrating this improvement with 80 % power and significance level 0.05 would require a sample size of 129. Any benefit from home uroflowmetry is likely to be far smaller than that from invasive PFS; powering to detect a 3 % improvement (the increase in diagnostic accuracy of mean Q_{max} compared to single Q_{max} predicted in Chapter 5) would require a sample size of 1290, which is clearly unfeasible here.

The decision was made, therefore, to measure instead the sensitivity to change of home uroflowmetry following disobstructive surgery, whilst piloting an investigation of home uroflowmetry parameters that may relate to good outcome. Thus the aim was to conduct an exploratory study of 30 men. The results could also then be used to power sample size calculations for follow-on studies (Lenth, 2013).

8.2.2 Recruitment

Ethical approval for the study was obtained from Newcastle & North Tyneside 1 Research Ethics Committee, covered by application 10/H0906/10 Assessment of home uroflowmetry: Amendment 3 (08/06/2011) which received favourable opinion on 15th July 2011 (see Appendix A3, page 241 onwards).

All men scheduled for disobstructive surgery at the Freeman Hospital were eligible for inclusion into the study. The exclusion criteria were the same as those listed in the previous chapter (see Section 7.2.2, page 129), with the addition of the following:

- Men for whom the primary reason for surgery was removal of cancerous tissue rather than relief of symptoms.

Suitable patients were identified in one of two ways:

- From the disobstructive surgery schedule list. These patients were contacted by telephone and an explanation of the study given. Those who agreed to take part attended the Freeman Hospital to give consent, complete an IPSS questionnaire and collect a PeePod.
- From their attendance at the surgery pre-assessment clinic at the Freeman Hospital, that is, patients who had been placed on the waiting list for disobstructive surgery. These patients were given an explanation of the study following their pre-assessment appointment and those who agreed to take part then gave consent, completed an IPSS questionnaire and collected a PeePod.

The majority of the patients approached were identified by my colleague Wendy Robson (Senior Research Nurse) and her research team, who also accompanied me during the consent process, and took consent on some occasions when I was unavailable.

All men who took part in this study carried out the following:

- Used the PeePod at home for one week and completed an IPSS questionnaire prior to their surgery.
- Used the PeePod at home for one week and completed a second IPSS questionnaire at least four months following their surgery*.

PeePod data were not made available to treating clinicians and therefore played no part in clinical decision making.

Patients' records were also checked pre- and post-procedure for relevant information such as diagnostic test results, the amount of prostate tissue resected during surgery, and the nature of any follow-on treatments or investigations.

8.3 Results

33 men were recruited into the study between January and September 2012. One man withdrew following the first period of recording due to ill health, a second man's prostate procedure was delayed, preventing timely follow-up, and a third participant's operation was postponed indefinitely following heart surgery. This left 30 full datasets available for analysis.

* Although three months has been used previously (Porru et al., 2002), the clinical members of the project team felt from experience that a marked improvement in storage symptoms occurs from month three to four.

The median age of the men who completed the study on the day of their surgery was 72 years (range 55 to 89 years). The median length of time between surgery and follow-up was 162 days (range 122 to 351 days). Table 8.2 shows the number of men who underwent each type of surgery.

Type of surgery	Number of men
TURP	16
HOLEP	6
KTP laser prostatectomy	3
TURP with BNI	2
HOLEP with BNI	1
TURIS	1
Laser BNI	1
Total	30

Table 8.2 *The types of surgery performed for men who completed this study.*

8.3.1 Patient reported outcome

The median total IPSS score prior to surgery was 21 (range 10 to 29), and following surgery was 7.5 (0 to 23), this symptomatic improvement being highly statistically significant ($p = 2 \times 10^{-6}$, Wilcoxon sign rank test). Figure 8.2A shows the percentage decrease in total IPSS score and IPSS QoL score following surgery for each participant, ordered by increasing percentage reduction in total IPSS score. These measures were strongly correlated ($\rho = 0.8$, $p = 1 \times 10^{-7}$, Spearman's rank correlation coefficient). Figure 8.2B shows how each symptom changed; all improved significantly ($p < 0.05$, Wilcoxon sign rank test).

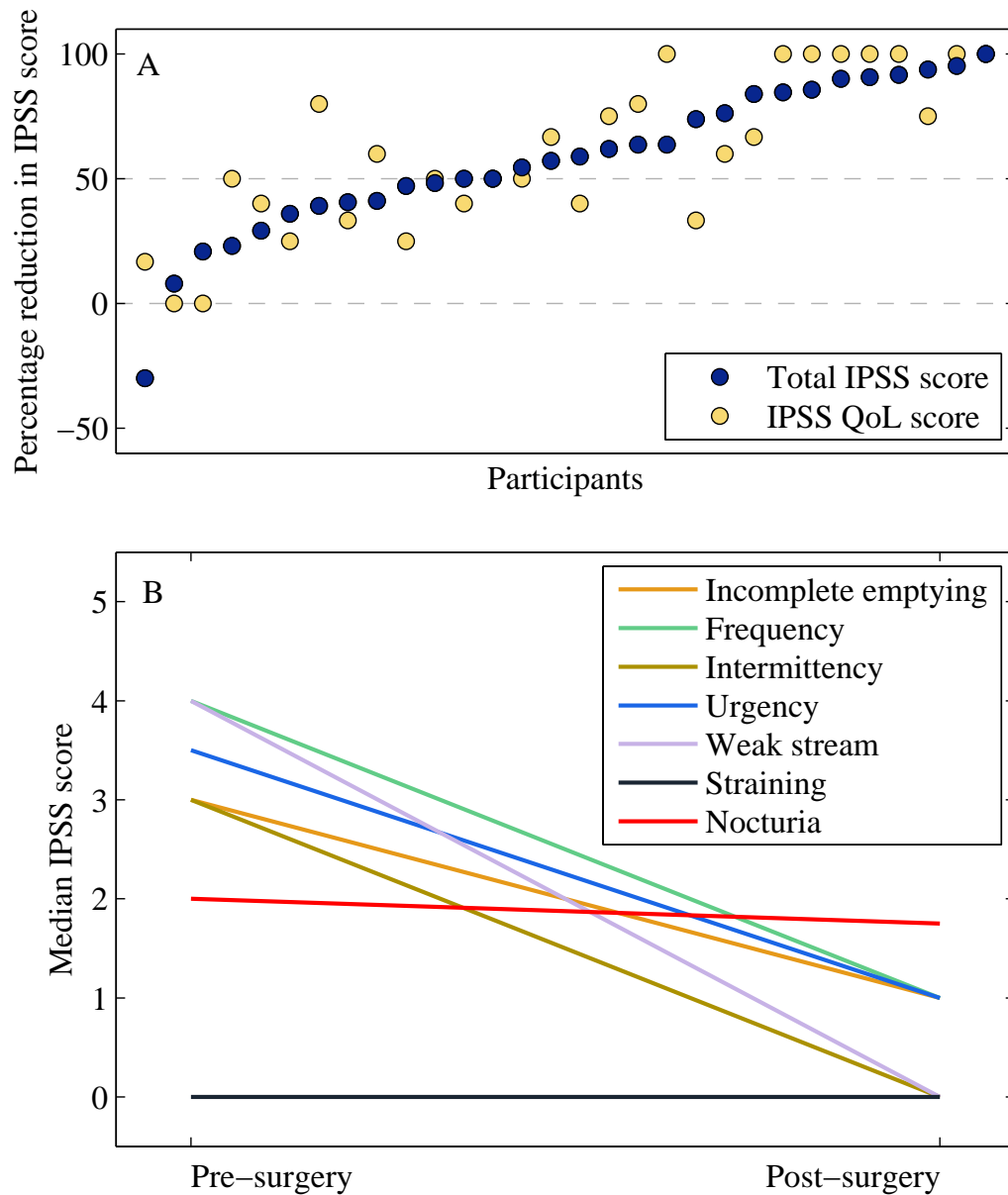


Figure 8.2 Patient reported outcome: (A) The percentage reduction in total IPSS score (blue) and IPSS QoL life score (yellow) for each participant following surgery, ordered by increasing percentage reduction in total IPSS score. (B) The change in median IPSS score across all participants for each symptom type.

Good symptomatic outcome was defined as either a reduction in total IPSS score of 50 % or more, as used by previous investigators (Porru et al., 2002; Harding et al., 2007). According to this criterion, 63 % (19/30) of participants experienced good symptomatic outcome from surgery. With the additional criterion of an improved post-procedure IPSS QoL score of 2 (*Mostly satisfied*) or less, this rose to 73 % (22/30). One man’s symptoms became worse; his total IPSS score increased from 10 to 13, although his IPSS QoL score decreased from 6 to 5.

8.3.2 Sensitivity to change

The treatment induced changes in a number of home urodiagnostic parameters are presented in Table 8.3. The following standard voiding and storage parameters were examined:

- Median[†] and maximum Q_{max}
- Median Q_{ave}
- Median and maximum V_{void}
- Median voiding time ($t_{voiding}$)
- Median time to Q_{max} (t_{Qmax})
- Median frequency of daytime voids
- Median frequency of nighttime voids (nocturia)

[†] Where multiple measurements of a parameter were obtained per individual, ‘median’ denotes the median of the medians. That is, a median value of the parameter was calculated for each individual, and then the median of this value across all individuals obtained, and compared pre- and post-surgery.

Among the literature reviewed in Section 4.3.2 (page 53 onwards), were studies that hypothesised differences in certain home urodiagnostic parameters between obstructed and unobstructed men. Therefore, the following were also compared pre- and post-surgery:

- Interquartile range (IQR) Q_{max} : Golomb et al. (1992) reported larger variability in Q_{max} for patients with symptomatic BOO than healthy men.
- The gradient of the linear relationship between V_{void} and Q_{max} according to a least squares fit: Sonke et al. (2002) reported that unobstructed patients had steeper Q_{max} versus V_{void} regression lines than obstructed patients.
- The value of Q_{max} at $V_{void} = 200$ ml according to this line of best fit: By examining the value of this regression line at $V_{void} = 200$ ml, Q_{max} may be controlled for voided volume. 200 ml was chosen as the largest volume included in all patients' V_{void} range prior to surgery.
- The ratio of median daytime Q_{max} to median nighttime Q_{max} : Witjes et al. (1997) found larger circadian flow rate variability in patients with higher grades of obstruction.

Figure 8.3 plots the change in median Q_{max} against the change in median V_{void} following surgery; these measures were strongly correlated ($\rho = 0.5$, $p = 0.002$, Spearman's rank correlation coefficient). Figures 8.4 to 8.9 show pre- and post-surgery Q_{max} versus V_{void} and pre- and post-surgery flow traces for each individual participant, ordered by increasing change in median Q_{max} following surgery. Figure 8.10 shows post-surgery versus pre-surgery median frequency (A) and post-surgery versus pre-surgery median nocturia (B).

A) Per void parameters

Parameter	Pre-surgery	Post-surgery	p-value	n (%)
	median	median		
Q_{max} (ml·s ⁻¹)	9.4	16.9	3×10^{-6}	80
Q_{ave} (ml·s ⁻¹)	4.0	7.0	3×10^{-6}	77
V_{void} (ml)	147	192	9×10^{-5}	50
$t_{voiding}$ (s)	44	26	5×10^{-6}	83
$t_{Q_{max}}$ (s)	8.0	6.8	0.001	57

B) Per patient storage parameters

Parameter	Pre-surgery	Post-surgery	p-value	n (%)
	median	median		
Frequency	8	6	7×10^{-5}	77
Nocturia	1	1	0.5	27

C) Per patient voiding parameters

Parameter	Pre-surgery	Post-surgery	p-value	n (%)
	median	median		
Maximum Q_{max} (ml·s ⁻¹)	13.9	24.8	1×10^{-5}	87
Maximum V_{void} (ml)	354	414	7×10^{-5}	80
IQR Q_{max} (ml·s ⁻¹)	3.2	4.1	0.002	77
Q_{max}/V_{void} gradient (s ⁻¹)	0.01	0.02	0.003	77
Q_{max} at 200 ml V_{void} (ml·s ⁻¹)	9.8	15.3	1×10^{-5}	90
Daytime/nighttime Q_{max}	1.1	1.0	0.6	50

Table 8.3 A comparison between pre- and post-surgery values of a number of home urodiagnostic parameters. *p*-values represent paired comparisons using Wilcoxon signed rank test. For (A) *n* denotes the number of men who experienced a significant improvement ($p < 0.05$) in the parameter according to Mann-Whitney *U*. For (B) and (C), *n* denotes the percentage of men who experienced an improvement in the parameter when one pre-surgery value was compared to one post-surgery value; no statistical test was used.

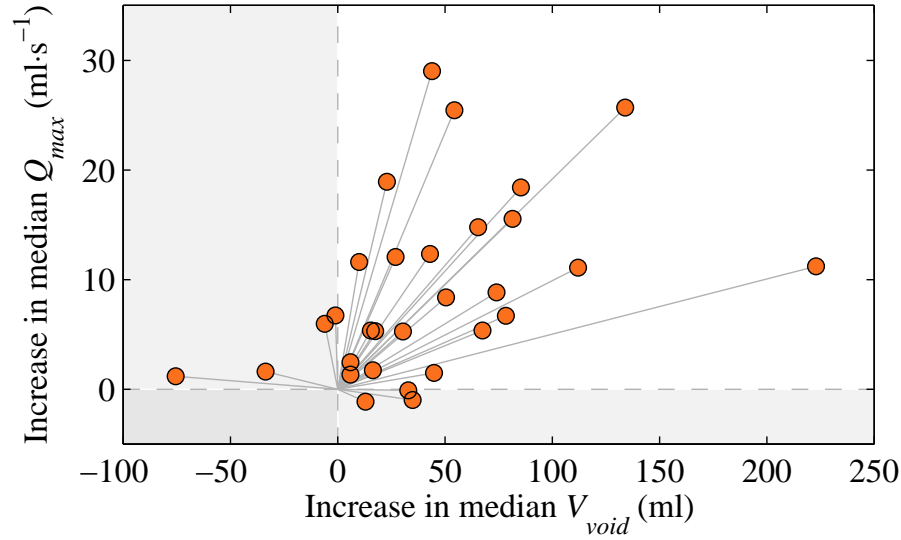


Figure 8.3 Change in median Q_{max} versus change in median V_{void} following surgery.

8.3.3 Predictive power

There are two approaches to investigating the prognostic power of a test to predict the outcome from treatment.

If outcome data are binary (good or poor outcome), unpaired pre-treatment parameters may be compared between the two groups, and the results reported as sensitivity and specificity. Or, patients may be grouped according to values of a pre-treatment parameter. The proportion of patients who experience good and poor outcome in each group can be reported as positive and negative predictive value.

Alternatively, if outcome data are scalar, or at least interval, a relationship can be sought between outcome and values of the test parameter. Although no diagnostically applicable threshold is produced, this method benefits from better resolution of outcome data and therefore better sensitivity to a relationship, if one exists. Given the small sample size in this study, to avoid division into subgroups resulting in further reduction in statistical power, this was the chosen method.

