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CRITICAL ANALYSIS OF THE CORRELATION BETWEEN URODYNAMIC AND NEUROUROPHYSIOLOGIC FINDINGS IN PATIENTS WITH MULTIPLE SCLEROSIS.

AIMS OF STUDY

Multiple sclerosis affects myelinated nerve fibres in the subcortical white matter, brainstem and spinal cord. Somatic as well as autonomic structures can be involved. Normal storage of urine and micturition requires an intact neuraxis, i.e frontal cortex, basal ganglia, thalamus, brainstem, cerebellum, thoracolumbar- and sacral spinal cord including interconnecting ascending- and descending neural pathways. Interconnecting pathways between the bladder/bladder-outlet and spinal cord (pelvic-, hypogastric- and pudendal nerves) are also essential for normal lower urinary tract function. During Neuro-Uro Physiological Investigation (NUPHI) we measure cortical evoked potential latencies of posterior tibial nerve (T.E.P.) and pudendal nerve (P.E.P.) for evaluation of dorsal column function. Sacral reflex latencies (bulbocavernosus reflex (B.C.R.) and urethro-anal reflex (U.A.R.)) are measured for the evaluation of peripheral- and sacral spinal function (S2 - S4).

With this study we aim to make a critical comparison of neuro-urophysiologic- and urodynamic (UDI) findings in 98 patients with multiple sclerosis in order to evaluate whether this limited investigation could enlighten the origin of lower urinary tract dysfunction in these patients.

PATIENTS AND METHODS

We investigated 98 patients (male 40, female 58), with a mean age of 37.6 years. Neuro -urophysiological investigation, as described above revealed 5 possible diagnoses: normal, pelvicus neuropathy (delayed UAR and normal BCR), sacral dysfunction (delayed or absent UAR and BCR, normal evoked potential latencies), suprasacral dysfunction (normal BCR and UAR, delayed or absent evoked potentials) and combined sacral- and suprasacral dysfunction. We used separate analysis for filling cystometry and micturition cystometry in each patient. Results of filling cystometry were classified as normal, hyposensitive (first sensation > 200 ml. and normal or high compliance) and hyperreflex (phasic contractions in the filling phase). Micturition during cystometry was classified as: normal or ineffective micturition (large residual urine and/or dyssynergic voiding).

RESULTS

The results of filling and voiding cystometry are given in the tables, compared with the results of NUPHI.

Looking at the filling phase of the cystometry we found that normal NUPHI results corresponded with normal urodynamic results in 80% of these patients. Abnormal NUPHI results corresponded with abnormal urodynamic results in 57.7%. Looking at the evacuation phase we found that normal NUPHI results

corresponded with normal UDI results in 89.7%. Abnormal NUPHI results corresponded with abnormal UDI results in 39.6% of these patients. The sensitivity of NUPHI for detecting disorders of storage function in cystometry was 83.8%; specificity was 57.7%. The sensitivity of NUPHI for detecting abnormalities in the evacuation phase of the cystometry was 81.5%; specificity was 39.6%.

Table 1: Filling-phase of cystometry and neuro-urophysiological investigation

NUPHI / UDI	NORMAL	PELVICUS NEUROPATHY	SACRAL LESION	SUP.SACRAL LESION	COMBINED (SUP)SACR
NORMAL	80.0% (24)	60.0% (3)	72.7% (8)	35.0% (7)	23.5% (4)
HYPOSENS	13.3% (4)	40.0% (2)	18.2% (2)	30.0% (6)	47.1% (8)
HYPERREFL	6.7% (2)	0	9.1% (1)	35.0% (7)	29.4% (5)

Table 2: Voiding-phase of cystometry and neuro-urophysiological investigation

NUPHI / UDI	NORMAL	PELVICUS NEUROPATHY	SACRAL LESION	SUP.SACRAL LESION	COMBINED (SUP)SACR
NORMAL	89.7% (26)	100% (5)	63.6% (7)	52.9% (9)	53.3% (8)
INEFF	10.3% (3)	0	36.4% (4)	47.1% (8)	46.7% (7)

CONCLUSIONS

The use of NUPHI for evaluation of lower urinary tract function in multiple sclerosis patients was introduced to localise MS-lesions and relate their localisation to lower urinary tract function. In the group of MS patients that we investigated, NUPHI abnormalities were found in 63.4%. The majority of patients with NUPHI abnormalities had no urodynamic abnormalities. Therefore NUPHI in its current form is not able to predict urodynamic abnormalities, especially not abnormalities in the evacuation phase. One possible explanation is incorrect diagnostic classification based on this NUPHI parameters. Since NUPHI measures almost exclusively sensory parameters it is hardly useful to predict the predominantly motor urodynamic parameters.

Additional thoracolumbar recordings of PEP for discriminating central- and peripheral sensory conduction and cortical recordings of evoked responses by stimulation of the vesico-urethral junction could improve current sensory investigation of the lower urinary tract. Motor evoked potentials of external urethral/anal sphincter by transcranial- and spinal magnetic stimulation are necessary for evaluation of corticospinal and reticulospinal tracts and measurement of central- and peripheral motor conduction. These additional measurements should allow more accurate evaluation of lower urinary tract (dys-)function in patients with multiple sclerosis.

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EFFECT OF INTRAVESICAL CAPSAICIN TREATMENT ON POSTTRAUMATIC SPINAL DETRUSOR HYPERREFLEXIA AND THE BLADDER COOLING REFLEX

AIMS OF STUDY

Capsaicin causes desensitation of C-fiber sensory afferents inducing

reversible suppression of sensory neuron activity. According to experimental studies there is reorganisation of the micturition reflex in the chronic spinal cat, the reflex being mediated by unmyelinated C-fibers which may be blocked by capsaicin (1). The bladder cooling reflex is also mediated by specific C-fiber afferents (2). Intravesical administration of capsaicin in patients has been found to increase bladder capacity and to reduce bladder pain (3, 4). We have prospectively studied the effect of topical capsaicin on bladder volume, detrusor contractility and the ice-water response in patients with traumatic high pressure spinal detrusor hyperreflexia in an attempt to reduce hyperreflexia.

MATERIAL AND METHODS

Seven male patients, mean age 32 years (range 15 - 61 ys), with chronic, traumatic spinal detrusor hyperreflexia (complete 4, incomplete 3) were prospectively studied. A medium fill cystometry was performed in the supine position using isotonic saline at room temperature. An ice-water test was performed by manual, rapid infusion (rate 200-300 ml/min) of sterile water at 0°. In patients with a cystometric capacity less than 200 ml, an ice-water volume corresponding to half the capacity was used. One-hundred ml of 2 mmol capsaicin dissolved in 30% alcohol was introduced into the bladder through an 8-F plastic catheter. The instillate was left within the bladder for 30 minutes and the vital signs were carefully monitored during this period. Cystometry and ice-water testing was repeated immediately after emptying of the bladder and again after 4 to 12 weeks follow-up.

RESULTS

As an immediate effect of capsaicin treatment, autonomic dysreflexia of varying degree was noted in all patients, in a few of them very marked and persistant. Patients with incomplete lesions got severe, burning, suprapubic pain. In all but one these symptoms disappeared shortly after bladder evacuation. In one man the pain continued for some days. Intense, hemorrhagic cystitis was found at cystoscopy. Otherwise, there were no side effects. In all but one patient bladder function parameters improved immediately after treatment and at 4-12 weeks follow-up. The bladder capacity increased from a median of 164 mls (range 27-300) to 230 (34-389) immediately post treatment compared to 268 (120-380) mls at follow up. The comparative figures for the maximal detrusor pressure were 90 (50-176), 75 (20-126) and 97 (24-160) cm H_2O.

CONCLUSION

Capsaicin improves bladder function in traumatic spinal hyperreflexia with distressing high pressure. The simultaneous reduction of micturition contraction pressure and the blocking of the bladder cooling reflex indicates that, in spinal man, the two reflexes are mediated by C-fiber afferents. The effect on detrusor pressure probably is dose dependant. The ice-water test may be used as a monitor to determine the dose of capsaicin needed to elicit therapeutic effects. Remaining questions are the duration of the response and how to reduce unpleasant immediate side effects of capsaicin administration.

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LESSONS LEARNT FROM 44 INTRAVESICAL INSTILLATIONS OF CAPSAICIN

AIMS OF STUDY

In experimental animals following disconnection of the sacral spinal cord from higher centres, a new segmental reflex arc becomes functional. Unmyelinated C fibres emerge as the predominant afferents from the lower urinary tract and establish volume determined detrusor hyperreflexia. Capsaicin appears to be selectively neurotoxic for these unmyelinated C fibres.
Since the first report in 5 patients of the use of intravesical capsaicin to treat severe detrusor hyperreflexia, 17 more have undergone this form of treatment. The earliest patients have now been followed up for 3 years.

PATIENTS AND METHODS

Forty four intravesical capsaicin instillations have been carried out in twenty two patients. Fourteen patients with spinal cord disease, (9 multiple sclerosis, 2 tropical spastic paraparesis, 1 arteriovenous malformation, 1 spina bifida, and 1 transverse myelitis) and 3 neurologically normal patients underwent urodynamic assessment before, during and after capsaicin instillation. All seventeen patients had significant frequency and incontinence. The remaining 5 patients had long term indwelling catheters and were bed bound, one in a vegetative state and four with severe progressive multiple sclerosis.
We are now performing intravesical capsaicin as an outpatient procedure in the urodynamic laboratory. Cystometry and flexible cystoscopy is carried out at the initial assessment. Two percent lignocaine is used prior to intravesical capsaicin instillation. Hundred mls of 1mmol or 2mmol solution of capsaicin dissolved in 30% alcohol in saline is used. No patient has had significant ill-effects during the procedure. Phasic detrusor contractions occur within a few minutes of intravesical capsaicin instillation in most patients. Cystometry is done four to twelve weeks after capsaicin instillation when a flexible cystoscopy is performed.

RESULTS

Cystometry in 14 patients with spinal cord disease revealed phasic detrusor hyperreflexia in eleven, the other three had poor compliance. Two of the neurologically normal patients had sensory urgency and one had idiopathic detrusor instability.
In eleven patients with spinal cord disease and phasic detrusor contractions the mean volume at first detrusor hyperreflexia increased from 132mls to 307mls and the mean bladder capacity rose from 157mls to 358mls. The mean maximum detrusor pressure decreased from 54 to 38cms H_2O. In seven patients the clinical improvement was highly satisfactory and they became continent with intermittent self catheterisation. The beneficial effects lasted for three to six months, after which they requested a repeat instillation. Two patients reported less episodes of urgency and urge incontinence between intermittent catheterisations.

The remaining 2 patients remained the same. There was no clinical or urodynamic improvement in the 3 patients with poorly compliant bladders nor the patient with primary detrusor instability. The 2 patients with sensory urgency also did not note any improvement in their symptoms. Three out of the 5 bedbound patients had a transient lessening of bypassing after capsaicin instillation but cystometry was not performed in all 5.

CONCLUSION

This study confirms that capsaicin sensory afferents exists in the human bladder and are functionally significant in detrusor hyperreflexia secondary to spinal cord disease. Intravesical capsaicin improves incontinence in some patients with spinal cord disease and detrusor hyperreflexia and the clinical benefit may be maintained by repeating the instillations at 3-6 monthly intervals.

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OUTCOME OF TRANSCUTANEOUS ELECTRICAL STIMULATION IN PATIENTS WITH DETRUSOR INSTABILITY.

AIMS OF STUDY

Electrical stimulation can modulate neural reflex behavior with respect to the urinary tract [1]. Surface contact stimulation procedures such as intra-vaginal and anal plugs [2] and transcutaneous electrical nerve stimulation (TENS) over the suprapubic [3] and of the Tibial and common Peroneal nerves [4] have been shown to be effective in modulating detrusor function. The aim of this prospective study was to assess the urodynamic and clinical outcome of TENS of the S3 dermatome in patients with idiopathic detrusor instability (DI) who have had an unsuccessful outcome with previous conservative treatments.

PATIENTS AND METHODS

We studied 20 patients with DI (8M:12F, mean age 52 years). Previous unsuccessful treatments included anticholinergic therapy (20), bladder over-distension (14), bladder transection (2) and S3 nerve root blockade (1).

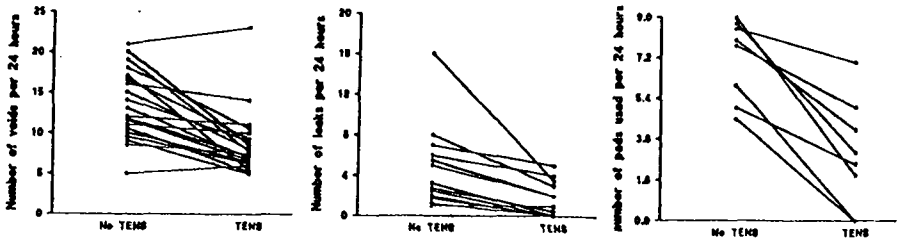
A dual channel transcutaneous nerve stimulator was used (COM-TENS). The device provided variable control of frequency, pulse width and current amplitude. Stimulation parameters were fixed at a frequency of 50Hz and a pulse width of 200 u sec. Patients were asked to control the amplitude to produce a tickling sensation under the two electrodes; placed bilaterally over the peri-anal region.

Objective assessment was performed using conventional cystometrogram (CMG) in a random fashion under three conditions: No TENS, TENS over S3 dermatome (TENS-S3) and TENS over T12 dermatome (TENS-T12) which acted as a placebo. Following a three week clinical trial with TENS-S3 an ambulatory urodynamic study (AM) was carried out with TENS-S3. Subjective outcome was assessed using a diary card documenting urinary frequency, urge incontinence and the use of pads; for one week prior to the study and during the three weeks of the clinical trial. In addition urinary symptom scores were analysed using a modified Frimodt Møller scoring system [5] (0-14 points).

RESULTS

The effect of TENS on urinary frequency, urge incontinence and in the use of pads is shown in figure 1. Improvement

Figure 1. Effect of TENS on 24 hour urinary frequency, urge incontinence and use of incontinence pads. Each value represents the mean number of episodes, one week prior to TENS therapy and in the last week of trial with TENS-S3.



in the 24 hour urinary frequency was observed in 14 patients. Urge incontinence experienced by 13 patients prior to the study improved in 12 patients. Of the eight patients regularly requiring pads, two were rendered completely dry. Pre and with TENS-S3 urinary symptom scores were 9 ± 3 (range 3-13) and 5 ± 2 (range 0-10) respectively.

Urodynamic (CMG) findings are summarised in table 1. Ambulatory study following three weeks of TENS-S3 therapy revealed the following: mean voided volume 282 ± 78 ml, maximum amplitude of DI 49 ± 44 cm H_2O and frequency of DI 1 ± 1 per minute.

Table 1. Effect of TENS on conventional CMG study.

	No TENS	TENS-S3	TENS-T12
Total bladder capacity (ml)	229 ± 125	337 ± 192	252 ± 202
Volume at first contraction (ml)	80 ± 65	128 ± 93	97 ± 65
Number of unstable peaks	5 ± 3	1 ± 1	4 ± 2
Frequency of contractions (/min)	2 ± 1	1 ± 1	2 ± 1
Maximum amplitude of unstable contractions (cm of H_2O)	46 ± 35	35 ± 36	34 ± 22

The effect of TENS on DI during CMG and AM urodynamic studies is shown in table 2. Although a significant number of patients noticed some improvement in their symptoms, five (25%) patients were rendered urodynamically stable on CMG and three (15%) patients on AM.

Table 2. Effect of TENS on DI during CMG (No-TENS, TENS-S3 and TENS-T12) and Ambulatory study with TENS-S3. Each value represents number of patients.

	No TENS	TENS-S3	TENS-T12	Ambulatory study
Unstable	20	15	20	17
Stable	0	5	0	3

CONCLUSIONS

We have studied a group of patients with severe DI refractory to conservative treatments. The study revealed that the use of TENS over the S3 dermatome produced significant changes in the urodynamic parameters and improvement in symptoms particularly regarding urinary frequency and urge incontinence. A significant reduction was also observed in the use of incontinence pads by these patients.

The precise mechanism regarding modulation of detrusor activity by electrical stimulation over the S3 dermatome remains unclear. The outcome of this study however, suggests an approach which may be beneficial in patients with DI refractory to conservative treatments and should be considered prior to enterocystoplasty or alternative surgical procedures.

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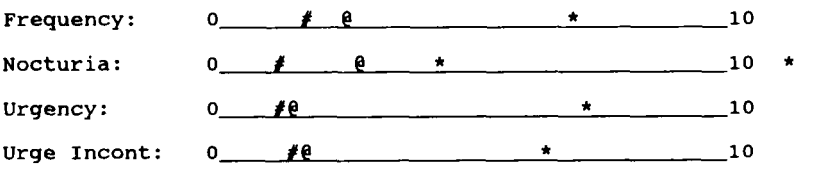
A RANDOMISED,CROSS OVER TRIAL COMPARING OXYBUTININ TAKEN THREE TIMES A DAY OR TAKEN"WHEN NEEDED".

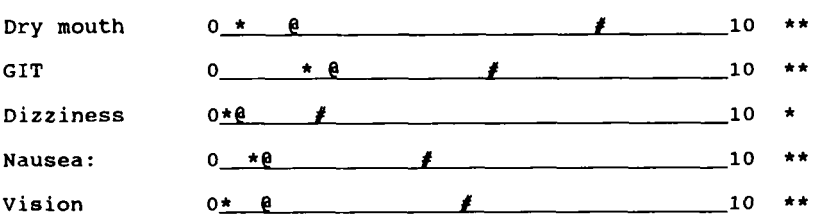
AIMS OF STUDY:
Oxybutinin is a powerful anticholinergic and smooth muscle relaxant(1). However cholinergic receptors exist throughout the body and therefore the main problem with the drug is the level of side-effects(2). Oxybutinin has a rapid onset (< 30 min.) and a short half life (5 hours)(1) and clinicians often use Oxybutinin on a "as necessary" (PRN) basis rather than a set dose regime. This has the advantage of achieving good control and less side effects and importantly gives the patient a sense of control over their bladder. The aim of this study was to compare a PRN schedule for Oxybutinin with routine Oxybutinin.

PATIENTS AND METHODS:
Eighty women with urodynamically proven detrusor instability were randomised to take 2.5mg Oxybutinin three times a day (TDS) or 2.5mg when necessary (PRN) for 6 weeks. They then stopped therapy for a two week wash out period and then crossed over into the other arm of the trial for another 6 weeks. Assessment included visual analogue Symptom score, visual analogue side effect score, urinary diary, 24 hour pad test, videocystourethrography and patient preference score. Two patients dropped out of the study. Both were in the TDS phase of the trial.

RESULTS:
Symptoms Score: * = Pre-treatment # = TDS @ = PRN (Median)



Side effect score:



Comparison of TDS vs. PRN * = $p < 0.05$ ** = $p < 0.01$
All others no sig. diff.

Urinary Diary:
Frequency was a mean of 11.1 times a day pre treatment and was 5.4 for the TDS group and 7.2 for the PRN group. Nocturia was 3.2 times a night pre treatment and was 1.1 for TDS and 1.9 for PRN. The number of incontinent episodes was 5.2 a day pre-treatment and was 1.4 for TDS and 1.8 for PRN. Comparing TDS versus PRN there was no significant difference in frequency, nocturia and number of incontinent episodes.

24 hour pad weighing test:
Median pad weight pre treatment was 37 g/24 hrs (IQR = 24-47). The median pad weight for the TDS protocol was 10 g/24 hr (IQR = 3-15) and for the PRN group it was 15 g/24 hr (IQR = 4-20). There was no significant difference between the TDS group and the PRN group.

Videocystourethrography:

	Pre-Treatment	TDS	PRN
First Sensation (mls)	105	190	184
Bladder Capacity (mls)	210	345	300
P Det-filling (cm H_2O)	16	9	9
Max P Det (cm H_2O)	19	11	12
Residual (mls)	45	75	49
Leak with D.I. (80 pts)	49	12	15

Both treatments were significantly better than pre-treatment ($p<0.05$) but there was no significant difference between the two treatment groups.

Patient Preference Score:

Of the 80 patients 62 preferred the PRN treatment and 8 preferred the TDS treatment. Eight preferred neither treatment.

CONCLUSIONS:

On subjective and objective testing Oxybutinin taken as needed gave results that were not statistically different to those on a set TDS regime. However the amount of side effects on the PRN regime was considerably reduced and patient preference was clearly for the more flexible regime. Patients should be encouraged to try this more flexible approach as it appears to give as good results, far less side effects and gives the patient a sense of control over their bladder.

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THREE DIMENSIONAL ULTRASOUND OF THE URETHRA AND URETHRAL SPHINCTER - A NEW DIAGNOSTIC TECHNIQUE

AIMS OF STUDY

Ultrasound enables the lower urinary tract to be visualised as well as the surrounding tissues. Three dimensional (3D) ultrasound scans a block of tissue allowing accurate measurements of tissue volumes within the block. Views of the pelvis obtained using 3D ultrasound are impossible to achieve by any other way and this should increase our understanding of the pathophysiology of urinary incontinence.

PATIENTS AND METHODS

Women with urinary symptoms were recruited prior to undergoing videocystourethrography. Seventy women had a perineal 3D ultrasound scan. The perineal scan is performed with the women lying supine using a 5 MHz mechanical probe (Kretz). The urethra and urethral sphincter

are visualised in the midline and the focus of the probe is adjusted to optimise the image. The 3D ultrasound scan takes 7-10 seconds, the ultrasound probe records 150 ultrasound "slices" as the probe scans 90 degrees on its axis. The images are digitised and combined by the ultrasound machine enabling the sonographer to view any structure within the volume of tissue scanned as a routine two dimensional ultrasound image or a three dimensional image can be reconstructed of the structures visualised.

The urethra, urethral sphincter and bladder neck were visualised in the sagittal plane. The urethral lumen and immediately adjacent tissues appear hypoechoic(black) this may extend from the urethral meatus to the bladder. This is surrounded along the mid length of the urethra by a homogenous round structure which thicker anteriorly than laterally or posteriorly. From pilot studies in cadavers, true cut biopsies of this area under ultrasound guidance have shown the tissue to be striated muscle. This structure is likely to be the rhabdosphincter.

Measurements were taken of the following structures in the sagittal plane (fig 1) the distance from the bladder neck to the start of the "rhabdosphincter"(a), the length of the "rhabdosphincter"(b), the distance from the bladder neck to maximal cross sectional area of the "rhabdosphincter"(c). The volume of the hypoechoic area "the urethra" and the volume of the "rhabdosphincter" (fig 2) were measured by taking between 10 to 15 cross sectional areas in the transverse plane. To obtain such an ultrasound image of the urethra in the transverse plane using a 2D ultrasound machine would involve scanning through the bony pelvis which is not possible.

RESULTS

All the women (42) with urethral sphincter incompetence had a continuous hypoechoic area from the bladder neck to the urethral meatus. Also some of the women with severe genuine stress incontinence had breaks in the continuous circle of the "rhabdosphincter" and it was replaced by hyperechoic areas. This may indicate damage to the urethral sphincter.

	Urethral Sphincter Incompetence (n=42)	Competent Urethral Mechanism (n=28)	Mann Whitney U Test
Distance (a)/mm	5.5 (3.8-6.2)	5.5 (2.2-8.3)	P > 0.05(NS)
Distance (b)/mm	18.8(16.8-21.9)	21.8(19.4-23.9)	P < 0.02
Distance (c)/mm	16.0(14.2-18.4)	17.8(15.2-20.1)	P > 0.05(NS)
Hypoechoic Volume/cm^3	0.8 (0.4-1.3)	0.5 (0.3-0.8)	P = 0.03
Total Sphincter Volume/cm^3	3.9 (2.3-4.7)	4.6 (3.4-6.1)	P = 0.02
True Sphincter Volume/cm^3	2.8 (2.0-3.8)	4.1 (2.9-5.4)	P = 0.03

CONCLUSION The "rhabdosphincter" is significantly smaller in women with urethral sphincter incompetence.The volume of the hypoechoic structure was significantly larger in this group of women and this may relate to the pressure exerted by surrounding structures. This may be useful in determining the pathophysiology of urethral sphincter incompetence as well as being a diagnostic tool.

FIG 1

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DYNAMIC 3-D MRI IMAGING OF THE PELVIC FLOOR

AIMS OF THE STUDY

The influence of voluntary pelvic floor contraction on the anatomical displacement of the structures surrounding the bladder was made. Axial, sagittal and transverse MRI were obtained from young, healthy volunteers in order to visualize the 3D configuration of the contracting pelvic floor. Our aim is to define the response of the normal pelvic floor to voluntary pelvic floor exercises so that rational comparisons can be made when imaging incontinent patients.

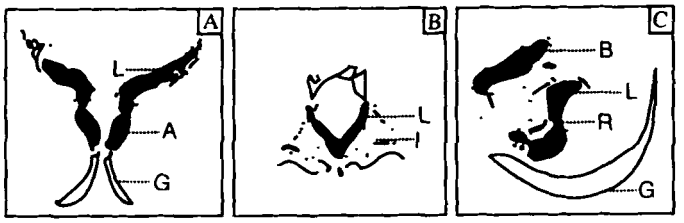
PATIENTS AND METHODS.

The 17 young, assymptomatic volunteers studied were trained to perform correctly pelvic floor

exercises. A Philips 1.5T Gyroscan having a 400mm field of view and an acquisition matrix of 180 x 250 pixels was used. Each plane consisted of 7 images 10mm thick and slices were separated by 12mm. Scanning time was 1:35min with the subject in the supine position. A sequence of images was obtained in the relaxed and contracted state with the subject maintaining a submaximal contraction for the duration of the scan. Images were color-coded and numerically subtracted to illustrate the differences between the two states and highlight the salient dynamic features of pelvic floor contraction. Using edge enhancement, measurements were made of the movement of the superior, lateral, anterior and posterior wall of the bladder. Distances are given in millimeters.

RESULTS.

Subtracted images clearly demonstrate the magnitude of displacement from the relaxed to the contracted state. The figure typically illustrates the outlines of the activated muscle groups in the (A): coronal, (B): axial, (C): sagittal. The filled in portions show compression and open portions show spaces that are vacated by the contraction. Coronal images transect the anal sphincter and the posterior levator ani. The sagittal image is taken at the midline and the axial at the level of the symphysis pubis.



Legend: A - Anal canal - I - Ischiorectal fossa
B - Bladder (posterior) L - Levator ani
G - Gluteal fossa R - Rectal motion

The analysis of the displacements measured by subtraction of the relaxed from contracted frames are tabulated below.

Coronal Displacement	
Superior bladder	5.9 ± 2.4 (3.1 - 10.9); n = 13
Lateral bladder	4.3 ± 1.8 (1.6 - 7.8); n = 13
Gluteal surface	3.9 ± 1.8 (1.6 - 7.8); n = 15
Sagittal Displacement	
Posterior bladder	6.3 ± 3.9 (1.6 - 10.9); n = 10
Gluteal surface	5.2 ± 2.3 (1.6 - 9.4); n = 14
Transverse Displacement	
Anterior urethral wall	3.3 ± 0.9 (1.6 - 4.7); n = 9
Levator ani surface	3.5 ± 2.0 (0 - 7.8); n = 17

Data are given as mean ± s.d., range, and number of observations..

CONCLUSIONS

Voluntary pelvic floor contraction produces changes in the support of the viscera by skeletal muscle in all three dimensions. The dynamic imaging obtained in these studies clarifies the direction and extent of compression of the normal pelvic floor that is produced by pelvic floor exercises in normal controls. It is suggested that these measurements set the framework upon

which comparisons can be made in patients with stress and/or detrusor incontinence. By identifying the specific muscle groups that are recruited during voluntary pelvic floor contractions, it may be possible to identify and localize the structure(s) that may be contributing to the symptoms. Previous dynamic MRI studies have been done in patients who were asked to strain. We believe that voluntary strain provides an indication of the passive elements of pelvic floor support, while contraction demonstrates the ability of the pelvic floor to actively support the visceral organs and suggests that it may be responsive to physiotherapy.

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PELVIC FLOOR STIMULATION IN THE TREATMENT OF GENUINE STRESS INCONTINENCE: A MULTICENTER PLACEBO-CONTROLLED TRIAL

AIM OF STUDY

To determine the efficacy of transvaginal electrical stimulation in treating genuine stress incontinence.

PATIENTS AND METHODS

This was a multicenter, prospective randomized, double-blinded placebo-controlled 15 week trial comparing the use of an active pelvic floor stimulator to a sham device. Thirty-five women used an active unit and 17 controls used sham devices. Seven day and daily voiding diaries were recorded during the trial. Urodynamic testing including pad testing and subtracted cystometry was done before and at the end of device use. Perineometry was measured at baseline and at the end of the trial. Patients scored their symptoms on visual analog scales, and completed quality of life questionnaires (SF-36) before and after therapy. Non-parametric rank sum tests and unpaired t-tests were used to assess treatment group balance at baseline, changes from baseline and outcomes at the end of treatments. Fischer's exact tests and Kruskal-Wallis exact tests for ordinal and continuous measures were used to compare groups for quality of life and improvement measures. Signed rank tests and paired t-tests were used to evaluate the significance of changes from baseline within each treatment group.

RESULTS

Significant improvements from baseline were found in patients using active devices but not in controls. Comparisons of changes from baseline between active device and control patients (Table) showed that active device patients had significantly greater improvement in weekly ($p=0.009$) and daily leakage episodes ($p=0.04$), pad testing ($p=0.005$) and vaginal muscle strength ($p=0.02$) when compared to controls. Significantly greater improvement was also found for visual analog scores of urinary incontinence ($p=0.007$), stress incontinence ($p=0.02$) as well as subjective reporting of frequency of urine loss ($p=0.002$), and urine loss with sneezing, coughing or laughing ($p=0.02$) when compared to controls. Pad testing showed that stress incontinence was cured or improved by 50% in 62% of patients using an active

device compared to only 19% of patients using sham devices (p=0.01). Voiding diaries showed a cure or 50% improvement rate in 48% compared to 13% of women using the sham device (p=0.02). No serious adverse effects were noted in either group.

Table: Significant changes in subjective and objective parameters between active and control patients after 12 weeks of pelvic floor stimulation*

	Active			Control			
	Pre-treatment mean	Post-treatment mean	Mean change	Pre-treatment mean	Post-treatment mean	Mean change	p Value (K-W)++
Objective							
Leaks per week	14.1	10.0	(4.1)	20.1	27.0	6.9	0.009
Leaks per 24 hours	3.0	1.8	(1.2)	2.6	3.4	0.8	0.04
Pad weight (gm)	45.3	15.4	(29.9)	30.0	32.3	2.3	0.005
Vaginal muscle strength (mm Hg)	10.6	15.2	4.6	10.0	8.9	(1.1)	0.02
Pads used per week	6.2	4.1	(2.1)	9.7	11.2	1.5	0.07
Subjective+							
Frequency of urine loss	3.1	2.4	(0.7)	2.8	2.9	0.1	0.002
Urine loss with sneeze/cough/laugh	4.1	3.2	(0.9)	3.4	3.5	0.1	0.02
Urine loss with running/exercising	3.8	3.0	(0.8)	3.6	3.3	(0.3)	0.19
Urine loss with walking/position changes	2.4	1.9	(0.5)	2.9	3.0	0.1	0.09
Visual Analog Scales:							
Severity of urinary incontinence	5.9	3.8	(2.1)	5.3	5.4	0.1	0.007
Severity of stress incontinence	7.1	4.8	(2.3)	6.6	6.3	(0.3)	0.02

* Numbers in parentheses are negative

\+ A decrease in value represents improvement

++ Comparison of mean changes

CONCLUSION

Pelvic floor stimulation was found to be a safe and effective therapy for genuine stress incontinence.

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PELVIC FLOOR DAMAGE AND CHILDBIRTH: A NEUROPHYSIOLOGIC FOLLOW UP STUDY

AIMS OF STUDY

Six years ago a study of 96 nulliparous women reported that childbirth causes damage to the nerve supply of the pelvic floor. However, this assessment was carried eight weeks post natally and the clinical significance of this damage was not clearly delineated. The objective of this study was to investigate the effect of time and further childbearing on the pelvic floor in a cohort of the 96 women originally studied and determine the relationship of any changes to the symptom of stress incontinence.

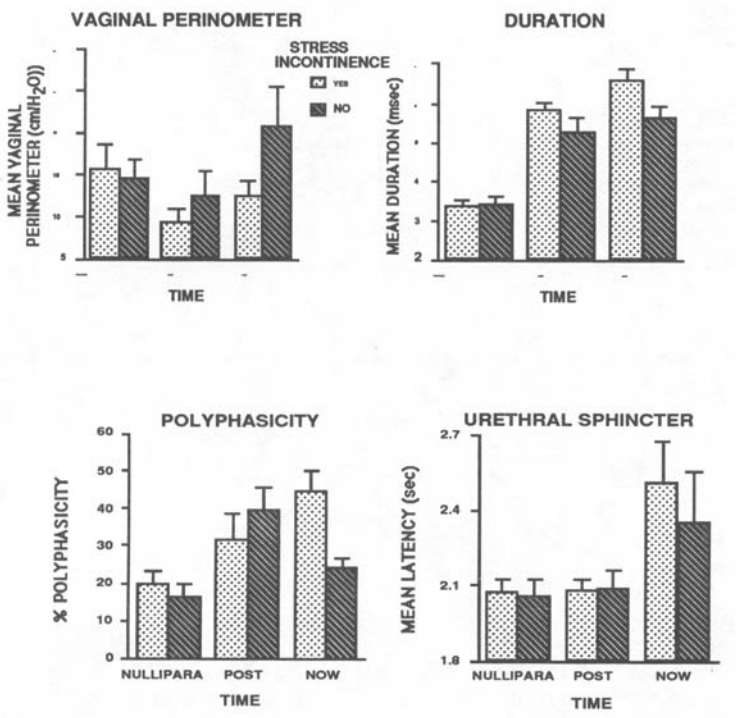
PATIENTS AND MEASURES

Seventy-six women were located and agreed to participate in this longitudinal cohort study. The study protocol included: history, physical exam, Q-tip^{tm} test, concentric needle EMG and quantitative motor unit analysis, pudendal nerve and perineometer measures. Thirty-one of the subjects provided only a history while

the remaining 45 completed the entire study protocol. Repeated measures ANOVA was used to determine the effect of time and further childbearing on the neurophysiologic and perineometer measures.

RESULTS

Parity did not independently effect outcome measures. Motor unit duration increased significantly for the group compared to their original post partum measure ($p<.001$), however the incidence of polyphasia remained the same. Latencies to the urethral and anal sphincters increased for the group over time as compared to the original postnatal record ($p<.001$). Perineometer measures increased for the group as a whole compared to the initial post partum measure. Fortyfive of the 76 respondents (60%) admitted to at least one stress incontinent episode in the last 3 months. Twenty (26%) had at least weekly episodes and thought their incontinence to be a problem. Women who complained of stress incontinence had a significantly longer measure of motor unit duration across all three time points (antepartum, postnatal and now) than those without($P<.05$). Urethral nerve conduction times, and motor unit polyphasicity increased significantly over time($P<.001$). Those women with stress incontinence exhibited a higher percent polyphasicity than continent women($p<.05$). There was a significantly more muscle strength in the continent women as compared to the incontinent women ($p<.001$).



CONCLUSIONS

Further changes in pelvic floor neurophysiology occur in time but do not appear to be related further childbearing. Women complaining of incontinence in this group had significantly longer measures of motor unit duration, urethral sphincter latencies and percent polyphasia compared to the asymptomatic women. The groups also differed in the perineometer measures of muscle strength.This would suggest that greater denervation damage correlates with diminished muscle function. The fact that absolute parity and further childbearing had no effect on the outcome measure would suggest majority of denervation- reinnervation occurs in the first birth. This supports epidemiological studies which failed to find a strong relationship with stress incontinence and increasing parity.

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THE NATURE OF URETHRAL PRESSURE VARIATIONS - SIMULTANEOUS EVALUATION BY PERINEAL VIDEO-SONOGRAPHY AND URETHROCYSTOMETRY

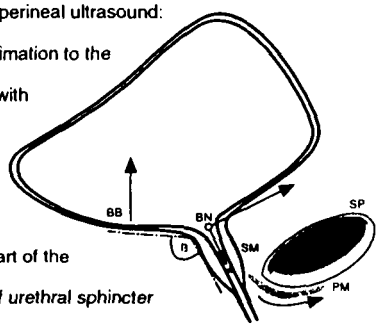
AIM OF STUDY

Urethral pressure variations (UPV) are a common finding in patients suffering from urinary stress incontinence and bladder instability as well as in normol controls. Among the various speculations on their origin, combined EMG and urethral pressure studies indicate that contraction and relaxation of smooth or striated urethral muscles seem to be the most likely cause (1). In addition, sonographic examinations have detected activity of the urethral and prepubic muscles (2). The aim of the present study was to simultaneously examine muscle activity by ultrasound and UPV by urethrometry in order to determine a correlation between them.

PATIENTS AND METHODS

In 15 women with urethral pressure variations, urodynamic evaluation with water filling cystometry, resting and stress urethral pressure profiles and uroflowmetry were performed. During water filling cystometry, there were simultaneous perineal video-sonography and urethrocystometry. Real-time ultrasound pictures and urodynamic curves were simultaneously monitored on a computer screen and registrated on video tape.

Fig. 1 shows schematically the morphologic changes seen by perineal ultrasound: Movement of the bladder neck (BN) with elevation and approximation to the symphysis pubis (SP) and elevation of the bladder base (BB) with an increase in angle ß are indirect signs of pelvic floor contractions. Contractions of the prepubic muscle (PM) are visualised as shortening of this fine muscular structure on the anterior border of the symphysis pubis leading to the middle part of the urethra. Shortening and opening of the urethra are the signs of urethral sphincter muscle contraction (SM) .

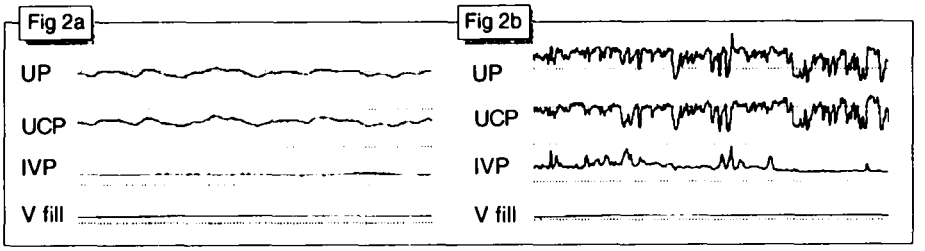


RESULTS

Simultaneous ultrasound and urodynamic evaluation in the 15 patients showed three types of muscle contractions leading to UPV: Type A - contractions of the pelvic floor muscle (N = 8). In this group two contraction patterns were found: Slow contractions with slow pressure variations and low amplitude (Fig 2a) and fast contractions with fast pressure variations and high amplitude (Fig 2b). Type B - fast contractions of the pelvic floor alternating with fast contractions of the prepubic muscle (N = 3). Type C - fast contractions of the urethral sphincter muscle (N = 2).

Fig. 2 shows two types of pressure patterns in patients with urethral pressure variations. a: Slow pressure variations with a slow rise and/or drop in urethral pressure between 15 and 30 cm H_2O for 3 - 10 sec. b: Fast pressure variations with a fast rise and/or drop in urethral pressure between 30 and 130 cm H_2O for 1 - 3

sec. UP = urethral pressure. UCP = urethral closure pressure. IVP = intravesical pressure. V fill = filling volume (isotonic saline water).



CONCLUSIONS

This is the first study to show that in addition to smooth muscle activity at least three different types of striated muscles contribute to UPV: The levator ani muscle, the prepubic muscle and the urethral muscle. The finding that the levator ani can act in a typical slow and fast contraction manner might indicate that either slow or fast twitch muscle fibre activity can predominate in this muscle.

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NEUROMODULATION OF THE MAXIMUM SHORTENING VELOCITY OF THE GUINEA PIG DETRUSOR MUSCLE

AIMS OF STUDY

The contractile properties of the bladder are determined by factors related to the detrusor muscle and factors related to the nervous system. The muscular aspect of bladder contractility is defined by the (hyperbolic) relationship between the shortening velocity v of the bladder circumference and the active detrusor pressure P(v) at that shortening velocity (Hill equation). The contractility of a particular bladder can be fully characterized by the intercepts of the hyperbole on both axes, i.e. by the parameters P_{iv} (active isovolumetric detrusor pressure) and v_{max} (maximum shortening velocity). The neurogenic control system of the urinary tract modulates bladder contractility, which effectively changes the values of P_{iv} and v_{max}. These parameters (might) also depend on the instantaneous bladder volume. In previous work the dependence of P_{iv} on the intensity of stimulation and bladder volume was measured in guinea pig bladders in vivo and in vitro [1]. In the present work v_{max} was measured in five guinea pig bladders in vitro, using electrical stimulation and the stop-flow technique to model its dependence on stimulation intensity and bladder volume.

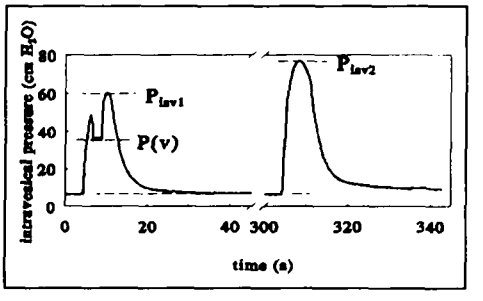
METHODS

Five male guinea pigs (895 to 1175 g) were urethane-anaesthetized. The bladder was excised and suspended in an organ bath from two catheters that had been inserted via the remaining part of the urethra: one 5 F catheter, which was connected to a disposable pressure transducer, and a stainless steel tube (inner diameter 1.7 mm), which was connected to an infusion pump. The bladder was stimulated electrically for 5.2 to 6.5 seconds at intervals of at least 5 minutes, using two parallel platinum electrodes (20 x 30 mm), one on each side of the bladder. The applied voltage was 10 V, while the pulse frequencies used were 25 and 200 Hz. The pulse width was adapted to the frequency to attain a duty cycle of 50%. Each measurement consisted of the following phases (see Figure): During the first 2 seconds of stimulation the bladder contracted isovolumetrically at the preset volume. During the following 1.2 to 2.5 seconds the bladder was emptied using the infusion pump at a preset flow-rate. During the last 2 seconds the bladder contracted isovolumetrically again at the resulting smaller volume. At least 5 minutes later an isovolumetric bladder contraction was induced once more by stimulating 6.5 seconds at this last volume. All contractions were sampled at a rate of 10 Hz with a personal computer and stored for further analysis.

The bladder emptying during the contraction simulated micturition. The bladder circumference shortening velocity v during this phase was calculated from the instantaneous volume and the flow-rate. The v values used ranged from 0.23 to 2.61 cm/s. The experimental procedure resulted in two active pressure values at the same volume: a value P(v) at the shortening velocity v caused by the pump and an isovolumetric value P_{isv1} (Figure). By dividing these two pressure values, data were obtained which were used to calculate v_{max} from the Hill equation. The resulting v_{max} values found for both stimulation frequencies were compared using the paired t test. The two isovolumetric pressure values P_{isv1} and P_{isv2} obtained at exactly the same volume were compared to study the effect of preceding shortening on the generated pressure.

RESULTS AND CONCLUSIONS

The calculated v_{max} values were independent of the bladder volume in the range studied, which complies with the sliding filaments theory. v_{max} averaged 3.75 ± 0.08 (SEM) and 3.00 ± 0.22 cm/s at the stimulation frequencies 200 and 25 Hz. These values were significantly different (p=0.015). A similar conclusion was drawn for P_{isv} previously [1], so that it can be concluded that both parameters characterizing bladder contractility depend on the intensity of stimulation. The two isovolumetric pressure values P_{isv1} and P_{isv2} in each measurement were generally largely different (Figure): the ratio P_{isv1}/P_{isv2} averaged to 0.67 ± 0.12 (SEM). It is known that striated muscle fibres generate less isometric force immediately after active shortening to a certain length compared to an isometric contraction at the same length without preceding shortening [2]. This shortening-induced weakening of contraction has been called "shortening-induced deactivation". The phenomenon is ascribed to a reduced affinity of the binding sites for calcium on the thin filaments [2]. Our data show that a similar shortening-induced deactivation occurs in the smooth muscle of the guinea pig bladder. No dependence of the ratio P_{isv1}/P_{isv2} on the shortening velocity was found in the range studied. Edman [3] showed that the degree of force reduction was not markedly affected by the shortening velocity in the range from v_{max} to 1/5 of v_{max}.



The effect of shortening on the isometric force has been demonstrated in whole muscle in situ [3] and might also exist in the human bladder. The duration of the effect is unknown from our experiments. If this period is not too short, it has implications for the clinically used stop-flow test. In this test the patient is asked to interrupt micturition. The isovolumetric pressure measured after interruption of voiding is used to assess bladder contractility. Deactivation would underestimate it.

