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**MD Thesis**

**Exploring the non-invasive diagnosis of bladder outlet  
obstruction using a penile cuff**

**Christopher Henry Blake. MB BS, FRCS, FRCS(Urol)**

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## **Declaration**

The work presented in this thesis is the candidate's own.

Christopher Blake  
January 2010

## **Abstract**

### **Introduction**

It has been proposed that all men should undergo invasive pressure flow studies (PFS) prior to bladder outlet surgery. However, expense and morbidity limit the use of this investigation.

A non-invasive technique for measuring bladder contractility using controlled inflation of a penile cuff has been developed. In work in an experimental model there is also evidence to suggest that this technique may be used to measure urethral opening pressure.

The purpose of this thesis is to validate the penile cuff technique and to confirm whether this may be used to diagnose bladder outlet obstruction (BOO) and obviate the need for invasive PFS prior to bladder outlet surgery. We also aim to elucidate whether cuff measurements can provide a non-invasive estimation of urethral opening pressure.

### **Methods**

118 patients were investigated with free flow rates, invasive pressure flow studies, free cuff test, simultaneous cuff test and invasive PFS, and voiding urethral pressure profile (VUPP) measurements.

Cuff pressure at flow interruption “ $p_{\text{cuff.int}}$ ” was compared with isovolumetric bladder pressure as a measure of bladder contractility. This was then used in conjunction with urinary flow rate to test a proposed non-invasive nomogram for diagnosis of bladder outlet obstruction.

Cuff pressure at which flow rate starts to fall “ $p_{\text{cuff.knee}}$ ”, proposed as a measure of urethral opening pressure, was compared with estimations of urethral opening pressure taken from invasive pressure flow studies and VUPP’s.

## **Results**

$p_{\text{cuff.int}}$  provides a valid estimation of isovolumetric bladder pressure. When used in combination with flow rate measurements this can be used to diagnose or exclude BOO in approximately two thirds of men, using a modification of the ICS nomogram.

Although  $p_{\text{cuff.knee}}$  does not correspond precisely with the previously described measures of urethral opening pressure, there is reasonable evidence to support our hypothesis that  $p_{\text{cuff.knee}}$  may provide a simple and non-invasive estimation of urethral opening pressure.

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The line A, B, C, E represents a compressive obstruction with low velocity, related to low  $p_{\text{dp}}$  and high  $p_{\text{ves}}$ , high  $p_{\text{uo}}$ , and large cross sectional area. The line A, B, D, E represents a constrictive obstruction with high velocity, high  $p_{\text{dp}}$ , high  $p_{\text{ves}}$ , low  $p_{\text{uo}}$ , and smaller cross sectional area. If the length of the compressive component at the FCZ (B to C) is very short then the profile of pressure changes for compressive and constrictive patterns may

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### **Statement of Conjoint work**

A group of researchers at the Freeman Hospital, Newcastle initiated the first work in the area of non-invasive urodynamics pertaining to this thesis. The main investigators on the project, based in Newcastle were Clive Griffiths, Michael Drinnan (Medical Physicists), Stuart McIntosh, and subsequently Chris Harding (Clinical Research Fellows).

As outlined in the Introduction to this thesis (Chapter 1.3) the cuff test investigated was designed and built by the medical physics department in Newcastle. Initial experimental work, allowing fine tuning of the prototype, was carried out in Newcastle; as was the first clinical work looking at the non-invasive measurement of isovolumetric bladder pressure using the cuff.

Subsequently the Newcastle group contacted Professor Paul Abrams at The Bristol Urological Institute, with a view to collaboration on the cuff project. They wanted a second centre, with a proven record in the urodynamic field, to independently assess the cuff test, and to see if the Newcastle results could be replicated by an investigator who had had minimal training in the technique (Chapter 4.1). If the results were replicated with similar outcomes, thus validating the Newcastle work, then it was planned to combine the data from the two centres in order to apply the findings to a larger population looking at the cuff test as a diagnostic tool (Chapter 4.2). The final part of the collaborative project was to explore some of the early experimental work from Newcastle

looking at urethral opening pressures and to try and apply this in a clinical study (Chapter 4.3). These three components were intended to provide the work for this thesis and to dovetail with the work already performed in Newcastle and planned for the future.

At the start of my project I spent a week in Newcastle being introduced to the cuff machine and technique and discussing the background and aims of my study in order that my data would be compatible and comparable with those of Newcastle for the validation and combined parts of my study; and to plan the new work exploring urethral opening pressures.

On my return to Bristol I initiated my thesis project and gained local ethical approval. I undertook all patient recruitment, patient investigation, data collection and data analysis in Bristol (Chapters 2 and 3) independent of the Newcastle researchers. Newcastle provided Bristol with a cuff machine and installed it, linking it up with our urodynamics equipment.

During the two years of my research post I visited Newcastle, along with my local supervisor Professor Paul Abrams, approximately every six months. The purpose of these meetings was to present my preliminary results, discuss and review progress on the project, and exchange ideas on the implications of our findings and areas for future research and development. These discussions covered all parts of my thesis, in particular the combining of both sets of data and development of the cuff nomogram. For the urethral opening pressure part of the study there was much interest in my results and I

was grateful to receive help with the interpretation of these from the medical physicists, who undertook a supervisory role in addition to my two formal supervisors.

### **Acknowledgements**

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The staff of the Regional Medical Physics Department, Freeman Hospital, Newcastle, who provided help and direction with the initiation of this project, as well as building our

equipment, and support throughout the project. In particular I would like to thank Clive Griffiths and Michael Drinnan for keeping me on the scientific straight and narrow. Finally, I would like to thank my wife for her unswerving patience and support.

## **Abbreviations**

A	Area
A-G	Abrams - Griffiths
BCI	Bladder contractility index ( $p_{det.Qmax}+5Q_{max}$ )
BNI	Bladder neck incision
BOO	Bladder outlet obstruction
BOOI	Bladder outlet obstruction index ( $p_{det.Qmax}-2Q_{max}$ )
BOR	Bladder outlet relation
BPE	Benign prostatic enlargement
BPH	Benign prostatic hyperplasia
BPO	Benign prostatic obstruction
CSA	Cross sectional area
Ch	Charrière
d	Distance
DO	Detrusor overactivity
DU	Detrusor underactivity
F	Force
FCZ	Flow controlling zone
g	Gravity
h	Height
ICS	International Continence Society
IPSS	International Prostate Symptom Score
LPURR	Linearized Passive Urethral Resistance Relation
LUTS	Lower urinary tract symptoms
m	Mass
MUCP	Maximum urethral closure pressure
NPV	Negative predictive value
p	Pressure
p <sub>abd</sub>	Abdominal pressure
p <sub>cuff.int</sub>	Cuff pressure at which urinary flow is interrupted
p <sub>cuff.knee</sub>	“Knee pressure”. Cuff pressure at which flow starts to decline towards zero during cuff inflation
p <sub>det</sub>	Detrusor pressure
p <sub>det.isv</sub>	Isovolumetric detrusor pressure
p <sub>det.minQ</sub>	Detrusor pressure at minimal flow
p <sub>det.Qbeg</sub>	Detrusor pressure at start of flow
p <sub>det.Qend</sub>	Detrusor pressure at end of flow
p <sub>det.Qmax</sub>	Detrusor pressure at maximum flow
p <sub>dp</sub>	Driving pressure

$P_{uo}$	Urethral opening pressure
$P_{ura}$	Urethral pressure
$P_{ura.max}$	Maximum urethral pressure
$P_{ves}$	Bladder pressure
$P_{ves.int}$	Bladder pressure at cuff interruption of flow
$P_{ves.isv}$	Isovolumetric bladder pressure
$P_{ves.Qbeg}$	Bladder pressure at start of flow
$P_{ves.Qend}$	Bladder pressure and end of flow
$P_{ves.Qmax}$	Bladder pressure at maximum flow
$P$	Power
PFS	Pressure flow studies
PPV	Positive predictive value
PVR	Post void residual
$Q$	Urinary flow rate
$Q_{max}$	Maximum flow rate
$r$	Radius
RUPP	Resting urethral pressure profile
$t$	Time
$T$	Tension
TURP	Transurethral Resection of Prostate
URA	Group specific urethral resistance factor
$v$	Velocity
VUPP	Voiding urethral pressure profile
$V_{void}$	Voided volume
$W$	Work
$\Delta$	Change in
$\rho$	Density

## **1. Introduction**

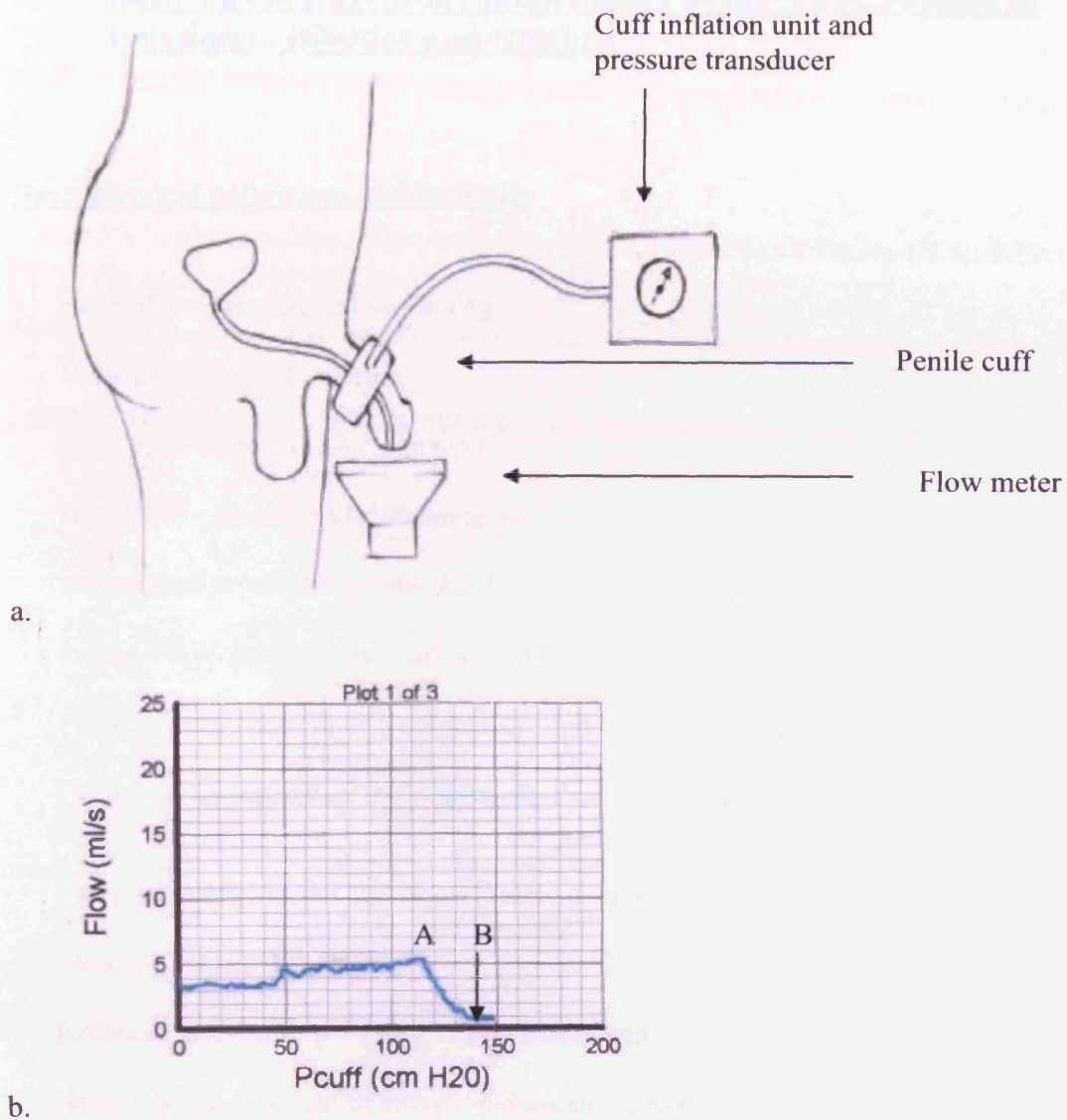
The purpose of this thesis is to validate a technique, using a penile cuff, inflated during voiding (Fig. 1.0a), for non-invasive assessment of detrusor contractility, and to confirm whether, in combination with free flow rate assessment, this can obviate the need for pressure-flow studies in some men prior to bladder outlet surgery. We are also trying to elucidate whether minimum urethral opening pressure may be measured non-invasively by comparison of cuff measurements (“the knee pressure”) (Fig. 1.0b), with voiding urethral pressure profiles and a value derived from the invasively measured minimum voiding pressure.

### **Hypotheses**

1. Cuff pressure at interruption of flow ( $p_{\text{cuff.int}}$ ) (Fig.1.b) corresponds to isovolumetric bladder pressure ( $p_{\text{ves.isv}}$ ).
2. That non-invasive urodynamics can reliably predict the presence or absence of bladder outlet obstruction (BOO) in a proportion of men being evaluated for lower urinary tract symptoms (LUTS).



3. In those patients with an identifiable “knee” pressure (Fig. 1.b), this corresponds to urethral opening pressure.



**Figure 1.0 a. Stylised representation of cuff machine. b. Plot of cuff pressure against flow during cuff inflation. Point A: “knee pressure” ( $p_{\text{cuff.knee}}$ ), point B: cuff pressure at flow interruption ( $p_{\text{cuff.int}}$ ).**

## **1.1 Basic Physics, Hydrodynamics and Physiology of Voiding in Relation to Bladder and Urethra**

### **Basic physical definitions and formulae**

Force (F) = pressure (p) x area (A)

Velocity (v) = distance/time

Flow (Q) = area (A) x velocity (v)

Work (W) = force (pA) x distance (d)

Incremental work ( $\Delta W$ ) = pA x  $\Delta d$

Power =  $\Delta W / \Delta \text{time} = pA \times \Delta d / \Delta t = pQ$

Pressure at the bottom of a column of fluid (p) = density ( $\rho$ ) x gravity (g) x height (h)

For water, and therefore approximately that of urine,  $\rho = 1 \text{ gml}^{-1}$ .

Potential energy (mass (m) gh) = kinetic energy ( $1/2 mv^2$ )

Thus  $p = gh = 1/2 v^2$

Bernoulli equation:  $p + 1/2 \rho v^2 + \rho gh = \text{constant}$

Based on conservation of energy and assuming density ( $\rho$ ) = 1, for a given urethral cross sectional area and an ideal fluid this may be presented:

intra-urethral pressure + constant x flow rate<sup>2</sup> = bladder pressure.

At constant flow a rise in velocity will lead to an associated fall in pressure.

### **Underlying concepts**

Micturition is a process under neuromuscular control, governed by the interplay between the expulsive action of the detrusor and urethral impedance to flow[1]. The only easily and accurately accessible parameters of voiding dynamics are bladder pressure, external flow rate and voided volume[2,3].

#### **Flow rate (Q)**

In urodynamic terms the rate of flow refers to the volume of urine that passes a given location in each unit of time and is measured in millilitres per second ( $\text{ml.s}^{-1}$ ). In the absence of ureteric reflux or a large bladder diverticulum it may be assumed that the rate of flow out of the bladder and through the urethra is equal to the externally measured flow rate[4]. Flow through a tube is a function of cross sectional area (A) and velocity (v) such that:

$$Q = v \times A$$

In benign prostatic obstruction (BPO) flow rate is governed by the prostatic urethra.[3]

## **Pressure (p)**

Pressure in urodynamic terms is expressed in terms of centimetres of water (cmH<sub>2</sub>O)[5].

It is a physical concept defined within a fluid as a force acting per unit area, to which no direction can be assigned[4], i.e. pressure is related to the force acting perpendicular to a surface in contact with the fluid.

$$p = \text{force (F)} / \text{area (A)}$$

## **Intravesical pressure ( $p_{\text{ves}}$ ), abdominal pressure ( $p_{\text{abd}}$ ) and detrusor pressure ( $p_{\text{det}}$ )**

In urodynamic practice intravesical pressure is defined as the pressure within the bladder; abdominal pressure is the pressure around the bladder, within the abdominal cavity, and can be estimated from the pressure within the rectum, vagina, or a bowel stoma. Detrusor pressure is that component of intravesical pressure that is created by forces within the bladder wall and is derived by subtraction of abdominal pressure from intravesical pressure ( $p_{\text{det}} = p_{\text{ves}} - p_{\text{abd}}$ ). During the work for this thesis these pressures have been measured per urethra and per rectum, using fluid filled catheters, with an external transducer using a reference level at the upper border of the symphysis pubis and zeroed to atmospheric pressure, i.e. atmospheric pressure = 0cmH<sub>2</sub>O, in line with the recommendations of the International Continence Society[6,7].

## **The mechanics of the bladder**

### **Storage or filling phase.**

Assuming the bladder to behave as a thin walled sphere then detrusor pressure is related to forces in the bladder wall:

$$p_{\text{det}} = F / \pi r^2$$

$$p_{\text{det}} = 2T/r \text{ (La Place's law)}$$

$$(r = \text{bladder radius, } T = \text{Tension, } \pi r^2 = \text{area of circle})$$

As the normally compliant bladder fills, the wall stretches. This leads to an increase in not only force and tension but also the radius.  $p_{\text{det}}$ , therefore, remains unchanged.  $F$ , and thus  $p_{\text{det}}$ , is also dependent on the rate of bladder filling. Therefore faster filling may result in a higher  $p_{\text{det}}$  being recorded[4].

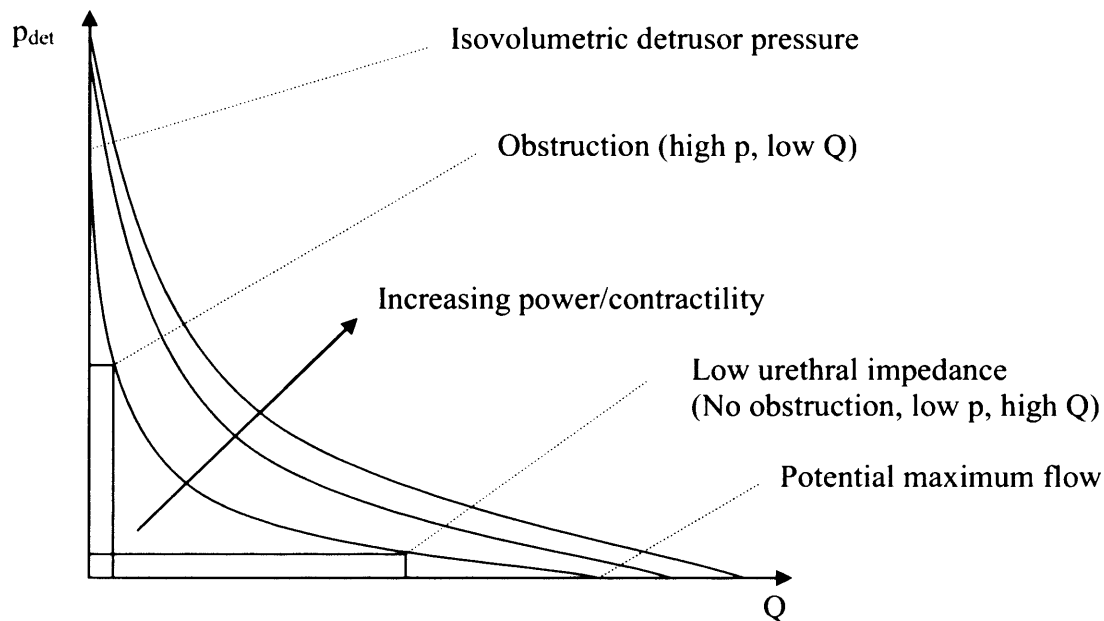
### **Voiding phase.**

At the start of micturition the detrusor contracts leading to an increase in  $F$  and thus  $p_{\text{det}}$ .  $p_{\text{det}}$  therefore reflects detrusor pump function. Abdominal straining, resulting in a raised  $p_{\text{abd}}$ , also acts to increase  $p_{\text{ves}}$ , although this is not required in normal voiding. However, if detrusor contraction is decreased, straining may help to facilitate voiding. Detrusor contraction provides the capacity to do work. For a given contraction pressure, more energy (per unit time) is required to produce a higher flow rate.

$$\Delta W = pA\Delta v$$

$$\text{Power} = \Delta W/\Delta t = pA\Delta v/\Delta t = pQ$$

Depending on urethral resistance, an adequate detrusor contraction may produce either a high  $p_{det}$  with a low maximum flow rate ( $Q_{max}$ ) or a low  $p_{det}$  with a high  $Q_{max}$  (Fig. 1.1.1) [2].



**Figure 1.1.1. Diagram illustrating the “trade off” between pressure and flow during bladder contraction, derived from the Hill equation[8]. Each curve represents a constant mechanical power generated by the contracting detrusor. If flow is interrupted  $p_{det}$  will move from the operating point on the curve to the isovolumetric value[4].**

Assessment of detrusor contraction and power thus requires measurement of  $p_{det}$  and  $Q$ . An alternative measurement that reflects detrusor contraction strength is the isovolumetric detrusor pressure ( $p_{det.isv}$ ) when  $Q = 0$  (Fig.1.1.1.). However, obtaining this value requires the interruption of the natural course of voiding. The mechanical

contraction strength generated by the detrusor ( $p_{det} \times Q$ ) does in fact vary during voiding because it is proportional to muscle fibre length and thus to bladder volume[3].

In normal bladder voiding, detrusor contraction continues until the bladder is empty. Duration of contraction is related to contractility[9]. A premature failure of this contraction before the bladder is empty is associated with a residual urine. Such a failure may be due to biochemical factors (such as an exhausted energy reserve, either due to detrusor underactivity or obstruction), mechanical factors (a thick bladder wall preventing collapse), temporal factors (an effect of myogenic detrusor rhythm) or neurological factors (an abnormal operation of voiding reflexes). A residual is due to an abnormality of detrusor function not a mechanical effect of the obstruction and thus may be due either to detrusor underactivity or bladder outlet obstruction or both[4].

## **The urethra**

### **Storage phase.**

The function of the urethra is to remain closed during filling, even in the presence of an increased bladder pressure, to prevent leakage of urine. The urethra has a number of properties that enable this to be achieved. It is collapsible and deformable with walls that are easily apposed. Any gaps remaining are blocked by a “mucosal seal”. Various forces promote apposition both intramural and extramural, in particular the contraction of the urethral and pelvic floor muscles. The urethral pressure at a given point along the urethra is the fluid pressure required to just allow fluid to flow past the point in question. The

maximal value of the urethral pressure ( $p_{ura.max}$ ) is the fluid pressure necessary to cause leakage through the urethra.  $p_{ves}$  is also able to cause leakage and so the difference between these pressures, the maximum urethral closure pressure (MUCP) is the reserve capacity of the urethra to prevent leakage.[4]

$$MUCP = p_{ura.max} - p_{ves}$$

The pressure needed to open the urethra rapidly is greater than the steady pressure needed to hold it open (the urethral opening pressure)[10]. This means that the reserve capacity to prevent a sudden leak may be greater than MUCP.

A minimum intraurethral fluid pressure is required to open the urethral lumen and keep it open. The calibre of the urethral lumen is dependent both on the distensibility and elasticity of the urethra as well as the internal static pressure. These vary along the urethral length[3].

An increase in abdominal pressure not only increases intravesical pressure but also MUCP by both mechanical effect on the proximal urethra and distal reflex activation of the periurethral muscles. This represents a natural defence against leakage[4].

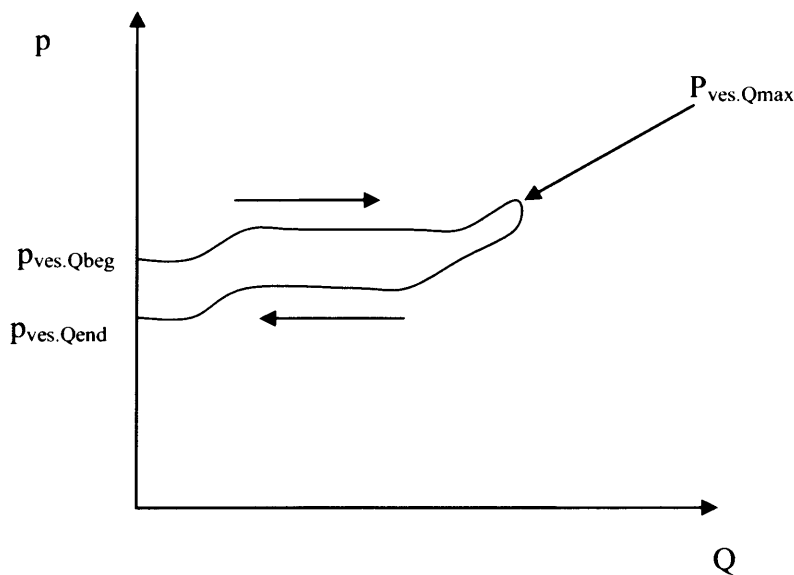
### **Voiding phase.**

Urethral resistance is the resistance presented to the contracting detrusor by the urethra. If resistance is high then the flow rate will be relatively low and the detrusor pressure high, and vice versa (Fig. 1.1.1). The elevated bladder pressure needed to force flow through



the urethra represents potential energy of the urine. Part of this energy is transformed into the kinetic energy of the external stream[4].

At the start of voiding the bladder contracts and the urethra relaxes. Initially the detrusor contracts in an isovolumetric fashion until  $p_{ves}$  achieves the minimum pressure required to open the urethra and urine enters the proximal urethral lumen. Once the proximal urethra is open the urine accelerates into the distal urethra and exits. Immediately before urine leaves the proximal urethra, static pressure is approximately equal to bladder pressure ( $p_{ves}$ ) and flow is 0. Thus urethral opening pressure ( $p_{uo}$ ) is approximately equal to the vesical pressure at which flow begins ( $p_{ves,Qbeg}$ ). This point may be identified from an x/y plot of pressure against flow (Fig. 1.1.2.)[3,11].



**Figure 1.1.2. Stylised representation of a plot of pressure against flow throughout the course of voiding.  $p_{ves,Qbeg}$  represents detrusor pressure at the point at which flow starts.  $p_{ves,Qend}$  represents the minimum vesical pressure during flow which, in**

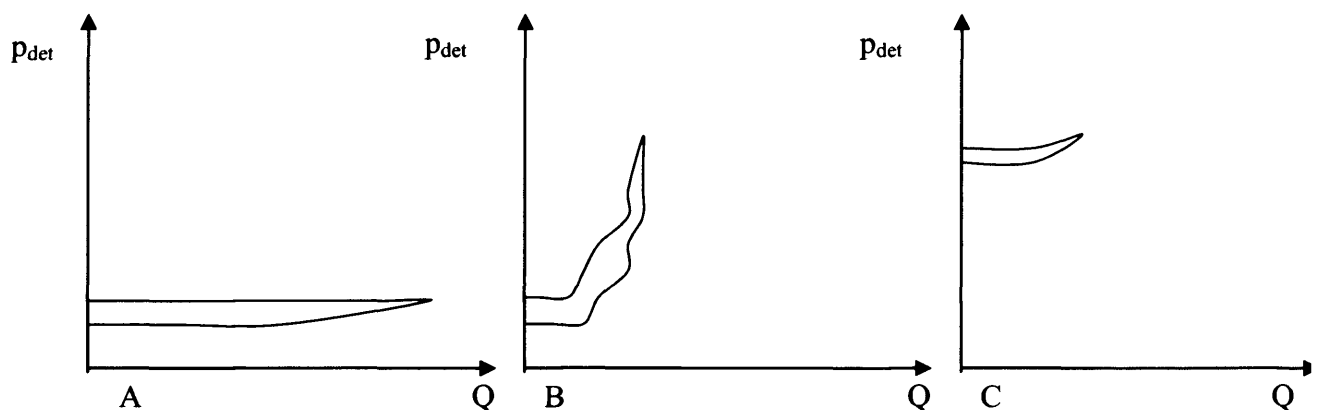
**this example is at the end of flow. Detrusor pressure at maximum flow ( $p_{det.Q_{max}}$ ) is used in conjunction with  $Q_{max}$  to diagnose obstruction.**

$p_{uo}$  is the minimum static pressure needed in the proximal urethra to allow flow. Only the component of  $p_{ves}$  that is greater than  $p_{uo}$  can act as the driving pressure, which can be converted into velocity and thus fluid flow[3]. At urethral opening, urine accelerates down the pressure gradient from proximal to distal. As the fluid velocity increases so the proximal static pressure falls. This would lead to collapse of the urethral lumen but for the rising detrusor pressure and power generated by the detrusor muscle. Thus not all pressure/energy generated by the bladder can be converted into velocity at the flow controlling zone because some pressure is needed to keep the outlet open[2,12].

Driving pressure ( $p_{dp}$ ) =  $p_{ves} - p_{uo} = 1/2v^2$  in the proximal urethra (from Bernoulli's equation above). Flow is proportional to both velocity and cross sectional area of the outlet. Therefore the properties of the flow controlling zone (FCZ), and its effect on flow, are governed by  $p_{uo}$  and the calibre of the urethral lumen. The relative highest opening pressure and relative smallest cross sectional area are located in the proximal urethra, at the level of the pelvic floor in normal men and in the prostatic urethra in those with BPO. The FCZ in BOO may be "compressive", as in BPO, with a raised urethral opening pressure or "constrictive", as with a urethral stricture, with a reduced cross sectional area. It is a reasonable approximation to consider the open FCZ as a tube with constant cross sectional area and constant static (lateral) pressure[3]. The relationship between  $p$  and  $Q$  during voiding is determined by the FCZ and is therefore dependent on  $p_{uo}$  and cross sectional area[2].

$p_{uo}$  is related to the mechanical properties of the urethra. If the urethra behaves as a perfectly elastic tube then the recorded pressure at start of flow should be the same as the pressure at the end of flow. In practice the  $p_{ves}$  at the end of flow is usually slightly lower than the  $p_{ves}$  at start of flow and this is due to delayed muscular relaxation and passive viscoelastic relaxation at the bladder outlet. This is often the case in BPO. The pressure at which the FCZ closes may be estimated by measuring voiding pressure 10mls prior to the end of voiding: the closing pressure ( $p_{ves,Qend}$ ) (Fig. 1.1.2.). This may be a more accurate measurement for the true minimum opening pressure required to allow flow[3,11].

In order to assess urethral resistance one must consider how flow rate and detrusor pressure vary during voiding: the bladder outlet relation (BOR) (Fig. 1.1.3.).

