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PREDICTING THE OUTCOME OF PROSTATECTOMY USING NON-INVASIVE BLADDER PRESSURE AND URINE FLOW MEASUREMENTS

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Take Home Message

This paper describes a prospective clinical study showing that pre-operative categorisation of bladder outlet obstruction using non-invasive measurement of bladder pressure by the penile cuff device can improve prediction of outcome following TURP.

Funding

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Conflict of Interest

The individuals conducting the study have no personal financial interest in the penile cuff device or Mediplus Ltd. The Departments of Urology and Medical Physics, Newcastle upon Tyne Hospitals NHS Trust are beneficiaries of royalty payments arising from commercial sale of the penile cuff device by Mediplus Ltd, High Wycombe, UK.

Abstract

Objectives: To determine whether categorisation of bladder outlet obstruction (BOO) using measurements of bladder pressure and urine flow obtained by a novel non-invasive medical device (the penile cuff test) improves prediction of outcome from endoscopic prostatectomy (TURP).

Methods: A consecutive cohort of 208 men undergoing TURP following standard assessment in our institution was recruited and 179 (86%) completed the protocol. Each subject underwent a penile cuff test prior to surgery and outcome was assessed by change in IPSS at 4 months. The proportion of men with good outcome (> 50% reduction in IPSS) was compared according to categorisation by the non-invasive bladder pressure and urine flow measurements.

Results: The cuff test was completed by 93% of men with 2% experiencing an adverse event. Men categorised as having BOO by the test (37% of total) had an 87% chance of a good outcome from TURP ($p < 0.01$) whilst of those deemed not obstructed (19% of total) 56% experienced good outcome ($p < 0.01$). For remaining men not categorised in these 2 groups 77% had good outcome which was identical to the result of the cohort as a whole (77%, $p > 0.05$).

Conclusion: Urodynamic categorisation using measurements obtained by the non-invasive penile cuff test improves prediction of outcome for men with LUTS undergoing TURP. This finding together with the ease and acceptability of the test suggest its suitability for office-based clinical use to assist men and their physicians in the selection for surgical treatment for relief of LUTS.

1. Introduction

Treatment options for men with lower urinary tract symptoms (LUTS) due to benign prostatic enlargement have increased over the last 20 years although surgical removal of tissue typically by transurethral resection (TURP) remains most effective [1]. This choice has focused the need for more precise diagnostic tests that can predict outcome and hence guide treatment selection [2]. Men with bladder outlet obstruction (BOO) defined by invasive pressure flow studies (PFS) have success rates following TURP 15-29% higher than those without obstruction but invasive PFS are not commonly performed because of patient discomfort, infection risk and cost associated with the need for skilled staff and specialised equipment [3]. Most UK urologists therefore suggest surgery on the basis of bothersome LUTS unresponsive to drug therapy and associated with reduced urinary flow with 65 - 75% of men achieving satisfactory symptomatic benefit [4]. Non-invasive tests that improve outcome prediction for men considering surgery would represent a useful addition to pre-operative assessment and several methods are being actively pursued [5].

We have developed a non-invasive bladder pressure measurement technique involving controlled inflation during voiding of a cuff placed around the penis [6]. The cuff pressure at which flow is interrupted ($p_{cuff.int}$) provides a valid and reproducible estimate of isovolumetric bladder pressure ($p_{ves.isv}$) – a measure of detrusor contraction strength [7]. Use of the device is well tolerated [8] and produces a plot from which maximum values of $p_{cuff.int}$ and peak urine flow rate ($Q_{max.cuff}$) can be read. These measurements can then be used on a pressure flow nomogram to categorise obstruction [9].

We have now performed a prospective study to determine whether pre-operative categorisation using the non-invasive pressure-flow nomogram improved prediction of TURP outcome compared to standard assessment alone.

2. Methods

Local Research Ethical Committee and institutional approval together with informed written consent were obtained and the protocol conformed to STARD guidelines [10].