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PUDENDAL NERVE VERSUS TIBIAL NERVE SOMATOSENSORY EVOKED POTENTIALS IN PATIENTS WITH MULTIPLE SCLEROSIS AND VOIDING DYSFUNCTION

AIMS OF STUDY

Pudendal nerve somatosensory evoked potentials (SSEP) have been introduced in evaluating patients with neurogenic disturbances of the bowel, bladder and sexual function, among them patients with multiple sclerosis (MS) (Haldeman 1982). They have been reported sensitive in disclosing disturbances of conduction along the somatosensory pathway in MS patients (Tackman et al. 1987, Bemelmans 1992, Eardley et al. 1991). It was the aim of our study to compare the sensitivity of pudendal nerve SSEP to the more established tibial nerve SSEP in MS patients with voiding dysfunction.

PATIENTS AND METHODS

Neurophysiological investigation was performed in 19 patients with clinically or laboratory supported definite MS (Poser et al. 1983). There were 12 females and 7 males, with a median age of 37 years (range 22-53). Median duration of disease was 4 years (range 0.25-13). Median Kurtzke grade was 3.5 (range 1.5-4.5), denoting mild to moderate neurological disability (Kurtzke 1983). One or more symptoms of voiding dysfunction (frequency, urgency and/or urge incontinence, hesitancy and retention) were present in all patients; 5 men also had erectile dysfunction. No patient had a history of diabetes mellitus, lumbar disc disease, of abdominal or pelvic surgery. All patients gave informed consent.

Cortical SSEP were detected with 2 silver/silver chloride cup electrodes attached with collodion to a cleaned and gently abraded scalp. Conducting jelly was introduced through a small hole at the top of the electrode. The recording electrode was placed 2 cm behind the vertex (Cz-2 position), and the reference electrode was attached to the forehead (Fz position).

Posterior tibial nerve was stimulated at the ankle. Square wave stimuli of 0.3 ms duration were applied at a frequency of 2 Hz with the intensity that produced small movements of toes. Dorsal nerve of penis/clitoris was stimulated with a square wave stimuli of 0.3 ms duration at a frequency of 1 Hz and intensity was 2-4 times sensory threshold.

Using a signal trigger and averaging technique the response to a minimum of 128 stimuli was amplified and

displayed. The procedure was repeated at least once and the latency of the first positive peak (P1) was measured.

The results were compared with those found in control subjects: 30 for tibial nerve SSEP (median age 36 years, range 22-61) and 33 for pudendal nerve SSEP (median age 34 years, range 18-55). Reference ranges were defined as mean ± 2.5 standard deviations.

RESULTS

There were 16 patients with a prolonged P1 latency of tibial nerve SSEP (> 46.0 ms). In one patient there was no response. An abnormality was thus found in 17 patients (89%), in 5 of them (29%) unilaterally.

Seven patients had prolonged P1 latency of pudendal nerve SSEP (> 50.7 ms), while in one patient no response could be elicited. That made pudendal nerve SSEP abnormal altogether in 8 patients (42%).

Eleven patients had normal pudendal and abnormal tibial responses, 7 bilaterally and 4 unilaterally. One patient had obviously abnormal pudendal response (P1 more than 3 standard deviations above the mean normal value) and a normal tibial response.

CONCLUSIONS

In a group of MS patients with mild and moderate neurological disability and voiding dysfunction, we found tibial nerve SSEP abnormal in 90% of patients, in one third of them unilaterally. Pudendal nerve SSEP was abnormal in 40%. Tibial nerve SSEP thus proved 50% more sensitive.

One possible reason for this discrepancy could be bilateral stimulation in evoking pudendal responses: in unilateral involvement of somatosensory pathways normal waveforms generated by the "good" side may mask the abnormality on the "impaired" side. By analogy with tibial responses, unilateral stimulation should increase sensitivity of pudendal nerve SSEP.

There also is a wider distribution of normal values of pudendal nerve SSEP latencies as compared to tibial nerve SSEP latencies which is reflected in standard deviations (3.6 VS. 2.3 ms). This may partly be due to a difference in definition of the appropriate stimulus intensity in tibial and pudendal nerve SSEP measurement.

As the pudendal central pathway may contain less myelin than the tibial (c.f. Rumpl et al. 1988), it might be less vulnerable to demyelination.

According to our results tibial nerve SSEP reveals more neurogenic abnormalities in MS patients with voiding dysfunction than pudendal nerve SSEP.

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EVALUATION OF S3 NERVE ROOT STIMULATION IN PATIENTS WITH IDIOPATHIC DETRUSOR INSTABILITY.

AIMS OF STUDY

Electrical stimulation of sacral nerve roots can modulate detrusor activity [1]. Recently permanently implantable neuroprostheses have been used, to stimulate S3 nerve roots, for a variety of voiding dysfunctions in patients mainly presenting with symptoms of urinary frequency, urgency and incontinence. Although the precise mechanism remains unclear, symptomatic benefits have been achieved in up to 75% of the cases [2]. The aim of this prospective study was to assess the effect of temporary sacral nerve root (S3) stimulation in patients with idiopathic detrusor instability (DI).

PATIENTS AND METHODS

Eleven patients were studied (3M:8F, median age 50 $\pm$ 11 years, range 31-66 years). All patients had urodynamic evidence of detrusor instability and have had unsuccessful outcomes with previous treatments including anticholinergic therapy (11), bladder over-distension (11), bladder transection (3) and sub-trigonal phenol injection (2). A bipolar pacing electrode was inserted into the S3 sacral foramen under local anaesthesia as previously described [3]. The electrode was coupled to an external pulse-generator for a 4-7 day period of test stimulation.

Objective assessment was performed using ambulatory urodynamic studies. Standard electromyography (EMG) equipment (Medelac-Neurostar) was used to obtain recordings from the distal foot and toe muscles, external anal sphincter and the urethral sphincter. Surface, concentric needle and a catheter mounted ring electrode was used for the respective recordings. Analysis of urinary frequency, incontinence and use of pads was performed to assess clinical outcome. In addition urinary symptom scores were analysed using a modified Frimodt Møller scoring system [4] (0-14 points).

RESULTS

Urodynamic findings are summarised in table 1. A significant improvement was observed in the mean voided volume and the frequency of unstable contractions during the stimulation period. Two patients were rendered urodynamically stable.

Table 1. Effect of S3 nerve root stimulation on ambulatory urodynamic study.

	No stimulation	S3-stimulation	
Mean voided volume (ml)	170 $\pm$ 53	263 $\pm$ 83	S
Frequency of unstable contractions(/hour)	5 $\pm$ 4	2 $\pm$ 2	S
Maximum amplitude of unstable contractions	53 $\pm$ 23	45 $\pm$ 35	NS

Paired t-test; $P<0.05$. S = Significant, NS = Not significant.

The effect of S3 nerve root stimulation on urinary frequency, urge incontinence and in the use of incontinence pads is shown in table 2. Pre and during stimulation urinary symptom scores were 10 $\pm$ 3 and 4 $\pm$ 3 respectively ($P<0.006$).

Evoked responses were obtained from the small muscles of the foot and great toe, on the side of the implanted electrode, at a sub-threshold current of 2 $\pm$ 1 mA, the maximum tolerated current being 5 $\pm$ 1 mA. This procedure provided evidence of satisfactory positioning of the electrode at sub-threshold stimulation during the study period. Anal sphincter EMG was abnormal in one patient (mean duration of potentials 15 $\pm$ 6 ms, 44% polyphasic activity). In the remaining 10 patients the mean duration of potentials was 7 $\pm$ 2 ms and the mean proportion of polyphasic activity was 18 $\pm$ 5%. No evoked potentials were obtained from the anal sphincter at sub-threshold or threshold stimulation. Using the catheter mounted ring electrode there was evidence of increased EMG activity in the region of the urethral sphincter in all patients at threshold stimulation.

Table 2. Results of S3 nerve root stimulation in patients with idiopathic detrusor instability.

	Number of patients	Benefit <50%	50%-75%	>75%	Satisfactory outcome (>50%)
Urinary frequency	11	7	3	1	36%
Urge incontinence	7	2	1	4	71%
Use of pads	7	1	2	3	71%

CONCLUSIONS

In patients with idiopathic detrusor instability refractory to conservative therapy, temporary stimulation of the S3 nerve roots produced significant changes in the urodynamic parameters and improvement in symptoms particularly regarding urge incontinence and in the use of pads. Our study revealed an increased EMG activity in the region of the urethral sphincter during S3 nerve root stimulation. This observation lends objective support to previously proposed hypothesis [2] of the neuro-modulation mechanism.

In summary the technique suggests a management option in patients with DI refractory to conservative therapy and should be considered prior to definitive surgical intervention in these patients.

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SELECTIVE DETRUSOR ACTIVATION BY VENTRAL SACRAL ROOT STIMULATION: INFLUENCE OF STIMULATION PARAMETERS

AIMS OF STUDY

The majority of spinal cord injury patients have urological problems due to detrusor hyperreflexia together with lost voluntary control of the lower urinary tract (LUT). An available method for restoration of urinary bladder control is artificial electrical stimulation of sacral ventral nerve roots [1]. These roots contain, among others, of two sets of efferent nerve fibers innervating the LUT, being small diameter preganglionic parasympathetic fibers innervating the detrusor muscle and larger somatic fibres, innervating the striated muscle of the urethral sphincter and the pelvic floor. Current stimulation methods are not selective with respect to muscle activation. Both detrusor and urethral sphincter are simultaneous activated, thus bladder emptying is only possible using the 'post-stimulus-voiding'-technique [1].

Recently, the possibility to activate both sphincter and detrusor independently has been demonstrated in dogs. This allows for two stimulation modes. First selective sphincter activation to regain continence and secondly selective detrusor activation to induce bladder emptying. Switching between the two modes can be done by changing the stimulus parameters as the same electrode is used in both stimulation modes.

In contrast to selective sphincter activation, selective detrusor activation is rather complex and comprises a combination nerve excitation and blocking. This requires precise tuning of the stimulus parameters. This abstract reports on possible pitfalls when applying an anodal block for selective detrusor activation.

METHODS

Selective activation of small fibers in a nerve trunk can be achieved using a tripolar cuff electrode consisting of a cathode flanked by two anodes [2]. Near the cathode, all fibers will be excited to produce an action potential (AP). These AP's propagate in both directions. Near the distal anode, the fibers will be hyperpolarized i.e. the transmembrane potential is pushed further away from the excitation threshold. If sufficiently hyperpolarized, an approaching AP fails to propagate through the hyperpolarized zone and will die out. As large fibers need less current for their blocking than smaller ones, the large fibers can be blocked selectively. As the activity in the small fibers can pass unhindered, selective small fiber activation is achieved.

The influence of stimulus parameters on anodal blocking has been investigated in 3 acute experiments using female dogs (beagle). After laminectomy and complete dorsal sacral rhizotomies a cuff electrode (contact separation: 2 mm) has been placed intradurally around a S2 ventral sacral root. Stimulation has been placed intradurally around a S2 ventral sacral root. Stimulation has been performed using a computer controlled stimulator, consisting of two synchronized current sources.

The induced AP's have been measured using an bipolar cuff electrode, placed extradural around the complete nerve root. The signal was amplified (1000x) and recorded using a digital oscilloscope connected to a personal computer.

RESULTS

The first factor influencing the blocking effects is the pulswidth. Using rectangular monophasic pulses with a pulse width below 200 μs AP's are generated at low currents (0.05-0.1 mA). Increasing the current does not result in any blocking because the blocking current is removed before the AP's arrive at the anode. Only when using wider pulses (>400 μs), the induced AP's could be arrested.

The second factor is the generation of an action potential at the end of a pulse. If blocking occurs, further increasing the current (>2-3 mA) will undo the blocking. This is due to anodal break excitation. The fibers are hyperpolarized by the anodal current. When the membrane potential falls back to resting level at the end of the pulse an overshoot occurs. If strongly hyperpolarized, the overshoot can reach the excitation level and excitation occurs. This can be prevented by adjusting the pulse shape so that the pulse does not end suddenly but gradually (e.g. linear in 300-500 μs).

A third disturbing effect can be the existence of a virtual cathode distal to the blocking anode. If the stimulation currents and the internal impedances are not balanced, current can flow external to the cuff, from the distal anode to the proximal anode. If sufficiently high, this current can excite fibers distal to the blocking site and thus undo the blocking. This can be prevented by adjusting the ratio between the two anodal currents.

CONCLUSIONS

Anodal blocking of nerve fibers in sacral roots to obtain selective detrusor activation, requires precise setting of the stimulus parameters. The pulse width must be sufficient wide and effects as anodal break excitation and excitation by a virtual cathode distal to the anode, can easily undo the blocking.

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NEUROMODULATION (SACRAL SEGMENTAL NERVE STIMULATION) AS A TREATMENT FOR URGE INCONTINENCE DUE TO DETRUSOR HYPERREFLEXIA IN MULTIPLE SCLEROSIS (M.S.) PATIENTS.

AIMS OF THE STUDY.

M.S.patients with urge incontinence due to detrusor hyperreflexia are usually treated conservatively with anticholinergics (combined with clean intermittent catheterization if significant residual urine volumes are present).It has been shown [1] that electrical stimulation of sacral somatic nerve afferents can induce detrusor inhibition in patients with detrusor hyperreflexia.Electrical stimulation of the S3 spinal nerve (carrying pudendal nerve afferents) is therefore a possible treatment option for patients refractory to conservative management.It was the aim of this pilot study to determine the clinical feasibility of this treatment option in M.S.patients.

METHODS.

Patients refractory to conservative treatment and having a bladder capacity of at least 150 ml were selected for this treatment, which implies implantation of a permanent Pisces Quad S3 foramen electrode (Medtronic) connected to a subcutaneously placed pulse generator.A permanent implant is only considered if the patient experiences a more than 50% reduction in pad use and /or number of leakages, during a 3-5 day test period.To date 5 women with a mean age of 50 years (range 39-62 years) underwent a test stimulation.Urodynamically they had a hyperreflexive bladder with (pts.2,3 and 4) or without (pt.1) detrusor sphincter dyssynergia.Under local anesthesia, a wire electrode was percutaneously placed in the left or the right S3 foramen,the choice of side being determined by the best pelvic floor muscle response on electrical stimulation.The pelvic floor muscle response is a biological indicator for the correctness of the wire electrode position and for the integrity of the nerve.Apart from the pelvic floor muscles, afferent somatic nerve fibers are stimulated with the aim to inhibit the micturition reflex.In one patient percutaneous placement of the electrode failed due to obesity.The wire electrode was connected to an external nerve stimulator (Frequency: 10-15Hz; Pulsewidth: 210 msec) and left in situ for 3-5 days.During the test period the patients kept a voiding/incontinence diary.which was compared to 2 previously kept baseline diaries.
All 4 women responded well during the test period and received a permanent implant.The average follow-up was 13.5 (range 6 - 18) months.The follow-up tests included voiding/incontinence diaries and urodynamic tests at 6 months post-implant.The diary and urodynamic results were compared to the baseline data.The follow-up urodynamic studies were performed with electrical stimulation on.

RESULTS.

The results of the voiding/incontinence diary parameters comparing the pretreatment situation with the latest follow-up are summarized in table 1.

Table 1.

		Pt.1	Pt.2	Pt.3	Pt.4
Follow-up (months)		18 mo	18 mo	12 mo	6 mo
No. of pads used / 24hrs	pre	3.1	3.7	4.6	6.0
	post	0	2	0	0
No. of leaks / 24hrs	pre	3.9	3.4	6.5	4.7
	post	0	1	0	0
Voiding.frequency / 24 hrs.	pre	11.8*	18.8	13.2*	15.0
	post	11.3*	12.6	8.7*	8.6
Average volume per micturition (ml)	pre	140	82	119	193
	post	159	121	360	113

*Voiding frequency includes spontaneous micturition and intermittent self-catheterizations.

The urodynamic data before the implant and 6 months following the implant are summarized in table 2.

Table 2.

		Pt.1	Pt.2	Pt.3	Pt.4
Bladder volume at 1st unstable contraction (ml)	pre	440	195	175	210
	6 mo	405	328	-**	106
Amplitude of 1st unstable contraction (cmH2O)	pre	32	32	48	14
	6 mo	18	46	-**	34
Bladder volume at maximum unstable contraction (ml)	pre	460	201	175	267
	6 mo	452	331	-**	155
Amplitude of maximum unstable contraction (cmH2O)	pre	56	35	48	14
	6 mo	25	46	-**	29
Bladder capacity (ml)	pre	478	201	177	267
	6 mo	452	331	490	157

**: no instability present.

DISCUSSION AND CONCLUSIONS.

In patients 1,2 and 3 urodynamic improvement goes along with improvement in voiding diary parameters.In patient 4 improvement in voiding diary parameters is seen although urodynamically the situation seems to have deteriorated.Three patients are dry, although instability is still detectable in 2 of these women during standard urodynamic tests.Symptomatically these patients do better than would have been expected on the basis of the urodynamic results.The overly provocative nature of medium-fill urodynamic tests could be a possible explanation for this discrepancy.The fact that urodynamic improvement is seen in 3 of these patients with neurogenic bladder disease supports the soundness of this approach.The symptomatic results obtained in these patients show that it is worthwhile to continue to explore this treatment option in selected multiple sclerosis patients.

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SACRAL NERVOUS SYSTEM INVOLVEMENT IN PATIENTS WITH MULTIPLE SCLEROSIS

AIMS OF STUDY

Multiple sclerosis (MS) is a common neurologic disease accompanied by a broad spectrum of voiding dysfunctions. A majority of these are thought to be a consequence of involvement of long pathways in the spinal cord. Little is known about clinical consequences and neurophysiological correlates of conus medullaris involvement in MS. It needs, however, to be considered that MS patients may have signs of damage to the peripheral sacral neuromuscular system due to childbirth or chronic constipation. It was the aim of our study to find the frequency of neurophysiological abnormalities denoting sacral nervous system involvement in a well defined group of MS patients, trying to correlate the abnormalities to parity and constipation.

PATIENTS AND METHODS

Sacral nervous system was neurophysiologically tested in 19 patients with clinically or laboratory supported

definite MS; there were 12 females (3 nulliparae) and 7 males, with a median age of 39 years (range 22-53). The median duration of disease was 4 years (range 0.5-20) and the median Kurtzke grade of neurological disability was 3 (range 1.5-8.5). Voiding dysfunction (frequency, urgency, hesitancy, retention and urge incontinence) and constipation were noted. No patient had a history of diabetes mellitus, lumbar disc disease or abdominal or pelvic surgery. All patients gave informed consent.

Concentric needle electromyography (EMG) in both sides of of the external anal sphincter was performed. The electrode was inserted centrally, frontally and posteriorly to the anal orifice (through a single skin penetration on each side) and positioned so as to produce crisp sound on the loudspeaker; fibrillation potentials and positive sharp waves were sought for and repetitively firing motor unit potentials (MUPs) analysed. On one side of anal sphincter, reflex responses to supramaximal electrical stimulation of the dorsal nerve of the penis/clitoris (pudendo-anal reflex, PAR) were recorded and their latencies measured.

Mean MUP duration, median MUP amplitude and percentage of polyphasic MUPs were determined for each patient. The results of neurophysiological investigation were compared with those from control subjects: 9 for EMG (median age 33 years, range 23-51) and 20 for PAR (median age 34 years, range 18-55). Reference ranges were calculated as mean ± 2.5 standard deviations. Mann-Whitney U test and Spearman rank correlation coefficient were used in statistical analysis.

RESULTS

Sixteen patients (84%) had voiding dysfunction and 11 patients (53%) constipation. Only 3 patients were neither constipated nor had voiding dysfunction. Both voiding dysfunction and constipation agreed well with neurological disability (Spearman R of 0.70 and 0.58, respectively).

Mean MUP duration was prolonged (> 9.2 ms) in 4 patients (21%), percentage of polyphasic MUPs was abnormally high (> 35%) in 5 (26%) and median MUP amplitude was abnormally high (> 0.6 mV) in one patient (5%). Considering MUP parameters together, 8 patients (42%) had abnormal anal sphincter EMG.

PAR was absent in one patient and latency was prolonged (> 48.7 ms) in 7; abnormality was therefore found in 8 patients (42%). Whereas in 6 patients both EMG and PAR abnormalities were found, 2 patients each had only either EMG or PAR abnormalities.

In summary, signs of sacral nervous system damage were found in 10 patients (53%).

Of 10 patients with abnormal EMG and/or PAR 6 were parous females (4 of them constipated) and 3 were constipated males. There was one nonparous female without constipation, who had abnormal EMG and PAR. She also had voiding difficulty. Of 9 patients with normal EMG and PAR there were 3 parous females (1 constipated), 2 nonparous females (1 constipated) and 4 males (2 constipated).

We were not able to show any significant difference in EMG and PAR parameters either between males and females or between nonconstipated and constipated patients. We also found no difference in duration of disease between patients with normal and abnormal EMG and/or PAR. There was no significant correlation between EMG and PAR abnormalities and neurological disability (Spearman R of 0.19 and 0.44).

CONCLUSIONS

In our group of MS patients with moderate median neurological disability a high percentage (53%) of EMG and/or PAR abnormalities (with good agreement between both) has been demonstrated. The patients had a high percentage of voiding dysfunction (84%) and constipation (53%), both apparently related to overall neurological disability. It does not seem possible to explain all neurophysiological abnormalities in our patients as a consequence of either childbirth or chronic constipation. Conus medullaris lesions at least in some of our MS patients remain a plausible possibility.

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URODYNAMIC DIFFERENTIATION OF DETRUSOR INSTABILITY AND DETRUSOR HYPERREFLEXIA

AIMS OF THE STUDY

Detrusor instability is defined as the contraction, spontaneously or on provocation, of the detrusor during filling whilst attempting to inhibit voiding. With demonstrable neurological disease the term "Detrusor hyperreflexia" is used [1]. Although the cause of unstable detrusor contractions is unknown, some have suggested that they may be a variant of normal, others have implicated urethral obstruction and others have proposed an intrinsic neurological deficit [2]. There are no urodynamic criteria for differentiating detrusor instability form detrusor hyperreflexia. This study examined the differences in urodynamic variables between the two diagnostic entities according to sex.

PATIENTS AND METHODS

2,332 Urodynamic records of patients with detrusor instability or hyperreflexia were examined (1,780 women, 552 men). 379 women and 233 men had detrusor hyperreflexia. The bladder capacity, postmicturition residual urine volume, bladder capacity at first sensation, the character of unstable activity [3], the impulse of isometric unstable force generated during contractions [3], the urethral opening pressures, and bladder velocity constant $Q^{\cdot}$ [2], were assessed. The Mann-Whitney test was used to test the difference between medians. The 95% confidence interval of the difference in median values and 'p' value is quoted.

RESULTS

Patients of both sexes with detrusor hyperreflexia had lower bladder capacities than those with detrusor instability (Females: 95%C.I. diff= 50,132 ml $p<0.001$: Males: 95% C.I. diff= 38,125 ml $p<0.001$). Post micturition residual volumes were higher in patients with hyperreflexia in both sexes (Females: 95%C.I. diff= 65,35 ml $p<0.001$: Males: 95% C.I. diff= 70,30 ml $p<0.001$). The impulse of unstable force generated during contractions was higher in men compared to women (95% C.I. diff=345,144 Ns

$p<0.001$) but there were no differences in either sex between the diagnostic groups. The character of the contractions differed amongst women where those with hyperreflexia showed greater degrees of motor summation during contractile activity ($p=0.001$). Such differences were not observed in men. Women with hyperreflexia had a lower detrusor velocity constant Q' (95% C.I. diff=4,10 ml sec^{-1} $p<0.001$) but men did not show this difference. Men with hyperreflexia had higher urethral opening pressure (95% C.I. diff=35,5 cm H_2O, $p=0.003$) in women it was similar in both groups. No differences were observed in either sex between the two diagnostic groups in the bladder capacity at first sensation of a desire to void. Sub-group analysis according to the neurological diagnoses did not show disease-specific changes.

CONCLUSION

We have demonstrated that detrusor instability and detrusor hyperreflexia differ in both sexes with respect to bladder capacities and postmicturition residual volumes. There are character differences in the form of unstable contractions and in detrusor shortening velocity in women. Men show differences in urethral opening pressure. The data support a urodynamic differentiation between the two entities but sex differences suggest that the diagnostic categories fail to explain the pathophysiological changes associated with neurological disease.

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DOES CYSTOPLASTY AT THE TIME OF AN ARTIFICIAL SPHINCTER IMPLANTATION INCREASE MORBIDITY ?

AIMS AND INTRODUCTION.

The artificial urinary sphincter (AUS) is established in management of sphincter weakness incontinence in neuropathic patients. Augmentation cystoplasty may be required for cystometrographically documented detrussor hyperreflexia and this is usually performed at the same time as the AUS implantation (1). We report our experience of the AUS in the neuropathic patient, with and without a cystoplasty.

PATIENTS AND METHODS.

A series of 90 patients with neurogenic bladder dysfunction

who underwent AUS implantation is presented. There were 75 males and 15 females with an age range of 13 to 62 years (mean 26). All patients have been followed up for a minimum one year after primary sphincter implantation, mean follow up was 4 and range 1 to 10 years. Pre operative video urodynamics demonstrated stress incontinence with 24 patients having an acontractile type bladder. Of 66 patients, with an intermediate type bladder 52 patients had a cystoplasty. 71 patients had congenital myelodysplasia and 19 had acquired cord lesions. Table 1 shows the neurological diagnosis.

TABLE 1 - DIAGNOSIS.

Congenital	Meningomyelocele	65
	Sacral agenesis	5
	Spinal angioma	1
Acquired	Spinal Injury	16
	Sacral Injury	1
	Spinal tumour	1
	Prolapsed IV disc	1

RESULTS.

83 patients (92%) are continent both by day and night. 3 are occasionally damp and controlled by pharmacotherapy and 4 have had a persistently bad result. Of the 66 patients with detrussor hyperreflexia 52 (79%) required a cystoplasty to achieve continence and 14 (21%) could be controlled with anticolinergics. Our re operation rate is 25 out of 90 (28%). Our complications include 6 infections, (2 of whom have been controlled with strong systemic antibiotics) 7 erosions, 8 system failures 2 pump failures and 1 sheered tubing. Table 2 shows the complications.

TABLE 2 - COMPLICATIONS.

Complication (n 90)	AUS+ Cys (n 52)	AUS (n 38)	Total
Redo	12 (23%)	13 (34%)	2
Inf	4 (7.7%)	2 (5.3%)	6
Erosion	4 (7.7%)	3 (8%)	7
System Fail	2 (3.8%)	6 (16%)	8
Pump Fail	1 (1.9%)	1 (2.6%)	2
Bl Perf	1 (1.9%)	-	
Rectal Perf	-	1 (2.6%)	1
Sheered tube	1 (1.9%)	-	1

All patients who had a cystoplasty at the time of a membranous urethra cuff implantation had the pump and balloon implanted at a later date usually 6 weeks later. There is no increase in morbidity when a cystoplasty is done simultaneous to an AUS implantation. 44 of the 52 patients (84.6%) with cystoplasty and 26 of the 38 patients (68%) without, perform intermittent catheterisation for high residues.

CONCLUSIONS.
Continence in excess of 90% is achieved in our neurogenic patients with an AUS implantation and this accords with other series (1). We recommend a simultaneous cystoplasty in patients with detrussor hyperreflexia.

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SYMPTOM SCORES AND THE SUBJECTIVE SEVERITY OF URINARY INCONTINENCE

AIMS OF THE STUDY

The subjective severity of urinary incontinence is traditionally measured with urinary symptom scores, urinary diaries or visual analogue scales. These measures are commonly used in prevalence studies and clinical trials, but have never been validated against quality of life questionnaires. Traditional methods alone provide only an assessment of the scale of urinary symptoms rather than a measure of the impact of urinary incontinence on the subjective health status of sufferers. Wyman et al[1] assessed the subjective impact of incontinence along with objective frequency, one of the most widely used severity measures, using the 'Incontinence Impact Questionnaire' and a urinary diary. They found only a modest correlation between the two.

In order to collect accurate clinical and prevalence data on the impact and severity of urinary incontinence, it is important to understand the relationship between the presence of urinary symptoms and their effect on the wellbeing of incontinence sufferers. We have used traditional symptom scores urinary diaries and quality of life questionnaires to determine the contribution of individual symptoms to the quality of life of incontinent women.

METHOD

700 women referred to a urodynamic unit for investigation of their lower urinary tract dysfunction were included in the study. All completed a detailed urinary symptom questionnaire a urinary diary, and a quality of life questionnaire. (Nottingham Health Profile NHP, (n = 295); Psychosocial Adjustment to Illness Scale PAIS, (n = 214); Short Form 36 SF36, (n = 182); or a new disease specific questionnaire (n = 194). Urinary symptoms of frequency, urgency, nocturia, stress incontinence, urge incontinence, bladder pain, voiding difficulties, and nocturnal enuresis were scored on a three point scale (0 = absent - 2 = very severe). All women completed a five day urinary diary documenting daytime frequency, nocturia, and incontinent episodes. 194 women were questioned regarding pad usage, fluid restriction, and change of underclothes (1 = never - 4 = all the time) as additional severity measures. The presence or absence of urinary symptoms was correlated (Pearson's correlation coefficient) with the results of quality of life scores using SPSS 5.0 statistical package.

RESULTS

Symptoms of frequency, bladder pain, urgency and urge incontinence correlated significantly ($p < 0.01$) with all domains of the disease specific questionnaire, SF36, total PAIS score, and index of health related distress, calculated from the NHP[2]. Daytime frequency of (> 10x/day) and nocturia of (> 3x/night) showed similar correlations although frequency of incontinence correlated poorly unless associated with symptoms of urgency. Whereas symptoms of frequency correlated well ($p < 0.01$) with urinary diary results, symptoms of nocturia correlated poorly. Accordingly the correlation of symptoms of nocturia, and quality of life scores was poor. Symptoms of stress incontinence, voiding difficulties and of pad usage showed poor correlation with quality of life measures. Severity indices of fluid restriction, and change of underclothes correlated significantly ($p < 0.01$) with disease specific questionnaire and SF36 questionnaire results.

CONCLUSION

The relationship of urinary symptoms and the subjective impact of lower urinary tract dysfunction is complex. Validated quality of life measures are undoubtedly the best measure of the subjective severity of urinary symptoms, although for large prevalence studies validated urinary symptom scores may be appropriate.

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5 YEAR FOLLOW UP OF PELVIC FLOOR MUSCLE EXERCISE FOR TREATMENT OF STRESS URINARY INCONTINENCE. CLINICAL AND URODYNAMIC ASSESSMENT.

AIMS OF STUDY

A short term cure rate of 60% after pelvic floor muscle (PFM) exercise for treatment of female stress urinary incontinence (SUI) was demonstrated 5 years ago. The aim of the present study was to evaluate clinically and urodynamically the long term effect.

METHODS

All 23 patients, mean age 51 years (range 30-70) who had participated in a 6 month intensive PFM exercise program 5 years ago, took part in the follow up study. This included:
1. Interview about the women's description of the condition and PFM exercise adherence.

2. Clinical examination consisting of vaginal palpation and measurement of PFM strength by vaginal squeeze pressure (Camtech microtip transducer, Camtech AS, Sandvika, Norway) with simultaneous observation of correct contraction.
3. Urodynamic assessment: After emptying the bladder and determining the residual urine, a double sensor microtip catheter 8 French with filling lumen (Camtech AS, Sandvika, Norway), was introduced into the bladder. Cystometry was performed with saline using a filling rate of 50 ml per minute. The bladder was filled to subjective capacity or a maximum of 250 ml. Two urethral pressure profiles were registered as the catheter was retracted at a speed of 2 mm per sec. The women were asked to cough repeatedly during the profile registration. Genuine stress incontinence was defined as any lack of positive closure pressure in the two registrations. Any visible leakage during the coughing was recorded. In addition a short pad test with standarized bladder volume was performed. This test has earlier been found to be 9 times more provocative than the ICS one hour test (1).

RESULTS

Among the 23 patients, three had been operated upon (one still not cured). Fourteen of the 20 patients (70%) were satisfied with the condition 5 years after cessation of organized training. Two were unable to contract the PFM correctly. PFM strength was mean 19 cm H_2O (95% CI: 13.2-24.9). Sixteen of the 23 patients (70%) were exercising the PFM on a regular basis, at least once a week.

Evaluated by the urodynamic assessment 11 of the 20 not treated surgically (56%), were found to have positive closure pressure. Fifteen (75%) of those not operated upon had no visible leakage during cough. In 7 of 23 women the finding of a positive or negative closure pressure did not correspond with observation of visible leakage during cough. Median leakage measured by the pad test was 10g (range 0-112). Six of the 20 patients not treated surgically had no leakage according to ICS criteria. Another 4 had less than 10 g leakage. Thus 50% of the patients leaked less than 10 g. There was a positive significant correlation between leakage measured by the pad test and the women's subjective grading of the condition ($r = 0.6$, $p < 0.01$).

CONCLUSIONS

The short term cure rate was maintained 5 years after cessation of the 6 month PFM exercise program. Seventy percent were still exercising at least once a week. There was a positive correlation between subjective grading of the condition and the pad test. However, this provocative pad test showed leakage in some women,

who never experienced incontinence during ordinary daily activities.

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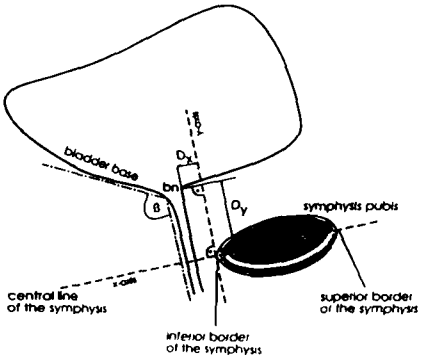
POSTPARTAL PELVIC FLOOR DAMAGE - IS CONNECTIVE TISSUE IMPAIRMENT MORE IMPORTANT THAN NEUROMUSCULAR CHANGES ?

INTRODUCTION

Pelvic floor damage after vaginal delivery is well known. Allen and Warrell were the first to assess neurophysiological changes of the pelvic floor in the individual patient by careful ante and post partal evaluation (1). However, the influence of vaginal delivery on active and passive mobility of the bladder neck is still unknown. It was the purpose of this study to assess pelvic floor contraction power and passive bladder neck mobility in a longterm evaluation before and after childbirth by clinical, perineometrical and sonographical methods.

PATIENTS AND METHODS

In an ongoing study 33 patients (13 primiparae, 13 multiparae and 7 patients with an elective ceaserean section [control group]) have been examined up to now. The examinations were performed on three occasions: 1.) 36th-42nd week of pregnancy, 2.) 3-7 days and 3.) 6 (5-10) weeks after delivery (so far 18 patients). Pelvic floor contraction and bladder neck mobility were assessed by digital palpation analogous to the Oxford-Grading, by perineometry with a perineometer based on air manometry and by perineal-ultrasound, using a 3.5-Hz-curved- linear-scanner with a standardized reproducible method recently described. Ultrasound of the urethrovesical unit was performed at rest, during voluntary contraction of the levator ani muscle and during straining, measuring the height (Dx) and the distance (Dy) of the inner urethral orifice in relation to the back of the pubic symphysis and observing funneling of the bladder neck and relaxation of the bladder base. The statistical test applied was the Wilcoxon signed rank test.



RESULTS

3-7 days after vaginal delivery the pelvic floor function assessed by digital palpation is significantly impaired ($p<0.001$). After six weeks it regains prenatal contraction power or is even stronger ($p=0.001$).
The perineometrical evaluated impairment of voluntary contraction power is also obvious soon after birth ($p<0.001$). Six weeks afterwards there is some improvement but not as far as the palpated one ($p<0.05$).
Sonographically the change of distance while contracting voluntarily is smaller than prenatally one week after delivery ($p=0.002$). Six weeks later there is an significant increase again. ($p<0.004$) In contrast, the passive mobility of the bladder neck is significantly increased one week after delivery ($p=0.01$) and is even greater in 9/18 (50%) patients 6 weeks post partum. 2/26(8%)patients show a relaxation of the bladder base soon after delivery. This increases to 10/18 (56%)patients six weeks later.
The birth weight of the infant or the length of the second stage of labour are not correlated to the degree of change in contraction power and passive mobility.
The control group showed no significant changes.

CONCLUSIONS

Voluntary contraction power is severely impaired after vaginal delivery but is reestablished about six weeks afterwards in most of the women. In contrast, the increase in mobility of the bladder neck and of relaxation of the bladder are even more obvious 6 weeks after delivery. The discrepancy between active contraction power on the one hand and passive mobility of the bladder neck as well as the relaxation of the bladder base on the other hand may originate from a faster recovery of the neuromuscular component (voluntary contraction) of pelvic floor function than the elastic component (over distention).

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MORPHOLOGICAL CHANGES IN THE PELVIC FLOOR IN PATIENTS WITH STRESS INCONTINENCE.

AIM OF STUDY

Previous histochemical studies of biopsy samples of the external anal sphincter, puborectalis and levator ani muscles have suggested that partial denervation of the pelvic floor occurs in patients with rectal prolapse and faecal incontinence.The possibility therfore exists that damage to the innervation of

the pelvic floor may also be a factor in the aetiology of urinary stress incontinence. Recent studies have, however,produced conflicting results and this study was therfore initiated to clarify the situation.

PATIENTS AND METHODS

Biopsies of the posterior part of the pubococcygeus component of the Levator Ani muscle were obtained from 30 incontinent women(age range 26-91), 30 age matched controls and 15 age matched control men. A small sample(n=10) of biopsies were obtained from nulliparous women. Cryostat sections, each 10 micrometres in thickness were processed to demonstrate histological structure using tissue actomyosin ATP ase activity. Sections comprising a minimum of 500 fibres were examined and the percentage of muscle cells showing evidence of pathological change recorded.

RESULTS

The results obtained demonstrated hypertrophy and atrophy of both type 1($p < 0.005$) and type 2 fibres($p < 0.001$) in patients with stress incontinence, and fibre type grouping ($p< 0.01$), changes that occur in muscle with evidence of denervation and re-innervation. There was also an increase in the proportion of type 1 fibres($p < 0.005$) and an increase in the proportion with centrally located nucleii($p < 0.005$) The differences in size were most marked when comparing pre and post-menopausal women(Type 1 $p < 0.05$,Type 2 $p < 0.001$) suggesting a hormonal influence on these changes which also increases with age and parity. The control groups demonstrated age related changes.

CONCLUSIONS

This data provides further evidence for the hypothesis that there has been neurological damage in patients with stress incontinence, initially at childbirth, and that these changes also increase with age as part of a multifactorial aetiology.

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HOW DOES SACROCOLPOPEXY AFFECT BLADDER FUNCTION AND PELVIC FLOOR ANATOMY? - A COMBINED URODYNAMIC AND MRI APPROACH

AIMS OF STUDY

Abdominal sacrocolpopexy provides effective correction of vault prolapse after hysterectomy and preserves vaginal function. Urinary incontinence and further prolapse can occur after sacrocolpopexy (1&2). MRI can accurately visualise pelvic floor anatomy and prolapse (3&4). This study aims to utilise pre and post operative urodynamics to assess bladder function and dynamic fastscan MRI, with and without Valsalva and abdominal pressure recording, to evaluate pelvic floor anatomy to determine the cause of incontinence and prolapse in relation to sacrocolpopexy.

PATIENTS AND METHODS

8 patients mean age 55.9 years (45-60) with marked symptomatic vaginal vault prolapse have completed this ongoing study to date. In addition to clinical assessment; a 1 hour pad test, sit and stand videocystourethrography and a MRI scan have been performed before and 2-3 months after sacrocolpopexy. Yearly follow up for 5 years is planned. One patient had a posterior repair for rectocele at the time of sacrocolopopexy. All MRI studies were performed on a 1.5 T GE Signa Advantage. Resting state images were obtained using fast spin echo proton density, T2 weighted and T1 weighted images in the coronal plane. Dynamic images were performed with a multiplanar fast spoiled gradient echo sequence in the sagittal plane. Sequential images at varying degrees of the Valsalva manoeuvre were obtained. Measurements were made using the pubococcygeal line (PCL) as reference (3), the vertical distances to the bladder neck, vaginal cuff and inferior rectal air were measured. Differences between means were analysed using paired two-tailed student t-tests.

RESULTS

The mean weight was 68.6Kg (59-90), mean height 1.65m (1.54-1.73), and mean parity 3.9 (1-7).The mean number of previous prolapse operations was 1.7 (1-4) and mean number of continence procedures was 1.5 (0-2).

Table 1 shows the vertical distances to the pubococcygeal line in the three pelvic compartments before and after sacrocolpopexy in cm. There were no significant differences in the change in mean distance (distance at valsalva - distance at rest) pre and postoperatively, in any of the three compartments. Preoperative clinical assessment showed 1 patient had a large cystocele and 2 had moderate cystoceles. Following sacrocolpopexy clinically both moderate cystoceles were no longer present and the large cystocele was smaller. This was confirmed by an increase in distance from bladder neck to the PCL on MRI postoperatively. There was no recurrence of vault prolapse at 2 month follow up. Preoperative clinical assessment revealed rectoceles in 7 of the 8 patients. Following sacrocolpopexy, examination at 2 months showed that 6 were no longer present. 1 patient had a posterior repair. In all patients postoperative MRI showed a significant decrease ($p<.05$) in distance from the rectal air to the PCL during Valsalva. 2 patients had detrusor instability preoperatively, 1 had complete symptom resolution with stable cystometry postoperatively. 1 patient developed de novo Genuine stress incontinence (GSI) with cystocele. This was associated with preoperative MRI findings of a lower bladder neck during Valsalva compared to other patients (-2.5 vs 0.8cm (next lowest)) and marked postoperative reduction in vertical bladder neck movement during Valsalva from 3.3 to 1.5cm (1.8 vs 0.8 (next)).

Table 1. Mean position and standard deviation (- denotes below the line)

Values in cm	PREOPERATIVE	POSTOPERATIVE	t-test
BLADDER NECK			
Rest	1.34 (0.59)	1.56 (0.98)	NS
Max Valsalva	0.33 (1.47)	0.71 (1.50)	p<.007
VAGINAL CUFF			
Rest	-2.19 (2.52)	4.10 (0.85)	p<.005
Max Valsalva	-2.66 (2.40)	3.59 (0.96)	p<.005
RECTUM			
Rest	-2.98 (2.16)	-1.55 (1.46)	NS
Max Valsalva	-4.23 (1.58)	-2.78 (1.08)	p<.05

CONCLUSIONS

MRI can provide objective quantification of prolapse and elegantly demonstrates the effect of sacrocolpopexy in the vaginal (middle) compartment. Sacrocolpopexy causes a significant (see table 1) upward movement of both anterior and posterior parts thus correcting concurrent cystocele and rectocele. Preoperative MRI correctly identified a cystocele which became clinically apparent postoperatively, suggesting it may be useful in preoperative planning of corrective surgery. One patient developed de novo GSI

her MRI findings pre and post operatively from the other patients; we aim to continue this study to confirm these findings.

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A MULTICENTER EXPERIENCE USING AN EXPANDABLE URETHRAL OCCLUSION DEVICE FOR MANAGEMENT OF URINARY STRESS INCONTINENCE.

Objective

This presentation represents findings of a multicenter, clinical trial to evaluate the efficacy and safety of a disposable, expandable occlusion device for the treatment of stress urinary incontinence in women. The trial is intended to measure the effects of daily patient use of the device over the short term and at four months. Following is a report on 33 patients with a minimum of four months of device use.

Protocol

Initial Visit--Patient history, physical exam, urine culture and urinalysis,CMG, cystoscopy, informed consent. Enrollees 18-75 years of age, have: symptomatic, stress incontinence, manual dexterity, no uropharmacologic meds, not pregnant.

One Week--Pad weight with and without device, urinalysis, urine culture, a one week voiding diary and quality of life profile. Patients were trained on insertion and began device use.

Monthly--Physical exam, return periodic diaries on device use and voiding experience, urine culture and urinalysis.

Four Months--CMG, cystoscopy, pad weight with and without device, urinalysis and culture, quality of life profile and diaries.

Patient Characteristics & Recruiting

Avg. Age: 51.39 years	Type of Incontinence (anatomic severity):	I	18%
Presence of Symptoms:		II	61%
Avg. Age at Onset- 35.9yrs		III	21%
Avg. Length of Symptoms-12.0yrs			
Previous Incontinence Surgery- 25%	Incontinence Classification (CMG)		
Patients Reporting Moderate Leakage on Urge Prior to Device Use-47%	Pure stress		87.9%
	Mixed		12.1%
	Urge		0%

Four Month Results

After four months of use, the results demonstrate that the urethral occlusion device is a highly effective means of preventing loss of urine associated with stress incontinence. The device remained securely positioned in the urethra blocking the passage of urine until the patient desired to void. Efficacy was objectively confirmed by comparative pad weight studies done without the device (average 28.68+/- 43.25 gm urine lost) versus with the device (4.12+/- 11.53 gm urine lost). Most patients (25, 80%) wore the device for between 2 and 5 hours and used an average of three devices daily. Patients reported that the device was easy to use initially and insertion had become a simple routine at four months. During initial use 18 patients (54%) reported an episode of discomfort either during insertion or while wearing the device. Comfort improved with daily use and experience with the device. On reaching four months, users indicated a high degree of satisfaction with device performance and reported remaining dry during use of the device. The women also reported a positive life style modification in their four month diaries and profiles.