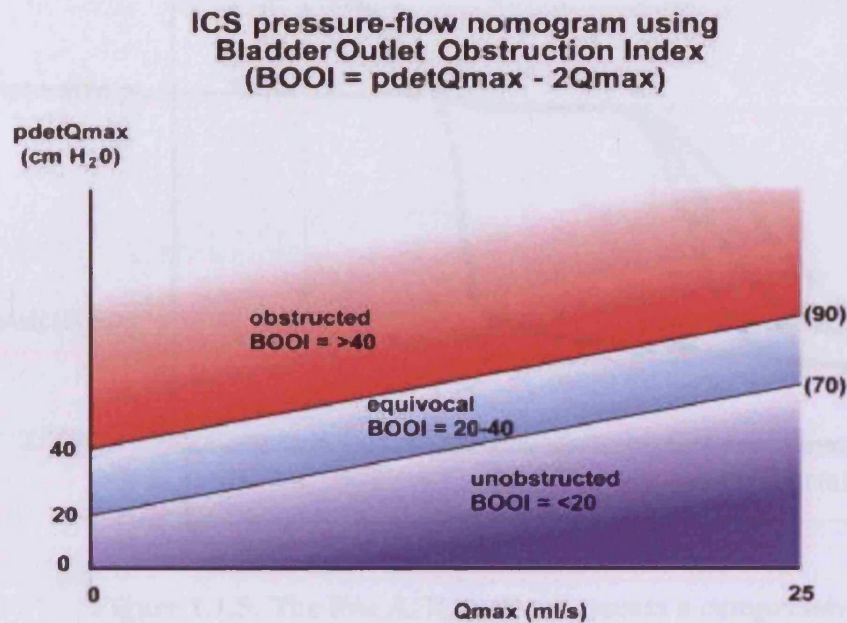


**Figure 1.1.3. Stylised representation of plots of pressure against flow in the course of a void. A: relaxed, unobstructed, distensible urethra allowing normal flow at low pressure. B: urethra obstructed by relatively rigid narrowing (“constrictive” obstruction), where flow is governed more by the cross sectional area of the FCZ. C: Distensible urethra with increased urethral opening pressure (“compressive” obstruction), flow rate is governed by the opening pressure at the FCZ[4].**

In the normal distensible urethra, with low relative resistance, this gives a nearly horizontal curve with a large change in  $Q$  for a small change in  $p_{det}$ , and a low opening pressure[3]. An upward curving slope indicative of a high pressure for a low flow, with low  $p_{uo}$  is suggestive of a “constrictive” obstruction, with little change in cross sectional area, whereas a “compressive” obstruction has a more horizontal curve, though at higher  $p_{uo}$ , leading to a low flow at high pressure. If resistance increases during voiding then pressure will increase and flow will fall[4]. Although the shape of this curve is related to urethral function, the actual values along the curve are related to detrusor function. Thus a normal shape with a reduced detrusor power produces a reduced  $Q_{max}$ . Bladder outlet resistance does not alter significantly with bladder filling, however, detrusor power does. Maximum voiding power increases with bladder filling up to volumes of 250-450mls (although this may be reduced at higher volumes) and for a normal shaped curve this increase in power gives a large rise in  $Q$  for a low rise in pressure. Therefore the greatest changes in  $Q_{max}$  occur in the lower volume range.

The diagnosis of BOO has relied on a number of nomograms: the URA, Schaefer’s and the Abrams Griffiths nomograms[13,14]. These three methods are fundamentally similar as they rely on the same measurements ( $Q$  and  $p_{det}$ ). They classify patients according to degree of bladder outlet obstruction, and differ only in terms of detail and complexity. As a result of the debate surrounding the use of these nomograms the International Continence Society have introduced a standardized ICS nomogram (Fig. 1.1.4.)[15,16].

This allows one to plot both the  $Q_{\max}$  and  $p_{\det.Q_{\max}}$  in order to diagnose bladder outlet obstruction.

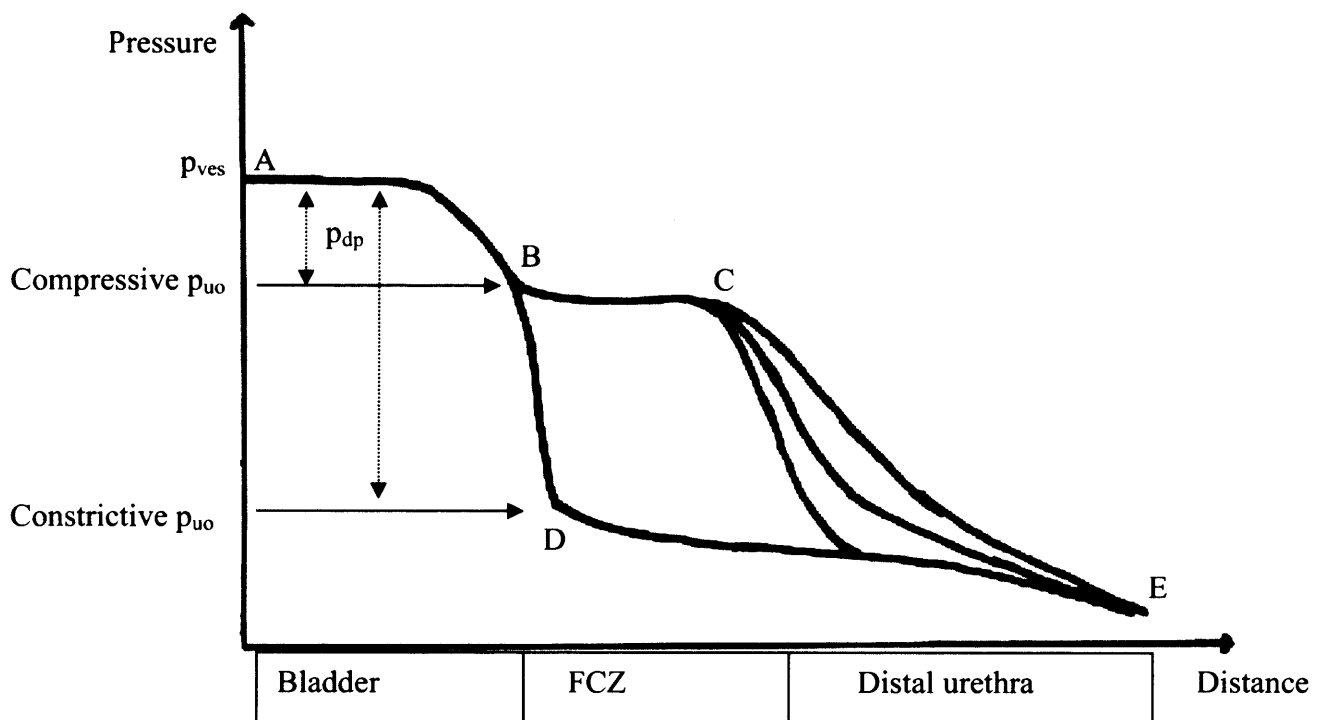


**Figure 1.1.4. The ICS nomogram for diagnosis of bladder outlet obstruction.**

#### Pressure distribution along the male urethra during voiding

During voiding, pressure falls along the urethra from bladder to distal urethra (Fig. 1.1.5).

The total available pressure is  $p_{\text{ves}}$ , which can be split into driving pressure ( $p_{\text{dp}}$ ), converted into velocity, and  $p_{\text{uo}}$ , i.e.  $p_{\text{ves}} = p_{\text{dp}} + p_{\text{uo}}$ . In a normal contractile bladder with normal outlet resistance at the FCZ,  $p_{\text{uo}}$  will be relatively low and thus a greater proportion of  $p_{\text{ves}}$  may be converted to velocity.



**Figure 1.1.5. The line A, B, C, E represents a compressive obstruction with low velocity, related to low  $p_{dp}$  and high  $p_{ves}$ , high  $p_{uo}$ , and large cross sectional area. The line A, B, D, E represents a constrictive obstruction with high velocity, high  $p_{dp}$ , high  $p_{ves}$ , low  $p_{uo}$ , and smaller cross sectional area. If the length of the compressive component at the FCZ (B to C) is very short then the profile of pressure changes for compressive and constrictive patterns may look similar. Downstream in the distal urethra (C to E and D to E) the pressure fall may be rapid or prolonged and may vary due to distal pressure gradients, for example at the pelvic floor, but this will not affect Q as this is unchanged downstream of the FCZ.**

With a compressive obstruction, such as in BPO, it is thought that the FCZ moves proximally from the pelvic floor to the bladder neck and prostate and the bladder operates at a higher  $p_{ves}$  with a higher  $p_{uo}$  at the FCZ, with subsequently a more pronounced pressure drop from the bladder neck/prostate across the pelvic floor[3,12]. In compressive obstruction  $p_{ves}$  is raised because it must overcome a raised  $p_{uo}$ . Once the urethra is open it has a large cross sectional area and therefore, despite a low velocity, related to the small pressure change across the FCZ, an adequate flow may be generated.

In constrictive obstruction  $p_{ves}$  is raised because although  $p_{uo}$  is still low the urethral cross sectional area is small. Therefore a large velocity is required, from a large pressure drop across the FCZ, to generate the same flow rate.

## **1.2 Lower Urinary Tract Dysfunction in Men**

Benign prostatic hyperplasia (BPH) is an age related histological change that may lead to non-malignant enlargement (BPE) of the prostate gland that may or may not result in bladder outlet obstruction in men[17]. In 2004-5, 28 000 prostatectomies were performed in the UK[18] and it is presumed that these operations are performed for the relief of bladder outlet obstruction (BOO)[13]. At our hospital this equates to approximately 250 per year for a catchment population of 475 000. However, it has been reported that prostatectomy, using current indications, fails to bring about symptomatic improvement in approximately one quarter of patients[19,20].

The diagnostic evaluation of these patients, presenting with lower urinary tract symptoms (LUTS), is an area of controversy and is primarily based on symptoms, prostatic enlargement and functional voiding variables such as flow rate and post void residual (PVR)[21].

There is, at best, only a poor association between LUTS and objective measures of voiding such as maximum flow rate ( $Q_{\max}$ ), post void residual and voided volume[22]. Equally there is little or no correlation between the various symptoms and pressure flow studies[23]. Low flow rate may be associated with either BOO[24,25] or detrusor underactivity (DU)[26]

Pressure/flow studies (PFS) are currently recognised as the gold standard for the diagnosis of bladder outlet obstruction. These do, however, come with a number of



disadvantages; they are time consuming, invasive and expensive. They also carry with them some morbidity to the patient. In the UK, the majority of men are offered prostatectomy on the basis of symptoms and a low  $Q_{\max}$ [19]. However, it has been suggested that use of pressure-flow studies should be mandatory prior to surgery[13]. It is, perhaps, the invasive nature of this test and its cost that limits its application[19] and a variety of non-invasive methods have been suggested to try and circumvent the need for “invasive” urodynamics[27].

### **Classification of Disorders of Bladder and Urethral Function**

As with any patient, assessment should start with a full history and physical examination. Lower urinary tract symptoms may be divided into storage symptoms, such as daytime frequency, urgency and nocturia, and voiding symptoms, such as hesitancy, slow stream and terminal dribbling[6]. Enquiry should also be made as to neurological symptoms and previous surgery. Physical examination, in all patients, should look for the presence of a palpable bladder or abdominal or pelvic masses, neurological signs in the lower limbs and loss of perianal sensation or anal tone (supplied by S2-4, the nerve roots carrying parasympathetic innervation to the bladder and urethra). In men, one should look for meatal stenosis, and prostatic size and consistency should be assessed. Following clinical assessment and urodynamic investigation it should be possible to classify patients into categories of storage or voiding dysfunction.

## **Vesico-urethral Storage Function**

**Disorders of bladder sensation during filling.** Sensation may be absent, reduced, normal or increased.

**Disorders of detrusor function during filling.** Detrusor overactivity is the urodynamic observation of involuntary detrusor contraction during the filling phase, which may be spontaneous or provoked. This may be neurogenic, in the presence of neurological disorders, or idiopathic. Such involuntary contractions may lead to detrusor overactivity incontinence. Bladder compliance describes the relationship between change in bladder volume and change in detrusor pressure; the normal bladder has high compliance, i.e. a large change in volume during filling with minimal change in pressure.

**Disorders of urethral function during filling.** The urethral closure mechanism during storage may be competent or incompetent. If incompetent it will allow leakage of urine in the absence of a detrusor contraction. Urodynamic stress incontinence is an urodynamic diagnosis where there is involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction.

## **Vesico-urethral voiding dysfunction**

**Abnormal detrusor activity.** The detrusor muscle may be underactive or acontractile leading to a reduced flow rate, prolonged void or failure to achieve complete bladder emptying.

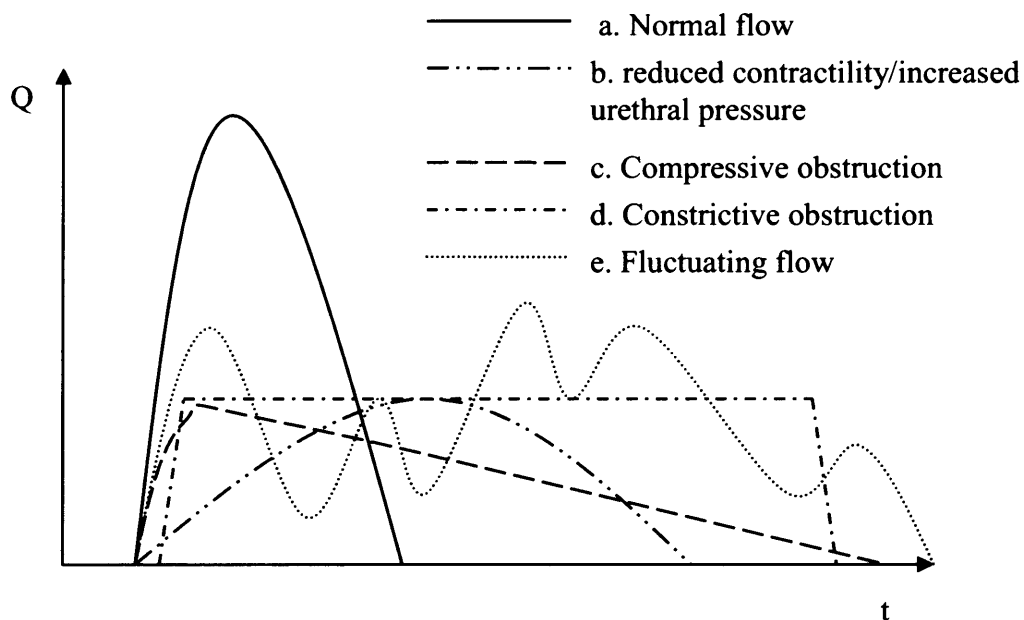
**Abnormal urethral function.** This may be due either to obstruction, which may occur at any point between bladder neck and external urethral meatus, such as an enlarged prostate or urethral stricture, or to urethral overactivity. Bladder outlet obstruction is the generic term for obstruction during voiding and is characterised by increased detrusor pressure and reduced urine flow rate as seen on urodynamic pressure/flow studies. Dysfunctional voiding is an intermittent or fluctuating flow rate due to involuntary contractions of the periurethral striated muscles, in neurologically normal individuals. Detrusor sphincter dyssynergia is where a detrusor contraction occurs concurrently with an involuntary contraction of the urethral/periurethral striated muscles; this typically occurs in patients with supra-sacral lesions of the spinal cord and is uncommon in lesions of the lower cord. Non-relaxing urethral sphincter obstruction usually occurs in patients with sacral or infra-sacral lesions of the cord and is characterised by a non-relaxing, obstructing urethra resulting in reduced urine flow[6].

### 1.3 Assessment of Bladder Outlet Obstruction

#### Flow rate Assessment[7]

Uroflowmetry is non-invasive and relatively inexpensive and is an indispensable first line screening test in those presenting with suspected lower urinary tract dysfunction. It produces both objective and quantitative information which reflects the relationship between detrusor and outlet function.

During normal flow the detrusor contracts and urethra relaxes. This produces a typical smooth bell shaped flow rate curve with a high  $Q_{\max}$ . Curves with other shapes: flat, asymmetric, intermittent or fluctuating suggest abnormal voiding but are not specific as to the cause of voiding dysfunction (Fig. 1.3.1).

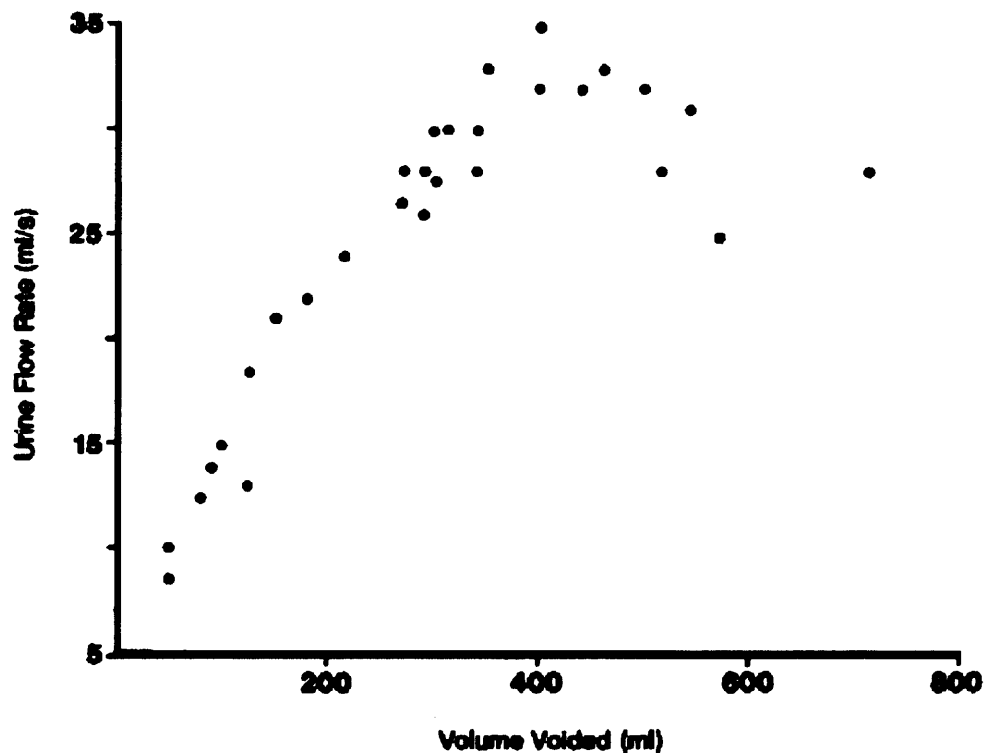


**Figure 1.3.1. A variety of common flow rate patterns.**

In normal voiding once  $p_{u0}$  is reached the urethra opens widely and the normally contractile detrusor produces a symmetrical flow pattern with high  $Q_{max}$  (Fig.1.3.1 a). The curve is smooth because its shape is determined by the kinetics of the detrusor contraction. If detrusor power is decreased or there is a constant increase in urethral pressure a longer, flatter curve will be produced with a lower  $Q_{max}$  (Fig.1.3.1 b). A constrictive obstruction, such as a urethral stricture, with a reduced urethral cross sectional area, will result in a plateau like flow curve (Fig.1.3.1.c). A compressive obstruction with an increased  $p_{u0}$  will produce an asymmetric curve with reduced  $Q_{max}$  and prolonged tail (Fig.1.3.1.d). This pattern may also be seen in patients with a weak detrusor. Fluctuations in flow rate (Fig.1.3.1.e) may be due to fluctuations in detrusor contraction, abdominal straining, or changes in outlet resistance, for example in pelvic floor contraction, intermittent sphincter activity. Although these patterns are identifiable in some patients, they are not present in all.

It is not possible to make a categorical diagnosis of BOO on the basis of flow rate alone. 88% of patients with a  $Q_{max} < 10 \text{ ml.s}^{-1}$  are obstructed but this falls to 57% of patients with  $Q_{max} 10\text{-}15 \text{ ml.s}^{-1}$  [28].

As the bladder volume increases the detrusor muscles become more stretched and there is an increase in the potential bladder power and work associated with the contraction. Thus at bladder volumes below 150mls  $Q_{max}$  is reduced. At volumes above 400-500mls the detrusor may become overstretched and contractility may decrease [7] (Fig.1.3.2.).



**Figure. 1.3.2. Multiple flow rates in the same patient at different voided volumes.**

$Q_{\max}$  is reduced at low and high voided volumes.

### **Pressure flow studies**

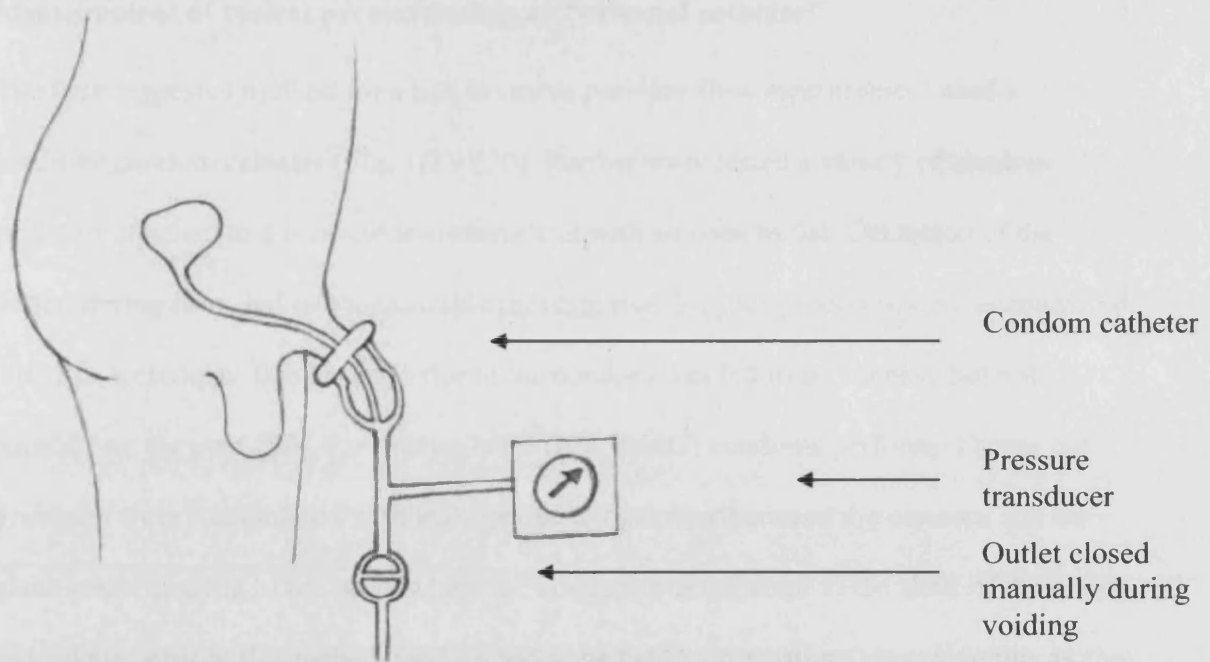
As discussed above simultaneous measurement of detrusor pressure and flow during voiding allows the demonstration of bladder outlet obstruction and such pressure/flow studies are currently the gold standard for diagnosing BOO. Patients with a high detrusor pressure during voiding in association with a reduced flow rate may be categorised as obstructed using the ICS nomogram and Bladder Outlet Obstruction Index (BOOI)[15,16](Fig.1.1.4.). Similarly patients with a low BOOI, either associated with

low voiding pressure and high  $Q_{\max}$  or low voiding pressure and low  $Q_{\max}$ , may be classified as unobstructed. In the latter case a measure of contractility may be used: the Bladder Contractility Index ( $BCI = p_{\det}Q_{\max} - 5Q_{\max}$ ).  $BCI < 100$  implies a weak detrusor and  $BCI > 150$  a strong detrusor[11,16].

### **Non-invasive Urodynamics**

#### **Non-invasive techniques for the measurement of isovolumetric bladder pressure**

Two promising techniques involve the non-invasive measurement of isovolumetric vesical pressure, coupled with a free flow rate, to achieve a diagnosis of bladder outlet obstruction. The first of these methods uses an external condom catheter (Fig.1.3.3.)[29,30] and the second an inflatable cuff around the penis (Fig. 1.0 a.)[31,32]. Both of these methods rely on the occlusion of urinary flow and measurement of the vesical pressure transmitted along the fluid column between the bladder and the site of occlusion.



**Figure 1.3.3: Modified condom catheter for non-invasive measurement of bladder pressure during voiding.**

The isovolumetric vesical pressure, thus measured, is that generated by the contraction of the bladder against a closed outlet. Theoretically this measurement should allow the differentiation between a low flow rate secondary to an obstruction as opposed to a low flow due to detrusor underactivity.

A third technique, which does not measure pressure directly, involves manual compression of the penile urethra during voiding (pinching the penis) and analysis of the resulting flow rate patterns. The principle underlying this technique is that the magnitude of flow rate change seen is proportional to the isovolumetric vesical pressure.



### **Measurement of vesical pressure using an “external catheter”**

The first suggested method for a non-invasive pressure-flow measurement used a modified condom catheter (Fig. 1.3.3)[30]. Further work tested a variety of condom catheters attached to a pressure transducer and with an open outlet. Occlusion of the outlet, during flow, led to a measurable pressure rise. Various problems were encountered with this technique. The pressure rise in the condom was felt to be “uneasy but not painful” on the penis[33]. Low compliance (less elastic) condoms performed better but problems were encountered with leakage due to backflow between the condom and the glans penis/foreskin to the point where the condom was adherent to the shaft of the penis. Indeed the penis with attached condom had to be held by the patient to prevent this as pressure increased[33].

In order to assess the potential diagnostic accuracy of this technique the results of invasive PFS were analysed for 297 patients[34]. Patients were classified using the urethral resistance parameter URA into obstructed and unobstructed groups. The mathematically derived detrusor contractility measure,  $W_{max}$ , [35] was used as an estimation of isovolumetric pressure and taken in conjunction with the  $Q_{max}$ , obtained from the PFS, this allowed correct identification of patients as obstructed/unobstructed in 89%.

Subsequent experiments by the same group looked at the effect that the interruption of flow had on voiding and at the relationship between maximum isovolumetric pressure and bladder volume, in 11 healthy volunteers[36]. Again an incontinence condom was

used, now stiffened with adhesive tape, to lower compliance by stopping the condom distending. Flow rates were not found to be significantly different with or without the condom, nor was “resumed flow” significantly altered by each interruption of the stream. Thus a number of measurements were possible from each void.

The isovolumetric pressure measurements taken between several voids, at low voided volumes, were not always consistent. This was thought to be due to closure of the urethral sphincter during interruption of the urinary stream, although the reasoning for this is unclear. However, at larger volumes a clearly defined optimum isovolumetric pressure/voided volume relationship was revealed with highest isovolumetric pressures seen at voided volumes of 150-320mls. This could certainly be explained by the increased work/power seen in more stretched detrusor muscle fibres (Fig.1.3.2.). Taking this into consideration, a reliable estimate of pressure could be obtained from a number of pressure measurements in a single void.

Again problems were encountered with this method. Leakage occurred from the condom in a small number of subjects (approx 5% of all voids) and these were excluded from the study. Some patients were also excluded because of involuntary closure of their urethral sphincters. Inappropriate sizing of the condom was also found to lead to problems: if the condom was too large it would accommodate too much urine and lead to a slowed pressure rise and an overshoot in flow, above steady state  $Q_{\max}$ , after voiding recommenced.

Validation investigations of the condom technique have also been undertaken by another Dutch group[37]. Various problems were highlighted. First was the determination of the ideal moment at which to interrupt flow, as stopping flow too early leads to an underestimation of  $Q_{\max}$ . Further problems were perceived as relating to pressure measurement: for good pressure transmission the bladder neck and urethra must remain open, as the “condom catheter” is occluded, in order to maintain a continuous fluid connection between the bladder and the point of pressure measurement (a side arm from the tube attached to the condom outlet). To measure isovolumetric pressure the bladder pressure and condom pressure must equilibrate, and this equilibration is dependent on the elastic properties of both the urethra, the condom and the sidearm connecting to the pressure transducer. The rate at which the pressure rise occurs in the condom is inversely proportional, both to the urethral resistance, and to the compliance in the condom and urethra: if the urethra/condom is more compliant equilibration will take longer, which in turn may result in inhibition of the detrusor contraction. Ideally occlusion of the outlet should be as proximal as possible to minimise the effect of compliance.

In conventional pressure/flow studies, abdominal pressure is measured in order to assess the effect of abdominal pressure changes on voiding function. This had not been done in van Mastrigt’s previous experiments and therefore it was not known to what extent abdominal straining might have affected the values of the isovolumetric measurements. Gommer showed that straining did result in a rise in intravesical pressure reflected in a higher condom pressure[37]. A subsequent study[38] has shown that abdominal straining interferes with the transmission of pressure from the bladder to condom. This was

assumed to be due to a compressive effect on the urethra/prostate above the pelvic floor. In younger (not obstructed) men straining results in an increase in flow and therefore will increase condom pressure, however, in BOO straining does not increase, and can decrease flow, which might reduce condom pressure[39].

A variety of condoms, with measures to reduce compliance were evaluated[37] These included the use of tape, cardboard and foil wrapped around the condom and were variously successful. The weight of the closure valve on the condom required this to be supported by the patient during the test, in order to prevent the condom from being pulled off.

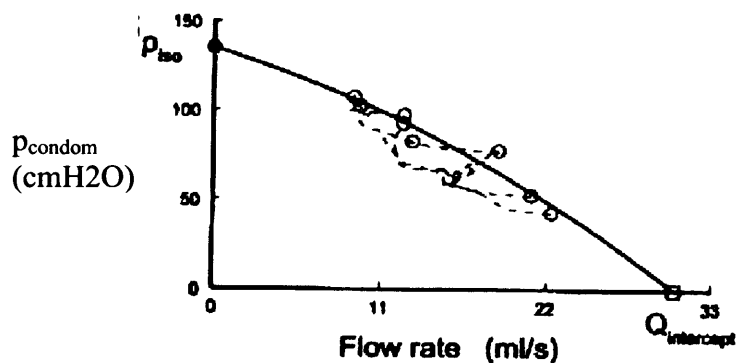
Radiographic studies of the urethra during occlusion of the catheter do show that the bladder neck and urethra remain open and that there is an open fluid connection between bladder and catheter[37]. Condom pressure rises rapidly when the flow valve is closed and this does allow good transmission of intravesical pressure to the condom and pressure transducer. However, simultaneous invasive measurements showed that, in a proportion of cases, condom pressure did not reach bladder pressure although condom pressure had reached a plateau. This was due to a continued rise in intravesical pressure after valve closure. This rise is due to the trade off between pressure and contraction velocity/flow during voiding: as the bladder changes from a partly isotonic contraction to an isovolumetric contraction, contraction velocity is converted into increased pressure[4,40] This, in turn, leads to a continued disparity between condom and bladder pressure, continuing distension within the urethra and condom and a steady state may not

be achieved[29]. The result is that by non-invasive measurement of the pressure in the condom, it is not possible to judge whether a steady state has been reached. Furthermore, if there is a prolonged time for pressure increase in the condom during interruption, detrusor inhibition may occur, with a consequent underestimation of  $p_{ves.isv}$ .

It was found that there was good agreement between externally and invasively measured pressures in non-obstructed patients ( $4.0 \pm 9.2 \text{ cmH}_2\text{O}$ , mean $\pm$ SD,  $n=15$ ) but less good agreement in obstructed patients ( $23.5 \pm 27.5 \text{ cmH}_2\text{O}$ , mean $\pm$ SD,  $n=11$ ). The reason for this is unclear and the authors have proposed a variety of explanations. It was felt that the relatively higher pressures seen in the obstructed bladder might have led to a greater difference between bladder and condom pressures and that steady state might not have been achieved[29]. An alternative explanation is that in obstructed men there is premature closure of the bladder neck and urethra[41]. Despite this, external pressures in the obstructed group were significantly higher than in the non-obstructed group. External pressures were also dependent on bladder volume[29].

A further development of this method has been to use a variable outlet resistance condom catheter[41]. This technique tries to circumvent some of the problems associated with the condom catheter. By altering the outlet resistance from the catheter, an estimate of isovolumetric pressure was made. This was achieved by fitting a second order polynomial curve to the various peak pressures versus flow rate for each outflow resistance, the intercept of this curve on the pressure axis at zero flow being taken as estimated isovolumetric pressure (Fig.1.3.4.). Flow was not completely obstructed and

therefore it was certain that a continuous column of fluid was present between bladder and condom and that the sphincter was open. This was also thought to reduce the risk of detrusor inhibition. The measured and estimated values were compared with non-invasively obtained isovolumetric pressures taken in the same normal subjects in a study the previous year. None had had an alteration in flow rate in the intervening period. Measurements were not validated against invasively obtained pressure data. In these normal subjects, the condoms again needed additional taping to reduce compliance, but no leakage was observed. Outlet resistance was increased in a stepwise fashion and by measuring the associated condom pressures an isovolumetric bladder pressure value was extrapolated. When compared to the previously obtained non-invasive isovolumetric pressures the mean difference between estimated and measured pressures was  $0 \pm 6$  (SD) cmH<sub>2</sub>O. However, it was again shown that for these measurements to be accurate a certain, minimum Q<sub>max</sub> of approximately 5-6 ml/sec was required[42].