2.1. Subjects

Sample size estimation showed that 200 men would be sufficient to demonstrate the minimum 10% improvement in outcome prediction suggested by studies using invasive PFS [3]. Therefore a consecutive cohort of 208 men with LUTS scheduled for TURP was recruited from a single institution during a 15-month period from December 2003 to February 2005. Prior selection for operation was independent of the study and made on the basis of bothersome LUTS and a reduced flow rate, after the exclusion of overt prostate cancer by digital rectal examination, PSA test and, if indicated, negative biopsies. For some men these standard criteria were supplemented by further investigation, typically invasive PFS.

2.2. Experimental protocol

Men completed the International Prostate Symptom Score (IPSS) and underwent an office-based penile cuff test prior to surgery with the IPSS repeated approximately 4 months following surgery to determine outcome. Subjects who were able to manage a second void following the cuff test also underwent standard uroflowmetry recording maximum flow rate (Q_{max}) and voided volume (V_{void}). Prior to conclusion of the study we decided to seek additional longer term outcome and patient satisfaction data by assessing patient-perceived outcome at 24 months. Available patients were contacted by telephone and were asked to rate the result of TURP on a 10 point scale from complete failure (0) to complete success (10). The patient and operating surgeon were unaware of the pre-operative study results and

researchers performing the assessments played no part in the standard clinical management of men recruited for the study.

2.3. Penile cuff test

A penile cuff (Mediplus Ltd, High Wycombe, UK) was placed around the penis and the subject was asked to void without straining into a uroflowmeter connected to the cuff machine (FM319, RMPD, Freeman Hospital, Newcastle-upon-Tyne, UK) [7]. Once voiding commenced the cuff was automatically inflated at 10 $cmH_2O\ s^{-1}$ until flow was interrupted or a safety cut-off of 200 cmH_2O was reached. The cuff then automatically rapidly deflated with resumption of flow allowing the process to be repeated until voiding was complete [7]. Maximum values of $p_{cuff.int}$ and $Q_{max.cuff}$ were read from the continuous plot of flow rate and cuff pressure obtained for each void (Figure 1a). These readings were then checked by a second observer blinded to the initial result.

2.4. Statistical analysis

Maximum $p_{cuff.int}$ and $Q_{max.cuff}$ recorded from the pre-operative penile cuff test were plotted on the non-invasive nomogram allowing classification of each subject as obstructed, not obstructed or diagnosis uncertain (Figure 1b) [9]. Successful symptomatic outcome was defined on the study protocol as a greater than 50% reduction in IPSS at the 4 month assessment with those achieving a lesser improvement categorised as having a poor outcome [11]. At 24 months patient-perceived success was defined as a rating of ≥ 7 on the 10-point scale. The number of men achieving good outcome is expressed as n {% (95% confidence interval)} using a binomial model. The proportion of men in each of the 3 groups categorised by the penile cuff test achieving a good outcome was then compared with outcome in the group as a whole. Likelihood ratios (LR = probability of correct result ÷ probability of

156 incorrect result) were used to assess prognostic accuracy whereby the higher the LR the more
157 discriminant the test. In order to provide a comparison using more conventional indices, this
158 exercise was repeated with standard 'free' uroflowmetry data using 10 ml s^{-1} and 15 ml s^{-1} as
159 a diagnostic cut-off values for BOO [12]. Categorical data were examined by chi-squared test
160 for trend with significance level set at 5%. Inter-observer variation was assessed by Bland-
161 Altman analysis.

3. Results

A total of 208 men already selected for TURP using standard institutional criteria were recruited. They progressed as shown in Figure 2 with 179 (86%) completing the initial protocol and 146 (70%) responding to additional telephone follow up at a mean (SD) of 24 (5) months. Characteristics of subjects and their operative findings were consistent with other series of men undergoing this surgery (Table 1) [4].

Of the 179 patients who completed the study 138 {77% (70-83%)} satisfied the pre-set criterion for a good symptomatic outcome at 4 months. For the 15 (7%) men in whom we were unable to achieve a valid measurement (test failures) but who subsequently underwent TURP, 11 (73%) achieved a good outcome. A total of 15 (9%) men were unable to attend for office follow-up and completed the post-operative IPSS by telephone. Of those patients contacted at 24 months, 112 {77% (69-83%)} rated the operation as successful.