Side Effects

Patients, achieving four month follow-up or greater have inserted 20,000+ devices during 6.9 months average use. Cystoscopy at four months, has shown no changes in bladder or urethral mucosa. In four patients, minor transient bladder irritation was observed between first and four month cystoscopy. All events resolved without medical intervention following brief suspension of device use. Routine urine cultures detected asymptomatic bacteriuria in 1 (3%) patient. This event resolved without treatment. Symptomatic urinary tract infections were reported in 7(21%) patients. All UTI's were treated with antibiotics and resolved quickly permitting continued device use. Urinalysis documented 8 (24%) patients with a transient red blood cell count in excess of 15 cells per high power field. Six patients (18 %) reported a transient event of gross hematuria associated with physical activities such as sports, jogging and aerobics. All resolved without medical intervention following a brief interruption of device use. Two devices migrated proximally. One device migrated into the bladder and was removed without consequence using a cystoscope. One device migrated into the proximal urethra and was withdrawn by the patient. Both patients continue to use the device satisfactorily. Overall, use of this device has demonstrated clinical side effects which are: easily recognized by the patient, readily treatable, and not likely to result in any permanent adverse sequelae.

Conclusion

The urethral occlusion device appears highly effective, relatively easy for females to use and safe. It holds promise as a excellent alternative for women with stress urinary incontinence, especially those in need of options beyond diapers and pads.

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EXTERNAL URETHRAL BARRIER FOR URINARY STRESS INCONTINENCE: A MULTI-CENTER TRIAL

AIM OF STUDY

Obvious drawbacks to current management options for women with stress urinary incontinence led to the development of a new biomedical device. It is intended to avoid discomfort, odor and skin

irritation associated with absorbent products by preventing urinary leakage. The aim of this study is to evaluate the safety and efficacy of this device.

PATIENTS AND METHODS

The device is a small foam shield worn externally over the urethral meatus. It is held in place by an adhesive gel and is easily removed for voiding and replaced. Women with symptoms of mild to moderate stress urinary incontinence were recruited at 12 incontinence centers in the U.S. to use the device. The 21-week protocol included a 1-week qualifying period, a 4-week control period, 12 weeks of device use, and 4 weeks of post-use surveillance. Safety was monitored with physical exam, vestibular cytology, vaginal smears and culture, and urine culture. Measures of efficacy included 12-hour home pad weight test, voiding diaries and symptom questionnaires. A cohort of patients underwent pre- and post-use cystometrograms. Post-void residual, presence of involuntary contractions, volumes of first sensation, fullness, and maximum capacity were reported. Statistical analysis was performed using a two-tailed t-test, and results are reported as mean (S.E.M.)

RESULTS

Enrollment totaled 411 women, and the protocol was completed by 346 participants with a drop out rate of 15.8%. Subjectively 273/346 (79%) of women reported at least 50% improvement in quality of life issues. The average number of leakage episodes per week decreased from a control of 14.2 (0.7) to 5.7 (0.4) in the 12th week of device use, $P < 0.001$. The pad weight test decreased from 15.6 gm (1.2) at baseline to 7.2 gm (1.2) in the 12th week of device use, $P < 0.001$. Safety issues revealed no increase in significant vaginal or urinary tract infection. Thirty-five (9%) of the 390 subjects who began device use reported skin irritation, but only 3 (0.8%) discontinued use for this reason. In the CMG cohort no clinically significant differences were noted in any of the parameters examined.

CONCLUSIONS

We report a new medical device which is safe and efficacious for the management of mild to moderate stress urinary incontinence in women, and which obviates the common problems associated with absorbent management products.

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URINARY INCONTINENCE AFTER RADICAL PROSTATECTOMY : IS PROFESSIONAL PELVIC FLOOR TRAINING NECESSARY?

AIMS OF STUDY

Urinary incontinence after radical prostatectomy is a significant and distressing problem. However most of the patients regain continence within a

few months after the operation. The aim of the study was to evaluate the usefulness of Pelvic Floor Training (PFT) performed under supervision of a physiotherapist to recover continence. We conducted a randomised study comparing two groups of patients : those who underwent intensive PFT directed by a physiotherapist and those who exercised on their own. Urinary continence was evaluated by pad weighing tests.

PATIENTS AND METHODS

102 consecutive patients (mean age : 65 - range : 51-77) who were subjected to radical prostatectomy (P. Walsh procedure) were evaluated for urinary continence. At Day 8 following the operation, patients were instructed about the mechanisms of urinary continence and pelvic floor exercises. No other treatment was initiated. Six weeks after the operation, a pad weighing test (Pad Test n°1) was performed according to the ICS recommendations : 59 (58%) patients lost < 1 gr of urine while 43 (42%) lost ≥1 gr. The patients who lost ≥1 gr were allocated randomly into 2 groups (Table I). Group A patients (n=21) were subjected to PFT directed by a physiotherapist consisting of two sessions of biofeedback and electrostimulation per week while Group B patients (n=22) performed pelvic floor exercises on their own without any medical supervision. At the 12th postoperative week (= 6 weeks after the first pad test) the randomized patients had a second pad test (Pad Test n°2) : of the 43 patients, 39 are evaluable (Table II), two did not reach, at the time of submission of the abstract, the 12th week of follow up and 2 are lost to follow up.

RESULTS

Table I : Results of Pad Test n°1 (at the 6th week post-prostatectomy)

	Amount of urine lost	n	Group A n	Group B n
G0	< 1 gr	59	-	-
GI	≥ 1 - 10 gr		13	14
GII	11 - 30 gr		2	3
GIII	>30 gr		6	5
			21	22
			43	

Table II : Comparison of Pad Tests N°1 and N°2 from the 39 evaluable patients

Group A				Group B			
Pad Test N°1	n	Pad Test N°2	n	Pad Test N°1	n	Pad Test N°2	n
GI	13	-> G0	11	GI	12	-> G0	12
		-> GI	2			-> GI	0
GII	2	-> G0	2	GII	3	-> G0	3
		-> GI	0			-> GI	0
		-> GII	0			-> GII	0
GIII	5	-> G0	4	GIII	4	-> G0	3
		-> GI	0			-> GI	1
		-> GII	0			-> GII	0
		-> GIII	1			-> GIII	0

DISCUSSION
No statistical significant difference was found between Groups A and B in terms of recovery of continence : the same proportion of patients in each group regained continence (Table II). Patients were then subdivided according to their histopathological stage or age category (50-59y/ 60-69y/ >70y) : no statistical significant difference was found in terms of recuperation of continence whatever the parameters considered. At this stage the question to be raised is whether patients regained continence as quickly in both groups. For this reason, in the future, patients will be evaluated by a supplementary pad test at the 9th postoperative week. The reasons why the majority of the patients regain continence in both groups might be multifactorial: patients selected for radical prostatectomy are in good physical condition and are rather young and care is taken at the operation to obtain a watertight urethrovesical anastomosis by placing 8 stitches instead of 4 as recommended by others.
CONCLUSION
We found no significant difference between the 2 groups of randomized patients : PFT directed by a physiotherapist compared to pelvic floor exercises without supervision does not seem to increase the final continence rate. However, the assistance of the medical staff is important from a psychological point of view since the patient benefits from a careful support and counseling.

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Can subvesical obstruction be assessed by symptom-scores?

Aims of the study:
Benign prostatic hypertrophy (BPH) can be depicted as a entity consisting of prostatic enlargement, prostatism and mechanical obstruction. The advent of new therapy modalities in BPH, as thermotherapy (TUMT), laserablation and alpha-blocking-agents, revived a worldwide interest in the evaluation of BPH. Prostatism can be quantified by questionaires. Rollema et. al (ICS1993) showed the lack of correlation between AUA-scores and mechanical obstruction (URA) and detrusor contractility (Wmax). The Boyarski- and the very extensive ICS-symptomscore (ICS-SS) were used in this study. The complex interactions, interrelationships and relative importance of the symptomscores and the other two components were subject of this study.

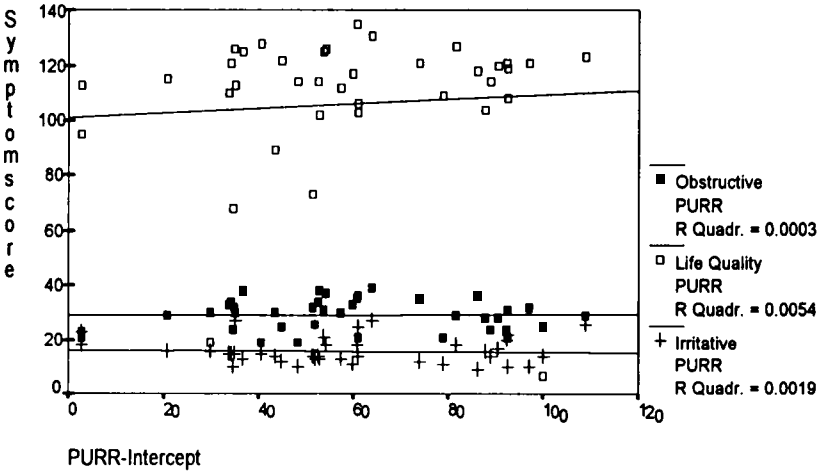
Patients and Methods:
We have included 42 BPH-patients (mean age 66 years). The prostatic size was measured by transrectal sonography. The subvesical obstruction was assessed in pressure-flow-analyses by computer-assisted urodynamics (AUDIT™). We have used the parameter PURR (Schäfer) in intercept and curvature and URA (Griffiths) for quantifying mechanical obstruction and the parameter Wmax. for detrusorcontractility. The ICS-SS was split into obstructive and irritative symptoms and an assessment of life-quality.

Results:
The Pearson correlationmatrix between the ICS-SS and the urodynamic obstruction parameter showed no significant correlations. A significant correlation (p= 0,008)was found between the irritative ICS-SS and Wmax. The regressioncoefficient r^2 of this relationship was only 0.07 % and not statistically significant (p=0.08). The three different

cumulated ICS-SS correlated significantly (p=0.000). The regression coefficients were: irritative vs. obstructive p=0.000, r^2=0.38269; irritative vs. life-quality p=0.0036, r^2=0.19132; life-quality vs. obstructive p=0 .7360 ,r^2= 0.00360

Pearson-Correlation	Irritative	Obstructive	Life-quality
PURR-intercept	-0.0842 p=0.596	-0.0529 p=0.739	-0.008 p=0.996
PURR-Curvature	0.1702 p=0.281	-0.0707 p=0.656	-0.0343 p=0.829
URA	0.1760 p=0.265	-0.0330 p=0.826	-0.0405 p=0.799
Wmax	0.2663 p=0.008	-0.1787 p=0.257	0.0805 p=0613
Prostatic Volume	0.1062 p=0.606	-0.0668 p=0.746	0.1755 p=0.391

The correlations between prostatic size and the cummulated ICS-SS were not significant. The multitude of differerent symptoms require, a multivariate (multivariable) analysis of variance (ANOVA and MANOVA) to discern the most important parameters. We found in our studies, with a relatively small number of patients, no significant differences of the individual symptoms on obstuctionparameters.



Conclusions:

The cummulated obstructive and irritative ICS-SS showed no significant correlations with the urodynamic parameters or the prostatic size. The significant correlaltion and regression show a reduction in lifequality by irritative symptoms. The value of the symptomscores or individual symptoms in assessing prostatism or the effects of BPH-treatment should be critically evaluated. The urodynamic investigation remains the only objective method in assessing subvesical obstruction.

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THE VOLUME DEPENDENCE OF FLOW-RATE

AIMS OF STUDY

For a long time it has been known that measured flow-rates are volume dependent. This dependence has been ascribed to the bladder geometry : at a constant bladder wall contraction velocity the flow-rate increases with the bladder volume to the power 2/3. When the maximum flow-rate Q_{max} is used as a diagnostic parameter it is common practice to use only values measured at voided volumes in excess of 150 ml, or to normalize the measured flow-rates using a nomogram or computerprogram. In the present study the physiological basis and diagnostic relevance of the volume dependence of flow-rate is verified and discussed.

METHODS

During consecutive periods of two to six weeks, ten healthy volunteers completed a voiding diary by voiding in standard plastic zipbags while measuring voiding time with a stopwatch. Each voided volume was weighed using an especially developed electronic pocket balance. Average flow-rate values were calculated by dividing the voided volumes by the voiding times.

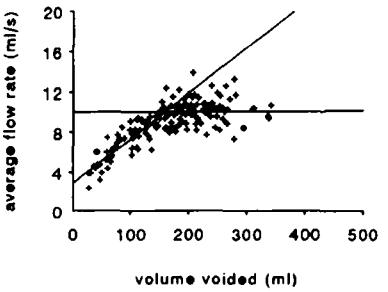

Fig. 1. Average flow-rate as a function of voided volume in a 33 year old healthy male.

RESULTS AND CONCLUSIONS

Figure 1 shows an example of the measured average flow-rates as a function of the voided volumes in one of the volunteers. In nine of the ten volunteers a pattern of increasing flow-rates at low voided volumes and more or less constant flow-rates at high voided volumes was found. This pattern was quantified by fitting two straight lines as illustrated in the figure. The intersection of the straight lines was called "threshold volume". The table shows for all volunteers this threshold volume, as well as the maximum voided volume and the modal volume (the most frequently voided volume). Although there is a large variation in the latter two estimates for different aspects of bladder capacity (which may be called mechanical and sensory capacity), the threshold volume is fairly constant in eight of the volunteers. It follows that the threshold volume is independent of

bladder capacity. Since there is a close relationship between average flow-rates and maximum flow-rates, the relation between average flow-rate and bladder volume should be similar to that between maximum flow-rate and bladder volume. Although (as in most free flow-rate measurements) the correct bladder volume is unknown (post void residuals were not determined) it is highly unlikely that the measured volume dependence can be entirely ascribed to the geometrical mechanism described in "aims". Fig. 2. shows the average contraction velocity of one of the volunteers which was far from independent of voided volume. In nine of the ten volunteers there was a similar significant decrease in average contraction velocity with increasing voided volume (regression analysis). Most likely this must be ascribed to a change in detrusor contractility. In one volunteer the average contraction velocity hardly decreased with voided volume. This was the 68 year male who also had the outlier *threshold volume in the table*. This volunteer had undergone a TURP and it is suggested that irreversible changes in detrusor contractility in response to the increasing prostatic obstruction are reflected in the measured data. It is concluded that it is highly unlikely that the volume dependence of flow-rate can be *entirely ascribed to a geometrical* mechanism. In addition to that mechanism probably the effective detrusor contractility decreases with the voided volume. This property of detrusor contractility can be quantified by determining a threshold volume in the relation between average flow-rate and voided volume as in the present study. It is suggested that this threshold volume might form a valuable source of information on irreversible changes in detrusor contractility in response to detrusor obstruction. It can be derived from non invasive measurements as in the present study.

Age	Sex	Modal vol. (ml)	Max. vol. (ml)	Thresh. vol. (ml)
23	♂	281	649	-
25	♂	113	592	152
33	♀	318	554	145
33	♂	178	512	159
37	♀	(188)	402	165
41	♂	170	456	159
41	♀	105	380	182
44	♀	59	1170	178
61	♂	138	406	128
68	♂	277	607	437

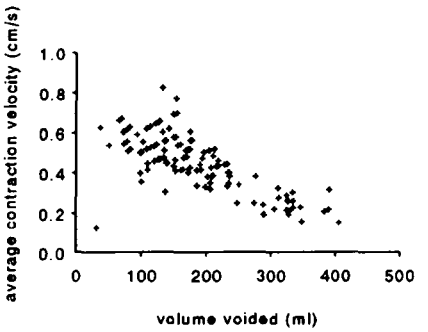

Fig. 2. Average contraction velocity as a function of voided volume in a 61 year old healthy male.

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ABDOMINAL STRAINING DURING VOIDING OF PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA.

AIMS OF STUDY

Variations in flow during one voiding of patients with prostatism are frequently interpreted as abdominal straining artifacts. Patients mention straining to start or to continue as a symptom but on the contrary a lot of patients state that straining has no positive effect on the flow.

A former study done in 46 subjects of whom 35 patients with benign prostate hyperplasia, showed that "requested straining" in all these patients had a negative effect on flow.[1] Analys of pressure/ flow relation during voiding is reported to be hampered by abdominal straining.[2] We performed this study to investigate the effect of "natural" straining on voiding and on the results of pressure/ flow analysis.

MATERIAL AND METHODS

Urodynamic investigations of 108 patients with benign prostatic hyperplasia were reviewed. Transurethral filling cystometry consisted of medium fill cystometry with water (20°C) until patients normal capacity was reached. When the patient expressed a strong desire to void, filling was stopped and micturition permitted. All patients have been asked to void "as usual". Abdominal and vesical pressures (P_{abd} and P_{ves}) were recorded with (transrectal and transurethral) 8F catheter mounted microtip sensors. Pressures were digitally sampled with a frequency of 8 Hz. Correction for time delay between detrusor pressure (P_{det}) and flow was usually 0.75 s but adapted when necessary.

A straining event was defined as an increase in P_{abd} of more than 20 cmH_2O with a duration of more than 1 s during voiding. Variations in flow were defined as significant when a positive or negative peak of more than 2 ml/s with a duration of more than 2 s was observed. Normally bladder outflow obstruction is investigated by means of a (detrusor pressure/ flow) P_{det}/Q plot, for analysis of the effect of abdominal straining in this study we used P_{ves}/Q graphs for comparison.

RESULTS

Spontaneous straining events were observed in 36 patients (33.3%). Significant flow variations were seen in 74 patients (68.5%). In 50 patients (69.4%) these flow variations were seen without any straining. Of the patients with straining events, 29 (80.5 %) showed significant flow variations.

Investigation of the P_{det}/Q graphs showed that straining resulted in pressure peaks parallel to the pressure axis of the graph. This means that during a straining event the P_{ves} pressure rise was not corresponding with an increase of flow in most of the patients. Of the patients performing spontaneous straining, 2 patients showed significant straining to start the voiding and 15 patients showed straining at termination of voiding. The flow and vesical pressure signal at the termination of voiding is badly synchronized because of pelvic floor activity ("milking") so it is impossible to conclude about the relation of vesical pressure and flow in this phase. In 5 of these (15) patients however, the straining resulted in a secondary detrusor pressure rise that resulted in subsequent voiding. The other 19 patients were straining during (mid-portion) flow or throughout the whole micturition. In 11 of these patients the straining had "triggered" a subsequent P_{det} rise with an increase in flow. None of these patients showed significant flow increase **during** straining events. The effect of straining on the flow was somewhat positive (between 1 and 2 ml/s) in 3 patients. These patients were moderate or not obstructed. Since all P_{ves}/Q effects were seen parallel to the pressure axis, the lower pressure border remained unaffected during straining events. Abdominal straining in these patients has no positive effect on the flow probably because of transmission of the abdominal pressure on the enlarged prostate and to the

subvesical region. The frequently observed variations in the flow in the not straining patients must be related to the "swaying" or discontinuation of the urine stream in the flowmeter funnel, to flowmeter (recorder) artifacts, or to dysfunctional voiding (with pelvic floor activity) due to the circumstances of the investigation.

CONCLUSION

Spontaneous abdominal straining during voiding was seen in 33.3% of the patients. Flow variations of more than 2 ml/s were seen in 68.5 % of the patients in 50% (of these) without any straining. Analysis of P_{ves}/Q graphs revealed that the flow rate was not significantly affected by the straining itself. In patients with straining during micturition, an increase of the flow rate can be noted because of a subsequent "triggered" detrusor pressure rise. In obstructed patients, abdominal straining never resulted in a flow rate increase, the lower pressure border of the pressure/ flow graph remains unaffected and P_{det}/Q analysis is not significantly influenced by the effect of abdominal straining during voiding.

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THE SIGNIFICANCE OF TERMINAL DRIBBLING IN MEN WITH LOWER URINARY TRACT SYMPTOMS

Aims : There has been little formal study of the significance of terminal dribbling in men with lower urinary tract symptoms (LUTS). Von Garrelts [1] reported that after reaching a peak, flow rate decreased at a rate that was slower than normal in men with BPH. Rollema [2] found that a prolonged descending leg of the flow curve trace both specific and sensitive for LUTS. We have studied the prevalence of terminal dribbling both as a symptom and as an objectively demonstrated abnormality of voiding, the association between the symptom of dribbling and objective evidence of its presence, and the relationship between terminal dribbling and bladder outflow obstruction (BOO).

Patients and Methods : To ascertain the prevalence of the symptom of terminal dribbling, 82 men presenting with LUTS (mean age 71 years, range 50-84) completed the ICS-BPH symptom questionnaire, question 18 of which asks "Does your urinary stream end in a dribble?" The prevalence of terminal dribbling on flow rate traces was assessed from 4 voids using a Dantec 1000 Urodyn flowmeter. Terminal dribbling was said to be present if the flow rate was less than 5 ml/s in the terminal 15 seconds of flow and the gradient of a line drawn between the peak flow and the end of flow was <25%. Pressure-flow studies were performed on a Dantec 5500 or Dantec Menuet multichannel recorder and patients were classified as obstructed or equivocally obstructed using the Abrams-Griffiths nomogram [3]. In a smaller number of men, the bladder contractility factor, WF [4], was calculated throughout the course of voiding and plotted against timne. The correspondence between subjective symptomatology and the objective assessment of terminal dribbling was analysed using a 5 x 5 table. The Chi square test was used in the comparison of pressure-flow findings across the groups who did and did not show terminal dribbling during voiding. The sensitivity, specificity and positive predictive value of terminal dribbling as a sign of BOO were also calculated.

Results : Thirty-eight patients (46%) complained of terminal dribbling most or all of the time and 21(26%) showed objective terminal dribbling on 3 or 4 of their flows. Of the 38 men complaining of terminal dribbling most or all of the time, 22 showed no evidence of terminal dribbling on any of 4 flows. In 53 men (65%), the response to the question about terminal dribbling agreed with the objective finding on flow traces.

Seventy-eight men had pressure-flow studies performed. The prevalence of BOO in those complaining of terminal dribbling most or all of the time (19 of 35) was similar (p=0.4) to those who said their flow ended in a dribble some of the time, occasionally or never (21 of 43). However, terminal on 3 or 4 flows was significantly (p<0.0001) related to the presence of BOO (Table). Terminal dribbling had a positive predictive value for BOO of 91% and a specificity for the presence of BOO of 95%. The sensitivity of terminal dribbling was less, with 50% of patients with BOO not having terminal dribbling on flow traces.

TABLE.
The relationship between objective evidence of terminal dribbling and BOO.
OBS - obstructed; UNOBS - equivocally / non obstructed; TD - terminal dribbling.

	OBS	UNOBS	Total
TD on 3 or 4 flows	20	2	22
TD on 0 - 2 flows	20	36	56
Total	40	38	78

In 10 men, 4 demonstrating terminal dribbling on 3 or 4 flows and 6 with no terminal dribbling of their free flows, WF was plotted against time during voiding. In those without terminal dribbling, WF was found to rise gently, reaching a peak just prior to the end of flow. In those with terminal dribbling, WF tended to peak just after the beginning of flow and then slowly declined towards the end of flow.

Conclusions : Terminal dribbling is a common symptom in men with LUTS and objective evidence of its presence can be found in 26% of cases. The association between the symptom of terminal dribbling and objective evidence of its presence is poor, and as a symptom it is not specific for BOO. However, its presence on flow curve traces is very specific for BOO and could thus prove clinically very useful to assist in the diagnosis of this condition. The finding that those men with terminal dribbling tended to show a declining level of WF throughout flow, compared to normal individuals who maintain bladder contractility, suggests that terminal dribbling arises as a reulst of bladder fatigue. This presumably is a consequence of the high pressures that these patients' bladders need to develop secondary to the presence of BOO.

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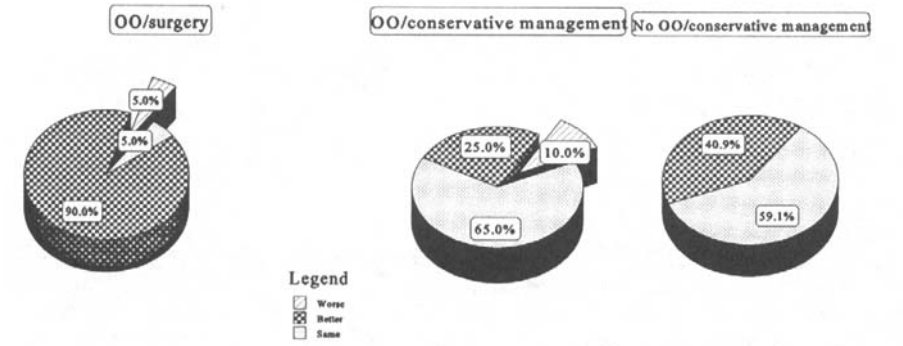
VOIDING PROFILOMETRY AS A DIAGNOSTIC AID IN PATIENTS WITH PROSTATISM: ASSESSMENT WITH POST-THERAPEUTIC SYMPTOM EVALUATION

Aims of Study: Although urodynamic assessment is strongly recommended for diagnosing outlet obstruction and planning management, its precise impact on post-therapeutic outcome is not well studied. Furthermore, many urodynamic techniques have not been clinically or experimentally validated. The value of any diagnostic test in determining therapeutic options must be based on its ability to improve treatment outcomes. Confirmation of outlet obstruction (OO) in a patient with symptoms of prostatism using a urodynamic test implies that relief of the OO will lead to significant relief of symptoms or improvement of morbidity. This assumes that the therapeutic modality itself does not create morbidity and the surgery is well executed. Similarly, when the urodynamic test diagnoses the absence of OO, conservative measures must not lead to deterioration of symptoms or functional status of the urinary tract. When a non-obstructed patient without a significant underactive or overactive detrusor shows signs of symptomatic or functional deterioration, either the urodynamic test failed to accurately characterize the outlet or a rapidly progressing morbid process of the outlet has occurred after the urodynamic assessment. Voiding profilometry is being used to diagnose outlet obstruction as an alternative to conventional pressure-flow studies, especially in disabled, non-ambulatory and elderly patients. The aim of this study was to assess the clinical utility of this technique. This clinical assessment will also validate the role of this technique in accurately separating obstructed and non-obstructed patients. Although the technique of measuring pressure gradients during voiding or during constant flow conditions has been verified in canine experiments, clinical validation of this technique is essential to assess its utility as a valuable diagnostic test.

Materials and methods: Patients with voiding dysfunction were urodynamically assessed by voiding profilometry, cystometry and contractility studies over the last 5 years. The severity of OO was determined using the results of voiding profilometry. Supra-membranous pressure gradients exceeding 10 cm H_2O were considered indicative of significant OO. Treatment was prescribed according to the determined severity of obstruction and patient symptoms. Patients with significant OO or symptoms were treated surgically (TURP, TUIBN), and those with lesser degrees of obstruction and symptoms were treated conservatively. The efficacy of this process was examined by requesting a selected population of surgically and conservatively treated patients to answer a questionnaire regarding their post-management symptoms. This survey included questions on the patient's urinary stream, voiding behavior (straining), hesitancy, intermittency, bladder emptying, incontinence, urge, nocturia and diuria. Each patient was instructed to respond to each question using a numerical scale. Patients were also given the opportunity to comment on how they felt since therapy and to report on any changes in their primary symptoms. Patients were asked to characterize their overall post-therapeutic status as better, same, or worse.

Results: Eighty conservatively managed patients and sixty surgically treated patients were surveyed. From the conservative treatment group, sixteen patients did not respond. Four patients were deceased (none due to urologic disease). Eighteen were excluded for a variety of reasons such as the onset of bladder cancer, spinal cord injury, and inability to complete the questionnaire. From the surgically treated patient group, 11 patients did not respond. Four patients were deceased (unrelated to surgery), and five did not complete the questionnaire. The results of the 82 remaining patient surveys (42 conservatively managed + 40 surgically treated) are shown below. Of the total survey population, 48.8% were moderately to severely obstructed and were treated with surgery. Conservative measures were applied in the remaining patients - 47.6% were mild to moderately obstructed and 52.3% were not obstructed. Approximately a third of both surgically treated and conservatively treated groups had concomitant detrusor dysfunction (detrusor instability or detrusor underactivity).



Conclusion: This retrospective study showed that accurate characterization of voiding dysfunction with voiding profilometry resulted in better post-operative outcomes than those reported in the literature. Post-operative outcomes in this study (5% of patients were unhappy with the outcome) were better than the reports of unsatisfactory outcomes in 21% of obstructed patients based on symptom score and flow rate[1], and 20% of obstructed patients diagnosed with pressure-flow studies[2]. Good outcomes were observed with non-obstructed patients treated conservatively, suggesting that voiding profilometry correctly identified patients with non-obstructive voiding dysfunction. The group of mild to moderately obstructed patients who showed symptomatic improvement with conservative management reinforces previous observations in the literature of the waxing and waning of BPH symptoms.

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TESTING THE EFFICACY OF TREATMENT FOR INFRAVESICAL OBSTRUCTION WITH PRESSURE FLOW DATA.

AIMS OF STUDY

At present infravesical obstruction can only be measured objectively using pressure-flow studies. Since one pressure-flow study in one patient comprises hundreds of pressure and flow-rate values, changes in response to experimental treatment options cannot be tested for statistical significance directly. It is necessary to characterize the pressure-flow data in terms of a limited number of parameters. Many methods have been proposed to reduce pressure-flow data to a few parameters or classes. Two of these are nomograms, the Abrams-Griffiths' nomogram [1] and Schäfers LPURR [2]. As a result of the limited number of classes these

nomograms have a limited resolution, i.e. only large changes in outlet resistance can be detected. Other methods analyse pressure-flow data using a computer program that calculates one or more urethral resistance parameters that have less limited resolution. One parameter methods such as URA [3] and OBI [4] have succesfully been used to statistically test the significance of changes in bladder outlet resistance for instance in response to an alpha blocker [5]. Since there is more information in the pressure-flow data than can be represented in one single parameter, there is an inevitable lack of accuracy in single urethral resistance parameters. It is possible to find examples where two clearly different pressure-flow plots are represented by the same parameter value. Multi parameter urethral resistance factors overcome this problem, but make it difficult to test the significance of changes in response to treatment. If one of the parameters improves and another deteriorates, it is unclear whether the patient has improved or not. A two dimensional classification system has been proposed to classify a two parameter urethral resistance factor [6], but like the nomograms this method suffers from the limited resolution inherent to a limited number of classes. The present paper describes and illustrates a method to test for significant changes in pressure-flow data using a two parameter urethral resistance factor.

METHODS

190 pressure-flow studies in 32 patients studied earlier [5] were reprocessed.

Three pressure-flow studies were done in each patient before treatment, and three studies after four weeks of treatment. 16 patients were treated with 4mg daily of an alpha blocker, doxazosin, and 16 patients with placebo. The study was randomized and double blind. The digitally stored pressure-flow data was reprocessed using the software packages Matlab, Qpro, Paradox and SPSS. The part of the pressure-flow data closest to the flow-rate axis was automatically detected and fitted with a first order orthogonal polynomial [4]. The pressure-flow plots were thus characterized in terms of the two parameters "average height" and "average slope". When fitted data was automatically compared with original data, six outliers were detected. Visual inspection showed these to be caused by artefacts in the original measurements, which were excluded from further analysis. The statistical significance of simultaneous changes in the two parameters "average height" and "average slope" was tested by applying the Wilcoxon matched pairs signed rank test to the sum of the parameters, normalized to the population means.

RESULTS AND CONCLUSIONS

parameter	treatment	before treatment		during treatment		significance Wilcoxon
		mean	sd	mean	sd	
average height [cm H_2O]	placebo	66	26	63	29	0.72
	4 mg	81	33	71	27	0.098
average slope [cm H_2O/ml/s]	placebo	4.5	4.6	4.6	3.7	0.57
	4 mg	5.3	4.0	4.8	4.0	0.21

The table shows that that both the average height and the average slope of the polynomial fitted to the pressure flow data decreased upon doxazosine treatment, but these changes were not significant. When average height and average slope were combined in a test variable by adding both values divided by the population means the Wilcoxon matched pairs signed rank test showed a significant change in this test variable in the 4 mg group ($p=0.030$) and no significant change in the placebo group ($p=0.76$). This demonstrates that the advantages of a single test variable for changes in urethral resistance can be combined

with the accuracy of a two parameter urethral resistance factor. The same approach could be applied to other two parameter resistance factors or directly to the data plotted in the Abrams-Griffiths nomogram. In the above patient groups testing for simultaneous changes in $-Q_{max}$ and $p_{det.qmax}$ also showed a significant change in the treatment group ($p=0.015$) and no significant change in the placebo group ($p=0.53$). In general however the approach with a test variable composed of average height and slope of a polynomial fitted to the pressure-flow data is more promising as the statistical nature of these parameters results in a better reproducibility. In the discussed patient population the reproducibility of the parameters was estimated by calculating the quotient of between patient variance and total variance as derived from variance analysis. This F-test value was 8.2 for average height, 4.4 for average slope, 7.3 for $p_{det.qmax}$ and 2.8 for Q_{max}. The higher F-values of the polynomial derived parameters signify the better within patient reproducibility of these.

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Watchful waiting in the treatment of prostatism complaints : Do urodynamic parameters change?

AIMS OF STUDY

Prostatism complaints are known to wax and wane in severity and do not necessarily correlate with objective findings. Whenever patients present themselves with considerable complaints without clear objective evidence for obstruction, or when patients due to different reasons do not want or can not undergo any treatment, the wait and see approach is often chosen. We conducted a prospective study to analyze the urodynamic changes after a period of 6 months of watchfull waiting.

PATIENTS AND METHODS

Between september 1992 to March 1994, 750 patients underwent a urodynamic investigation because of prostatism complaints. All patients underwent a full screening program, consisting of patient history, physical examination (including DRE), blood and urine analysis (including PSA), TRUS of the prostate, renal ultrasound, uroflowmetry, urodynamic investigation with pressure/flow-analysis, and urethrocystoscopy. Patient complaints were measured using Madsen and IPSS symptom scores. When symptoms were not too pronounced or patients did not want any treatment, a wait and see pollicy was conducted. After 6 months, uroflowmetry and urodynamic investigations were repeated.

RESULTS

In 103 patients a wait and see approach was chosen. Baseline characteristics: Average age 65 years (range: 43-86); Mean prostate volume (planimetric) of 40.8 cm^3 (range: 19-114); mean PSA-level (Hybritech) of 3,5 ng/ml (range: 1,0-25). Uroflowmetry: all patients had a voided volume of at least 100 ml, with an average maximum flow rate of 13.1 ml/s (range: 4.7- 30.0) and an average post-voiding residual urine of 51.8 ml (range 0-220). Symptomscores: The average Madsen symptom score was 10.6 (range 2-22) and an average IPSS of 14.8 (range 1-31).

The urodynamic findings of these 105 BPH-patients are presented in table 1 and table 2a/b:

Table 1: Cystometry parameters:

CYSTOMETRY	MEAN	RANGE
Capacity (ml)	453	164 - 823
Compliance (ml)	41.9	5 - 240
Instable detrusor	10/103 (9.7%)	

Table 2a: Pressure/flow parameters:

PRESSURE FLOW ANALYSIS	MEAN	RANGE
Pdet at Qmax (cm H_2O)	54.8	9 - 150
URA (cm H_2O)	28.1	0 - 91
Pmuo (cm H_2O)	30.5	0 - 78
Atheo (mm^2)	4.7	1.1 - 16.0

Table 2b: LPURR obstruction grading according to Schäfer.

LPURR	Number of patients (%)
0	14 (13.6)
1	24 (23.3)
2	30 (29.2)
3	13 (12.6)
4	14 (13.6)
5	6 (5.8)
6	2 (1.9)

Until now, 25 patients had a repeated urodynamic investigation after 6 months. The urodynamic parameters before and after 6 months of watchfull waiting are presented in table 3:

Table 3: Urodynamic changes after 6 months.

	BEFORE		AFTER		
	mean	range	mean	range	p-value (Wilcoxon)
Qmax (ml/s)	13.5	5.5 - 25	13.0	6.0 - 26	0.97 ns
Residual urine (ml)	49.2	0 - 220	52.1	0 - 300	0.35 ns
Pdet at Qmax (cm H_2O)	55.0	15 - 116	47.5	16 - 89	0.28 ns
URA (cm H_2O)	31.0	10 - 67	28.2	12 - 57	0.27 ns
Pmuo (cm H_2O)	27.2	1 - 69	21.9	3 - 48	0.33 ns
LPURR	2.3	0 - 5	1.9	0 - 4	0.23 ns
Atheo (mm^2)	4.0	1.3 -8.2	4.2	1.2- 7.7	0.56 ns

CONCLUSIONS

This group of patients with prostatism complaints and who received watchfull waiting showed no major changes in parameters after 6 months follow up. However we must keep in mind that this is only a limited group of patients and that the majority of patients have mild symptoms and urodynamic obstruction is less pronounced.

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THE URETHRAL RESISTANCE EQUATION IN THE DIAGNOSIS OF THE MECHANISM OF BLADDER OUTFLOW OBSTRUCTION

AIMS OF STUDY

It has been suggested that two particular mechanisms contribute to male outflow obstruction. The first is benign prostatic hyperplasia, the second is contraction of the prostatic, urethral and bladder neck smooth muscle during micturition. The latter mechanism has led to an interest in the use of alpha 1_c adrenoreceptor blocking agents for the treatment of obstructive symptoms. The ability to discern the dominant obstructing mechanism urodynamically may confer a therapeutic advantage. Theory suggests that applying the urethral resistance equation to the voiding pressure/flow plot would be a means of aiding subclassification of obstruction [1]. A videocystometrogram images the urethra during voiding. It is claimed that an attenuated prostatic urethral outline indicates obstructive prostatic hypertrophy, whereas "trapping" of contrast within the prostatic urethra during a stop test is indicative of bladder neck dyssynergia (a dynamic obstruction) [2]. Analysis of the pressure flow plot can be used to identify a rigid (or constrictive obstruction), an elastic (or compressive obstruction), and relative combinations of the two [2]. In addition, measurement of the urethral opening pressure over micturition provides information on the amount of change in urethral resistance.

This study tested the null hypothesis that videourodynamic diagnosis of obstructive prostatic hypertrophy and bladder neck dyssynergia would not correlate with a voiding pressure/flow plot differentiation of constrictive and compressive obstruction nor with the change in urethral opening pressure.

PATIENTS AND METHODS

80 consecutive male patients with lower urinary tract symptoms of outflow obstruction were studied. Their age range was 42 to 84 years (mean 62.9). They underwent a videourodynamic study and a simultaneous voiding pressure/flow plot recording. The videourodynamic findings were classified so that 42 patients showed prostatic urethral attenuation, 28 had prostatic urethral trapping and 10 had both.

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NITRIC OXIDE SYNTHASE (NOS) ACTIVITY IN URETHRA, BLADDER, AND BLADDER SMOOTH MUSCLE CELLS

AIMS OF STUDY

Rabbit urethral relaxation in response to transmural electrical field stimulation (EFS) has been shown to be mediated by non-adrenergic, non-cholinergic (NANC) nerves. The findings that EFS induced urethral relaxation is inhibited by N^G-nitro-L-arginine (NNA), a nitric oxide synthesis inhibitor and by methylene blue, a soluble guanylyl cyclase inhibitor, is consistent with EFS causing the release of nitric oxide (NO) which in turn activates the enzyme guanylyl cyclase with the formation of cyclic GMP (cGMP) and subsequent urethral relaxation. The bladder on the other hand is relatively resistant to the relaxant effects of EFS and of nitrovasodilators such as sodium nitroprusside but relaxes completely in response to 8-bromo cyclic GMP (8-Br-cGMP). We have undertook a study to clarify the role of the nitric oxide-cGMP signal transduction pathway in the urethra, bladder, and bladder smooth muscle cells. This pathway consists of:

$$\text{L-arginine} \xrightarrow{\text{NOS}} \text{L-citrulline} + \text{NO}$$

NO in turn activates the enzyme guanylyl cyclase with the subsequent formation of cGMP and in smooth muscle a relaxation response.

METHODS

Smooth muscle cells were isolated and cultured after collagenase-pronase digestion of bladder dome smooth muscle. Phenotype and purity were confirmed by immunofluorescence using smooth muscle alpha actin antibody. Guanylyl cyclase activity was measured in bladder and urethral supernatant fractions by determining the conversion of GTP to cGMP. cGMP was quantified after acetylation with a radioimmunoassay. NOS activity was measured in supernatant and particulate fractions of urethra, bladder and bladder smooth muscle cells as the formation of L-[^{14}C] citrulline from L-[^{14}C] arginine and isolation of the citrulline by AG 50W-X8 column chromatography. Citrulline formation was verified by thin-layer chromatography.

RESULTS

Bladder and urethra contain both soluble and particulate NOS activities. NOS activity in the soluble fraction of bladder and urethra was NADPH and calcium dependent and was inhibited more by N^G-nitro-L-arginine (NNA) which preferentially inhibits a constitutive NOS (cNOS) than by canavanine (CAN) which preferentially inhibits an inducible NOS (iNOS). These data are

consistent with a constitutive nitric oxide synthase (cNOS) as seen in neuronal tissues. NNA is a more potent inhibitor of soluble urethral NOS, when compared to bladder NOS and this may account for differences in the relaxant response of urethra and bladder to EFS. Both bladder and urethra contain soluble sodium nitroprusside sensitive guanylyl cyclase activity, with the basal and stimulated levels being higher in the urethra than in the bladder. NOS activity in soluble and particulate fractions from bladder smooth muscle cells is 1.5±0.4 and 2.7±0.4 pm citrulline/min/mg protein, respectively. Canavanine (100 μM) inhibits the soluble and particulate NOS activity in bladder smooth muscle cells by 66±13% and 80±9%, respectively. Lipopolysaccharide (LPS) (0.1 μg/ml) increased soluble NOS activity in bladder smooth muscle cells by 390% after an 18 hr. incubation.

CONCLUSIONS

These data are consistent with EFS causing the release of NO which in turn activates guanylyl cyclase with the formation of cGMP and subsequent urethral relaxation. Bladder smooth muscle cells contain an NOS activity which can be increased by LPS. The function of the bladder NOS has not been determined (Supported by NIH Grants DK38311 and DK 47548).

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NITRIC OXIDE SYNTHASE-CONTAINING NEURONS IN RAT MAJOR PELVIC GANGLIA - COMPARISONS TO OTHER AUTONOMIC GANGLIA

AIMS OF STUDY

Nitric oxide (NO), formed by nitric oxide synthase (NOS), has probably an important transmitter role in NANC (non adrenergic non cholinergic) neurotransmission in the genitourinary tract. In rat, a frequently used experimental model, the major pelvic ganglia (MPG) are major sources for pelvic innervation. By the use of specific antisera to NOS and neuropeptides the content of cell bodies in the MPG containing NOS and/or neuropeptides was investigated and compared to other autonomic ganglia.

METHODS

Autonomic ganglia in female rats were investigated by the use of double labelling immunocytochemistry and subsequent NADPH diaphorase staining. The contribution of NOS-immunoreactive (IR) innervation by the MPG to genitourinary innervation was analyzed following decentralization or extirpation of the MPG.

RESULTS

MPG. NOS-immunoreactivity was seen in a large proportion of neuronal cell bodies.

VIP-IR cell bodies (somewhat less frequent NOS-IR cell bodies) were also generally NOS-IR, however, some lacking NOS-immunoreactivity were observed. Cell bodies with NPY-immunoreactivity generally coincided with adrenergic cell bodies (tyrosine hydrolase(TH)-IR) and only few NPY-IR cell bodies were seen displaying NOS-immunoreactivity. TH-IR cell bodies were observed in large amounts and were different from NOS-IR cell bodies. Extirpation of the MPG caused a total disappearance of the NOS-innervation of the uterine cervix and urinary bladder, whereas no apparent change was seen following decentralization.
Nodose ganglia contained NOS-IR cell bodies in less frequencies than the MPG.
Coeliac ganglion only contained NOS-IR varicose terminals that formed "basket-like" net-works around adrenergic cell bodies.
Superior cervical ganglia contained no NOS-IR cellbodies.
Dorsal root ganglia. NOS-IR cell bodies were most frequent in the thoracic and lumbal regions. The NOS-IR cell bodies also showed CGRP-immunoreactivity.
Trigeminal ganglia contained only few NOS-IR cell bodies that lacked no CGRP-immunoreactivity, which was seen in a large number of other cell bodies.

CONCLUSIONS

In the autonomic ganglia studied the MPG presented the largest number of NOS-IR cell bodies, which, most likely, is a major source for pelvic nitrergic innervation as judged from the denervation experiments. The co-localization of NOS- and VIP-immunoreactivities might indicate a co-operative smooth muscle relaxatory role for NO and VIP in the genitourinary tract. The presence of NOS-IR cell bodies in the dorsal root and trigeminal ganglia could speak for a sensory role of NO.

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THE INVOLVEMENT OF THE L-ARGININE / NITRIC OXIDE PATHWAY IN RABBIT PROSTATIC SMOOTH MUSCLE

AIMS OF STUDY

Recent studies support the idea of nitric oxide (NO) as the non-adrenergic non-cholinergic (NANC) neurotransmitter in the relaxation of trigonal and urethral smooth muscle. However, with regard to prostatic smooth muscle, this mechanism has not been completely elucidated. Thus, the present study, using the isolated precontracted strips of rabbit prostate, investigated whether the NANC nerve-mediated relaxation is present in the prostate, and the L-arginine / NO pathway is involved in this relaxation.