**Figure 1.3.4. Condom pressures as a function of flow rate measured at 3 voidings in the same subject. Highest condom pressures and flow rates were automatically selected (open circles). Second order polynomial was fitted to these points and separately measured isovolumetric pressure ( $p_{iso}$ ).  $Q_{intercept}$ : flow rate axis intercept.[41]**

A recent study has compared the classification of patients using invasive PFS, externally measured bladder pressure (by the condom method) and flow rate. 30% of patients could be correctly classified on the basis of free flow rate ( $Q_{\max} < 4.5 \text{ ml/sec}$ : obstructed,  $Q_{\max} > 13.8 \text{ ml/sec}$ : unobstructed). In the remaining patients, who could not be classified correctly by flow rate alone, a combination of flow rate and external pressure were used in comparison to PFS diagnosis. If obstructed and equivocal groups, as defined by the ICS nomogram, were taken together this led to an agreement with PFS diagnosis in 90%. However, if unobstructed and equivocal groups were taken together the agreement fell to 67%[38].

The condom method of obtaining an isovolumetric bladder pressure measurement, although in theory possible, does have some significant problems. First are practical considerations with the condom itself. Compliance of the condom leads to a prolonged time for pressure to reach a steady state. Various methods have been attempted to reduce compliance by taping the condom with various materials (tape, cardboard, film and foil) and by preloading the condom by stepwise occlusion of the outlet. This does indeed reduce compliance but at the expense of simplicity. Pressure rise in the condom can cause back leakage but this seems to have become less of a problem over the course of the series of experiments.

In summary, for bladder pressure to be measured accurately, as previously mentioned, a continuous column of fluid (urine) between bladder and condom is required: this has been confirmed to occur radiologically. However, if the pressure rise in the condom is too

prolonged this can lead to involuntary inhibition of the detrusor contraction or closure of the external sphincter[37]. Many of these experiments have been done without the simultaneous invasive measurement of bladder pressure, which would be needed to validate the technique. Where intravesical pressure has been measured, the technique is less accurate at low flow rates ( $Q_{max} < 5-6$  ml/sec). At present, this technique is not ready to replace invasive urodynamics but is being used in a longitudinal study to assess the natural history of detrusor contractility in response to age related prostatic enlargement[43]. The aim of this study is to recruit 1200 healthy male volunteers and to assess their condom pressures, flow rate, prostatic volume on ultrasound and International Prostate Symptom Score.

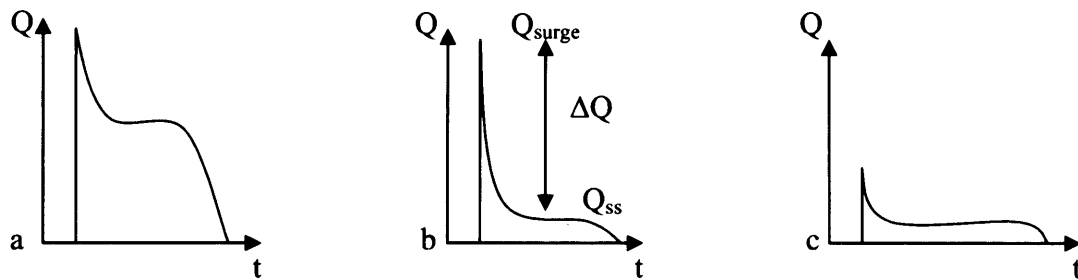
#### **Measurement of bladder pressure using penile compression by a cuff**

It has been proposed that inflation of a cuff around the penis during voiding should give a cuff pressure that equates to the isovolumetric pressure in the bladder, similar in principle to the non-invasive measurement of blood pressure. This has been done in two ways, by occluding the urethra prior to the initiation of voiding, then releasing the pressure to allow voiding[31], and by occluding the urethra after voiding has commenced[32].[44]



### *The cuff deflation technique*

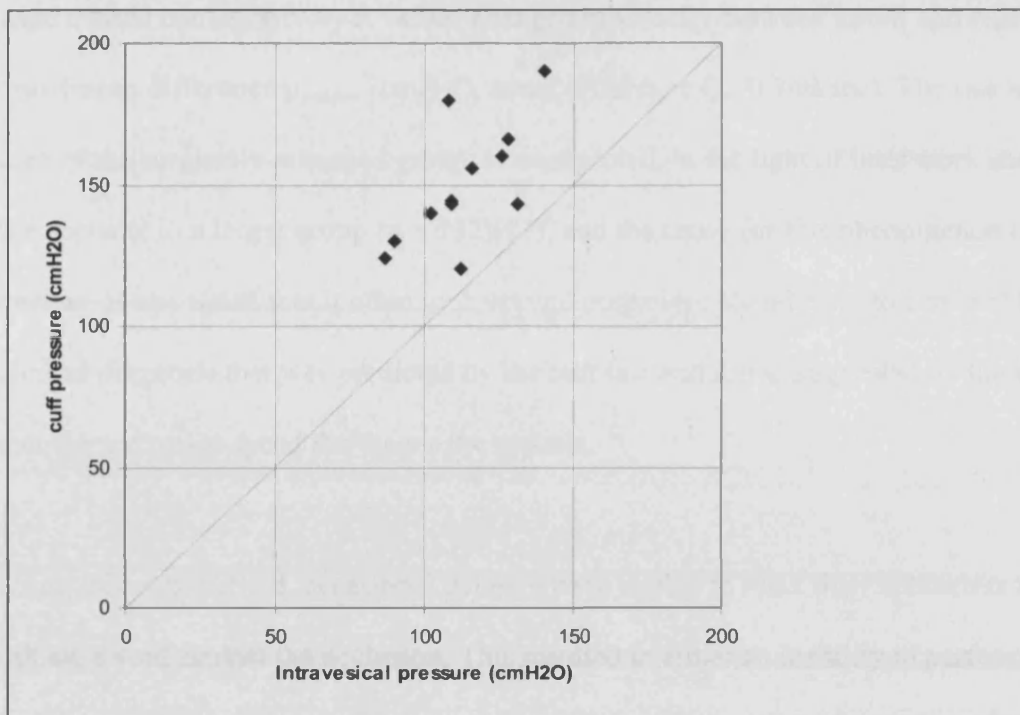
The first of these methods uses a cuff to obstruct the urethra[31,45]. In the original description, the cuff was wrapped around the penile shaft and inflated to a pressure of 250cmH<sub>2</sub>O. Subjects were then asked to initiate voiding against the occluded urethra. Theoretically this allowed the bladder to contract in an isovolumetric fashion and for a column of urine to develop between the bladder and cuff and for pressure to be transmitted down the open urethra to the point of occlusion. This was not validated radiologically. As the patient felt urine entering the urethra he would release pressure from the cuff, by means of a button, allowing the cuff to slowly deflate until flow commenced, at which point intraurethral pressure should be equal to or greater than cuff pressure. Once a flow rate of 1ml/sec was detected in a flow meter, the cuff was rapidly deflated to allow voiding. When the cuff deflated rapidly a characteristic surge of flow ( $Q_{\text{surge}}$ ) was seen as urine was expelled from the distended urethra, which then settled to a more normal, steady state flow ( $Q_{\text{ss}}$ )(Fig 1.3.5.).



$Q_{ss}$  = steady state flow,  $Q_{surge}$  = peak flow

**Figure 1.3.5. Characteristic flow patterns seen after release of the compressed urethra during voiding. a. Normal flow with normal contractility. b. Low flow, normal contractility. c. Low flow, reduced contractility.[31,46]**

In 13 subjects simultaneous invasive pressure flow studies were also undertaken. These experiments showed cuff pressure to be generally higher than intravesical (isovolumetric) pressure with a mean difference ( $\pm$ SD) of  $37\text{cmH}_2\text{O} \pm 16\text{cmH}_2\text{O}$  (Fig. 1.3.6.). Some of this difference is explained by the difference in height between the pressure transducer at the level of the symphysis pubis and the penile cuff plus a small pressure transmission loss through the tissues of the penis. The technique was shown to be reproducible and without complication[31].



**Figure 1.3.6. Non-invasive penile cuff pressure using the deflation technique against simultaneously measured intravesical bladder pressures.**

In a subsequent double blind study, the same group compared cuff pressure studies, before and after treatment, with the clinical assessment and management of a group of 26 patients[45]. The ratio between isovolumetric pressure and steady state flow, derived from the cuff test, was calculated ( $R = p_{ves.isv}/Q_{ss}^2$ ) and used as a measure of obstruction.  $R > 3$  was taken as evidence of obstruction,  $R < 1$  as unobstructed and  $R$  value between 1 and 3 as mild to moderate obstruction, on the grounds of their response to treatment. This information was not made available to the clinician and all management decisions were made on conventional clinical grounds. All patients who had undergone prostatic surgery (TURP or prostatotomy) had a significant reduction in  $R$  value post operatively, with an average increase in  $p_{ves.isv}$  of 33cmH<sub>2</sub>O and increase in  $Q_{ss}$  of 11ml/sec. In those men who

were treated conservatively R values changed minimally between initial and repeat cuff tests (mean difference  $p_{ves.isv}$  7cmH<sub>2</sub>O, mean difference  $Q_{ss}$  0.3ml/sec). The rise in  $p_{ves.isv}$ , seen in the surgically managed group, is unexpected, in the light of later work showing the opposite in a larger group (n = 132)[47], and the cause for this phenomenon is unclear. It was noted that it often took several outpatient attendances to arrive at the same clinical diagnosis that was predicted by the cuff test and it was suggested by the authors that the test might speed the diagnostic process.

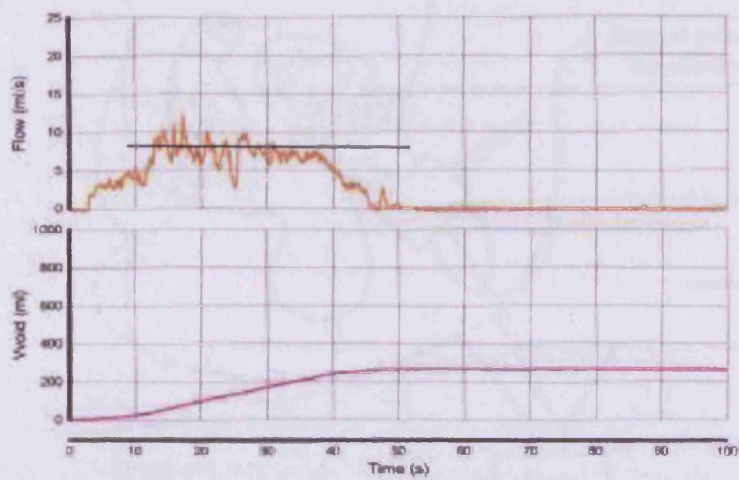
Using this cuff method, occasional patients were unable to relax their sphincters and initiate a void against the occlusion. This resulted in either an inability to perform the test or, in those patients being eventually able to void, a falsely low cuff pressure. During distension of the urethra, inadvertent sphincter or bulbar muscle contraction could squeeze urine through the cuff, which led to the premature release of the cuff before full isometric pressure had been reached and thereby giving a falsely elevated cuff pressure reading.

#### *The cuff inflation technique*

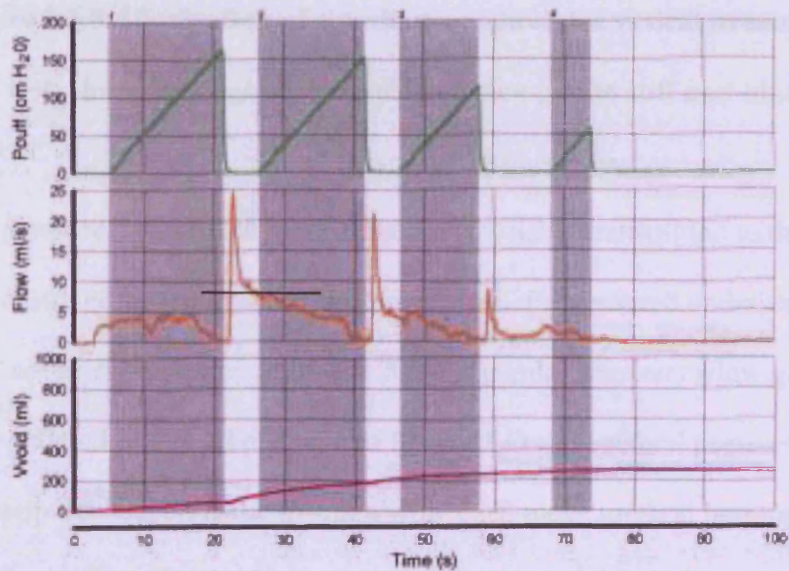
In a series of experiments[48-50] a group in Newcastle, UK, has explored the use of a penile cuff, automatically progressively inflated, after voiding has commenced, until flow ceases, to measure isovolumetric intravesical pressure(Figure 1.0a.). The cuff is inflated at a rate of 10cmH<sub>2</sub>O/sec to a maximum of 200cmH<sub>2</sub>O. Once flow has ceased the cuff is rapidly deflated and voiding resumes with an initial surge of flow followed by the

resumption of a steady state flow that approximates to that preceding flow interruption (Fig 1.3.7.). A number of cycles of inflation can be undertaken during each void. This technique relies on the principle that, at the time of urethral occlusion, the urethra and bladder neck remain open (confirmed radiologically in unpublished work [51,52]) and that therefore the bladder pressure will be equivalent to penile urethral pressure exerted by the cuff . If this is the case then the occlusion pressure in the cuff must be greater than or equal to bladder pressure, allowing for the height difference between bladder and cuff (Fig.1.3.8.), for flow to cease.

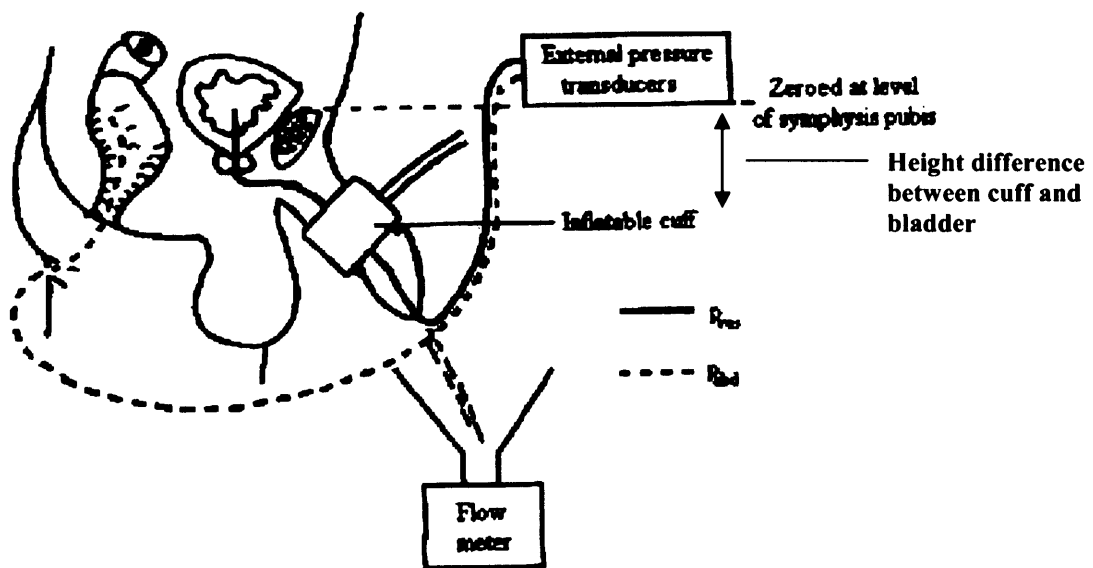
a.



b.



**Figure 1.3.7. a. Free flow rate[7] and b. flow rate during cuff test from the same patient. Note similar  $Q_{\max}$  and prolonged voiding associated with cuff test.**



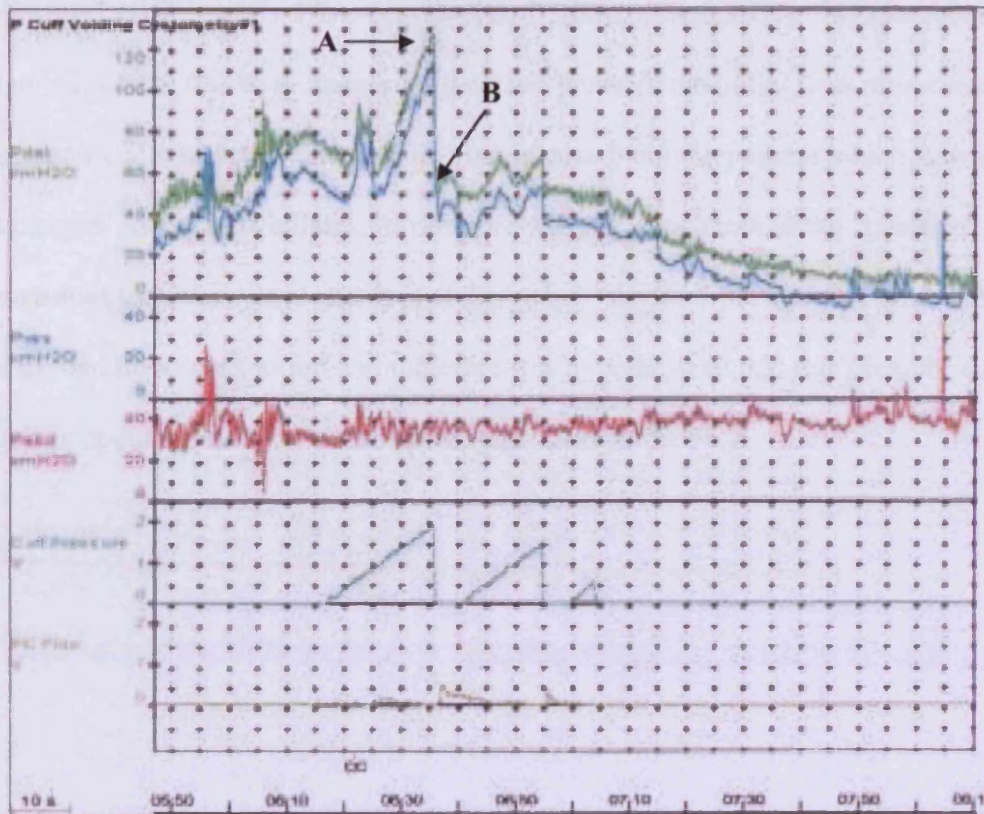
**Figure 1.3.8. Illustration of simultaneous invasive vesical pressure measurement and cuff test, showing height difference between penile cuff and bladder.**

The pressure generated by cuff inflation is reliably transmitted to the urethra as demonstrated by the intraurethral pressure (IUP) measured under the middle of the penile cuff; wider cuffs (approximately 1.5 times penile diameter) allow greater accuracy. Cuffs were inflated to a fixed pressure of 120cmH<sub>2</sub>O and urethral pressures measured with a microtip transducer, using a 46mm wide cuff, mean urethral pressure ( $\pm$ SD) under the middle of the cuff was  $120.8 \pm 8.9$ cmH<sub>2</sub>O, compared to  $95.0 \pm 9.9$ cmH<sub>2</sub>O under a 28mm wide cuff. A soft cuff material also yielded less erratic results particularly at lower cuff pressures. This was thought to be related to unfolding of creases in the cuff walls during inflation[53].

Simultaneous invasive urodynamics have shown that this method of controlled interruption of voiding does give a reliable estimate of isovolumetric bladder pressure with a mean difference of cuff pressure  $14.5 \pm 14.0 \text{ cmH}_2\text{O}$  greater than bladder pressure. This difference is thought mainly to be due to the height difference between the bladder pressure transducer zeroed at the level of the symphysis pubis and the cuff [49]

A rise in bladder pressure between maximum flow ( $Q_{\text{max}}$ ) and interruption was also demonstrated[44,49]. This rise is, as above, due to the trade off between pressure and contraction velocity/flow during voiding: as the bladder changes from a partly isotonic/isometric contraction to an isovolumetric contraction, contraction velocity is converted into pressure. Thus as flow falls to zero, pressure increases[4]. When pressures in the cuff, within the urethral lumen and within the bladder were compared there was seen to be a close relationship between vesical and urethral pressures. Urethral pressure increased with cuff pressure as the cuff was inflated. As expected, when urethral pressure reached vesical pressure, flow ceased[54]. After deflation of the cuff, and following recovery of urinary stream, detrusor pressure ( $p_{\text{det}}$ ) and bladder pressure ( $p_{\text{ves}}$ ) return to their pre interruption levels (Figure 1.3.9.). The fact that changes in  $p_{\text{ves}}$  mirror those in  $p_{\text{det}}$ , shows that abdominal pressure remains a constant factor during the test, that is, that there is no abdominal straining.



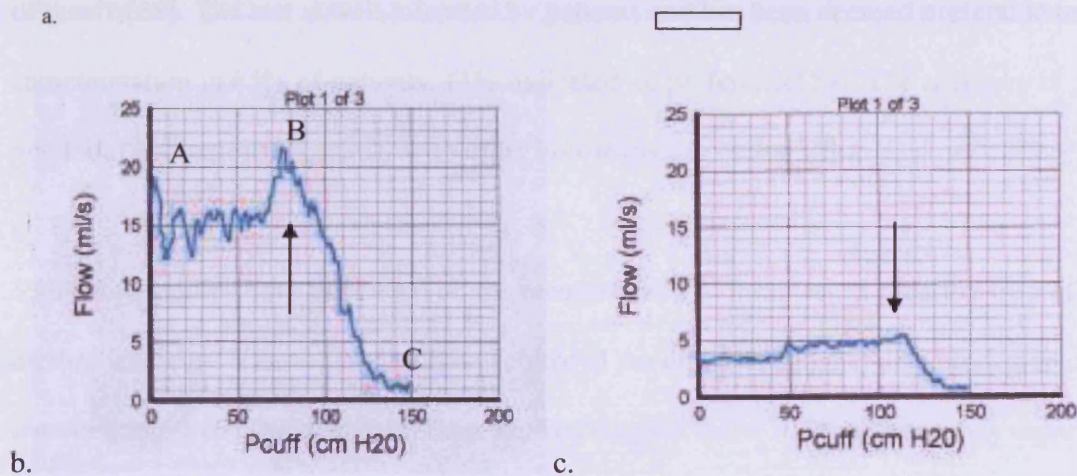
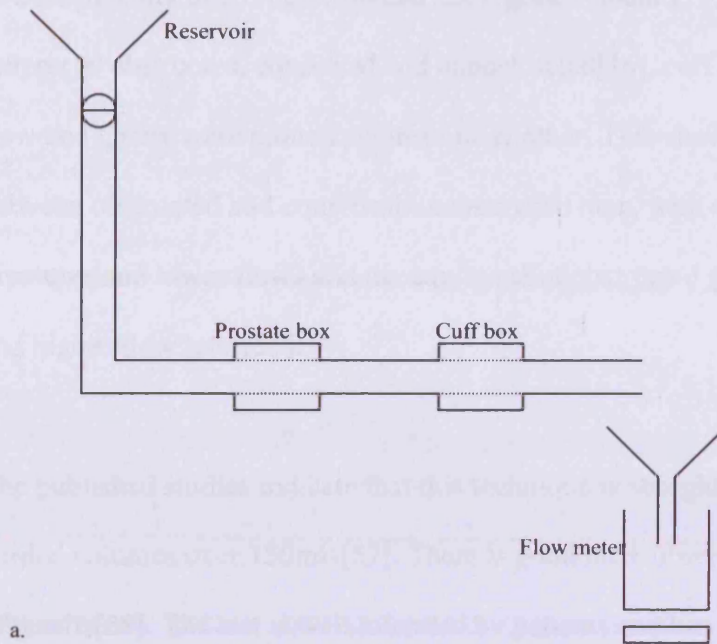


**Figure 1.3.9. Simultaneous recording of intravesical pressure (pves), abdominal pressure (pabd) and cuff pressure. As the cuff inflates detrusor pressure rises to an isovolumetric peak (A). As it deflates detrusor pressure (pdet) returns to its pre interruption level (B).**

Using an experimental model, designed to provide an analogy of the bladder/outlet/cuff system (Figure 1.3.10.a) [48,55], cuff pressures were plotted against flow at a variety of fixed “prostatic” pressures, mimicking increasing opening pressure at the prostate. These plots were qualitatively and quantitatively similar to clinical recordings. The characteristic shape of these pressure/flow studies shows a plateau phase of initial steady state flow (Figure 1.3.10.b: A to B), followed at a certain pressure by a decline to zero

(Figure 1.3.10.b: B to C). Flow ceases as cuff pressure rises above “bladder pressure”

(Figure 1.3.10.b: C). With increasing prostatic pressure the initial flow rate is lower and the pressure at which flow starts to decline is raised; but the point at which flow stops is unchanged. As the cuff inflates, its pressure will rise above that of the “prostate” and thence start to govern flow rate. It is at this point, “the knee pressure” (Figure 1.3.10.b and c), that flow starts to fall and therefore it is hypothesized that this pressure equates to prostatic opening pressure, or the opening pressure at the FCZ.



**Figure 1.3.10. a.** Diagram of experimental model. Reservoir is at a height of 120cm to give a fixed head of pressure. Pressures in the prostate box may be set to simulate increasing bladder outlet obstruction. Pressure in the cuff box is increased linearly during flow to simulate cuff inflation. Two traces taken from the experimental model both with a “bladder pressure” of 120cmH<sub>2</sub>O. **b)** “prostate pressure” was set at 80cmH<sub>2</sub>O; **c)** “prostate pressure” set at 110cmH<sub>2</sub>O. “Knee” pressures indicated by arrows.

In a small study of 33 men who had undergone standard PFS and were classified by ICS criteria as obstructed, equivocal and unobstructed[16], cuff pressure at interruption of flow and Qmax were plotted against one another. This showed a clear differentiation between obstructed and equivocal/unobstructed men, with obstructed men having higher pressures and lower flows and the equivocal/unobstructed group having lower pressures and higher flow rates[56].

The published studies indicate that this technique is straightforward and reproducible for voided volumes over 150mls[57]. There is good inter-observer agreement in the analysis of results[58]. The test is well tolerated by patients and has been deemed preferable to catheterisation in 85% of patients, 11% indicated no preference[59]. The accuracy is good and compares favourably with other non-invasive results[31].

Validation studies have depended on the measurement of intravesical pressure by a 6Ch urethral catheter. Various studies have looked at the effect of catheter size on degree of obstruction[60-62]The data from these studies suggest that a 10Ch catheter may cause a reduction in flow and increase in voiding pressures, albeit not necessarily affecting grade of obstruction, but that an 8Ch catheter does not cause an obstruction. In order to assess whether the presence of a catheter during simultaneous invasive and non-invasive measurements has an effect, a study has been performed recently to compare the difference between  $p_{ves.isv}$  and  $p_{cuff.int}$  measured simultaneously with both a 6Ch double lumen catheter and a 16G (approximately 4.8Ch) epidural catheter. The difference between  $p_{cuff.int}$  and  $p_{ves.isv}$  was on average 1.74cmH<sub>2</sub>O greater when measured with the

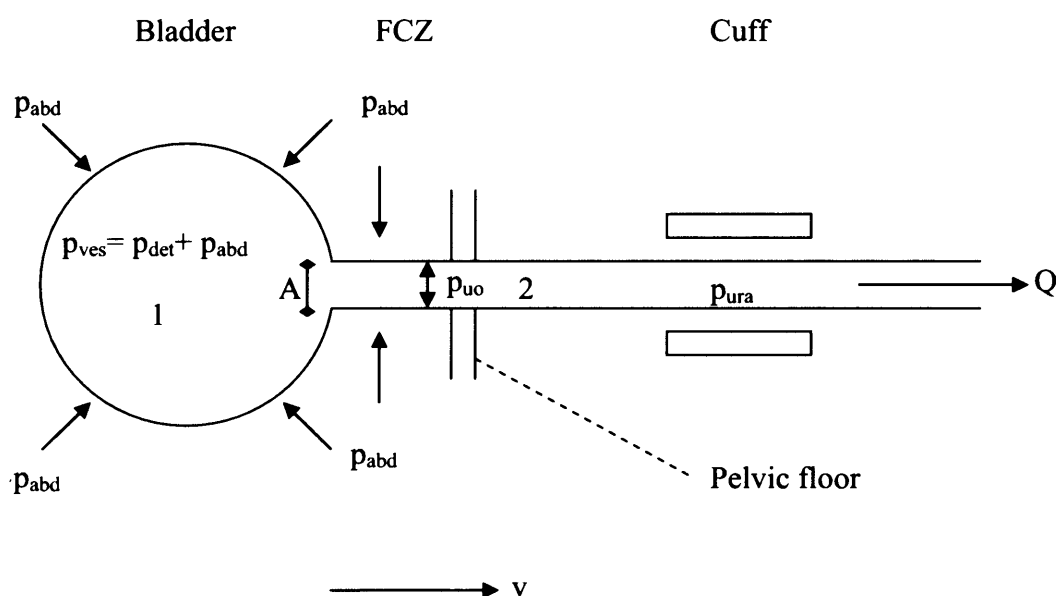
larger catheter[63]. This small but consistent difference may also help to explain some of the measured difference between  $p_{\text{cuff.int}}$  and  $p_{\text{ves.isv}}$ , not explained by the height difference between bladder and cuff. As with all of these non-invasive techniques, in the absence of a rectal catheter it is not possible to know what effect abdominal pressure plays, however across groups of patients the mean abdominal pressure is approximately 40cmH<sub>2</sub>O[49]and thus a correction could be applied.

Both the cuff deflation and inflation techniques do allow measurement of isovolumetric bladder pressure. Cuff pressure is generally slightly higher than bladder pressure, and most of this is likely to be associated with the height difference between cuff and bladder. In combination with flow rate measurement it would appear that this allows classification of patients into obstructed and unobstructed groups. Urethral pressure measurements suggest that the bladder neck and urethra do remain open during the test and this has been confirmed radiographically. Using the cuff inflation technique, with multiple measurements during voiding, detrusor contraction does not appear to be inhibited by the interruption of flow. This technique is reported as simple to perform and well tolerated by patients and may provide clinically useful information on bladder contractility, particularly in those men with a low flow rate and high isovolumetric pressure.

### **Physics of the cuff test**

As discussed above, urinary flow rate is dependent on both cross sectional area of the bladder outlet (A) and urinary velocity (v) (Fig. 1.3.11.). The velocity is determined by

the difference in pressure between the bladder and urethra distal to the FCZ (points 1 and 2). The pressure in the bladder is made up of detrusor pressure and abdominal pressure.  $p_{uo}$  is the pressure intrinsic to the outlet that must be overcome to allow the urethral lumen to open and flow to start.

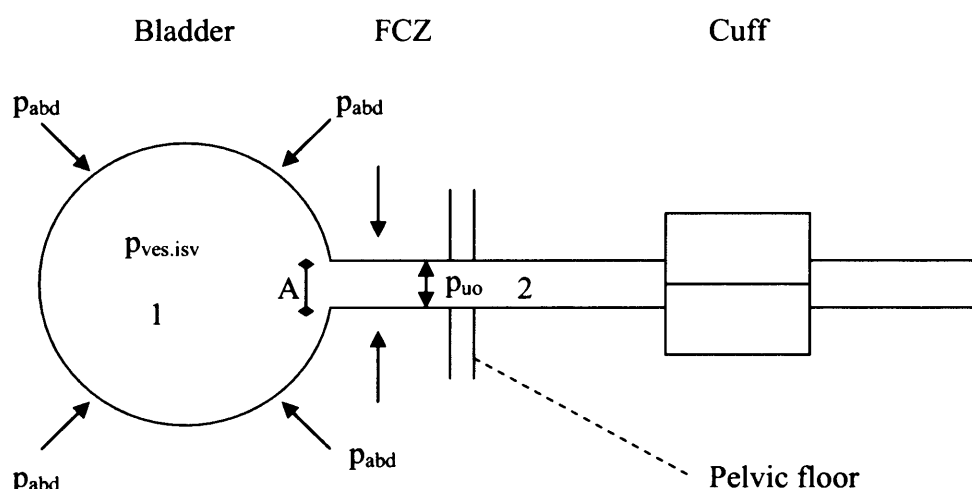


**Figure 1.3.11. Stylised diagram of male outflow tract during voiding, cuff deflated.**

As the cuff inflates during voiding the intraurethral pressure ( $p_{ura}$ ) under the cuff increases. Until cuff pressure rises above  $p_{uo}$  it will not affect flow (Fig 1.0b. Point A – the “knee” pressure). However, after this point the cuff starts to affect what is happening at the FCZ, by reducing the pressure difference across it, and urine velocity and hence flow will start to decrease until flow stops (Fig. 1.3.12). At this point there is no longer a pressure difference across the “real” flow controlling zone and the detrusor contracts under isovolumetric conditions. The pressure at point 2 is now the same as at point 1 and



cuff pressure mirrors bladder pressure. As the cuff is distal to the level of the pelvic floor it is not affected by abdominal pressure. Therefore the cuff estimates the total pressure upstream:  $p_{ves.isv}$ .