Cuff inflation was well tolerated although 8 (4%) men were unable to void and 4 (2%) experienced adverse events; 3 having self-limiting urethral bleeding and 1 terminating the test due to pain. A recording suitable for analysis could not be made in 3 (1%) subjects. Reading of $p_{cuff.int}$ by a second observer showed good agreement with the initial reading with a mean (SD) difference of 0.5 (3.8) cmH_2O. Readings of the first observer were used for data analysis throughout.

Excluding test failures, the non-invasive pressure-flow nomogram categorised 71 (40%) men as obstructed, 36 (20%) were not obstructed and 72 (40%) were in the areas of diagnostic uncertainty (Figure 3). The predictive value of nomogram classification for 4-month IPSS outcome including test failures and 24-month patient rating outcome is shown in Table 2.

We obtained a separate reading for Q_{max} using standard uroflowmetry for 138 (77%) men. Analysis using a cut-off value of 10 ml s^{-1} showed that good outcome at 4 months was seen in 52 of 65 men {80% (68-89%)} with $Q_{max} \leq 10$ ml s^{-1} (LR for good outcome = 4.0) and in 48 of 73 men {66% (54-77%)} with $Q_{max} > 10$ ml s^{-1} (LR for poor outcome = 0.5) compared to 73% (64-79%) overall ($p < 0.03$, LR = 2.7 for good outcome). Similarly if 15 ml s^{-1} was used as a diagnostic cut-off value 86 of 113 {76% (67-84%)} men with $Q_{max} \leq 15$ ml s^{-1} had a good outcome at 4 months (LR = 3.2 for good outcome) compared to 14 of 25 {56% (35-76%)} of men with $Q_{max} > 15$ ml s^{-1} (LR = 0.8 for poor outcome) and 73% (64-79%) overall ($p > 0.05$).

4. Discussion

Population ageing and male health promotion concerning early diagnosis of prostate disease has resulted in large numbers of older men seeking medical advice concerning LUTS. After initial exclusion of prostate cancer, it is argued that the decision to treat and the choice of treatment can be helped by differentiating between BOO and detrusor underactivity which requires measurement of bladder pressure and urine flow during voiding [13,14]. To overcome the practical disadvantages of invasive PFS a number of groups have attempted to measure bladder pressure indirectly, chiefly by interruption of flow [15]. Our technique plots an estimate of isovolumetric bladder pressure, $p_{cuff.int}$, and a measurement of maximum flow rate, $Q_{max.cuff}$, on a nomogram to allow categorisation into obstructed, not obstructed or diagnosis uncertain groups [9]. The present study tested the usefulness of this approach in a clinically relevant setting and demonstrated that a 10% improvement in prediction of good outcome was achieved with few test-related adverse events. Men whose measurements fall in the obstructed area have an 87% chance of a good outcome which is reassuring and encourages the use of ablative procedures for symptom relief. Conversely those classified as not obstructed have a much reduced chance of benefit and might prefer to put up with their symptoms. For the 45% of men whose obstructive category remained uncertain the chance of a good outcome was intermediate and similar to that predicted by standard assessment. The choice for these men would be to accept the moderate risk of unsatisfactory symptom relief or undergo further testing, perhaps by invasive PFS, to clarify their urodynamic status.

At first glance the 10% improvement in prediction of good outcome appears modest. It should be noted however that the overall success rate without cuff test categorisation (77%) was at the upper end of previous audit results [4] and that the 87% success rate in men classified as obstructed was similar to that achieved by invasive PFS in previous studies (79 -

93%) [3]. It could also be argued that the risk of failure is a more pertinent criterion for these men and this was reduced by over 40%; from 23% to 13%. Finally the difference in good outcome between the obstructed and not obstructed groups defined using non-invasive data (31%) is at the upper end of the range seen with invasive classification (15 – 29%) [3]. The high prevalence both of the condition and surgical intervention may also increase the impact of small improvements in outcome prediction. In England, where 15 000 men undergo TURP for LUTS each year, good outcome could be predicted with greater certainty for 6000 men whereas for the 3000 men classified as not obstructed the risk - benefit ration would merit more careful consideration and a proportion might opt for continued surveillance [16].