METHODS

The prostate, urethra and bladder were removed from male adult rabbits (Japanese white) immediately after the animals were sacrificed. The prostatic strips were taken from the inside of prostate. Muscle strips lacking the mucosa were also taken from the detrusor and proximal urethra. The strips were suspended in organ bath containing oxygenated Krebs solution, and their tensions were recorded with an isometric transducer. Transmural stimulation of nerves was performed by means of an electrical stimulator connected to two platinum electrodes (supramaximum voltage, 0.8ms, 4-30Hz). The responses of precontracted strips to electrical stimulation and administration of NO ($NaNO_2$) were determined.

RESULTS

Prostatic strips precontracted by 10^{-5}M noradrenaline (NA) showed a frequency-dependent relaxation in response to electrical stimulation (Fig.1), which was blocked by 10^{-6}M tetrodotoxin. Maximum relaxation was obtained at 12 to 16 Hz. Pretreatment with guanethidine (10^{-6}M), propranolol (10^{-6}M), atropine (10^{-6}M) and indomethacin (2×10^{-5}M), respectively, did not alter the maximum relaxation of prostate. N^{G}-nitro-L-arginine (L-NOARG), 10^{-6} to 10^{-4}M, dose-dependently inhibited the relaxant response, and the responses were changed to contractions at the dose of 10^{-4}M (Fig.1). However, D-NOARG (10^{-4}M) did not show any effect. L-arginine (10^{-3}M) significantly enhanced the relaxant response. In the urethral strips precontracted by NA, the same NANC nerve-mediated relaxations were obtained, whereas the detrusor strips precontracted by carbachol (5×10^{-6}M) exhibited no relaxant responses . The maximum relaxation was 41.3± 1.8% of NA-induced tone in the prostate and 58.9 ± 2.8% in the urethra. Administration of NO (10^{-5} to 10^{-3}M) caused transient and concentration-dependent relaxations in precontracted muscle strips from the detrusor, urethra and prostate. The extents of relaxant responses to exogenous NO were the greatest in the prostate and in the order of prostate > urethra > detrusor (Fig.2).

CONCLUSIONS

The results show that the NANC nerve-mediated relaxation which involves the L-arginine / NO pathway can be demonstrated in the rabbit prostate. Since the relaxant effect of exogenous NO is greater in the prostate than that in the detrusor, there would be a possibility that a NO-donor like nitroglycerine is available for pharmacological management of urinary obstruction in BPH.

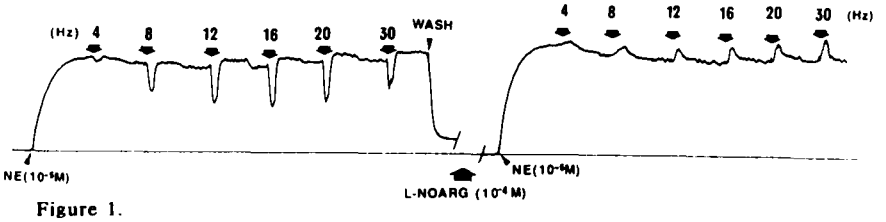

Figure 1.

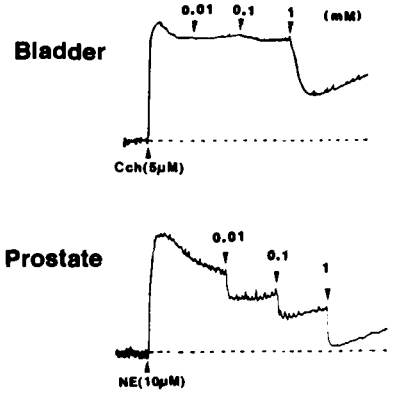

Figure 2.

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ENZYME ACTIVITY IN MITOCHONDRIA ISOLATED FROM RABBIT BLADDER MUSCLE AND MUCOSA FOLLOWING PARTIAL URINARY OUTLET OBSTRUCTION

AIMS OF STUDY

In previous investigations in our laboratory it was demonstrated that following partial urinary outlet obstruction in the rabbit oxidative metabolism of bladder tissue was depressed and glycolysis increased. This metabolic change was accompanied by a decrease in activity in bladder homogenates of two important mitochondrial enzymes,citrate synthase and malate dehydrogenase. The present study is concerned with the problem of whether mitochondria from obstructed tissue are in fact deficient in their ability to oxidize substrates and thereby generate ATP for muscular contraction.If this be true is there a recovery of enzyme activity with time after the initial insult to the tissue?

METHODS

Partial urinary outlet obstruction was produced in male New Zealand white rabbits. After 1,3 and 7 days the animals were euthanized and the bladders removed. Enzyme determinations were made in whole bladder homogenates and in mitochondria isolated by differential centrifugation from the muscle and mucosal part of the bladder.The activities of two essential enzymes in electron transport,NADH-cytochrome C reductase(NCCR) and cytochrome oxidase(CO) as well as citrate synthase (CS) were measured.

RESULTS

Following urinary outlet obstruction bladder weight increased progressively until at day 7 whe bladder weighed 3 times that of the control.

The results of the enzyme measurements are presented in table 1.In whole bladder homogenates enzyme activity was markedly depressed at day 1 following obstruction and, except for CO, activity was still below normal after 7 days.The results with muscle mitochondria showed a marked decrease in activity of the three enzymes studied at day 1 after obstruction.This was followed by a dramatic increase in the activities NCCR and CO with the activity of NCCR fully restored at day 7 and the activity of CO already close to the control value 3 days following obstruction.

CS activity of the muscle mitochondria was similarly affected by obstruction but the return toward normal was less pronounced than for the enzymes of the electron transport chain.As seen from the table the results of the experiments with mitochondria isolated from the mucosa were almost identical to the results obtained with muscle mitochondria.

Enzyme Activity in nmols/min/mg protein.

	Control	1 Day	3 Days	7 Days
		Whole Homogenates		
NCCR	60±4	33±5*	37±3*	44±4*
CO	39±4	20±1*	31±3+	33+4+
CS	93±9	45±3*	48+5*	59+3*
		Muscle Mitochondria		
NCCR	405±23	160±26*	274±37*+	394±11+
CO	164±18	44±1*	141±11+	134±17+
CS	286±25	160±24*	183±14*	206±28
		Mucosal Mitochondria		
NCCR	371±57	148±8*	228±41*	377±8+
CO	137±37	60±9*	123±11+	131±14+
CS	421±48	257±49*	305±43	351±13

Number of determinations 6-9 in each group.

*Significantly different from control.

+Significantly different from 1 day obstruction.

CONCLUSIONS

The results of these experiments show conclusively that mitochondria from both the muscle and the mucosal part of the rabbit bladder are severely damaged metabolically 1 day following partial urinary outlet obstruction.This is the time at which the bladder suffers from overdistension,edema and probably ischemia.As time progresses there is a remarkable recovery of enzyme activity that is complete for cytochrome oxidase 3 days after obstruction and for NADH-cytochrome C reductase at 7 days.The return of citrate synthase activity to normal is less complete. Studies in our laboratory are now being made to clarify the molecular mechanisms involved in the restoration of mitochondrial enzyme activity following the acute initial mitochondrial damage produced by obstruction.In contrast to the defect in mitochondrial enzymes observed early following obstruction the decrease in enzyme activity observed with whole homogenates 7 days after obstruction appears to be caused primarily by there being fewer mitochondria per unit mass in the obstructed tissue.

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MITOCHONDRIAL ENZYME ACTIVITY OF THE URINARY BLADDER -- EFFECTS OF OUTLET OBSTRUCTION AND RELIEVING OBSTRUCTION

AIMS OF STUDY

Experimental obstruction of the bladder outlet has been shown to result in impaired

contractility of the urinary bladder. In rabbits the impaired bladder contractile function was found associated with decreased concentration of high energy phosphates and reduced regional blood perfusion of the detrusor muscle. These functional, metabolic and microcirculatory impairments were also found recovered concurrently and gradually by relieving outlet obstruction. However, it is still unknown that what is/are the mechanism(s) directly involved in the reduced high energy phosphates concentration in the obstructed bladder. Impaired mitochondrial enzyme activity might be an important factor. The aims of this study are to investigate the effect and the reversibility of outlet obstruction on the mitochondrial enzyme activity in the rabbit urinary bladders.

METHODS

Mild bladder outlet obstruction was induced by placing a silicone ring around the bladder neck of male New Zealand rabbits. Following two weeks of obstruction, one group of animals(n=5) was sacrificed. The outlet obstruction was relieved by removing silicone ring in other three groups of animals. These animals were sacrificed one(n=5), two(n=5) and four(n=4) weeks after relieving obstruction. Six normal male New Zealand rabbits were served as controls. Fresh detrusor muscle was minced thoroughly with a pair of sharp scissors. After treatment with nargarse, the minced tissue was homogenized in a glass tissue homogenizer. The homogenate was centrifuged to obtain the mitochondria. The mitochondria was further broken to expose enzymes on membranes with twice freeze-thaw technique using liquid nitrogen. Activity of key mitochondrial enzymes in tricyclic acid cycle, citrate synthase(CS) and malate dehydrogenase(MD), and in electron transport chain, succinate cytochrome c reductase(SCCR), NADH-cytochrome c reductase(NCCR) and cytochrome c oxidase(CCO) was assayed. Tissue content of high energy phosphates was determined by high performance liquid chromatography(HPLC).

RESULTS

The results can be summarized as follows: (1) The bladder weight was significantly increased after outlet obstruction, however, it was reduced gradually following relieving obstruction. (2) The obstructed bladder contained significantly less phosphocreatine and ATP than those of control bladders. The concentration of phosphocreatine and ATP was increased gradually toward the control level after relieving obstruction. (3) The activity of all assayed enzymes was reduced by two weeks of outlet obstruction. Relieving obstruction recovered enzyme activity gradually, but at various recovery rate for different enzymes. Activity of TCA cycle enzymes, CS and MD, was regained as the control level four weeks after relieving obstruction. For enzymes in electron transport chain, NCCR was recovered most quickly, whose activity was mostly recovered one week after relieving obstruction. Four weeks after relieving outlet obstruction, the activity of CCO was improved as the control level. However, the activity of SCCR, which receives the electrons from succinate, was still not recovered completely four weeks after relieving obstruction.

	NCCR	SCCR	CCO	CS	MD
Control	287.0±22.8	123.3±6.6	266.1±27.7	53.4±5.7	261.1±21.3
Obstruction	207.9±18.0*	63.8±6.4*	182.5±15.6*	33.9±3.4*	125.0±10.6*
Rel. 1 week	215.3±28.8	51.4±5.3*	175.4±8.0*	24.5±4.1*	151.9±9.6*
Rel. 2 weeks	322.3±14.5	80.5±4.7*	180.1±8.6*	41.7±3.2*	194.3±11.4*
Rel. 4 weeks	223.3±14.2	58.7±6.2*	208.2±22.9	58.4±3.0	238.0±16.3

(* : significantly different from the control group, $p < 0.05$)

(enzyme activity is expressed as nmole/min/mg mitochondrial protein.)

CONCLUSION

In summary, this study showed that bladder outlet obstruction induced a reduction in high energy phosphates concentration and mitochondrial enzyme activity of the detrusor muscle. Furthermore, the reduced enzyme activity could be recovered gradually by relieving outlet obstruction. These findings indicate that impaired mitochondrial enzyme function might be a significant factor for the deranged energetic metabolism and functional impairment of the urinary bladder following outlet obstruction.

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NEUROKININ A INDUCED BLADDER HYPERACTIVITY IN CONSCIOUS NORMAL RATS

AIM OF STUDY

Capsaicin-sensitive primary afferent neurons have been shown to be involved in the regulation of various micturition-related reflexes in the urinary bladder of several species, including humans. These afferents may be of importance in the pathogenesis of detrusor hyperactivity induced by irritants in rats, and in bladder hypersensitivity disorders and detrusor hyperreflexia in humans. In patients with such disorders, intravesical capsaicin caused a long-lasting symptom improvement (1, 2). It has previously been shown that tachykinins, particularly neurokinin A, seem to be involved at the peripheral level in detrusor hyperactivity induced by irritants (3). In the present study, this hypothesis was tested by studying the effects of intra-arterial (i.a.) and intravesical administration of substance P, neurokinin A, and neurokinin B to unanesthetized, normal rats undergoing continuous cystometry.

METHODS

Female rats were used. A polyethylene catheter was inserted into the bladder through the dome. For administration of drugs, a catheter was implanted into the caudal abdominal aorta. Cystometric investigations were performed the following day without any anesthesia. Intravesical pressure and micturition volumes were

recorded continuously. Drug effects on cystometric parameters were assessed for 60 min and compared with the baseline values, as described previously (4).

RESULTS

Substance P, given i.a. in concentrations of 0.1 and 1.0 nmol x kg^{-1} increased micturition pressure ($p<0.05$, n=7). I. a. neurokinin A , 0.1 nmol x kg^{-1} (n= 6), increased micturition pressure ($p<0.05$), and basal pressure ($p<0,01$), and decreased bladder capacity ($p<0.01$). These changes were still more pronounced after 1.0 nmol x kg^{-1} (n= 12); micturition pressure ($p<0.001$) and basal pressure ($p<0.001$) increased, and bladder capacity ($p<0.001$), micturition volume ($p<0.001$), and residual volume ($p<0.01$) decreased. The neurokinin-2 receptor antagonist SR 48,968 (100 nmol x kg^{-1}) did not suppress the effects of i.a. neurokinin A (1.0 nmol x kg^{-1}; n=7). I.a. neurokinin B (n=7) caused no changes of the cystometric pattern.

Intravesical neurokinin A (10 µM; n=6, but not 1 µM; n=4) increased micturition pressure ($p<0.05$), decreased bladder capacity ($p<0.01$) and micturition volume ($p<0.01$). These effects were counteracted by i.a. SR 48,968 (20 nmol x kg^{-1}; n=6). Intravesical substance P (10 µM; n=5) or neurokinin B (10 µM; n=5) caused no changes in cystometric parameters.

CONCLUSION

Neurokinin A, but not substance P or neurokinin B, stimulated micturition when given intravesically. The effect of neurokinin A was inhibited by the neurokinin-2 receptor selective antagonist SR 48,968, confirming that the effect was mediated by stimulation of neurokinin-2 receptors. Given i.a near the bladder, neurokinin A produced an increase in basal intravesical pressure before initiating micturition, suggesting that the tachykinin had a direct contractant effect on the detrusor smooth muscle. This effect was not observed when the tachykinin was given intravesically, and could not be blocked by SR 48,968. The reasons for this are unclear , but it cannot be excluded that the micturition reflex elicited by i.a. neurokinin A, which caused a pronounced detrusor smooth muscle contraction, was mediated by other pathways than the reflex initiated via the neurokinin-2 receptors stimulated on intravesical administration of the tachykinin. Neurokinin-2 receptors in the urothelium may thus be targets of, e.g., irritants known to produce bladder hyperactivity.

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STRETCH INCREASES SECRETION OF PARATHYROID HORMONE RELATED PROTEIN BY CULTURED BLADDER SMOOTH MUSCLE CELLS

AIMS OF STUDY

Parathyroid hormone-related protein (PTHrP) immunoreactivity is detected in vascular and nonvascular smooth muscle cells [1]. Exogenous PTHrP inhibits smooth muscle contractility [2] and PTHrP gene expression in the rat bladder correlates with the degree of bladder distension [3]. Thus, the synthesis of PTHrP may be regulated by mechanical stretch of the bladder smooth muscle cells. If PTHrP reduces bladder muscle tonicity, it may be involved in the adjustment of bladder compliance during urine storage distension.

METHODS

Smooth muscle cells from the bladder body, base and urethra of the female rat were isolated by enzymatic disaggregation. PTHrP secretion in response to mechanical stretch (10 cpm, 20% elongation) was measured in cell cultures grown in Dulbecco's modified Eagle medium containing 10% fetal bovine serum. Samples from the culture medium, together with protease inhibitors, were analysed for PTHrP by an immunoradiometric assay. Organ bath experiments of isolated smooth muscle strips from the bladder body and the base were performed to investigate direct effects of exogenous PTHrP (1-34) on smooth muscle.

RESULTS

Time-course studies revealed that PTHrP secretion in stretched cells exceeded control levels 4-24 h after initiation of stretch. Maximum secretion was achieved after stretch for 8 h (Figure 1). PTHrP levels in culture medium from bladder body smooth muscle cells increased from 1.9 ± 0.3 pmol/l to 4.4 ± 0.8 pmol/l ($n = 3$, $P < 0.01$) when stretched for 8 h. Cycloheximide (5μg/ml), a protein synthesis inhibitor, inhibited basal and stretch-induced PTHrP secretion. Stretch of smooth muscle cells from the bladder base and urethra also increased PTHrP production (Figure 1).

PTHrP (1-100nM) produced relaxation of carbachol-contracted bladder body and base preparations by 15 ± 2% (n = 4) and 45 ± 4% (n = 4), respectively. PTHrP (100nM) did not affect bladder body contractions elicited by K^+ (124mM) or α-β MeATP (10μM). Concentration-response relations to carbachol (10nM-0.1mM) were also unaffected by PTHrP pretreatment.

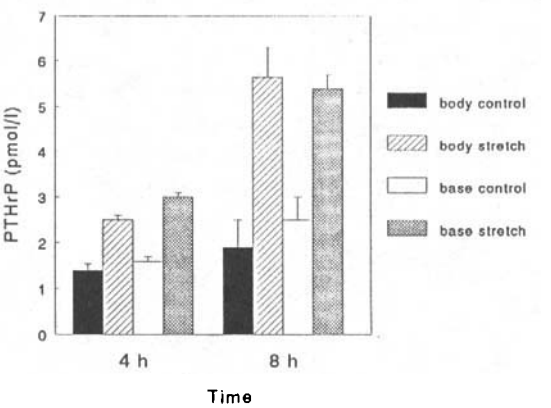

Figure 1. Effects of mechanical stretch on PTHrP secretion by cultured bladder body and base smooth muscle cells. The data shown are from one representative experiment.

CONCLUSION

PTHrP secretion increases in response to stretch of isolated urinary tract smooth muscle cells raising the possibility of an autocrine and/or paracrine action of the peptide. Inhibition of PTHrP production by blockade of protein synthesis indicates that the secreted PTHrP is newly synthesized rather than derived from stored sources. The responsiveness of bladder body preparations to PTHrP was modest, while the relaxant effect of PTHrP in the bladder base was more pronounced. PTHrP may facilitate bladder accomodation during filling by a direct effect on the smooth muscle. In addition, PTHrP may have a paracrine effect on vessels regulating blood flow during bladder distension or modulating the threshold for afferent nerve firing.

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URETHRAL PRESSURE MEASURMENT IN CONSCIOUS AND ANAESTHETISED MINI-PIGS

Aim of study

We believe that the pig is the best animal model for study of the function and dysfunction of the lower urinary tract. We wished to extend the use of this model to obtain baseline urethral pressure data under anaesthesia and to allow urethral pressure measurement in the conscious minipig to validate data obtained in experiments under anaesthesia.

Methods

Female Yucatan mini-pigs were used, some of which had had no previous urethral surgery (control animals), some of which had previously had extraperitoneal partial urethral obstruction with a silver ring placed just distal to the bladder neck (obstructed animals) and some of which had previously had sham obstruction without placement of a ring (sham-operated animals). Conscious urethral pressure was measured with a single catheter-mounted transducer, inserted during a very brief and light halothane anaesthetic and urethral pressure under anaesthesia was measured with two catheter-mounted transducers. Anaesthesia was with halothane and nitrous oxide:oxygen, without premedication. The bladder was filled to 100ml except in some obstructed animals with residual urine of greater than this amount.

Results

Urethral profilometry showed a high pressure zone about 3-4 cm from the bladder neck, distal to the site of urethral obstruction in the obstructed animals. The site of obstruction could seen reliably during profilometry and was distal to the site of maximal urethral pressure ($p_{ura\ max}$). There was no significant difference between $p_{ura\ max}$ in the control, sham and obstructed groups. During urethral pressure profilometry under anaesthesia (1% halothane) in 27 animals, the median $p_{ura\ max}$ was 96 cmH_2O. In continuous recording from the site of $p_{ura\ max}$ under anaesthesia (1% halothane), the median value in 11 animals was 71 cmH_2O. Spontaneous variations in $p_{ura\ max}$ were seen under anaesthesia: the median variation was 5 cmH_2O. Conscious urethral pressures were recorded in 5 sham animals: the median $p_{ura\ max}$ was 60 cmH_2O. In both conscious and anaesthetised animals, $p_{ura\ max}$ fell before a void.

Conclusions

This study has shown that under anaesthesia, the female Yucatan mini-pig has a zone of considerable urethral pressure, higher than that previously obtained in experimental animals. For the first time, urethral pressures have been recorded in a conscious large animal which is a good model of human lower urinary tract function. These values are similar to those seen in conscious women. Spontaneous variations in $p_{ura\ max}$ are seen and $p_{ura\ max}$ falls before voiding. We suggest that this model should be used for further investigation of urethral function and dysfunction.

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MEASUREMENT OF BLADDER STIFFNESS USING A NEW BIOSENSOR IN NORMAL AND CHRONICALLY OBSTRUCTED RABBIT BLADDER

AIMS OF STUDY

We have developed a new sensor made of piezoelectric transducer (PZT), which can measure

the stiffness of biological materials. In the present study, we introduce this biosensor for the evaluation of bladder compliance. Thus, using rabbits, animal experiment was performed to examine the accuracy of this measurement system for bladder stiffness and compare these stiffness data with cystometric compliance data. In addition, we evaluate whether the sensor can detect any changes in bladder stiffness that may be produced as a result of chronic partial bladder outlet obstruction.

METHODS

The principle of stiffness measurement using the sensor is based on the frequency shift (Δf) of the resonant frequency in the vibrating of PZT when subjected to a different loading impedance. Theoretically, the Δf is dependent on the stiffness of the contact region. This Δf was measured by the sensor in rabbit bladder in vivo and calibrated to the actual stiffness which was accurately determined using a displacement transducer. In order to measure Δf and stiffness simultaneously, the sensor was combined with the displacement transducer.

Eight normal rabbits (3.5 to 4.0 kg) were anesthetized with pentobarbital, and their urinary bladders were exposed. Δf and stiffness were recorded from several regions of the empty bladder. Cystometry was then performed to determine the compliance of the whole bladder.

The identical measurements were repeated in the 6 rabbits whose bladder neck had been partially obstructed for 3 to 7 weeks.

RESULTS

In the normal rabbit bladder, Δf from the sensor was -962.5 ± 29.8 Hz while the stiffness calculated from displacement transducer was 4.1 ± 0.14 g/cm. The cystometric compliance of normal bladder was 21.6 ± 4.71 ml/cmH_2O. In the chronically obstructed bladder, compliance was significantly decreased to 5.8 ± 3.25 ml/cmH_2O ($p < 0.05$), whereas the stiffness was significantly increased to $6.803 + 0.887$ g/cm ($p < 0.001$). Associated with this increase in stiffness as well as a decrease in compliance, Δf increased to -650.618 ± 62.118 Hz ($p < 0.001$). The obstructed bladder showed the various degrees of stiffness (5.701 to 8.203 g/cm). These values, including the stiffness of normal bladder, were related to the Δf measured by the sensor. Figure 1 shows the result of this analysis and demonstrates that Δf increased with an increase in stiffness, significantly ($r=0.966$, $p < 0.001$).

CONCLUSIONS

The present study demonstrates that this senor is sufficiently sensitive to the changes in the stiffness of the bladder wall caused by chronic obstruction. Our results suggest that the sensor can predict the stiffness of pathologic bladder which is consistent with the compliance measured cystometrically. The clinical implication of using the sensor is that cystoscopic measurement of bladder stiffness can be made, since the sensor is easily mounted on a ureteral catheter and passed through the cystoscope to bring it into contact with bladder wall.

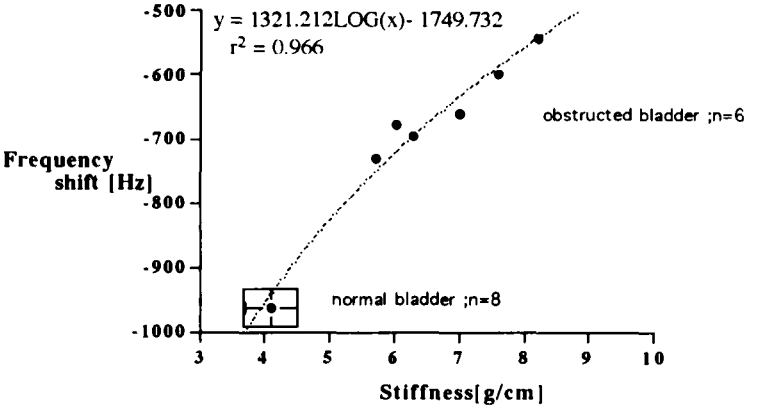

Figure 1 correlation between frequency shift and stiffness

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CONTRACTILE RESPONSES OF THE SEROSAL LAMINA OF THE RABBIT BLADDER FOLLOWING PARTIAL OUTLET OBSTRUCTION.

AIMS OF STUDY:

Partial outlet obstruction of the rabbit bladder stimulates a significant increase in bladder mass and alterations in the contractile responses to autonomic stimulation, and a decreased ability of the bladder to empty efficiently and fully. Structurally, partial outlet obstruction induces an expansion of the serosa to form an extrinsic connective tissue layer (ECT) outside the elastic lamina. Recent studies indicate that mesenchymal cells within this extrinsic layer differentiate into myofibroblasts and subsequently into fetal-type smooth muscle cells after 30 days of chronic partial outlet obstruction. The specific aim of this combined study was to determine if this extrinsic layer of fibrous connective tissue develops contractile properties and to correlate these contractile properties with the histochemical characterization of the smooth muscle cells within the ECT.

MATERIALS AND METHODS:

Partial outlet obstruction in rabbits was surgically created by placing a 8 Fr catheter next to the urethra and placing a 0 silk suture loosely around the urethra. The catheter was removed and the incision closed. At 30 and 60 days following obstruction, each rabbit (N = 6) was euthanized and the bladder surgically excised. The ECT was isolated, dissected free of underlying smooth muscle, and mounted in isolated baths containing 30 ml Tyrode's solution at 37°C containing glucose and equilibrated with 95% O_2, 5% CO_2. After 1 hour incubation, 2 grams tension was placed on each strip and the maximal responses to field stimulation (80V, 1ms, 1--32 Hz), bethanechol (0.1--500 uM), and KCl (120 mM) were determined. The maximal responses of isolated strips of smooth muscle were determined simultaneously. It should be stressed that it is not possible to isolate strips of the serosa from control bladders, and thus these studies do not have any contractile data from control rabbits.

Immunohistochemistry was performed on unfixed cryosections (7 µm thick) of control, 30 and 60 day obstructed bladders. Sections were incubated with the primary antibody [SMA (smooth muscle α-actin); SMD2 (smooth muscle myosin); NMG2 (non-smooth muscle myosin); VI (Vimentin); and D (Desmin)] at 37°C in

a humidified chamber for 30min. Each was then washed 2X with PBS and incubated under identical conditions with the secondary rabbit IgG TRITC-conjugated Ab (Dako, Dakopatts), washed 2X and mounted with Elvanol. Cryosections were inspected with a Zeiss Axioplan epifluorescence microscope.

RESULTS:

The mean weights of the bladders at 30 days after partial outlet obstruction were 11.5 +/- 3.5g; at 60 days it was 18.6 +/- 4 g. The mean weight of bladders from age-matched control rabbits was 2.1+/- 0.4g. All strips of detrusor smooth muscle isolated from the obstructed rabbits responded to FS, bethanechol, and KCl.

The isolated strips of serosa responded with one of two types of response. For the 30 day bladders, 70% of the strips responded only to KCl with a relatively small response (1.1±.2 g/100mg tissue): response type 1. The remaining 30% of the strips responded to both bethanechol and KCl with approximately equal responses (2.0±.5 g/100mgT; 2.4±.4 g/100mgT respectively): response type 2. For the 60 day bladders, there was a shift to approximately 70% of the strips showing response #2 and 30% showing response #1. No strips at either time period gave significant responses to field stimulation.

The ECT of 30 day obstructed bladders was reactive to SMA, and SMD2. These two probes are specific markers for smooth muscle cells (SMC). The ECT was also reactive with NMG2 and VI. These second two markers are for fibroblasts. The ECT at 30 days did not react with D, another specific marker for SMC. The smooth muscle-type cells present in the ECT of the 30 day obstructed bladders can be considered myofibroblasts expressing smooth muscle myosin or SMC of the fetal type.

In contrast, the cells within the ECT of 60 day obstructed bladders contained desmin and was locally negative for NMG2, indicating a maturation towards adult SMC. As the rabbits progressed from 30 days of partial outlet obstruction through 60 days, the serosal cells that contain the smooth muscle-specific proteins organized themselves around the elastic lamina (original serosal lamina) and at 60 days they locally concentrated in small bundles. At neither time period did the serosal lamina react with anti-gynatophysin, a specific marker for neuronal innervation.

CONCLUSIONS:

The results of this study clearly demonstrate that the serosal lamina isolated from rabbits that were partially obstructed for 30 days develop contractile properties. At 30 days, the contractile response is primarily limited to KCl (membrane depolarization) whereas by 60 days the response to KCl increases and a response to bethanechol (muscarinic agonist) develops. The development of the contractile response at 30 days parallels the identification of smooth muscle cell-types within the lamina whereas at 60 days the response to bethanechol parallels the development of adult-type SMC and the organization of the SMC into small muscle bundles. Our current theory is that as myoblasts differentiate into smooth muscle cells, they develop the ability to contract to KCl (generalized depolarization). These smooth muscle cells are isolated from each other and do not have functional muscarinic receptors. As the cells develop and form junctions with other smooth muscle cells, they develop functional muscarinic receptors and thus develop the ability to respond to bethanechol. This clearly demonstrates that muscarinic receptors can develop in the absence of innervation. At 30 and 60 days after partial outlet obstruction, these SMC are not innervated, and thus do not respond to field stimulation. Thus, even though the extrinsic lamina at 30 and 60 days develops the ability to respond to both KCl and bethanechol, without neuronal innervation of the lamina the serosa cannot participate in the neuronal stimulation of bladder contraction.

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EFFECTS OF ACUTE DIURESIS AND DIABETES ON MICTURITION AND BLADDER MASS

AIMS OF STUDY

Studies from many laboratories have demonstrated chronic effects of diuresis on micturition, cystometry, bladder mass, and contractile characteristics. Diabetes mellitus and diabetes insipidus both produce increases in volume of urine excreted, in micturition frequency and bladder capacity, and in bladder mass. In addition, diuresis induced by sucrose in rats or furosemide in rabbits results in qualitatively similar changes. This study examined the temporal relationship between functional changes and the diuresis-induced increases in bladder mass.

METHODS

Diabetes was induced in male SD rats (300-325g) by a single injection of streptozotocin (65mg/kg, ip), and confirmed by monitoring body weight and measurement of urine and serum glucose. Sucrose-diuresis was produced by replacing the drinking water with 5% sucrose in water. Controls received water to drink. Diuresis in male NZW rabbits (2-3kg) was induced by implantation of Alzet 2ML2 osmotic pumps containing furosemide (10mg/ml), infusing 200μg/hr. Each rabbit received 4.8mg furosemide/day. Controls were implanted with saline-containing pumps. Micturition was monitored using metabolic cages. Animals were usually placed in the cages for 2-3 days before starting treatment and then monitored for 7-14 days. Data presented are total daily urine output, mean micturition frequency during the dark cycle (19:00 - 07:00) when the animals are actively feeding and drinking, the maximal micturition volume (which approximates cystometric capacity), and bladder weight determined on separate groups of animals treated as described above. For all groups the data are normalized between the mean value of the group during the control period prior to the onset of diuresis, or of the control group (0%) and the maximal value obtained during the experimental period (100%).

RESULTS

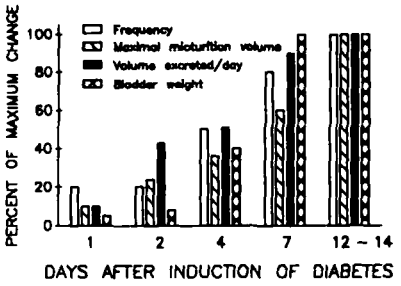
Control rats kept in metabolic cages and drinking water for up to 14 days showed no significant age-related or temporal changes in micturition parameters or bladder weight. Diabetes induced progressive increases in total volume of urine excreted, frequency of micturitions, maximal micturition volume, and in bladder weight (figure 1). 7-14 Days was required for micturition parameters or bladder mass to reach maximal values. In contrast, sucrose-diuresis induced maximal changes in drinking and micturition during the first day, followed by a slight decline and then a gradual increase back towards maximal values (figure 2). The increases in bladder mass occurred more rapidly than those of the diabetics, probably related to the earlier effects on micturition. The effects of furosemide were similar to those observed with sucrose; increases in micturition parameters were maximal within 2-3 days and followed by increases in bladder weight (figure 3). Micturition parameters for control rabbits did not alter significantly over the study period. In all groups, increases in micturition frequency occurred in parallel with increases in maximal micturition volume and total daily urine volume.

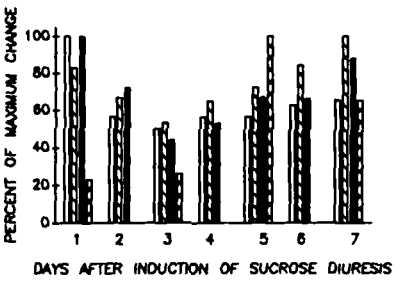
The absolute increase in urine volume was much greater in the diabetic rats than the other 2 groups (13-fold increase vs. 6-fold) (table 1). Similarly, diabetic rats had 5-fold increases in maximal micturition volume compared to 3-fold in the sucrose and furosemide groups. However, the increases in bladder mass were much slower to reach maximal values in the diabetics, even though an increase in maximal micturition volume of the same magnitude as the other 2 groups was seen within 5 days after induction of diabetes, and similar increases in urine volume within 4 days.

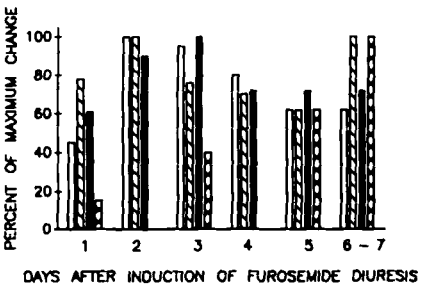
TABLE 1.	Freq (per hr)	Max Vol (ml)	Daily Vol (ml)	Bladder (mg)
Diabetic - Minimal	1.75 ± 0.22	1.20 ± 0.20	16 ± 4	123 ± 4
Diabetic - Maximal	5.35 ± 0.51	6.45 ± 1.37	211 ± 12	214 ± 6
Sucrose - Minimal	1.22 ± 0.19	0.75 ± 0.19	9 ± 2	110 ± 5
Sucrose - Maximal	4.40 ± 0.19	1.92 ± 0.31	55 ± 9	140 ± 10
Furosemide - Minimal	0.15 ± 0.03	27.0 ± 4.1	55 ± 10	1850 ± 160
Furosemide - Maximal	0.88 ± 0.03	82.1 ± 24.4	363 ± 111	2640 ± 300

CONCLUSIONS

Theoretically, an increase in micturition frequency should be sufficient to handle diuresis without any changes in micturition volume. However, in all groups, micturition volume and frequency increased in parallel, and were followed by increases in bladder mass. These findings indicate that the acute changes in the diabetics are unlikely to be due to sensory impairment.







The data indicate that increases in volume, rather than in pressure, are likely to be the initiating event which determines the onset of micturition. In particular, the data obtained with the diuresis-induced animals, when compared to diabetics, suggest that it is the rate of increase in intravesical volume which is primarily responsible for re-setting the micturition reflex.

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HIGH FREQUENCY OSCILLATIONS DURING VOIDING IN THE RAT: SIMULTANEOUS FLOW RATE AND PRESSURE MEASUREMENTS

AIMS OF STUDY

The voiding contraction in the rat is characterized by three phases (see Fig. 1); a rise in bladder pressure, a

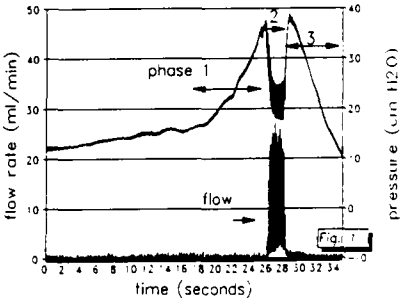
decrease on which usually a series of pressure oscillations are superimposed and a re-rise followed by a decline to base line values [1]. Accurate flow-rate measurements have not been published for the rat and the cause and function of the high frequency pressure oscillations remain unclear. It has been suggested that the oscillations are caused by contractions of the striated musculature of the urethra. In this study, flow-rate measurements with an ultrasonic flowmeter are described. The flow pattern is analyzed in relation to the oscillations in the intravesical pressure.

METHODS

Male Wistar rats (450 g) were anesthetized with urethane (1.2g/kg i.p.). The urinary bladder and the distal part of the urethra were exposed through an abdominal incision. A 24G needle connected to a pressure transducer was inserted into the bladder dome. The bladder was filled using an infusion pump (room temperature saline, infusion rate 0.1 ml/min) while the pressure was recorded through the same needle. A Transonic flow probe was placed around the distal (most superficial) part of the urethra. Both pressure and flow-rate signals were recorded by computer at a sampling rate of 100 Hz. The bladder was filled until the pressure rose steeply or until the first drop of urine/saline appeared. The voided volume was collected in a glass funnel. After voiding, the residual volume was removed from the bladder with a syringe attached to the inserted needle. Sixteen contractions from 3 animals were analyzed. The (statistical) analysis was restricted to the second phase of the voiding contraction which is characterized by high frequency oscillations (t-test, correlation).

RESULTS AND CONCLUSIONS

The pressure and the flow-rate signal are shown in Fig. 1, the three phases of the voiding contraction are indicated by arrows. Fig. 2 shows the second phase of the contraction during which flow took place in more detail. The flow pattern is characterized by several peaks which correspond to changes in pressure. The mean flow rate was 7.0 ± 1.7 ml/min (range 4.5 -10.3 ml/min) (n=16), the maximum flow rate was 35.3 ± 9.0 ml/min (range 26.5-50.0 ml/min). The frequency of pressure and flow oscillations was the same and very constant (mean 7.8 ± 0.5 Hz). Flow peaks coincided exactly with pressure peaks during the oscillations. The first assumption therefore was, that the flow peaks were caused by contractions of the bladder. The high frequency however renders this possibility unlikely. When the magnitudes of the flow peaks were correlated with the previous maximum pressure values (max) during the oscillations, an average correlation of 0.02 was found, when the flow peaks were correlated with the previous minimum pressure values, a significant negative correlation of - 0.31 was calculated. When the flow maxima were correlated with the pressure decrease (max-min) just prior to the flow peak, a highly significant correlation emerged (R= 0.49, $p<0.001$)(Fig. 3). This suggested that a flow maximum corresponds to the previous pressure minimum. Furthermore, because of the length of the urethra, and the position of the probe (about 4.5 cm from the bladder outlet) a time delay has to be considered. The delay between both signals was about 0.08 seconds. Combining this delay with the distance between pressure and flow measuring probes, results in a mean fluid velocity of 0.6 ± 0.1 m/sec.



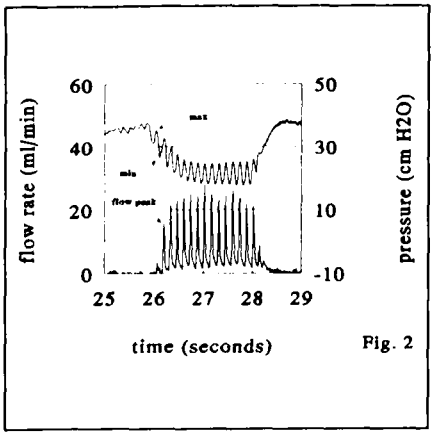


Fig. 2

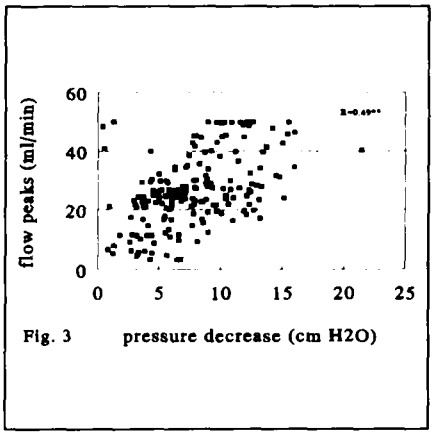


Fig. 3

Our data support the view that the pressure changes in the bladder are caused by contractions of the urethra [1,2]. Opening of the urethra thus causes a flow-rate which in turn causes a decrease in intravesical pressure, bladder contractions do not cause peak flows. Whether the high fluid velocity (0.6 m/sec) of the emitted drops of urine is caused only by the intermittent relaxation of the striated sphincter or by an additional propulsing mechanism of fast travelling contraction waves through the urethral wall, remains as yet unclear.

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AB Medical generously provided a Transonic flowmeter for the experiments described above.

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IN VITRO RESPONSE OF HUMAN BLADDER SMOOTH MUSCLE IN UNSTABLE OBSTRUCTED MALE BLADDERS: A STUDY OF PATHOPHYSIOLOGICAL CAUSES ?

AIMS OF STUDY.

The likely causal link between male bladder outlet obstruction and detrusor instability remains unexplained. Studies (1, 2) have demonstrated a post junctional supersensitivity in animal models, but few studies have identified this in the human. A single study (3) suggested that human bladder muscle that showed unstable characteristics had an altered α adrenergic contractile response to noradrenaline. Previous studies have identified a non-adrenergic non-cholinergic (NANC) response or change in NANC neurotransmitter levels in the unstable bladder. Unfortunately, few studies have looked at the in vitro response of human bladder smooth muscle in the unstable obstructed male due to shortage of tissue. A novel modification of existing technique of muscle collection and in vitrostudy has facilitated the investigation of the above hypotheses on human tissue.

METHODS.

Men on a waiting list for surgery had videocystometrograms, using ICS guidelines and were defined on this basis as either stable obstructed (n=16) or unstable obstructed (n=21) and an age matched control group (n=10), comprised patients undergoing endoscopic bladder procedures with no evidence of bladder outflow obstruction. All entered under

informed consent and local ethical committee approval.

At their operation, cold cup bladder muscle biopsies were taken and set up in tissue baths with Tyrodes solution, at 37°C and gassed with 95% O_2 and 5% CO_2. After 60 minutes equilibration under 1 gram tension the contractile responses were measured using UFI 1030 transducers, using a MacLab 8 system to record and analyse the data.

Cumulative dose response curves were obtained with acetyl choline (10^{-7} - 10^{-3} M) and antagonised with atropine (10^{-8} - 10^{-6} M). The tissue was also field stimulated between parallel platinum electrodes (0.5ms, 40Hz, 15v) and the response to atropine and other antagonists was studied, with Tetrodotoxin to verify the neural response.

Cumulative experiments with the α agonists phenylephrine, noradrenaline and methoxamine were obtained and compared against the cholinergic agonist acetyl choline and K^+.

RESULTS.

Between 4-6 biopsy specimens were obtained from each male bladder with low morbidity (<0.33%). There was a 70% viability rate for tissue at the muscle strip experiments.

EC_{50} values for acetyl choline were 5.2×10^{-4} M for control (n=22 strips), 3.4×10^{-4} M for stable (n=35) and 3.3×10^{-5} M (n=41) for the unstable group ($p<0.0001$). The pA_2 values for atropine varied between 8.0 - 8.9 but there was no statistical difference between the three groups.

Using field stimulation, no NANC response could be found in stable (n=7) or control (n=7) bladder strips. However, 15/21 unstable muscle strips revealed a definite NANC component (25% of the original response), this contraction was eliminated by tetrodotoxin.

The addition of phenylephrine produced no contractile response in the stable (n=37 strips) or control (n=18) groups but 5 of 72 unstable strips contracted. Methoxamine and noradrenaline produced a relaxant or a non response in all of the study groups. Propranolol was also used to block any β relaxant affect, but this did not draw out any further α adrenergic effect. All of the muscle strips studied were demonstrated to be viable as they exhibited a forcible contraction to the application of K^+.

CONCLUSIONS.

This technique of in vitro muscle testing has much to recommend it ; and allows a reliable, safe method for the collection of human bladder smooth muscle in large sample numbers for physiological and pharmacological experiments. In particular, it allows the safe collection of human bladder specimens from routine endoscopic procedures and allows muscle strip experiments to carried out using standard tissue baths and pressure transducers. This should allow research in this area to be more successful and plentiful.

This study illustrates an exaggerated response in unstable obstructed bladder strips to acetyl choline which is likely to be via a post junctional supersensitivity. This agrees with previous animal studies. We have demonstrated an apparent marked NANC component peculiar to unstable obstructed detrusor smooth muscle as opposed to stable or control. This is non-specific and requires further study to localise the possible neurotransmitter involved. This study has been unable to confirm the previous report that there is an α adrenergic contractile response seen in the unstable obstructed human bladder. It therefore seems unlikely that an altered adrenergic response plays a significant role in the genesis of obstructive detrusor instability.