**Figure 1.3.12. Outflow tract at flow interruption due to cuff inflation.**

### **The Manual penile compression-release manoeuvre: Analysis of flow patterns to identify Bladder Outlet Obstruction**

The manual penile compression-release manoeuvre (pinching the penis) during voiding with analysis of the pattern and magnitude of flow rate change[46] is a simple method, which also seeks to categorise patients into obstructed and unobstructed groups.

An American group has focused their attention on the characteristic flow patterns produced following compression and release of the urethra during flow in order to diagnose obstruction. This has been achieved in patients and asymptomatic volunteers using manual compression and release of the urethra [46]. Patients were assessed using free flow rates and voiding urethral pressure profiles[64], to assess the presence and degree of obstruction. In addition a continuous outlet occlusion test[65], using a catheter balloon to occlude the bladder neck during voiding, was used to assess isovolumetric pressure and therefore detrusor contractility, in order to validate the pinch test.

Comparison of these flow patterns, which are similar to those obtained with the cuff test, with invasive urodynamics suggests that the magnitude of change in flow rate (between  $Q_{ss}$  and  $Q_{surge}$ ) is determined by the magnitude of the isovolumetric pressure generated. Patients with low flow rates may be separated into obstructed and detrusor underactivity groups by the height of the surge in flow rate (Fig 1.3.5.). In the obstructed group with normal detrusor function there is an initial high  $Q_{surge}$  followed by a fall to a low  $Q_{ss}$  (Figure 1.3.5.b). In contrast, patients with reduced detrusor contractility have a much lower  $Q_{surge}$  with a similarly low  $Q_{ss}$  (Figure 1.3.5.c). Subjects with detrusor overactivity, in the absence of obstruction, again had a distinctive pattern, a high  $Q_{surge}$  followed by a high  $Q_{ss}$  which was similar to a normal unobstructed flow rate (Figure 1.3.5.a).  $Q_{surge}$  tended to be higher in detrusor overactivity (DO) than in the normal group and this was thought to be due to an increase in detrusor contractility associated with DO. Normal volunteers generally had a higher  $Q_{ss}$  commensurate with their higher free flow rates.



In order to compare the flow patterns seen between the various diagnostic groups the change in flow rate ( $\Delta Q$ ) was expressed as a percentage of  $Q_{ss}$ , the Penile Compression Release Index (PCR Index =  $[Q_{surge} - Q_{ss} / Q_{ss}] \times 100$ ) (Fig 1.3.5.b). PCR indices were significantly higher in patients with BOO or DO compared to those with detrusor underactivity, normal contractility without obstruction and normal volunteers. PCR indices between the latter three groups were not significantly different. Patients with BOO may be distinguished from unobstructed patients with DO by their lower  $Q_{ss}$ . All patients with DO were considered together without differentiating between those with or without concomitant obstruction. To determine the discriminating ability of this technique receiver-operating-characteristic (ROC) curves were used and showed that a PCR index of 100% to detect BOO had a sensitivity, specificity, positive and negative predictive values of 91,70,74 and 89% respectively. Reproducibility was assessed, in a small number of patients and volunteers, and a good correlation was shown between repeated tests ( $r = 0.77$ ,  $p = 0.002$ ).

These patterns are reliable as long as the flow controlling zone (FCZ) [2] is proximal to the urethral compression, as for example in benign prostatic obstruction. If the FCZ is distal to the point of urethral compression then no spike of  $Q_{surge}$  is seen, for example in men with distal urethral strictures or meatal stenosis. A similar pattern was seen in 2 normal volunteers with flow rates  $>30$  ml/sec. In these subjects the FCZ appeared to be at the meatus.

This technique is extremely simple and does not involve pressure measurements.

Radiographic studies showed that penile compression does lead to distension of the urethra proximal to the site of compression. Successful tests were performed in 93% of patients. However, in a few cases there were problems with the patients' understanding and ability to direct the increased stream into the funnel of the flow meter. As with all these techniques, abdominal pressure measurement may be necessary to improve the accuracy of this test as straining was shown to affect the results. The pinch test may prove to be a useful tool in identifying obstructed men with low free flow rates and normal detrusor contractility.

As described above, a number of novel techniques have been proposed to assess voiding function in men, in order to avoid the need for invasive pressure-flow studies (Table 1.3.1) and each comes with potential sources of error and artefact (Table 1.3.2). A non-invasive measure of bladder pressure, allied to a free flow rate, would give a very useful diagnostic adjunct to the assessment of men with LUTS.

Of the methods discussed above, those using a penile cuff, inflated during voiding and resulting in an interruption of flow, or penile squeeze, would seem the most likely to be clinically useful. With each compression/void cycle of the penile cuff an impulsive flow rate, albeit brief, is generated. These appear to have the same spike/plateau configuration as those from the manual penile compression/squeeze method, but give additional useful information, giving two indications of detrusor contractility or obstruction from the one test.

In order to assess this, studies have been performed to validate the PCR index using data derived from the cuff test. These show that the PCR index is related to isovolumetric pressure and thus detrusor contractility and confirm the original findings, suggesting that the PCR index has an improved ability to predict obstruction than flow rates alone (positive predictive values 69% vs. 51%)[66]

**Table 1.3.1. Comparison of different non-invasive techniques.**

Characteristic		Condom	Cuff deflated during voiding	Cuff inflated during voiding	Pinch test
Physiological variable measured	Pressure	Yes	Yes	Yes	No
	Flow	Yes	Yes	Yes	Yes
Validation		Yes	No	Yes	Yes
Sources of artefact		<ul style="list-style-type: none"> <li>- Leakage from condom</li> <li>- Compliance within system</li> <li>- Failure of bladder and condom pressures to equalise</li> <li>- Inhibited voiding</li> </ul>	<ul style="list-style-type: none"> <li>- Inhibited voiding</li> <li>- Premature cuff release</li> <li>- Delayed cuff release</li> </ul>	<ul style="list-style-type: none"> <li>- Inhibited voiding</li> <li>- Small/stiff cuff</li> </ul>	<ul style="list-style-type: none"> <li>- Relies on patient compliance</li> <li>- inhibited voiding</li> </ul>
Reproducible		Yes	Yes	Yes	Yes

**Table 1.3.2. Possible sources of artefact in non-invasive urodynamics.**

<b>Measured isovolumetric pressure</b>	
Too high	Straining
Too low	Detrusor inhibition Sphincter closure Increased compliance (condom/urethra)
<b>Measured flow</b>	
Too high	Rebound surge from distended system (condom/urethra)
Too low	Inhibited void/detrusor contraction Failure of relaxation in sphincter/pelvic floor

### **Measurement of voiding urethral pressure profiles**

It has been demonstrated that if pressure is measured in a fluid filled tube under conditions of flow through an end hole catheter, the kinetic energy of flow is converted into end (total) pressure. This end pressure is greater than pressure measured through a side hole, the lateral pressure (static pressure), by an amount equivalent to the kinetic energy of flow. This pressure difference (dynamic pressure) is determined by the velocity of the fluid. Thus: total pressure = dynamic pressure + static pressure[67]. In the bladder and urethra this equates to:  $p_{ves} = p_{dp} + p_{uo}$ .

As discussed above, during voiding, pressure falls along the urethra from the bladder to the external urethral meatus (Fig. 1.1.5.). The pattern and magnitude of this fall is affected by the presence of any obstruction and measurement of these pressure changes should, in theory, allow measurement of urethral opening pressures. A number of groups have attempted the measurement of these pressure changes during voiding in both experimental models[12,68,69] and patients[67,70,71] as voiding urethral pressure profiles(VUPP's). This technique uses the withdrawal of a catheter through the urethra, during voiding, allowing simultaneous measurement of vesical and urethral pressures and thus the pressure changes in the urethra.

### Measurements in experimental models.

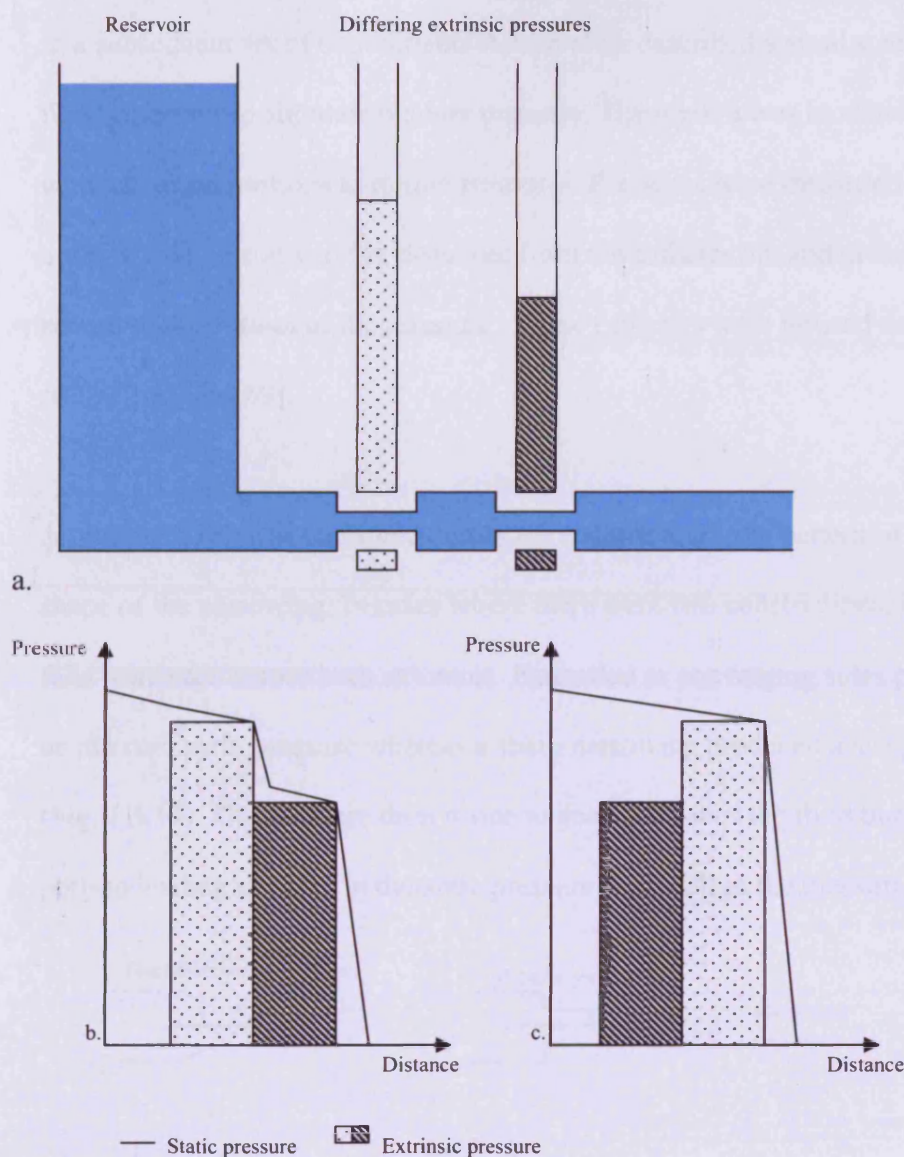
In a bladder/urethral model, using a water filled reservoir giving a fixed head of pressure, to simulate the bladder, and flexible latex tubes, to simulate the urethra, Scott et al.

[12]demonstrated that flow through the system was related to the pressure difference between the reservoir pressure and a circumferential extrinsic pressure applied to the flexible tube by a separate reservoir of fluid (Fig1.3.13.a). In other words:

$Q \propto \text{reservoir pressure} - \text{extrinsic pressure}$  (or  $Q \propto p_{\text{ves}} - p_{\text{uo}}$ ).

The static pressure distribution within the model during flow was measured by passing into its lumen a hollow steel probe with a side hole 10cm from the tip. As the probe was withdrawn along the lumen, it was seen that as well as some minor pressure gradients associated with acceleration and friction there was a sudden fall in static pressure at the downstream side of the area of extrinsic pressure. This fall in pressure was approximately equal to the extrinsic pressure. It was also seen that if two areas of extrinsic pressure were present then both would produce a pressure gradient. However if the distal extrinsic pressure was greater this would mask the proximal pressure changes (Fig. 1.3.13.b and c).

If this model is thought of in terms of bladder and urethra then the reservoir pressure ( $p_{\text{ves}}$ ) must be higher than the extrinsic pressure ( $p_{\text{uo}}$ ) to allow flow and the fluid pressure ( $p_{\text{dp}}$ ) must be more than or equal to extrinsic pressure to maintain flow. The pressure difference along the urethra leads to fluid acceleration and therefore flow.

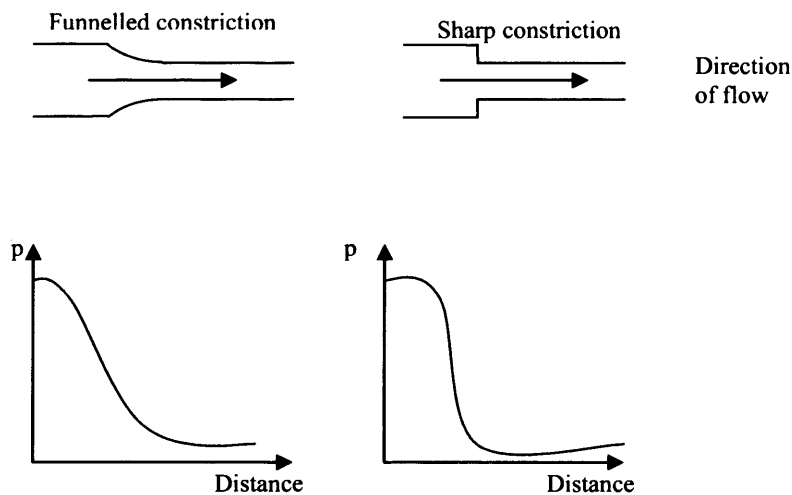


**Figure 1.3.13. a. Reservoir/urethra model in which changes in static pressure may be measured using a side hole catheter withdrawn down a flexible tube under conditions of flow with two areas of differing extrinsic pressure. b) Area of higher pressure is proximal and a fall in static pressure is seen at distal end of both areas of compression. c) Area of higher pressure is distal and masks area of proximal lower pressure[12]**



In a subsequent set of experiments Asklin et al. described a similar model using a water filled reservoir to simulate bladder pressure. The urethra was modelled using glass tubes with narrowed portions to mimic strictures. Pressures were measured using catheters with a single side hole at varying distances from the catheter tip, and pressure transducers were zeroed to the bottom of the reservoir. These catheters were infused during withdrawal at a rate of 1ml/min[69].

A pressure drop was measured across the constrictions, the pattern of which varied with shape of the narrowing. In cases where there were two constrictions, in series, pressure falls were seen across both strictures. Funnelled or converging sides produced a more gentle decline in pressure whereas a sharp narrowing produced a steeper fall in pressure (Fig. 1.3.14). The pressure drop is due to acceleration of the fluid through the narrowed portion leading to a rise in dynamic pressure and a fall in the measured static pressure.



**Figure 1.3.14. Illustration showing different pressure change patterns across funnelled and sharp constrictions.**

The fluid filled catheter which showed the most reliable measurements was that in which the side holes were far enough from the tip to allow the tip to remain in the reservoir/bladder as the side hole passed the entire length of the tube/urethra. This ensured that the catheter exerted a constant effect along the length of the urethra.

Palmer and Desmond also studied voiding pressure profiles in a model using a fixed reservoir of water and a flexible tube with constrictions provided by metal washers. Pressure changes were measured using a fluid filled catheter with two side holes 6cm from the tip, the catheter being infused at a rate of  $2\text{ml}\cdot\text{min}^{-1}$  [68]. For a given constriction the pressure drop measured across the constriction increased with increasing reservoir pressure, however the pressure measured distally, downstream of the constriction, remained constant. Likewise for a given constriction flow rate increased with increasing reservoir pressure. By measuring the flow rate and pressure fall across the constriction it was possible to calculate the cross sectional area of the constriction; this calculated area remained constant for each size of narrowing independent of reservoir pressure.

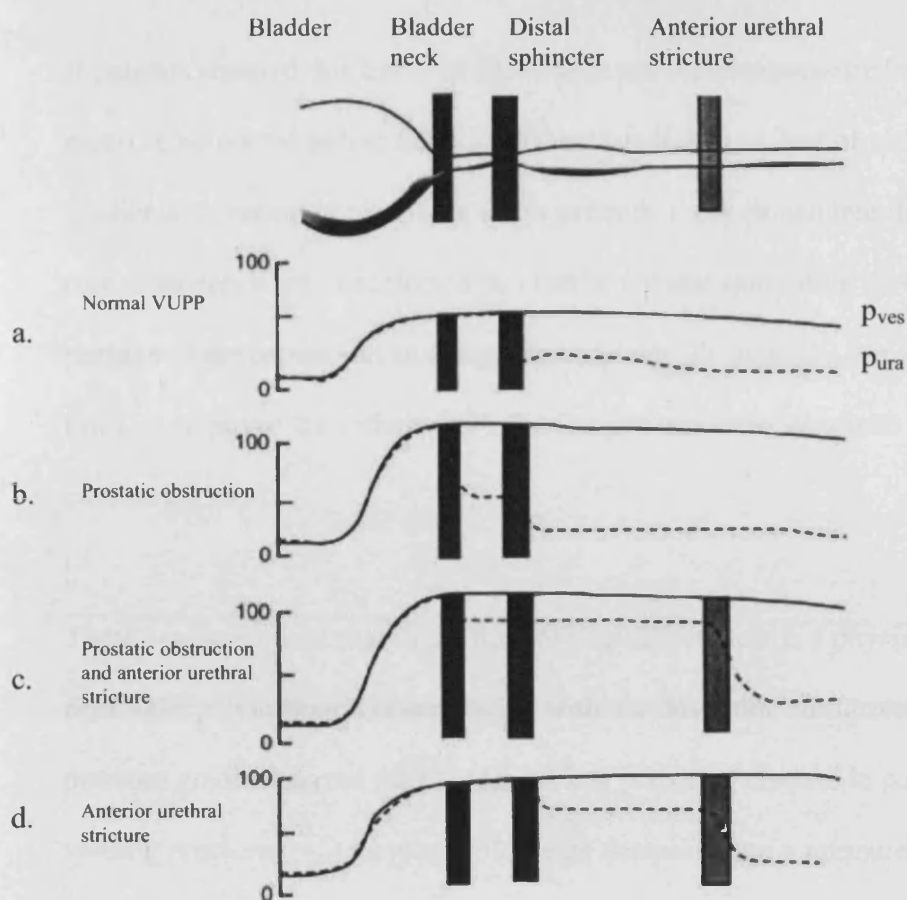
### **Measurements in patients**

The measurement of voiding urethral pressure profiles in men has been pioneered by Yalla. In a series of experiments he measured voiding profiles in a number of patient groups, with varying voiding dysfunctions, as well as in normal asymptomatic controls [67,72-74]. He used a 10Ch triple lumen catheter with two channels opening at the tip, for bladder filling and measurement of intravesical pressure, and one channel

opening through two side holes 10cm proximal to the tip, in order to measure the pressure changes along the urethra during voiding. Prior to voiding, resting urethral pressure profiles were recorded using the Brown-Wickham method[75] in order to identify the anatomical landmarks of bladder neck, external sphincter/pelvic floor and bulbar urethra. In order to further clarify the location of the catheter, with radio opaque markings, the procedure was carried out under fluoroscopy. Patients were then asked to void either supine or standing whilst the catheter was withdrawn. Yalla states that catheter withdrawal may be by hand or mechanical, although if a mechanical puller is used more care must be taken to prevent catheter expulsion [76].

In the normal subjects the supramembranous urethra was found to be isobaric with the bladder (Fig 1.3.15.a.). At the level of the pelvic floor/external sphincter a pressure drop was seen. Distal urethral pressure tended to be in the range 25-30cmH<sub>2</sub>O with  $p_{det}$  in the range 50-70cmH<sub>2</sub>O[76]. In patients with a clinical diagnosis of BPO a different pressure distribution was seen, dependent on the anatomic distribution of the prostate. There was a characteristically higher voiding pressure with pressure falls seen in the region of the bladder neck, followed by a plateau in the prostatic urethra and a further fall in pressure at the pelvic floor[74](Fig. 1.3.15.b). The magnitude of pressure fall at the bladder neck/prostate is proportional to the degree of prostatic compression. If the pressure fall at the bladder neck is very large ( 70-80cmH<sub>2</sub>O with  $p_{det}$  in the region of 100cmH<sub>2</sub>O) then a pressure fall may not be seen across the pelvic floor, suggesting that the obstructed urethra is narrower than the membranous urethra[76]. Following TURP in some of these patients, voiding pressure was reduced and the pressure fall across the bladder neck and

prostate was abolished. Similarly in patients with bladder neck obstruction, a large pressure drop (mean 53 cmH<sub>2</sub>O, range 20- 110cmH<sub>2</sub>O) from an elevated voiding pressure was seen at the bladder neck[73]. Post operatively this was abolished, although if a post operative stricture recurred (mean drop 31cmH<sub>2</sub>O, range 15-65 cmH<sub>2</sub>O) or there was residual obstruction, a pressure gradient could still be measured. If the penis was compressed during voiding the bladder and urethra upstream of the compression became isobaric, with a pressure fall across the site of obstruction. Similarly if a distal stricture was present this could prevent the identification of a more proximal obstruction (Fig. 1.3.15c). A fall in pressure across the bladder neck/prostate is suggestive of obstruction[70,77,78] and a distal intraurethral pressure of greater than 25-30cmH<sub>2</sub>O is suggestive of a distal urethral stricture[77]. When compared to measurements taken from invasive pressure flow studies the pressure gradient was found to correlate significantly with  $p_{uo}$  ( $r = 0.609$ ,  $p < 0.001$ )[77].



**Figure 1.3.15. Voiding urethral pressure profiles under various outlet conditions.**

Solid lines represent intravesical pressure ( $p_{ves}$ ) and broken lines represent urethral pressure ( $p_{ura}$ ) a. Under normal conditions there is a low voiding pressure with a fall in pressure across the distal sphincter. b. In prostatic obstruction voiding pressure increases and a pressure gradient develops across the bladder neck and prostate. A further drop in pressure is seen in the region of the distal sphincter, similar to that seen in the unobstructed patient. c. If a distal urethral stricture is also present the pressure change across the bladder neck and prostate is masked and a further pressure fall occurs across the stricture. d. If an anterior urethral stricture is present with a normal prostate and bladder neck then again the pressure fall across the pelvic floor may be masked. If the stricture is severe then the entire urethra proximal to the stricture may be isobaric with the bladder.[64]

If patients strained this led to an increase in intravesical pressure but did not affect distal pressure below the pelvic floor. This therefore had the effect of accentuating pressure gradients. In repeated profiles in some patients it was shown that the patterns and measurements were not affected by bladder volume (providing flow was maintained), passage of the catheter in an antegrade or retrograde direction during the void, or by infusion or not of the catheter[67]. Similar patterns were seen with both 10Ch and 5Ch catheters[73,74].

These results suggest that in the normal population there is a physiological pressure fall across the pelvic floor, corresponding with the flow controlling zone, but there is no pressure gradient across the bladder neck or proximal urethra. In patients with BOO voiding pressure ( $p_{det}$ ) increases, flow rate decreases and a pressure gradient develops across the site of obstruction (bladder neck and prostate) which takes on the role of the FCZ.

In order to accurately measure intraurethral pressure during voiding the catheter should be withdrawn once flow is established[64]. The catheter should be small enough to prevent any flow disturbance, the side hole should face laterally and be in contact with the fluid layers[76]. Multiple side holes would reduce the chance of entrapment of the catheter against the urethral wall, however, under conditions of flow and catheter withdrawal this should not occur[79]. Entrapment would be suggested by a rise in intraurethral pressure above vesical pressure[76]. Asklin et al performed similar studies in patients using an 8Ch catheter with single eyeholes at 5 and 25cm from the tip[71].

They reported similar findings to Yalla's group and noted that the side holes, of the two urethral lumens, must be far enough apart to allow the catheter tip, measuring vesical pressure, to remain in the bladder while the area of interest in the urethra is being studied. This allows any effect of the catheter to remain constant between the bladder and urethra.

## 1.4 **Summary**

### **Hypothesis 1**

A reduced urinary flow rate may be related to either bladder outlet obstruction or detrusor underactivity[3,4,24,25]and as such is not an ideal tool for the diagnosis of obstruction[22,28].

Currently the best accepted method of determining bladder contractility and therefore obstruction is by the simultaneous invasive measurement of vesical pressure and flow rate during voiding, which in conjunction with the ICS nomogram may be used to diagnose obstruction[15,16].

An alternative measure of bladder contractility is isovolumetric bladder pressure[3,4]. Work using a penile cuff suggests that this may be used to measure isovolumetric bladder pressure[49]. As part of this thesis we look to reproduce this work and validate the previously published results.

### **Hypothesis 2**

If the cuff test can give a reliable estimation of isovolumetric bladder pressure, this could then be used in conjunction with flow rate to provide a clinically useful tool to provide a non-invasive diagnosis of obstruction. If so, is it possible to construct a nomogram, similar the ICS nomogram to facilitate such a diagnosis?



### Hypothesis 3

Whilst looking at further possible applications of the cuff test it has been noted, in work using an experimental model, that the shape of the curves generated by measurement of simultaneous cuff pressure and flow may give a measurement of urethral opening pressure at the flow controlling zone (Fig1.0.b)[55]. [48]In the “compressive” model of obstruction  $p_{uo}$  should be increased and thus if “knee pressure”, as measured by the cuff test, did represent  $p_{uo}$  then this might again give useful information as to degree of obstruction.

We look to explore the nature of the knee pressure generated by the cuff test by comparing it to currently accepted methods of estimation of  $p_{uo}$  taken from invasive pressure flow studies and voiding urethral pressure profiles, and its relationship to obstruction.

## **2. Materials and methods**

The work for this study was undertaken in the Urodynamics Unit of the Bristol Urological Institute, Southmead Hospital, Bristol. The project was initiated in September 2001, recruitment of patients started in December 2001 and clinical investigation took place between January 2001 and March 2003.

Application for ethical approval for our study was made to the local Research Ethics Committee at Southmead Hospital, Bristol. The standard application form was submitted in November 2001 and ethical approval was granted on 20 December 2001 (Project 130/01, Appendix A).

Funding for the study came from 2 main sources. The author worked as a clinical fellow in the Urodynamics Department at Southmead Hospital, providing a clinical urodynamic service and drew a salary from the hospital. Funding for the cuff machine and disposables was provided by Mediplus, UK who own the patent for the cuff machine and were planning to market it for non-invasive urodynamics if our research proved its efficacy.

The project was planned and executed by the author. The study was designed in collaboration with the Medical Physics Department, Freeman Hospital, Newcastle. Recruitment and investigation of patients was undertaken by the author. The staff of the Urodynamic Department, Southmead Hospital assisted with clerical support for booking patient appointments and nursing support in conducting urodynamic tests. Data

acquisition and analysis was carried out by the author and statistical advice was provided by Miss Kate Parry, Research and Development Unit, Southmead Hospital. Supervisors for the project were Professor Paul Abrams, Bristol Urological Institute, and Mr Julian Shah, Institute of Urology, University College, London.

In order to test our hypotheses, men with LUTS referred to our department, were recruited into the trial. Each patient underwent free flow rate investigation and at a subsequent visit underwent a free cuff test, resting urethral pressure profile measurement, invasive filling cystometry and pressure flow study, simultaneous invasive pressure flow study and cuff test and voiding urethral pressure measurement. General demographic data was obtained including age, height, weight, predominant symptoms and IPSS score.

## **2.1 Recruitment**

Men with LUTS were recruited from outpatients and from the urodynamic waiting list. Approximately 200 were approached of whom 139 agreed to take part. 118 were investigated, 6 attended but declined to take part on the day of investigation, 1 patient was not able to be catheterised (having had a previous TURP), 4 initially took part but dropped out after the initial pressure flow study for reasons of frailty, 1 patient suffered a stroke resulting in an indwelling catheter prior to attending. 9 patients did not attend their urodynamic appointments. Each patient was given a patient information sheet at the time of recruitment and written informed consent was obtained immediately prior to investigation (see Appendix B).

## **2.2 Free flow rates**

Flow tests were performed in accordance with the guidelines set down by the International Continence Society[7]. Patients were asked to attend the flow clinic in our department with a full bladder and perform a free flow test by passing urine into a spinning disc flow meter (Dantec, Denmark). They were then asked to drink and, when feeling a normal desire to void, perform a further flow rate. This procedure was repeated to obtain a total of three flows. For each flow test the Q<sub>max</sub>, voided volume (V<sub>void</sub>) and post void residual volume (PVR), assessed using ultrasound, were recorded.

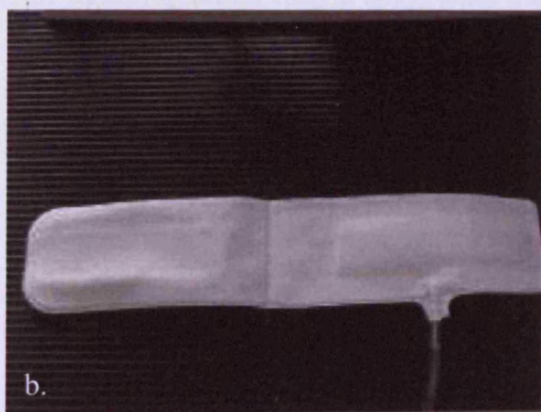
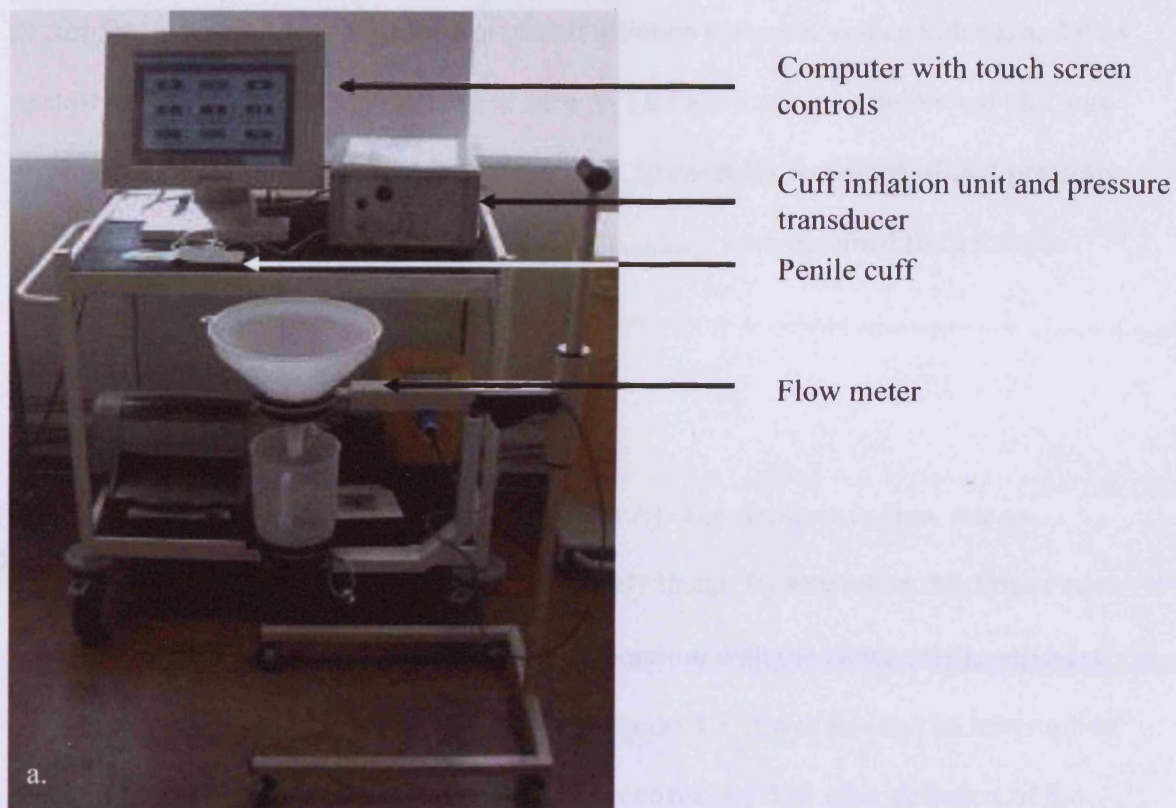
## **2.3 Urodynamic and cuff studies**

Having attended for urodynamic assessment a full history and clinical examination, consisting of abdominal, digital rectal and neurological assessment, were performed by the author. The investigations were explained again to the patients and written consent obtained. At the end of the study patients were asked to complete an IPSS questionnaire.