The next question is whether addition of the cuff test gave better prediction of outcome than existing tests known to define BOO, chiefly invasive PFS and 'free' uroflowmetry. Direct comparison with invasive PFS was not an aim of the present study but of the 49 men who underwent both investigations a good outcome was seen for 32 of the 44 (73%) men with BOO on invasive studies compared to 17 of the 18 (94%) men categorised as obstructed using non-invasive data. It should be noted however that for 22 (45%) of these men the non-invasive diagnosis was uncertain and that any comparison is severely compromised by selection bias. Fair comparison with 'free' uroflowmetry was hampered by the fact that a low flow rate was part of the standard selection criteria for TURP and by our inability to capture complete data for this purpose. Despite these caveats the cuff test was better than flow rate alone both in terms of improvement in prediction of good outcome over standard assessment where a 7% advantage was seen and by improved separation of obstructed and not obstructed groups with a 10% advantage. Consideration of the LR also shows that categorisation using the non-invasive nomogram (LR = 6.7) gave improved prognostic accuracy over flow rate alone (LR = 4.0). At present we are unable to categorise 45% of men using cuff test

measurements. This includes 15 (7%) men in whom we could not obtain an acceptable recording, a proportion similar to invasive PFS [17]. Whilst this does not affect the predictive value of plots in the obstructed and unobstructed areas it does mean that these men would require further testing to more accurately predict their likely outcome and represents a drawback that the cuff test has in common with invasive studies.

The categorising of health states using cut-off values of continuous variables in the nomogram and outcome definition is a shortcoming of our study since small numerical differences may change category. We have persisted with this approach because it fits with current practice in the assessment of men with LUTS and it is reassuring that longer term outcome using a simple patient rating scale were similar overall to that seen at 4 months with IPSS. In the future, a Bayesian approach may be more appropriate whereby the results of the cuff test would add to those of other assessments to either increase or decrease clinicians' perception of the probability of obstruction or treatment benefit [18]. This probability-based approach may also help identify the significant number of men (10% of our sample) destined to have a good outcome from prostate ablation despite being classified as not obstructed. It is also possible that use of alternative single or multiple criteria such as voiding symptom scores or other indices may be useful in this regard [19].

The sample of men used in the present study had already been selected for surgery in a single UK institution on the basis of severe symptoms and reduced urinary flow rate. They therefore represent a particular sub-group of the population of men complaining of LUTS and it remains uncertain whether the encouraging results of the present study are repeatable in different centres and across different patient groups. We currently feel that the cuff test works well as an elective extension to 'free' uroflowmetry since it potentially reduces the number of

men requiring PFS by over 50% and allows individual patients a more informed choice. It could be argued however that patient benefit is confined to the 37% of men who are categorised as obstructed with the rest requiring additional investigation to establish urodynamic diagnosis. Further studies are certainly needed to clarify these issues and establish the role of the test earlier in the assessment of men with LUTS due to BPE prior to selection for surgery. We are currently conducting a multi-centre trial to address some of these issues.

5. Conclusion

For men with bothersome LUTS considering surgical options for symptom relief, this simple office- based test allows categorisation of bladder outflow obstruction using non-invasive pressure and flow measurements. The improved prediction of outcome from TURP that results from this categorisation can aid patient and physician in their choice of treatment.