These findings suggest that the pathophysiology seen in detrusor dysfunction associated with the obstructed male bladder is likely to be multifactorial in aetiology. However, this is the first functional work to completely test the above hypotheses in the human bladder obstructed by benign prostatic hyperplasia. Further work should concentrate on human pathophysiological study rather than rely upon extrapolation from animal models.

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THE AMBULATORY MONITORING OF THE UPPER URINARY TRACT: OUR PRELIMINARY RESULTS

INTRODUCTION

The Whitaker investigation measures the pressure in the renal pelvis and bladder while perfusing the omolateral upper urinary tract at a fast urine flow rate (10ml/min).

Considering that the diuresis in the normal is almost 0.7 - 1.5 ml/min it should be noted that the Whitaker test is a non physiological investigation. The aim of this study is to stress the criticism of the Whitaker test and to present the technology and the methodology of the ambulatory monitoring of the upper urinary tract. The preliminary results are reported.

MATERIALS AND METHODS

Since February 1st 1994 a new computerized recording system for the simultaneous ambulatory monitoring of the upper and lower urinary tract has been introduced in our urodynamic practice.

The system (MMS-Medas) continuously records and stores pelvis, vesical, abdominal, detrusoral and urethral pressure signals for up to 24 hours. It consists of a set of 6Fr flexible microtip pressure transducers connected to a microprocessor recorder carried on a belt.

The pelvis pressure microtip patient is connected directly to the nephrostomy while the other transducers are positioned into the bladder, urethra and rectum. The system is completed with the uroflowmeter line (weight-uroflussometry) and leak line (using a thermometric pad). The uroflowmeter is connected to the recorder every time that the patient (pt) is ready for micturition. The basic phase of our trial (not closed at this moment) is to investigate pts without upper urinary tract (UUT) obstruction and pts with UUT obstruction. The pts selected were nephrolithiasis pts with normal renal function and treated by percutaneous surgery .

The holter monitoring was carried out before removing the nephrostomy kept in place after percutaneous treatment in nonobstructive group and before the treatment in obstructive group. The total amount of the ambulatory monitoring investigation time was 21 hrs 7 min. (min.1/2 hr, max 3 hrs 27 min. range 2 hrs 31.8 min.). We report our preliminary results in six UUT nonobstructed and in four UUT obstructed pts.

RESULTS

Ten pts (7 M, 3 F, aged 5+76, mean 44.3) 6 nonobstructed (5 nephrolithiasis, 1 VUR) and 4 obstructed pts (ureteral obstruction) underwent AMUUT (Tab. I). The renal function was normal in all pts (Cr. 0.7+ 1.5 mg/dl). In our data significant difference was observed in pelvis pressure when the pts changed position (clinostatism vs orthostatism and viceversa). So that while the average range in clinostatism the nonobstructed pts was 2 + 19 cm water and in the obstructed was 15 + 39, instead in orthostatism in nonobstructed pts was 5 + 34 and in the obstructed group was 22 + 107. Moreover, as we observed, in obstructed pts the intrapelvic pressure remain always more than 45 cm water and in different events more than 100 cm water when the pressure become symptomatic (renal pain). Comparing the pelvis pressure and detrusoral pressure in pts that had simultaneous recording not variation of the pelvis pressure was noted during bladder filling or micturition in both of the group.

DISCUSSION

It should not be assumed that every dilated upper urinary tract is obstructed but the high intrapelvic pressure is damaging to the nephron.. For this reason the upper urinary tract obstruction needs accurate diagnosis in terms of pressure. A voiding cystourethrogram is an essential part of diagnostic evaluation not only to rule out reflux but also to ensure that no abnormality of the lower urinary tract is responsible for the upper urinary tract dilation.

A radionuclide diuretic renogram is especially helpful in distinguishing nonobstructive from obstructive dilation but not which is the pressure in the system.The Whitaker test could seem to be an excellent method for differentiating nonobstructive from obstructive dilation. Unfortunally, this test has some drowbecks; namely: a) the fast flow-rate, b) the temperature of the irrigation fluid, c) the short investigation time. It is known that many key points of the testing could be altered by a,b,c. Moreover, the geometry of the system, compliance, the step-off pressure between kidney and bladder at the end of the examination, it could be altered in the final evaluation of the test. The above consideration suggest that the holter monitoring can be a more physiological test in upper urinary tract evaluation because: 1.the time of the investigation could be much longer, 2.the irrigation of the system is its own diuresis. 3.the geometry of the system does not change, 4.the temperature is not altered because it is body temperature, 5. the step-off pressure between pelvis and bladder is evaluated in more different time, 6.it is possible to correlate many events during the micturition phase and the pelvis pressure line, 7. the value of the compliance can be more accurate, 8. it allows simultaneous execution of IVP or radionuclide study, 9. much more

Moreover our data seems to show that in the upper urinary tract the pressure significantly changes during daily activities, as showed by AMUUT, otherwise undetcted by traditional Whitaker test. In this view AMUUT will probably allow to understand more in physiology and symptoms of the upper urinary tract.

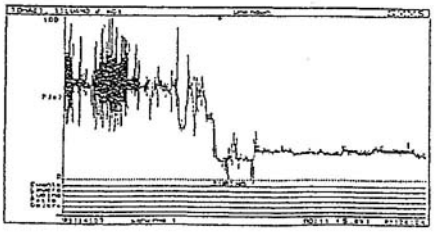
CONCLUSION

The Whitaker test arose from the need to precisely assay the possible presence of obstruction in dilated upper urinary tracts, but many points in methodology are debatable. The simultaneous holter monitoring of the upper

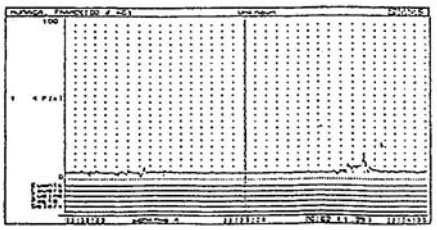
and lower urinary tract seems to be a more physiologic way of evaluating the upper urinary tract.
The comparison of results obtained with the standard Whitaker test and with AMUUT larger series will clarify the indications and value of both methods.

Tab. I

Pts	Age	Pathology	Holter Hours	Timing Mins	Pelvis Clino	Pr Ortho	Pressure lines used
B.B (M)	74	Nonobstructive	2	24	5÷13	29÷34	4 (pyel,ves, ura, rectum
B.A (M)	61	Obstructive	3	27	32÷38	45÷50	4 (" " ")
C.A (M)	33	Obstructive		30		22÷107	1 (pyel)
C.M (F)	5	Nonobstructive	1	30	5÷9	7÷15	3 (pyel,ves,ura)
D.G (M)	76	Nonobstructive	3	23	15÷19	20÷28	3 (")
F.A (M)	57	Obstructive	3	2	20÷24	33÷50	1 (pyel)
M.A (F)	33	Nonobstructive	2	11	4÷7	7÷15	4 (pyel,ves,ura, rect.)
M.F (M)	53	Nonobstructive	2	47	8÷11	25÷33	1 (pyel.)
R.S (F)	19	Nonobstructive	2	28	2÷5	5÷6	4 (pyel,ves,ura, rect.)
T.S. (M)	32	Obstructive	3	16	16÷20	56÷107	1 (pyel)



obstructed



nonobstructed

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RENAL IMPAIRMENT IN MEN WITH URINARY RETENTION DETECTED USING CYSTATIN C: A NOVEL MARKER OF GFR

AIMS OF STUDY

Bladder outflow obstruction can result in upper urinary tract obstruction and renal impairment by glomerular and tubular damage, a decrease in renal blood flow and, thus, a decrease in the glomerular filtration rate (GRF). Serum creatinine is a poor indicator of subtle changes in renal function and creatinine clearance must vary by about 30% for there to be a 95% chance that a real change in GFR has occurred (1). Cystatin C is a low molecular weight protein (13.8 kD) which is synthesised naturally by most nucleated cells. Cystatin C

has been shown to be a better measure of GFR than serum creatinine or creatinine clearance (2). We present the results of a study on the effect of urinary retention on the serum level of this novel marker of GFR.

PATIENTS AND METHODS

Nineteen men (mean age 63 years, range 48 - 80 years) who presented in retention of urine had serum creatinine, cystatin C and GFR measured within 24Hrs of catheterisation. Cystatin C was measured by PETI (Particle Enhanced Turbimetric Immuno) assay. GFR was calculated from iohexol clearance following a bolus injection of iohexol (5.0 ml, OMNIPAQUE® 300mg I/ml). Iohexol concentration in timed (+120, +180, +240 mins) serum samples was measured by HPLC (High Pressure Liquid Chromatography). Calculated GFR was standardised for height and weight and used as a reference against which to compare serum cystatin C levels.

RESULTS

Using the normal ranges for serum creatinine ($\leq$125 μmol/L) and cystatin C ($\leq$1.1 mg/l) the patients could be divided into three groups. Mean ± standard deviation shown. (*P < 0.05 compared to Group A)

GROUP	NUMBER	CREATININE μmol/L	CYSTATIN C mg/l	GFR ml/min
A	11	105 ± 11	0.88 ± 0.11	98 ± 14
B	4	105 ± 13	1.66 ± 0.30*	49 ± 15*
C	4	217 ± 126*	2.36 ± 1.59*	38 ± 19*

CONCLUSIONS

1) Men presenting with urinary retention may have a decreased GFR despite a normal serum creatinine.

2) Serum cystatin C concentration is a more sensitive index of renal impairment than serum creatinine in men with urinary retention.

3) Measurement of serum cystatin C concentration may replace serum creatinine levels in the investigation of men with bladder outflow obstruction.

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A CLINICAL COMPARISON OF THE MEMOKATH PROSTATIC STENT WITH TRANSURETHRAL RESECTION OF THE PROSTATE

AIMS

This clinical study compares the results of insertion of a Memokath with transurethral resection of the prostate (TURP) for the relief of bladder outlet obstruction (BOO) due to benign prostatic hyperplasia (BPH) in elderly or unfit patients.

PATIENTS AND METHODS

The Memokath (R), a second generation intraprostatic spiral stent, is made of NiTinol, a 'memory' alloy with memory for shape, and remarkable thermo-elastic properties that make it easy to insert and, if necessary, remove (1). It is placed over a flexible or rigid telescope and inserted under local anaesthetic. When in position, warm water at 50 C is injected which causes the lower end of the stent to expand, release the telescope and anchor itself in the prostatic cavity.

Between January 1993 and January 1994 a prospective study was performed on 30 consecutive patients who had Memokaths inserted for prostatism due to BPH. All were aged over 75 years (mean 75.9 (+/-7.4), or anaesthetic risk grade ASA (2) III or IV (mean 2.6 +/-0.7). Postoperatively the patients were reviewed at 1 month, 3 months and then six monthly when AUA symptom scores (3) and maximum urinary flow rates were recorded. The same data was collected from 30 age matched patients (mean 74.4 +/-7.6), with a mean ASA grade 2.5 (+/-0.87) who underwent TURP for BPH during the same period. Mean follow up after Memokath insertion was 6.6 months (+/-4.3), and 7.2 months (+/-4.2) after TURP.

Students 't' test was used for statistical analysis.

RESULTS

The Memokath failed in 8 patients due to obstruction by mucosal ingrowth in 5 and migration in 3. This compares with an unsuccessful outcome in 3 TURP patients.

AUA symptom scores in the remaining 22 patients with Memokaths improved from a mean 20.9 (+/-6.4) to 10.1 (+/-7.4) (p=0.0001). In the TURP group the score improved from 15.8 (+/-6.2) to 8.0 (+/-6.3) (p=0.0002). Residual symptoms in the Memokath group were urgency in 2 and unconscious leakage in 1, whilst 3 patients had urge incontinence after TURP.

The mean maximum flow rates improved significantly after TURP from 8.8 (+/-3.2) to 15.2 (+/-7.2) (p=0.0095), but after Memokaths insertion the improvement from 7.9 (+/-2.9) to 10.6 (+/-4.1) did not reach significance (p=0.17) despite good symptom relief.

There were no medical complications after Memokath insertion, but after TURP 2 patients required transfusion, 2 had clinically evident urinary infections, and 1 had a chest infection. Two Memokath patients died of unrelated causes at 4 and 12 months post insertion. The hospital stay was less than 1 day for Memokath insertion, compared to 7.4 days (+/-3.6) for TURP.

Seven patients that obstructed after Memokath insertion were treated with a TURP, and 1 with long term catheterisation. The 3 failures after TURP were treated by repeat TURP (1), catheterisation (1), and self intermittent catheterisation (1).

Even after accounting for the additional cost of treatment of Memokath failures, the cost of a Memokath insertion and follow up was still less than half that of a TURP.

CONCLUSIONS

This study shows that compared to a TURP Memokath insertion is a simple, safe and cheap but less reliable alternative in elderly or unfit patients with BOO.

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Laser prostatectomy: a desobstructing treatment modality?

AIMS OF STUDY

Laser therapy for benign prostatic hyperplasia recently became available. In view of morbidity, this new treatment modality seems preferable to TransUrethral Resection of the Prostate (TURP). To replace TURP, laser therapy of the prostate should at least be able to achieve desobstruction of voiding. The best method to measure the grade of obstruction is pressure-flow analysis. In order to measure the change in obstruction parameters before and 6 months after laser treatment of the prostate, pressure-flow analysis was used.

PATIENTS AND METHODS

Between November 1992 and March 1994, a hundred and ten patients with symptomatic BPH have been treated with laser therapy, using different devices. All patients underwent a full screening program, consisting of patient history, physical examination (including DRE), blood and urine analysis (including PSA), TRUS of the prostate, renal ultrasound, uroflowmetry, and urethrocystoscopy. All patients got a complete urodynamic investigation, including a pressure/flow-analysis (IPSS=International Prostate Symptom Score, Qmax=maximum flow, Atheo=computed urethral area during voiding, Pmuo=minimal urethral opening pressure, URA=extrapolated minimal urethral opening pressure, LPURR=obstruction class according to Schäfer). The same analysis were performed before and 6 months after treatment.

RESULTS

Pessure/flow-data of 27 patients are available for analysis. Baseline characteristics: average age 64.4 years (range:51-76); mean prostate volume (planimetric) of 44.4 (range:24-78); mean PSA-level (Hybritech) is 4,0 ng/ml (range: 1-12).

Changes in subjective parameters, objective parameters and urodynamic parameters are presented in the following table:

	IPSS	Qmax (ml/s)	Residual urine (ml)	Atheo (mm^2)	Pmuo (cm H_2O)	URA (cm H_2O)	LPURR
BEFORE	22.8	8.3	104	2.30	41	47	3.6
AFTER	6.6	18.3	24	7.81	19	19	1.1

Statistical analysis of the parameters showed a p-value < 0.001 for all parameters (Wilcoxon paired-rank test). Although there is a marked increase of the Qmax, this finding is insufficient proof for the desobstructing capabilities of laser treatment. Using pressure flow studies we could unequivocally demonstrate that laser treatment is a desobstructing treatment modality.

CONCLUSIONS

Pressure flow analysis clearly showed that with laser prostatectomy a significant reduction of outflow obstruction can be reached. This is in conjunction with the symptomatic improvement.

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CONTINUOUS OUTLET OCCLUSION TEST: A SIMPLE, CLINICAL URODYNAMIC TECHNIQUE TO ASSESS DETRUSOR CONTRACTILE PERFORMANCE.

Aims of Study: Assessment of detrusor contractility is essential for an accurate characterization of lower urinary tract function. Pressure-flow (PQ) studies are currently used to determine detrusor contractility based on Hill's force-velocity relationship. These tests can be cumbersome and technically not feasible in non-ambulatory and elderly populations. Alternate methods of assessment using the isometric contraction have been proposed, but not widely accepted. We have been using the continuous occlusion test (COT) routinely as an alternate method of contractility assessment, particularly in patients who are not amenable to PQ studies. The aims of this study were to establish the most effective method of generating an isometric contraction and to compare the detrusor contractile performance determined by COT with the performance derived from PQ studies.

Materials and methods: Isometric evaluation and PQ studies were performed in 75 men with prostatism. Three methods of isometric evaluation were performed. The COT was performed by carefully positioning the Coolsaet catheter balloon at the bladder neck prior to the onset of a detrusor contraction. The bladder neck was occluded during the entire detrusor contraction without allowing urinary flow around the catheter. Simultaneous EMG of the external sphincter in 8 patients demonstrated that the striated sphincter remained silent during the COT, indicating a lack of inhibitory feedback and possible facilitation of maximum detrusor activation. In each patient, additional isometric tests were conducted during separate contractions by voluntary interruption of flow (VIF) and by balloon occlusion of the bladder neck (BOBN) during the mid-voiding phase[1]. The magnitude of the isometric contraction (P_{iso}), the maximum slope of the detrusor contraction ($\Delta P/\Delta t$), and the nature of the detrusor activation were determined. In the same patient, pressure-flow studies were performed and contractility parameters (WF[2], estimated P_{iso}, estimated velocity of shortening[3],Schäfer's contractility nomogram[4]) were derived. Correlations were made between the contractility parameters derived from the COT, VIF, BOBN, and PQ studies.

Results: P_{iso} was significantly higher using the COT compared with VIF ($p=0.001$, $n=45$) . P_{iso} and $\Delta P/\Delta t$ determined from BOBN were not significantly different ($n=63$) from those derived from COT. P_{iso} and $\Delta P/\Delta t$ derived from COT were significantly correlated with the estimated P_{iso} and estimated velocity of shortening derived from PQ studies, respectively ($r=0.79$, $p<0.001$ and $r=0.55$, $p<0.001$). WF calculated from PQ studies showed good correlation with P_{iso} derived from COT ($r=0.64$, $n=49$). Contractility parameters using BOBN and VIF showed weaker correlations with parameters derived from PQ studies.

Conclusion: The COT appears to provide the best method of generating consistent isometric contractions. With the BOBN and VIF, sudden changes in the outlet during the mid-voiding phase may

cause discomfort and reflex inhibition of detrusor activation, thus precluding a more accurate determination of contractility parameters. The good correlations between the contractility parameters derived from COT and PQ studies indicate that the COT can be used effectively as an alternative to PQ studies to assess detrusor contractile performance.

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POST-NATAL CONTINENCE SURVEY AT GENERAL PRACTITIONER CLINICS IN THE UK

AIMS OF THE STUDY

There is an increasing trend in the UK for post-natal examinations to be carried out by the general practitioner (GP). However, only 14% of women readily admit to stress incontinence to their GP. This study aims to investigate the prevalence of incontinence in women presenting to their GP for post-natal review and to identify any significant aetiological factors.

PATIENTS AND METHODS

A total of 565 women attending their GP for post-natal check-up took part in this multi-centre study. A self-completed questionnaire detailed information on continence, age, parity, weight of baby, mode of delivery and incidence of epidural anaesthesia.

RESULTS

The sample consisted of 272 (48%) primiparous and 293 (52%) multiparous women, and 106 (19%) of the total population reported bladder problems (such as leaking when coughing or sneezing) at a mean of 7 (sd 2) weeks post-partum. There was no significant difference between the incidence of incontinence in the primiparous (17%) and multiparous (20%) women. A comparison of the primiparous and multiparous women showed that the two groups are

different in the respect of maternal age, weight of baby and mode of delivery. Therefore, in order to investigate the aetiological factors appropriately, only the data from the primiparous women was further analysed and this is shown in the table. Statistical comparisons are by the Chi-squared test.

Essentially the results show that neither baby weight nor epidural anaesthesia are significant factors in the development of bladder problems in the primiparous group. However, there is a significant increase in the prevalence of these problems with maternal age in this group. Additionally, it can be seen that mode of delivery significantly influences the incidence of bladder problems and, if this is analysed in detail, the women who had a forceps delivery are more likely to end up with bladder problems at the post-natal review ($p = 0.03$). Only 4% of the primiparous women with bladder problems had them before pregnancy and this is significantly less than the 44% whose problems started during pregnancy or the remaining 52% whose problems developed after the birth ($p = 0.0001$ and $p = 0.00002$ respectively).

FACTOR	BLADDER PROBLEM	NO BLADDER PROBLEM	SIGNIFICANCE
MATERNAL AGE			
Under 20	4 (9%)	42 (91%)	
20 - 30	30 (17%)	149 (83%)	p = 0.04
Over 30	13 (28%)	33 (72%)	
BABY WEIGHT (kg)			
Under 3.2	14 (14%)	85 (86%)	
3.2 to 3.6	19 (19%)	81 (81%)	p = 0.58
Over 3.6	14 (19%)	58 (81%)	
TYPE OF DELIVERY			
Normal	28 (15%)	159 (85%)	
Forceps	13 (31%)	29 (69%)	p = 0.02
Caesarian	4 (11%)	32 (89%)	
Other	2 (50%)	2 (50%)	
EPIDURAL ANAESTHESIA			
Epidural	22 (21%)	84 (79%)	p = 0.29
No Epidural	24 (15%)	136 (85%)	

TABLE. ANALYSIS OF DATA FROM PRIMIPAROUS WOMEN

CONCLUSIONS

1 in 5 women visiting their GP for post-natal review have urinary incontinence. Because the majority of these women fail to volunteer urinary problems, GP's need to be aware of their prevalence and specifically ask about them. For many, incontinence will arise from pelvic laxity due to unavoidable childbirth trauma to the pelvic floor and its nerve supply. Referral to a physiotherapist specialising in the strengthening of the pelvic floor muscles may be the most appropriate therapy.

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AGE ASSOCIATED CHANGES IN DETRUSOR SENSORY FUNCTION IN WOMEN WITH LOWER URINARY TRACT SYMPTOMS

AIMS OF STUDY

It is known that ageing is accompanied by changes in motor function of the lower urinary tract, that sensory fibres run in close association with motor fibres [1], and that changes in sensory function occur in association with dementia [2]. This study aimed to examine a urodynamic measure of bladder sensation in relation to age and lower urinary tract pathology.

PATIENTS AND METHODS

Urodynamic studies were performed on 1708 adult women presenting to an incontinence clinic with symptoms of lower urinary tract dysfunction. Patients with diabetes mellitus or diseases of the nervous system were excluded. A water cystometrogram was done, during the filling phase of which subjects were asked to indicate the point at which they first felt a desire to void. The volume infused so far, the bladder capacity at first desire to void (BCFDV), was taken as a measure of bladder sensation. Where physically possible, before voiding, the urethral meatus was inspected during coughing whilst standing to detect leakage indicative of genuine stress incontinence.

Statistics: classification data were analysed for differences between groups using the Chisquare test with Yates' correction. The median with 95% confidence intervals was used to describe the distribution of quantitative data. Comparison between age groups was achieved with the Kruskal-Wallis test, quoting the test statistic H and the degrees of freedom. The 95% level of confidence was used to reject the null hypothesis.

RESULTS

1708 women with lower urinary tract symptoms were studied, mean age 54.3 years (sd=16.7,range 20-95). Detrusor instability was present in 1141 (66.6%) patients and absent in 567 (33.3%), the incidence being higher in older age groups (χ^2=55,df=7, p<0.01). Testing for genuine stress incontinence was possible in 1249 (73%) patients, being present in 524 (31%) and absent in 725 (43%). Testing was precluded in 459 (27%) patients by uncontrolled unstable detrusor contractions.

Maximum bladder capacity fell from the seventh decade onwards (H=121, df=7,p<0.001), but capacity at first desire to void (BCFDV) rose from the third to the eighth decade, then dropped significantly in the ninth and tenth (H=30,df=7,p<0.001).

This age related rise in BCFDV was well seen in patients with unstable bladders (H=26.4,df=7,p<0.001), or stress incontinence (H=20.5, df=7,p=0.005), or both (H=17,df=7,p=0.019), but was less clear in those without instability (H=18,df=7, p<0.01) or without stress incontinence (H=12,df=7,p=0.1).

Those who could not be tested for stress incontinence had lower bladder capacities (median=350mls,95% C.I.=320,375) than those who could be tested, regardless of result, and no age-related differences in BCFDV (H=9,df=7,p=0.255). Vaginal atrophy rose with age, (χ^2=331,df=7, p<0.001), whereas anterior vaginal wall prolapse fell (χ^2=65,df=7,p<0.001). In those with prolapse there was no age-related difference in BCFDV (H=7.9,df=7,p=0.35), and a low overall median value of 141.5mls (95% C.I.=129,150). A history of gynaecological surgery did not influence the results.

CONCLUSION

This study provides evidence that total bladder capacity is reduced in association with old age in women with symptoms of lower urinary tract dysfunction. By contrast, bladder capacity at first desire to void increases with age in women with stress incontinence and/or detrusor instability from the third decade until at least the eighth decade, falling in the ninth decade in those with detrusor instability, possibly due to the overriding influence of a fall in total bladder capacity.

This increase with age in bladder capacity at first desire to void suggests a decreased sensitivity to filling, although the frequency and urgency seen in the elderly might have led one to expect the opposite.

As our patient selection eliminated those with overt neurological disease it is likely that the defect in sensation lies peripherally, either in the bladder wall, mediated by changes in the density or balance of neurotransmitters, or alternatively in the proximal urethra, where evidence of defective function has been found.

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BLADDER INSTABILITY- A CHAOTIC RESPONSE OF THE URINARY CONTROL MECHANISM

AIMS OF STUDY To explain a much greater incidence of urine loss(p<0.005) after hand-washing provocation in a group with low bladder compliance on filling cystometry, as opposed to a similar group with detrusor instability(DI), in terms of the Chaos theory and the micturition reflex.

MATERIALS AND METHODS Fast fill subtracted cystometry(ICS standards and nomenclature) using Gaeltec microtransducers was performed on 169 women with urinary incontinence using a 5 channel Ormed system 5000. Mean age:50 yrs (35-71 yrs), mean parity 2.6.After filling to 500mls or point of discomfort,the patient,with transducers in situ,washed her hands at a sink. RESULTS DI was noted in 40 patients during filling cystometry; 24 (60%) of these actually lost urine following hand-washing.Of 16 patients with a low compliance bladder,13 (81%)lost urine on hand-washing. Using the X^2 test, X^2=23.59 with 1D.F. the difference between the detrusor instability and low compliance groups is highly significant(p <0.005). Mean cystometric capacity: DI group:448mls (range 191-545 mls);for the low compliance group:459 mls (range 381 - 500mls).

DISCUSSION It is generally accepted that, in the main, both DI and low compliance patterns reflect the detrusor's reaction to filling..i.e., despite statistical differences between the two groups,it is likely that smooth muscle contraction lies at the core of both conditions, especially as bladder smooth muscle predisposes to tonic contraction(1).It is hypothesized that:there are two chaotic"attractors"(2)for the micturition control system,"open"(O)and"closed"(C) FIG1.Micturition is a classical"feedback" system, FIG2."Open"(O), unbroken lines = micturition reflex; "closed"(C),broken lines = musculo-elastic closure force(S) *plus* a discrete cortical inhibitor,also"C,but equating with "r"in the iterative equation.It is hypothesized that filling activated the detrusor to contract in both groups.

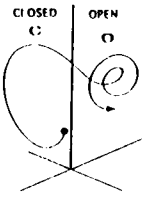


FIG 1

In the low compliance group of 16 patients("stable closed"), FIG3,contraction of the striated sphincter "S",FIG2, during filling closes urethra firmly,resulting in raised detrusor pressure(3).i.e,the micturition reflex was totally controlled and was urodynamically expressed with a low compliance pattern.The DI pattern seen in 40 patients during filling indicates that the micturition reflex has

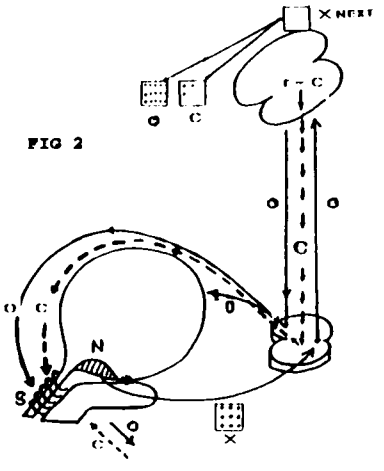
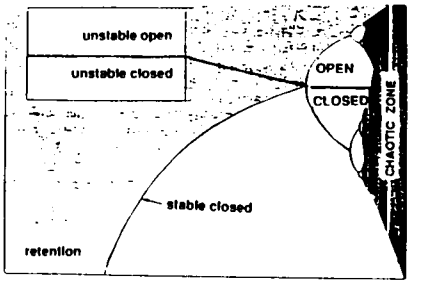


FIG 2



$$X_{NEXT} = r\,X\,(1-X)$$

FIG 3

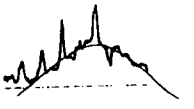


FIG 4

$$X_{NEXT} = r\,X\,(1-X)$$

overcome the"stable closed" mode, FIG3. The system is swinging between"unstable open",and "unstable closed" modes,FIG3,(or"O"and"C,FIG1),urodynamically expressed in a detrusor instability pattern,FIG4.The time delay inherent in

feedback systems allows "C", FIG2, to act,temporarily reverting the system to the "closed" attractor,FIG1, creating the classical bell-shaped curve of a feed-back system,FIG4.Feedback can be quantitatively expressed in the iterative equation,$X_{next}=rX(1-X)$."r", a constant for a set circuit, can be equated to a valve, regulating how many"X" impulses deriving from nerve stimulation at "N" pass through.The cortical inhibitor(broken arrows) functions as this valve. As "r" increases beyond 3,X_{next} breaks into 2 cycles,"unstable open", and "unstable closed", FIG3, then into 4, 16 cycles, until the chaotic zone is reached. Even there, periods of regularity may be seen. This concept explains how many patients with even quite severe bladder instability (having entered the chaotic zone,FIG 3) may have periods of normal function from time to time.The sharp rises in urine loss with "handwashing" in 13 low compliance patients can be explained by hand-washing suddenly counter-acting the discrete cortical inhibitor.This sharply swings the system from "closed" to "open", FIG1.

CONCLUSION Broadening the concept of DI to include non-linear (chaotic) control systems may help explain many anomalies found in this subject.

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THE ANTIDIURETIC EFFECT OF IMIPRAMINE IN ADULT NOCTURNAL ENURESIS.

AIMS OF STUDY

Patients suffering from primary monosymptomatic nocturnal enuresis are often characterized by polyuria at night. The polyuria seems frequently to be caused by a diminished nocturnal increase in the secretion of antidiuretic hormone, arginine-vasopressin (AVP) (1). The mechanisms behind the defect circadian rhythm are still unsolved. Medical treatment of nocturnal enuresis includes DDAVP, a synthetic vasopressin analogue or imipramine. Where DDAVP substitutes a relative lack in nocturnal plasma vasopressin levels, the mode of action of imipramine in nocturnal enuresis is still unknown.
Previous studies of renal excretion of vasopressin suggest that imipramine increases vasopressin secretion (2,3). However the effect of imipramine on diuresis and plasma vasopressin levels is still unknown. The aim of the present study was to test the hypothesis that imipramine causes antidiuresis induced by increased vasopressin secretion.

PATIENTS AND METHODS

In 16 adult patients (mean age 23y, range 15-48y) with primary monosymptomatic

nocturnal enuresis and 10 healthy controls (mean age 27y, range 24-32y) studies of nocturnal plasma vasopressin levels, urine volume and composition were performed before and after treatment with imipramine (1 mg/kg BW perorally at 8 p.m.). During both studies the subjects received a standardized fluid intake of 25 ml/kg BW/24h. All patients had a frequency of 3 or more wet nights per week and showed a normal urinary flow rate and urinalysis.

RESULTS

Without treatment patients with nocturnal enuresis did not have a significantly larger urine production than normals (0.94± 0.51 vs. 0.59± 0.25 ml/kg BW/h, n.s.) although their urine was less concentrated (546± 226 vs. 803± 181 mosm/kg, p <0.05). Imipramine did not reduce urine output in normals (0.59± 0.25 to 0.62± 0.25 ml/kg BW/h, n.s.). However, in the patient group a significant reduction in urine output was seen (0.84± 0.46 to 0.64± 0.34 ml/kg BW/h, p <0.05). Analogously, reciprocal changes were observed in urine osmolality in this group after treatment (597± 220 to 700± 291 mosm/kg, p <0.05). The administration of imipramine was not associated with an increase in plasma vasopressin in any of the groups.

CONCLUSIONS

An antidiuretic effect of imipramine was demonstrated in adult nocturnal enuretics. The antidiuretic response does not seem to be caused by increased pituitary release of vasopressin as no changes in plasma vasopressin levels were detectable. This indicates different modes of action of imipramine and DDAVP although both drugs probably depend on reduction in urine output for complete treatment response.

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TREATMENT OF URGENCY AND INCONTINENCE IN ELDERLY PATIENTS WITH PROPIVERINE HYDROCHLORIDE

AIMS OF THE STUDY

Verification of the efficacy of Propiverine hydrochloride (Prop) in the therapy

of urgency and urge-incontinence by final assessment by the patient and the treating physician compared with the results of a non-invasive urodynamic method (uroflow). This limitation of urodynamics was accepted because of the intensive cardiologic investigations (four times 24h-ECG) carried out in the internal part of the study.

STUDY DESIGN

The study was designed as double-blind, randomized, placebo-controlled parallel group trial. After 14 days of placebo wash-out patients received placebo or Prop (15 mg t.i.d.). Uroflows (twice on each trial day) with sonographic determination of the residual urine were carried out on day -14 (visit 1), on day 0 (visit 2), both under placebo, and during treatment phase on day 6 (visit 3, reaching saturation level) and on day 28 (visit 4, steady state level). Urological investigations and detailed psychometric evaluations were performed approx. 1h to 4h after morning dose. Additional parameters: Gaudenz questionaire (visit 1, 2, 4), laboratory (visit 1, 2, 4), micturition diary throughout the study, trough level of trial drug on visit 4.

PATIENTS

Age above 60 years, both sexes, suffering from urgency or urge-incontinence. Micturition volume between 100 ml and 300 ml and residual urine volume <20% of micturition volume on visit 1.

RESULTS

1. The ***final assessment*** on visit 4 by patient and investigator (under double-blind conditions) showed a most significant difference between placebo and Propiverine hydrochloride for the improvement of the urgency (n = 93) and incontinence (additional in 76 of 93 patients). But also the clinical symptoms of the patients in the placebo group improved, due to the preoccupation with their micturition habits and regimen (table 1). Without symptoms of urgency or improved were 89% in verum, 48% in placebo group (investigator's assessment 85% and 43%). Without incontinence or improved were 89% in verum, 47% in placebo group.

table 1: no. of *assessments* on visit 4

	URGENCY, n = 93				**INCONTINENCE**, n = 76			
	VERUM		PLACEBO		VERUM		PLACEBO	
assessed by	inv.	pat.	inv.	pat.	inv.	pat.	inv.	pat.
free of sympt.	14	12	04	05	18	18	10	10
improved	26	30	16	17	16	16	08	08
unchanged	07	05	26	24	04	04	20	20
worsened	00	00	00	00	00	00	00	00
total no.	47	47	46	46	38	38	38	38

2. The ***micturition volume*** increased in the placebo group from 195 ml on average (visit 1) to 221 ml (visit 4), in the verum group from 188 ml to 239 ml. The differences were as well as the changes in residual urine volume and in peak flow statistically not significant.

3. The evaluation of the ***micturition diaries*** resulted not in a statistically significant difference between verum and placebo. Reasons for the missing significance could be the large variability of external influences on urgency and miction resulting in a large standard deviation and the partly incomplete recor-

ding of micturition data by the patient.

4. The intraindividual comparison of the ***stress- and urge-scores*** of the ***Gaudenz*** questionaires on visit 2 and 4 showed a decrease of the urge-score and an increase of the stress-score. The changes in the verum group were significantly higher than in the placebo group.

table 2: relative change of Gaudenz-scores from visit 2 to visit 4 (n = 82)

	VERUM	PLACEBO
Urge	-6.1	-1.0
Stress	+4.0	+1.2

CONCLUSIONS

Even if uroflow is often used in diagnostic procedures considering the lower inconvenience for the patient compared to invasive methods, it was not a suitable method to prove the efficacy of the therapy of urgency and incontinence.

The evaluation of patient's micturition diaries was affected by the incompleteness and low reliability of the redording of such data.

The final assessment by patient and treating physician under double-blind conditions proved the benefit of the therapy with Propiverine hydrochloride with a high level of significance. This result was confirmed by the scores of the Gaudenz questionaire. Despite the non-significant results of the chosen urodynamic method we consider the level of improvement of the clinical symptoms to be important for the life quality of patients with urgency and incontinence.

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POSSIBLE INDUCTION OF CARDIAC DYSRHYTHMIA IN ELDERLY PATIENTS UNDER THERAPY WITH PROPIVERINE HYDROCHLORIDE

AIMS OF THE STUDY

Propiverine hydrochloride (Prop) is used for therapy of urgency and urge-incontinence because of its anticholinergic and spasmolytic effects, assuming a Calcium-antagonistic mechanism. In recent literature Terodiline hydrochloride (Ter), used for the same indications, was suspected to induce disturbances of heart rhythm (torsades de pointes), but evidence was not provided until now. Even if chemical structures are different, this study was initiated to prove the safety of Prop in the therapy of urgency and incontinence of elderly patients.

STUDY DESIGN

The study was designed as double-blind, randomized, placebo-controlled parallel group trial. After 14 days of placebo wash-out patients received placebo or Prop (15 mg t.i.d.). 24h- ECGs were carried out from day -14 to -13 (vis1), from -1 to day 0 (vis2), both under placebo, and during treatment phase from day 6 to 7

(vis3, reaching saturation level) and from day 27 to 28 (vis4, steady state level). All ECGs were recorded with the same type of recorder (Holter recorder mod. 2448/2, ela medical) and were sent to Cologne for central evaluation.

PATIENTS

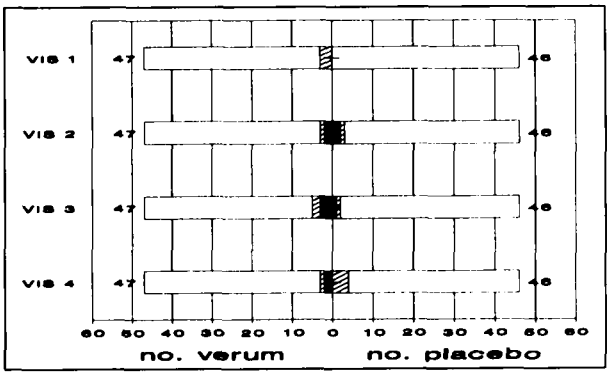
Age ≥ 60 years, both sexes, Lown classes 0 up to IVa on visit 1, no severe heart diseases, no pathological changes of electrolytes. Patient suffered from urgency or urge-incontinence.

RESULTS

93 patients (47 verum, 46 placebo) were evaluable, 73 of them belonged on all visits to the Lown classes 0 to IIIb.

graph 1: Lown classes

- IVb
- IVa
- IIIb - 0



20 patients belonged to Lown class IVa or IVb, but 7 only during wash-out phase (table 1, group 1). Two of the remaining 13 patients belonged to classes IVa/IVb during wash out and treatment phase (table 1, group 2). 11 patients showed Lown classes IVa/IVb only during treatment phase (table 1, group 3), 6 of them belonged to the verum group, 5 to the placebo group.

table 1: patients with Lown classes IVa, IVb
(C = 1x couplett, T = 1x triplett, S = 1x salve per 24 hours)

PHASE ●	WASH OUT		PLACEBO		WASH OUT		VERUM	
VISIT ●	1	2	3	4	1	2	3	4
group 1: IVa, IVb only during wash out phase	I	IVa(C)	0	0	IVa(C)	IIIb	IIIb	II
	0	IVb(T)	0	0	IIIb	IVb(C,T)	I	II
					I	IVb(S)	I	0
					IVa(C)	I	0	I
					I	IVa(C)	I	0
group 2	0	IVb(S)	0	IVa(3C)	IVa(4C)	IIIa	IVa(3C)	IIIa
group 3: IVa, IVb only during therapy phase	I	I	IIIb	IVa(C)	I	I	IIIb	IVa(C)
	0	0	0	IVa(C)	I	I	I	IVb(T)
	I	IIIa	IVa(C)	IIIa	I	I	IVa(C)	0
	IIIa	I	I	IVa(2C)	I	0	IVb(T,S)	0
	I	0	IVb(S)	0	0	0	IVb(S)	I
					0	I	IVb(C,T)	IVb(T)

In none of the patients the cardiac dysrhythmia was longer lasting, all events consisted of one, two or three ventricular extrasystoles within 24 hours, which is not more than the rate of the spontaneous variability.

Heart rate (F[min], F[max], F[average]) was also not influenced by study medication.

CONCLUSIONS

The distribution of cardiac events, i.e. Lown classes IVa and IVb, to both groups - placebo and Prop - is accidental and indicates no development during treatment phase. The other ECG parameters as well indicate no difference between Prop and placebo. Therefore it can be assumed that Propiverine hydrochloride does not induce any disturbances of the heart function, which is important for the safety of the therapy of urgency and incontinence of elderly patients.

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ANTICHOLINERGIC THERAPY: THE NEED FOR CONTINUED SURVEILLANCE.

AIMS OF THE STUDY

There are many different treatments available for the management of detrusor instability, a testament to the fact that none is perfect, and all have their disadvantages. Drugs with anticholinergic properties are commonly prescribed for this condition, and studies have shown that they improve both urodynamic parameters and urinary symptom scores. The major drawback of anticholinergic medication is the accompanying antimuscarinic side effects, which may limit the compliance with treatment of many women.

Unfortunately the majority of studies of anticholinergic therapy have been performed under the costly and inevitably short term constraints of the controlled clinical trial. As a consequence there are little data available regarding the duration of treatment compliance, long term efficacy, and which patients are most likely to comply with and benefit from treatment. The aims of this study were to assess the medium term subjective efficacy of anticholinergic therapy, the frequency or treatment limiting side effects, and risk factorss for treatment failure.

METHOD

191 women with videourodynamically diagnosed detrusor instability (134) or idiopathic low compliance (57) and symptoms of urgency and frequency of micturition were included in the study. All women completed the Nottingham Health profile a generic health status questionnaire, and the Hospital Anxiety and Depression scale (HAD) a psychological status questionnaire prior to videourodynaic investigations. Following urodynamic investigation women were commenced on conventional anticholinergic therapy with outpatient bladder drill by the investgating doctor or their referring clinician. Nine to twelve months following diagnosis women were contacted again and asked to complete a detailed urinary symptom and outcome questionnaire and a further copy of the NHP.

RESULTS

The mean age was 39.4 years (range 19 years - 72 years) and the mean duration of symptoms 3.8 years. Only 13 (6.8%) women felt that their condition had completely resolved, 94 (49.2%) that it had improved, 73 (38.2%) were the same, and 11 (5.8%) worse. Nine (4.7%) women had used anticholinergic for less than 2 weeks, 61 (31.9%) for less than 1 month, and 117 (61.3%) for less than 3 months. 71 (37.2%) women had discontinued treatment due to unacceptable side effects and of these 33 (46.5%) had used treatment for less than 1 month, although 37 (52%) felt that medication had been helpfull whilst they could tolerate it. The presence of residual urinary symptoms for all patients is shown in Table 1. Even disregarding women discontinuing treatment due to side effects the results of treatment were poor (urgency 40%, frequency 35%, nocturia 22.5%, urge incontinence 25%)

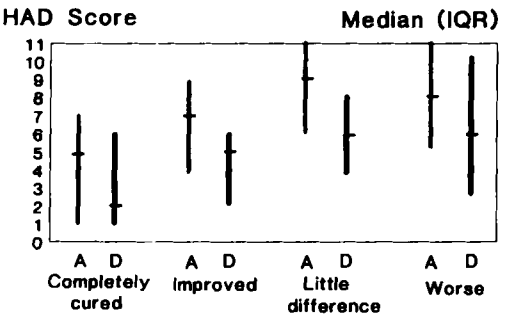
Table 1. Urinary symptoms 9-12 months following urodynamic diagnosis and commencement of anticholinergic therapy. (n=191)

SYMPTOM	% (n)
Frequency (>7x/day)	41.4 (79)
Urgency	45.0 (86)
Nocturia (>=2x/night)	35.6 (68)

SYMPTOM	% (n)
Urge Incontinence	28.8 (55)
Protective pad usage	43.9 (84)
Urinary symptoms problematic	47.1 (90)

There was no significant correlation of age and treatment outcome although women with a shorter duration of symptoms were significantly more likely to be cured or significantly improved ($p<0.05$ Kruskall Wallis 3df). NHP scores showed that women who considered their general health to be good or very good were more likely to be cured, as were women with lesser degrees of work, homelife, social, sexual, and recreational impairment. Results of Part 1 of the NHP showed that women with higher scores in the domains of energy, and emotion, were significantly more likely to fail to respond to treatment ($p<0.05$ Kruskall Wallis 3df). HAD scores showed similar results and women with higher levels of anxiety and depression were more likely to have a poor treatment outcome (Figure 1).

Figure 1. HAD score and treatment efficacy. A=Anxiety, D=Depression. ($p<0.01$ Kruskall Wallis 3df)



CONCLUSION

The medium term subjective efficacy of anticholinergic therapy in this study is disappointing, and failed treatment and residual urinary symptoms are common. Antimuscarinic side effects are a major obstacle to the success of anticholinergic therapy, and hopefully the introduction of sustained release, intravesical instillation, and other routes of administration may partly overcome this problem. Women with a longer duration of symptoms, greater levels of anxiety and depression and poorer quality of life are less likely to be cured. The longer term assessment and review of the treatment of detrusor instability is essential if we are to understand these problems and maximise our treatment efficacy.