### **Free cuff test**

Patients were requested to attend with a full bladder. At the start of the investigations they were then asked to perform a cuff test, without invasive monitoring. Due to a lack of suitable equipment we were unable to perform ultrasound bladder volume measurements prior to voiding. A specially designed, flexible, inflatable plastic cuff, similar to a neonatal blood pressure cuff, (Mediplus, UK) was placed around the penile shaft, as close

as possible to the base, with the inflation tube alongside the ventral aspect. Cuffs are manufactured from Rectaleen PVC and are retained in position with Velcro. They are available in two sizes “large” (48mm x 220mm) or “small” (38mm x 180mm). The largest fitting cuff was used. The patients were asked to void, without straining, into a load cell flow meter attached to the cuff machine. The cuff machine is a custom built pneumatic system under microprocessor control with the penile cuff connected to a pressure transducer (Type FM319, Regional Medical Physics Department, Freeman Hospital, Newcastle, UK) (Fig. 2.3.1). As soon as a flow rate of more than  $1\text{ml.s}^{-1}$  for 2 seconds is detected in the flow meter the cuff automatically inflates in a linear fashion at a rate of  $10\text{cmH}_2\text{O.s}^{-1}$ . The cuff continues to inflate until flow stops. Once flow has stopped, less than  $0.5\text{ml.s}^{-1}$  detected by the flow meter, the cuff rapidly deflates and flow resumes. As flow resumes the cuff reinflates. This cycle continues until voiding is complete. For safety the cuff will inflate to a maximum of  $200\text{cmH}_2\text{O}$  when it automatically deflates, if flow has not been interrupted.



**Figure 2.3.1. a. The cuff machine supplied by the Regional Medical Physics Department, Freeman Hospital, Newcastle.**

**b. and c. Penile cuff**

A plot was generated for each cuff test of cuff inflation pressure, voided volume and flow against time (Fig. 2.3.2. upper half). For each cuff inflation cycle an individual plot was obtained of cuff pressure against flow (Fig. 2.3.2. lower half). Readings of cuff pressure at flow interruption ( $p_{\text{cuff.int}}$ ) and knee pressure ( $p_{\text{cuff.knee}}$ ) were obtained from these individual plots.

$p_{\text{cuff.int}}$  is measured on the x axis (Fig. 2.3.2. point A). The decrease in flow rate as interruption is approached is usually approximately linear. By extending this line to zero, interruption pressure may be estimated. In collaboration with the Newcastle group a set of standard exclusion rules were developed (Appendix C). It was felt that an interruption pressure could not be estimated if: there was no recovery of flow after deflation of the cuff (ignoring initial surge), suggesting that detrusor contraction was not maintained (Fig 2.3.3a); flow was not interrupted (Fig 2.3.3b); there was more than one pressure at which flow was interrupted (Fig 2.3.3.c); a flow trace was erratic with sudden fluctuations in flow rate (fig 2.3.3c); or if a trace was inconsistent with others from the same void.

$p_{\text{cuff.knee}}$  was estimated at the point at which flow rate changed from an approximately horizontal curve to a more vertical curve as it approached zero (Fig.2.3.2. point B). The presence or absence of a measurable knee pressure was classified as 3: definitely present, 2: probably present, 1: probably not present or 0: definitely not present

**Figure 2.3.2. (next page) Printout obtained from cuff test performed in a 78yr old man, presenting with voiding LUTS and an IPSS of 24. A large cuff was used. In the upper half is plotted cuff pressure ( $p_{\text{cuff}}$ ), flow rate and voided volume ( $V_{\text{void}}$ ) against time. In the lower half cuff pressure is plotted against flow for each cuff inflation cycle. From the lower individual traces may be estimated  $p_{\text{cuff.int}}$  and  $p_{\text{cuff.knee}}$ . By extrapolating the approximately linear fall in flow rate to the x axis it is possible to estimate  $p_{\text{cuff.int}}$ : point A, in this case 100cmH<sub>2</sub>O.  $p_{\text{cuff.knee}}$  is estimated at the point where flow rate starts to fall: point B, in this case 80cmH<sub>2</sub>O. The knee pressures in this case were classified as 3 (definitely present) in the first two inflations (graphs 1 and 2 of 5) and 1 (probably not present) in the third inflation (graph 3 of 5), and 2 (probably present, point C:  $p_{\text{cuff.knee}} = 60 \text{ cmH}_2\text{O}$ ) in the fourth inflation (graph 4 of 5). Pressure flow plot for the fifth cuff inflation is not shown.**

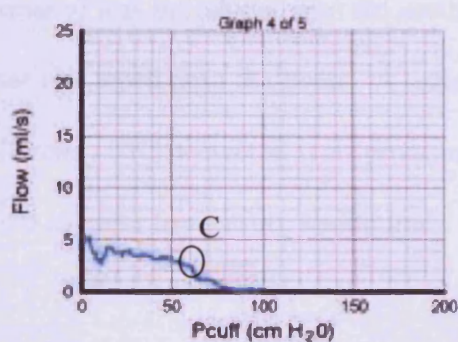
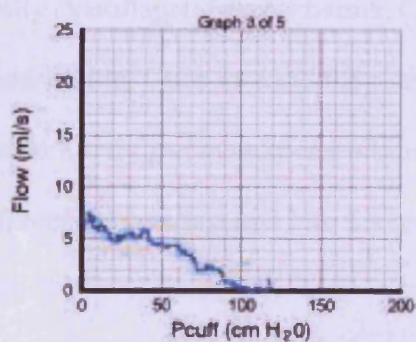
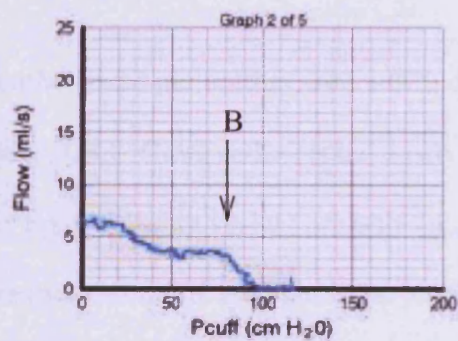
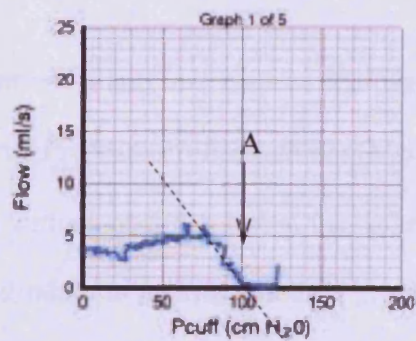
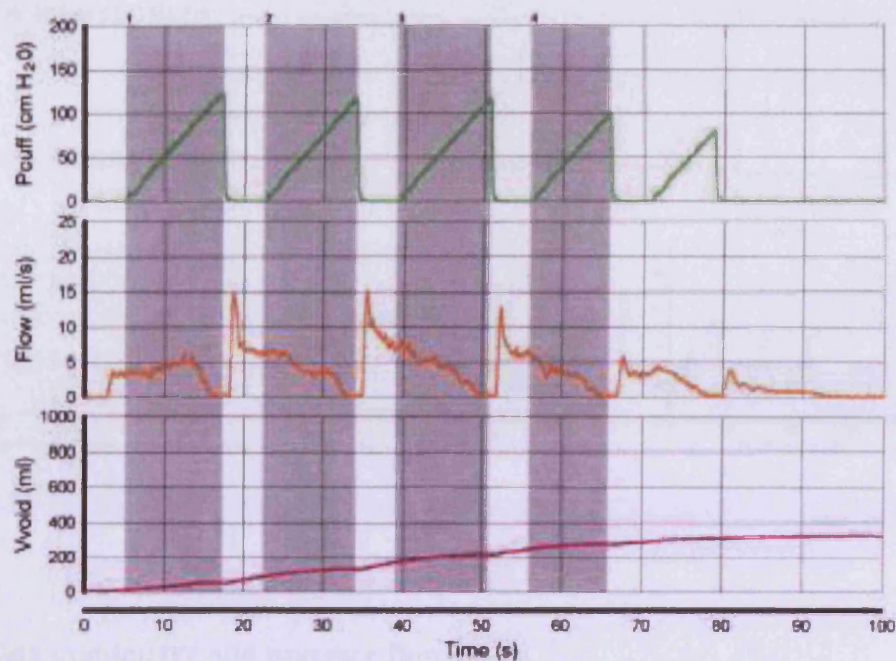


Figure 2.3.2. (Legend on previous page)

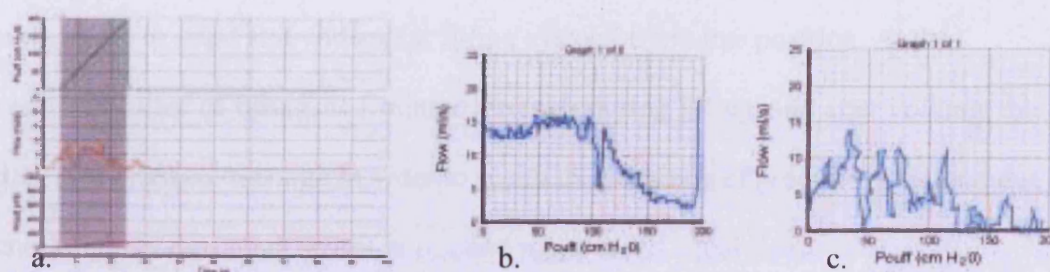
DO NOT USE FOR DIAGNOSIS

**NON-INVASIVE BLADDER TEST**

DO NOT USE FOR DIAGNOSIS



**Figure 2.3.3** Traces from three different patients showing: a. failure of flow recovery after cuff deflation, b. failure of flow interruption, c. erratic flow with multiple flow interruptions.



#### **Invasive filling cystometry and pressure flow study.**

Having performed a cuff test, each patient was catheterised per urethra with a 6Ch double lumen Urethral Pressure Profile catheter (Mediplus, UK). These catheters have two lumens each with an opening, one at the catheter tip to measure vesical pressure ( $p_{ves}$ ) and one 7cm proximally to measure urethral pressure ( $p_{ura}$ ). 10ml of 1% lignocaine local anaesthetic jelly (Instillagel, Farco-Pharma, Germany) was introduced into the urethra prior to catheterisation. Once inserted the catheter was taped onto the penis. A rectal catheter manufactured from manometer tubing (Portex, UK) protected at its proximal end by a vented finger cot was inserted into the rectum in order to measure abdominal pressure ( $p_{abd}$ )

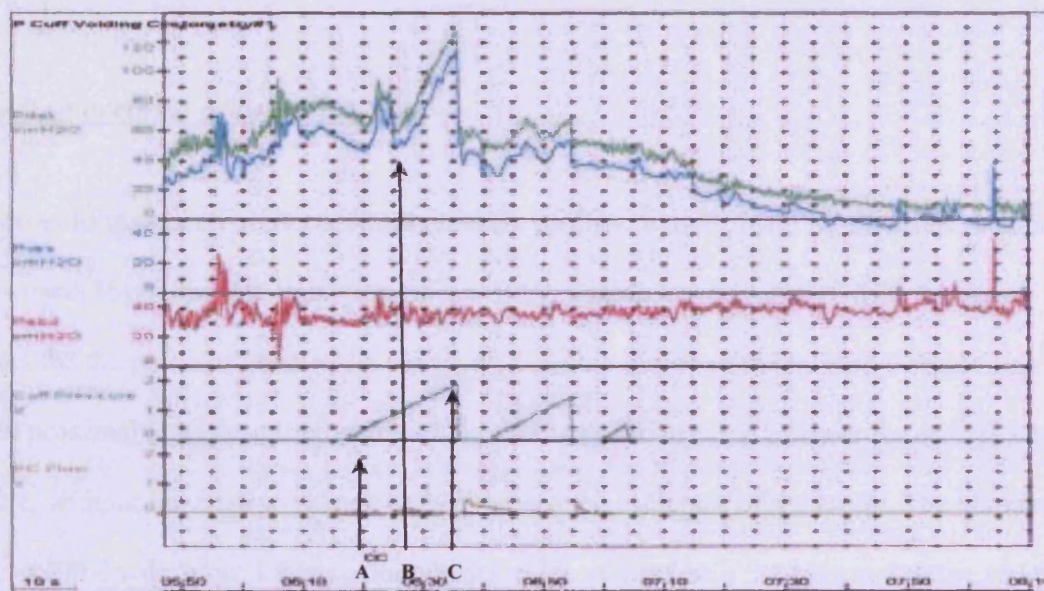
Invasive urodynamics were performed in accordance to the recommendations of the International Continence Society[7] using a “Duet” urodynamic machine (Dantec, Denmark). Both lumens of the urethral catheter, and the rectal catheter, were fluid filled, with normal saline, and connected to external pressure transducers (Dantec, Denmark) zeroed to atmosphere and levelled at the upper border of the symphysis pubis. Patients were asked to stand and underwent filling cystometry in this position. At the commencement of filling, at 1 minute intervals during filling, and after voiding, the patient was asked to cough in order to verify the accuracy of pressure measurement, checking that the cough spikes in  $p_{ves}$  and  $p_{abd}$  were of equal size.

Patients were filled at a rate of  $50\text{ml}\cdot\text{min}^{-1}$  with room temperature normal saline. The presence or absence of detrusor overactivity was noted. If severe detrusor overactivity was encountered during filling the filling speed would be reduced, to allow adequate bladder filling. At cystometric capacity, when the patient described a normal desire to void, the patients were instructed to void into the flow meter. Simultaneous recordings were made of intravesical pressure ( $p_{ves}$ ), intraabdominal pressure ( $p_{abd}$ ), detrusor pressure ( $p_{det}$ ), by subtraction of  $p_{abd}$  from  $p_{ves}$ , and flow rate. From these recordings, measurements were taken of: detrusor and intravesical pressures at maximum flow ( $p_{det.Qmax}$  and  $p_{ves.Qmax}$ ), maximum flow rate ( $Q_{max}$ ), voided volume, minimum detrusor and intravesical pressures at urethral opening[3] (start of flow) ( $p_{det.Qbeg}$  and  $p_{ves.Qbeg}$ ), detrusor and vesical pressures at minimum flow[11] (10mls prior to the end of flow) ( $p_{det.Qend}$  and  $p_{ves.Qend}$ ) and  $p_{abd}$ . From the  $Q_{max}$  and  $p_{det.Qmax}$  was calculated the Bladder Outlet Obstruction Index (BOOI) and Bladder Contractility Index (BCI)[16].



### Simultaneous invasive pressure flow studies and cuff test

Having completed the routine pressure flow studies the urethral catheter was left in situ and the patients were then refilled, standing, with room temperature normal saline at a rate of  $50\text{ml}\cdot\text{min}^{-1}$ . The presence or absence of detrusor overactivity was again noted. When the patient felt a normal desire to void, filling was stopped and a penile cuff was reapplied as described above. Again the patients were asked to void without straining and the cuff was inflated and deflated automatically, throughout voiding. The cuff machine was linked to the urodynamic equipment allowing simultaneous recording of  $p_{\text{ves}}$ ,  $p_{\text{abd}}$ ,  $p_{\text{det}}$ , cuff pressure ( $p_{\text{cuff}}$ ) and flow (see Fig. 2.3.4.). For each cuff inflation cycle an individual plot of  $p_{\text{cuff}}$  vs.  $Q$  was obtained (Fig. 2.3.2).



**Figure 2.3.4. Simultaneous recording of  $p_{\text{det}}$ ,  $p_{\text{ves}}$ ,  $p_{\text{abd}}$ ,  $p_{\text{cuff}}$  and flow rate. Due to the linkage of the cuff machine to the Dantec urodynamic equipment 2 “V” on the cuff pressure scale represents  $200\text{cmH}_2\text{O}$ . As flow is detected by the cuff machine the cuff**

**starts to inflate (point A). As cuff pressure increases  $p_{det}$  and  $p_{ves}$  start to rise (point B) to an isovolumetric peak. As flow ceases the cuff deflates and  $p_{det}$  and  $p_{ves}$  fall back to pre-inflation levels (point C).**

For each cuff inflation cycle various measurements were taken. From the individual traces of cuff pressure and flow:  $p_{cuff.int}$ ,  $p_{cuff.knee}$ , as above, and flow rate. From the combined recordings of bladder and abdominal pressures with cuff pressures: detrusor and intravesical pressures prior to cuff inflation ( $p_{det.pre}$  and  $p_{ves.pre}$ ), detrusor and intravesical pressures at knee pressure ( $p_{det.knee}$  and  $p_{ves.knee}$ ), detrusor and intravesical pressures at cuff interruption pressure ( $p_{det.int}$  and  $p_{ves.int}$ ), and highest detrusor and intravesical pressures at the end of flow ( $p_{det.isv}$  and  $p_{ves.isv}$ ).

### **Voiding urethral pressure profiles**

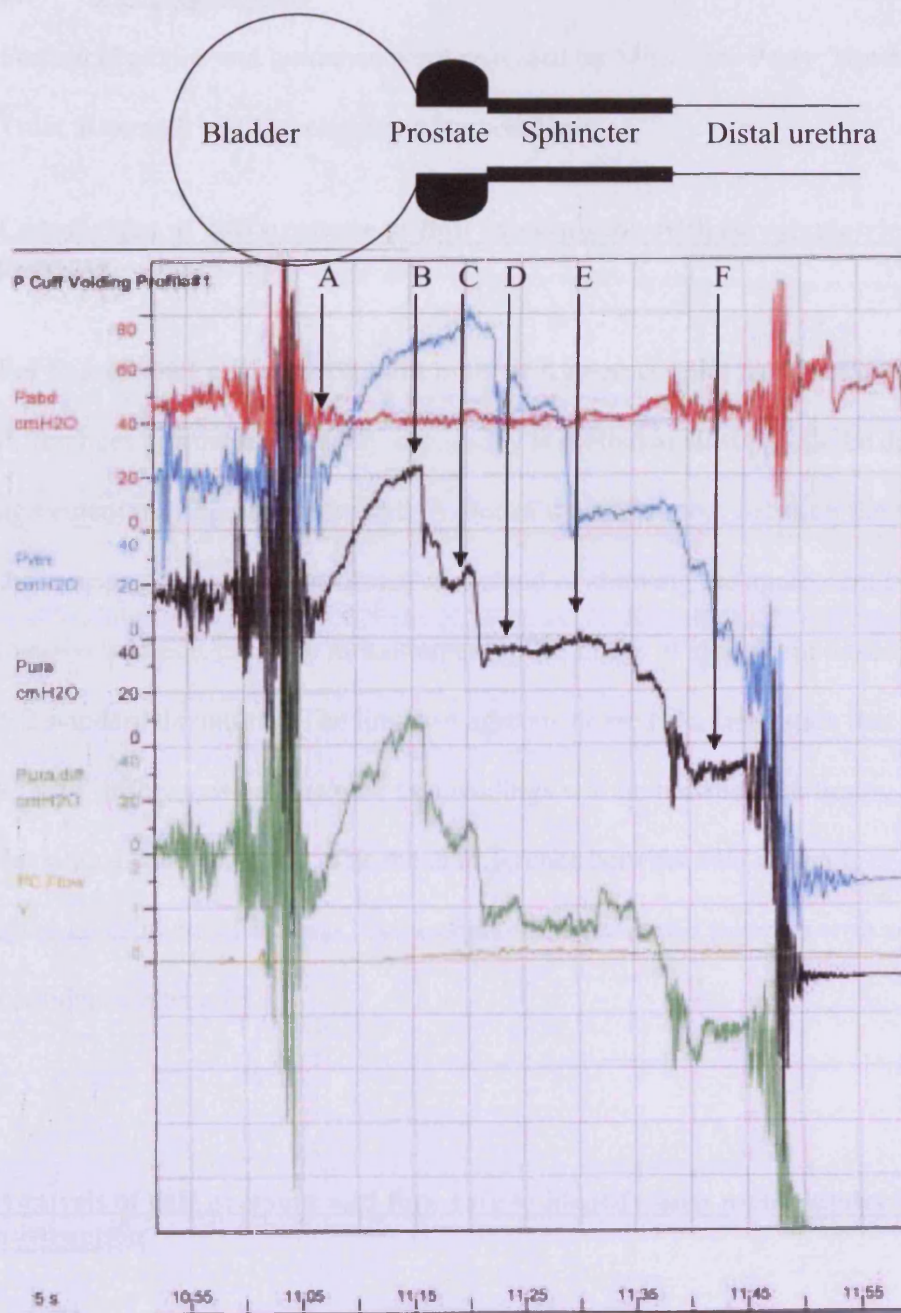
In order to measure voiding urethral pressure profiles, a modification of Yalla's technique was used[76]. Although Yalla describes a 10Ch double lumen catheter with two side holes for the proximal lumen, we used a 6Ch double lumen catheter, with a single side hole proximally, as described above. This enabled us to use one catheter for each fill/void cycle, without the need to change catheters between each part of the study. The bladder was refilled with room temperature normal saline at  $50\text{ml}\cdot\text{min}^{-1}$ . At normal desire to void filling was stopped. The proximal lumen of the catheter was attached to a third pressure transducer, allowing simultaneous measurement of intraurethral pressure (at the proximal side hole),  $p_{ves}$  (at the catheter tip) and  $p_{abd}$ . The catheter was orientated with the proximal

side hole facing laterally. Once voiding was established the catheter was withdrawn.

Initially in these experiments a mechanical pulling device was used at a pull of 5mm.sec<sup>-1</sup>.

<sup>1</sup>. Subsequently a manual pull at approximately the same speed was adopted.

At the start of voiding both catheter side holes, proximal and distal, are in the bladder. As the detrusor contracts, pressures measured at the bladder and urethral ports both rise and are similar (Fig. 2.3.5 point A to B). Once flow is established the catheter is withdrawn and as the proximal side hole passes through the bladder neck and into the prostatic urethra the measured pressure is seen to fall below that of intravesical pressure (Fig. 2.3.5 point B) to a plateau (Fig. 2.3.5 point C). A subsequent pressure drop is then seen as the urethral port moves from the prostatic urethra to the external sphincter and pelvic floor area where a further plateau of pressure is seen (Fig.2.3.5. point D); this is often followed by a transient rise in pressure (Fig. 2.3.5 point E) as the catheter passes into the distal urethra (Fig. 2.3.5. point F). Pressure measurements were taken at each of these points: points B, C, D, E and F.



**Figure 2.3.5. Voiding urethral pressure profile.** Abdominal pressure ( $p_{abd}$ ), intravesical pressure ( $p_{ves}$ ), urethral pressure ( $p_{ura}$ ), subtraction of vesical pressure from urethral pressure ( $p_{ura.diff}$ ). See text for details.



## **2.4 Data Analysis**

Statistical advice and guidance were provided by Miss Kate Parry, North Bristol NHS Trust, Research and Development Support Unit.

### **Comparison of cuff pressure at flow interruption with isovolumetric bladder pressure.**

For this analysis a Bland-Altman Limits of Agreement plot has been used, plotting differences against means [80]. If  $p_{\text{ves.isv/int}}$  is plotted against  $p_{\text{cuff.int}}$  the degree of agreement may be gauged by eye. A plot of the differences between the variables against their mean gives a more informative method of showing the agreement between the invasive and non-invasive measurements. The limits of agreement described are the mean  $\pm 2$  standard deviations. The limits of agreement are calculated such that approximately 95% of differences between the two readings will lie between the limits, i.e. 2 standard deviations from the mean. The mean difference between two methods of measurement gives an estimate of the bias. All estimates are presented together with associated 95% confidence intervals.

### **Analysis of cuff pressure and flow rate to identify men with bladder outlet obstruction**

By plotting  $p_{\text{cuff.int}}$  against free flow rates and flow rates taken from the cuff test we hope to identify those men with poor flow associated with high non-invasively measured detrusor contractility (i.e. obstructed on standard pressure flow studies) who would be



expected to do well from bladder outlet surgery (TURP/BNI) and those with a low flow rate associated with a low detrusor contractility (i.e. unobstructed) who would be expected to do less well from surgery.

### **Identification of patients with knee pressures**

In order to find the proportion of patients in whom identifiable knee pressures are found and to see if the presence or absence of a knee pressure is related to diagnosis of either obstructive grade (obstructed, equivocal, unobstructed) as defined by BOOI (using  $p_{det,Q_{max}}$  and  $Q_{max}$ ) from invasive pressure flow studies, or detrusor overactivity a Chi-square test has been used.

### **Comparison of knee pressure with urethral opening pressure**

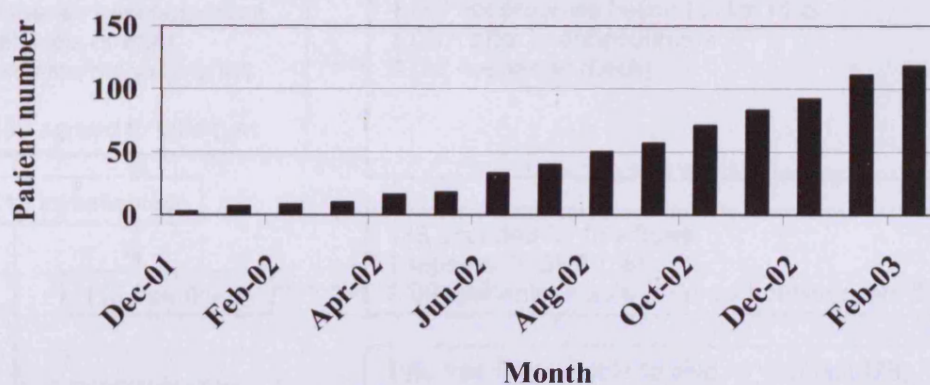
Limits of agreement plots have been used to compare knee pressures with the various measures of urethral opening pressure discussed in the introduction. From invasive pressure flow studies:  $p_{ves,Q_{beg}}$  and  $p_{ves,Q_{end}}$ , and from the voiding urethral pressure profiles the various pressures and pressure gradients measured in the proximal urethra.

### **3. Results**

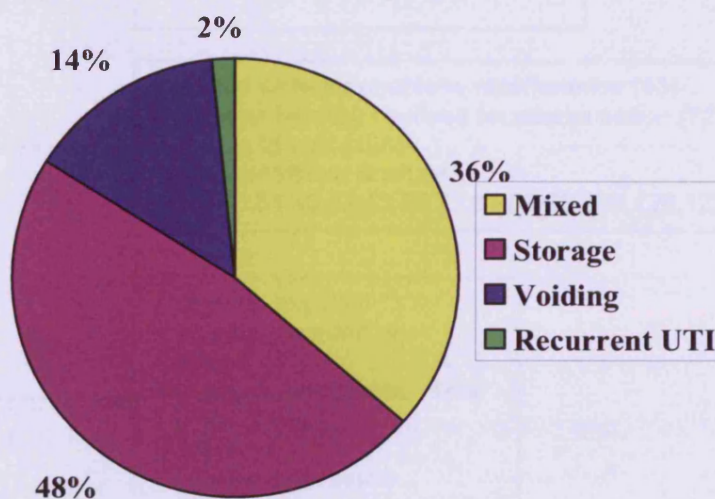
#### **3.1 Population data**

118 men were investigated between 17 January 2002 and 31 March 2003 (Fig 3.1.1. and 3.1.2). Patient ages ranged from 39 to 86 with a mean age of 65.4 years (SD 9.7). 56 had storage symptoms, 17 voiding symptoms, 43 had mixed (storage and voiding) LUTS, and 2 complained of recurrent urinary tract infections (UTI) (Fig.3.1.3). The mean IPSS score was 18.2, SD 6.9, range 0-33. Body Mass Index ranged from 18.1 to 36.3 with a mean of 26.3 (SD 3.5).

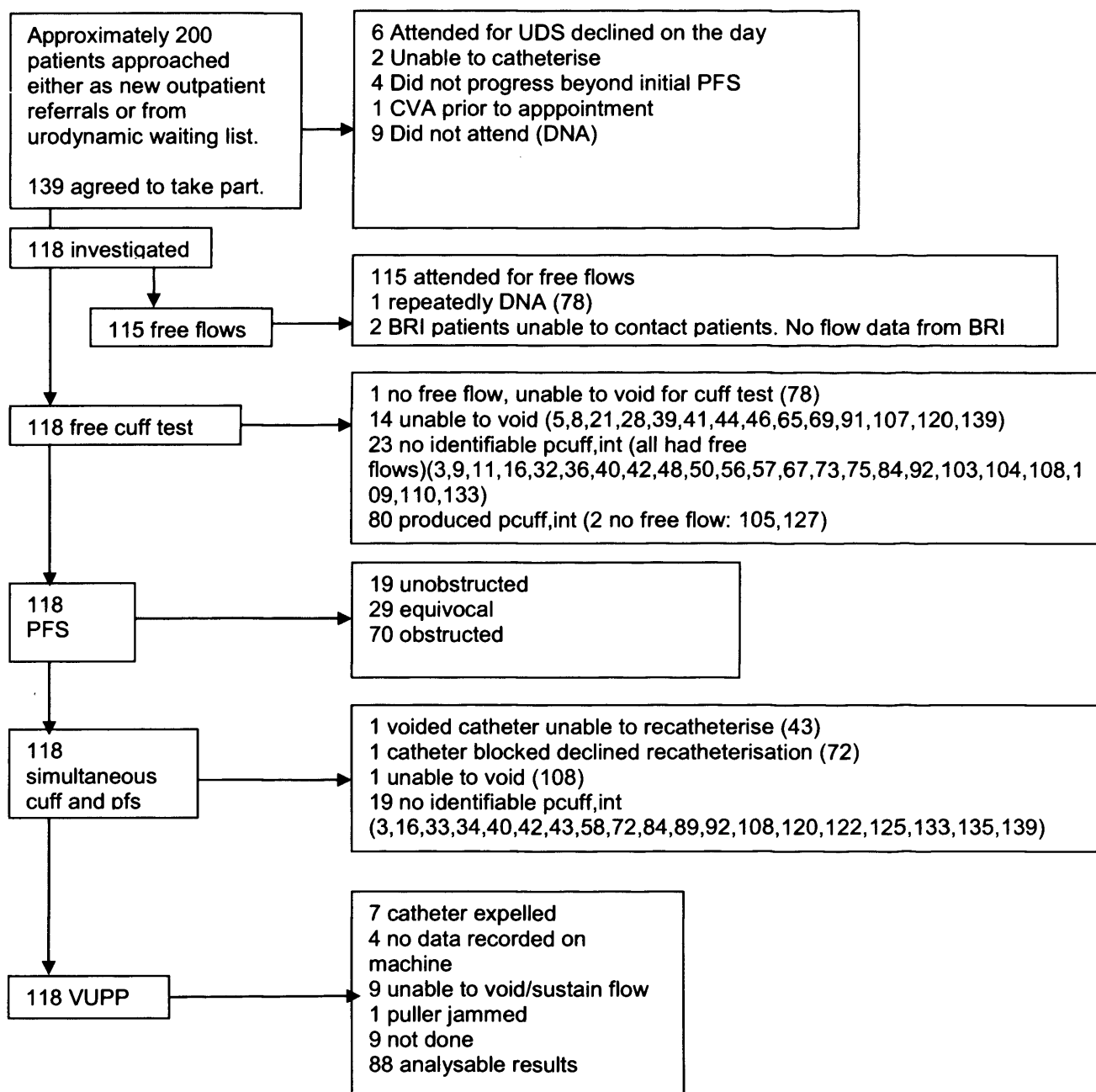
**Figure 3.1.1. Number of patients investigated between January 2002 and March 2003**



**Figure 3.1.2. Presenting symptoms**



**Figure 3.1.3. Flow chart of patients investigated.**



### 3.2 Free flow rates

115 patients attended for free flow rate assessment. 1 patient repeatedly did not attend and 2 patients from another hospital, on whom flow rates were not available, declined a further appointment.