6. Acknowledgements

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7. References

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8. Tables

Table 1: Characteristics of patient cohort

Variable	Descriptive
Number of patients	179*
Age mean (range)	69 (47 – 88) years
Pre-operative IPSS (0-35) mean (SD)	22 (7)
Pre-operative IPSS QoL (0-5) mean (SD)	4 (1)
Pre-operative Q_{max} mean (SD)	10.8 (4.7) ml s^{-1}
Pre-operative residual volume mean (SD)	130 (123) ml
Pre-operative invasive PFS performed (%)	49 (27)
Resected weight mean (SD)	16.7 (12) g
Men with prostate cancer in resected prostate (%)	19 (11%)
Surgical success rate %	77%

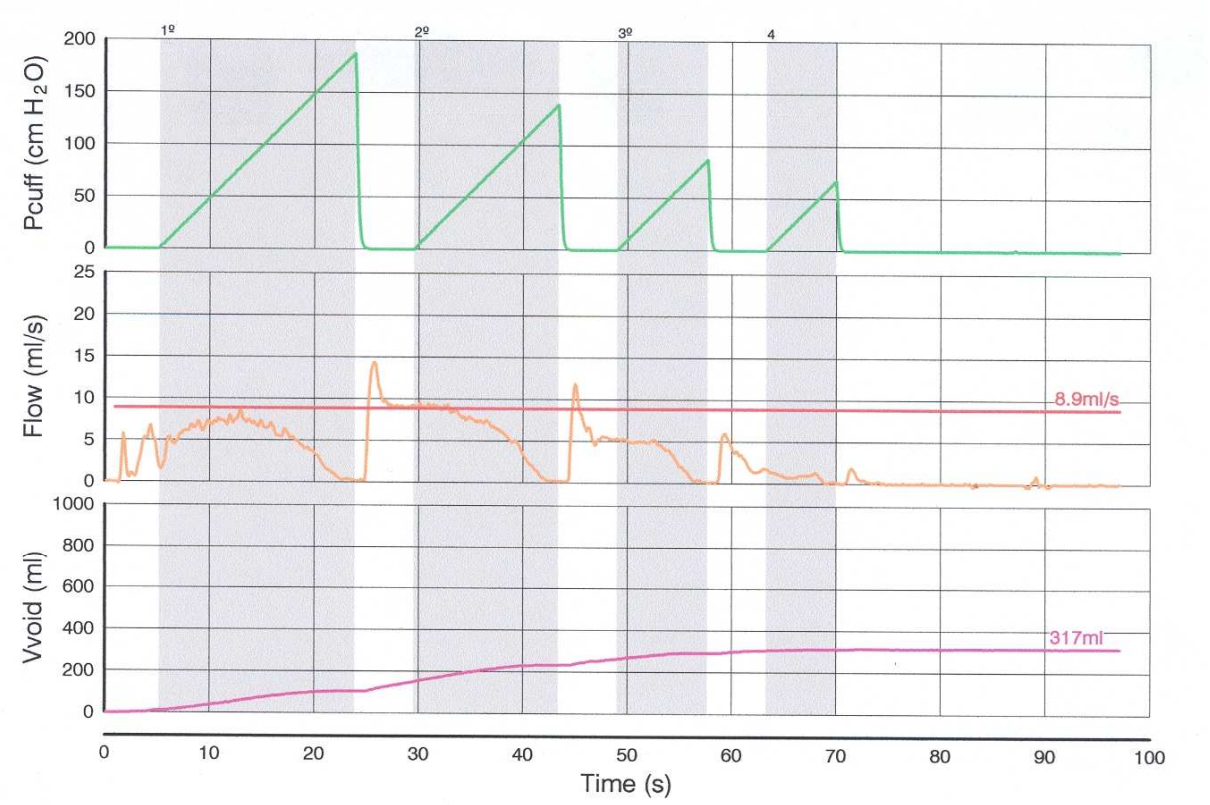
*Excludes 15 subjects for whom cuff test measurements were not obtained

Table 2: Surgical outcome for all subjects overall and following classification into obstructed, uncertain and not obstructed groups according to the nomogram. Outcomes were measured by IPSS questionnaire at 4 months, and separately by telephone interview at 24 months. Numbers (n) of subjects in each group achieving a good outcome compared to the total together with percentage good outcome (95% confidence intervals) are given. To assess prognostic accuracy likelihood ratios (LR) are given where LR = probability correct result ÷ probability of incorrect result (LR 5 – 10 = moderate change, LR = 2 – 5 small change).