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THE IN VITRO PHARMACOLOGICAL PROFILE OF TOLTERODINE-A NEW AGENT FOR THE TREATMENT OF URINARY URGE INCONTINENCE.

AIMS OF STUDY

Tolterodine, (+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, is a new muscarinic receptor antagonist intended for the treatment of urinary urge incontinence. The present investigation was undertaken to characterize the basic pharmacological profile of tolterodine *in vitro*.

METHODS

The affinity of tolterodine for muscarinic receptors was determined both in functional *in vitro* studies on isolated urinary bladder strips using carbachol as agonist and in radioligand binding studies using (-)^{3}H-QNB as tracer on homogenates of urinary bladder and parotid gland from guinea pigs. Potential effects of tolterodine at α-adrenergic and histamine receptors were evaluted in the rat portal vein (*vs.* noradrenaline) and guinea pig ileum (*vs.* histamine), respectively. Calcium antagonist properties were evaluated in isolated urinary bladder (K^{+}-*depolarisation*), spontaneously beating right atrium and electrically paced papillary muscle from the guinea pig.

RESULTS

Tolterodine effectively (IC_{50}: 14±0.4nM, n=5) inhibited contractions of isolated urinary bladder strips induced by carbachol (3μM). The concentration-response curve to carbachol was shifted in parallel, towards higher concentrations, in the presence of tolterodine (30-500nM). The maximal contractile response to carbachol was, however, not depressed. This is consistent with a simple and competitive mechanism of action at the bladder muscarinic receptors. The affinity of tolterodine for bladder muscarinic receptors determined in the functional studies (K_B:3.0±0.2nM, n=15) was virtually identical to that of oxybutynin (K_B:4.4±0.6nM, n=14).

The radioligand binding studies confirmed this, since tolterodine and oxybutynin were found to bind with similar affinities to the muscarinic receptors in the bladder (Table 1). However, with respect to its binding affinity in the parotid gland, tolterodine was 8 times less potent than oxybutynin (Table 1).

Table 1. Affinity (K_i, nM) for muscarinic receptors, determined by radioligand binding studies in guinea pig urinary bladder and parotid gland*)

Drug	Urinary bladder	Parotid gland
Tolterodine	2.7 ± 0.2	4.8 ± 0.3
Oxybutynin	4.0 ± 0.4	0.62 ± 0.05

*)Data are mean ± SEM of 5-6 experiments

Tolterodine was found to be highly selective for muscarinic receptors. Thus, blockade of α-adrenergic (portal vein IC_{50}: 2800±220nM, n=5) and histamine (ileum IC_{50}: 380±61nM, n=5) receptors could be demonstrated only at concentrations much higher than those needed for a complete inhibition of carbachol-induced urinary bladder contractions (IC_{50}: 14±0.4nM, n=5). Similarly, the calcium antagonist activity of tolterodine (urinary bladder: IC_{50} 6500±530nM n=5; atrium: IC_{50} 5200±390nM n=5; papillary muscles: IC_{50} 6800±1200nM n=3) was approximately 400 times lower than its antimuscarinic activity in the bladder.

CONCLUSIONS

Tolterodine is a potent and competitive muscarinic receptor antagcnist, without significant activity at α-adrenergic receptors, histamine receptors or calcium channels. With respect to its antimuscarinic actions on the urinary bladder, tolterodine was equipotent to oxybutynin. However, the affinity of tolterodine for muscarinic receptors in the parotid gland was 8 times lower than that of oxybutynin. This is consistent with the selectivity of tolterodine for urinary bladder contractions over salivation, that has been observed *in vivo*, in the anaesthetized cat.

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TOLTERODINE-A NEW AGENT WITH TISSUE EFFECT SELECTIVITY FOR URINARY BLADDER

AIMS OF STUDY

The dosage and effectiveness of traditional antimuscarinic drugs for treatment of urge incontinence has been limited by cholinergic side effects mainly dryness of the mouth. It is therefore desirable to develop a new antimuscarinic drug with tissue effect selectivity for the urinary bladder. In the search for such a drug there was a need for an experimental animal model measuring effect on urinary bladder pressure, salivation and heart rate simultaneously. Tolterodine ((+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine) was chosen as a drug candidate from our urge incontince research programme. The present study was undertaken in order to evaluate the *in vivo* functional selectivity of tolterodine on urinary bladder, salivary gland and heart tissue. Oxybutynin and atropine were included as reference compounds.

METHODS

The effects of tolterodine, oxybutynin and atropine on urinary bladder contractions induced by acetylcholine were studied in the anaesthetized cat. The effects on basal heart rate and electrically stimulated salivation were simultaneously monitored. At the beginning of each experiments, a dose-response curve for bladder pressure was obtained by administering acetylcholine intra-arterially within 3 sec. in doses of 0.5, 1, 2, 4 and 8 µg/kg. From these bladder pressure responses, a submaximal dose of acetycholine was selected (1 to 4 µg/kg). This dose produced a short-lasting (<1 min.), substantial (>9 cm H_2O) and reliable (at least two responses with less than 15% variation) increase in bladder pressure. Acetylcholine was administered before and approximately 9 minutes after each dose of test substance.

The duct of the submandibular gland was exposed in the neck, and cannulated with a PE10 catheter. The parasympathetic chorda-lingual nerve of the submandibular

gland were exposed and cut as far proximally as possible. The peripheral stump of the nerve was placed on a bipolar electrode and stimulated supra-maximally (6V, 2ms) at variable frequencies (0.5-5 Hz) during a period of 2 min. The electrical stimulation was performed before and approximately 7 minutes after each dose of test substance. The amount of saliva secretion was expressed per 2 minutes period. The test substances were given at increasing doses by intravenous infusion via the right femoral vein .

RESULTS

Tolterodine, oxybutynin and atropine produced a dose-dependent inhibition of the acetylcholine induced urinary bladder pressure, with ID_{50} value of 105±14, 200±23 and 15±2 nmol/kg (mean ±SEM) (48±6, 79±9 and 5±1 µg/kg), respectively. The threshold doses (ID_{30}) were estimated to: tolterodine 19±4 µg/kg; oxybutynin 33±5 µg/kg; atropine 3±1 µg/kg.

Tolterodine, oxybutynin and atropine produced a dose-dependent inhibition of the electrically stimulated salivary secretion from submandibular gland, with ID_{50} values of 268±47, 104±12 and 22±3 nmol/kg (mean±SEM)(122±21, 41±5 and 8±2 µg/kg), respectively. The threshold doses (ID_{30}) were determined graphically to be: tolterodine 63±14 µg/kg; oxybutynin 20±3 µg/kg and atropine 4±1 µg/kg.

Atropine inhibits both salivation and bladder pressure in the similar dose range, whereas oxybutynin affected the salivation at a dose lower than that needed to inhibit bladder contraction. In contrast to oxybutynin, tolterodine was more effective on the urinary bladder, i.e. bladder pressure was inhibited at a dose approximately one third of that affecting the salivation

Neither of tolterodine, oxybutynin nor atropine caused no significant effect on heart rate in this study.

Table 1. The dose of test substance giving 30 (ID_{30} nmol/kg) or 50 % inhibition of the urinary bladder contraction and salivary secretion in the anaesthetized cat (Data are mean ± SEM, n=5)

Drug	ID_{30} Urinary bladder	ID_{30} Salivary gland	ID_{50} Urinary bladder	ID_{50} Salivary gland
Tolterodine	42±9	138±31	105±14	268±47
Oxybutynin	83±13	50±7	200±23	104±12

CONCLUSION

In this experimental model the unselective drug atropine affects bladder contraction and salivation within the same dose range. Oxybutynin also produced an effect on the bladder contraction but at significant higher doses than those affecting salivation. In contrast to these drugs, the new agent tolterodine affects the urinary bladder pressure at doses significantly lower than those affecting salivation. Thus, tolterodine differs from traditional antimuscarinic drugs by being more effect selective for the urinary bladder as compared to the salivary gland.

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MODULATION OF MICTURITION BY TERFLAVOXATE

AIMS OF STUDY.

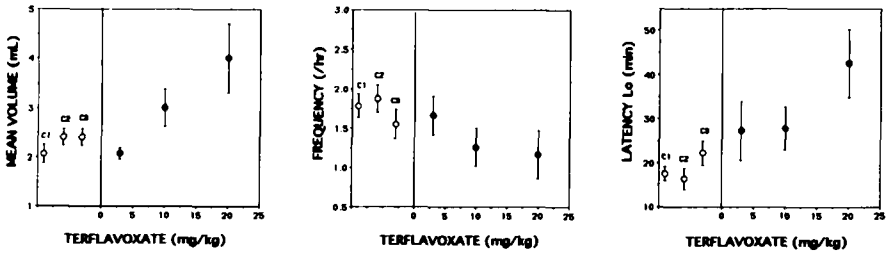
The present study was designed to evaluate the effect of Terflavoxate in modulating the bladder storage and micturition characteristics using non-invasive monitoring techniques on non-anesthetized rats. Since the role of pharmacotherapy for the treatment of detrusor incontinence aimed toward increasing bladder capacity, minimizing leakage and, consequently, the number of micturitions, we developed an animal model that incorporates the monitoring of these parameters.

METHODS.

Micturition studies were undertaken in 31 young (4 months) female Wistar rats weighing approximately 316±6gm. Each rat was evaluated on four separate occasions and each study was separated by an interval of 7 days. Two control periods (C_1, C_2) were first done without pharmacologic stimulation, followed by a single dose of Terflavoxate. A post-control study (C_3) was done after the Terflavoxate dose to establish the reliability of the original non-Terflaavoxate values. Micturition studies were done by the subcutaneous injection of a loading dose of saline 5ml together with 1mg/kg of furosemide. In experimental studies, Terflavoxate 3, 10, 20mg/kg was added to the loading dose.

Micturition studies were done by placing the rats in a restrainer under which a urine volum sensor was attached and connected to a recorder[1] . Parameters measured were the mean volume voided (V) after a latency period, Lo (min) following the placebo/drug injection and the frequency of voiding F (min^{-1}). Monitoring of individual micturitions provided data to calculate V, F, Lo and leakage. Statistical analysis was performed using the paired t-test comparing (C_2) values with Terflavoxate. Data are presented in terms of mean ± S.E.M.

RESULTS.



Analysis of the results show that Terflavoxate produces a dose-dependent response on the

micturition parameters tested. The figure above illustrates that Terflavoxate produces an increase in mean bladder volume, a lowering of the frequency of micturition and a prolongation of the latency of Lo. Significant differences were observed for V at 20mg/kg ($p<0.003$) and for F at 10mg/kg ($p<0.001$) and 20mg/kg ($p<0.001$).

When compared to baseline (C_2), there was a significant increase in Lo at 3mg/kg ($p< 0.05$), 10mg/kg ($p<0.02$) and at 20 mg/kg ($p<0.0001$).

DISCUSSION.

These observations lend supporting evidence to existing data, indicating that Terflavoxate produces suppression of efferent activity by effecting increased mean voided volume and associated decrease in the frequency of micturition. These observations further suggest that Terflavoxate suppresses the volume evoked micturition threshold producing a prolonged Lo and, consequently, decreased F. Although the precise physiological mechanism responsible in contributing to these results cannot be identified directly from this experimental design, it has been suggested that IV Terflavoxate produces efferent suppression of pelvic nerve discharges[2]. The observations made in the present study provides further experimental support to these reported observations and verifies their applicability to a non-anesthesized animal model that is not instrumented with a urethral catheter.

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THE BEHAVIOURAL RESPONSE INDUCED BY INTRAVESICAL INSTILLATION OF CAPSAICIN IN RATS AS A MODEL OF URETHRAL NOCICEPTION.

Introduction

The recent clinical use of intravesical instillation of capsaicin for the management of various kinds of detrusor hyperreflexia prompted further experimental investigations about mechanisms through which capsaicin affects motility and sensory input from the lower urinary tract in laboratory animals. Recently, the behavioural response induced by the intravesical instillation of capsaicin through an indwelling catheter has been characterized in conscious, freely-moving rats: animals respond with an intense licking directed toward the abdominal and perineal areas of the skin, and this behaviour has been interpreted as indicative of vesical pain. However, once instilled into the bladder, capsaicin stimulates micturition producing the passage of the irritant through the urethra; therefore the capsaicin-induced behavioural response could represent a model of

urethral rather than vesical nociception. In the present study the behavioural response induced by the intravesical instillation of capsaicin has been furthermore characterized by means of surgical or pharmacological manipulations.

Material and Methods

Male Wistar rats (n=82) weighing 300-350 g were anaesthetized with chloral hydrate (360-400 mg/kg, i.p.). A polyethylene catheter (PE 50) was implanted in the bladder dome. The catheter was tunneled subcutaneosly, exteriorized at T2-T3 level. Some experiments were performed after surgical manipulations which include: the bilateral surgical ablation of pelvic ganglia, the bilateral section of pudendal nerves and the ligature of the proximal urethra near to the insertion of ureters. The abdominal wall or back muscles (for pudendal nerve cutting) were sutured by means of a silk ligature and the skin with wound clips. Experiments were carried out 48 h after surgery. Pharmacological pretreatments included: systemic capsaicin pretreatment (50 or 150 mg/kg, s.c., 96 h before) and topical treatment with lidocaine or tetrodotoxin (infused into the bladder through the implanted catheter at a flow rate of 150 µl/min for 60 min, 10 min before). For cystometrycal and behavioural recordings rats were placed in plexiglass cylinders (diameter 20 cm, hight 30 cm). 0.5 ml of 50 µM capsaicin solution or its vehicle (1% ethanol in saline) were instilled into the urinary bladder in 10 sec. Time (sec) spent in licking perineal or abdominal skin was immediately recorded for 15 min after capsaicin instillation. Results were evaluated by means of analysis of variance.

Results

The intravesical instillation of capsaicin (25 nmol/rat in 0.5 ml) caused an intense perineal licking which started about 10-30 sec from capsaicin administration and lasted for about 15 min. Instillation of the capsaicin vehicle had no effect. Systemic capsaicin pretreatment at the dose of 150 mg/kg, but not at 50 mg/kg (4 days before in each case), reduced the the time spent in licking following the acute intravesical instillation of capsaicin. Bilateral ablation of pelvic ganglia did not modify the capsaicin-induced perineal licking during the first 5 min and prolonged the effect of capsaicin for the remaining 10 min obsevation period when compared to sham-operated rats. In urethra-ligated rats, capsaicin was instilled intravesically and left *in situ* for 15 min: in these conditions the capsaicin-induced licking was greatly reduced. In rats subjected to the section of pudendal nerves, the intravesical instillation of capsaicin did not evoke any behavioural response, thus confirming the indications about the involvement of pudendal urethral afferents. Infusion of tetrodotoxin (1 and 10 µM) during cystometry reduced the amplitude of micturition contractions, whereas infusion of lidocaine (100 mM) induced overflow incontinence in 4 out 6 animals. Tetrodotoxin pretreatment did not modify the licking induced by intravesical instillation of capsaicin, while lidocaine abolished the effect of capsaicin.

Discussion

The present findings demonstrate that the behavioural response produced by the intravesical instillation of capsaicin in rats is mainly, is not exclusively, produced by the stimulation of urethral afferents travelling in the pudendal nerves rather than by irritation of bladder afferents. This conclusion is based on the followings : a) pelvic ganglionectomy did not abolish but even prolonged the duration of licking produced by intravesical capsaicin; b) placing a ligature

between the bladder and urethra largely prevented the behavioural response to intravesical capsaicin; c) section of pudendal nerves likewise blocked the response to intravesical capsaicin. Interestingly, the behavioural response to capsaicin was abolished by the local infusion of lidocaine but not by tetrodotoxin; both drugs, although at different extents, inhibited the distension-induced micturition contractions, indicating that the concentrations of the two agents were high enough to affect motor nerves in the bladder wall. The failure of tetrodotoxin, as opposed to lidocaine, to block the behavioural response to capsaicin may be related to the presence of afferent fibers possessing a tetrodotoxin-resistant condutcion mechanism, as it has been demonstrated to occur at central endings of capsaicin-sensitive small dorsal root ganglion neurons and in the soma of a group sensory neurons projecting to the bladder.

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POSSIBLE TACHYPHYLAXIS AFTER CHRONIC ORAL ADMINISTRATION OF NIMODIPINE: EFFECT ON RAT DETRUSOR CONTRACTION.

AIMS OF STUDY

The influx of calcium through potential-operated and receptor operated calcium channels is an important trigger for smooth muscle contraction. Considerable research work has been devoted to the effect of calcium antagonist on the contractile response of mammalian detrusor muscle to establish an effective treatment for detrusor hyperactivity. In vivo and in vitro animal studies demonstrate the effectiveness of calcium antagonists in reducing detrusor muscle contractile response (Bo & Burnstock 1990, Diederichs et al 1992). From these results one would expect the treatment of detrusor instability with calcium antagonists to be very effective, unfortunately this is not reflected in clinical practice. Because most in vivo studies in animals were performed after a single dose of calcium antagonist we investigated the effect of chronic oral administration of nimodipine on the contractile response of isolated rat detrusor muscle, which would more closely mimic the situation in man. We compared this with a single oral dose. Nimodipine was used because we have found it to be the most effective in reducing isolated human detrusor muscle contraction.

METHODS

In vitro treatment

To establish the stability of nimodipine in our bladder tissue samples we removed the bladders from male Wistar rats (300-400g), killed by a blow to the head followed by dislocation of the neck. Strips of bladder muscle (4mm x 1mm) were suspended in a 50ml organ bath chamber containing Krebs solution at 37°C aerated with 95% oxygen and 5% carbon dioxide. The strips were passed through two circular parallel electrodes connected to a Digitimer Stimulater delivering 1-80 pulses per second, voltage 10, pulse width 0.5msec, in ten second trains at 2 minute intervals. The

samples were allowed to equilibrate for one hour under a tension of 10mN after which they were stimulated with 1, 5, 10, 20, 40, 60, 80pps to obtain a frequency response curve. When consistent responses had been achieved nimodipine, 0.1μM, was added to the bath and after 15 minutes incubation a second frequency response curve was obtained. The tissues were washed and stimulated at intervals of 30, 45 and 60 minutes.

In vivo treatment

One group of 6 male Wistar rats (350-400g) were treated for 8 days with nimodipine 5.14mg/Kg daily, administered by gastric intubation. The nimodipine was dissolved in 0.5ml vehicle prepared by mixing 96.6g polyethylene glycol 400, 6.0g glycerine and 10g water. Two groups of 6 rats received either the vehicle only or no treatment and one group of 5 rats received only one dose of nimodipine. After the treatment period rats were killed and bladders removed and placed in 10mls Krebs solution. Strips of detrusor muscle was prepared and mounted in the organ bath as previously described except the samples were kept in the original 10ml Krebs solution and not washed. Tissues were equilibrated for 45 minutes under a tension of 10mN then stimulated as described to obtain frequency response curves. The responses were recorded as an increase in tension. Statistical analysis was carried out using one way analysis of variance followed by Dunnett's corrected t test.

RESULTS

In vitro treatment

Nimodipine significantly reduced the maximum contractile response to electrical field stimulation by 52% ($p<0.01$). After washing and re-stimulation at intervals of 30, 45 and 60 minutes the contractile response was significantly reduced by 44%, 34% and 30% respectively compared to controls ($p<0.01$).

In vivo treatment

There was no significant difference in the maximum contractile response of rat detrusor muscle between those treated for 8 days with nimodipine and those given just the vehicle and controls (no treatment). The response of detrusor muscle from rats treated with one dose of nimodipine was significantly reduced by 66% compared to controls.

CONCLUSIONS

Our results demonstrate that nimodipine was reasonably stable in our detrusor samples and was not easily washed out of the tissue. Treatment with nimodipine for 8 days had no effect on rat detrusor contractile response whereas a single oral dose significantly inhibited detrusor contraction. These results suggested that repeated oral dosage with nimodipine was producing desensitization. This may have certain implications for the treatment of detrusor instability with calcium antagonists.

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NEUROPHYSIOLOGIC PREDICTORS OF SURGICAL OUTCOME

AIMS OF STUDY
Evidence of neurophysiologic damage in women with stress incontinence is well documented. To date the clinical usefulness of electrodiagnostic examination in predicting surgical outcome has not been determined. The aim of this study was to determine the relationship between electrodiagnostic findings and outcome of anti incontinence surgery.

PATIENTS AND METHODS
Motor unit fiber densities of the pelvic floor and nerve conduction times to the anal sphincter, pubococcygeus and urethral sphincter were obtained in 71 women prior to an anti-incontinence procedure. Outcomes were defined as either: dry-stress test negative and no complaint of stress incontinence; or wet: stress test positive and complaint of stress incontinence. All women were seen and assessed clinically and urodynamically prior to their operation and exhibited genuine stress incontinence. Patients were then examined at least six months post operatively, both clinically and urodynamically, to determine surgical results.
To determine the relationship of electrodiagnostic findings to outcome the data was analyzed using an ANCOVA (analysis of covariance) with BMI, age, parity, previous surgery and MUCP as covariates. Discriminant function analysis (DFA) was then carried out with surgical outcome as the dependent variable and electrodiagnostic measures as predictors. Due to missing data the number of subjects analyzed by DFA was only 57.

RESULTS
Fifty one of the subjects underwent a fascial sling and 20 underwent colposuspension. Eight of the patients had a prior vaginal surgery. Fifty five of the 71 women analyzed (77%) were dry by objective criteria. Mean follow up time was 9.91 months. ANCOVA analysis revealed a significant effect of previous surgery for anal sphincter latency ($F=8.1$, $df=1,63$, $p<.01$) and urethral sphincter latency ($F=14.1, df=1,62$, $p<.001$). Those women who had prior surgery had a significantly longer latency to the urethral sphincter. No significant relationship was found between the covariates(BMI, age, parity and MUCP and electrodiagnostic findings). In the discriminant function analysis on patients without prior surgery, none of the variables were significant predictors of outcome. In patients with previous surgery the following variables explained 68% of the variance: Anal sphincter latency, age, and BMI. The relationship between age and outcome was that younger women were more likely to be wet.

CONCLUSION
The results of this study show that conduction times and motor unit fiber density were not clinically useful in predicting outcome in this retrospective study. Interestingly those women with previous surgery and significantly longer latencies to the urethral sphincter were also those with the highest percentage of surgical failures. This finding may suggest that denervation injury during surgical repair may represent a predisposing factor to adverse surgical outcome. A prospective analysis to examine patients electrodiagnostically both pre and post surgery, may reveal electrodiagnosis post surgically as clinically useful.

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AMBULATORY URODYNAMICS: A PREDICTOR OF DE-NOVO DETRUSOR INSTABILITY AFTER COLPOSUSPENSION

INTRODUCTION

Following colposuspension there is an increased incidence of detrusor instability(1). No specific cause can be found but it may be either a result of the operation due to excessive dissection, or detrusor instability which was not diagnosed prior to surgery. Ambulatory urodynamics appears to be the most sensitive method of detecting detrusor instability(2). This study attempts to determine, using ambulatory urodynamics, whether detrusor instability which develops after colposuspension is present preoperatively.

PATIENTS AND METHODS

All women entered into this study had moderate to severe genuine stress incontinence diagnosed on videocystourethrography. Thirty four women have been recruited. Ambulatory urodynamics was performed one day prior to surgery. All the women underwent a modified Burch colposuspension. The ambulatory urodynamic test lasts four hours, a single solid-state 8F microtransducer (Gaeltec) with two pressure transducers is inserted into the bladder and a separate solid-state microtransducer is inserted into the rectum. The pressures are recorded on a solid-state ambulatory system (Gaeltec). The women are asked to drink a standard 180ml cup of fluid every 30 minutes and also keep a diary of any events during the test. The results are interpretated on a computer, with the patient present, at the end of the ambulatory study.

The women were all seen six weeks after the colposuspension and notes were made of any urinary symptoms. Nine months after the colposuspension urinary symptoms were evaluated and videocystourethrography is performed.

RESULTS

The mean age of this group of women was 49 years (sd 11) and four women had undergone previous continence surgery (anterior vaginal repair). After undergoing ambulatory urodynamics eleven women (34%) were diagnosed as having detrusor instability. Five of these women, on close questioning, had developed symptoms of urgency and nocturia postoperatively. The other women were asymptomatic. Three women have had videocystourethrography nine months postoperatively. One of these women had detrusor instability on ambulatory urodynamics. She has developed symptoms of nocturia (twice nightly) since the operation and has occasional urgency. On videocystourethrography she was found to have detrusor instability.

CONCLUSION

These are preliminary results but they appear to indicate that detrusor instability which develops de-novo after continence surgery

may be present preoperatively and can be detected on ambulatory urodynamics, although not on a single conventional laboratory test.
1. Long-term follow-up of detrusor instability following the colposuspension operation. BJU (1985) 58: 138-142
2. Ambulatory monitoring and electronic measurement of urinary leakage in the diagnosis of detrusor instability and incontinence. BJU (1991) 68: 148-152

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EFFECT OF CHILDBIRTH ON LONG-TERM SUCCESS OF SURGERY FOR STRESS INCONTINENCE AND PROLAPSE

AIM OF STUDY

Surgical correction of stress incontinence and prolapse is usually delayed until after childbearing is completed. The purpose of this study was to determine whether pregnancy and the route of delivery influence the long-term results of surgery for stress incontinence and genital prolapse.

PATIENTS AND METHODS

We surveyed over 900 medical records from seven community hospitals to identify 72 women aged 15 to 40 years who had had surgery for genital prolapse or urinary incontinence with preserved fertility. A five-page questionnaire was mailed to eligible subjects regarding subsequent deliveries and recurrent or new symptoms of stress incontinence or prolapse. Questions were designed to differentiate urge and stress incontinence. A subset of women were examined for objective confirmation of symptoms.

RESULTS

The mean age of the study subjects was 28.5 years (95% C.I. 18.7-38.3). Of 40 responders, 21 had subsequent deliveries, and the time from operation to delivery ranged from 11 months to six years. Six women were delivered by cesarean (four to preserve the previous repair and two for obstetric indications), and 15 women were delivered by the vaginal route. Three women reported a recurrence of symptoms prior to the pregnancy. Of the remainder, 8/18 (44%) had recurrent symptoms after delivery. Recurrence of symptoms was unaffected by the route of delivery. Eight of 19 women who had not undergone subsequent pregnancies reported a recurrence of their original symptoms, five had new symptoms, and nine were asymptomatic. Including the 3 subjects who had a recurrence prior to pregnancy, the recurrence rate unrelated to childbirth was 50% (11/22). Examination of 13 women confirmed stress incontinence in subjects reporting these symptoms, but demonstrated genital prolapse to or beyond the introitus in some women who had denied symptoms of prolapse.

CONCLUSION

Recurrence of symptoms in young women after surgery for stress incontinence or genital prolapse is more common, regardless of whether there is a subsequent pregnancy and delivery. Cesarean section seems to confer no protection over vaginal delivery. Further prospective studies should determine the reason for the high rate of recurrence in young women after such surgeries.

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COLPOSUSPENSION A.M. BURCH- AN 18-YEAR FOLLOWUP STUDY.

Objectives:

Long term experience with colposuspension a.m. Burch in patients with urinary stress incontinence.

Methods:

In a retrospective study 960 patients with clinical and urodynamical verified genuine stress incontinence were in the periode 1974-1992 treated with colposuspension a.m. Burch. The medical records were reviewed and a standardized questionaire was completed which quantitated all voiding symptoms and patients satisfaction. Followup was done in 1993.

Results:

771 patients returned the questionaire. 78 patients had died. 111 were lost to followup. The median age was 46, with a range of 32-75 years. Median parity was 2, range 1-7. Postoperatively 30% had cystitis and 5,3% had wound infection. The subjective successrate using life analysis was 54% after 18 years. Among successes and failures were voiding difficulty, frequency, nocturia and Burch pain syndrome 28%, 41%, 10%, 20% and 66%, 81%, 35%, 37%, respectively. $p< 0.01$ (Chi-square test). Age, body-mass-index, parity and hysterectomy were of no risk in the outcome of surgery.

Conclusion:

The high subjective cure rate reported in short term studies appears to decline significantly with time. Furthermore voiding problems are a frequent and permanent complication both among successes and failures.

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THE EFFECT OF THE ALPHA-1-ADRENOCEPTOR SELECTIVE AGONIST MIDODRINE ON MILD TO MODERATE FEMALE STRESS-INCONTINENCE.

INTRODUCTION

Urinary incontinence, a condition chracterized by involuntary loss of urine, is a major clinical problem affecting 30 % of the home-dwelling elderly and 40-50% of institutionalized populations. Stress urinary incontinence is commonly seen in women and is identified by daytime loss of small to moderate amounts of urine associated with Valsalva manoeuvres, i.e. coughing, sneezing, etc.
Midodrine Hydrochloride is a prodrug, which after absorption is rapidly transformed to an active metabolite, ST 1059, a potent and selective α_1-adrenoceptor agonist. Compared to its effects on isolated human arteries, ST 1059 was ten times more effective on human urethral smooth muscle (1). Since long, midodrine has been used in the treatment of hypotension and in alleviating symptoms of stress urinary incontinence. However, a controlled clinical trial of its effect in stress incontinence has apparently not been performed.

AIMS OF STUDY

The aim of this study was to evaluate the efficacy and safety of oral Midodrine (5, 7.5 and 10 mg/day) for the treatment of mild to moderate stress urinary incontinence.

PATIENTS AND METHODS

A randomized, double-blind, placebo-controlled, multicenter design was used. 96 adult females with mild to moderate stress urinary incontinence were selected fullfilling the following criteria.
- the female patient is between 18-70 years of age.
- the patient must have a history of urinary incontinence and has proven a urinary stress incontinent episode during urodynamic filling cystometry up to 75 % of the bladder capacity in sitting and/or standing position while coughing.

The patient was randomized to recieve either placebo or midodrine in a daily dosage of 5.0, 7.5 or 10 mg for 4 weeks.
Efficacy was based on an improvement in incontinence, demonstrated by an increase in the Maximum Urethral Closure Pressure (MUCP) at rest. Other efficacy parameters assessed were the pressure transmission ratio (PTR) and the pad weight test. The subjective improvement of the patient was based upon the number of pad changes and a global assessment of patient and physician.
Safety was controlled by checking blood pressure every two weeks before and after medication, furthermore blood and urine analysis were performed before and after completion of the study.

RESULTS

The study (including 96 patients) will be completed in July 1994. The results presented below are from the first 48 patients and comprise MUCP, PTR, pad test and physician assesment. There was an increase in MUCP in all 4 groups, the change being statistically significant in the 5.0 mg and 7.5 mg groups. The PTR, the increment in urethral pressure on stress as a percentage of the simultaneously recorded increment in intravesicular pressure,was not changed comparing the placebo with the treated patients.

The pad test, (modified 20 minute pad test) was performed before and after 4 weeks of treatment. In the placebo group the netto urine loss was significantly increased (*P<0.05). There was a tendency of decreased urine loss in the treated groups and a significant decrease in the group treated with 10 mg of midodrine.
The investigators assesment showed a improvement in all three groups, significance was reached with 5.0 and 10 mg midodrine compared to placebo.

Furhermore no significant blood pressure change was found in either group.

CONCLUSIONS

The aim of this study was to evaluate the efficacy and safety of oral Midodrine in females with stress incontinence. The results of this interim analysis showed that the drug caused a minor increase in MUCP, but no changes in PTR. The known large variations in MUCP, and the inclusion of women with MUCP values within the "normal range" may contribute to this. There was a decreased urine loss in the midodrine treated women, as reflected by the pad test, and no changes in blood pressure.
This suggests that midodrine may be clinically useful in women with mild to moderate stress incontinence.

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PROGNOSTIC FACTORS AFFECTING THE OUTCOMES OF PUBOVAGINAL SLING

AIMS OF STUDY

To determine pre-operative factors that would predict outcomes following pubovaginal sling, for stress incontinence in women.

PATIENTS AND METHODS

A retrospective analysis of 106 women who underwent pubovaginal sling (PVS) from 1983 to 1993 was done. All patients had a preoperative history, physical examination, and videourodynamic study (VUDS). In addition, since 1990 each patient had a voiding diary and 24 pad test. Individual symptoms (stress, urge, urge incontinence and urinary frequency) and urodynamic

findings (Pdet at capacity, cystometric capacity, presence of unstable bladder contractions, volume at which the unstable contractions occurred, absence of detrusor contraction and urethral obstruction) were compared to status at last postoperative followup (cure, improved, failure, urge incontinence and urinary retention). Urethral obstruction was defined as a sustained detrusor pressure greater than 30 cm H20 and a flow of less than 12 ml/s. Postoperative assessment was identical to the preop assessment except urodynamics were only performed on symptomatic patients. Exclusion criteria included neurogenic bladder (7), coexistent bladder exstrophy (1), pelvic irradiation (3), and bladder augmentation at time of PVS (2). Follow-up was not available on 3 patients. For each category of results, the patients were divided into 2 groups, for example with and without urinary retention.

RESULTS:

Overall, 82% were cured, 9% improved, 3% failed because of SUI and 6% failed due to urge incontinence. 1% developed urinary retention requiring intermittent catheterization. There was no significant statistical differences between any of the historical or urodynamic variables and the outcome of surgery with the single exception of those with preoperative urge incontinence (UI) and postoperative UI ($p<0.05$). 23 women had UI postoperatively occurring at least once per week; Of these 23 women, 20 had symptoms of UI preoperatively, but only 7 had detrusor instability (DI) demonstrated at cystometry. Pre-operative cystometric capacity in the 23 women ranged from 200 - 700 ml (mean=410 ml). Postoperatively, cystometrogram confirmed detrusor instability in 10 of 17 women, 3 of whom had urethral obstruction. Six women declined postoperative urodynamics because they did not consider their symptoms severe enough to warrant further treatment.

Sixty-seven (67) women did not have postoperative urge incontinence: 23 women had urge incontinence preoperatively and 12 had detrusor instability on cystometrogram.

CONCLUSIONS

In this study, neither cystometry nor historic features were of prognostic value. The only variable which predicted outcome was a preoperative history of urge incontinence. A woman with urge incontinence preoperatively had a 46% chance of persistent urge incontinence. New onset of urge incontinence in the postoperative period is uncommon (3.3%). These data suggest that a history of urge incontinence, not cystometric detrusor instability, is the only risk for the development of postoperative outcome.

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PERIURETHRAL COLLAGEN FOR FEMALE GENUINE STRESS INCONTINENCE: RESULTS AT 2-3 YEAR FOLLOW UP.

AIMS OF STUDY

Periurethral Bard Contigen collagen injection is a simple office technique used to correct stress incontinence. Early and six month cure rates of 41-61% are reported (1&2). The mechanism of action is uncertain but an increased functional urethral length and decreased maximum urethral closure pressure are reported in cured patients (3). We wish to determine if periurethral collagen injection is an effective long term treatment for urethral sphincter incompetence in a targeted population of women with reduced bladder neck mobility and poor urethral function.

PATIENTS AND METHODS

60 women, mean age 64 years (range 20-90) with urethral sphincter incompetence received collagen injections under local anaesthetic under cystoscopic vision. Observation of bladder neck mucosa movement with gentle needle movement helped ensure correct placement. Collagen was injected at 9 o'clock and 3 o'clock positions until submucosal bulking occurred; the goal was total lumen occlusion. A maximum number of 3 injection sessions were allowed. Subjective and objective assessment including one hour pad test, cystometry and urethral pressure profiles were obtained at 3 and 12 months. At 24 months a pad test, uroflowmetry and endovaginal ultrasound of the bladder neck were performed.

RESULTS

The mean parity was 2 (0-7) and mean weight 67kg (46-91). The mean number of previous continence procedures was 1.6 (0-4). The mean number of collagen injection sessions was 1.6 (1-3) with an average injected volume of 19mls (5-55) per subject. Subjective and objective cure rates are outlined in Table 1. Table 2 illustrates urodynamic variables in patients with objective success and failure. There were no long term complications.

Table 1 Subjective and Objective cure rates

	Subjective	Objective
3 months (n=59)	86%	61%
12 months (n=54)	77%	54%
24 months* (n=29)	68%	48%

* (range 24-37)

Table 2 Urodynamic variables in objective cure and failure

	Success		Failure	
	Pre (GAX)	Post	Pre (GAX)	Post
MUCP rest cmH2O	26.0	24.3	26.2	23.6
MUCP stress cmH2O	19.0	23.4	20.2	26.1
FUL cm	2.3	2.8	2.5	2.6
Peak flow rate ml/s	26		24	

Of the patients with objective cure at 2 years, 87% had fair, good or excellent bulking at injection. Of the objective failures 50% had bulking adjudged to be poor. Endovaginal ultrasound at 2 years follow up showed no clear evidence of collagen.

CONCLUSIONS

Collagen injections may continue to be effective at 2 years follow up, although there is some decline with time. FUL and clinical assessment of bulking may be more useful than MUCP for predicting success. There is no significant decrease in peak flow rate after treatment. No long term complications are reported.

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IS THERE AN IRRITABLE BLADDER

IN THE IRRITABLE BOWEL SYNDROME ?

AIMS OF STUDY

The pathophysiology of detrusor instability (DI) and irritable bowel syndrome (IBS) are poorly understood. In IBS altered small bowel and colonic motility (1), lowered oesophageal and colonic pain thresholds (2) and symptoms of urinary dysfunction (3) are reported. Pharmacological agents used to treat bowel spasm also exert an effect on the bladder and have been used in the management of DI and sensory urgency. The only previous urodynamic study of patients with IBS reported a prevalence of DI of 33% (4), however two thirds of the subjects were postmenopausal. This study aims to investigate bladder function

and oesophageal pain and perception in premenopausal female patients with documented IBS to see if they are altered.

PATIENTS AND METHODS

14 premenopausal patients, mean age 28 years (20-42), with IBS (normal upper GI endoscopy and oesophageal motility) were recruited from Gastroenterology clinic. None had presented with urinary symptoms. Severity scores for IBS were calculated on the six most discriminatory of Manning(5) criteria:
pain relieved by bowel action, looser stool with onset of pain, more frequent stool with onset of pain, abdominal distension, urgency of defaecation and incomplete emptying. Urodynamic diagnosis was made after clinical assessment and twin channel subtracted cystometry. Balloon distension studies were performed using a latex balloon placed above the lower oesophageal sphincter. The balloon was filled with increments of air (1ml) and volumes for perception and pain recorded before and after sensitisation with 0.1N HCl.

RESULTS

On direct questionning eight patients had symptoms of urgency and frequency. Five of these patients (36%) had detrusor instability and 3 (21%) had sensory urgency. There was no significant difference in symptom severity scores in patients with detrusor instability (mean score 9.8), or stable bladders with or without symptoms of sensory urgency (mean score 7.6). No significant differences were found in balloon distension volumes for oesophageal perception (7.6ml +/- 1.3 vs 6.1ml +/- 0.9) or pain (10.8ml +/- 1.3 vs 9.6ml +/- 1.0) before and after acid perfusion.

CONCLUSIONS

A 36% prevalence of detrusor instability in this premenopausal study group is much higher than the 5% expected prevalence in the normal premenopausal population. The prevalence may be even greater as ambulatory monitoring can provide evidence of detrusor instability in 60% of patients with sensory urgency (6). The high prevalence of detrusor instability and sensory urgency suggest that IBS may be part of a generalised disorder of smooth muscle. IBS symptom severity scores were not predictive of DI. Oesophageal perception and pain thresholds were lower in patients with IBS compared to controls but were not predictive of DI.

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THE VALUE OF A PATIENT ADMINISTERED HOME FLOW TEST COMPARED TO OFFICE UROFLOWMETRY IN THE EVALUATION OF PROSTATISM PATIENTS.

AIMS OF STUDY

Variables obtained from uroflowmetry are important criteria for the decision to treat prostatism patients. However, office uroflowmetry is often done inadequately by these patients. In the present study the value of a simple home flow test was studied.

PATIENTS AND METHODS

Four hundred and twenty-one consecutive patients without any intervening diseases referred to our department were included. Before the first visit a symptom questionnaire(*symptom score*) was send to the patient together with a *home flow test* (HFT) chart. To perform an adequate HFT the patient should measure on ten different occasions the time in whole seconds from the start of micturition until 100 ml of urine had been voided. The mean value was used for the analysis. At the first visit the patients were specifically asked to come with a full bladder in order to do uroflowmetry with an adequate volume of urine in the bladder. The maximal flow (Q_{max}) and the voided volume(V_{comp}) were recorded. The *Residual urine* was measured and *cystoscopy* was performed.

RESULTS

The symptom questionnaire was filled in by 100% and HFT by 78.1%. Uroflowmetry was completed by 84.1% the rest being unable to micturate in the office. If uroflowmetries with a V_{comp} < 150 ml are considered inaccurate, Q_{max} could only be classified in 37.8% of the patients. The mean Q_{max}(±SD)was 9.7±5.9 ml/sec and the mean HFT was 22.2±17.3 sec/100 ml. HFT was correlated to Q_{max}(R=0.36, p<0.001). The symptom score was stronger correlated to HFT(Rs=0.37,p<0.001) than to Q_{max}(Rs=-0.18,p<0.001) and the same was the case with each single symptom. The positive predictive value of a HFT > 30 sec/100ml in predicting a Q_{max} < 10 ml/sec was 0.95 and the positive predictive value of a HFT < 10 sec in predicting a Q_{max} > 10 ml/sec was 0.75.

CONCLUSIONS

Home flow test is a cost-effective measurement which may be used for classification of flow in prostatism patients. It is better correlated to the *symptoms of these patients* than Q_{max} and it can be measured adequately in a larger proportion of the patients compared to single routine uroflowmetries.

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RELIABILITY OF FREE UROFLOWMETRY USING REPEATED MEASUREMENTS OF HOMEFLOWMETRY IN MALES

Introduction

A prerequisite for a measuring technique is that the measurements obtained with it are reliable. Results of measurements of urinary flow rate patterns show considerably large biological variation. Golomb et al.[1] noted a statistically significant larger standard deviation in the Peak Flow Rate (Qmax) recordings in BPH patients as compared to controls: 87.5 % of the patients showed a difference of at least 1 SD, and 47% a SD of at least 2, whereas in the controls these values were 50% and 12.5% respectively. On the other hand, in pharmacological trials for BPH, the effect-sizes in terms of increase in Qmax and Mean Flow Rate (Qmean) are usually small, generally not more than a few ml/s. If uroflowmetry is applied as an endpoint in clinical trials for BPH, there is a need for assessing the reliability of repeated measurements. The question is, what should the absolute magnitude of change be to conclude that the flow rate of an individual patient has improved? How many measurements are required? By assessing the relative magnitudes of the various sources of measurement error, important ones can be detected.

Material and Methods

140 Men with micturition disorders, most of them 'prostatism', were recruited. After a routine screening procedure, they collected a Home-Flowmeter. We asked them to complete a small questionaire. As they voided at home in a container, the digitalized data of their flows were stored in the memory chips of a portable recorder. During one measurement period, a maximum of 75 Flow rates could be recorded. Artefacts in the flow rate patterns were digitally corrected. Irregular shapes of flow curves were accepted as typical voiding patterns if occurring repeatedly and if two observers agreed. The

various parameters according to the ICS were determined. For statistical analysis, we used an approach which is known as Generalizability Theory.[2] This theory allows estimation of error variances in actually obtained measurements, to be subsequently used for projections to different conditions of measurements, in this case the number of repeated flow rate measurments. The parameters of measurement error may be interpreted as the range of absolute values for an individual patient, which would be found with a 65% certainty (Standard Error of Measurement, SEM) and with a 95% certainty (confidence interval, CI) when the measurements would be infinitly repeated using a different sample of flow rate measurments. The Smallest Detectable Difference (SDD) is the smallest real, non-error, change in performance on an individual level, that can be measured. Based on our material, we estimated these values for single, double and multiple measurements.

Results

Out of a series of 140 men, 100 of them, mean age 63,5 (range 30-85, SD. 10.1) had a series of at least 19 flow rate measurements that could be analyzed. In this sample, the mean Qmax was 11,6 ml/s (SEM 2.6, CI 5.3, SDD 7.2) and mean Qmean was 6.3 ml/s (SEM 0.8, CI 1.6, SDD 2.3). Based on our data set, the SEM, CI and SDD of mean Qmax and mean Qmean are estimated for repeated measurements (Table).

		Number of repeated flow rate measurements							
		1	2	3	10	20	50	75	100
Qmax	SEM	11.5	8.16	6.66	3.65	2.58	1.63	1.33	1.2
(ml/s)	CI	22.5	16.3	13.1	7.2	5.1	3.2	2.6	2.3
	SDD	31.9	23.0	18.4	10.1	7.1	4.5	3.7	3.2
Qmean	SEM	3.5	2.50	2.05	1.12	0.79	0.50	0.41	0.35
(ml/s)	CI	6.9	4.9	4.0	2.2	1.5	1.0	0.80	0.69
	SDD	9.8	6.9	5.7	3.1	2.2	1.4	1.13	0.97

Conclusions

Many flow rate measurements are necessary. The reliability of Qmax is lower than Qmean. At an individual level, approx. 50 measurements are sufficient to detect a difference in Qmax of 2 ml/s.