Maximum flow rate, voided volume and post void residual were recorded in each of three voids and highest Qmax was identified, as representative of maximum achievable flow.

In concordance with previously published work, mean Qmax, Vvoid and PVR all increased across the three voids (paired t-test Qmax 1-2,  $p = 0.06$ ; Qmax 1-3,  $p = 0.01$ ) (Table 3.2.1.)[81].

**Table 3.2.1 Free flow rate data obtained from three consecutive voids performed by each patient in the flow clinic (n=115).**

	1 <sup>st</sup> Void			2 <sup>nd</sup> Void			3 <sup>rd</sup> Void			Best
	Qmax	Vvoid	PVR	Qmax	Vvoid	PVR	Qmax	Vvoid	PVR	Qmax
	(ml/s)	(ml)	(ml)	(ml/s)	(ml)	(ml)	(ml/s)	(ml)	(ml)	(ml/s)
Range	2-36	33-512	0-637	4-37	48-685	0-694	3-35	86-694	0-467	5-37
Mean	12.6	228.2	93.3	13.1	251.7	105.3	14.2	268.7	111.5	14.9
SD	6.2	111.7	117.6	5.8	124.9	122.1	6.2	139.6	109.8	6.3

### **3.3 Urodynamic and cuff studies**

The 118 patients who attended for urodynamic and cuff studies each underwent a free cuff test on arrival, prior to catheterisation. They were then catheterised as discussed above (section 2.3). The patients then underwent resting urethral pressure profile measurement, invasive filling cystometry and pressure flow studies, followed by a second filling cystometry and simultaneous invasive pressure flow studies and cuff test. Finally a third fill was performed followed by voiding urethral pressure profile measurement.

#### **Free cuff test**

Of the 118 patients 15 were unable to void (13%), 23 voided but produced no identifiable  $p_{\text{cuff.int}}$  (19%), by the standard analysis rules (Appendix C), and 80 patients produced an identifiable  $p_{\text{cuff.int}}$  (68%). In those patients who produced more than one identifiable  $p_{\text{cuff.int}}$  the highest value was taken (mean 113.6cmH<sub>2</sub>O, SD 42.7cmH<sub>2</sub>O, range 25-190cmH<sub>2</sub>O). 85 patients used a large cuff and 33 a small cuff. Highest  $p_{\text{cuff.int}}$  was taken as it was assumed that this would best represent the maximal contraction pressure generated by the bladder.

73 patients (62%) produced an identifiable  $p_{\text{cuff.knee}}$  (mean 75.6cmH<sub>2</sub>O, SD 36.7cmH<sub>2</sub>O, range 10-160cmH<sub>2</sub>O) of which 26 (36%) were classified as definitely present, 26 (36%) were classified as probably present and 21 (28%) as equivocal.

Highest  $Q_{\text{max}}$  was also measured (mean 9.7 ml.s<sup>-1</sup>, SD 5.4 ml.s<sup>-1</sup>, range 2-25ml.s<sup>-1</sup>).

The cuff test was straightforward to perform, although in one patient, with a large hydrocoele, there was difficulty in fitting a cuff. 5 patients found the cuff inflation uncomfortable at flow interruption (4.2%) and 3 experienced a small amount of self-limiting urethral bleeding (2.5%). Otherwise the cuff test was well tolerated.

### **Invasive filling cystometry and pressure flow studies**

118 patients underwent invasive filling cystometry and pressure flow studies. During filling 78 patients (64%) showed evidence of detrusor overactivity.

70 patients (59%) were found to be obstructed (BOOI > 40), 29 (25%) were equivocal for obstruction (BOOI 20-40) and 19 (16%) were unobstructed (BOOI <20). 24 patients (20%) had reduced bladder contractility (BCI <100), 59 (50%) had normal contractility (BCI 100-150) and 35 (30%) had strongly contractile bladders (Table 3.3.1.).

**Table 3.3.1. Pressure flow data obtained from single void in each patient (n=118)**

	Q <sub>max</sub> (ml.s <sup>-1</sup> )	P <sub>det.Qmax</sub> (cmH <sub>2</sub> O)	P <sub>ves.Qmax</sub> (cmH <sub>2</sub> O)	P <sub>abd</sub> (cmH <sub>2</sub> O)	BOOI	BCI
Mean	11	80	119	39	59	132
SD	4	37	36	16	39	38
Range	3 - 27	20 - 187	60 - 231	2 - 114	-10 - 127	59 - 271

Theoretical urethral opening pressures were also measured[11]; detrusor and vesical pressures at the start of flow,  $p_{det.Qbeg}$  and  $p_{ves.Qbeg}$ , were available for all 118 patients. In 23 patients (19%) an after contraction was seen at the end of voiding which would have given a falsely elevated value for the detrusor and vesical pressures at the end of flow,  $p_{det.Qend}$  and  $p_{ves.Qend}$ , these values were therefore discounted (2 sample t-test  $p_{det.Qend}$ ,  $p=0.01$ ;  $p_{ves.Qend}$ ,  $p=0.05$ ) (Table 3.3.2.).

**Table 3.3.2 Urethral opening pressures taken from invasive pressure flow studies**

	$p_{det.Qbeg}$ (n=118) (cmH <sub>2</sub> O)	$p_{ves.Qbeg}$ (n=118) (cmH <sub>2</sub> O)	$p_{det.Qend}$ (n=95) (cmH <sub>2</sub> O)	$p_{ves.Qend}$ (n=95) (cmH <sub>2</sub> O)
Mean	80	117	56	100
SD	41	40	31	33
Range	13-232	53-248	12-196	39-235

#### **Simultaneous invasive pressure flow studies and cuff test**

Of the 118 patients who underwent standard pressure flow studies, 1 voided his catheter and attempted recatheterisation failed, one patient declined recatheterisation after his catheter became blocked. Of the 116 patients who underwent further filling cystometry 52 (45%) showed evidence of detrusor overactivity.



During simultaneous PFS and cuff test, one patient voided his catheter and declined recatheterisation, for one patient the urodynamic equipment failed to record any voiding data and one patient was unable to void after bladder filling. The patient who was unable to void had also been unable to void during the free cuff test.

Two patients found the cuff uncomfortable at flow interruption, one who had experienced similar discomfort during the free cuff test and one who had not. One patient who had experienced bleeding after the free cuff test, again had a small amount of bleeding after the combined cuff and pressure flow tests.

From the traces of cuff pressure against flow (Fig 2.3.2.)  $p_{\text{cuff.int}}$ ,  $p_{\text{cuff.knee}}$  and maximum flow rate were recorded. In those patients where more than one  $p_{\text{cuff.int}}$  was recorded during the void the highest value was used. Of the 113 patients who successfully underwent simultaneous PFS and cuff test, 17 did not produce an identifiable  $p_{\text{cuff.int}}$  (15%) (flow not stopped 7, failure of flow recovery 4, multiple stops/erratic flow 6). Of these 17, 8 failed to produce an identifiable  $p_{\text{cuff.int}}$  in both the free cuff test and simultaneous cuff test with invasive pressure flow monitoring.

In those patients in whom more than one knee pressure was recorded the highest value was recorded. 103 patients produced an identifiable knee pressure.

**Table 3.3.3. Cuff pressure at flow interruption, knee pressures and highest Q<sub>max</sub> from simultaneous pressure flow studies and cuff test.**

	P <sub>cuff.int</sub> (n=96) (cmH <sub>2</sub> O)	Highest p <sub>cuff.knee</sub> (n=103) (cmH <sub>2</sub> O)	Q <sub>max</sub> (n=113) (ml.s <sup>-1</sup> )
Range	70 - 200	25 - 170	3 - 21
Mean	129	92.8	8.3
Median	125	90	8
SD	34.3	32.6	3.1

From the simultaneous recordings of vesical pressure and cuff pressure (Fig 2.3.4.), vesical pressure prior to cuff inflation (p<sub>ves.pre</sub>), vesical pressure at knee pressure (p<sub>ves.knee</sub>), vesical pressure at p<sub>cuff.int</sub> (p<sub>ves.int</sub>) and highest vesical pressure at the end of flow (p<sub>ves.isv</sub>) were measured (Table 3.3.4.). In some patients vesical pressure at the end of flow continued to rise after flow interruption thus making p<sub>ves.isv</sub> higher than p<sub>ves.int</sub>.

**Table 3.3.4. Vesical pressures: prior to cuff inflation ( $p_{ves.pre}$ ), at knee pressure ( $p_{ves.knee}$ ), at cuff interruption pressure ( $p_{ves.int}$ ) and the highest pressure at the end of flow ( $p_{ves.isv}$ )**

	$p_{ves.pre}$ (n=103)  (cmH <sub>2</sub> O)  corresponding to  Highest $p_{cuff.knee}$	$p_{ves.knee}$ (n=103)  (cmH <sub>2</sub> O)  corresponding to  Highest $p_{cuff.knee}$	$p_{ves.int}$ (n=96)  (cmH <sub>2</sub> O)	$p_{ves.isv}$ (n=96)  (cmH <sub>2</sub> O)
Mean	111	109	113	123
SD	34	32	32	33
Range	55-208	56-204	63 - 193	64 – 193

### **Voiding urethral pressure profiles**

Of the 116 patients who underwent simultaneous PFS and cuff test 7 declined a further fill. 109 remaining patients underwent voiding urethral pressure profile measurement. In 8 patients the catheter was expelled during pressure measurement, these patients were not recatheterised. In 4 the urodynamic equipment failed to record any data. 7 patients were unable to void. In one patient the mechanical puller jammed and in one patient no interpretable results were obtained because the proximal catheter lumen was not in the bladder at the start of voiding. 88 patients produced interpretable results. Urethral

pressure measurements were taken at various points along the profile (Fig.2.3.5.) and pressure gradients between these points were calculated.

Pressures were measured (Table 3.3.5) at the bladder neck (Fig.2.3.5. point B), at the pelvic floor (Fig.2.3.5. point D) and in the distal urethra (Fig.2.3.5. point F). In some patients a plateau was seen within the prostatic urethra (67/88, 76%) and a rise in pressure at the distal pelvic floor (79/88, 90%) (Fig.2.3.5. points C and E respectively); where these occurred, pressure measurements were also taken at these points. Pressure gradients were calculated from the bladder neck to prostatic plateau (Fig.2.3.5. point B to C), bladder neck to pelvic floor plateau (Fig.2.3.5. point B to D), bladder neck to distal pelvic floor (Fig.2.3.5. point B to E), and bladder neck to distal urethra (Fig.2.3.5. point B to F).

**Table 3.3.5. Urethral pressure measurements taken during voiding (see text above)**

	Voiding urethral pressure measurements (cmH <sub>2</sub> O)								
	Bladder neck	Prostate plateau	Pelvic floor plateau	Pelvic floor peak	Distal urethra	Pressure fall bladder neck to prostate plateau	Pressure fall bladder neck to pelvic floor plateau	Pressure fall bladder neck to pelvic floor peak	Pressure fall bladder neck to distal urethra
Mean	102	65	37	45	-6	37	65	56	108
Median	98	62	34	43	-8	32.5	60	50.5	104.5
SD	30	21	15	15	15	23	31	32	34
Range	46-95	33-133	5-91	18-82	-37-43	9-125	13-172	8-166	39-232

## **4. Comparative data analysis and discussion**

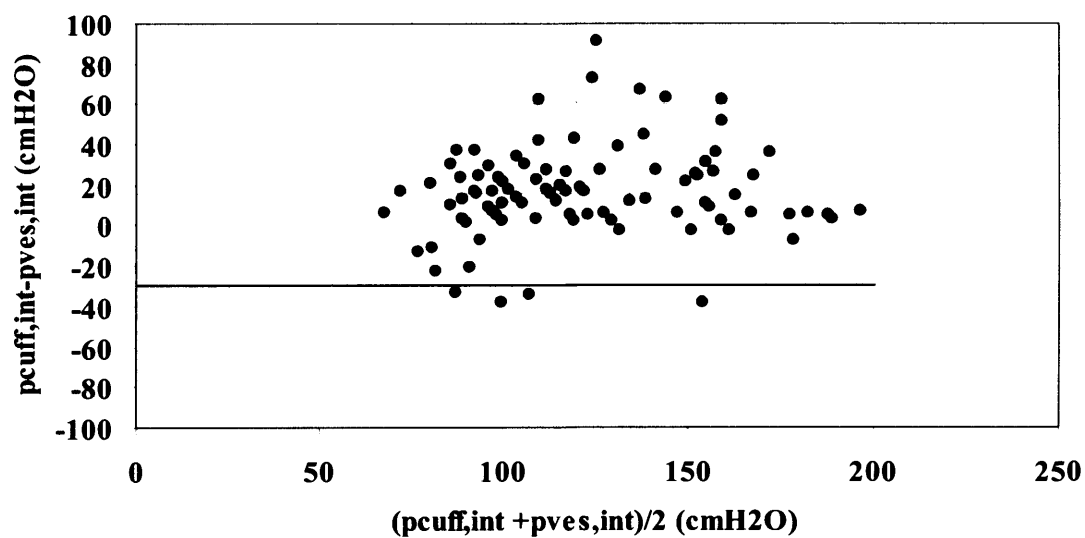
### **4.1 Comparison of cuff pressure at flow interruption with isovolumetric bladder pressure**

#### **Results**

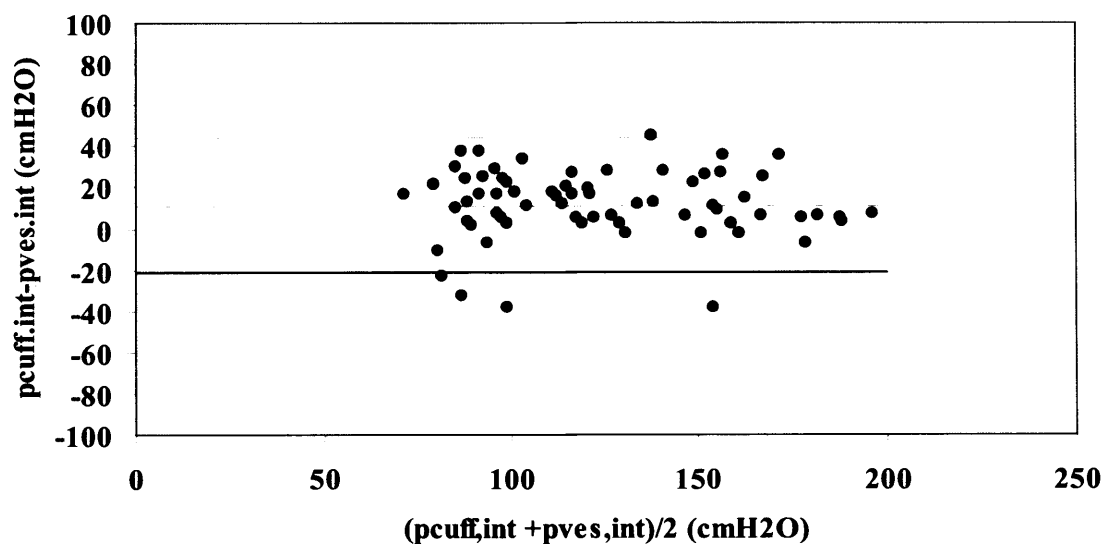
The highest cuff pressure at flow interruption ( $p_{\text{cuff.int}}$ ) was compared to the corresponding bladder pressure ( $p_{\text{ves.int}}$ ). A Limits of Agreement plot was constructed for all patients (Fig.4.1.1), those using large cuffs (Fig. 4.1.2.) and those using small cuffs (Fig. 4.1.3). The estimates of the mean difference and the limits of agreement are given (Table 4.1.1.).

Figure 4.1.1 shows a consistent bias for  $p_{\text{cuff.int}}$  to be greater than  $p_{\text{ves.int}}$  with a mean difference between the two measurements of 16cmH<sub>2</sub>O. Standard deviation of the mean difference was 23cmH<sub>2</sub>O giving limits of agreement 46cmH<sub>2</sub>O above and below the mean difference. Figure 4.1.2 shows large cuffs giving a smaller mean difference (11cmH<sub>2</sub>O), although a similar bias, between  $p_{\text{cuff.int}}$  and  $p_{\text{ves.int}}$  with narrower limits of agreement resulting from a smaller standard deviation (16cmH<sub>2</sub>O). Conversely small cuffs (26% of those with measurable  $p_{\text{cuff.int}}$ ) showed a much wider variation with mean difference of 28cmH<sub>2</sub>O and limits of agreement 56cmH<sub>2</sub>O above and below the mean. Table 4.1.1 shows the mean differences and limits of agreements for each group. As these are in themselves estimates of the population values 95% confidence intervals are also presented, which again show a small degree of variation around the mean and limits, less marked for large cuffs and more noticeable for small.

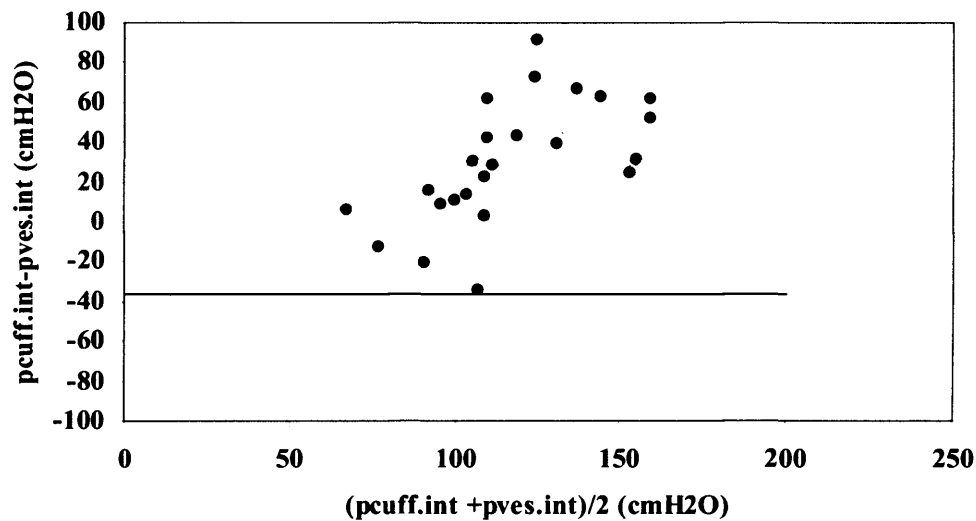
**Figure 4.1.1. Limits of agreement plot for pcuff,int and pves,int large and small cuffs. n=96**



**Figure 4.1.2. Limits of agreement plot for pcuff,int and pves,int large cuffs only. n=71.**



**Figure 4.1.3. Limits of agreement plot for  $p_{\text{cuff.int}}$  and  $p_{\text{ves.int}}$  small cuffs only.  $n=25$ .**



**Table 4.1.1. Mean difference and limits of agreement between  $p_{\text{cuff.int}}$  and  $p_{\text{ves.int}}$  with corresponding 95% confidence intervals. Large and small cuffs,  $n=96$ . Large cuffs,  $n=71$ . Small cuffs,  $n=25$ .**

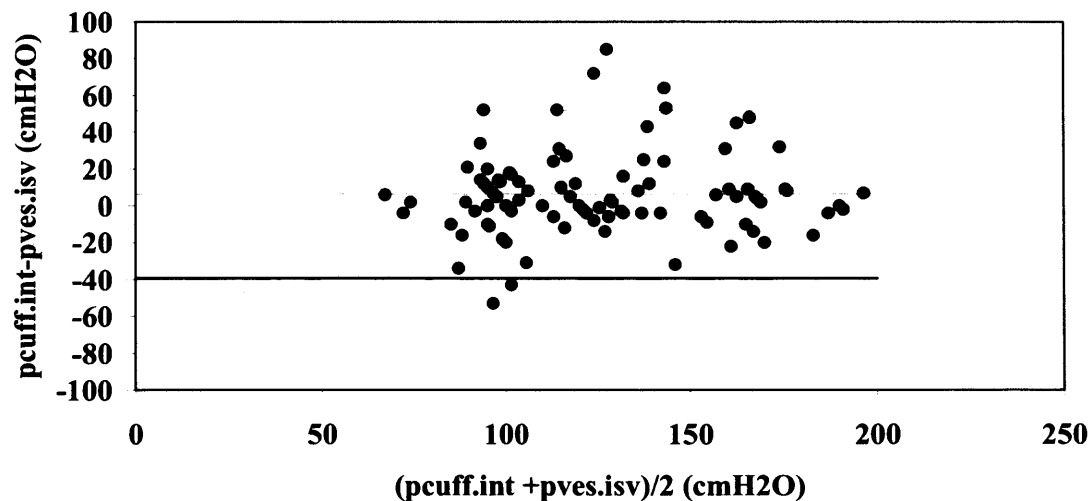
		Estimate	95% confidence intervals
Mean difference	All cuffs	15.6	11.0 – 20.3
$(p_{\text{ves.int}} - p_{\text{cuff.int}})$ (cmH <sub>2</sub> O)	Large cuffs	11.3	7.4 – 15.2
	Small cuffs	28.0	15.2 – 40.9
Upper limit of agreement (cmH <sub>2</sub> O)	All cuffs	60.8	52.8 – 68.8
	Large cuffs	43.9	37.2 – 50.6
	Small cuffs	92.1	69.9 – 114.3
Lower limit of agreement (cmH <sub>2</sub> O)	All cuffs	-29.5	-37.5 – -21.5
	Large cuffs	-21.3	-28.0 – -14.6
	Small cuffs	-36.0	-58.2 – -13.8



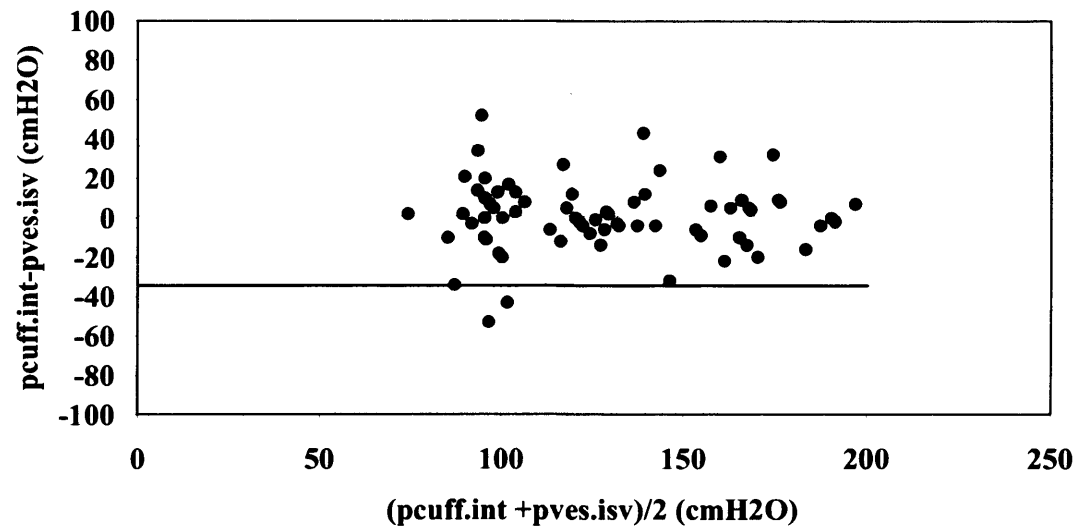
Highest  $p_{\text{cuff.int}}$  was also compared to the highest bladder pressure at the end of flow for the corresponding cuff inflation ( $p_{\text{ves.isv}}$ ). Again Limits of Agreement were used and large and small cuffs were assessed together and separately (Figs 4.1.4, 4.1.5 and 4.1.6 respectively). Estimates of mean difference and limits of agreement are given in Table 4.1.2.

Figure 4.1.4 again shows a positive bias of  $p_{\text{cuff.int}}$  over  $p_{\text{ves.isv}}$  but to a lesser degree than for  $p_{\text{ves.int}}$  (mean difference for all cuffs 6cmH<sub>2</sub>O, standard deviation 23cmH<sub>2</sub>O). Small cuffs showed a much wider variation than large cuffs compared with the invasively measured pressures (mean difference  $\pm$  SD: large cuffs 1  $\pm$  18 cmH<sub>2</sub>O, small cuffs 21  $\pm$  29cmH<sub>2</sub>O).

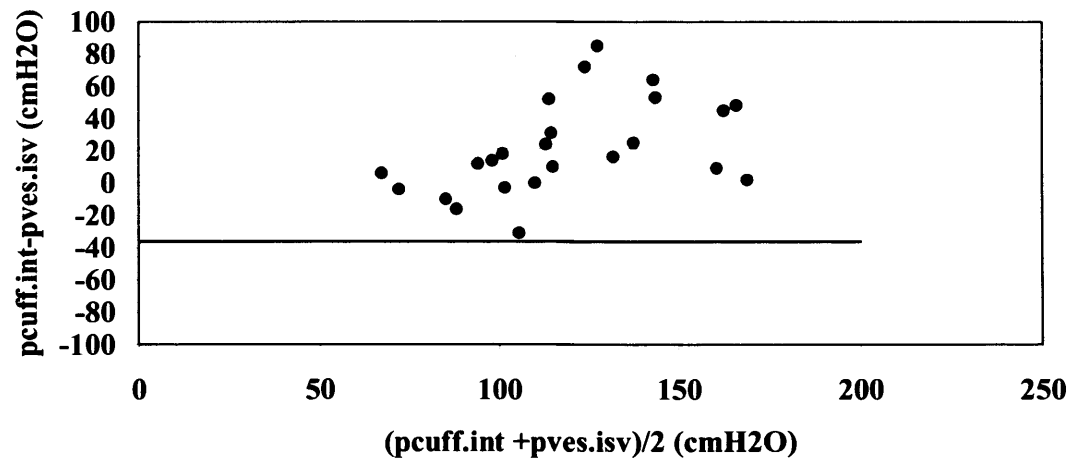
**Figure 4.1.4. Limits of agreement plot for  $p_{\text{cuff.int}}$  and  $p_{\text{ves.isv}}$ , large and small cuffs, n=96**



**Figure 4.1.5. Limits of agreement plot for pcuff.int and pves.isv,  
large cuffs only, n=71.**



**Figure 4.1.6. Limits of agreement plot for pcuff.int and pves.isv  
small cuffs only n=25**



**Table 4.1.2. Mean difference and limits of agreement between  $p_{\text{cuff.int}}$  and  $p_{\text{ves.isv}}$  with corresponding 95% confidence intervals. Large and small cuffs, n=96. Large cuffs, n=71. Small cuffs, n=25.**

		Estimate	95% confidence intervals
Mean difference ( $p_{\text{ves.isv}} - p_{\text{cuff.int}}$ ) (cmH <sub>2</sub> O)	All cuffs	6.3	1.6 – 10.9
	Large cuffs	1	-3.2 – 5.2
	Small cuffs	21.3	9.8 – 32.8
Upper limit of agreement (cmH <sub>2</sub> O)	All cuffs	51.8	43.8 – 59.9
	Large cuffs	36.4	29.1 – 43.6
	Small cuffs	78.7	58.8 – 98.6
Lower limit of agreement (cmH <sub>2</sub> O)	All cuffs	-39.3	-47.3 - -32.2
	Large cuffs	-34.4	-41.6 - -27.1
	Small cuffs	-36.1	-56.0 - -16.2

## **Discussion**

Our data is consistent with previously published work[49] and shows reasonable agreement between cuff pressure at flow interruption and simultaneous intravesical pressure, measured invasively. Taking all cuff sizes, cuff pressure in this study overestimates intravesical pressure by a mean ( $\pm$  SD) of 15.6 ( $\pm$  22.6)cmH<sub>2</sub>O. This is in part due to the height difference between the bladder and cuff, however, the measured height difference is less, approximately 8-10cmH<sub>2</sub>O[82]. When large and small cuffs are

analysed separately then the large cuffs do give a much closer approximation to the measured value. From experimental work it has been shown that narrower cuffs transmit pressure less well to the penile urethra and it is this that is likely to be the cause of the differences seen[53]. The limits of agreement show, however, that there is a degree of variability between the two measurements, invasive and non-invasive. This may partly be inherent to the cuff test but may also be related to the fact that intravesical pressure is changing as flow stops and its value is dependent on the point at which it is measured.

The assumption has been made that intravesical pressure at point of flow interruption is the maximum contraction pressure generated by the bladder. However, we see that in many cases the pressure continues to rise after flow has stopped. This means that, while operating under isovolumetric conditions, the bladder is acting under conditions of increasing contractility and power[4,83]. There is a close correlation between  $p_{\text{ves.int}}$  and  $p_{\text{ves.isv}}$  ( $r=0.93$ ) but there is a consistent and measurable difference between them (mean 9.4cmH<sub>2</sub>O, SD 11.2cmH<sub>2</sub>O). This effect means that isovolumetric and maximum contraction pressures, although similar, are not necessarily the same thing.

This raises the question as to what is the nature of isovolumetric pressure? Isovolumetric pressure is, by definition, the result of bladder contraction at a fixed volume. However, this appears to vary according to the point at which it is measured. In other words  $p_{\text{ves.int}}$  is *an* isovolumetric pressure but may not be the *maximum* bladder contraction pressure. As a result of the differences between these various measures,  $p_{\text{cuff.int}}$  provides a closer

approximation to  $p_{ves.isv}$  (maximum contraction pressure) than  $p_{ves.int}$  (isovolumetric pressure at flow interruption), although this may well be a mathematical coincidence.

It has been shown that  $p_{cuff.int}$  falls after TURP[47] and that with obstruction the bladder compensates generating higher isovolumetric pressures[84,85]. If the bladder responds to increasing obstruction over a prolonged period it may be that the rise in pressure from flow interruption to maximum contraction pressure, that we have demonstrated, is evidence of an acute compensation to a sudden increase in urethral resistance.

The cuff test was found to be straightforward to perform and generally well tolerated. Patient discomfort from cuff inflation was similar to that reported elsewhere[49,59] and less than that reported from other non-invasive techniques (16%)[43]. Urethral bleeding (3 patients, 2.5% in our series) has not been previously reported for the cuff test but has been reported using other non-invasive techniques in the order of 7-16%[43,86], particularly in patients taking anticoagulants. All bleeding was self limiting and is likely to be due to the pressures applied to the urethra by cuff pressure approaching 200cmH<sub>2</sub>O.

## **Conclusion**

In this study we have shown that cuff pressure at flow interruption does correspond to simultaneously measured intravesical pressure. This may be slightly different to isovolumetric pressure but in clinical practice this is unlikely to be of great significance.

We believe that our study validates the use of the penile cuff technique to estimate intravesical pressure at or approaching isovolumetric conditions and that this information could be used as part of the basis for a non-invasive pressure flow nomogram to diagnose bladder outlet obstruction in men.