	All subjects	**Pre-operative cuff test nomogram classification**		
		Obstructed	**Uncertain**	**Not obstructed**
Good outcome (IPSS @ 4 months)	n = 149 of 194*	n = 62 of 71	n = 67 of 87*	n = 20 of 36
	77% (70-83%)	87% (77-93%)	77% (67-85%)	56% (40-71%)
	LR = 3.3	LR = 6.7	LR = 3.3	LR = 0.8
		p < 0.01	N.S.	p < 0.01
Good outcome (Patient rating @ 24 months)	n = 112 of 146	n = 53 of 60	n = 45 of 57	n = 14 of 29
	77% (69-83%)	88% (78-95%)	79% (66-89%)	48% (30-68%)
	LR = 3.3	LR= 7.3	LR = 3.8	LR = 1.1
		p < 0.01	N.S.	p < 0.01

* For those assessed at 4 months the total number of subjects and the number of men categorised as diagnosis uncertain includes 15 men in whom we failed to get valid cuff measurements but who subsequently underwent TURP

Figure 1a: Pressure flow recording from the penile cuff test for a single void showing reading of maximum $p_{cuff.int}$ (168 cmH_20) and $Q_{max.cuff}$ (8.9 ml s^{-1}) for a voided volume of 317 ml.


1º
2º
3º
4
Pcuff (cm H2O)
Flow (ml/s)
8.9ml/s
Vvoid (ml)
317ml
Time (s)