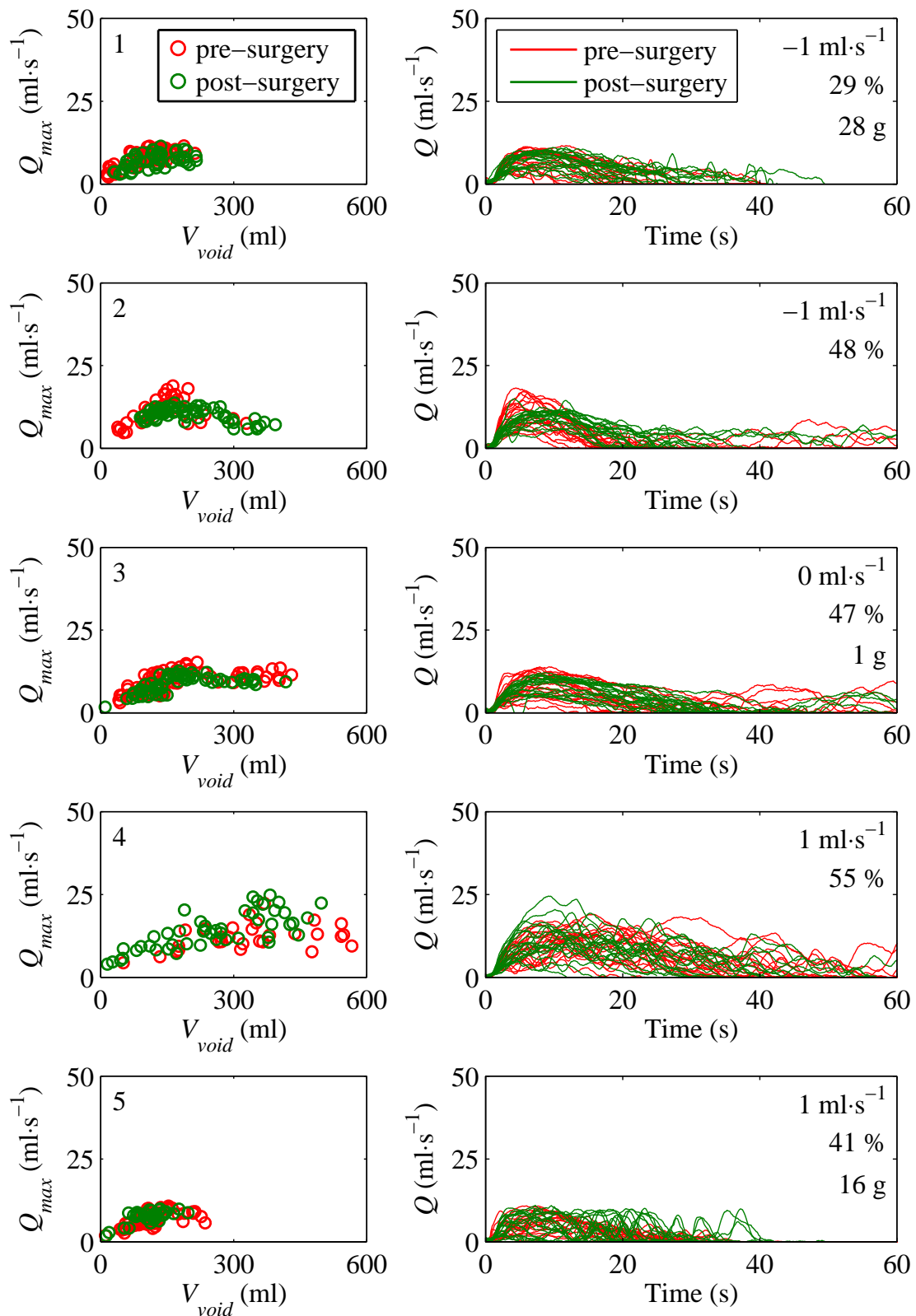


Figure 8.4 Pre- and post-surgery Q_{max} versus V_{void} (left) and pre- and post-surgery flow traces (right). Patients are ordered by increasing change in median Q_{max} , shown at the top of each flow trace plot. Percentage reduction in total IPSS score and, where measured, resected prostate weight are also shown. For clarity, a maximum of 20 pre- and post-surgery flow traces are displayed. Patients 1 to 5.

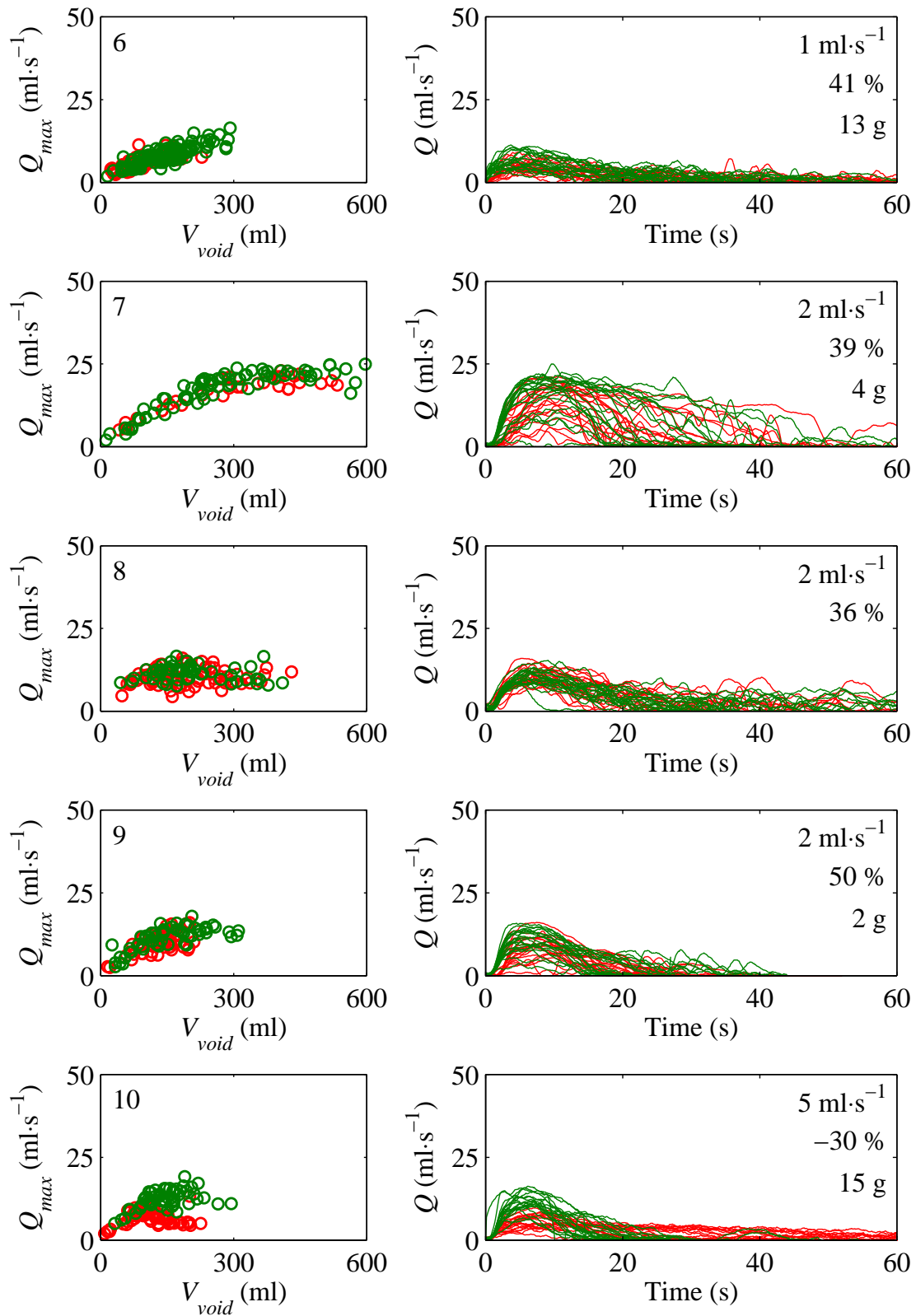


Figure 8.5 For the full caption and legends, see Figure 8.4, page 165. Patients 6 to 10.

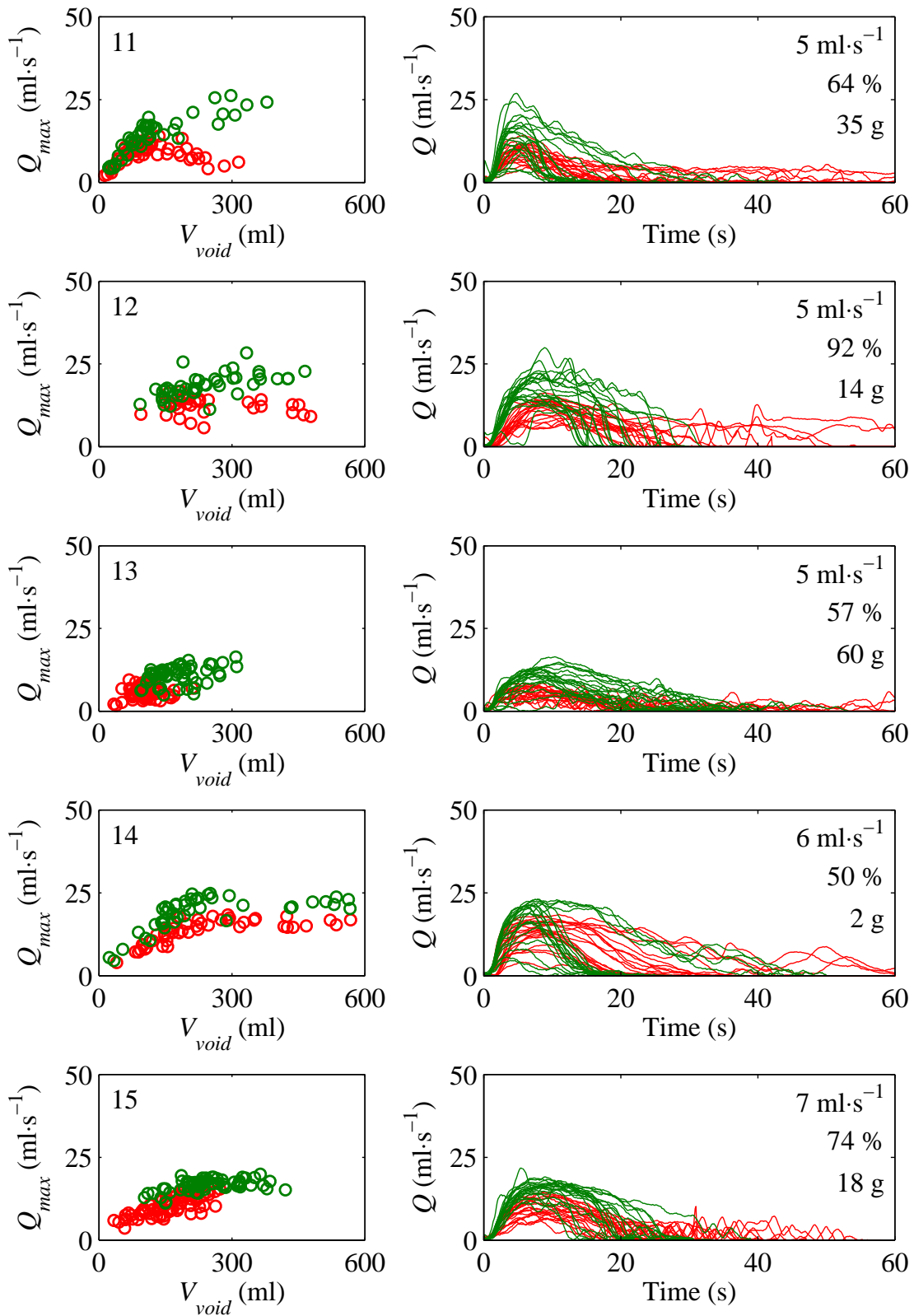


Figure 8.6 For the full caption and legends, see Figure 8.4, page 165. Patients 11 to 15.

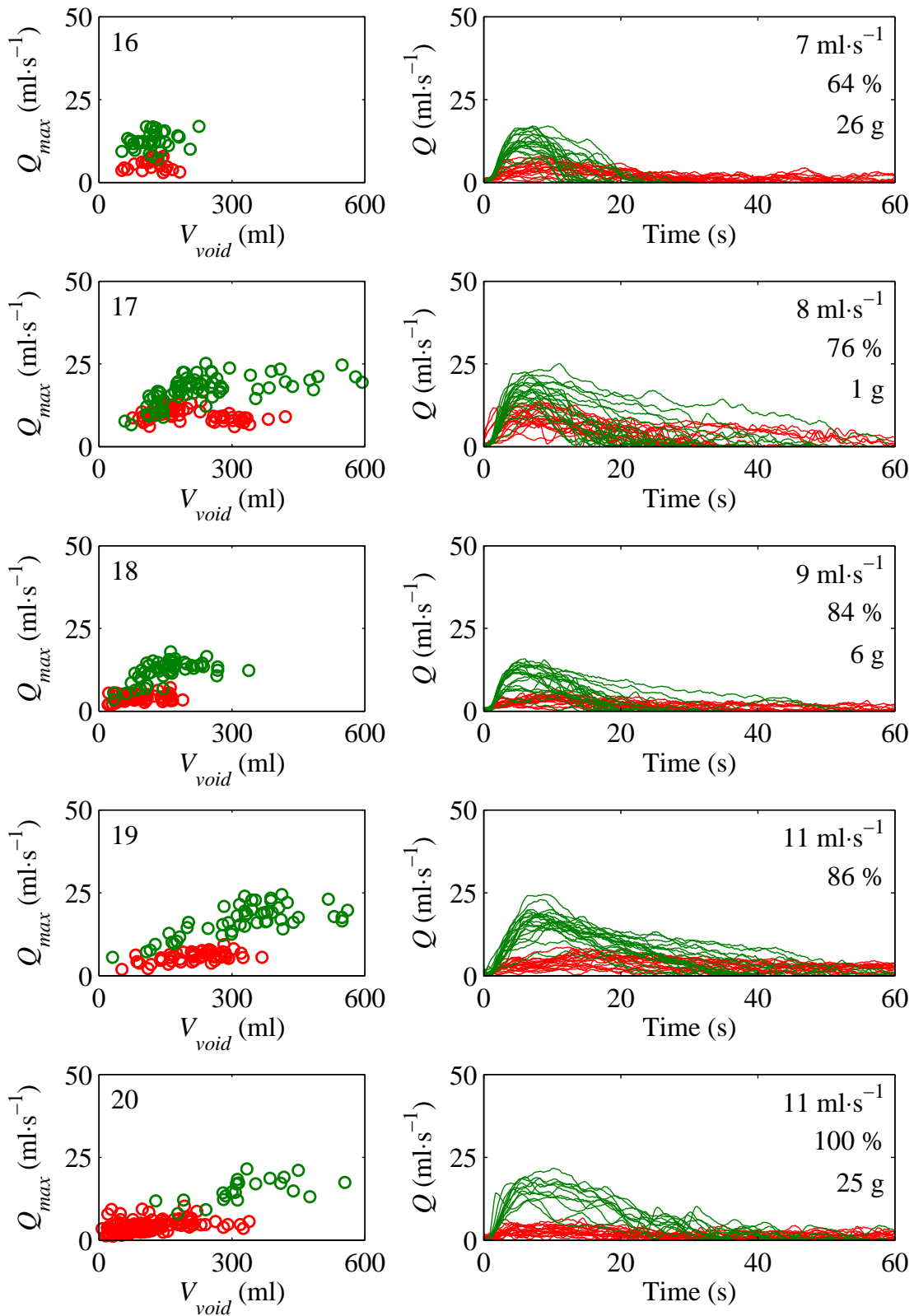


Figure 8.7 For the full caption and legends, see Figure 8.4, page 165. Patients 16 to 20.