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A RANDOMISED CONTROLLED TRIAL OF URODYNAMIC INVESTIGATIONS PRIOR TO CONSERVATIVE TREATMENT OF URINARY INCONTINENCE IN THE FEMALE.

AIM OF STUDY Most females with urinary incontinence have a mixed pattern of urinary symptoms and it is normal practice to investigate them by way of urodynamic investigations prior to treatment, in order to establish a diagnosis. The aim of this study was to determine whether prior to first line conservative treatment (bladder retraining and/or physiotherapy) establishing a urodynamic diagnosis and tailoring treatment accordingly actually produced a better outcome than simply treating patients with both treatments together without prior investigations.

PATIENTS AND METHODS Sixty patients complaining of frequency, urgency, nocturia, urge incontinence and stress incontinence were recruited to the trial. Exclusion criteria included any previous treatment for their incontinence, symptoms of haematuria, recurrent dysuria or voiding difficulty, or infection on urine culture. Patients were randomly allocated to either undergo urodynamic investigation by way of uroflowmetry and subtracted filling and voiding cystometry and have treatment appropriate to their urodynamic diagnosis, or to have no investigations but be treated with pelvic floor exercises and bladder retraining as part of a 5 day in patient programme. For the group investigated pelvic floor exercises were used for genuine stress incontinence (gsi), bladder retraining for detrusor instability (di) or hypersensitive bladder and self catheterisation for voiding difficulty.

The treatment period was 3 months. Assessment was made pre and post treatment by way of urinary diary (frequency, nocturia and incontinence episodes), pad test (degree of urinary leakage) and subjective questionnaire including a visual analogue score. Analysis of results pre and post treatment and comparison of change between the 2 groups was performed using t-tests or a Mann Whitney U test where appropriate.

RESULTS Twenty seven patients were allocated to have investigations and 33 were treated without investigation. Twelve patients did not complete the trial, leaving 48 patients available for analysis. In the group investigated 13 patients had gsi, 9 had gsi and di combined, 2 had gsi and a hypersensitive bladder, one had di alone, one had gsi and voiding difficulty and one was normal.

The 2 groups were well matched for age, parity and degree of urinary leakage prior to treatment. The results of treatment are shown in Table 1. Values given are means with (standard deviations). There was a statistically significant improvement post treatment for every parameter studied, other than for loss on pad testing which was not significant for either group. The comparison of improvement between the 2 groups was not significantly different for any parameter. The percentage of patients cured or improved to the extent

that they did not require further treatment was 60% for the group investigated, 71% for the group not investigated, and 67% for the trial overall. This equates well with the cure rates as assessed by the number dry on pad testing at the end of the trial, (65%, 75% and 71%), and those with no incontinence episodes per week, (50%, 57% and 54%).

Table 1

parameter	overall (n=48)		investigated (n=20)		not investigated (n=28)	
	pre	post	pre	post	pre	post
frequency (voids/day)	10.4 (3.9)	6.4 (1.4)	10.4 (3.9)	6.9 (1.3)	10.0 (3.6)	6.0 (1.4)
nocturia (voids/night)	2.1 (1.4)	0.8 (1.0)	2.2 (1.8)	0.9 (1.2)	2.0 (1.1)	0.8 (0.9)
incontinence (times/week)	12.5 (4.1)	3.1 (2.9)	13.5 (4.5)	3.6 (3.1)	11.0 (3.6)	3.0 (2.8)
pad test (loss in g.)	17.6 (26.6)	4.8 (16.1)	21.3 (24.1)	6.0 (19.3)	13.9 (29.0)	3.9 (11.1)
Visual analogue score	7.3 (2.0)	3.8 (2.7)	7.6 (1.5)	4.1 (3.0)	7.0 (2.3)	3.4 (2.4)

CONCLUSIONS Conservative treatment with bladder retraining and pelvic floor exercises combined as an inpatient treatment is an effective first line treatment for female patients with a mixed pattern of urinary incontinence. Undertaking urodynamics and tailoring the treatment to the results did not improve the outcome. Even considering those who did not complete the trial as failures, over half the patients entering the trial did not require further treatment. This suggests that patients presenting with an uncomplicated story of urinary incontinence can be treated conservatively without prior urodynamics allowing us to concentrate the resources required for invasive investigations and treatments for those who fail.

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THE REPRODUCIBILITY OF A NEW METHOD TO MEASURE LEAK POINT PRESSURE IN PATIENTS WITH GSI

AIMS OF STUDY

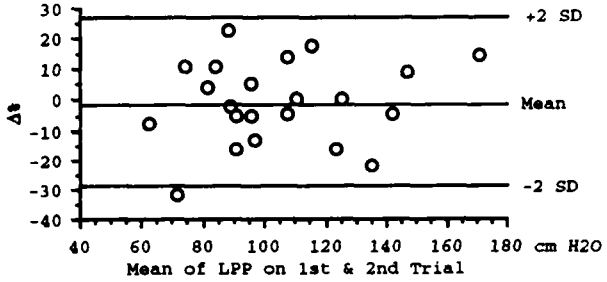
Traditional urodynamics are time consuming and expensive, their reproducibility sometimes questionable. With a foreseeable increase in the number of patients seeking treatment for urinary incontinence, it is of great importance that there are inexpensive, easily interpreted and reproducible methods to evaluate treatment. We present a new method for determining cough induced leak point pressure (LPP) in women with genuine stress incontinence (GSI). The aim of this study was to evaluate the reproducibility of the method.

PATIENTS AND METHODS

Twenty-four patients with a mean age of 49,3 years (range 37-64), who had a urodynamically established diagnosis of GSI, were included in the study. LPP was determined in a semi-recumbent and/or standing position on two separate occasions, one to four weeks apart. To record abdominal pressure increase above the baseline value, a micro tip catheter was placed in the fornix of the vagina. Urinary leakage was detected by measuring distal urethral electrical conductance (DUEC) with a silastic probe placed in the urethra. The DUEC and pressure measurements were recorded simultaneously on a polygraph. With a standardised bladder filling of 300 ml, the patient was asked to cough with gradually increasing strength until leakage was detected. Two to three such series, with a pause of 15-20 seconds between series, were performed in the semi-recumbent position and then repeated in the standing position. The average of the highest pressure recorded without leakage and the lowest pressure recorded with concomitant leakage was used as the LPP.

RESULTS

For 20 patients, there were recordings both in the standing and semi-recumbent position. For two patients, there were recordings only in the semi-recumbent position and for another two only in the standing position. The median of LPP in the recumbent position was 96,5 cm H_2O (range 71-173) and 98,5 cm H_2O (range 60-180) on initial and repeat investigation respectively. The corresponding figures for the standing position was 99,0 cm H_2O (range 65-158) and 98,0 cm H_2O (range 60-183). Since there was no significant difference in reproducibility between results obtained in the semi-recumbent and standing position, data will be presented for the standing position only. The regression line for the correlation between two observations was $y=4,7+0,95 \cdot x$ ($r=0,76$). The absolute difference between initial and repeat measurements increased with increasing LPP, whereas the percentual difference was independent of LPP. The mean of the percentual difference between measurements was -1,1 (SD=13,8). To visualise the agreement between tests, the percentual difference in LPP between initial and repeat testing was plotted against the mean of the LPP on initial and repeat testing in the same patient:



DISCUSSION

By this method of determining LPP, urethral competence was assessed while creating minimal interference to its function. The test was easy to perform; since patient position did not alter reproducibility, measurements in the recumbent position can be left out. A difference between recordings of more than 28% carries a 95% probability of representing a true difference. The reproducibility of this method thus seems better than that of other quantitative tests, e.g. pad tests. The method should be of value in detecting GSI as well as in following the results of treatment in individual patients. It should also be useful in comparing results between centres. To validate the method further, it should be tested against other measures for GSI.

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SINGLE FIBRE EMG AND FIBRE DENSITY IN PATIENTS WITH URETHRAL SPHINCTER DYSFUNCTION.

AIMS OF STUDY

Single fibre EMG (SFEMG) and fibre density (FD) estimation is a well established method which gives a quantitative measure of the degree of denervation/reinnervation in the skeletal muscles. The method also has proved of diagnostic as well as of prognostic value in patients with external anal sphincter dysfunction. The method has however not gained much approval in evaluation of urethral sphincter dysfunction. The urethral sphincter is small and recording single muscle fibres within the sphincter is technically difficult. Furthermore, obtaining enough single fibre potentials to calculate a reliable FD may be time consuming. In addition there is no normative data on FD in the urethral sphincter. The muscle has a continuous activity or tonus and the motor unit potentials

are small and often difficult to distinguish from spontaneous abnormal fibrillation potentials with a conventional concentric EMG needle. Interpretation of conventional EMG from the urethral sphincter thus can be ambiguous.

PATIENTS AND METHODS

In the present preliminary study we have successfully recorded single fibre signals from 25 patients with various forms of urethral sphincter dysfunctions.The results were compared to those obtained from concentric needle EMG and to conventional manometric parameters of the urethral sphincter function.

RESULTS

Our results confirm that the pathophysiology of urethra dysfunction is different in patients with central and peripheral nerve lesions. Thus, FD was low (normal ?) in patients with a dysfunction caused by central nervous diseases while significantly higher in various types of peripheral nerve lesions.

FD estimation was as a rule more accurate than conventional EMG. In several patients SFEMG showed a clearly increased FD while the concentric EMG was normal or equivocal.

CONCLUSIONS

We think SFEMG and estimation of FD is a better method for diagnosis of urethral sphincter dysfunction than conventional concentric EMG. FD is superior in differentiating between peripheral and central nervous causes. When normative FD data from the urethral sphincter are established, the method alsc will offer a quantitative picture of the degree of denervation and reinnervation of the muscle and thus be of importance for prognosis and further treatment. We propose that the method should be included in the routine examination of all patients with various forms of urethra dysfunction.

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ABNORMAL SPINAL MRI IN PATIENTS WITH VOIDING DYSFUNCTION

AIMS OF STUDY

Indications for spinal cord magnetic resonance imaging (MRI) in patients with voiding dysfunction are currently unclear.In addition, the high incidence of abnormal findings in asymptomatic patients (57%) complicate interpretation of results [1]. We asked whether one or more historical, physical, urodynamic, or ultrasonographic parameters were predictive of an abnormal MRI in patients presenting to urology clinic with voiding dysfunction.

METHODS

The neurourologic history, physical exam, urodynamics, and ultrasonography findings were correlated to MRI in all urology patients undergoing imaging from 1991-1993.The neurourologic history including queries for combined bladder, bowel and sexual dysfunction, history of spinal cord injury or trauma, history of multisystem or familial neurologic complaints, and previously diagnosed myelomeningocele was obtained. Physical exam evaluated lumbosacral dermatomes and lower back abnormalities. Urodynamics included cystometrograms with the addition of electromyography or fluoroscopy as indicated. Ultrasonography was reviewed in respect to bladder wall thickness, presence or absence of hydronephrosis, and post void residual. Blinded review of MRI studies was performed by a neuroradiologist. Chart review documented management of abnormal MRI findings after neurosurgical review.Multivariate analysis was performed to demonstrate single or additive value of study parameters in deciding to obtain an MRI.

RESULTS

Twenty-eight patients from 2 to 77 years of age (18 female, 10 male) underwent spinal cord imaging for suspected, but undiagnosed, neurologic disorders. Abnormal lumbosacral exam findings (8/11,73%), changes in urodynamic parameters in myelomeningocele patients (3/3,100%), and the presence of detrusor sphincter dyssynergia (DSD) (2/2,100%) demonstrated the highest correlation with spinal cord pathology as determined by MRI Other historical, physical, or urodynamic parameters were not predictive of spinal cord pathology. Presence of incontinence or elevation of post void residual also failed to predict spinal cord patholgy. Overall, 13 of 28 patients (47%) demonstrated abnormalities on MRI. However, only 8/28 (28%) of the abnormalites were felt to contribute to voiding dysfunction or required surgical intervention as determined by neurosurgical review.

CONCLUSIONS

The presence of abnormalities on lumbosacral exam, presence of DSD, or changes in urodynamic parameters in myelodysplastic patients warrant

spinal cord imaging. Other findings such as combined bladder, bowel, and sexual dysfunction are not highly correlated with spinal cord abnormalities.Larger prospective studies are needed to determine the value of MRI in the evaluation of patients with voiding dysfunction and suspected neurologic disease. It remains to be determined which subtle abnormalities detected by spinal MRI can contribute to voiding dysfunction

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ULTRASOUND BLADDER WALL MEASUREMENT - A NON-INVASIVE SENSITIVE SCREENING TEST FOR DETRUSOR INSTABILITY

AIMS OF STUDY

Laboratory cystometry has been found to be less sensitive in diagnosing detrusor instability than ambulatory urodynamics, but the later technique is labour intensive and time consuming. A non-invasive screening technique for detecting detrusor instability would be useful.

METHODS

One hundred and eighty women with urinary symptoms were studied. All women voided prior to being scanned. The bladder was imaged using a 5MHz transvaginal ultrasound probe, women were only included if the post-micturition residual was measured to be less than 30 mls. The bladder wall thickness at the dome, anterior bladder wall and trigone were measured at double magnification. The women then underwent videocystourethrography(VCU). A pilot study indicated that women with a bladder wall thickness greater than 5mm were more likely to have detrusor instability(1). Thus if the mean bladder wall thickness was found to be greater than 5mm and detrusor instability was not diagnosed the women underwent ambulatory urodynamics for 5 hours on a separate day.

RESULTS

The diagnoses on videocystourethrography were:

Diagnosis	Detrusor Instabilit	Genuine Stress Incont.	Mixed Incontin.	Sensory Urgency	Voiding Difficult.	Normal UDS
Numbers	43	52	43	5	3	34

Forty two women with a stable cystometry but with a mean bladder wall thickness greater than 5mm, and they underwent ambulatory urodynamics.

Of these women thirty six had detrusor instability. One hundred and eight women had a mean bladder wall thickness greater than 5mm. The median and interquartile range for all the women studied are shown in table 2.

Seventeen women had a mean bladder wall thickness less than 3.5mm, three women had detrusor instability on VCU, four women had normal urodynamics and on ambulatory urodynamics none of these women had detrusor instability. The positive predictive value of a mean bladder wall thickness greater than 5mm to diagnose detrusor instability is 94%. VCU in these women had a positive predictive value of 65%. In the group of women with a mean bladder wall thickness less than 3.5mm the positive predictive value for diagnosing genuine stress incontinence for VCU was 76% and for mean bladder wall thickness it was 82%.

Bladder wall thickness for the group studied: TABLE 2

Diagnosis	Median	Interquartile Range	Mann Whitney U Test
Detrusor Instability	6.3	5.3 - 7.7	P < 0.0001
Other groups	3.9	3.4 - 4.5	

CONCLUSION

Measurement of bladder wall thickness with transvaginal ultrasound is a sensitive screening method for diagnosing detrusor instability in certain women and may be also be useful in excluding detrusor instability in a smaller group of symptomatic women.

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DOSE THE MENSTRUAL CYCLE INFLUENCE CYSTOMETRY ?

AIMS

The lower urinary tract and genital tracts share a common embryological origin therefore steroid hormones influencing the genital tract may also affect bladder and urethral function. Increased urethral pressures have been reported in premenopausal women compared to postmenopausal women; administration of oestrogens to postmenopausal women caused a rise in urethral

pressure measurements (1 & 2). There is an isolated case report that detrusor instability is more severe during menstruation, a prostaglandin mediated effect (3). Taking these facts into consideration it would seem likely that cystometry may be affected by the menstrual cycle. In this retrospective study we wish to determine the relationship between menstrual phase and urodynamic diagnosis.

PATIENTS AND METHODS

Consecutive case records of 687 patients attending the urogynaecological outpatients were analysed. One hundred and twenty four (18%) women were still having regular menstrual periods. The date of the first day of the last menstrual cycle and urodynamic diagnosis was extracted. Thirteen patients with recurrent urinary infection and one with a fistula were excluded.

RESULTS

Forty two (38%) mean age 35.3 years (range 22-48) complained that their urinary symptoms were adversely influenced by their menstrual cycle, the symptoms of the other 68 mean age 35.2 years (range 25-50) were unaffected.

Table 1 shows the timing and results of urodynamic investigation in 42 patients whose symptoms are affected by their menstrual cycle (none were performed during menstruation).

AFFECTED	NORMAL	DI	GSI	DI & GSI
FOLLICULAR	5(12%)	10(24%)	3(7%)	2(5%)
LUTEAL	11(26%)	10(24%)	1(2%)	0

Table 2 shows the timing and results of urodynamic investigation in 68 patients whose symptoms are unaffected by their menstrual cycle.

UNAFFECTED	NORMAL	DI	GSI	DI & GSI
FOLLICULAR	1(1.4%)	17(25%)	12(18%)	4(6%)
LUTEAL	9(13%)	11(16%)	3(4%)	4(6%)
MENSES	2(3%)	2(3%)	1(1.4%)	2(3%)

In both affected and unaffected groups the majority of normal cystometric diagnoses were made in the luteal phase of the cycle. Diagnoses of GSI, DI and mixed GSI and DI were most frequently made in the follicular phase of the cycle. More normal cystometric diagnoses were made in the affected group (38%) compared to the unaffected group (17.4%).

CONCLUSIONS

The results of this preliminary study indicate that the timing of cystometric evaluation may influence detection of a positive

diagnosis. The luteal phase may not be the correct time to make an accurate diagnosis especially in patients whose symptoms are affected by their menstrual cycle.

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EVALUATION OF mRNA ENCODING MUSCARINIC RECEPTOR SUBTYPES IN HUMAN DETRUSOR MUSCLE

AIMS OF STUDY

The muscarinic receptor (MR) is pharmacologically classified into M_1, and M_2 and M_3 subtypes on the basis of the characteristic responses to putative selective MR antagonists. Those that exhibit a high affinity for pirenzepine, AF-DX 384 and pFHHSiD are designated M_1 (nerve tissue), M_2 (cardiac) and M_3 (smooth muscle/glandular) receptors, respectively. When the MR subtypes in the same tissue are studied, however, there is a limitation to the pharmacological methods or binding assays because these MR antagonists are relatively selective for each subtype.

Recently, complementary DNA for the MRs were cloned(1), suggesting a molecular biological classification of MR into m_1, m_2, m_3, m_4 and m_5 subtypes. Thus, instead of the pharmacological methods, the MR subtypes in a given tissue can be discriminated by evaluating mRNA encoding these subtypes. The present study was undertaken to determine the MR subtypes corresponding to m_1 to m_5 genes in human detrusor muscle. In addition, the tissue location of the subtypes was studied by the in situ hybridization method.

METHODS

Detrusor muscle was obtained form patients who were urodynamically normal at the time of operation. The total RNA was extracted from detrusor muscle and the corresponding cDNA were obtained by reverse transcription. Primers were designed on the basis of nucleotide sequence for each human MR subtype and cDNA was

amplified by polymerase chain reaction (PCR). Agarose gel electrophoresis was performed to validate the RT-PCR products. In order to evaluate the tissue location of MR subtypes, synthetic probes which discriminate among each mRNA subtype were labelled with digoxigenin. Cryostat sections of detrusor muscle were hybridized with a labelled probe and developed using a dig.-detecting kit.

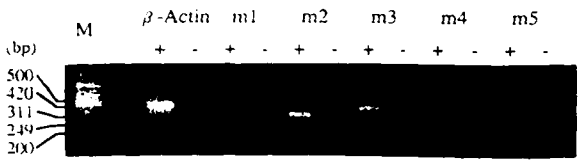
RESULTS

In human detrusor muscle, mRNAs encoding m_2 and m_3 subtypes were strongly detected by the RT-PCR method. However, the PCR products derived from m_1, m_4 and m_5 subtypes were not detected (Fig. 1). The amounts of these products were calibrated using plasmid DNA which contained either m_2 or m_3 RT-PCR products, and the cDNA concentrations for m_2 and m_3 mRNA subtypes were calculated to be 0.46 and 0.58 attomole/ μg of total RNA, respectively. The presence of both m_2 and m_3 mRNA subtypes in detrusor muscle was also confirmed by the in situ hybridization. In the sections of detrusor, the synthetic probes were clearly hybridized with the mRNA encoding m_2 and m_3 subtypes. In contrast, no hybridizable mRNA was found for m_1,m_4 and m_5 receptors. The m_2 and m_3 receptors were located in the muscle, and not in the interstitial region.

CONCLUSIONS

In the present study, both m_2 and m_3 MR subtypes were distinctively detected in human detrusor muscle. Since the molecular biological subtypes m_1, m_2 and m_3 are considered to correspond approximately to the pharmacological subtype M_1, M_2 and M_3, respectively, the results of this study suggest that human detrusor muscle possesses $M_2(m_2)$ as well as $M_3(m_3)$ receptors. With regard to functions of these subtypes, the $M_3(m_3)$ receptors seem to mediate detrusor contraction through activation of phosphatidylinositol turnover, as generally demonstrated in the visceral smooth muscle. However, the presence of the $M_2(m_2)$ subtype in the detrusor muscle is of interest, but its functional role is unkown. It may be speculated that the $M_2(m_2)$ receptor in the detrusor muscle couples with inhibition of adenylate cyclase and regulates the contraction of bladder smooth muscle.

Figure 1.



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CHANGES IN CHOLINERGIC AND PURINERGIC NEUROTRANSMISSION IN PATHOLOGIC BLADDER OF CHRONIC SPINAL RABBIT

AIMS OF STUDY

It is generally accepted that urinary bladder receives a dual excitatory innervation from cholinergic and purinergic nerves. However, our recent study(1) has demonstrated that anticholinergic agents such as Oxybutynin and Atropine markedly suppress a hyperreflexic detrusor contraction in chronic spinal rabbit rather than a micturition contraction in normal rabbit. This may suggest a possibility that a cholinergic transmission becomes dominant in the bladder of paraplegic animal. Thus, the present study was undertaken to determine whether a postganglionic neurotransmission is altered in this type of pathologic bladder.

METHODS

Urinary bladders taken from 10 normal male rabbits(3kg in weight) and 12 chronic spinal rabbits were used in this experiment.In order to make spinal rabbits,a laminectomy was performed at the T_{10} segment and the spinal cord was transected.These rabbits with detrusor hyperreflexia and detrusor sphincter dyssynergia(DSD) were sacrificed 28 days after laminectomy.Detrusor muscle strips(1× 5mm) were prepared and mounted by means of silk ligatures in organ bath(5ml) containing oxygenated Krebs solution.Transmural stimulation of nerves was performed with the preparations suspended between platinum electrodes,using an electric stimulator(supramaximum voltage,0.5msecduration,20Hz frequency). The responses to electrical stimulation and agonists were determined by recording the isometric tension of muscle strips.

RESULTS

Both normal and pathologic detrusor strips contracted frequency dependently in response to electrical field stimulation.These contractions were abolished by tetrodotoxin(1μM).As a maximum response was obtained at 20Hz in both strips,this frequency of stimulation was used for the following analysis.In normal detrusor strips,atropine dose-dependently reduced the contractile responses to electrical stimulation and left an atropine resistant contraction at the concentrations from 0.5 to 1.0μM(Fig.1 and Fig.2).The atropine resistant contraction(1.0μM atropine) was completely abolished by desensitization of purine receptors with repeated exposure to α, ß-methylene ATP(10μM).Thus,the atropine sensitive(cholinergic) and the atropine resistant (purinergic) components were 41.5±7.0%(n=15) and 58.5±7.0%(n=15) of the control response, respctively.However,in pathologic detrusor strips,an inhibitory effect of atropine was more potent than that in normal strips(Fig.1 and Fig.2).The cholinergic component was increased to

75.0±7.1%(n=15).The atropine resistant contraction was also abolished by pretreatment with α,β-methylene ATP,and thus,the purinergic component was decreased to 25.0±7.1%(n=15). Acetylcholine(0.1 to 90μM) and ATP(0.01 to 4mM) produced the dose dependent contractions of detrusor strips.The dose-response curves for each agonist did not show the significant differences between normal and pathologic detrusor.

CONCLUSIONS

The present study demonstrates that in the pathologic bladder obtained from chronic spinal rabbit,the contribution of cholinergic transmission to detrusor contraction is considerably increased whereas the purinergic component is decreased.Thus,it is suggested that the postganglionic neurotransmission may be shifted to a cholinergic dominance in hypereflexic bladder with DSD.However,a mechanism causing this change remains unsolved.

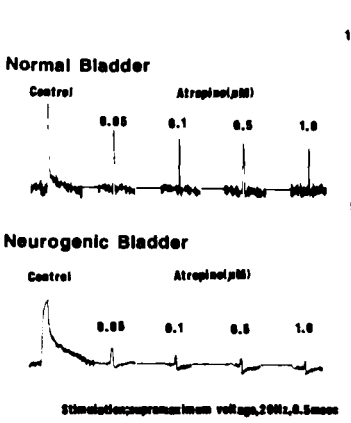

Fig.1

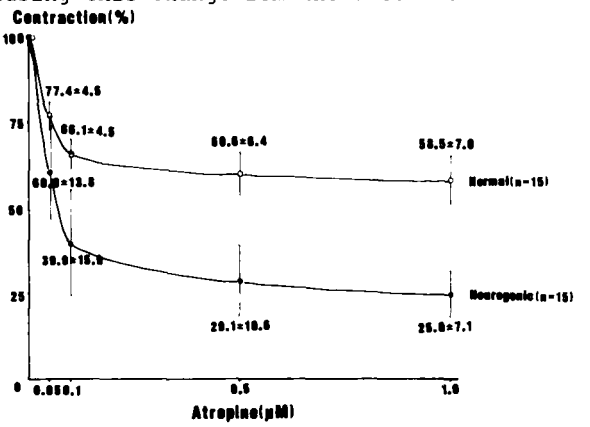

Fig.2

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SUBTYPE OF NEUROKININ NK_2 RECEPTOR MEDIATING CONTRACTION OF HUMAN URINARY BLADDER

AIMS OF STUDY

Neurokinin A is a neuropeptide which acts via NK_2 receptors to contract many smooth muscle tissues including human bladder. NK_2 antagonists may therefore be potentially useful to treat detrusor instability. Recent work has suggested that there may be two NK_2 subtypes. For example, the competitive peptide antagonists L 659,877 and R396 had an affinity more than 10 times higher in the hamster trachea compared with the endothelium denuded rabbit

pulmonary artery whereas the opposite selectivity was reported for MEN 10,207 (1,2). Human bladder contains only NK_2 receptors. Therefore the aim of these experiments was to use these compounds to see if the NK_2 receptor mediating contraction of human bladder resembled pharmacologically one of these putative subtypes and also to use the novel NK_2 peptide antagonist GR 94800 (3) and the novel non-peptide NK_2 antagonist SR 48,968 (4), to see if they showed any selectivity.

PATIENTS AND METHODS

Human bladder (n=15) was obtained at the time of elective surgery from patients with functionally normal bladders (age range 35-60 years). Detrusor muscle strips from the bladder dome were set up *in vitro* in Tyrode solution at 37°C. A maximal contraction to NKA ($3x10^{-6}$M) was measured first in each strip followed by either a control concentration-effect curve to NKA or one in the presence of an antagonist. Antagonist concentrations were equilibrated for at least 15 minutes. Their effect was measured as the dose-ratio of the NKA EC_{50} in the presence and absence of the antagonist from which pA_2 values were calculated.

RESULTS

Neurokinin A ($1x10^{-9}$-$3x10^{-6}$M) contracted human bladder strips with a pD_2 of 7.72±0.06 and maximum contraction of 2.00±0.38g. Preliminary experiments showed that the presence of the peptidase inhibitors thiorphan, amastatin, bestastin, phosphoramidon and captopril did not alter the potency of NKA. All five antagonists moved the NKA curve in parallel to the right and no decrease in maximum contraction was observed. Schild plots based on the dose ratio shifts of these curves gave pA_2 values (and slopes ± SEM) as follows: L 659,877 7.1 (1.0±0.1), MEN 10207 5.8 (1.0±0.1), R396 6.4 (1.0±0.1), GR 94800 9.4 (1.1±0.2) and SR 48,968 9.3 (1.0±0.1).

CONCLUSIONS

The affinities of the antagonists in human bladder do not fit either pattern of the two proposed subtypes. For example, while the affinity of L 659,877 is close to that reported in the rabbit pulmonary artery, that for MEN 10,207 is close to that in the hamster trachea and that for R396 and SR 48,968 fall midway between those reported in the other two tissues. GR 94800 had a similar affinity in the human bladder to the rat colon (which is similar to the hamster trachea for the other antagonists). This pattern of affinities cannot be explained by the presence of a mixed population of both subtypes. There is currently no firm evidence for the existence of both subtypes within a single species and so the different pharmacological profiles could be explained by species heterogeneity of NK_2 receptors rather than the existence of true NK_2 subtypes. These results suggest that the human NK_2 receptor in the bladder is different to both the rabbit and hamster NK_2 receptor and that differences between all three may partly be due to species heterogeneity.

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α_{1C}-ADRENOCEPTOR IN HUMAN PROSTATE: CORRELATION WITH CLONED α_1-ADRENOCEPTOR SUBTYPES

AIMS OF STUDY

Benign prostatic hyperplasia (BPH), can be treated therapeutically using α_1-adrenoceptor antagonists e.g. prazosin. This blocks the contraction of smooth muscle due to the release of noradrenaline from sympathetic nerve terminals. It has been demonstrated that the contraction of human prostate is mediated by an α_{1C}- and not via an α_{1A}- or α_{1B}-adrenoceptor subtype (1). This classification was based on the effects of the alkylating agent chlorethylclonidine and the affinity of the competitive antagonist WB 4101. The aim of the present work was to compare the affinities in the prostate of a number of competitive antagonists which have some subtype selectivity with their affinities in binding studies using membranes from rat 1 fibroblast cells expressing only one of the three cloned receptor subtypes (2).

PATIENTS AND METHODS

Human prostate (n=12) was obtained at transurethral prostatectomy from patients aged 60-85 years. Muscle strips were set up *in vitro* in Tyrode solution at 37°C and cumulative concentration-contraction curves were recorded isometrically. Antagonists were equilibrated for 30 minutes. Their effect was measured as the dose-ratio of the noradrenaline EC_{50} in the presence and absence of the antagonist from which pA_2 values were calculated.

RESULTS

The antagonists shifted the noradrenaline concentration-contraction curve in parallel to the right with no apparent reduction in the maximum response. The calculated pA_2 values (and Schild slope ± SEM) were as follows: WB 4101 9.0 (0.9±0.1), 5-methyl urapidil 8.6 (1.0±0.2), phentolamine 7.6 (1.1±0.1), benoxathian 8.5 (1.0±0.2) and spiperone 7.3 (1.0±0.1). These values have been correlated with K_i values for the same antagonists published for the cloned α_1-adrenoceptor subtypes in rat 1 fibroblast cells (2). The correlation coefficient (and slope of the regression line ± SEM) for the affinities in the prostate with cloned rat α_{1a}-, hamster α_{1b}- and bovine α_{1c}-subtypes were 0.74 (0.77±0.41), -0.32 (-0.17±0.30) and 0.95 (0.82±0.15) respectively.

CONCLUSIONS

A series of 5 competitive antagonists has been compared at α_1-adrenoceptors in human prostate. The best correlation of the functional data with the binding data from cloned receptor subtypes in cell lines supports the conclusion that an α_{1C}-adrenoceptor subtype mediates noradrenaline contractions in human prostate. These results provide further support for a selective α_{1C}-adrenoceptor antagonist having the potential to be prostate selective and to advance the treatment of BPH.

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HAVE ALPHA$_{1A}$-ADRENOCEPTORS A FUNCTIONAL ROLE IN MEDIATING CONTRACTIONS OF THE HUMAN PROSTATE.

AIMS OF THE STUDY

It has been shown that the human prostate expresses mRNA for the three cloned adrenergic receptors; alpha$_{1A}$, alpha$_{1B}$ and alpha$_{1C}$ (1). The role each subtype plays in contraction of prostatic smooth muscle is not clear, but previous studies have suggested that contraction of the human prostate is mediated primarily via alpha$_{1C}$-adrenoceptors (2). However, thirty percent of the mRNA coding for alpha$_1$-adrenoceptors in the prostate codes for the alpha$_{1A}$-adrenoceptor subtype and whether this receptor plays a role in functional responses is unclear.

It has been suggested that responses mediated via the alpha$_{1A}$-adrenoceptor involve the influx of calcium through L-type calcium channels. Thus, nifedipine markedly reduces the alpha$_{1A}$-adrenoceptor mediated contractions of the rat vas deferens, but has no effect on the alpha$_{1B}$-mediated contractions of the rat spleen (3). In this study nifedipine and also abanoquil, a selective alpha$_{1A}$-adrenoceptor antagonist (4), have been used to evaluate the role of alpha$_{1A}$-adrenoceptors in contraction of the human prostatic smooth muscle.

METHODS

Human prostate tissue, obtained from transurethral resection procedures, were set up under 1g tension in tissue baths in Krebs-bicarbonate solution at 37°C, aerated with 95% O_2 and 5% CO_2. Cumulative concentration-response curves were obtained to noradrenaline in the absence and in the presence of 1μM nifedipine, or abanoquil(10 or 30nM). All responses were obtained to noradrenaline in the presence of cocaine (10μM) and corticosterone (10μM) to block uptake of noradrenaline and propranolol (1μM) to antagonise ß-adrenoceptors.

RESULTS

Nifedipine had no significant effect on the noradrenaline EC_{50} values, the mean values (with 95% confidence limits) being 5.6(1.8-20)μM and 10(2.6-40)μM in the absence and presence of nifedipine respectively (n=6). Calcium channel blockade did however significantly reduce the maximal responses of prostatic contraction to noradrenaline. Maximum responses were reduced by 44±5.6% from 0.79±0.09g to 0.45±0.06g (n=6) in the presence of 1μM nifedipine (P<0.005).

Abanoquil (10nM) produced rightward shifts of noradrenaline concentration-response curves, significantly increasing (P<0.05) EC_{50} values from 2.6(0.97-6.8)μM to 19(2.9-127)μM (n=6). This concentration of abanoquil caused a slight reduction (30±6%) in the maximum

response of the tissue to noradrenaline from 1.35±0.39g to 0.92±0.27g. Increasing the concentration of abanoquil 3-fold to 30nM did not result in any further shift of the concentration-response curves and produced a similar reduction in the maximal response of the tissue to noradrenaline, (30±7%).

CONCLUSIONS

This study provides the first functional evidence supporting a role for $alpha_{1A}$-adrenoceptor mediated contraction in the human prostate. The substantial component of the response resistant to antagonism by abanoquil would suggest that the predominant receptor subtype in this tissue is the $alpha_{1C}$-adrenoceptor. This study however, demonstrates that the $alpha_{1A}$-adrenoceptor subtype is also implicated in the responses of the prostate to noradrenaline.

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REC 15/2739, A NEW α_1-ANTAGONIST SELECTIVE FOR THE LOWER URINARY TRACT: IN VIVO STUDIES.

AIM OF THE STUDY

Rec 15/2739 (N-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide) is a new highly selective $alpha_1$-blocker synthetized in Research Department (IT-MI91A408, 1992; US 888775, 1992), within a project aiming to discover new selective antagonists for the treatment of benign prostatic hyperplasia (BPH). The aim of this study was to simultaneously evaluate the effects of Rec 15/2739 and currently used reference compounds on the prostatic urethral contractions and systemic blood pressure in animal models suitable to investigate the dynamic phase of BPH. The main unwanted

side effect typical of this class of compounds (orthostatic hypotension) was also studied.

METHODS

In male anaesthetised dogs and rabbits, blood pressure (BP) and intraurethral prostatic pressure (IUP) were monitored via Mikro-tip pressure transducers introduced into the aortic arch through the right common carotid artery and the external urethral meatus, respectively.

In dogs, the increases of IUP were evoked by electrical stimulation of hypogastric nerves (HGN: 10 V, 15-30 Hz, 5msec, 7 sec), or by intraarterial administration (iliac artery) of noradrenaline (NA: 0.5-1 µg/kg) . In rabbits, increases in IUP were obtained by i.v. injection of NA. The compounds were tested intravenously (i.v.) in cumulative way and/or intraduodenally (i.d.) in a single dose. The ratio between the doses effective in lowering diastolic BP (ED_{25}) and in inhibiting the IUP increase (ID_{50}), was assumed as an index of selectivity for the lower urinary tract. Orthostasis was studied in conscious dogs and rats.

RESULTS

After i.v. administration in dogs, the potency of Rec 15/2739 in antagonizing the IUP increase was similar to prazosin and (R)-YM-12617, but higher than that of phentolamine and terazosin (see table). The effects on DBP were more variable, with ED_{25} ranging from 77 to 243 µg/kg. This variability was most likely a consequence of the inherent variability in the degree of anaesthesia. Nevertheless, the effects of Rec 15/2739 on DBP were clearly lower than those exerted by the reference compounds.

The "uro-selectivity index" of our novel compound in this animal species was significantly higher than that of prazosin, terazosin, phentolamine and (R)-YM-12617. A better selectivity than that observed with (R)-YM-12617 was also retained after intraduodenal administration. After i.v. administration in rabbits, Rec 15/2739 was less potent than (R)-YM-12617 in inhibiting the urethral contractions induced by NA, however its hypotensive effects were again low and its "uro-selectivity index" significantly higher than that of the reference compound.

Compound	Animal species	Agon.	Route	Urethra (ED_{50})	DBP (ED_{25})	ratio
Rec 15/2739	dog	NA	i.v.	2.4	243.1	101.29
(R)-YM-12617	dog	NA	i.v.	1.1	11.4	10.36
Prazosin	dog	NA	i.v.	3.6	6.6	1.83
Phentolamine	dog	NA	i.v.	12.6	124.4	9.87
Rec 15/2739	dog	HGN	i.v.	3.2	76.9	24.03
(R)-YM-12617	dog	HGN	i.v.	4.5	15.5	3.44
Prazosin	dog	HGN	i.v.	10.2	10.0	0.98
Terazosin	dog	HGN	i.v.	19.9	77.9	3.91
Rec 15/2739	dog	HGN	i.d.	53.1	1652.0	31.11
(R)-YM-12617	dog	HGN	i.d.	12.9	50.0	3.88
Rec 15/2739	rabbit	NA	i.v.	5.5	36.9	6.71
(R)-YM-12617	rabbit	NA	i.v.	1.5	1.1	0.73

In conscious rats i.v. Rec 15/2739 (1-10 mg/kg) produced a a dose-related reduction of tilt induced blood pressure increases, but did not convert the

pressor response to depressor (i.e. did not induce orthostatic hypotension). Prazosin and terazosin inhibited the blood pressure response at doses ≥ 0.01 and ≥ 0.03 mg/kg, respectively, and both induced orthostatic hypotension at doses ≥ 0.1 mg/kg. Similar results were observed in conscious dogs, where Rec 15/2739 produced less blockade of the tilt response than terazosin, and did not induce orthostatic hypotension at i.v. doses < 1 mg/kg.

CONCLUSIONS

These in vivo studies indicate that Rec 15/2739 inhibits prostatic urethral contractions at very low doses, distinctly below those required to obtain an effect on blood pressure. Rec 15/2739 is a potent and higly uro-selective α_1-antagonist, with minimal risk of unwanted cardiovascular side-effects. This agent is currently under investigation for the symptomatic treatment of BPH.

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REC 15/2739, A NEW α_1-ANTAGONIST SELECTIVE FOR THE LOWER URINARY TRACT: IN VITRO STUDIES.

AIM OF THE STUDY

Rec 15/2739 (N-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide) is a new highly selective alpha$_1$-blocker recently synthesized in our laboratories (1), within a project aiming to discover new, more selective α_1-antagonists to be used in the symptomatic treatment of benign prostatic hyperplasia (BPH). The aim of the present study was to provide the receptor binding profile of the compound and to evaluate its functional α_1-antagonist activity on two different tissues (receptors): rabbit urethra (α_{1a}) and rat aorta (α_{1b}), in comparison to selective α-antagonists.

METHODS

1. **Receptor binding studies:** the affinity of Rec 15/2739 and reference compounds for α_2- and β-adrenoceptors, 5-HT$_{1a}$ and 5-HT$_2$ serotonergic and D2 dopaminergic receptors was evaluated as displacement of specific tritiated ligands from different membrane preparations (2). The affinity of the compounds for the α_1-adrenoceptors was evaluated as displacement of specific [^{3}H]prazosin binding from membranes of rat cerebral cortex (α_1), rat hippocampus pretreated with chloroethylclonidine (α_{1a}), rat liver (α_{1b}), rabbit liver (α_{1c}), human prostate tissue (α_{1HP}) and from cloned $\alpha_{1a/d}$ (rat), α_{1b} (hamster) and α_{1c} (bovine) - receptors expressed in rat fibroblast cells (obtained from S. Cotecchia, University of Lausanne - CH). 2. **Functional studies:** the functional α_1-antagonistic activity of the compounds was studied on noradrenaline-induced contractions of rabbit urethra and rat aorta strips. Antagonist potency was

expressed as pA_2 values by Schild regression analysis.

RESULTS

1. Receptor binding studies

Rec 15/2739 showed higher affinity for α_1-adrenergic (K_i: 10.01 nM) and 5-HT_{1a} serotoninergic receptors (K_i: 6.1 nM) than for α_2-adrenoceptors (K_i: 92.4 nM), D_2 dopaminergic (K_i: 100.2), 5-HT_2 (K_i: >500 nM) and β-adrenergic receptors (K_i: 4282 nM). Binding of Rec 15/2739 to 5-HT_{1a} receptors was competitive and the compound behaved as an agonist or partial agonist on forskolin-stimulated adenylate-cyclase activity.

The affinity of Rec 15/2739 for the α_1-adrenoceptors was further investigated on the animal α_1-adrenoceptor subtypes and on α_1-adrenoceptor of human prostate.

Table: affinity (K_i nM) for α_1-adrenoceptor subtypes.

compounds	Native α_{1a}	Native α_{1b}	Native α_{1c}	Cloned $\alpha_{1a/d}$	Cloned α_{1b}	Cloned α_{1c}	Prostate α_{1HP}
Rec 15/2739	1.34	11.10	6.07	43.95	60.68	0.41	2.04
prazosin	0.93	0.36	0.99	2.79	0.56	1.21	0.29
terazosin	5.81	3.55	31.21	84.81	31.07	43.17	n.d.
(R)-YM-12617	0.20	4.06	0.80	4.56	6.80	0.22	0.29
phentolamine	16.37	89.33	34.70	97.02	236.30	34.35	13.46
spiperone	37.81	1.55	22.22	27.87	8.29	24.52	8.31
5-CH_3urapidil	4.66	220.24	17.41	800.84	1222.90	2.10	6.89

In native receptors, Rec 15/2739 and (R)-YM-12617 proved selective for the α_{1a}- versus α_{1b}-adrenoceptor subtypes, in contrast to prazosin. Studies utilizing the cloned adrenoceptors indicated that the compound is very selective for the cloned α_{1c}-subtype. The affinity of the tested compounds for α_1-adrenergic receptors of human prostate (α_{1HP}) correlated with the affinity for native α_{1a}- and native and cloned α_{1c}-adrenergic subtypes.

2. Functional α_1-antagonistic activity

Rec 15/2739 was studied in comparison to the aforementioned α_1-antagonists. Rec 15/2739, in both tissues, behaved as a competitive antagonist. Its potency on rabbit urethra (pA_2: 8.60) was similar or better than that of prazosin (pA_2: 8.15), whereas on rat aorta the compound (pA_2: 8.84) proved 25 fold less potent than prazosin (pA_2: 10.24). Furthermore, our results confirmed the reported α_1-subtype distribution for these tissues.

CONCLUSIONS

Rec 15/2739 showed a high affinity for α_1-adrenergic receptors. The high affinity for α_1-adrenoceptors in human prostate was comparable to that found for α_{1a} and for α_{1c}-adrenergic subtypes. Our compound also showed a potent functional α_1-antagonistic activity, selective for the α_{1a}-subtype in comparison to prazosin. Since the contraction of human prostate is reportedly mediated by α_{1a}-adrenoceptors (3) and/or α_{1c}-adrenoceptors (4), Rec 15/2739 is a prostate selective alpha blocker that may be useful as a treatment for BPH.

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THE ABRAMS-GRIFFITHS NUMBER: A SIMPLE WAY TO QUANTIFY BLADDER OUTFLOW OBSTRUCTION

Aims of Study : Bladder outflow obstruction (BOO) can only be defined by pressure-flow (PQ) measurement. Methods of expressing the degree of BOO have preoccupied members of ICS for many years. The old methods of urethral resistance calculation have been abandoned, to be superseded by newer methods that relate pressure to flow. These methods vary in their complexity and some require computer analysis. This study looks at a simple way of quantifying the degree of obstruction and compares the Abrams-Griffiths (AG) number with group-specific urethral resistance factor, URA (1) and Schäfer's method of assessing outflow obstruction (2).

Patients and Methods : The urodynamic tracings of 100 patients who had pressure-flow studies before and after prostatectomy were reviewed. The maximum flow (Qmax), detrusor pressure at maximum flow (PdetQmax) and minimum voiding pressure (Pmuo) were noted for each PQ recording. Each PQ plot can be represented by an AG number which can be easily calculated by the equation : AG number = PdetQmax - 2Qmax. To obtain an AG number from the PQ plot, a line is drawn through the PdetQmax/Qmax point, parallel to the upper line of the AG nomogram (3), to intersect with the pressure axis, at which point the Ag number is read off (see Fig 1). An AG number of greater than 40 is considered to be "obstructed". Griffiths' URA factor and Schäfer's grade of obstruction (LPURR) were determined for each set of PQ data. The AG number was compared to URA and Schäfer's method.