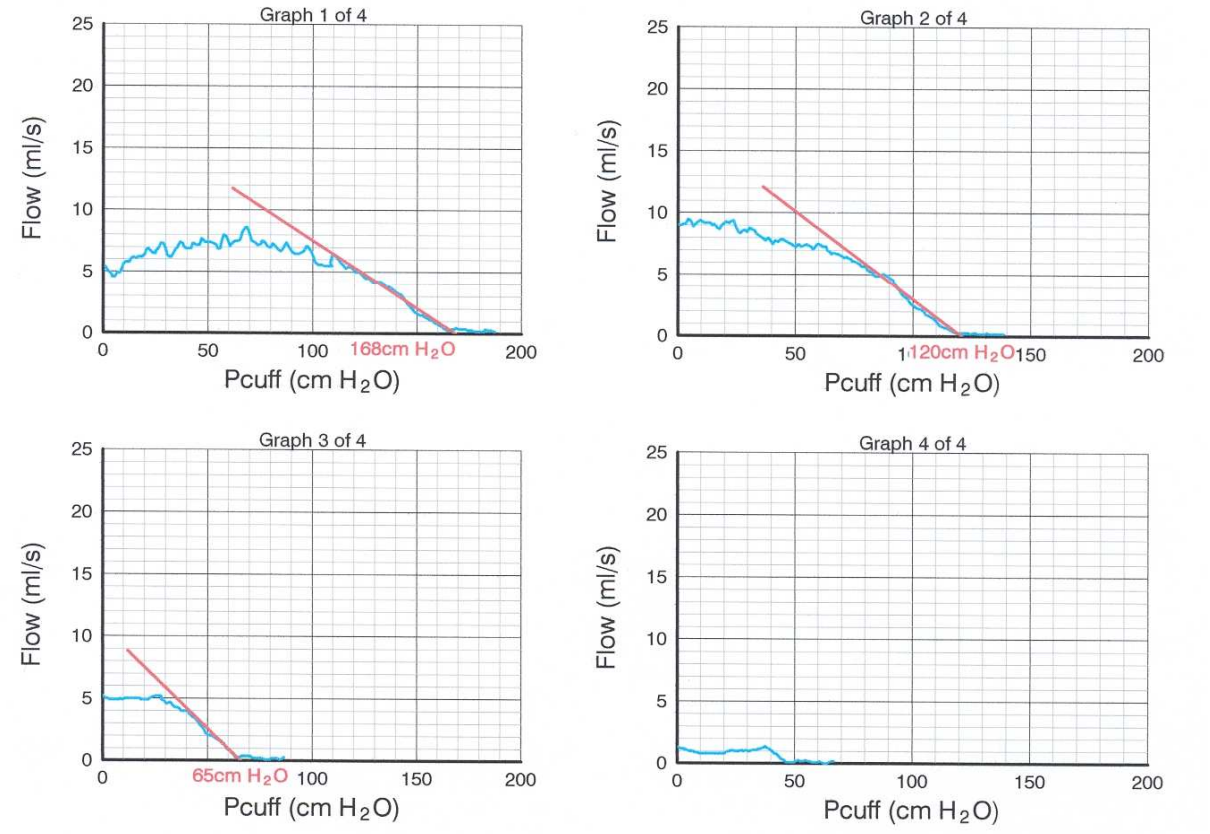

Graph 1 of 4
Flow (ml/s)
168cm H2O
Pcuff (cm H2O)
Graph 2 of 4
Flow (ml/s)
120cm H2O
Pcuff (cm H2O)
Graph 3 of 4
Flow (ml/s)
65cm H2O
Pcuff (cm H2O)
Graph 4 of 4
Flow (ml/s)
Pcuff (cm H2O)

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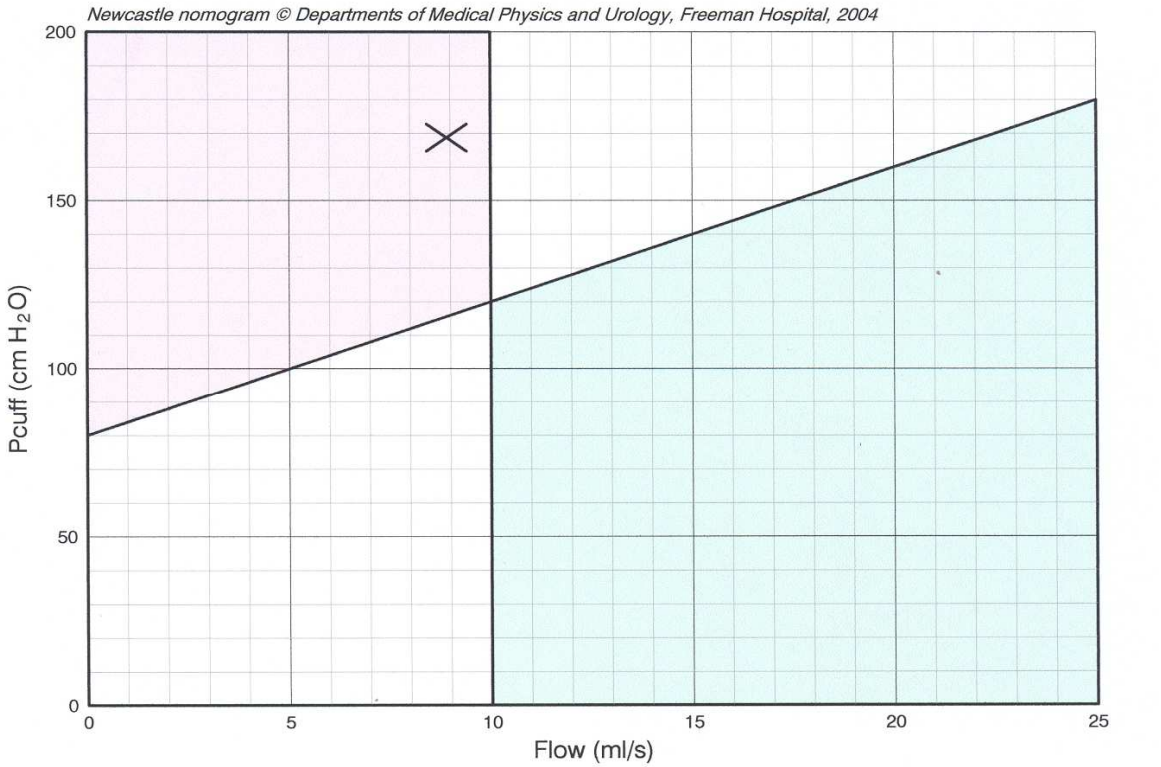
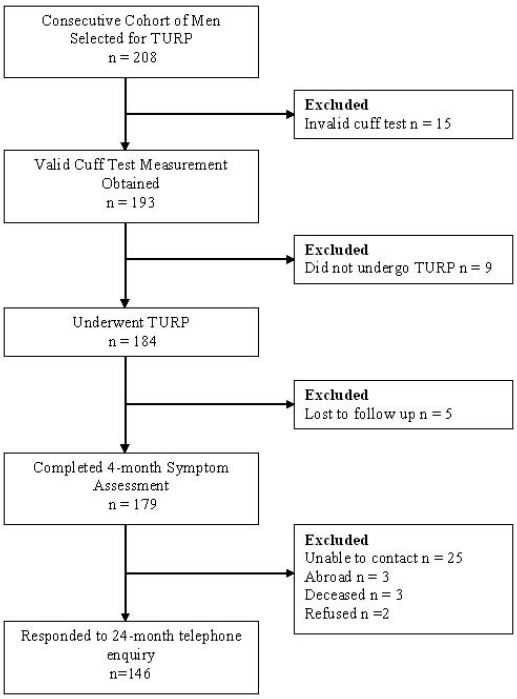
Figure 1b: Plotting of the measured readings for the subject's pressure flow plot (Figure 1a) for maximum $p_{cuff.int}$ and $Q_{max.cuff}$ on the non-invasive nomogram categorises the subject as obstructed.