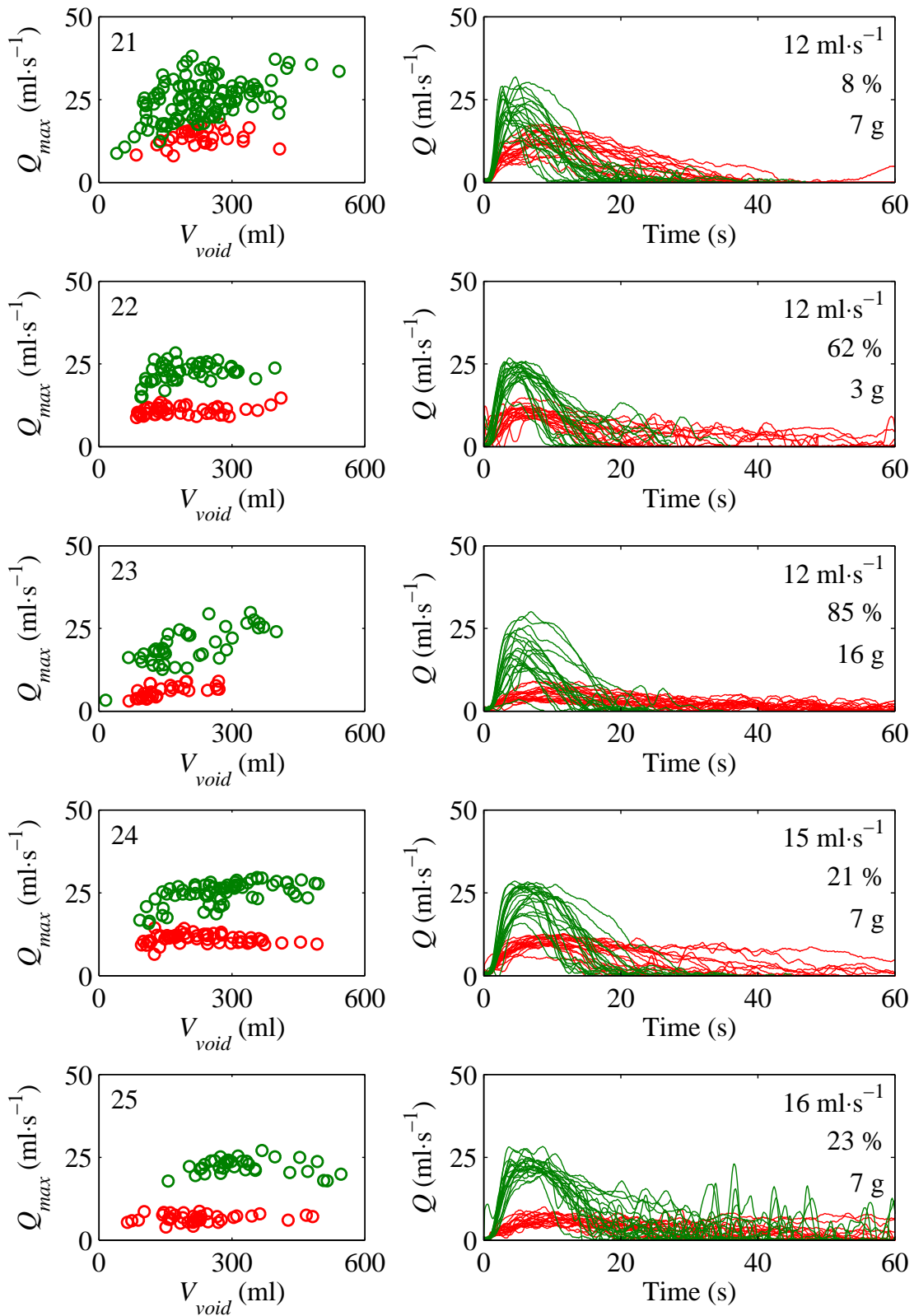


Figure 8.8 For the full caption and legends, see Figure 8.4, page 165. Patients 21 to 25.

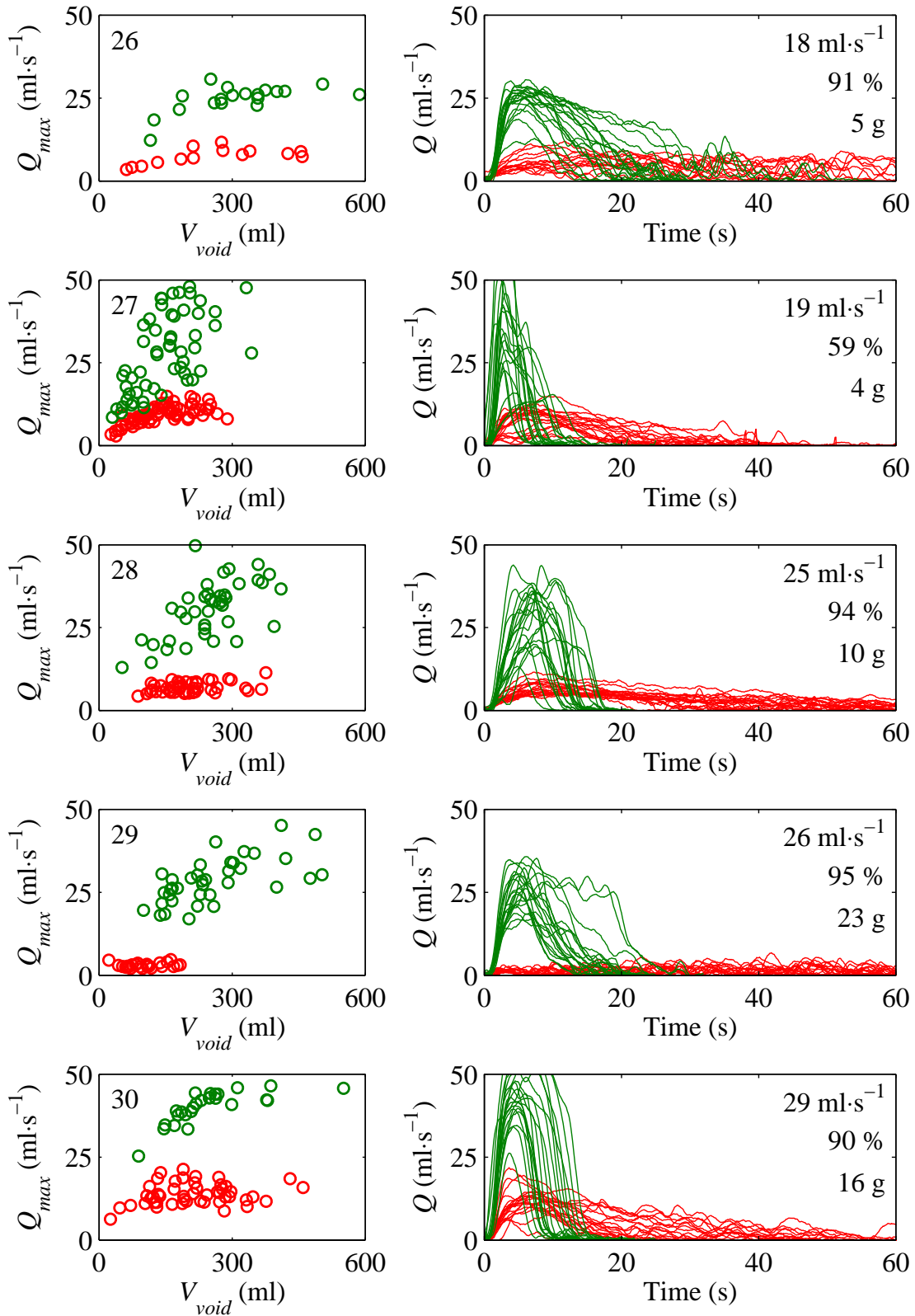


Figure 8.9 For the full caption and legends, see Figure 8.4, page 165. Patients 26 to 30.

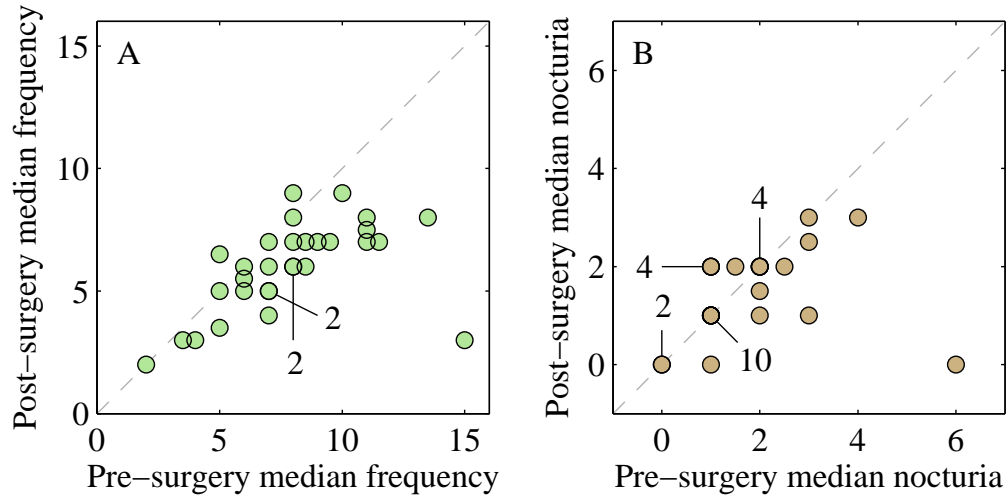


Figure 8.10 Changes in storage parameters following surgery: (A) Post-surgery versus pre-surgery median frequency and (B) post-surgery versus pre-surgery median nocturia. Dotted lines represent identity. Values represent the number of overlapping points.

Good correlation implies good predictive power. Spearman's rank analysis is based upon the position of datapoints' ranks rather than the values themselves and therefore does not require a linear relationship and does not require the nature of the relationship to be known. Thus, the relationship between home urodiagnostic parameters and outcome from surgery was investigated using Spearman's rank correlation analysis.

The 'predictors' were pre-surgery values of the parameters listed in Table 8.3 that changed significantly following surgery. The 'responses' (one subjective parameter, one objective voiding parameter and one objective storage parameter) were as follows:

- Percentage change in total IPSS score
- Absolute change in median Q_{max}
- Absolute change in median frequency

Table 8.4 presents the correlations between these predictors and responses. Omission of any predictor or response signifies that none of its correlations were significant. Figure 8.11 plots regression information for the best predictors of subjective outcome (namely, the value of Q_{max} at $V_{void} = 200$ ml as a predictor of percentage reduction in total IPSS score) and objective outcome (namely, the interquartile range of Q_{max} as a predictor of change in median Q_{max}). Both were best described by an inverse relationship, that is, of the following form, where a and b are constants:

$$response = \frac{a}{predictor} + b \quad (8.1)$$

		Response	
		Reduction in total IPSS score (%)	Change in median Q_{max} (ml·s ⁻¹)
Home urodiagnostic predictor	Median Q_{max}	$\rho = -0.37$ p = 0.047	$\rho = -0.24$ p = 0.2
	Median $t_{voiding}$	$\rho = 0.37$ p = 0.047	$\rho = 0.44$ p = 0.02
	IQR Q_{max}	$\rho = -0.24$ p = 0.2	$\rho = -0.48$ p = 0.007
	Q_{max}/V_{void} gradient	$\rho = -0.16$ p = 0.4	$\rho = -0.39$ p = 0.04
	Q_{max} at $V_{void} = 200$ ml	$\rho = -0.39$ p = 0.03	$\rho = -0.29$ p = 0.1

Table 8.4 *The predictive value of home urodiagnostic data. Correlations for which $p < 0.05$ are highlighted in green, the strength of the relationship being indicated by the tint of the highlight.*

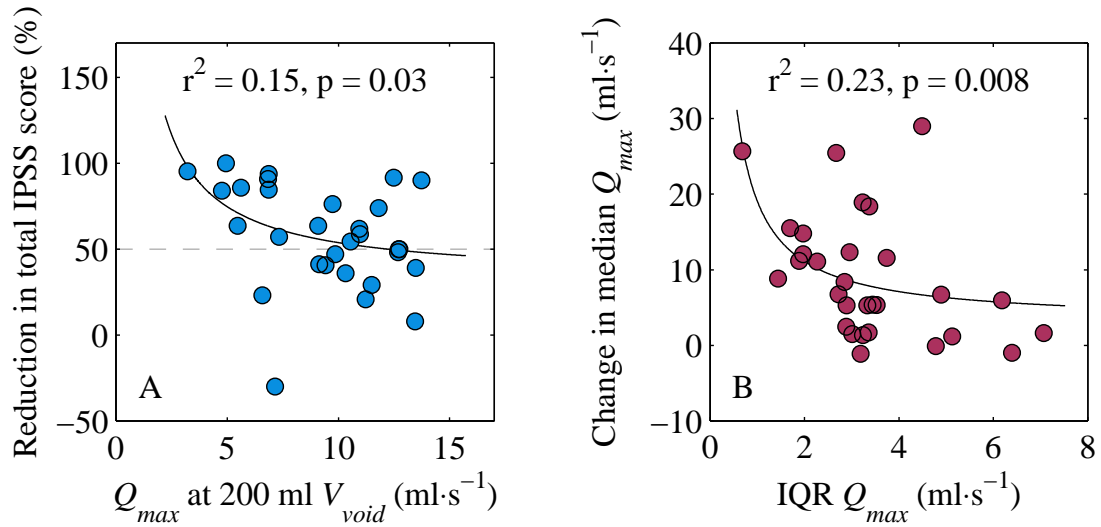


Figure 8.11 (A) Reduction in total IPSS score (%) versus the value of Q_{max} at $V_{void} = 200$ ml and (B) change in median Q_{max} versus IQR Q_{max} , with inverse regression lines, r^2 values, and F -test p -values.

On examining the pre-surgery notes of the patients involved in this study, there was a diagnosis of BOO from either invasive or non-invasive pressure-flow measurements in 8 cases (27%), for 5 patients (17%) pressure-flow measurements either did not detect BOO or were inconclusive, and there was no record of pressure-flow measurements having been carried out prior to surgery in the remaining 17 cases (57%). Figure 8.12 compares the increase in median Q_{max} in patients grouped according to results from invasive or non-invasive pressure-flow measurements. There was no difference in response in terms of change in Q_{max} when the obstructed group was compared to all other patients ($p = 1$, Mann-Whitney U, although samples of this size could only detect a large difference) and a confirmed diagnosis of BOO did not guarantee a large increase.

There was no relationship between the weight of prostate tissue resected and the increase in median Q_{max} ($\rho = -0.05$, $p = 0.8$, Spearman's rank correlation coefficient; Figure 8.13).

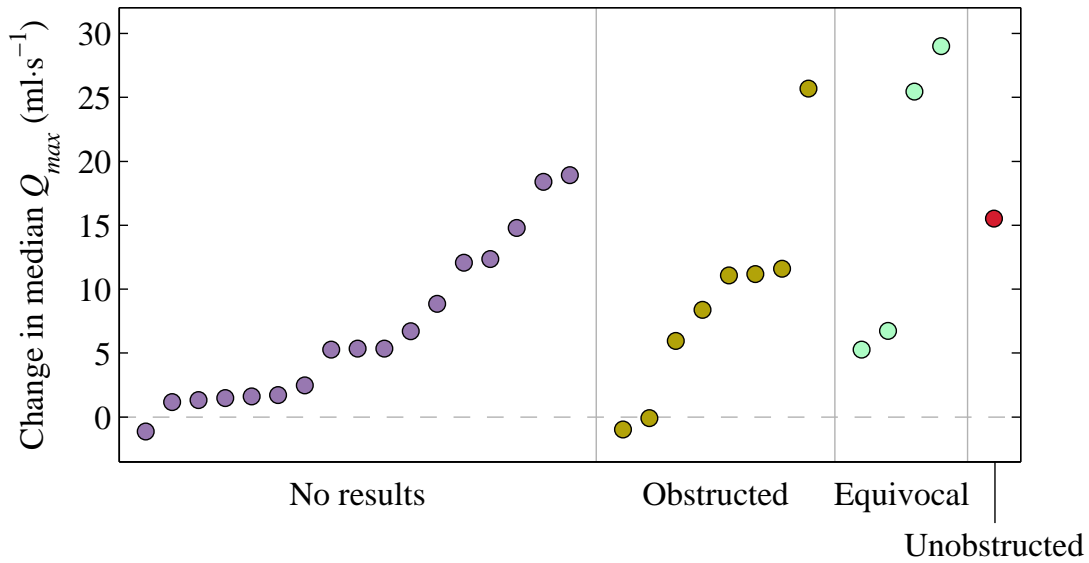


Figure 8.12 The change in median Q_{max} for patients grouped according to results from invasive or non-invasive pressure-flow measurements.

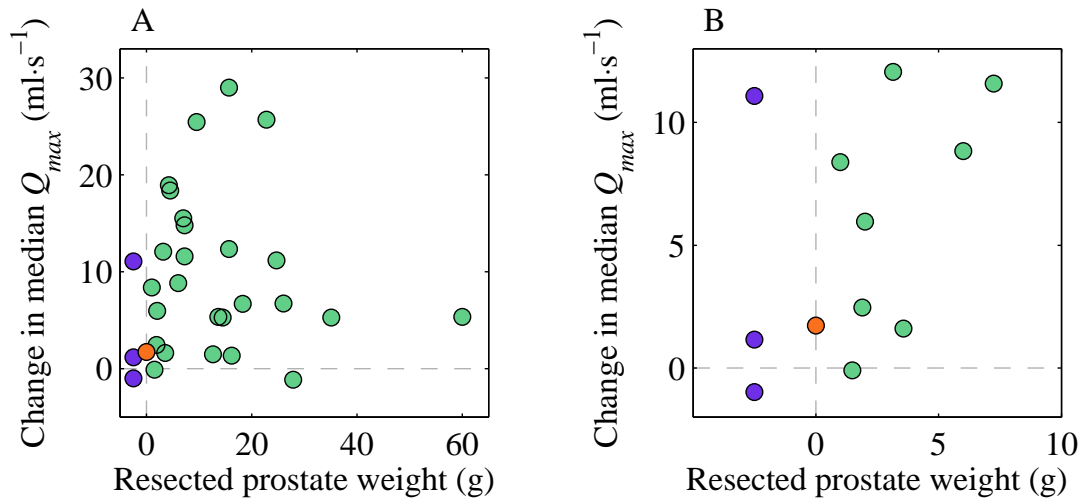


Figure 8.13 Change in median Q_{max} following surgery versus resected prostate weight: (A) All patients, and (B) the same plot focussed upon the region of smaller change in median Q_{max} and lower prostatic weight resected. One patient for whom there was no prostate tissue resected (BNI only) and three for whom prostate tissue was vapourised and could not therefore be collected (Greenlight laser prostatectomy) are shown in orange and purple, respectively.