#### **4.2. Comparison of cuff pressure at flow interruption with flow rate to identify men with bladder outlet obstruction: construction of a nomogram**

As discussed previously, using invasive pressure flow studies, men may be classified into obstructed, equivocal and unobstructed groups by plotting  $Q_{\max}$  and  $p_{\det.Q_{\max}}$  on the ICS nomogram. During non-invasive bladder pressure measurement, however,  $p_{\text{cuff.int}}$  is measured rather than  $p_{\det.Q_{\max}}$ . Cuff interruption pressure ( $p_{\text{cuff.int}}$ ) differs from  $p_{\det.Q_{\max}}$  in two important ways. First,  $p_{\text{cuff.int}}$  includes abdominal pressure ( $p_{\text{abd}}$ ) and, second,  $p_{\text{cuff.int}}$  estimates isovolumetric bladder pressure ( $p_{\text{ves.isv}}$ ) as flow is zero at the time of measurement. In collaboration with the group in Newcastle, we hypothesise that by adjustment of the ICS nomogram to allow for both the inclusion of  $p_{\text{abd}}$ , and the rise to isovolumetric pressure, a modified nomogram could be constructed for use with non-invasive cuff test data to classify bladder outlet obstruction with sufficient accuracy for clinical use. For the construction of the modified nomogram, data from Bristol and Newcastle was used. This nomogram was then validated against invasive PFS for the combined data and the Bristol data alone.

##### **Development of a non-invasive nomogram**

On the ICS nomogram (Figure 4.2.1a), the line separating obstructed patients (O) from equivocal (E) and unobstructed (U) patients intercepts the vertical axis at 40 cm H<sub>2</sub>O and has a slope of 2 cm H<sub>2</sub>O per ml s<sup>-1</sup>. The position and slope of this line need to be adjusted to allow for the inclusion of abdominal pressure (step 1) and the dependency on flow rate

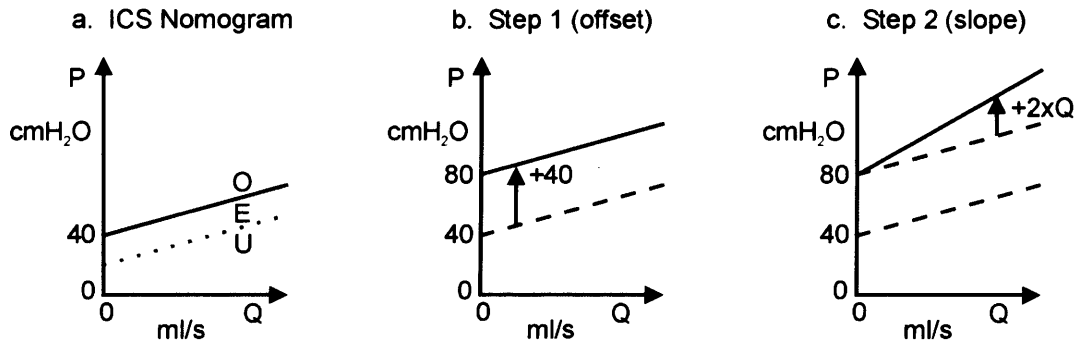
of the increase in bladder pressure that occurs if established voiding is interrupted (step 2).

Step 1: Newcastle have previously reported a mean (SD) abdominal pressure during voiding of 35 (9) cm H<sub>2</sub>O in 100 patients[87]. Allowing for the additional mean (SD) measured height difference between the bladder and cuff of 8.8 (1.4) cm[82], we hypothesise that for non-invasive data the 'obstruction line' should be moved upwards by 43.8 cm water. For simplification we round this to the nearest 10 cm H<sub>2</sub>O, giving a 'y' axis intercept of 80 compared to 40 cm H<sub>2</sub>O (Figure 4.2.1b).

Step 2: Figure 4.2.2 demonstrates the pressure rise during interruption ( $p_{\text{det.isv}} - p_{\text{det.pre}}$ ) for 64 inflation cycles in 13 subjects[88]. The line of 'best fit' for the data has a slope of 1.71 cm H<sub>2</sub>O per ml s<sup>-1</sup>. A similar factor of 2 cm H<sub>2</sub>O per ml s<sup>-1</sup> was deduced from data in a separate study[89]. To allow for a typical pressure rise during interruption of 2 cm H<sub>2</sub>O times  $Q_{\text{max}}$ , the slope of the 'obstruction line' should therefore be increased from 2 to 4 cm H<sub>2</sub>O per ml s<sup>-1</sup> (Figure 4.2.1c). ).

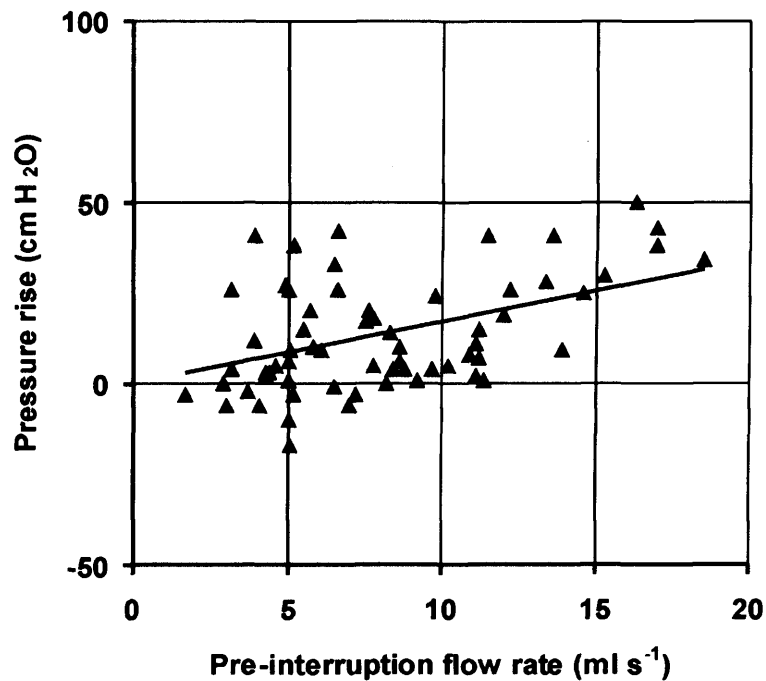
These steps allowed construction of a proposed non-invasive pressure-flow nomogram that could then be prospectively validated.





**Figure 4.2.1**

**Stages in transition from the ICS nomogram (a) to the modified nomogram for non-invasive bladder pressure data. Step 1 (b) allows for abdominal pressure and cuff height; and step 2 (c) allows for the isovolumetric rise in pressure during interruption. See text for further explanation.**



**Figure 4.2.2. Pressure rise during interruption as a function of flow rate prior to interruption. The regression line has a slope of 1.71 cm H<sub>2</sub>O per ml s<sup>-1</sup>.**

### **Patients**

Combined invasive and non-invasive pressure-flow data were obtained from men recruited in the two separate institutions (Newcastle and Bristol). At both sites, ethical approval was obtained and men were recruited, following informed consent, from those referred for PFS to investigate LUTS.

### *Invasive pressure-flow studies and 'gold standard' classification of obstruction*

PFS was performed, as described previously, according to ICS 'Good Urodynamic Practices' guidelines[7], in the standing position. Detrusor pressure at maximum flow ( $p_{det.Q_{max}}$ ) and maximum flow rate ( $Q_{max}$ ) were obtained and plotted on the ICS nomogram[15] for classification of obstruction.

### **Non-invasive cuff test**

A "free" cuff test was performed in each patient, as described previously, in the absence of invasive urodynamic catheters, in order to mimic as much as possible the cuff test under clinical conditions of use. Identical equipment (Type FM319, Regional Medical Physics Department, Newcastle upon Tyne, UK) and procedure were used at both locations.

### **Analysis**

For each cuff inflation cycle, flow rate was plotted against cuff pressure, allowing for a delay of 1 s in the flow measurement. Cuff interruption pressure was thereby estimated (to the nearest 5 cm H<sub>2</sub>O) for each inflation cycle. For each cuff cycle the standard exclusion rules were applied (Appendix C). In addition, measurements for voided volumes of < 150 ml were also excluded since reliability of measurement of both  $p_{cuff.int}$  and  $Q_{max}$  is significantly reduced[82]. The highest measured  $p_{cuff.int}$  during each cuff test was used throughout. The maximum flow rate  $Q_{max}$  for the voiding cycle was measured,

discounting the surges occurring immediately after release of the cuff pressure following interruption.

For each patient,  $p_{\text{cuff.int}}$  was plotted against  $Q_{\text{max}}$  on the modified nomogram, using a symbol to indicate their standard classification according to the ICS nomogram from the separate invasive PFS. A chi squared test was performed to test the null hypothesis that the modified nomogram had no ability to classify obstructed patients. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for points lying above and below the 'obstructed line' on the modified nomogram in comparison to their invasive classification as obstructed or equivocal/unobstructed.

The classification of obstruction using the modified nomogram was also compared with classification using the commonly applied criterion of  $Q_{\text{max}} < 10 \text{ ml s}^{-1}$  [22].

## **Results – combined patients**

### **Patients**

In Newcastle 151 patients with a mean age of 63 (range 20 – 88) were studied. Of these, 107 were suitable for analysis having provided both a PFS study and at least one cuff inflation cycle that passed the exclusion criteria, and in 86 the cuff test voided volume was at least 150 ml. In Bristol 118 patients with a mean age of 66 (range 39 – 81) were studied with 78 providing both PFS and at least one acceptable cuff inflation, and 58 had

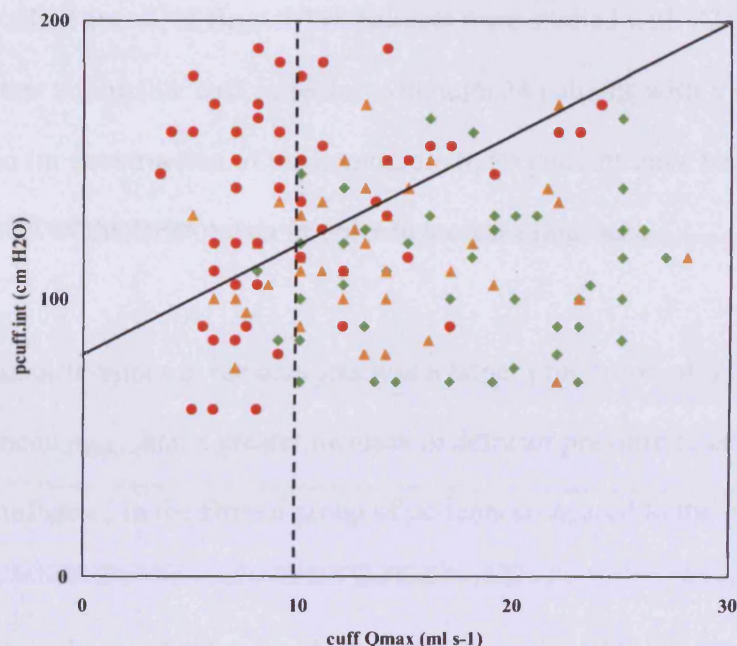
a voided volume of at least 150 ml. Overall, 144 (54%) of 269 men recruited had full data.

### **Invasive classification**

Use of invasive data classified 56 as obstructed, 42 as equivocal and 46 as unobstructed.

### **Nomogram and prediction of obstruction**

Figure 4.2.3 illustrates the result of plotting the data on the modified nomogram. For patients above the proposed 'obstructed line' ('y' axis intercept 80 cm H<sub>2</sub>O and slope of 4 cm H<sub>2</sub>O per ml s<sup>-1</sup>) the positive predictive value (PPV) for obstruction was 68% and sensitivity 64%. For patients below the line the negative predictive value (NPV) for equivocal/unobstructed was 78% and specificity 81%. The chi squared test demonstrated that it was extremely unlikely the proportion of unobstructed above the line occurred by chance ( $\chi^2 = 29.8$ ;  $p \ll 0.001$ ).



**Figure 4.2.3**

**Modified nomogram with data for 144 patients showing classification from invasive PFS and ICS nomogram by the symbol used: ● obstructed; ▲ equivocal; ◆ unobstructed.**

*Prediction of obstruction using  $Q_{\max}$  less than 10 ml/s*

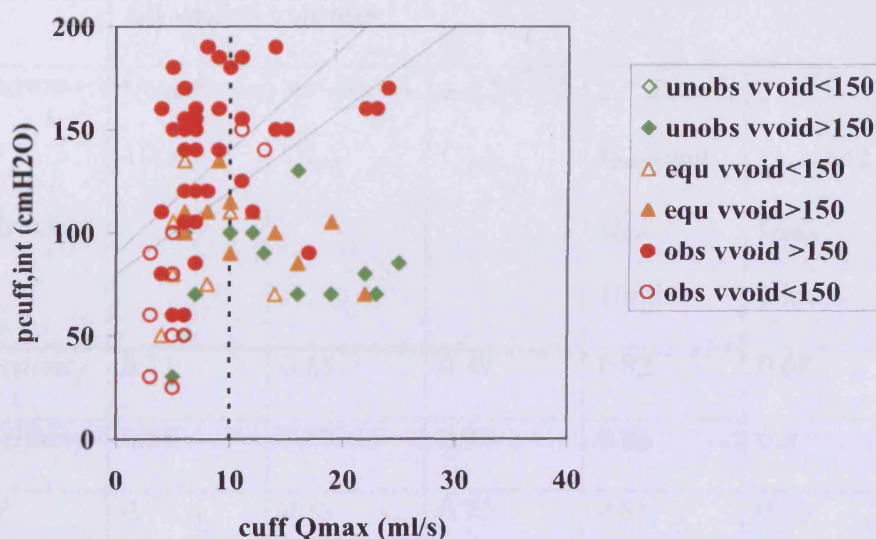
Applying a criterion of  $Q_{\max}$  less than 10 ml/s alone as a predictor of obstruction we found: PPV 77%, sensitivity 59%, NPV 77%, specificity 89%. However for the 68% of patients where both criteria either agreed the patient was obstructed (top left quadrant of Figure 4.2.3) or agreed the patient was equivocal/unobstructed (bottom right quadrant of Figure 4.2.3) the PPV was 88% (23 of 26) and the NPV was 86% (64 of 74).

## **Results – Bristol patients**

As described above, in Bristol 118 patients were studied with 82 providing both PFS and at least one acceptable cuff inflation. Although 24 patients with  $V_{void} < 150\text{mls}$  were excluded for construction of the nomogram these patients have been included for assessment of the Bristol data in order to increase numbers.

The main differences in the data sets was a larger proportion of obstructed patients, a higher mean  $p_{abd}$ , and a greater increase in detrusor pressure to isovolumetric pressure on cuff inflation, in the Bristol group of patients compared to the Newcastle group.

Of the Bristol patients 51 were obstructed on invasive PFS, 18 were equivocal and 13 were unobstructed. The mean value of  $p_{abd}$  for 121 patients who underwent standard pressure flow studies was  $38.7\text{cmH}_2\text{O} \pm 15.7\text{ cmH}_2\text{O}$  (SD) thus an upward move in the line separating obstructed from equivocal/unobstructed of  $47.5\text{cmH}_2\text{O}$  rounded to  $50\text{cmH}_2\text{O}$  and a “y” axis intercept of  $90\text{ cmH}_2\text{O}$ . For the Bristol patients the rise to isovolumetric pressure was approximately 3 times. These differences give an equation to the line separating obstructed from equivocal/non obstructed of  $y = 90 + 5Q_{max}$  rather than  $y = 80 + 4Q_{max}$ . Our data is plotted with both of these lines and a line representing  $Q_{max} = 10$  in Figure 4.2.4.



**Figure 4.2.4 Plot of  $Q_{\max}$  vs.  $p_{\text{cuff,int}}$ . Patients classified by ICS obstruction grade and voided volume.  $n=82$ .**

Sensitivity and specificity, positive and negative predictive values were calculated for each of these criteria as well as a combination of each slope/y-intercept with  $Q_{\max} < 10 \text{ ml.s}^{-1}$  (table 4.2.1). Values for combined data shown in brackets.



**Table 4.2.1 Sensitivity, specificity, positive and negative predictive values for differing criteria for obstruction using proposed nomogram. Bristol data shown for all voided volumes and  $V_{\text{void}} > 150\text{mls}$ , combined Bristol/Newcastle data in brackets.**

	<b>All voided volumes</b>						
Criterion for obstruction	$Q_{\text{max}} < 10\text{ml.s}^{-1}$	$y = 80 + 4 Q_{\text{max}}$	$y = 90 + 5 Q_{\text{max}}$	$y = 80 + 4 Q_{\text{max}}$ and $Q_{\text{max}} < 10\text{ml.s}^{-1}$	$y = 90 + 5 Q_{\text{max}}$ and $Q_{\text{max}} < 10\text{ml.s}^{-1}$	$y = 80 + 4.5 Q_{\text{max}}$	$y = 80 + 4.5 Q_{\text{max}}$ and $Q_{\text{max}} < 10\text{ml.s}^{-1}$
Sensitivity	0.71	0.65	0.49	0.82	0.68	0.59	0.76
Specificity	0.58	0.87	0.94	0.86	0.9	0.87	0.82
PPV	0.73	0.89	0.93	0.88	0.90	0.88	0.83
NPV	0.55	0.6	0.53	0.78	0.67	0.56	0.75
	<b>Voided volumes &gt; 150 mls</b>						
Sensitivity	0.69(0.59)	0.74(0.64)	0.59(0.45)	<b>0.81(0.70)</b>	0.70(0.53)	0.69(0.59)	0.78(0.64)
Specificity	0.73(0.89)	0.91(0.81)	0.95(0.94)	<b>0.89(0.95)</b>	0.94(0.97)	0.91(0.86)	0.89(0.96)
PPV	0.82(0.77)	0.93(0.68)	0.96(0.83)	<b>0.97(0.88)</b>	0.95(0.90)	0.93(0.73)	0.91(0.88)
NPV	0.57(0.77)	0.67(0.78)	0.58(0.73)	<b>0.76(0.86)</b>	0.67(0.81)	0.63(0.77)	0.73(0.84)

In those 18 Bristol patients, included in the nomogram, in whom a small cuff was used, 10 were correctly classified as either obstructed or unobstructed using the proposed nomogram ( $y = 80 + 4Q_{\text{max}}$  and  $Q < 10\text{ml.s}^{-1}$ ), 3 were incorrectly classified and 5 fell into either the top right or bottom left quadrants. Taking large cuffs alone did not greatly alter sensitivity (0.78), specificity (0.87), PPV (0.88) or NPV (0.76).

## **Discussion**

### **Modified nomogram**

The provisional ICS nomogram is currently the recommended method for classifying obstruction from invasive PFS data[15]. The boundary between obstructed patients and others is a feature common to earlier proposed nomograms[11,90]. Our hypothesis was that suitable adjustment of this boundary would allow use of non-invasive pressure flow measurements obtained with the penile cuff test to categorise men as obstructed. The subsequent prospective study presented here validates the proposed modified nomogram and suggests that non-invasive measurements are clinically useful.

The proposed offset correction (Step 1, above) was made to allow for abdominal pressure and the height difference between the bladder and the cuff. The abdominal pressure reading for the Bristol patients was measured as a baseline at the start of filling. It has been shown that abdominal pressure falls during voiding compared to the filling phase[87]. The Bristol measurements correspond with the published storage phase measurements and it may well be that this is the cause of the discrepancy between the Bristol and Newcastle readings.

The slope correction (Step 2, above) was made to allow for the isovolumetric rise in bladder pressure as flow is reduced to zero[2,4]. The correction was based on measurements from clinical data recorded during simultaneous cuff and PFS studies. The dependency of the rise in bladder pressure during interruption on flow rate is expected[4,60] though the observed magnitude is less than that predicted by Schäfer's

LPURR nomogram[11]. Published data suggest the discrepancy is not due to inhibition of bladder contraction[88]

In a separate study to investigate bladder contractility in a larger group of men undergoing simultaneous invasive and non-invasive PFS[91] it has been shown that bladder contractility increases with increasing degree of obstruction. Unobstructed patients showed an increase in detrusor pressure from normal voiding to isovolumetric conditions in the order of  $2Q_{\max}$ , equivocal patients  $2.2 Q_{\max}$  and obstructed patients increased by a factor of  $3Q_{\max}$ . The Bristol group of patients showed a larger proportion of obstructed patients and the Newcastle unobstructed/equivocal. This might suggest that an increase in slope of  $2.5Q_{\max}$  might be more appropriate, for the combined data, to take into account these differences.

Of all the various possible adjustments for both offset correction (Step 1) and slope correction (Step 2) for the obstructed/non obstructed line on the proposed nomogram,  $y = 80 + 4Q_{\max}$  is probably the best in terms of both sensitivity and specificity, with or without the addition of  $Q_{\max} < 10\text{mls}^{-1}$ , than any of the alternative potential criteria discussed above (Table 4.2.1)

### *Cuff interruption pressure*

The rationale for the proposed nomogram depends on  $p_{\text{cuff.int}}$  being a reliable estimate of  $p_{\text{ves.isv}}$ . This was previously demonstrated in studies in Newcastle[49,82] and has been validated by ourselves as part of this thesis. In these studies measurements were made

with a urethral catheter in situ during the cuff test which may have influenced the results. This will not be a factor in the present study where the cuff test was performed without a catheter present. Though isovolumetric pressure is not routinely used in the assessment of obstruction, it is a valid assessment of bladder contractility[4], and the correction to the slope of the nomogram compensates for the difference in isovolumetric pressure compared to pressure at maximum flow.

### *Q<sub>max</sub>*

$Q_{\max}$  from the same cuff study was plotted on the new nomogram. It should be noted the surge following release of cuff pressure was discounted, because it relates to release of urine from the distended proximal urethra. Simultaneous video fluoroscopy that shows clear expansion of the bulbar and penile urethra proximal to the cuff during interruption[51,92]. For the combined group of patients classified invasively as obstructed in this study, the mean cuff  $Q_{\max}$  ( $8.7 \text{ ml s}^{-1}$ ) is close to the mean free  $Q_{\max}$  ( $9.5 \text{ ml s}^{-1}$ ) obtained in the large, multi-centre ICS 'BPH' study for patients classified as obstructed by the same invasive criterion[22]Comiter found a similar mean  $Q_{\max}$  ( $9.3 \text{ ml s}^{-1}$ ) in over 100 men classified as obstructed using a different invasive criterion[93]. In a separate study [94]the Newcastle group found good agreement between  $Q_{\max}$  measured during a cuff test and a free flow test conducted on the same visit [mean difference ( $\pm$ SD) of  $0.1 (\pm 2.9) \text{ ml s}^{-1}$ ;  $n = 40$  patients]. In Bristol, patients underwent free flow rate evaluation at a separate visit where three free flows were undertaken. In the Bristol group, those patients subsequently classified as obstructed on PFS had a mean ( $\pm$ SD)  $Q_{\max}$  of  $13.4(\pm 4.8) \text{ mls}^{-1}$  at free flow. Thus a  $Q_{\max}$  of  $10 \text{ mls}^{-1}$  would seem to be a clinically

reasonable figure to use as an additional criterion for obstruction on the proposed nomogram. It would be feasible to use  $Q_{\max}$  from a separate free flow study but from a practical standpoint, there is an advantage to using the same voiding cycle and this is also consistent with the practice of using invasive flow and pressure measurements from the same voiding cycle in the ICS nomogram.

*Prediction of obstruction (using invasive PFS as 'gold standard')*

In this study, the sensitivity, specificity, PPV and NPV for detection of obstruction by both the modified nomogram and the flow rate criterion of  $< 10 \text{ ml s}^{-1}$  are similar confirming that both techniques provide clinically useful data. Both sets of figures are much better than for flow rate alone in the ICS 'BPH' study[22]. There is a clear further improvement in predictive value when both methods are in agreement: either both indicating obstruction (PPV 85%) or both indicating equivocal/unobstructed (NPV 90%). These accuracy rates indicate that the classification is clinically useful and suggest that the new technique, in addition to flow rate alone, can play a useful role in the management of patients with LUTS.

For the 32% in the lower left or upper right quadrants of Figure 4.2.3, where the modified nomogram and flow rate criteria do not agree, the diagnosis is less certain and further investigation may be required. These findings are similar to those of Comiter et al[93] who also proposed a 'four quadrant' nomogram using invasive data.

### *Exclusions*

The rules for an acceptable interruption cycle (Appendix C) are pragmatic, with the aim of ensuring reliable data. After applying the rules, at least one satisfactory measurement was obtained in 90% of patients who performed the test twice[82]. We have recently demonstrated that this can be markedly improved by prior scanning to estimate the volume in the bladder, maximal use of a larger size cuff and more precise patient instruction (unpublished).

The result of a conventional flow rate test is generally considered acceptable if the voided volume exceeds 150 ml. We have found a similar criterion applies to the cuff test. It has been shown that a voided volume of < 150 ml resulted in reduced likelihood of any cuff inflation cycle passing the exclusion criteria and, if it did,  $p_{\text{cuff.int}}$  was less repeatable[82]. Therefore, at present, exclusion of data where  $V_{\text{void}}$  is < 150ml would seem appropriate. Ultrasonic imaging to assess bladder volume prior to a cuff test may help to avoid this difficulty.

### **Clinical role**

The data presented here suggest the non-invasive cuff inflation test used with the modified nomogram can provide information useful in the management of individual patients by predicting their likely classification from a PFS. A prospective clinical study is underway to assess the proposed nomogram in relation to the outcome of elective prostatectomy and preliminary results are encouraging[47,95,96].

## **Conclusion**

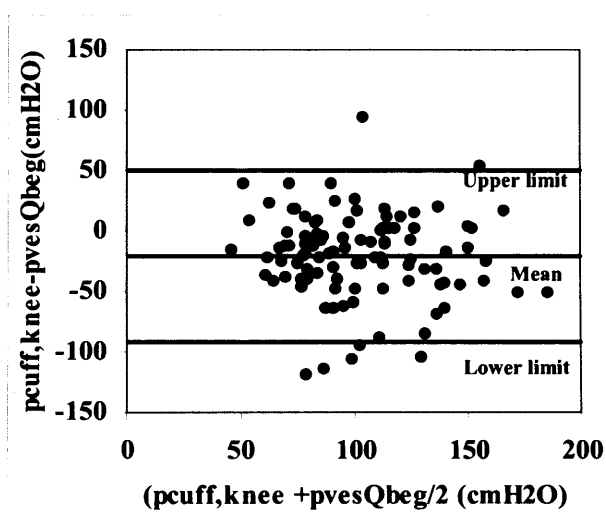
We have proposed a modification to the ICS nomogram for predicting obstruction from non-invasive pressure-flow data. We have tested the modified nomogram prospectively using data from two centres, with invasive PFS as ‘gold standard’, and found it to be particularly useful when non-invasive pressure flow measurements are used in combination with the frequently used criterion of  $Q_{\max} < 10 \text{ ml s}^{-1}$ . Assessment of the technique in relation to outcome from surgery is underway.

### 4.3 Non-invasive assessment of urethral opening pressures: making sense of the relationship between flow rate and penile cuff pressure

#### Comparison of “knee” pressure and measures of urethral opening pressure derived from standard pressure flow studies

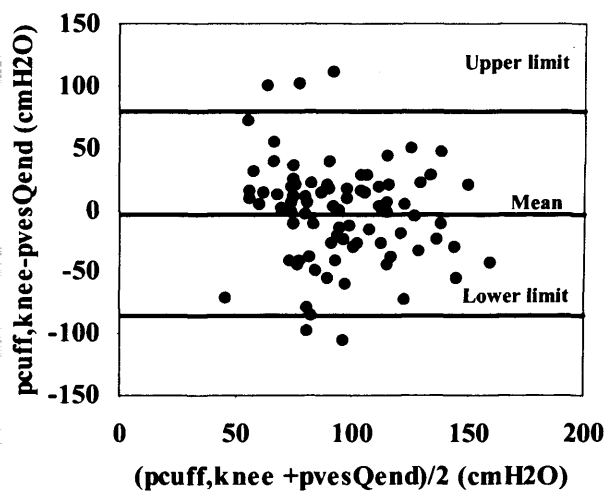
Knee pressures were compared with estimates of urethral opening pressure derived from invasive pressure flow studies, vesical pressures at the start and end of flow ( $p_{ves.Qbeg}$  (Fig. 4.3.1) and  $p_{ves.Qend}$  (Fig. 4.3.2) respectively), using a Bland-Altman Limits of Agreement plot. Limits of agreement were calculated to assess the levels of agreement between the two different methods of measuring urethral opening pressure (penile cuff and pressure flow studies) (Table 4.3.2.).

**Figure 4.3.1. Limits of agreement plot for  $p_{cuff,knee}$  and  $p_{ves.Qbeg}$ .  $n=103$ .**





**Figure 4.3.2. Limits of agreement plot for  $p_{\text{cuff,knee}}$  and  $p_{\text{ves,Qend}}$  (after contractions excluded). n=83.**



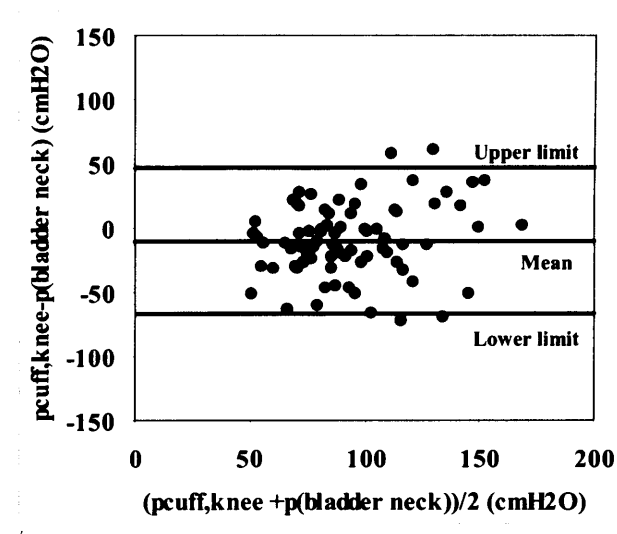
These plots show the mean difference between the two measures and the spread of data. The upper and lower limits are each two standard deviations from the mean and 95% of the population lie between these.

#### **Comparison of “knee” pressure with urethral pressures obtained during voiding urethral pressure profile measurements**

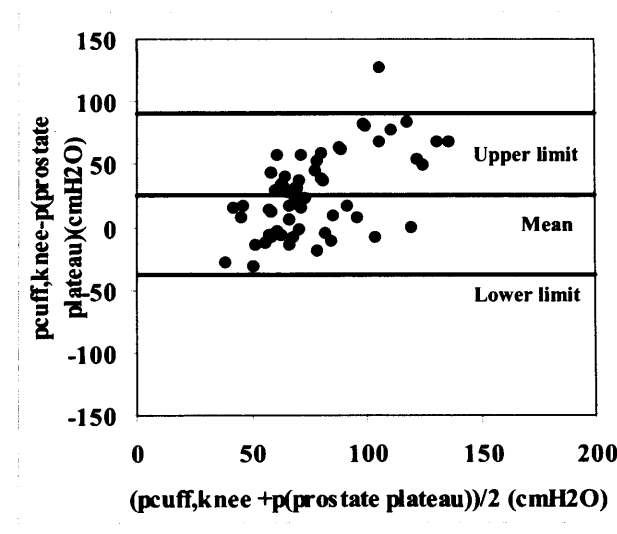
As discussed previously, the likely location for the flow controlling zone, in normal men and men with BPO, but not men with distal urethral strictures, lies between the bladder neck and pelvic floor. Thus it is at these locations that the  $p_{\text{uo}}$  is most likely to be measured using VUPP (Fig 2.3.5). Knee pressures were compared (Fig. 4.3.3, 4.3.4, 4.3.5, 4.3.6) with the pressures measured at these locations. Distal urethral pressure in all cases was close to zero. Of those 88 patients who had interpretable voiding pressure

profile data, 80 had corresponding knee pressure data. Again Bland-Altman Limits of Agreement plots were used with limits corresponding to  $\pm 2SD$  and their associated 95% confidence levels (Table 4.3.1).