435 **Figure 2:** Patient flow chart for study



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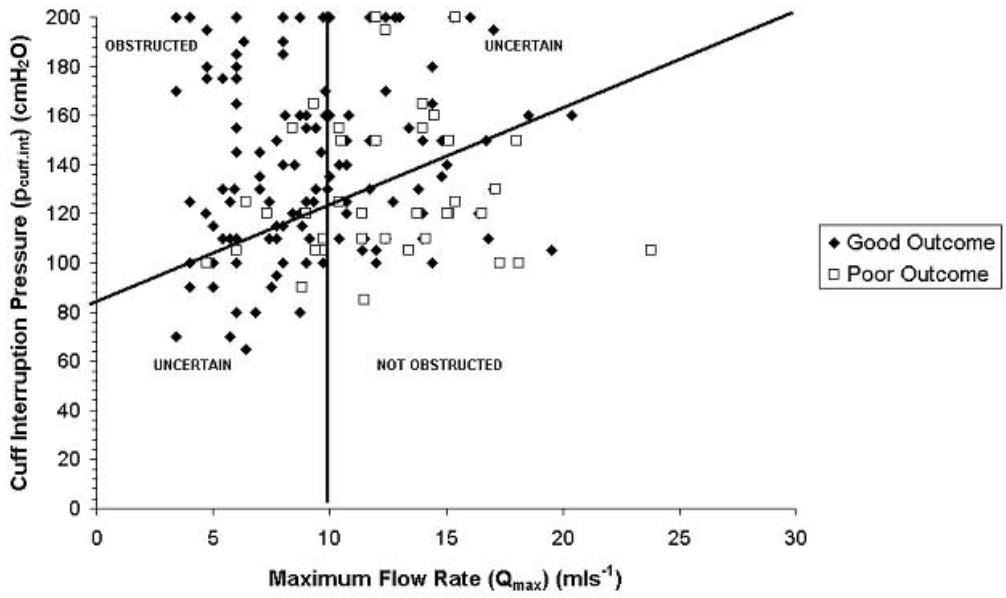
437

438 **Figure 3:** Pre-operative nomogram position. The nomogram is divided into diagnostic

439 quadrants according to flow and pressure cut-off lines. The points are labelled

440 according to subsequent symptomatic outcome as determined by change in

441 IPSS at 4 months.



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