8.4 Discussion

In general, patients were satisfied with the symptomatic outcome from their surgery; all but one reported a reduction in total IPSS score. 63 % experienced ‘good’ symptomatic outcome, which is somewhat lower than subjective success rates measured previously (Neal et al., 1989; Harding et al., 2007). This increased to 73 % if those with good post-surgery IPSS quality of life scores were included. This poorer than expected result may stem from less stringent inclusion criteria surrounding flow rate and IPSS score.

8.4.1 Home urodiagnostic changes following surgery

A variety of home urodiagnostic parameters were compared pre- and post-surgery and the majority showed a statistical improvement. The most significant were maximum and average flow rate and the related variable voiding time, which decreased markedly from 44 to 26 seconds.

The parameter which changed in the highest proportion of patients (90 %) was the value of Q_{max} at $V_{void} = 200$ ml according to the least squares best fit linear regression relationship for Q_{max} versus V_{void} . The ratio of daytime to nighttime Q_{max} did not change following surgery, challenging the notion that circadian variability is higher for obstructed patients.

As discussed in Section 3.5 (page 47), long-term changes to detrusor function associated with chronic obstruction can lead to both overactivity during storage and underactivity during voiding, but treatment of obstruction appears to reverse these effects. Thus, one would expect an increase in V_{void} and a reduction in frequency as overactive symptoms regress following surgery. Overall, a statistically significant improvement was observed for both of these parameters.

On an individual level, half the participants experienced a statistically significant increase in V_{void} ; this is consistent with the estimate that overactivity is found in 50 % of men with BOO (National Institute for Health and Clinical Excellence, 2010). Despite time to follow-up being fairly evenly distributed from four to eight months (with the exception of two patients restudied at 10.5 and 11.5 months), there was no correlation between time to follow-up and percentage reduction in frequency ($\rho = -0.005$, $p = 1$) or increase in V_{void} ($\rho = -0.2$, $p = 0.2$, Spearman's rank correlation coefficient). This suggests that overactive symptoms tend to improve most within the first four months following surgery.

Overall, nocturia did not change following surgery, although one fortunate fellow who saw a decrease from six to zero voids per night may disagree (Figure 8.10).

8.4.2 Responses of flow and volume to surgery

It is extremely interesting to observe the varying responses of flow rate and voided volume to surgery between individuals, presented in Figures 8.4 to 8.9.

In several patients there was an increase in both flow rate and flow rate variability; a shift towards the 'normal' pattern suggested by various flow-rate, volume nomograms (Siroky et al., 1979; Kadow et al., 1985; Haylen et al., 1989), the clearest examples being patients 21, 27, 28 and 29. For some, there was an accompanying increase in V_{void} (21 and 29) and for others there was not (27 and 28). Again, an increase in V_{void} could signify a reduction in overactivity, or more efficient emptying of the bladder.

In several other patients, surgery had far less impact upon the relationship between Q_{max} and V_{void} , as for patients 15, 22, 24 and 25. The pre-surgery pattern was shifted, either upward to higher flow rates (patients 22 and 24), or diagonally towards both higher flow rates and larger volumes (patients 15 and 25).

It appears that for a proportion of men, normal dependency of flow rate upon bladder volume was restored by surgery, and for others it was not. In the latter group, perhaps morphological changes within the bladder resulting from long-term obstruction, observed during animal trials, have left the bladder with irreversible, or less easily reversible, stiffness.

Other notable cases include patient 6, for whom the improvement in flow rate resulted only from the addition of voids between 200 and 300 ml (improved storage in the absence of any supposed precursory improvement in voiding), and patient 11, whose improvement in flow rate was modest at low volumes and marked at high.

8.4.3 Why would flow rate fail to improve?

Men who undergo disobstructive surgery are expected to experience, and told to expect, an improvement in flow rate as a result of reduced outlet resistance. This ought to be clearly demonstrable from home urodiagnostics given that multiple measurements narrow the confidence intervals surrounding an average Q_{max} .

It is surprising therefore that six patients did not experience a significant increase in Q_{max} (defined either as a decrease in median Q_{max} , or an increase with $p > 0.05$ according to Mann Whitley U; patients 1 to 5 and 7 on Figures 8.4 and 8.5). For this suboptimal response there are a number of possible explanations, discussed below.

Absence of obstruction One may instinctively attribute an unsuccessful operation, in terms of little or no improvement in flow rate, to an absence of obstruction prior to surgery, that is, an incorrect diagnosis. However, definitions of obstruction are somewhat arbitrary calculations involving Q_{max} and $p_{det.Q_{max}}$. Even men who are not deemed to be obstructed by one or another pressure-flow

nomogram ought to experience an increase in Q_{max} due to the reduction in outlet resistance according to the urethral resistance relation (see Section 2.4.1, page 14). This is providing that the tissue removed constituted the flow controlling zone, as discussed later.

Further, in this study, even men with obstruction confirmed by pressure-flow measurements did not necessarily experience a large increase in flow rate following surgery. One man was deemed to be unobstructed; his median Q_{max} increased by $16 \text{ ml}\cdot\text{s}^{-1}$.

Reduction in voiding pressure Bladder outlet obstruction is defined by a combination of Q_{max} and $p_{det.Qmax}$. Therefore, it is possible for surgery to disobstruct a patient and bring about a change in one but not the other. Tammela and Kontturi (1995) reported results from pressure-flow studies in 27 men with BOO, at baseline and following four years of treatment with a 5α -reductase inhibitor. For the majority of patients, $p_{det.Qmax}$ decreased and Q_{max} increased. However, at least one man moved from the obstructed to unobstructed region of the Abrams-Griffiths nomogram with no change in flow rate; $p_{det.Qmax}$ fell from 86 to 17 cmH_2O whilst Q_{max} remained at $13 \text{ ml}\cdot\text{s}^{-1}$. Overall, the decrease in $p_{det.Qmax}$ was statistically significant ($p < 0.001$) whereas the increase in Q_{max} was not (p value not reported)[‡].

The reason lies in the nature of the BOR (see Section 2.4.2, page 17). Disobstructive treatment in a man with severe obstruction will induce a larger decrease in pressure and a smaller increase in flow rate than in a less obstructed man. This concept, illustrated in Figure 8.14, could go some way towards explaining the variation in the response of flow rate to treatment found in this study.

[‡] Due to reasons relating to the study design, these comparisons were performed in two subgroups of 12 and 15 patients.

The main difference between the work by Tammela and Kontturi and the present study is the nature of the treatment. Surgical intervention is intended for men with severe obstruction and should have a large effect on both pressure and flow rate; one may envisage a change from point A to D on Figure 8.14. Further, even if a man who becomes unobstructed following surgery does not experience an increase in flow rate, his flow trace should move from an obstructed pattern towards a normal bell-shaped curve. From Figures 8.4 and 8.5, this does not appear to be the case for the patients in question.

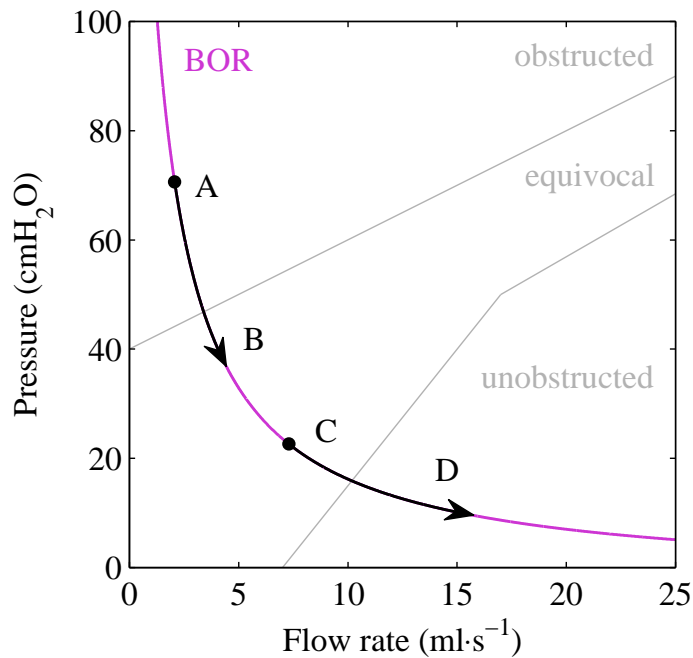


Figure 8.14 *The effect of disobstructive treatment on severe and mild obstruction according to the bladder output relation. The path from point A to B represents the effect for a man who begins with severe obstruction; there is a large decrease in pressure and a small increase in flow rate. Conversely, for a man with mild obstruction there is a small decrease in pressure and a large increase in flow rate; from C to D. The pink curve shows the bladder output relation and the Abrams-Griffiths nomogram is underlaid in grey. This is a simplified model in which only the urethral resistance relation, and not the bladder output relation, changes following surgery.*

Post-surgery scarring Formation of scar tissue at some point in the bladder outlet (bladder neck or urethra) following surgery resulting in constrictive obstruction may negate any benefit from reduction in outlet resistance. Patient 3 (Figure 8.4), subsequent to his follow-up in this study, was diagnosed with post-surgery bladder neck stenosis[§] and treated with a BNI. As discussed in Section 3.3.1 (page 31), constrictive obstruction is characterised by a decreased flow rate and flatter flow curve, indicated by his post-surgery flow rates. Patient 2's post-procedure plots appears to exhibit these characteristics to an even larger extent; perhaps he too suffered surgical scarring, although if this is the case the condition is at the time of writing undiagnosed. Patient 17 was diagnosed post-surgery with a urethral stricture which was corrected by an optical urethrotomy (urethral incision) prior to his follow-up in this study.

Decreased contractility Bladder contractility measured non-invasively has been found to decrease significantly when remeasured several months following surgery for BOO (Harding et al., 2005). It is possible, therefore, that in some patients the reduction in outlet resistance allowing an initial increase in flow rate was counterbalanced over subsequent months by a decrease in bladder contractility. This finding is incongruent with the theory that surgery reverses the adverse effects that obstruction has on the bladder, and requires further investigation.

Resected tissue weight Although weight of resected prostate tissue and increase in median Q_{max} did not correlate, there were a small number of cases where little tissue was removed and response in terms of increase in flow rate was poor (Figure 8.13B). However, it seems unlikely that were obstructive tissue

[§] Although the reason cited for this was discomfort as opposed to dissatisfaction with the outcome from his operation.

present it would not be removed; this would be poor surgical technique. Prostatic regrowth, which is to the order of 1 g per year (Capitán et al., 2011), may be a contributing factor in patients who had a small amount of tissue resected and more time between surgery and follow-up.

Flow controlling zone The remaining possibility is that the site of the operation, the prostatic urethra and / or bladder neck, was not the flow controlling zone. In a condition more commonly observed in females, symptoms of overactive bladder force patients to contract their pelvic floor in order to maintain continence or postpone voiding. If prolonged, the resulting ‘overactive sphincter’ would present as an obstructive pattern and would not necessarily be discerned during the diagnostic work-up for BOO.

There was no evidence that patients with signs of overactivity, characterised by low voided volumes and high frequency, experienced less improvement in flow. Again, the size of samples involved in this study may lack the power to demonstrate a relationship of this nature.

8.4.4 Predictive value

An attempt was made to predict subjective and objective outcome from pre-surgery home urodiagnostic parameters. Bonferoni correction for multiple comparisons would decrease the p-value denoting significance from 0.05 to 0.002[¶]. No correlations achieved this; possibly a reflection of the inadequacy of the sample size.

[¶] 11 predictors and three responses amounted to 33 comparisons ($n = 33$); for Bonferoni correction, the largest p-value for significance falls to α/n .

Nevertheless, a number of home urodiagnostic parameters were good predictors of the response of Q_{max} to surgery (Table 8.4). (The reader will recall from Section 5.8, page 91, that the effect of regression to the mean is almost eradicated in cases where an average value calculated from multiple measurements is used.) In particular, the variability of Q_{max} described by its interquartile range predicted the increase in median Q_{max} far better than median pre-surgery Q_{max} itself. The fact that less variable flow rates are more likely to improve following surgery could be taken into consideration during the clinical decision making process.

Unsurprisingly, as symptoms are known to correlate poorly with objective measures of LUT function, home urodiagnostic parameters were less successful at predicting subjective outcome. The value of Q_{max} at $V_{void} = 200$ ml, according to the linear regression relationship for Q_{max} versus V_{void} , performed best, having a marginal edge over median Q_{max} and median $t_{voiding}$. Surgical success rates in terms of symptomatic improvement are better for obstructed patients by 15 to 29 % (Homma, 2001). Given that this parameter controls flow rate for volume, it may better separate patients with low flows secondary to obstruction from those who pass small volumes, with a low flow rate, due to overactivity.

8.5 Conclusion

The most crucial outcome from treatments for BOO is of course that reported by the patient. However, objective assessment is also important to verify the intended mechanism of the treatment. The aim of disobstructive surgery is to reduce outlet resistance and increase flow rate; symptomatic improvement is presumably secondary to this. Would a surgeon put resector-to-prostate in the knowledge that the patient's flow rate would remain unchanged as a result of the surgery?

This study has revealed interesting and considerable variation in the response of objecting voiding parameters to surgery. Whilst some men emerged with unchanged, or even slightly diminished, flow rates, others were able to void with supranormal flows of up to $80 \text{ ml}\cdot\text{s}^{-1}$! The reasons for this variation remain uncertain. A number possible explanations for poor response were discussed, and the variability of Q_{max} found to be a good predictor.

The PeePod has emerged as a useful tool to study these subtle changes within, and differences between, individuals. There could be value in using home urodiagnostics throughout clinic trials for treatment of LUTS, which may shed light on the mechanisms of medical and surgical interventions.

Here ends the investigation of home urodiagnostics in the familiar setting of secondary care. The final leg of this journey takes us to pastures new: an evaluation of the PeePod in general practice.

Chapter 9

Home urodiagnostics in primary care

9.1 Introduction

So far, this thesis has described evaluation of the PeePod in patients recruited from secondary care. This was an obvious place to begin because in the urology clinic, uroflowmetry is an established test. The resulting data are familiar to clinicians and the device can be assessed in the context of the conventional alternative. However, secondary care is only the latter part of the story for men with LUTS. Their pathway usually begins with a visit to a GP who will follow their own investigative protocol, and perhaps subsequently make the decision to refer for specialist assessment.

Specialist care is costly and so, to improve the efficiency of NHS care, those in general practice are being asked to do more and refer less. Financial incentives have already been placed upon reductions in rates of referral. In relation to urology, there is a growing body of opinion in the literature and amongst organisations such as NICE that a large proportion of men with LUTS are not being managed appropriately in primary care (Morant et al., 2008; Quinlan et al., 2009; Kirby et al., 2010).

Could access to additional diagnostic information, such as that provided by the PeePod, help GPs to meet the increasing demands being placed upon them? Although not primarily designed with this purpose in mind, the simple, portable nature of the PeePod lends itself to implementation in primary care. At present, NICE recommend that flow-rate measurements are not offered to men with LUTS at initial assessment. This statement, however, is based upon a lack of evidence to support the practice rather than the existence of evidence against.

The aim of this chapter is to assess the feasibility and utility of the introduction of home urodiagnostics into the early clinical pathway of men with LUTS, beginning with an investigation of the current management of these men by local GPs.