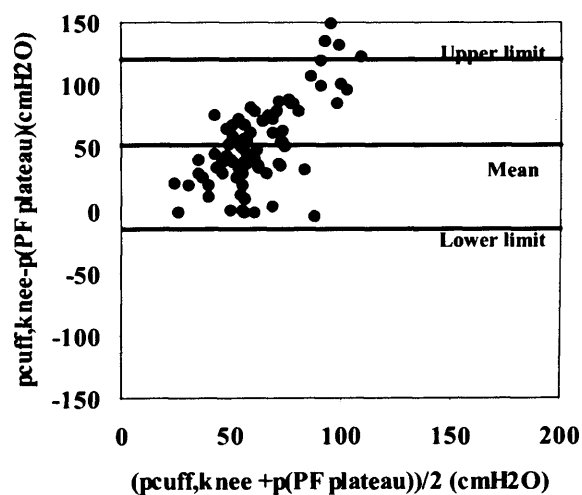
**Figure 4.3.3. Limits of agreement plot for  $p_{\text{cuff.knee}}$  and  $p_{\text{(bladder neck)}}$ . n=80.**



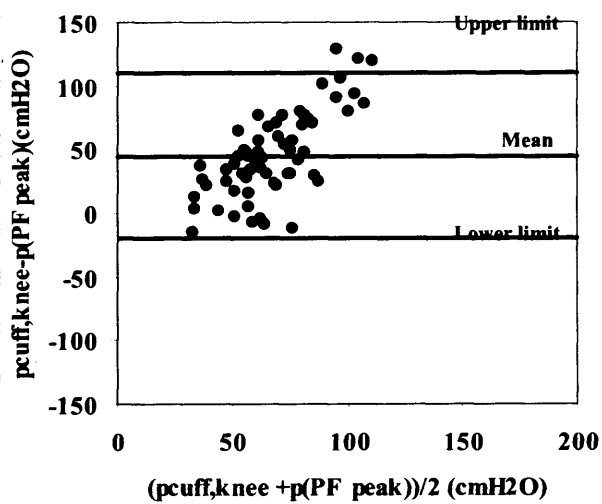
**Figure 4.3.4. Limits of agreement plot for  $p_{\text{cuff.knee}}$  and  $p_{\text{(prostate plateau)}}$ . n=60.**



**Figure 4.3.5. Limits of agreement plot for  $p_{\text{cuff.knee}}$  and  $p_{\text{(pelvic floor plateau)}}$ .  $n=80$ .**



**Figure 4.3.6. Limits of agreement plot for  $p_{\text{cuff.knee}}$  and  $p_{\text{(pelvic floor peak)}}$ .  $n=71$ .**



**Table 4.3.1. Limits of agreement between  $p_{\text{cuff, knee}}$  and urethral opening pressures derived from invasive pressure flow studies and between  $p_{\text{cuff, knee}}$  and urethral pressure measurements and pressure gradients derived from voiding urethral pressure profiles.**

	$p_{\text{cuff, knee}} - p_{\text{ves.Qbeg}}$	$p_{\text{cuff, knee}} - p_{\text{ves.Qend}}$	$p_{\text{cuff, knee}} - p_{\text{(bladder neck)}}$	$p_{\text{cuff, knee}} - p_{\text{(prostate plateau)}}$	$p_{\text{cuff, knee}} - p_{\text{(pelvic floor plateau)}}$	$p_{\text{cuff, knee}} - p_{\text{(pelvic floor peak)}}$
N	103	83	80	60	80	71
Mean difference (cmH <sub>2</sub> O)	-20.5	-3.2	-9.9	26.1	52.6	45.0
95% confidence interval	-27.5 to -13.5	-12.2 to 5.9	-16.3 to -3.6	18.0 to 34.8	45.0 to 60.2	37.3 to 52.7
SD(cmH <sub>2</sub> O)	35.4	41.2	28.2	32.6	33.9	32.5
Lower limit of agreement (cmH <sub>2</sub> O)	-91.4	-85.4	-66.4	-38.7	-15.2	-20.0
Upper limit of agreement (cmH <sub>2</sub> O)	50.4	79.1	46.5	91.5	120.5	110.0

Table 4.3.1. shows the magnitude of difference between  $p_{\text{cuff.knee}}$  and the various measured estimates of  $p_{\text{uo}}$ .

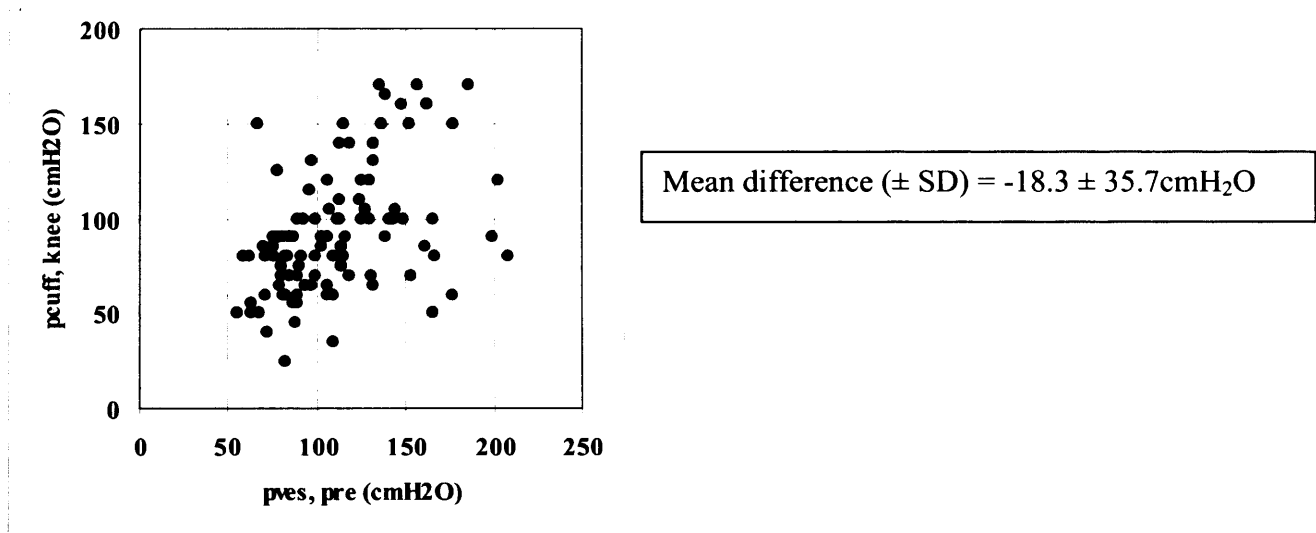
Of the estimations of  $p_{\text{uo}}$  taken from invasive PFS, vesical pressure at the start of flow ( $p_{\text{ves.Qbeg}}$ ) is consistently greater than  $p_{\text{cuff.knee}}$ . Vesical pressure at the end of flow ( $p_{\text{ves.Qend}}$ ), however, is much closer to  $p_{\text{cuff.knee}}$  with a mean difference ( $\pm$ SD) of -3.2 ( $\pm$  41.2) cmH<sub>2</sub>O.

When compared to the pressures taken from the VUPP's,  $p_{\text{cuff.knee}}$  is less than the pressure measured at the bladder neck but greater than the pressure at the “prostatic plateau”, suggesting that it falls somewhere between the two.

### **Comparison of knee pressure with vesical pressure under normal flow conditions**

For the 103 patients for whom simultaneous cuff and invasive data were available  $p_{\text{cuff.knee}}$  was compared with vesical pressure measured at the point at which cuff inflation commenced ( $p_{\text{ves.pre}}$ ), i.e. under conditions of normal established flow, using a scatter plot (Fig. 4.3.7). This shows that just prior to cuff inflation vesical pressure is equal to or greater than  $p_{\text{cuff.knee}}$ , in the majority of patients.

**Figure 4.3.7. Scatter plot of  $p_{\text{cuff, knee}}$  VS.  $p_{\text{ves, pre}}$**



## **Discussion**

### **Knee pressure and its relationship to urethral opening pressure**

#### *Knee pressure and invasive pressure flow data*

If the two methods of measurement (i.e. knee pressure and theoretical opening pressure taken from the invasive PFS) were equivalent and any differences in readings between the two methods could be attributed to chance variation, one would expect that any difference in readings would be just as likely to be positive as negative. Furthermore in order to accept that both methods are equivalent any differences within the limits of agreement would have to be considered negligible.

Comparison of  $p_{\text{cuff.knee}}$  with  $p_{\text{ves.Qbeg}}$  did not show a particularly close relationship to knee pressure, however, comparison with  $p_{\text{ves.Qend}}$  showed a much closer relationship to knee pressure with a mean difference of -3.2 cmH<sub>2</sub>O. This supports our hypothesis that knee pressure represents opening pressure, given that  $p_{\text{ves.Qend}}$  may be a better measure of opening pressure than  $p_{\text{ves.Qbeg}}$  [3,11]. However, the limits of agreement are wide, suggesting that there is quite a degree of variation in results between the two methods of measuring opening pressure.

The reasons for this variation are unclear but are likely to be multifactorial. Assessment of opening pressure from invasive pressure flow studies measures the theoretical  $p_{\text{uo}}$ .  $p_{\text{ves.Qend}}$  is therefore an estimation of  $p_{\text{uo}}$  and thus in itself may show variation from the true figure. If there is variation in both methods then these may compound each other.

A further source of error may be related to the cuff measurements and pressure flow measurement being taken from separate voids. It has been shown that there is some variation between  $p_{det.Qmax}$ ,  $p_{det.Qbeg}$  and  $p_{det.Qend}$  between successive voids on pressure flow data[97-100]. This effect appears to vary in magnitude between studies although the trend is for detrusor pressures to reduce in subsequent voids, without a change in  $Q_{max}$ , suggesting a reduction in opening pressure. In our study standard invasive pressure flow studies were performed first followed by a repeat fill and combined PFS and cuff test. The vesical pressure measurements were taken from the first void and the cuff pressure measurements from the second. If simultaneous vesical and cuff pressure measurements are taken from the same void a systematic difference of approximately 10cmH<sub>2</sub>O is seen due to the height difference between cuff and bladder. A reduction in detrusor pressure between first and second voids may help to explain both some of the variability between  $p_{cuff.knee}$  and  $p_{ves.Qend}$  as well as the smaller difference between  $p_{cuff}$  and  $p_{ves}$  seen in this comparison[49].

#### *Knee pressure and voiding urethral pressure profile measurements*

Voiding urethral pressure profile measurement is not a standard urodynamic technique in our unit. Thus there were some initial teething problems with the technique resulting in the failure of the equipment to record any usable data in 4 patients. Problems were also encountered with the mechanical puller. The main problem with this was the tendency for the catheters to be expelled during voiding. Therefore a manual pull was subsequently adopted. In a personal communication with Professor Yalla, who has pioneered this

technique, his unit has also abandoned the use of mechanical pullers due to the problem of catheter expulsion.

Of the comparisons discussed above none show a definite relationship between knee pressure and the various pressure measurements taken during voiding urethral pressure profiles. Knee pressures do appear, however, to have some degree of similarity with both pressures measured at the bladder neck and with the pressure gradient between the bladder neck and distal urethra. From the VUPP measurements,  $p_{\text{cuff.knee}}$  lies consistently between the pressures measured at bladder neck and prostate.  $p_{\text{cuff.knee}}$  is also slightly less than the total pressure change from bladder neck to distal urethra, mean difference ( $\pm$ SD)  $-16.1 \pm 33.5 \text{ cmH}_2\text{O}$ . If  $p_{\text{cuff.knee}}$  does represent opening pressure, as suggested by the  $p_{\text{ves.Qend}}$  comparison, then it would appear that the opening pressure component of the FCZ lies between the bladder neck and prostate, where pressure is falling rapidly, and may exist over a short distance that we are not able to measure using VUPP, rather than over a longer distance producing a plateau of pressure. This may be explained by the fact that the pressure fall on VUPP, across the FCZ, is related both to changes in pressure and in cross sectional area. Thus the pressure falls in both compressive and constrictive obstructions. The value of  $p_{\text{cuff.knee}}$  should represent  $p_{\text{uo}}$  and the rate of decrease in flow after  $p_{\text{cuff, knee}}$ , i.e. the slope of the curve, should relate to cross sectional area[48].

Theoretical and experimental work suggest that  $p_{\text{uo}}$  should correspond to the plateau pressures seen within the VUPP[3,12,67]. However, a subsequent paper[77] suggested a correlation between the pressure gradients across an area of obstruction and  $p_{\text{uo}}$ . Although



this is in contradiction to the earlier work in experimental models and humans, if the distal urethral pressure is low, approaching zero, the magnitude of the gradient and the pressure at the plateau would be similar.

#### *Knee pressure and normal flow conditions*

Another interesting characteristic of the knee pressure is that when compared to vesical pressure prior to cuff inflation, in other words under conditions of established flow, vesical pressure is generally equal to or higher than knee pressure (Fig. 4.3.7: to the right of the diagonal line). The line is offset by 10cmH<sub>2</sub>O to allow for the difference in height between bladder and cuff. Thus, the knee pressure may allow estimation of the minimum pressure present in the bladder under flow conditions or the “minimum voiding pressure”. This again would fit with the concept of knee pressure being related to opening pressure because for conditions of flow to occur, the bladder must generate a pressure at least as great as opening pressure to open the urethra. Equally as cuff pressure rises the knee pressure is the point at which cuff pressure rises above voiding pressure, i.e.  $p_{ves}$ . This does not however appear a good point at which to measure  $p_{ves}$  non-invasively as there is much more variation between cuff pressure and vesical pressure at this dynamic point compared to the point of flow interruption.

## **Relationship between knee pressure and bladder outlet obstruction**

### *Association between the presence of a knee pressure and degree of bladder outlet obstruction.*

A knee pressure is not seen in all cuff inflation cycles and in some cases was better defined than others. The presence or absence of a knee pressure was therefore graded as “definitely not” present, “equivocal”, “probably” present or “definitely” present. The confidence with which a knee pressure was seen was compared with obstruction grade (obstructed, equivocal, not obstructed) and degree of contractility (strong, normal, weak) obtained using invasive PFS. There was insufficient data to analyse the data based on all four categories. For the purposes of analysis, presence of a knee pressure was classified as “definitely not/equivocal” vs. “probably/definite” (Table 4.3.2). This comparison showed an association between obstruction grade and the presence of a well defined knee pressure ( $\chi^2=8.28$ ,  $p=0.02$ ,  $n=103$ ). The proportion of probable/definite knees increased with increasing levels of obstruction. No relationship was seen between knee pressure and contractility ( $\chi^2=5.11$ ,  $p=0.78$ ,  $n=103$ )

**Table 4.3.2. Obstruction grade vs. presence of a knee pressure**

Obstruction grade	Presence of a knee pressure		Total
	definitely not / equivocal	probably / definitely	
Not obstructed	12	5	17
Equivocal	11	13	24
Obstructed	20	42	62
Total	43	60	103

BPO is thought to be related to an increase in the compressive component at the FCZ and thus if knee pressure does correspond to urethral opening pressure one would expect a higher and, therefore more obvious knee pressure, to be seen with increasing obstruction, as was found.

#### *Knee pressure and surgery*

A further study in Newcastle has looked at changes in knee pressure before and after TURP. Their early results have shown that there is a general trend within the study population for knee pressure to fall as a result of surgery[95] This is borne out in paired data showing a reduction in knee pressure in individuals after surgery. Thus it would appear that surgery to treat bladder outlet obstruction leads to a reduction in knee

pressure. These observations further support the theory that  $p_{\text{cuff.knee}}$  may represent urethral opening pressure at the flow controlling zone which, as discussed earlier, would occur in the region of the prostate in men with BPO, and one would expect this to be reduced following TURP.

#### *Knee pressure and urethral opening pressure: clinical utility*

Bladder outlet obstruction and the resulting reduction in urinary flow rate are the result of a complex relationship between urethral calibre, the “constrictive” component, and the difference between vesical “driving” pressure and urethral opening pressure, the “compressive” component. In benign prostatic obstruction it has been suggested that the main component is a decrease in urethral distensibility and therefore an increase in opening pressure[2,3]. If  $p_{\text{cuff.knee}}$  is a non-invasive measure of urethral opening pressure: does this add a useful adjunct to the non-invasive diagnosis of obstruction using the penile cuff technique?

The ICS Nomogram and BOOI evolved from the Abrams-Griffiths nomogram and number[14,90], the Schaefer Linearized Passive Urethral Resistance Relation nomogram(LPURR)[11] and Griffiths’ group specific Urethral Resistance Factor (URA)[101]. All work in a similar way using  $p_{\text{det.Qmax}}$  and  $Q_{\text{max}}$ , to diagnose the presence and degree of bladder outlet obstruction. Although the various cut off values for obstruction used vary slightly, results using each method are similar[13,102]. Both the A-G number(BOOI) and URA are mathematical estimations of detrusor pressure at minimal flow ( $p_{\text{det.minQ}}$ ) or urethral opening pressure[3,11]. In his LPURR Schaefer uses  $p_{\text{uo}}$

derived from invasive pressure flow studies ( $p_{det.Q_{end}}$ ) to provide a “quality control” to support a diagnosis based on using the single point of ( $Q_{max}$ ,  $p_{det.Q_{max}}$ ). Griffiths and Schaefer give cut offs of 28 and 30cmH<sub>2</sub>O respectively for  $p_{uo}$  as the boundary between no obstruction and mild obstruction. This falls into the equivocal zone of the Abrams-Griffiths nomogram which gives a value of 40cmH<sub>2</sub>O as its criterion. 40cmH<sub>2</sub>O also corresponds to the border between Groups II and III on the LPURR nomogram, or mild to more definite obstruction. If we take then an opening pressure of  $p_{det} \geq 40\text{cmH}_2\text{O}$  as representing obstruction can we apply this concept to knee pressure to help diagnose obstruction?

As discussed above the cuff technique provides an estimation of vesical pressure rather than detrusor pressure. The difference between these two is the abdominal pressure component. As in step 1 of the development of the modified cuff nomogram, it is possible to add an average abdominal pressure component of 40cmH<sub>2</sub>O, giving a cut off of  $p_{cuff.knee} \geq 80\text{cmH}_2\text{O}$  to diagnose obstruction.

For the 73 patients who produced an identifiable knee pressure in their free cuff test  $p_{cuff.knee} \geq 80\text{cmH}_2\text{O}$  as the basis for diagnosing obstruction had a sensitivity of 0.70, specificity of 0.81, positive predictive value of 0.86 and negative predictive value of 0.61. For the patients in whom voided volume was greater than 150ml the figures were slightly improved: 0.83, 0.75, 0.85, and 0.71 respectively. Thus  $p_{cuff.knee}$  alone does not provide a better way of diagnosing obstruction than the modified nomogram.

If  $p_{\text{cuff.knee}}$  does not in itself provide a useful diagnostic tool, can it improve the diagnostic accuracy of the modified nomogram? Of the Bristol patients, on whom knee pressure data was available; those in the lower left quadrant on the modified nomogram, one obstructed patient had a  $p_{\text{cuff.knee}} \geq 80\text{cmH}_2\text{O}$  as did one equivocal patient. In the lower right quadrant four of the five wrongly classified obstructed patients had a  $p_{\text{cuff.knee}} \geq 80\text{cmH}_2\text{O}$  as did two equivocal and one unobstructed patient. Of the four equivocal patients falling into the top left quadrant of the nomogram only two had produced identifiable knee pressures. These were 70 and 80cmH<sub>2</sub>O respectively. Thus for the 29 patients falling outside the “obstructed” zone of the nomogram  $p_{\text{cuff.knee}} \geq 80\text{cmH}_2\text{O}$  had a sensitivity of 0.55, specificity of 0.77, PPV of 0.55 and NPV of 0.77 for predicting obstruction. Again  $p_{\text{cuff.knee}}$  does not improve on the classification of  $Q_{\text{max}}$  and  $p_{\text{cuff.int}}$ .

## **Conclusions**

Although knee pressure in these studies has not corresponded precisely with the previously described measures of urethral opening pressure we believe that there is reasonable evidence to support our hypothesis, based on findings in the experimental model, that knee pressure may be used as a simple and non-invasive measure of urethral opening pressure.

On the basis of these results it would appear that knee pressure is probably not useful clinically as a tool for improving the diagnosis of bladder outlet obstruction.

## **5. Conclusions and ideas for further research**

This study was undertaken in collaboration with the group at the Freeman Hospital, Newcastle. Its aims were threefold.

The first was to take their technique using a penile cuff and reproduce their work in order to confirm their results that cuff pressure at flow interruption was a valid measurement of isovolumetric bladder pressure and to see if the technique was easily transferable to a unit with no experience of it.

This work was undertaken in Bristol by the author using identical methods and with equipment supplied by the Regional Medical Physics Department in Newcastle. Our results were both quantitatively and qualitatively similar to those of the Newcastle group. They showed a mean difference between  $p_{\text{cuff.int}}$  and isovolumetric bladder pressure of  $14.5 \pm 14.0 \text{ cmH}_2\text{O}$  [49] and in Bristol we found a mean difference of  $15.6 \pm 22.6 \text{ cmH}_2\text{O}$ . Use of a large cuff gave better results than a small cuff and this confirms experimental data which suggests pressure is more faithfully transmitted to the urethra by a wider cuff than a narrower one[53]. 4.2% of patients found the test uncomfortable and 2.5% experienced limited urethral bleeding. The test, in our study, was well tolerated and has previously been shown preferable by patients to invasive urodynamics[59]. The incidence of discomfort and bleeding are similar to those reported for invasive urodynamics[103,104]; no urinary tract infections or episodes of acute retention have yet been reported following the cuff test.

Given that our results were similar and used an identical technique the second part of our study was a joint undertaking with Newcastle to develop a nomogram for the cuff test and attempt to validate it with our combined data, in order to diagnose bladder outlet obstruction.

The ICS nomogram is currently the most widely accepted method for diagnosis of bladder outlet obstruction. We took this as our starting point and adapted it from the use of  $Q_{\max}$  and  $p_{\det.Q_{\max}}$ , taken from invasive pressure flow studies, to use  $Q_{\max}$  and  $p_{\text{cuff.int}}$ , taken from the cuff test. The demographics of the patient groups in Bristol and Newcastle were broadly similar although a higher proportion of the Bristol patients were obstructed on invasive pressure flow studies. Although there were slight variations between the Bristol and Newcastle groups of patients, in terms of mean abdominal pressure and the mean increase in vesical pressure from conditions of flow to isovolumetric, this did not make a great difference in the parameters chosen for the modified nomogram. When compared to classification of the patients by invasive pressure flow studies, the nomogram showed a sensitivity for diagnosing obstruction of 0.64, specificity of 0.81, PPV of 0.68 and NPV of 0.78. Addition of  $Q_{\max} < 10 \text{ ml.s}^{-1}$  as a criterion for obstruction increased the sensitivity and specificity of the new nomogram to 0.70 and 0.95 respectively with a PPV of 0.88 and NPV of 0.86, for those patients lying in either the top left or bottom right quadrants (68%); in other words those obstructed or unobstructed by both criteria.



Invasive urodynamics in our unit costs approximately £38 for the disposable items. A penile cuff costs £5 and will give a reliable diagnosis of obstruction in just over two thirds of patients. We therefore believe that the cuff test provides a cheap, simple alternative to invasive pressure flow studies as a first line investigation in those patients being considered for bladder outlet surgery.

The third part of this thesis was to explore the relationship between cuff inflation pressure and flow rate. In particular we have investigated the hypothesis that the “knee” pressure, seen as flow starts to decline during cuff inflation, is related to urethral opening pressure, as suggested by work in an experimental model. Urethral opening pressure rises in the “compressive” model of bladder outlet obstruction associated with benign prostatic enlargement and thus, if this was an easily measured parameter, would this be useful clinically?

We measured urethral opening pressure using previously accepted methods from the literature of invasive pressure flow studies and voiding urethral pressure profiles. We compared these measured estimations of opening pressure with knee pressures derived from the cuff test. Although knee pressures did not have as close an association with the measured pressures as  $p_{\text{cuff.int}}$  does to  $p_{\text{ves.isv}}$ , there was reasonable evidence to support our hypothesis.

On the basis of this we have looked to see if  $p_{\text{cuff.knee}}$  could be used for diagnosing bladder outlet obstruction or improve the sensitivity of  $p_{\text{cuff.int}}$  and flow rate on the cuff nomogram.  $p_{\text{cuff.knee}}$  was not found to add to the non-invasive diagnosis of obstruction in this group of patients.

### *Directions for further research*

Non-invasive measurement of isovolumetric bladder pressure to diagnose bladder outlet obstruction is a new technique. To further assess its usefulness it is important to see if it is sensitive to change after surgery, whether it can predict outcome from surgery and thus be useful in guiding patients towards or away from invasive treatment.

If non-invasive urodynamics is to become a widespread technique it would need to be integrated into clinical practice. This is most likely to be achieved by adding the cuff test to the routine of the flow clinic but would also require raising familiarity and interpretation of the technique with the wider community of clinicians.

The presence of a knee pressure, on the basis of experimental work, is thought to be related to a “compressive” obstruction. It would be interesting to look at patients with urethral stricture disease, who in theory have a “constrictive” model of obstruction to see if they also display a knee pressure and whether this is sensitive to change after stricture surgery.

## **6. List of publications**

### **Journal Articles**

Non-invasive techniques for the measurement of isovolumetric bladder pressure. A review.

Journal of Urology. January 2004. Volume 171(1): pp12-19.

C H Blake, P Abrams.

A nomogram to classify men with lower urinary tract symptoms using urine flow and non-invasive measurement of bladder pressure.

Journal of Urology. October 2005. Volume 174(4 Pt 1):pp1323-6.

C Griffiths, C Harding, C H Blake, S McIntosh, M Drinnan, W Robson, P Abrams, P Ramsden, R Pickard.

### **Abstracts in Peer Reviewed Journal**

Non-invasive estimation of bladder pressure using a penile cuff. The new pressure-flow study?

BJU International. June 2003. Volume 91, Supplement 2 pp95

C H Blake, L Baldry, A Hassine, P Abrams..

Non-invasive bladder pressure: the case for using a modified ICS nomogram.

Neurourology and Urodynamics. 2003. Volume 22(5) pp367.

C J Griffiths, C H Blake, C Harding, S McIntosh, M J Drinnan, W Robson, P D Ramsden, P Abrams, R S Pickard.

### **Abstracts in Proceedings of Learned Societies**

Non-invasive urodynamics. New information on bladder contractility in men.

Proceedings of International Continence Society, UK. 10th Annual Meeting 24-25 April 2003. pp4.

C H Blake, A Hassine, L Baldry, P Abrams.

Evaluation of the non-invasive estimation of bladder pressure using a penile cuff. An alternative to pressure flow studies in men?

Proceedings of International Continence Society 33rd Annual Meeting, Florence, Italy, October 2003. pp374-5.

C H Blake, L Baldry, A Hassine, P Abrams.

Assessment of minimum voiding pressure using a penile cuff.

Proceedings of International Continence Society 33rd Annual Meeting, Florence, Italy. October 2003. pp366-7.

C H Blake, L Baldry, A Hassine, W Bevan, P Abrams.

Combination of non-invasive urodynamic parameters from a single penile cuff test for diagnosis of bladder outlet obstruction.

Proceedings of International Continence Society 34th Annual Meeting, Paris, France. September 2004. Abstract number 334.

M Drinnan, C Harding, C H Blake, S McIntosh, W Robson, R Pickard, P Abrams, P Ramsden, C Griffiths

A non-invasive method for the measurement of urethral opening pressures.

Proceedings of International Continence Society 35th Annual Meeting, Montreal, Canada. September 2005

C H Blake, W Bevan, A Hassine, L Baldry, P Abrams

## 7. Appendices

### Appendix A: Ethics approval

North Bristol   
NHS Trust

20 December 2001

Clinical Governance Directorate  
Beaufort House  
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Mr C Blake  
Clinical Research Fellow in Urology  
SMH

Dear Mr Blake

**PROJECT 130/01: VALIDATION OF TECHNIQUE FOR NON-INVASIVE ASSESSMENT OF  
BLADDER CONTRACTION PRESSURE AND ASSESSMENT OF MICTURATING URETHRAL  
PRESSURE PROFILES TO ESTABLISH PROSTATIC OPENING PRESSURE NON-INVASIVELY**

I am pleased to inform you that the Southmead Local Research Ethics Committee has approved your application in respect of the above project.

Approval is given on the understanding that:-

- a) Any ethical problems arising in the course of the project will be reported to the Ethics Committee;
- b) Any change in protocol will be reported to the Ethics Committee;
- c) An annual progress report will be submitted and a brief final report on completion.

Yours sincerely

Mrs S B Bowman  
Administrator  
Southmead Local Research Ethics Committee

**Appendix B:      Patient information sheet and consent form.**

**EVALUATION OF A NEW NON-INVASIVE  
TECHNIQUE FOR DETERMINING VOIDING  
PRESSURE IN MEN WITH LOWER URINARY  
TRACT SYMPTOMS SUGGESTIVE OF BLADDER  
OUTLET OBSTRUCTION**

**A New Test for Prostate Obstruction**

***Patient information***

There are several different ways of deciding whether men with troublesome urinary symptoms have a significant blockage to the passage of urine caused by the prostate gland, which lies at the exit to the bladder. Symptoms alone are not an accurate guide and we commonly use a test called a flow rate to help us diagnose a blockage problem. However, flow tests can be misleading and unless the flow is very poor it can be difficult to be certain whether men will benefit from surgery to the prostate gland. The most accurate way of diagnosing a significant blockage is with a bladder pressure flow test. This involves passing narrow tubes (catheters) into the bladder and rectum (back passage). You will be having one of these pressure flow tests as part of your assessment.

We are investigating a new non-invasive bladder pressure test, which has been developed in Newcastle. It is called non-invasive because we think it can measure the bladder pressure whilst you pass urine without the need to pass a catheter into the body. This non-invasive test involves the wrapping of a small pressure cuff around the shaft of the penis. The cuff is inflated as you pass urine. This cuff is like the cuff put on your arm to measure blood pressure but it is much smaller. The pressure required to stop the flow of urine is an indicator of the pressure generated by the bladder muscle.

If you are willing to take part we would like to perform this non-invasive bladder pressure test as well as the usual pressure flow test so that we can compare the two tests and see whether the new technique is accurate. The new technique has been evaluated on healthy staff volunteers without any problems.

**Evaluation of a new non-invasive technique for determining voiding pressure in men with lower urinary tract symptoms suggestive of bladder outlet obstruction**

**Consent Form**

*Please cross out  
as necessary*

Have you read the Patient Information Sheet?	Yes / No
Have you had an opportunity to ask questions and discuss this study?	Yes / No
Have you received satisfactory answers to all your questions?	Yes / No
Have you received enough information about the study?	Yes / No

To whom have you spoken?.....

Do you understand that you are free to withdraw from the study:

- At any time?
- Without having to give a reason for withdrawing?
- And without affecting your future medical care? Yes / No

Do you agree to take part in this study? ..... Yes / No

I have agreed to take part in this clinical study to compare conventional pressure flow measurements recorded by the passage of a narrow tube (catheter) down the penis into the bladder with measurements obtained with a small inflatable cuff which is attached to my penis whilst I urinate. I understand that my participation is entirely voluntary and if I wish to withdraw from the study at any stage I may do so without compromising in any way my clinical care.

I certify that I have read the information sheet and agree to participate in the study.

Signed..... Date.....

(Name in block letters) .....

Signed (Researcher): Date

**Appendix C:      Rules for deciding if an individual inflation should be excluded from analysis.**

1.      No recovery of flow after deflation of the cuff (ignoring initial surge).
2.      Flow is not interrupted.
3.      More than one pressure at which flow is interrupted.
4.      Erratic flow trace with sudden fluctuations in flow rate.
5.      Trace is inconsistent with others from the same void.

Assuming the individual inflation is included for analysis (i.e.: none of the above applies), some guidance in reading the interruption pressure is useful. The decrease in flow rate as interruption is approached is usually approximately linear. Extending this line to zero is a good way of estimating the interruption pressure.

Each small rectangle on the flow rate v cuff pressure plot represents 1 ml of urine (a pressure increase of 10 cm water takes 1 s). If the above method does not include the last ml or thereabouts, this is not seen as a problem.



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