9.2 Are NICE guidelines implemented in primary care?

As a basis for our investigation, we looked to NICE clinical guideline 97: *The management of lower urinary tract symptoms in men*, published in 2010 (National Institute for Health and Clinical Excellence, 2010). According to this evidence-based report, at initial assessment all men with LUTS should be offered the following:

- Physical examination of the abdomen and external genitalia.
- Digital rectal examination (DRE).
- Urinalysis.
- Men with bothersome LUTS* should also complete a frequency-volume chart.

Thereafter, guidelines diverge according to the type of LUTS that predominates (storage, voiding or post micturition).

* NICE define bothersome LUTS as those that are “*worrying, troublesome or have an impact on quality of life*”. Non-bothersome LUTS are presumably those that a man is happy to live with, but that prompt him to seek reassurance regarding serious disease.

We conducted surveys to determine which tests and treatments were administered in primary care for men with LUTS. The tests and treatments selected for inclusion were those from NICE clinical guideline 97 that are feasible for use in primary care.

9.2.1 Methods

Prostate assessment audit 100 consecutive patients in attendance at four local specialist prostate assessment centres were surveyed as to which investigations and treatments they had received in primary care. These clinics are for men whose initial assessment did not indicate the presence of serious disease (those with suspected cancer would follow a different route) but by implication had bothersome LUTS.

Questionnaires were completed by the clinician providing the clinic, who gave an explanation of the investigation or treatment where necessary. Patient's referral notes were also checked.

My role included questionnaire design, data entry, presentation and analysis using SPSS (IBM, Armonk, USA) and MATLAB software packages, and interpretation. My colleague Chris Harding (consultant urologist) instructed participating centres, distributed and collected questionnaires, and registered and reported the audit internally.

Survey of general practitioners In addition to the above, 40 local GPs completed a similar survey regarding how often they used NICE pathway investigations and treatments for men with LUTS. For each, they were asked to choose from *Never*, *Less than half the time*, *More than half the time* and *Always*, for each of Initial presentation, First review and Second review (see Appendix A5, Section A5.2, page 250 onwards).

The survey was circulated amongst GPs known to the project group and members of local Primary Care Research Networks. It could be completed either as an online survey[†] or by entering the results into an Excel (Microsoft, Redmond, USA) spreadsheet or hard copy.

9.2.2 Results

Prostate assessment audit The participating prostate assessment centres are listed below, with the number of questionnaires contributed by each in brackets.

- North Tyneside General Hospital (37)
- Freeman Hospital, Newcastle upon Tyne (27)
- Queen Elizabeth Hospital, Gateshead (20)
- Hexham Hospital (16)

The median age of the patients included in the survey was 66 years (range 46 to 90 years), the median symptom duration was six months (range three weeks to 12 years), and the median number of visits to primary care prior to referral was two (range one to ten visits). Figure 9.1 shows the percentages (also frequencies, given that 100 men were surveyed) of men who received each investigation and treatment in primary care.

Survey of general practitioners The median number of male patients with a new complaint of LUTS seen per month by the respondents was four (range one to 30 per month) (Figure 9.2). For ease of presentation and interpretation, given that the survey produced a large amount of data, the results were used to calculate

[†] <http://www.surveymonkey.com/s/J6Q2TQG>

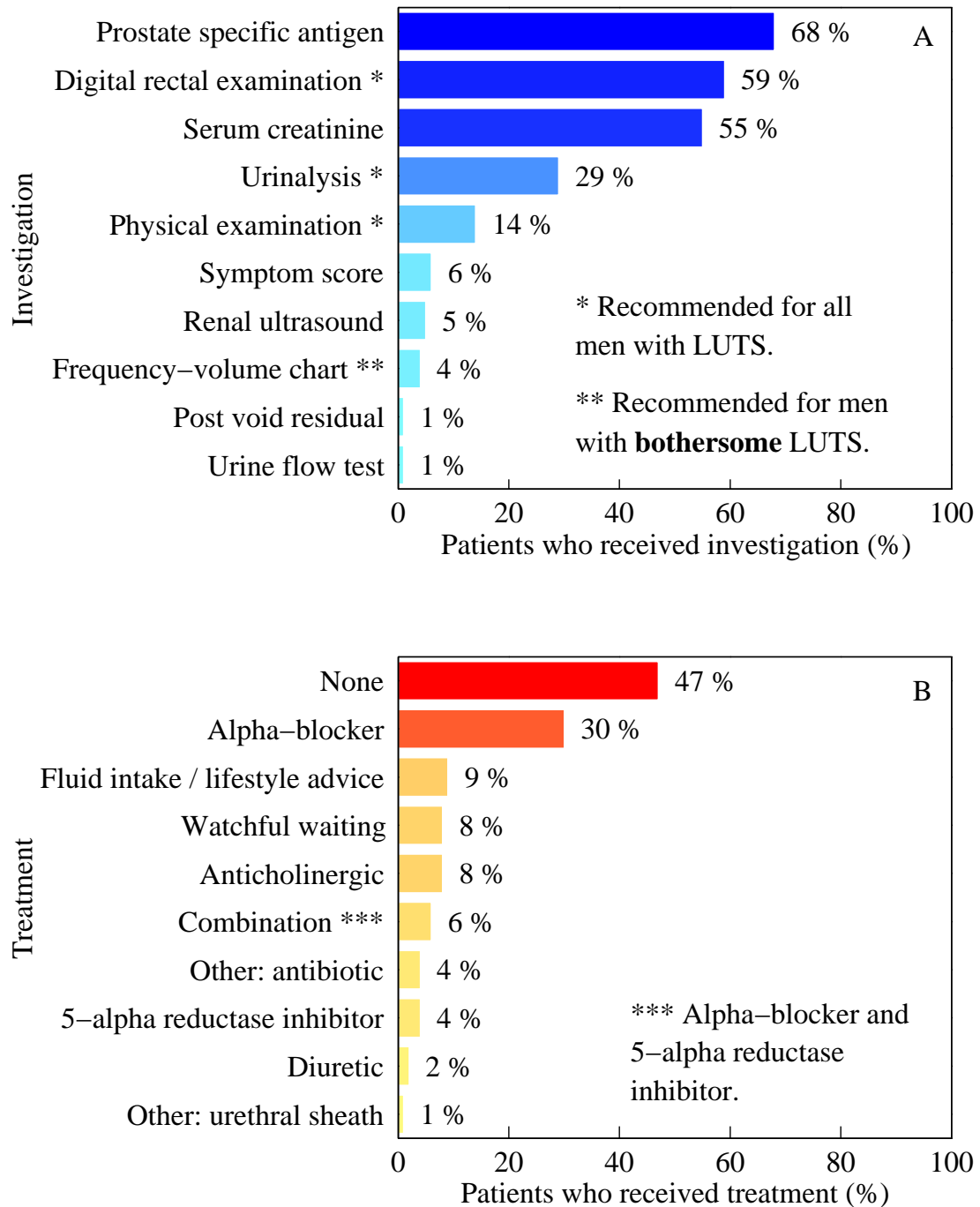


Figure 9.1 The percentage of men who received a variety of (A) investigations and (B) treatments in primary care, based upon an audit of 100 men referred to specialist assessment at local prostate assessment centres.

a likelihood score for each appointment type. This reflected the probability that each investigation and treatment would be used at each appointment, calculated according to Equation 9.1. The results are shown in Figure 9.3.

$$\text{likelihood (\%)} = \frac{\frac{1}{3}n_{<half} + \frac{2}{3}n_{>half} + n_{always}}{n_{total}} \quad (9.1)$$

Where:

$n_{<half}$ = number of responses of *Less than half the time*

$n_{>half}$ = number of responses of *More than half the time*

n_{always} = number of responses of *Always*

n_{total} = total number of responses

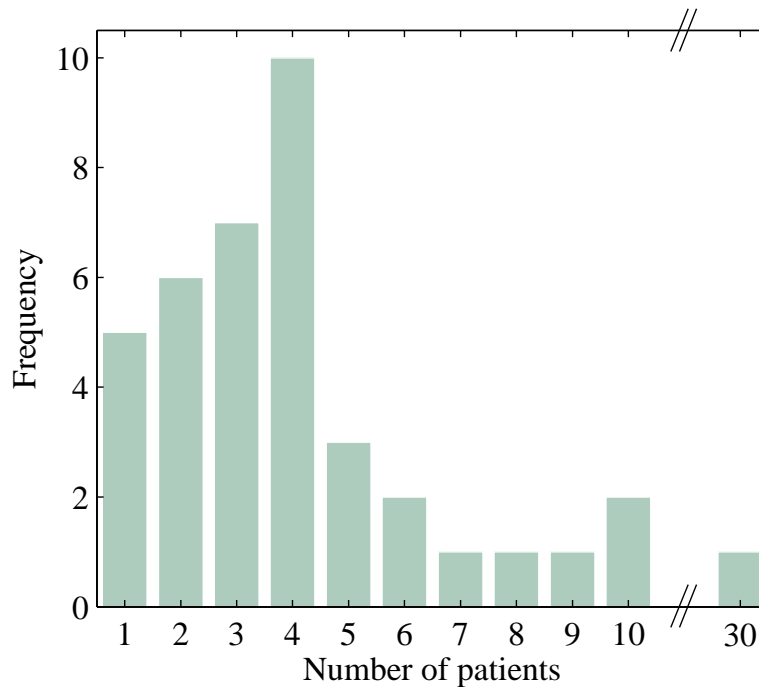


Figure 9.2 The number of male patients with a new complaint of LUTS seen per month by GPs who responded to our survey.

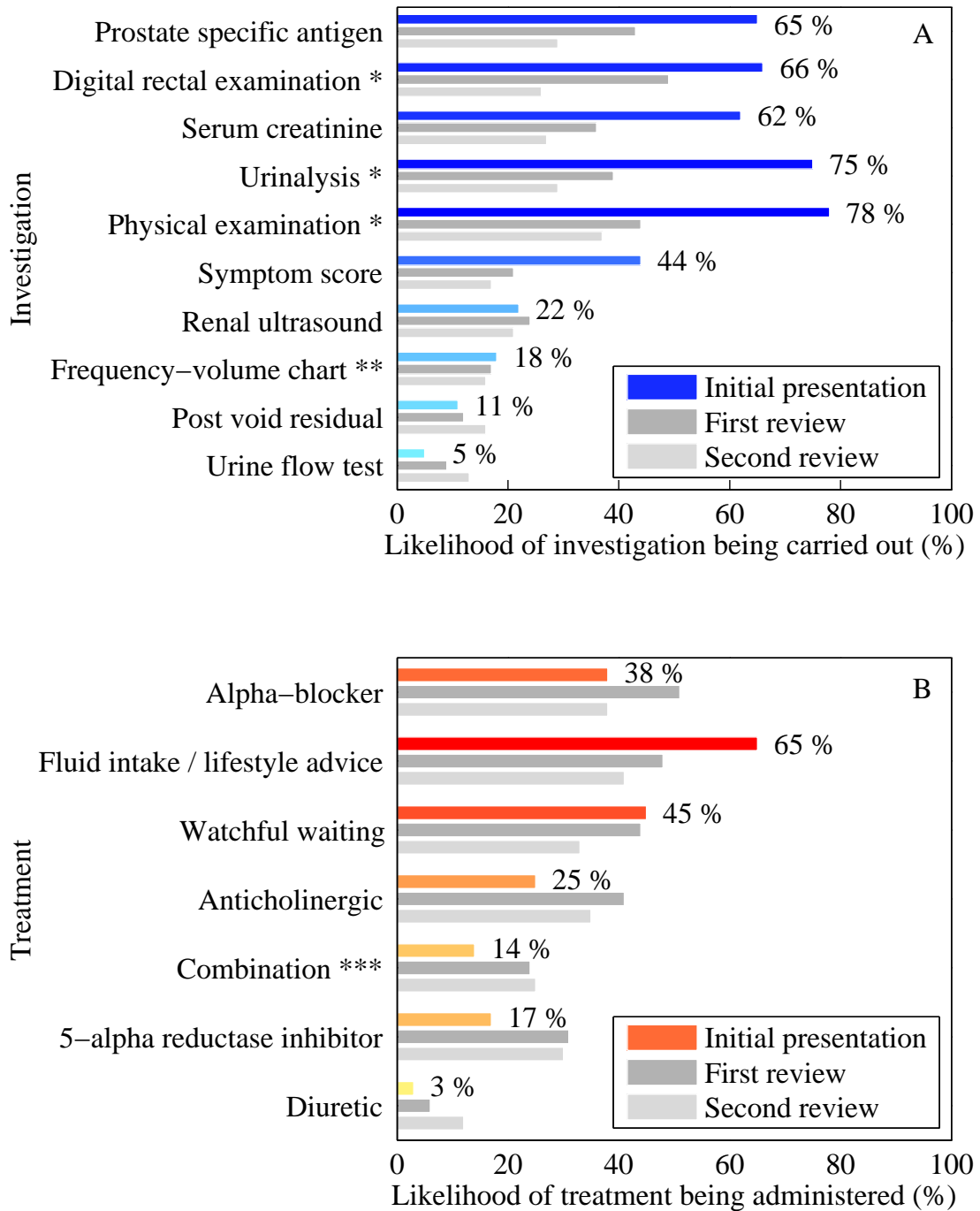


Figure 9.3 The likelihood of men with LUTS receiving a variety of (A) investigations and (B) treatments in primary care at initial presentation (blues / reds), first review (dark grey) and second review (light grey), based upon a survey of 40 local GPs. For the asterisks key see Figure 9.1.

9.2.3 Discussion

Naughty or NICE? According to our audit of patients in attendance at prostate assessment clinics, whose LUTS are presumably bothersome, the four investigations recommended for initial assessment by NICE were actually performed in just 59 (DRE), 29 (urinalysis), 14 (physical examination) and 4 % (FVC) of cases (Figure 9.1A). According to the GPs themselves, these tests are performed more frequently, but there is still an admission that they are not offered to all men. In particular, there is just an 18 % likelihood of a frequency-volume chart being completed at initial presentation. As patients may not recall each and every investigation[‡], the truth is likely to lie somewhere between reports from patients and GPs, which are subject to recall bias and estimation bias, respectively.

Concerning treatments, conservative measures, such as fluid management, are most likely to take place at initial presentation, whilst medications are most likely to be prescribed at the first GP review visit. A large discrepancy was found between rates of fluid intake and lifestyle advice reported by patients (9 %) and GPs (65 %), most likely indicating that not all patients perceive conservative management such as this as a form of treatment. A symptom score questionnaire, such as the IPSS, should be completed by men considering treatment. Although half of those surveyed received some form of treatment, only 9 % recalled completing such a questionnaire during their assessment in primary care.

It is difficult to draw a conclusion about the appropriateness of treatments administered to the group of patients surveyed in the prostate assessment clinics, given that this depends upon the results of various investigations. However,

[‡] Although, as articulated by Mr Harding: “*Not many people forget a finger up their a**e!*”

according to NICE, men with uncomplicated[§] LUTS should only be referred for specialist assessment once medical treatment has failed. Half of the men surveyed reported no form of treatment in primary care. Although we don't have information regarding the proportion of complicated LUTS in the patients surveyed, it is unlikely that as many as half fell into this category.

Why are there these discrepancies between guidelines and practice? There are a number of possible factors, discussed below.

Investigative priorities It is clear from both surveys that exclusion or detection of serious disease is being prioritised. Results from PSA testing and DRE, the most commonly performed investigations amongst our prostate assessment group, can indicate possible prostate cancer. This emphasis may leave little time for investigation of less serious, benign disease, as facilitated by tools such as frequency-volume charts and, if treatment is being considered, IPSS questionnaires. Is this practice justified?

A prospective study of over 20,000 men found that LUTS were associated with detection of early, localised prostate cancer, given that men with LUTS were more often screened for such, but not of advanced cancer. This led to the conclusion that prostate cancer does not cause LUTS (Martin et al., 2008). Therefore, LUTS should no more warrant investigation of prostate cancer than any other complaint commonly reported by a similar demographic. Still, to many men's minds, and perhaps some GPs', prostate disease is synonymous with prostate cancer. Brown et al. (2003) found in a small group of men with uncomplicated LUTS and no evidence of prostate cancer that over two thirds were worried regarding cancer at initial presentation.

[§] NICE define complicated LUTS as recurrent or persistent urinary tract infection, retention, renal impairment that is suspected to be caused by lower urinary tract dysfunction, or suspected urological cancer.

Guideline despair General practitioners require knowledge of an enormous number of different medical conditions, many of which are associated with some form of clinical guidance. From January 2009 to December 2012, NICE alone published 79 clinical guidelines, which represents a new several hundred page document every two to three weeks.

The GPs who completed our survey generally saw only a handful of patients per month with a new complaint of LUTS (Figure 9.2). Several major disease areas, such as cardiovascular and respiratory, are covered by the Quality and Outcomes Framework[¶], meaning that practices receive financial reward for adherence to relevant guidelines. This is not the case for LUTS. Therefore, with relatively few cases, and lack of incentive, many GPs may be unfamiliar with the fine detail of clinical guideline 97. They may also feel that their learning is better spent on diabetes and cancer than honing interpretation of frequency-volume charts. Referral to secondary care may seem like the more efficient option from an NHS care perspective.

With GPs being expected to improve their management of men with LUTS, but having little incentive to do so, what could be done to overcome this apparent stalemate?

[¶] <http://www.nice.org.uk/aboutnice/qof>

9.3 Home urodiagnostics in primary care feasibility study

This chapter began with the idea that home urodiagnostics could aid the primary care assessment of men with LUTS. Indeed, an investigation of current practice has highlighted areas which fall short of guideline recommendations. In particular, more men should be offered conservative and medical treatments prior to referral for specialist care. Could home urodiagnostics provide the missing link to guide general practitioners to an appropriate management decision?

In order to test the feasibility and utility of home urodiagnostics in primary care, a study of the PeePod was conducted at five practices within local primary care federation Hadrian Primary Care Alliance^{||}. Ethical approval for the study was obtained from Newcastle & North Tyneside 1 Research Ethics Committee, covered by application 10/H0906/10 Assessment of home uroflowmetry: Amendment 4 (11/11/2011) which received favourable opinion on 14th December 2011 (see Appendix A3, page 241 onwards).

9.3.1 Methods

Two meetings were conducted at each site prior to beginning the study. At the first, the general concept of the project and device was presented, and at the second, details of the study were discussed. The participating GPs were required to recruit men with LUTS to use the PeePod for one week. No exclusion criteria surrounding symptom severity, symptom duration, treatment status, or number of previous primary care consultations were imposed.

^{||} <http://hadrianpca.co.uk>

Patients were asked to complete an IPSS questionnaire and a survey to provide feedback about the PeePod, by answering the questionnaire described in Section 7.3.1 (page 134) in relation to the PeePod (see Appendix A5, Section A5.1, page 247 onwards).

Participant identification, recruitment, consent, and instructing of the patient regarding use of the PeePod were performed by the GPs. I prepared devices and study site files, retrieved data from used devices, compiled PeePod reports and acted as the point of contact for recruiting sites.

The recruitment target was 25 patients, with the intention that each practice would recruit five men.

9.3.2 Results

24 patients were recruited between February and September 2012. The participating members of Hadrian Primary Care Alliance are listed below, with the number of patients recruited by each in brackets.

- Branch End Surgery, Stocksfield (1)
- Burn Brae Medical Group, Hexham (3)
- Ponteland Medical Group, Ponteland (5)
- Sele Medical Practice, Hexham (9)
- White Medical Group, Ponteland (6)

One device was returned containing no data; the patient probably voided into the jug prior to placing it onto the pod. This left 23 sets of data for analysis, two of which did not include an IPSS questionnaire.

The median age of the recruited patients was 68 (range 61 to 77 years), the median total IPSS score was 12 (range 2 to 26) and the median IPSS QOL score was 3 (range 1 to 6).

Eight patients had a current prescription of an α -blocker, one patient of an α -blocker and 5 α -reductase inhibitor in combination, and one patient of an antimuscarinic, all for treatment of LUTS.

Symptoms versus objective voiding data The PeePod data provided objective measures of frequency, weak flow and nocturia to allow correlation of these parameters with subjective IPSS scores, using Spearman's rank correlation coefficient. For frequency $\rho = 0.4$, $p = 0.07$, for weak flow $\rho = -0.3$, $p = 0.3$, and for nocturia $\rho = 0.6$, $p = 0.009$. These results are illustrated in Figure 9.4.

Reporting PeePod reports were provided to the GPs for comment. Initially, the reports contained only the supertrace, electronic frequency-volume chart, summary statistics, Siroky nomogram and selection of individual flow traces (Figures 6.5 and 6.6, pages 107 and 108). However, GPs fed back that these results, being unfamiliar, were of little use alone.

Therefore, subsequently, the data were reviewed by Chris Harding (consultant urologist), along with the patient's history, relevant medications, IPSS questionnaire, and results from PSA and DRE where available. Chris then provided a short recommendation on patient management to append to the PeePod report.

All 23 reports were reviewed and annotated as such. Nine recommended that the current management strategy be altered, as summarised in Table 9.1. Nine recommended a first treatment or continuation of the current plan, and five were deemed to be normal.

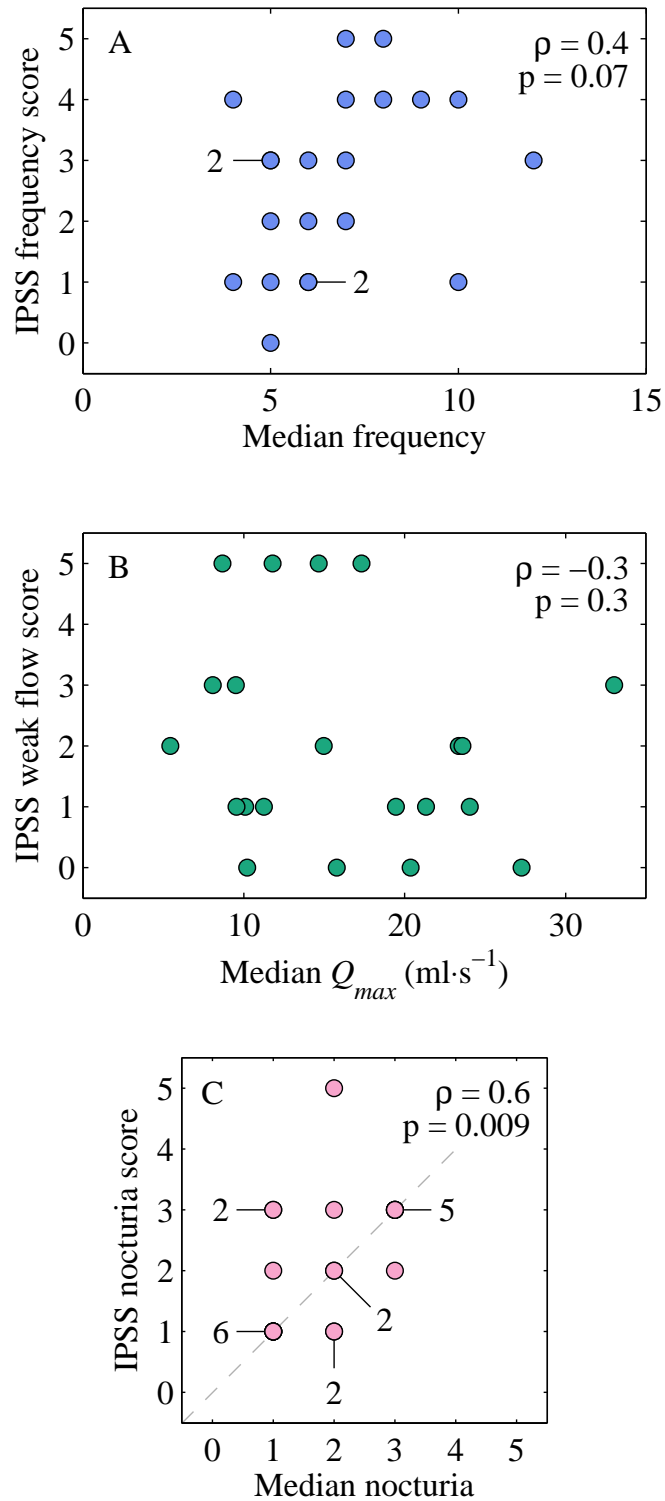


Figure 9.4 Scatter plots showing the relationship between objective parameters as measured by the PeePod and subjective symptoms as measured by the IPSS questionnaire, for (A) frequency, (B) weak flow and (C) nocturia. ρ and p denote correlation according to Spearman's rank correlation coefficient. Values represent the number of overlapping points. For (C), the dotted line represents identity (this is the only plot in which the two parameters being compared are measured on equivalent scales).

Existing management	Suggested management	Number of patients
α -blocker	Antimuscarinic	5
α -blocker	5 α -reductase inhibitor	3
α -blocker	Referral	1

Table 9.1 *The existing and suggested management of nine patients whose PeePod reports and relevant background were reviewed by a consultant urologist.*

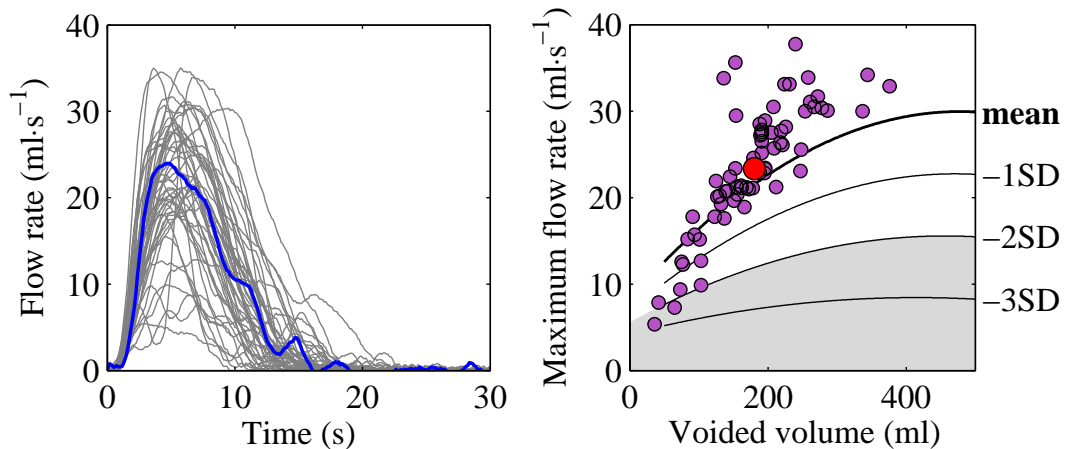
Case studies Three interesting case studies are presented on the following pages to demonstrate the potential value of home urodiagnostics in the patients studied. For each, the patient's history and symptoms are described, followed by a summary of findings from the PeePod report, plus discussion of the implications of these results.

CASE STUDY 1

History A 65 year old male with a two to three year history of urgency, urge incontinence and nocturia three to four times a night. His symptoms as recorded on an IPSS questionnaire were predominantly storage (urgency = 5, frequency = 4, nocturia = 3) with voiding symptoms to a lesser extent (intermittency = 5, weak stream / straining = 2). The patient had a current prescription of an α -blocker (tamsulosin) and 5α -reductase inhibitor (finasteride).

PeePod results Above average flow rate (median $Q_{max} = 23 \text{ ml}\cdot\text{s}^{-1}$), highly variable according to voided volume, with a large proportion of low volume voids (median $V_{void} = 180 \text{ ml}$) but normal bladder capacity (maximum $V_{void} = 375 \text{ ml}$). Flow curves appeared normal with no evidence of intermittency. Median frequency was eight and nocturia, three.

Comments This patient's prescribed medications indicate that he had been managed according to a suspected diagnosis of bladder outlet obstruction. This management decision may have been influenced by the apparent presence of voiding symptoms, which were unsubstantiated by the PeePod data. The data strongly suggest a case of overactive bladder; the patient could be managed accordingly.



CASE STUDY 2

History A 77 year old male complaining of difficulty initiating urination and frequency. His IPSS questionnaire reported mild to moderate voiding symptoms (intermittency = 3, weak stream = 1) and mild storage symptoms (frequency / nocturia = 1). The patient had been prescribed an α -blocker (tamsulosin).

PeePod results A maximum flow rate within the normal range, particularly given the patient's age (median $Q_{max} = 21 \text{ ml}\cdot\text{s}^{-1}$). Consistently large voided volumes (median $V_{void} = 440 \text{ ml}$) and high bladder capacity (maximum $V_{void} = 900 \text{ ml}$). Flow curves appeared to be normal with little evidence of intermittency. Normal frequency at four times per day.

Comments This man's voiding symptoms could in part be due to distention of the bladder past its most efficient point, given the consistently large voided volumes. He could be counselled in this regard and reassured that his results are normal.

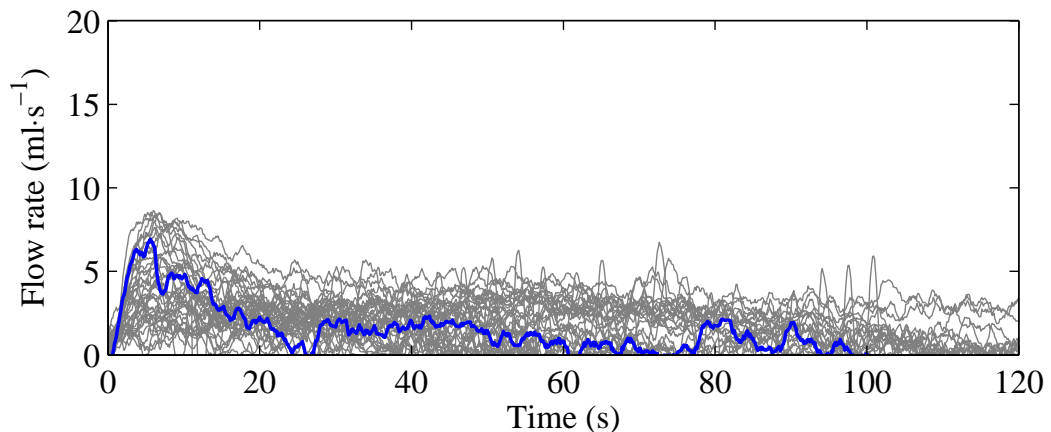
Hour / Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
6 am	424 ml	437 ml		880 ml	898 ml		481 ml
7 am						454 ml	
8 am			143 ml				
9 am				505 ml			
10 am			588 ml				
11 am	189 ml	220 ml			395 ml		384 ml
Midday						309 ml	
1 pm							
2 pm			609 ml				
3 pm							
4 pm						201 ml	
5 pm	183 ml	191 ml			180 ml		
6 pm			281 ml				
7 pm				411 ml			
8 pm							
9 pm							
10 pm				724 ml			
11 pm	429 ml		576 ml		501 ml	391 ml	
Midnight							506 ml
1 am							
2 am		591 ml					
3 am							
4 am							
5 am							
Total	1225 ml	1439 ml	2197 ml	2520 ml	1974 ml	1355 ml	1371 ml

CASE STUDY 3

History A 73 year old male complaining of nocturia three times per night, variable flow, hesitancy, and terminal dribbling. His IPSS questionnaire showed mixed storage (frequency = 3, urgency = 1) and voiding (intermittency = 4, weak stream / straining = 2) symptoms. He had trialled an α -blocker (tamsulosin) but discontinued this due to intolerable side effects such as dizziness.

PeePod results A consistently low maximum flow rate (median $Q_{max} = 6 \text{ ml}\cdot\text{s}^{-1}$, range 2 to $10 \text{ ml}\cdot\text{s}^{-1}$), particularly at high volumes, always with terminal dribble, and an average flow time of over 90 seconds. Frequency almost hourly on some days and nocturia three times per night. A normal bladder capacity of 400 ml.

Comments The PeePod report strongly suggests a case of advanced bladder outlet obstruction. The patient's flow rate is very low with an obstructive pattern. There is likely to be a degree of detrusor over- and underactivity secondary to BOO. If the patient wished, it would be appropriate to refer him to specialist care with a view to discussing surgical intervention, particularly as he was unable to tolerate medical treatment.



GP feedback Following completion of the study, the GPs leading the research at each site were asked to provide feedback regarding the study, including the value of the PeePod report, once annotated. Two provided a short statement to the effect that patients found the device acceptable and easy to use. The remaining more detailed responses are given below**.

“I found the [PeePod] reports useful as they were an additional diagnostic tool, enabled better evidence based treatment instead of a trial of treatment, and improved the patients’ quality of life more quickly. They also prevented the need for some referrals. Some examples:

[A] 65 year old man presented with [urgency] and occasional urge incontinence. He had nocturia 3-4/night. I initially gave some lifestyle advice and tamsulosin, but [on the basis of the PeePod report] I changed him to an anticholinergic, and reinforced evening fluid reduction. His symptoms had improved at the next appointment. I suspect I would have got there in the end with trial and error but with PeePod I got there quicker, with fewer appointments, and less cost of medication/time.

One report came back with a very high urine output so I discussed fluid intake in detail and it did appear he was drinking excessive quantities of fluids, these were reduced and symptoms improved.

One result came back as fairly normal, [although] the patient reported poor flow and frequency, so they could be reassured without the need for trying medications and referral.”

Dr Tom Schatzberger, Sele Medical Practice

** Redaction key: [] = word(s) inserted or replaced for clarity, ... = word(s) removed.

“Broadly speaking [the PeePod] was universally embraced by the patients as an interesting option. The ones who had previously had the pleasure of a trip to the [urine flow clinic at the Freeman Hospital] were very clear that it was preferable. They found it easy to use. From my perspective the clinical insight offered by the team on the report was very helpful and added weight to my attempts at managing their care in primary care.”

Dr Matthew Thomas, Ponteland Medical Group

“[The] PeePod device was used with relative ease and no reported problems in all of our patients... Suggestions fed back to us regarding each patient were straightforward and useful. [It was] good to be able to reassure one patient that his flow rate was actually within normal limits rather than his perception that it was slow. [It was] also useful to be advised that another patient’s symptoms were suggestive of [detrusor overactivity] according to his PeePod result ... enabling us to give appropriate lifestyle advice and consider bladder training.”

Dr Nick Hargreaves, Burn Brae Medical Group

Patient opinion The median ‘burden score’ was 0 (*Not at all burdensome*) (range 0 to 3), indicating that all participants experienced very little inconvenience when using the PeePod at home. The median ‘willingness to repeat’ score was 10 (*Very willing*) (range 2 to 10); all but five patients gave a score of 10. The results are shown in Figure 9.5. There was no difference between the scores from these patients and those from patients recruited from secondary care, as described in Section 7.3.1 (page 135) (Mann-Whitney U, $p = 0.8$ and 0.9).

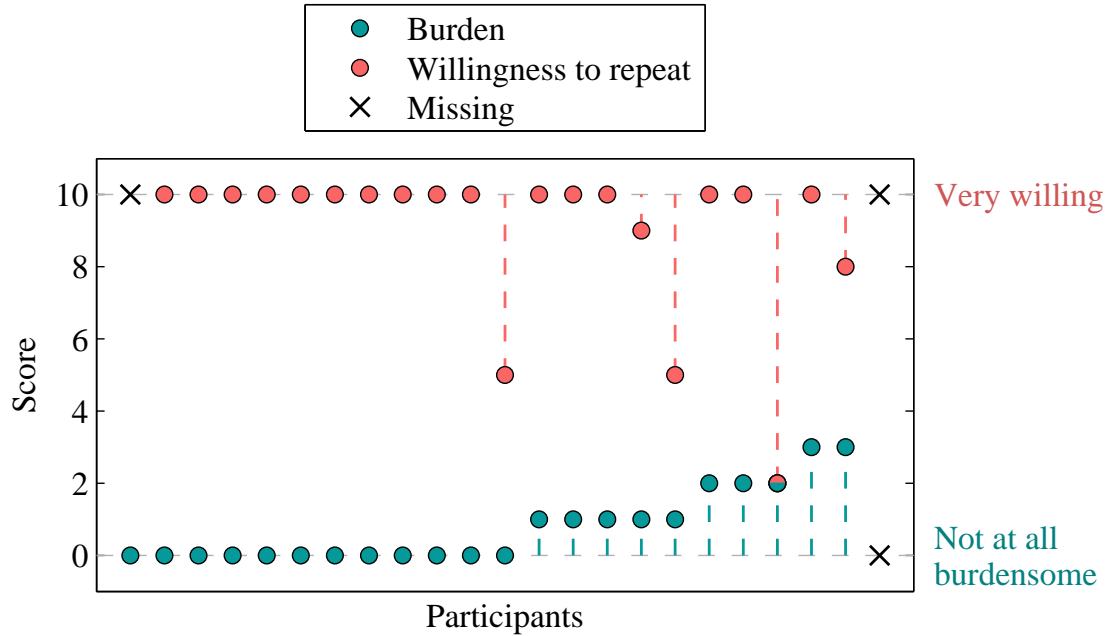


Figure 9.5 *PeePod* burden (brown) and willingness to repeat (blue) scores from each participant as recorded on a questionnaire. Patients are ordered by increasing burden followed by decreasing willingness to repeat.

9.3.3 Discussion

What could home urodiagnostics contribute to the primary care assessment of men with LUTS? Once serious disease has been ruled out, GPs are often left with the decision to focus upon treating either the prostate or the bladder. Treatment for obstruction is more effective in those with a low flow rate, hence clinical trials exclude those with Q_{max} above a certain threshold. The same applies to treatment for overactivity in relation to storage symptoms such as frequency and nocturia; a lower limit is often applied. Therefore, knowledge of parameters such as flow rate, frequency and nocturia would be of great benefit to GPs for the initial assessment of men with LUTS.

An appreciation of a patient's storage difficulties can be obtained from their description of such. Patients are rather good at estimating how often they pass urine during the day and night, probably owing to the impact of this on their quality of life. This is reflected by reasonable agreement (and low p-values) between subjective and objective measures of frequency and nocturia in this study, despite the small sample size (Figure 9.4A and Figure 9.4C).

The same could not be said for patients' own evaluation of their flow rate (Figure 9.4B), and other investigators have drawn the same conclusion on the basis of much larger studies (Reynard et al., 1998; de la Rosette et al., 1998). This could be an important contributing factor towards the high failure rate of α -blocker medication, estimated to be around 50 % if prescribed in primary care on the basis on symptoms rather than flow rate (Norg et al., 2006). Therefore, objective measurement of a patient's flow rate, along with its relation to voided volume and storage parameters, could be an extremely valuable early tool.

One may argue that a conventional frequency-volume chart plus office-based urine flow test is equally valuable. However, firstly, a conventional flow test does not lend itself to being administered within primary care. GPs may at present request the test for patients under their care from a secondary care provider, but as there is little incentive to do so rather than refer, this is rare. Just one man in our prostate assessment audit had performed a urine flow test prior to referral. Secondly, a combined electronic report enables automated analysis, which, as discussed below, may be crucial. Thirdly, certain information which proved to be valuable during this study is only determinable from multiple measurements of flow.

By way of example, three case studies were presented, illustrating the value of home urodiagnostics in the early assessment of men with LUTS. The first demonstrated how GPs could be directed towards the most appropriate management strategy, in this case away from that of obstruction and towards

overactivity. The second man could be reassured that his urinary function was normal. It is not just about avoiding referrals, but also expediting the referral of those who truly warrant it, as in the third case. According to one urologist who examined all 23 cases, over a third were likely to have gained from a different management strategy.

Appreciation of these benefits was shared by the GPs involved in the feasibility study. They described arriving at the correct management decision more quickly, improving efficiency by avoidance of ineffective medications resulting from ‘trial and error’, and having the confidence to reassure men whose results were normal. However, an important observation was made. They requested that the reports include expert interpretation, and in fact felt otherwise unable to comment on their utility.

This raises the following question: If home urodiagnostics was to become available within primary care, would it suffer the same fate as frequency-volume charts: a valuable and yet, due to the investment required to understand and interpret them, underused tool?

Interpretation Any new tool requires investment of resources for development and testing of training strategies and materials. It may be possible to train all GPs in the full interpretation of home urodiagnostic data. However, given the issues discussed in Section 9.2.3, this seems impractical and therefore unrealistic.

An alternative, and perhaps more feasible, approach could be for this role to fall to one accredited GP with a Special Interest^{††} (GPwSI) for each practice or group of associated practices, to whom men with LUTS were directed. (Although, at the time of writing there was no GPwSI framework for urology.)

^{††} <http://www.rcgp.org.uk/clinical-and-research/clinical-resources/gp-with-a-special-interest-gpws-i-accreditation>

A third option would be for home urodiagnostic data to be interpreted by a specialist and a recommendation returned to primary care, the model tested during this study. This would appear to be an ideal scenario for GPs; they could be extremely confident in the decisions made, whilst retaining patient management within primary care. It remains to be seen how urologists would perceive this arrangement.

Finally, the nature of home urodiagnostic data allows a degree of automated analysis. A number of the early investigations performed commonly for men with LUTS are relatively simple to interpret. PSA is compared to an age-dependent threshold (Table 3.2, page 43); a high level may indicate cancer. Serum creatine is compared to a normal range; a high level may indicate renal disease. For DRE, the prostate is reported as either nodular (cancer?) or smooth, enlarged (BPE?) or small. At the very least, home urodiagnostic parameters could be reported with respect to normal ranges, and abnormal values flagged.

Slightly more involved, but feasible, would be to include recommendations based upon the data. Unfortunately, the workings of a urologist's brain cannot be translated into an algorithm, but simple guidance may be sufficient to lead GPs through conservative management options. Suggested strategies could be built into nomograms such as that illustrated in Figure 9.6: a plot of median Q_{max} versus 24 hour frequency separating likely cases of normal, overactive, obstructed, and mixed. Volume-related observations could be covered by alerts, such as the following:

- ! Polyuria - discuss fluid intake.
- ! Low voided volumes - consider bladder training.
- ! Nocturnal polyuria - consider an afternoon diuretic.

The complexity would lie in prioritisation of recommendations where multiple parameters fell outside normal ranges, and accounting for situations in which previous treatments had failed. Of course, any such tool would require extensive development and testing.

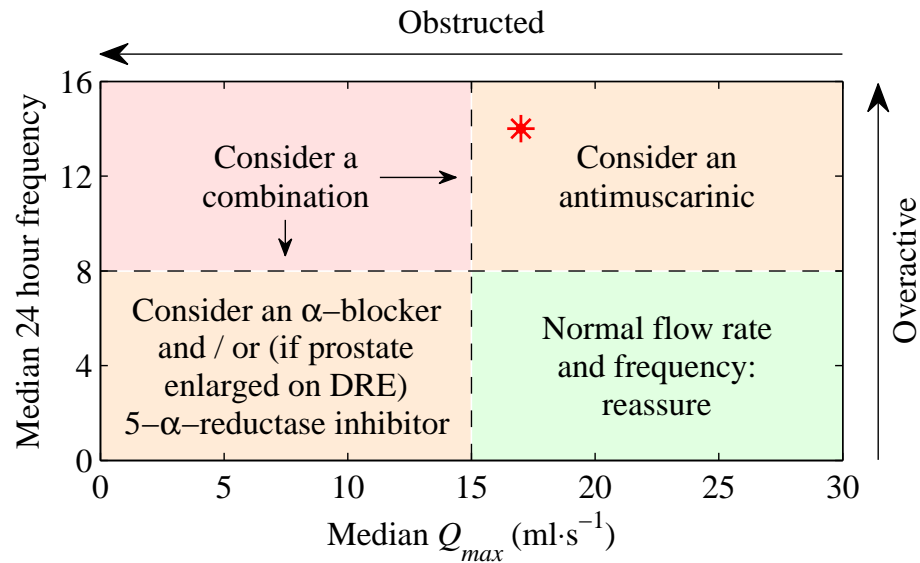


Figure 9.6 An example of a simple draft nomogram that could translate home urodiagnostic data into basic recommendations for patient management. The red marker indicates the patient's position on the nomogram.

9.4 Conclusion

According to NICE, at present, three quarters of men who consult their GP due to LUTS are referred for specialist assessment, but over 60 % of those referred could be managed conservatively (National Institute for Health and Clinical Excellence, 2013). Therefore, those in primary care are likely to come under increasing pressure to improve the management of men with LUTS without referral to secondary care.

The combination of home urodiagnostics with symptom scores, PSA and DRE appears to be a powerful tool to guide the initial management of men with LUTS. However, GPs are unlikely to adopt a technology that requires a large amount of time or expertise to administer. The success of a device such as the PeePod in this environment would require careful consideration and evaluation of models of implementation, particularly surrounding interpretation of the resulting data.

Chapter 10

Conclusion

10.1 Summary of conclusions, strengths and limitations

The aim of this thesis was to investigate the value of home urodiagnostics in the assessment of men with lower urinary tract symptoms.

A review of the literature revealed a host of devices previously used to measure flow in the home. None fulfilled guideline recommendations whilst being designed and costed for widespread use. A small number of underpowered studies reported that an individual's average Q_{max} had no better diagnostic accuracy for obstruction than a single value. Although the review was conducted systematically, heterogeneity in the designs of studies identified did not allow meta-analysis.

A novel, theoretical method of calculating the accuracy of a mean Q_{max} to diagnose bladder outlet obstruction was presented. This predicted benefit for thousands of men in the UK per year. Similarly, the capability of single and average values of Q_{max} to measure the effect of medical treatment on flow rate was calculated. This showed that the use of conventional uroflowmetry to measure medication

effect is unwarranted. Substantial improvement was predicted when multiple measurements are averaged in an individual. Confidence in the knowledge that medical treatment has had a measurable effect on the LUT would no doubt benefit both clinicians and patients. Although the spread of flow rates were later found to be non-Gaussian in some patients, introducing a potential source of error in these calculations, this was an elegant method of estimating the clinical accuracy of multiple measurements of flow.

In the remaining chapters of this thesis, a novel device was used to obtain home urodiagnostic information in patients. A comparison of home and conventional urodiagnostics in a group of men with LUTS revealed undeniable patient preference towards home-based assessment. Flow rates recorded in the clinic were significantly lower than those at home, a concern for interpretation of clinic voids. Diagnostically, there was increased confidence amongst surveyed clinicians in home data without a corresponding increase in consistency of diagnosis. Perhaps the clinical significance of these new data is not yet known; its potential value is not being maximised. It would have been advantageous if the true urodynamic diagnosis for each patient was known, allowing more conclusive analyses.

Next, home urodiagnostics was performed by a group of men before and after disobstructive outlet surgery. This revealed for the first time that 20 % of participants did not experience an improvement in flow rate, an extremely surprising result. This statement may come under criticism from the clinical perspective, disputable as it may be, that only obstructed men will experience benefit from surgery. Again, to silence those critics, the study design would have gained from urodynamic confirmation of obstruction in each participant. This study showed home urodiagnostics to be a highly sensitive tool to measure objective outcome from treatment of obstruction in an individual and a group.

Multiple measurements allowed calculation of parameters which may better separate obstructed and unobstructed patients than flow rate alone. The parameter that changed in the highest proportion of patients, and best predicted subjective outcome, was the predicted value of Q_{max} at $V_{void} = 200$ ml according to the linear regression relationship for Q_{max} versus V_{void} . This, along with alternative methods of quantifying the relationship between Q_{max} and V_{void} , should be further investigated and evaluated in larger samples under more strict inclusion criteria.

Finally, home urodiagnostics was evaluated in a primary care setting, where at present most men with LUTS are treated empirically with an α -blocker. The results suggested that the addition of flow and volume data would help to guide GPs to the most appropriate management decision more quickly and with greater confidence, be that treatment for obstructions or overactivity, reassurance or referral. It is in this setting, perhaps, where home urodiagnostics shows most promise.

The patients recruited into the studies described in this thesis had varying underlying causes of LUTS. Inability to relate home urodiagnostic observations to specific disease mechanisms made interpretation of the results difficult at times. In retrospect, a study of home urodiagnostic data in a cohort with known urodynamic diagnoses may have been the best place to start. However, this would have presented practical issues given that relatively few men undergo urodynamic investigation, and even fewer emerge with a single definitive diagnosis. Further, the ability of urodynamic observations to predict surgical outcome is itself unproven and under question.

The PeePod has now had extensive clinical field testing in the patients for whom it is intended. Aside from this research, the device was specifically requested for clinical use in four patients who were unable to pass urine in the flow clinic.

Overall, the device was used by more than 100 patients with a success rate of over 99 %. This included one patient with Alzheimer’s disease and another in his 10th decade of life. It is clearly fit for purpose.

In conclusion, this work has shown that home urodiagnostics is a feasible alternative to conventional assessment and should improve the experience of men under assessment for LUTS. Larger clinical investigations should be performed to verify the beneficial effects measured and predicted within this thesis.

10.2 The future

The next step, therefore, will be to conduct a clinical trial using patient reported outcome in the most appropriate setting. A robust and adequately powered study, in which patients are randomised between home urodiagnostic and conventional assessment, should enable evidence-based recommendations to be made by decision-making bodies such as NICE. Application processes are underway for a randomised controlled trial involving patients referred to our secondary care benign prostate assessment clinic. Outcome measures will include symptomatic outcome, as measured by the IPSS questionnaire, and test efficiency, defined as the percentage of tests completed successfully according to a set of clinically important criteria. We hope that independent groups will conduct their own research into home urodiagnostics to further validate our findings. As an aside, a large database of normative home urodiagnostic data would also be beneficial.

On a slightly different note, there has been interest over the years in the PeePod’s suitability for use in adult females and paediatrics. Flow rate measurements are often performed for men in order to discern an obstructive pattern. Whilst obstruction of the female bladder outlet can occur, urogynaecology is chiefly concerned with the opposite complaint: incontinence. Therefore, measurements

of flow rate are of less value in female patients, who make up around one in ten visits to the flow clinic. However, the electronic voiding diary may be of more worth. The next engineering challenge could be to adapt the device with use by women (ShePod?) or children (PeeweePod?) in mind.

Regarding the future of home urodiagnostics in general, it is likely to gain momentum from the current trend towards home health and telemonitoring. As the next generations age, their adeptness with, and reliance upon, ‘personal digital assistants’ will no doubt bring about further change to diagnostics and health monitoring. A variety of healthcare ‘apps’ are already available, allowing users to monitor sleep patterns, diet and exercise, and a multitude of symptoms, to name but a few. Urology is no exception, with the recent development of several digital voiding diaries*. In addition to voided volumes, these allow symptoms and other important information such as episodes of incontinence and sensations of urgency to be documented. One can envisage in the near future a union of services like these and devices such as the PeePod, giving a complete picture of a patient’s LUTS in one place. Careful consideration would then need to be given to how this new combination of information is utilised.

10.3 Concluding message

The science of medicine is so often concerned with the big picture, clinical trials and overall trends, which masks the story of each patient. New methods by which we can study patients in more detail allow us to better understand their condition. After all, shouldn’t healthcare be about the individual?

* Examples include <http://www.ip-voiding-diary.com>, <http://www.elaros247.org.uk/services/>, and <http://www.urologysite.com/ElectronicBladderDiary>.

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Appendices

A1 Intellectual property


A1.1 Patent

Title	Urine flow measuring apparatus
Application numbers	UK: 1113749.4 International: PCT/GB2012/051941
Priority date	10/08/2011
Applicant	Newcastle upon Tyne Hospitals NHS Founda- tion Trust
Inventors	Michael Whitaker Michael Drinnan Alison Bray Clive Griffiths Robert Beckwith

A1.2 Trademark

Mark text	PeePod (text only)
Status	Registered
Class	10 - Surgical, medical, dental and veterinary apparatus and instruments, artificial limbs, eyes and teeth; orthopaedic articles; suture materials; sex aids; massage apparatus; supportive bandages; furniture adapted for medical use.
Filing date	11/05/2010
First advert	Journal 6846
Publication date	30/07/2010
Registration date	08/11/2010
Next renewal date	11/05/2020
List of goods or services	Class 10 - Medical apparatus, instruments and devices; urine flowmeters; parts and fittings for the aforementioned goods.
Proprietor	Newcastle upon Tyne Hospitals NHS Foundation Trust
ADP number	0970114001

A2 Registration of PeePod with the MHRA

<p>Safeguarding public health Our Ref: IVD000536</p> <p>Mr Michael Drinnan Regional Medical Physics Department Freeman Hospital Freeman Road Newcastle Upon Tyne NE7 7DN United Kingdom</p> <p>03 June 2010</p> <p>Dear Mr Michael Drinnan,</p> <p style="text-align: center;">IN VITRO DIAGNOSTIC MEDICAL DEVICES REGULATIONS 2002: REGULATION 44 Registration of manufacturers of <i>In-Vitro Diagnostic</i> Medical Devices and devices for Performance Evaluation</p> <p>Thank you for informing the Competent Authority of the company's details and for supplying the medical device information.</p> <p>Your registration has been recorded based on your declaration that you have determined that the device(s) fall within the definition of "In vitro diagnostic medical device", and that you have classified it/them correctly taking into account the intended purpose(s) and mode(s) of action. In accepting your registration, I should make clear that the Competent Authority does not examine each individual notification and therefore cannot and does not necessarily endorse these determinations. Neither does this letter represent any form of accreditation or approval by the UK Competent Authority.</p> <p>Your registration is based upon your declaration on the RG3 form and means that you should now be operating under the In Vitro Diagnostic Medical Devices Directive and the 2002 Regulations for the products you asked us to register, by fully complying with the essential requirements, CE marking those products or labelling them as such.</p> <p>If you stop placing devices on the market or if you are not complying with the Regulations you should inform us as required by the Regulations. You should be aware that it is an offence to place on the market CE marked devices that do not comply with the Regulations.</p> <p>The information you provided has been recorded against the reference number shown at the top of this letter, which we ask you to quote in all future correspondence and communications.</p> <p>Please inform us of any changes to:</p> <ul style="list-style-type: none">• the company information• additional generic groups of devices or, for Annex II or Self-Test devices, additional devices• discontinuation of a generic group of devices or, for Annex II or Self-Test devices, discontinuation of devices <p>Please use RG3, the Registration form, to tell us about any of these changes. A fee of £70 is payable for each change or set of changes notified.</p> <p><small>Medicines and Healthcare products Regulatory Agency Market Towers 1 Nine Elms Lane London SW8 5NQ T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk RegMivd Vers 3 Oct 2008</small></p>	
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Thank you for registering the following generic groups of devices

Part 5: IVDs which are not Annex II and not self-test devices

*For reagents, reagent products, calibration and control materials:
group by common technological characteristics and/or analytes*

New products: None

For performance evaluation: None

Neither: None

For other IVDs, group by appropriate indications

New products: None

For performance evaluation: None

Neither: None

Part 6: IVDs which are Annex II or self-test devices

***For reagents, reagent products, calibration and control materials:
group by common technological characteristics and/or analytes***

New products: None

***For performance evaluation:
PEEPOD***

Neither: None

For other IVDs, group by appropriate indications

New products: None

For performance evaluation: None

Neither: None

If you have any queries regarding your registration, please do not hesitate to contact us.

Yours sincerely



Sean Williams
Regulatory Affairs Administrator

Tel No: 0207 084 3325
Fax No: 0207 084 3112
Email: sean.williams@mhra.gsi.gov.uk

RegMivd Vers 3 Oct 2008

A3 Ethical approval



National Research Ethics Service **Newcastle & North Tyneside 1 Research Ethics Committee**

TEDCO Business Centre
Room 002
Rolling Mill Road
Jarrow
NE32 3DT

Telephone: 0191 428 3564
Facsimile: 0191 428 3432

24 March 2010

Miss Alison Bray
RMPD
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
NE7 7DN

Dear Miss Bray

Study Title: Assessment of home Uroflowmetry
REC reference number: 10/H0906/10
Protocol number: 1

Thank you for your letter of 09 March 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.
Where the only involvement of the NHS organisation is as a Participant Identification



National Research Ethics Service
Newcastle & North Tyneside 1 Research Ethics Committee

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13 May 2010

Miss Alison Bray
RMPD
The Freeman Hospital
Freeman Road
Newcastle upon Tyne
NE7 7DN

Dear Miss Bray

Study title: Assessment of home uroflowmetry
REC reference: 10/H0906/10
Amendment number: Amendment 1 05/05/2010
Amendment date: 05 May 2010

The above amendment was reviewed at the meeting of the Sub-Committee held on 11 May 2010.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter	Alison Bray	05 May 2010
Notice of Substantial Amendment (non-CTIMPs)	Amendment 1 05/05/2010	05 May 2010
Protocol	Version 2	05 May 2010
Participant Information Sheet: Patient Information Sheet	Version 3	05 May 2010
Participant Information Sheet: Volunteer Information Sheet	Version 3	05 May 2010
Questionnaire: Uroflowmetry Study Participant Guide	Version 2	05 May 2010
Summary/Synopsis	Version 2	05 May 2010
Questionnaire: Questionnaire 1 for Prostate UK Readers	Version 2	05 May 2010
Questionnaire: Questionnaire 1 for Study Participants	Version 2	05 May 2010



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Newcastle & North Tyneside 1 Research Ethics Committee

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13 October 2010

Miss Alison Bray
RMPD
Freeman Hospital
Freeman Road
Newcastle upon Tyne
NE7 7DN

Dear Miss Bray

Study title: Assessment of home uroflowmetry
REC reference: 10/H0906/10
Amendment number: Amendment 2 05/10/2010
Amendment date: 05 October 2010

The above amendment was reviewed at the meeting of the Sub-Committee held on 12 October 2010.

Ethical opinion

Favourable Opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	Amendment 2 05/10/2010	05 October 2010
Protocol	Version 3	05 October 2010
Summary/Synopsis	Version 2	05 October 2010
Participant Information Sheet: Volunteer Information Sheet	Version 4	05 October 2010
Participant Information Sheet: Patient Information Sheet	Version 4	05 October 2010
Questionnaire: Uroflowmetry Study Participant Guide	Version 3	05 October 2010



National Research Ethics Service
NRES Committee North East - Newcastle & North Tyneside 1

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15 July 2011

Miss Alison Bray
RMPD
Freeman Hospital
Freeman Road
Newcastle upon Tyne
NE7 7DN

Dear Miss Bray

Study title: Assessment of home uroflowmetry
REC reference: 10/H0906/10
Amendment number: Amendment 3 08/06/2011
Amendment date: 08 June 2011

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter	Alison Bray	10 June 2011
Notice of Substantial Amendment (non-CTIMPs)	Amendment 3, 08/06/2011	08 June 2011
Participant Information Sheet: Comparison of Home and Clinic Uroflowmetry	Version 5.1	08 June 2011
Participant Information Sheet: Home Uroflowmetry TURP Outcome Study	Version 5.2	08 June 2011
Participant Consent Form: Comparison of Home and Clinic Uroflowmetry	Version 3.1	08 June 2011
Participant Consent Form: Home Uroflowmetry TURP Outcome Study	Version 3.2	08 June 2011
Summary/Synopsis	Version 4.1	08 June 2011
Summary/Synopsis	Version 4.2	08 June 2011
Protocol	Version 4	08 June 2011
Questionnaire: Uroflowmetry Questionnaire	Version 1	08 June 2011
PeePod User Instructions	Version 1	08 June 2011



Health Research Authority

NRES Committee North East - Newcastle & North Tyneside 1

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14 December 2011

Miss Alison Bray
RMPD
Freeman Hospital
Freeman Road
Newcastle upon Tyne
NE7 7DN

Dear Miss Bray

Study title: Assessment of home uroflowmetry
REC reference: 10/H0906/10
Amendment number: Amendment 4 11/11/2011
Amendment date: 11 November 2011

The above amendment was reviewed at the meeting of the Sub-Committee held on 13 December 2011.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

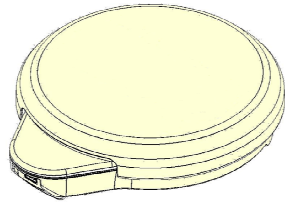
Approved documents

The documents reviewed and approved at the meeting were:

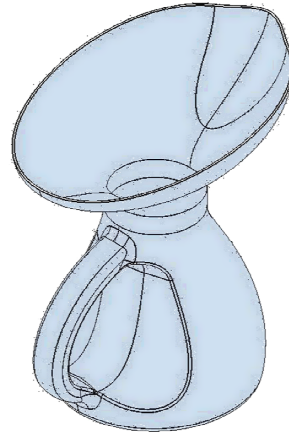
Document	Version	Date
Covering Letter	Alison Bray (RMPD)	11 November 2011
Notice of Substantial Amendment (non-CTIMPs)	Amendment 4 11/11/2011	11 November 2011
Protocol	Version 5	11 November 2011
Participant Information Sheet	Version 5	11 November 2011
GP/Consultant Information Sheets	Version 1	11 November 2011
Questionnaire: PeePod Questionnaire	Version 1	11 November 2011
Letter of invitation to participant	Version 1	11 November 2011
Flow Test Appointment Letter	Version 1	11 November 2011
Investigator CV	Matthew James Thomas	
Investigator CV	Dr Tom Schatzberger	
Investigator CV	Dr Richard James Holdsworth	
Investigator CV	Dr Nick Hargreaves	

A4 PeePod user instructions

PeePod user instructions



POD



JUG

Before using the PeePod for the first time, you must remove the pull tab from the bottom of the POD to activate the batteries.

- 1) Place the POD on top of the closed toilet lid, or on top of a flat surface which makes the PeePod a comfortable height to pass urine into.
- 2) Place the JUG on top of the POD – a green light on the POD will start flashing to tell you it is ready to use. **There is no on or off switch – the PeePod automatically knows when to turn itself on and off.**
- 3) Pass urine into the JUG – try to aim for the hole in the middle to minimise splashing. The green light on the POD will flash more quickly to tell you it has detected flow. **Try not to knock the jug during use.**
- 4) Once you have finished, pour away the urine and rinse out the JUG. **Do not rinse or submerge the POD. If necessary, wipe the POD with damp toilet roll or a wet wipe.**

A5 Study questionnaires

A5.1 Home versus conventional urodiagnostics

Participant study ID: _____

Home versus conventional urodiagnostics

Date: _____

Please answer the following questions by circling the number that reflects your response.

1. Please rate the burden of using the PeePod.

Not at all burdensome Very burdensome

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Why? _____

2. Please rate the burden of completing a frequency volume chart.

Not at all burdensome Very burdensome

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Why? _____

3. Please rate the burden of attending hospital for a urine flow test.

Not at all burdensome Very burdensome

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Why? _____

4. In the future, if you required investigation for urinary symptoms, how willing would you be to repeat using the PeePod at home?

Not at all willing Very willing

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Why? _____

5. In the future, if you required investigation for urinary symptoms, how willing would you be to repeat completing a frequency volume chart at home?

Not at all willing Very willing

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Why? _____

6. In the future, if you required investigation for urinary symptoms, how willing would you be to repeat the hospital urine flow test?

Not at all willing

Very willing

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Why? _____

7. In the future, if you required investigation for urinary symptoms, which would you prefer to repeat?

- Hospital flow test and frequency volume chart
 PeePod

Why? _____

8. Any further comments?

Thank you for completing this questionnaire.

A5.2 General practitioner survey

GP LUTS survey

1. Approximately how many men with a new complaint of lower urinary tract symptoms (LUTS) do you see per month? _____

2. For men with LUTS, please indicate how often you assess each of the following (tick one per assessment for each of Initial presentation, First review and Second review):

	Initial presentation			First review			Second review		
	Never	Less than half the time	More than half the time	Always	Never	Less than half the time	More than half the time	Always	
Prostate specific antigen (PSA)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Abdomen / genital examination	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Digital rectal examination (DRE)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Voiding diary / frequency volume chart	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Urine dipstick	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Symptom score questionnaire (e.g. IPSS)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Creatinine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Renal ultrasound scan	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Urine flow test	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Residual urine ultrasound scan	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other: _____ (please state)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other: _____ (please state)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other: _____ (please state)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

3. For men with LUTS, please indicate how often you use each of the following management options (tick one per option for each of Initial presentation, First review and Second review):

	Initial presentation			First review			Second review			
	Never	Less than half the time	More than half the time	Never	Less than half the time	More than half the time	Never	Less than half the time	More than half the time	Always
Fluid intake / lifestyle advice	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Watchful waiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
α -blocker e.g. tamsulosin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5- α reductase inhibitor, e.g. finasteride	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
α -blocker and 5- α reductase inhibitor combination	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anticholinergic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diuretic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other: _____ (please state)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other: _____ (please state)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other: _____ (please state)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