Results : 85% of the urodynamic traces were suitable for analysis. Table 1 shows the pre and post-operative diagnosis expressed according to AG number (>40=obstruction), URA (>29=obstruction) and Schäfer's LPURR (grade III to VI=obstruction). Table 2 shows the correlation between the AG number and URA.

TABLE 1: Pre and post-operative diagnosis of BOO using AG number, URA and LPURR in 85 patients (OBS=obstruction, UNOBS=equivocal/non-obstructed).

	AG no.		URA		LPURR	
	Unobst.	Obst.	Unobstr.	Obst.	Unobst.	Obst.
Pre-operative	12	73	11	74	12	73
Post-operative	77	8	82	3	80	5
Total	89	81	93	77	92	78

TABLE 2 : Correlation between AG number and URA in 85 patients (pre-operative and post-operative results combined)

		URA	
		Unobst.	Obst.
AG Number	Unobst.	86	3
	Obst.	7	74

The agreement between AG number and URA is 160/170=**94%**. Similar comparisons between the 3 methods against each other were also made. The agreement between the AG number with LPURR was **98.2%** and that between URA and LPURR was **94.7%**.

Figure 2 represents a scattergram of AG numbers and URA of these 85 patients. The Pearson's correlation coefficient for AG number against URA was **0.9** with a coefficient of determination (r^2) of **0.82**.

Conclusions : The agreement between the 3 different methods of diagnosing BOO is excellent. It remains to be seen as to whether there are advantages in using the more complex methods of PQ analysis. The AG number is very easy to calculate and does not require a computer. There is no ambiguity in grading the degree of obstruction as can occur with Schäfer's method. Like URA, it gives a continuous variable which allows small changes to be assessed by statistical methods.

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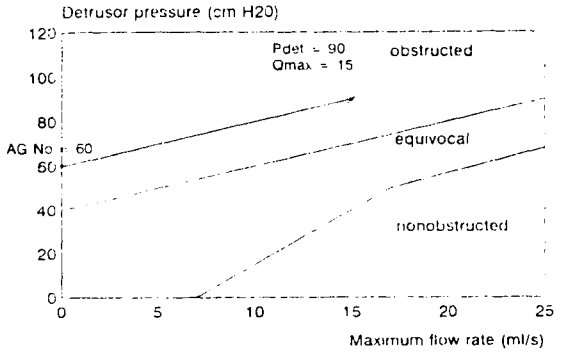
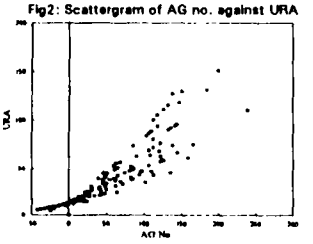
Fig.1:Abrams-Griffiths nomogram
Derivation of AG number





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SYMPTOMS OF PROSTATISM IN A COMMUNITY-BASED SAMPLE OF MEN WITHOUT PROSTATE CANCER BETWEEN FIFTY-FIVE AND SEVENTY-FOUR YEARS OF AGE.

AIMS OF THE STUDY.

This study was undertaken in order to study the prevalence of symptoms of prostatism in the community and the correlations between these symptoms and other measures of benign prostatic hyperplasia (BPH), such as flow rate, postvoid residual urine volume and prostate volume.

METHODS.

A community-based population of men between 55-74 years of age was created on the basis of the municipal population registry.In the present study we only included men without a history of a previous prostate operation and without prostate cancer.Prostate cancer had been excluded with a reasonable degree of certainty by serum PSA, digital rectal examination and transrectal ultrasound followed, if necessary, by prostate biopsies according to a strict protocol.A total of 502 men was finally included in this analysis.The International Prostate Symptom Score (IPSS) was administered to these men.This is a numerical symptom scoring system which grades the presence of 7 symptoms on a discrete scale of 0 (symptom never present) to 5 (symptom always present).These 7 symptoms are: incomplete emptying, increased frequency, intermittency, urgency, weak stream, hesitancy, and nocturia.Based upon American Urologic Association-conventions three subclasses for the resulting total score have been defined:minor (IPSS 0-7), moderate (IPSS 8-19) and severe (IPSS 20-35) symptoms [1].Uroflowmetry (ml/sec) was done using a Dantec Urodyn 1000 flowmeter.The following parameters were noted:maximum flow rate, average flow rate, delay time, total voiding time, total flow time and voided volume.The postvoid residual urine volume (ml) was computed using an Aloka machine with a 3.5 MHz handheld probe using the formula $\pi/6$x(width)x(height)x(depth).The prostate volume was measured by transrectal ultrasonometry with a 7 MHz Bruel and Kjaer multiplane sector scanning probe.The planimetric technique of volume measurement was used

RESULTS.

Overall,6 % and 24 % of the men were severely and moderately symptomatic respectively.There is a discrepancy between the results of a detailed questionnaire such as the IPSS (only 12% of the men scored 0) and the men's global perception of their voiding function (88% of the men claimed to have "no voiding complaints" when answering a global intake question).There is a weak correlation between the IPSS and total prostate volume ($r=0.19;p<0.001$) and between the IPSS and physiologic measures such as maximum flow rate ($r=-0.18;p<0.001$) and postvoid residual urine volume ($r=0.25;p<0.001$).Equally weak correlations were found between the scores on the individual symptom questions of the IPSS and selected flowmetry variables and postvoid residual urine volume when correlating these variables to the IPSS questions that can be assumed to be a measure of the same variable:the "feeling of incomplete emptying" was poorly correlated with residual urine volume ($r=0.14;p=0.01$).Furthermore, intermittency was weakly correlated with total flow time divided by total voiding time ($r=-0.20;p<0.001$) and the symptom weak stream was poorly correlated with the maximum flow rate ($r=-0.19;p<0.001$) and the average flow rate ($r=-0.22;p<0.001$).Hesitancy was poorly correlated with the delay time ($r=0.13;p=0,0081$).There is a very weak correlation between the IPSS and age ($r=0.09;p=0.04$).Of the individual symptoms, only the

prevalence of nocturia increases significantly with age (p=0.002).

DISCUSSION AND CONCLUSIONS.

Surprisingly, the correlations between symptoms and other measures of BPH are better in this community-based population than in a group of clinical BPH patients reported about by others [2].Despite of this, the correlations are still only weak to moderate in this population.Based on the weak correlations between symptoms and other measures of BPH, it is concluded that symptom scores should not be used as a preselection criterium in the determination of the prevalence of clinical BPH as has been done by some investigators [3} and that other measures for the condition such as prostate volume and physiologic measures of voiding function should be combined with symptoms and be considered simultaneously in the determination of the prevalence of clinical BPH.

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Is there a Relationship between Symptomatic Benign Prostatic Hypertrophy and Cardiac Autonomic Dysfunction ?

INTRODUCTION

An increased risk of long-term mortality from cardiovascular disease following Transurethral Prostatectomy (TURP) compared to Open Prostatectomy (OP) was reported in a retrospective study by Roos et al (1). This difference is unexplained (bias on selection, co-morbidity, factors related to TURP, factors related to the type of benign prostatic hyperthrophy (BPH)). <<The idea that a TURP lasting 40 minutes causes a fatal heart attack 8 years later is not easy to accept>>(2). TURP is mainly chosen for small glands when OP is performed for big glands; small glands are often more precociously and more intensively symptomatic (3). The following question was arised: <<Do patients with symptomatic small prostates have greater sympathetic nervous system activity than those with relaxed large prostates, activity that also stimulates the heart?>>(4).

AIM

The aim of this research was to test the hypothesis that patients with Symptomatic Small Volume BPH may have altered autonomic control of cardiovascular function (Cardiac Autonomic Dysfunction).

MATERIAL AND METHODS

From October 1992 to December 1993, 50 patients with Symptomatic Small Volume BPH were prospectively evaluated. Selection criteria were the following: a) candidate to TURP; b) age 45 to 65 years; c) sonographic prostate volume less than 40 grams. Exclusion criteria were the following: hypertension under medical treatment, diabetes, history of cardiac disease, and previous miocardial infarction.

Fifteen age-matched asymptomatic subjects were evaluated over the same period as a control group.

The evaluation included the following cardiovascular autonomic tests (5-7):

Lying-to-Standing (LS), Standing-to-Lying (SL2), Deep Breathing (DB), Valsalva Ratio (VR), and Power Spectral Analysis of heart-rate variations.
The comparison of group means was conducted with the Student t test for paired and unpaired data, with 0.05 as the significant level (2 sided).
RESULTS
The results are showed in the following tables.

	CONTROL GROUP M (SD)	SYMPTOMATIC BPH M (SD)	p	
number	15	50		
age	56.3(11.7)	59.2(5.4)	0.18	ns
LS	1.229(0.156)	1.101(0.063)	0.000015	***
SL2	1.356(0.133)	1.285(0.104)	0.034	•
DB	23.5(9.3)	18.6(6.7)	0.029	•
VR	1.75(0.31)	1.60(0.27)	0.089	ns

Power Spectral Analysis on Lying:

		CONTROL GROUP M (SD)	SYMPTOMATIC BPH M (SD)	p	
low frequency	LF	551(660)	257(259)	0.012	•
	LFu	57.9(21.7)	59.3(24.8)	0.84	ns
high frequency	HF	243(278)	211(445)	0.79	ns
	HFu	33.1(16.9)	28.8(18.9)	0.43	ns
ratio	LF/HF	2.96(3.02)	6.54(14.39)	0.34	ns

COMMENT
Patients with symptomatic less than 40 grams BPH showed altered cardiovascular autonomic tests in comparison with a normal control group. This suggests impaired neural control of heart activity.
As Cardiac Autonomic Dysfunction is a well known cause of unexpected death and is related to very poor prognosis in other diseases such as diabetes, further studies are needed to understand the clinical impact of the observed results.

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CORRELATIONS BETWEEN PRESSURE-FLOW AND MUPP CRITERIA FOR OUTLET OBSTRUCTION

AIMS OF STUDY

Current UDS methods for diagnosing outlet obstruction include pressure-flow (P/Q) analysis[1,2] and micturitional urethral pressure profilometry (MUPP).[3] P/Q studies may be difficult to perform in elderly or disabled patients, and may fail to yield interpretable data in up to 25% of patients, even in experienced laboratories. Moreover, there is no consensus on adjusting P/Q analysis for either urinary flow scatter due to the urethral catheter or flow signal delay. The MUPP may identify the site of obstruction, especially in patients for whom P/Q studies are not feasible. However, only one study has compared the MUPP with P/Q for obstruction diagnosis.[4] To better understand the relationship between these two methods, we compared MUPP and P/Q studies in older men with prostatism.

PATIENTS AND METHODS

We retrospectively analyzed prospective UDS data from 115 men (mean age 69±6 [range 51-84]) consecutively presenting to a Veterans Administration urology clinic for evaluation of prostatism. Eighty-six (75%) consented to multichannel videoUDS evaluations; age (69±6) and the prevalence of comorbid conditions were similar in men tested and not tested. Criteria for outlet obstruction were pressure gradient >10 cmH_2O in the supramembranous urethra during voiding for MUPP, and linear PURR[1] ≥ grade 2 and the P/Q nomogram[2] for P/Q.

RESULTS

Interpretable MUPP studies were completed in 85 men (99%), while interpretable P/Q studies were completed in only 52 (60%) (McNemar test, $p<.00001$). The one incomplete MUPP was due to inability to void, while incomplete P/Q studies were due to technical difficulties (22), patient factors (10), and after-contraction precluding Pmuo determination (2). Men with incomplete P/Q studies were not more likely to be obstructed by MUPP criteria than men with complete P/Q (71 v. 75%, $p=0.69$). The prevalence of obstruction was 73% by MUPP, 79% by linear PURR, and 47% by the A-G nomogram (35% were "equivocal").

Although PURR obstruction grades did not correspond to a discrete range of MUPP gradients, the mean MUPP gradient increased with increasing PURR grades. Agreements between the three criteria were examined using several analytic methods. Cohen's kappa was used to assess the concordance of obstructed/not obstructed diagnoses between criteria ($K>.40$=good and $>.80$=excellent concordance); $K=.57$ for MUPP v. PURR ($p=.00002$),

.38 for MUPP v. A-G nomogram ($p=.01$), and .84 for PURR v. A-G nomogram ($p<.00001$). The Spearman rank correlation was used to assess the correlation between actual values of the MUPP and PURR; $r=.70$, $p<.00001$. This good correlation was corroborated by the McNemar test for correlated proportions in matched pair analyses for MUPP and PURR; the same test showed correlation between the A-G nomogram and both MUPP and PURR.

Using PURR as the criterion ("gold") standard for obstruction, the MUPP's sensitivity for obstruction = 88%, specificity = 73%, and positive predictive value = 92%; using the Abrams-Griffiths nomogram as the standard, MUPP sensitivity = 73%, specificity = 70%, and positive predictive value = 86%; that is, nearly every patient classified as obstructed by MUPP was obstructed by either P/Q criteria.

CONCLUSIONS

The MUPP agrees closely with linear PURR and Abrams-Griffiths nomogram P/Q diagnoses of outlet obstruction in men with prostatism, but can be completed in a higher percent of patients, especially the elderly and disabled.

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THE CLINICAL APPLICABILITY OF ABRAMS-GRIFFITHS NOMOGRAM AND LINEAR PURR IN COMPARISON TO CHESS-CLASSIFICATION

AIMS OF STUDY

Due to an increased number of alternative treatment modalities in BPH-patients, the question is raised for the quantification of the outlet resistance. In this connection, it must be noted that not only the question of the presence of a mechanical obstruction has to be clarified but also the definition of treatment effects has to be quantified in the different new therapies. It is generally accepted that the pressure flow plot (URR) is the basic guideline to define any obstruction and the passive urethral resistance relation (PURR) to define the mechanical obstruction component. Therefore, the judgement of different methods of pressure flow analysis should be carried out in accordance to its analytical power based on URR and PURR. The minimal level for the definition of footpoint and slope of PURR is shown by two pairs of corresponding pressure - flow values, normally the minimum voiding detrusor pressure and the pressure at maximum flow. In methods of analysis using only one point of the plot (pressure at maximum flow), (Abrams/Griffiths-Nomogram, URA), the user works under the condition that 1. the pressure at maximum flow describes PURR in adequate quantities (A-G-Nomogram) or 2. the pressure intercept of a theoretical low pressure area calculated on the basis of the pressure at maximum flow (URA) is identical to PURR, concluding a sufficient value for the description

of mechanical resistance. Although the linear PURR is based on a two parameter model, the 7-classes-nomogram reduces it back to one parameter with the implication of an inverse proportionality between the opening pressure and slope. After the documentation of the limitations of the one parameter model URA at last year's ICS meeting, the goal of this present study is to investigate the A-G-Nomogram and the linear PURR Nomogram according to their applicability and accuracy in comparison to the two parameter based CHESS Classification.

PATIENTS AND METHODS

To investigate the applicability of the linPURR Nomogram the linear PURR from analogous pressure flow curves of 197 male patients with different grades of obstructions were determined after correction of the pressure flow delay and then projected onto the nomogram. In a further group of 118 BPH-patients a computerized pressure-flow measurement with AUDIT™ (FM Wiest) was performed and the CHESS Classification was defined on the basis of PURR-curvature and PURR-intercept with the pressure axis. In a second analysis for these curves the classifications according to A-G-Nomogram and linPURR were performed to investigate the compatibility of both concepts with CHESS.

RESULTS

In 197 analogous curves a precise classification of obstruction with linPURR (the line is lying in one nomogram area) was only possible in 25.4 %. In ¾ of all cases the line crossed over 2 or more areas of the nomogram (Fig. 1). The further analysis in comparison to CHESS (n=118) showed that the reason for the overlapping is to be found in the different slopes according to the pressure axis-intercept (Fig. 2: A3, B4, C4 and D4 are too flat and D1 is too steep). The analysis according to A-G-Nomogram (n=118) showed a total obstruction rate of 81%. 18% of patients were eqivocal, 1% normal. The projection of Qmax/Pqmax-points dependent on their pressure-axis-intercept of the underlying PURR according to CHESS (A-D: increasing pressure) resulted in (Fig. 3): Normal: A: 100%, equivocal: A: 35%, B: 35%, obstructed: B: 34%, C: 43%, D: 23%. The A-G-Classification according to different PURR-curvatures (1-4 decreasing steepness): Normal: 1: 100%, equivocal: 1: 34%, 2: 50%, 3: 16%, obstructed: 1: 14%, 2: 31%, 3: 32%, 4: 23%. The total analysis of the compatibility of the A-G-Nomogram and CHESS showed that only the CHESS-classes A1 to B2 are differentiated in equivocal (40-91%) and obstructed (0-60 %) areas whereas from class B3 onwards all cases were classified as obstructed.

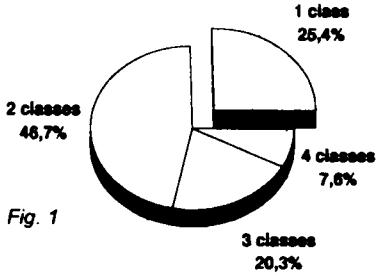

Fig. 1

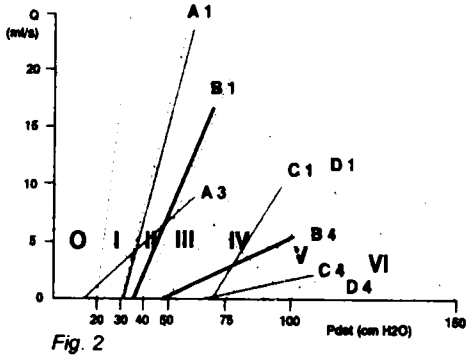

Fig. 2

CONCLUSIONS

Due to the fact that the PURR-intercept and PURR-curvature are not interdependent the two parameter CHESS-Classification was developed. Taking this into account, the analysis of linear PURR shows that 75% of linear PURR curves do not fit onto the nomogram due to the different slopes. As a result of the mentioned independency, the linear PURR classification 0-VI fails in the same way as the URA. The A-G-Nomogram with its one point concept and 3 classes only is much too unspecific to describe the obstruction in detail and the treatment effects of today's usual treatment spectrum of BPH.

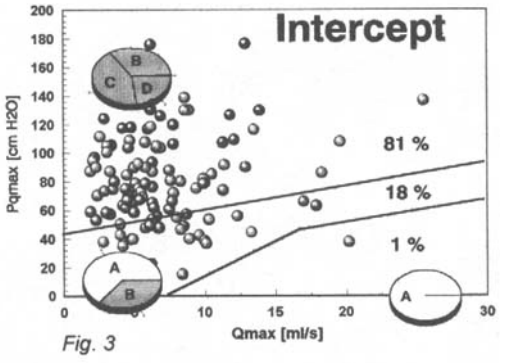

Fig. 3

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ICS-BPH STUDY : BACKGROUND AND DESIGN

INTRODUCTION : There has been an explosion of interest in the treatment of older men with lower urinary tract symptoms (LUTS). Traditionally, selection for treatment has been based on the assessment of symptoms, physical findings and the results of investigations such as excretion urography and endoscopy. Although the urodynamic community accepts the need for objective evaluation by uroflowmetry and pressure-flow studies, it is likely that most elective treatments still proceed without urodynamic evaluation. Clinicians justify not doing urodynamics by stating that the patient is interested in symptoms not urodynamic findings. To enable symptoms to be quantified symptom scores have been constructed : as in the Boyarsky, Madsen-Iversen, Maine, AUA-IPSS and Danish symptom scores. These scores have been variously validated, the AUA-IPSS being the most intensively validated although not against any objective criteria such as UDS. Symptom scores have been used to define which patients should be submitted to surgery. As well as looking at total symptoms, clinicians have divided symptoms into two groups, "obstructive" (voiding symptoms) and "irritative" (filling symptoms).

In 1991, the ICS became concerned by the lack of objective data, firstly, to justify the reliance on symptoms in selecting older men for treatment for presumed bladder outflow obstruction (BOO), and secondly, to justify the separation of symptoms into so-called "obstructive" and "irritative" groups. The ICS planned the ICS-"BPH" study with the aims :

1. To investigate the relationship between the results of urodynamic studies and a wide range of urinary symptoms (Phase I).
2. To develop and validate an ICS-BPH symptom score for use in research and clinical practice (Phase I).
3. To undertake an observational study of the outcome of treatments for outflow

obstruction secondary to BPH according to current clinical practice (Phase II).

4. To develop and refine the methodology to undertake a randomised controlled trial of prostatectomy versus 'watchful waiting' (Phase III).

The current reports are concerned only with Phase I of the ICS-BPH study.

PATIENTS AND METHODS : To date (March 1994). 880 patients have been entered by 27 centres and analysis is available for the first 658 patients.Each patient has completed the ICS-BPH symptom questionnaire, which consists of 20 urinary symptoms, 4 sexual function questions and 7 quality of life questions. Each of the urinary questions asks for the presence and severity of the symptom (graded from 1 ["not at all"] to 5 ["all of the time]) and follows this by asking "how much of a problem is this for you?" (graded from 1 ["not a problem"] to 4 ["a serious problem"]). In addition the patient has completed a 7 day frequency-volume chart. Central to the ICS-BPH study is high quality urodynamics and each centre has been asked to conform to minimum quality standards for their multiple flow studies and pressure-flow. Cystometry should be performed standing (or sitting if necessary), using water at medium fill rates (20 - 50 ml/min) and using a catheter no larger than 8 Ch. In addition the surgeon has completed a patient information record, detailing demographic details and essential urological information, including an estimation of prostatic size, the results of free flows and pressure flow studies, diagnosis and treatment scheduled. Patients are included if they are over 45 years old, fit for prostatic surgery, with symptoms and if a frequency volume chart has been completed and urodynamics performed. Exclusion criteria include prostate cancer, renal disease, previous prostatic surgery and patients taking drugs known to have a lower urinary tract effect.

RESULTS : The mean age of the 658 patients is 67 years (range 46 - 88). Most come from Europe (74%), with the remainder from Japan, Australia, Canada, Egypt and Taiwan. The majority are married (86%) and retired from work (71%). Most live in towns or suburbs (83%) and in a house(62%).

CONCLUSIONS : Whilst this study is ambitious there has been excellent recruitment and Phase I should be completed by the end of 1994, when 2,000 patients will have been entered. From 1st January 1995 only those patients who will also be available for Phase II (the assessment of outcomes) will be accepted for inclusion in the study, such as patients included in two international multicentre studies of 5 alpha reductase inhibitors : these studies, each lasting a year, have pressure-flow studies performed at the beginning and end of the treatment period. Phase III will include patients entered into randomised controlled trials only, such as the recently funded trial comparing transurethral prostatectomy with laser prostatectomy and watchful waiting.

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THE ICS-BPH STUDY : PRELIMINARY FINDINGS CONCERNING THE RELIABILITY OF THE ICS-BPH QUESTIONNAIRE

AIMS OF STUDY : The ICS-BPH study is a large international study which aims to investigate the relationships between urodynamic data and a wide range of urinary symptoms, problems, and aspects of quality of life. A major aim of the study is to develop a valid and reliable questionnaire for use in research, clinical practice and community studies. This paper presents results concerning the reliablility of the questionnaire as assessed by a test-retest analysis.

PATIENTS AND METHODS : All patients recruited to the ICS-BPH study complete a new wide-ranging questionnaire concerning the presence of urinary symptoms, the degree of problem they cause, sexual function, and issues associated with quality of life. Some factors relating to the validity and reliability of the questionnaire can be ascertained from the overall sample of 658 men. Others can be obtained from the analysis of sub-groups or other samples. This paper discusses some of these findings, and focusses on a test-retest analysis in which forty English-speaking patients from two of the active centres participating in the ICS-BPH study were asked to complete the questionnaire again within two weeks of completing the first one. The analysis of these data allows the assessment of the test-retest reliability of the questionnaire, particularly the stability of individual items.

RESULTS : The ICS-BPH questionnaire is intended to be self-completed, and in the overall sample of 658 men, the questionnaire was completed by 91% unaided. The numbers of missing items on the symptom questions was very low - at approximately 1%. Sexual function questions have rather more missing data as one might expect, but these are still low at 7-14%. This evidence, plus data gathered from in-depth interviews, suggests that the questionnaire is well understood by patients and is easily completed. The ICS-BPH questionnaire is divided into four sets of items: the presence of 20 urinary symptoms; the degree of problem caused by 19 symptoms; issues associated with sexual function (4 symptom and 4 problem questions); and issues associated with quality of life (7 questions, but only 4 are suitable for this analysis).

The reliability of individual questions is assessed in a test-retest analysis by the movement of responses between the two completed questionnaires for each individual. Responses for the whole group changed by at most one category between the two tests in 7 urinary questions, 11 urinary problem questions, 2 sexual symptom questions, 2 sexual problem questions, and 2 quality of life questions. For those with responses moving more than one category, it is mostly only one individual (in 40) that is involved. The least reliable items include six urinary symptoms: frequency (4 cases moving more than one category), hesitancy (2 such cases), straining to continue (2), intermittency (4), incomplete emptying (5), and post-micturition dribble (3). It is,

of course, possible that these symptoms might have changed in terms of frequency and severity between the two test periods. Only one urinary problem has such lower reliability: problem with a weak stream (2 cases). Of the sexual function and quality of life questions, only the perception that the sex life is spoilt by urinary symptoms (4), and reducing fluid intake (2) have this lower reliability.

CONCLUSIONS : The ICS-BPH questionnaire is easily understood and completed. The results of this preliminary test-retest analysis suggest that the majority of questions also have good reliability. Final assessment of the validity and reliability of the questionnaire awaits further investigation. For example, aspects of the construct validity of the questionnaire will be examined by the ability of the questionnaire to differentiate between a symptomatic population and an age-matched community sample. A wide range of statistical analyses will be undertaken to assess the reliability and internal consistency of the questionnaire. A detailed assessment of the relationships between urodynamic data and questionnaire responses will be undertaken to determine the most effective method of scoring and weighting the individual items in the final questionnaire, by using statistical techniques such as factor analysis and multiple regression/multiple logistic regression.

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THE ICS-BPH STUDY : THE EFFECTS OF URINARY SYMPTOMS ON QUALITY OF LIFE

AIMS OF STUDY : The ICS-BPH study is a large international study which aims to investigate the relationships between urodynamic data and a wide range of urinary symptoms, problems, and aspects of quality of life. A further major aim of the study is to develop a valid and reliable questionnaire for use in research, clinical practice and community studies. This paper presents results concerning the reported effects of urinary symptoms on various aspects of quality of life, including sexual function.

PATIENTS AND METHODS : These preliminary results focus on the first 658 men recruited to the study. The ICS-BPH questionnaire asks men to report the frequency of urinary symptoms, and also to assess the degree of bother that they cause. The questionnaire also contains specific questions which focus on issues concerned with sexual function and the effects of symptoms on daily life.

RESULTS : The urinary symptoms which are reported to be the most prevalent are not those which are reported to be the most bothersome. Amongst the total sample, the most common symptoms (reported at least occasionally) are reduced stream (92%), terminal dribble (92%), intemittency (86%), hesitancy (84%), incomplete emptying (80%), nocturia (74%), and urgency (72%). The most bothersome (reported to be at least a bit of a problem) are frequency (89%), nocturnal incontinence (87%), urge incontinence (85%), miscellaneous incontinence (85%), nocturia (84%), and post-micturition dribble (83%). Urinary symptoms can have severe effects on the men's quality of life. Only 21% report that their symptoms do not interfere with their lives, with 43% indicating that their urinary symptoms interfere with their lives a little, 25% somewhat, and 10% a lot. In terms of spending the rest of their lives with their urinary symptoms as they are now, most would not be happy: 29% have mixed feelings, 27% are mostly disatisfied, 21% very unhappy, and 2% desperate. Not surprisingly, incontinence is clearly identified as a bothersome symptom and one which impinges on everyday life. For example,19% report that they have to change underpants during the day, with 2% having to change outer clothes, and 1% have to wear pads.

It is clear that urinary symptoms are commonly tolerated for some time before treatment is sought: 30% report that they had been affected by their urinary symptoms for more than three years; with 19% bothered for 2-3 years, 32% for 1-2 years, and 14% for less than one year. In an attempt to gain some control over their urinary symptoms, many men limit their liquid intake: 23% occasionally reduce their drink intake, with 17% doing this sometimes, 6% most of the time, and 2% all of the time.

Sexual symptoms and problems are also highly prevalent in these men. 58% report problems with the rigidity of erections, 58% reduced or no ejaculate, and 15% pain on ejaculation. One question in the ICS-BPH questionnaire directly addresses the issue of how much the men feel that their sex life has been affected by their urinary symptoms. 41% report that their sex life has been spoilt by their urinary symptoms. Of these, 20% feel it has been spoilt a little, 11% somewhat, and 9% a lot.

CONCLUSIONS : The ICS-BPH questionnaire indicates that urinary symptoms are very prevalent in this group of men with suspected bladder outflow obstruction secondary to BPH. Some of the symptoms, particularly those associated with incontinence and frequency, are also highly bothersome. Many of the symptoms traditionally associated with bladder outflow obstruction are thus common, but are not perceived to be particularly troublesome compared with socially embarrassing symptoms such as frequency and incontinence. Further analyses will explore the relationships between particular symptoms and aspects of quality of life.

It is of great interest that the majority of men report some sexual difficulty, and that over 40% feel that their sex lives have been spoilt by their urinary symptoms. These findings demand further investigation to define the relationships between sexual function and lower urinary tract pathophysiology.

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THE ICS-BPH STUDY : THE ASSESSMENT OF LOWER URINARY TRACT SYMPTOMS

AIMS OF STUDY : The ICS-BPH study is a large international study which aims to investigate the relationships between urodynamic data and a wide range of urinary symptoms, problems, and aspects of quality of life. A major aim of the study is to develop a valid and reliable questionnaire for use in research, clinical practice and community studies. This paper presents results concerning the frequency of 20 urinary symptoms firstly in the whole sample and secondly within subgroups according to age and clinical diagnosis.

PATIENTS AND METHODS : Men are recruited into the ICS-BPH study if they are over 45 years of age, have symptoms suggestive of bladder outflow obstruction and are fit enough to undergo prostatic surgery if appropriate. They are excluded if they have significant other urological disease (such as prostate cancer), neurological disease, previous prostatic surgery, or are taking medication active on the lower urinary tract. These preliminary results focus on the first 658 men recruited to the study. The mean age of the men is 67 years (range 46 to 88). 20% are aged between 46 and 59 years, 43% between 60 and 69 years, and 37% 70 years and over. The majority were "obstructed" according to the clinician, with 61% given a diagnosis of "classical obstruction", 23% "questionable obstruction", 9% "unobstructed", and 7% some other diagnosis.

RESULTS : Urinary symptoms are highly prevalent in the total sample, with reduced stream reported to occur at least occasionally by 92%; terminal dribble by 92%; intemittency by 86%; hesitancy by 84%; incomplete emptying by 80%; nocturia by 74%; and urgency by 72%. The majority of those who have symptoms report that they occur occasionally (less than one third of the time) except for reduced stream and terminal dribble. Reduced stream and terminal dribble are reported to be present all or most of the time by 50% and 42% respectively, with 16% and 14% reporting it all of the time. Intermittency, hesitency and incomplete emptying are the only other symptoms reported to occur most or all of the time by more than 20%, and all of the time by more than 5%.

Several urinary symptoms are related to age. Chi square analyses indicate that nocturia, urgency and urge incontinence have a positive association with age ($p=0.007$, 0.009, and 0.033 respectively). In contrast, burning, straining to start, straining to continue, and incomplete emptying have a negative association with age ($p=0.070$, <0.001, $=0.009$ and $=0.007$ respectively). Some reported urinary symptoms are associated with the three main clinical diagnosis assigned by the clinician at the time of data collection. Men with "classical obstruction" tend to report a more reduced stream ($p=0.004$) and more intermittency ($p=0.018$) than men who are "unobstructed". "Obstructed" men tend to report lower levels of frequency ($p=0.031$), burning ($p=0.023$), and nocturnal incontinence ($p<0.001$) than "unobstructed" men. "Obstructed"

men are also more likely to have experienced acute urinary retention than "unobstructed" men (p=0.050).

CONCLUSIONS : The ICS-BPH questionnaire indicates that urinary symptoms are highly prevalent in this group of men. Reduced stream and terminal dribble are the most commonly reported symptoms, both in terms of the numbers of men who experience them, and their severity. A small number of symptoms in this preliminary analysis are shown to have an association with age or clinical diagnosis. Final analysis will relate each symptom to validated urodynamic findings, rather than to the clinicians' diagnoses. Relationships will be explored between single symptoms and clusters of symptoms, and the urodynamic diagnoses of bladder outflow obstruction, detrusor instability, and detrusor underactivity.

This study provides the only opportunity to indicate whether a symptom scoring system can be disease-specific, that is, have a reasonable specificity for a diagnosis such as bladder outflow obstruction. Furthermore the study will indicate whether or not it is reasonable to use collective terms such as "obstructive" and "irritative" to describe groups of symptoms.

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THE ICS-BPH STUDY : FLOW RATE ANALYSIS

AIMS OF STUDY : The ICS-BPH study is a large international study which aims to investigate the relationships between urodynamic data, uroflowmetry, and a wide range of urinary symptoms, problems, and aspects of quality of life. This paper presents results from the analysis of the uroflowmetry and examines the relationships between flow rates and age and clinical diagnosis.

PATIENTS AND METHODS : Patients recruited to the ICS-BPH study complete a questionnaire covering a wide range of urinary symptoms, problems, and issues associated with quality of life and sexual function. Patients receive a physical examination, undergo full urodynamic studies, and are asked to provide three free flows. The mean age of the men is 67 years (range 46 to 88). 20% are aged between 46 and 59 years, 43% between 60 and 69 years, and 37% 70 years and over. The majority were obstructed according to the clinician, with 61% given a diagnosis of 'classical obstruction', 23% 'questionable obstruction', 9% 'unobstructed', and 7% some other diagnosis. For the purpose of this analysis, the highest flow rate achieved by each individual man was selected, and the data from this free flow used to assess voided volume, flow rate, and residual urine.

RESULTS : In total, 628 men (out of a total sample of 658) provided at least one free flow. 382 (61%) men performed three free flows, 177 (28%), two free flows and 67 (11%) one. The highest flow rate was selected for analysis: 5% had a flow rate of less than 5 ml/s, 35% 5 to 9 ml/s, 35% 10 to 14 ml/s, and 25% 15 ml/s or more; 27% had a voided volume of less than 150 ml; and 58% had residual urine of less than 50 ml, 29% between 50 and 149 ml, and 13% 150 ml or more.

Qmax from the free flow was compared with the Qmax obtained in the pressure flow studies. The pressure flow Qmax tended to be lower than the free flow Qmax; commensurately, there was a crude agreement between the two measures of only 38%. Although there was no clear direction to the discrepancies, the crude agreement between the two measures for volumes voided was also low (51%).
The residual urines recorded during pressure flow studies tended to be larger than those recorded on free flow measurement. The crude agreement between the two measures for residual urine was approximately 35%.

There was a strong association between diagnosis and flow rates: men with a clinical diagnosis of classical obstruction tended to have lower flow rates than men who were unobstructed or questionably obstructed ($p<0.001$).
Although the older men tended to have a lower flow rate than the younger men, there was not a statistically significant relationship between flow rate and age ($p=0.230$).

CONCLUSIONS : Free flow rates tended to be higher than flow rates measured during pressure-flow studies. The precise reasons for this are unclear. However, further investigation will focus on whether or not this is due to patient inhibition, lower voided volumes, or a combination of factors.

A relatively large percentage of these patients (25%) had flow rates of 15m/s or more which supports the conclusions of previous studies that one third of men with lower urinary tract symptoms do not have bladder outflow obstruction. However, a proportion of these patients will be shown to be obstructed with supra-normal voiding pressures: high flow - high pressure. A similar problem exists in differentiating low flow secondary to bladder outflow obstruction from that secondary to detrusor underactivity: low flow - low pressure.

Final Phase I analysis will be able to give an authoritative statement as to the sensitivity and specificity for flow studies in the diagnosis of bladder outflow obstruction.

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THE ICS-BPH STUDY : PRESSURE-FLOW STUDIES, QUALITY CONTROL AND INITIAL ANALYSIS

AIMS OF STUDY : The ICS-BPH study is a large international study which aims to investigate the relationships between urodynamic data and a wide range of urinary symptoms, problems, and aspects of quality of life. A major aim of the study is to develop a valid and reliable questionnaire for use in research, clinical practice and community studies and which will be validated in comparison with urodynamic findings. This paper presents results concerning the urodynamic quality control, and preliminary findings.

PATIENTS AND METHODS : Patients recruited to the ICS-BPH study complete a questionnaire, receive a physical examination, provide three free flows, and undergo full urodynamic studies. Whilst no attempt was made to impose a standardised urodynamic technique, each participating centre was requested to use certain basic methods, for example, water cystometry, with abdominal pressure measurement, and using narrow guage catheters (4Ch or less) for measuring pressure. A document entitled *ICS-BPH Study: Urodynamics - quality control* was circulated to each centre, together with a questionnaire seeking information on details of urodynamic technique, to be completed and returned with two sample pressure-flow traces before commencing the study. In order to validate the measurements from the pressure-flow traces sent in by the 27 centres, data quality control and analysis was performed blind, in a single centre, using the original or a copy of the urodynamic trace(s) from each patient. Each trace was examined for scaling, zero-setting, artefacts and checking of the detrusor pressure signal by regular coughs both before and after voiding. This validated data were then used in a new nomogram which includes the following methods of assessing obstruction: Abrams-Griffiths (A-G), URA, Schäfer (Sch), DAMPF, and OBI.

RESULTS : To date, 443 traces have been validated. Compliance with the defined standards was somewhat variable, with quality often excellent in "less well-known" centres. 60% of recordings showed obvious artefacts. One half of these could be easily corrected, and were due to common problems, such as, a difference in pressure transmission to the pves. and pabd. traces, incorrect position of the zero line, and spikes and other irregularities in the pves. trace, usually due to movement. One third of artefacts were less easy to correct, such as periodic loss of a signal (usually pabd.), pressure rising above full scale deflection (usually pves.), slow drift in a pressure trace, and loss of the pves. catheter during voiding. A small percentage (10%) of traces could not be analysed due to a lack of scaling or indicated zero position, or complete loss of a pressure or flow signal. Analysis was more difficult with small scale computer printouts.

After validation, 61% of patients were classified as obstructed (on A-G and

Sch III-VI), 21% were classified as equivocal or mild obstruction (A-G, Sch II), and 18% unobstructed (A-G, Sch 0-I). The severity of obstruction according to Sch showed the following correlations with: maximum flow rate (Pearson correlation -0.43, p<0.001), residual urine (0.032, p=0.64), prostate volume (0.17, p=0.007), and history of retention (0.07, p=0.21).

CONCLUSIONS

Analysis (excluding A-G) showed that all methods gave similar results in terms of grading the severity of obstruction, and at this stage it is not possible to determine whether any particular method of pressure-flow analysis should be adopted as standard. Further work is required to compare "on-line" analysis with "off-line" methods. The value of a precise urodynamic diagnosis will be assessed by comparison with the clinician's diagnosis. Whilst certain relationships can be shown between urodynamic diagnosis and other urological features, it has to be remembered that the apparently high level of statistical significance is largely due to the numbers in the study. The correlation co-efficients indicate that these associations may be clinically irrelevant.

The ICS-BPH study is the only multi-centre study examining the quality of pressure-flow traces. Modern urodynamic equipment has presented new problems in analysis. Almost all machines are unable to correct artefacts and most list the key pressure-flow measurements at the end of the recording. It is clear that clinicians must meticulously examine the trace for artefacts before accepting the computer's statement of key readings such as Qmax and pdet.Qmax. This aspect of pressure-flow analysis requires further investigation which may necessitate the development of guidelines.

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IS URINARY STRESS INCONTINENCE HEREDITARY?

AIMS OF STUDY

Stress urinary incontinence is a common disorder among women. Its prevalence varies from 5% to 10%. Factors which have been suggested as contributing to this disorder include parity, estrogen deficiency and surgical procedures in the pelvis.
It is also suggested that a genetic defect in the connective tissue is a major factor in the etiology of stress incontinence.[1]

In order to investigate this last theory, we, in this study examined the familial tendency towards stress incontinence.

PATIENTS AND METHODS

Two hundred and fifty-nine women, who were diagnosed as suffering from urinary stress incontinence, were interviewed about the coexistence of typical complaints of stress incontinence among their first degree female members (i.e., mothers, sisters, daughters). The control group included 165 women who attended the gynecology clinic for other reasons, and who denied any kind of micturition disorder. The two groups were identical with regard to their mean age, parity, maximal birth weight and the number of first degree female family members.

RESULTS

We found a prevalence of 20.1% stress incontinence in the families of the incontinence group, compared with 6.5% in the families of the control group ($p<0.05$). The occurrence of stress incontinence was 35.2% among the mothers and 19.9% among the sisters of the incontinence group; this compared with 12.7% in the mothers ($p<0.005$) and 6.5% in the sisters ($p<0.005$) of the control group. Although complaints of stress incontinence were more common among daughters of women in the incontinence group (6.5%), compared to the daughters of the control group (3.2%) the difference was not significant.

CONCLUSIONS

We conclude that stress incontinence is about 3 times more prevalent in first degree female family members of women who suffer from this disorder, in comparison with those of continent women. This familial tendency does not relate to age, parity or maximal birth weight. Hence it might reflect an inherited factor that predisposes the development of stress incontinence.

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GAUGING THE SUCCESS OF SURGERY FOR GENUINE STRESS INCONTINENCE:CAN WE IMPROVE ON THE COLPOSUSPENSION?

AIMS OF THE STUDY

Many different surgical procedures have been described for the treatment of genuine stress incontinence. Burch colposuspension has previously been shown to offer sustained long term urodynamic and symptomatic improvement making it the surgical treatment of choice for many doctors[1]. In an attempt to reduce surgical morbidity and hospital costs minimally invasive procedures are becoming increasingly popular. These have been introduced on the basis that the increased cost and morbidity of prolonged operating time, costly disposables and uncertain long term efficacy, are more than offset by the reduction in patient morbidity and shorter inpatient stay.

Undoubtedly subjective health status assessments of patient morbidity are likely to be important determinants for the selection of these procedures in favour of established surgical techniques. To date however there have been no published studies documenting the improvement in quality of life of women undergoing colposuspension or other forms of incontinence surgery, using validated quality of life questionnaires.

In an attempt to understand the improvement in health status of patients undergoing colposuspension, and to set standards for the comparison of other surgical procedures, we have conducted an interventional quality of life study of women undergoing colposuspension.

METHOD

230 women with videourodynamically diagnosed moderate or severe genuine stress incontinence undergoing colposuspension were included in the study. Prior to urodynamic investigation all women completed a detailed urinary symptom questionnaire, and a validated quality of life questionnaire (either the Nottingham Health Profile NHP, or the Psychosocial Adjustment to Illness Scale. Modified Burch colposuspension was susequently performed in our unit or by the patients referring doctor.

At least six months following surgery the women were contacted again and asked to complete the same quality of life questionnaire as previously and a detailed follow up symptom questionnaire.

RESULTS

The mean age of the patients was 47.6 years (range 32-70 years), and the mean duration of symptoms was 4.9 years (range 6 months- 16 years). 82% of the women had no previous bladder neck or major pelvic surgery. The mean elapsed time since surgery was 8.4 months (range 6.2 - 13 months).

54.3% (125) of women felt that they were completely cured, 30.9% (71) significantly improved, 8.7% (20) little different, and 6.1% (14) worse. 91.3% (210) wished they had been investigated sooner, and 93.9% (216) felt they would advise other women to undergo surgery for the same complaint. Postoperative urinary symptoms (Table 1) were greater amongst women who had undergone previous bladder neck surgery although interestingly the subjective assessment of the success of surgery was the same as those undergoing their first procedure.

Table 1. Significant symptoms following colposuspension

Frequency (>7x/day)	23.9% (55)	Voiding difficulties	30.0% (69)
Nocturia (> = 2x/night)	34.3% (79)	Prolapse	7.0% (16)
Urgency	15.2% (35)	Urinary tract infections	12.2% (28)
ANY residual incontinence	19.1% (44)	Dyspareunia	11.7% (27)

Results of QOL scales were impressive with significant improvement in QOL assessed by both the PAIS and the NHP. Tables 2 and 3 (* = $p<0.01$ Wilcoxon test)

Table 2. Nottingham Health Profile and PAIS scores before and after surgery.

PAIS score (n = 136) Mean (Sd)	Before	After
Vocation *	2.8 (2.8)	1.9 (1.7)
Domestic *	3.3 (2.7)	2.4 (1.7)
Sexual *	4.6 (5.1)	3.2 (4.4)
Social *	4.7 (3.8)	2.6 (3.2)
Psychological *	6.7 (4.1)	4.4 (3.8)

NHP score (n = 94) Mean (Sd)	Before	After
Social isolation *	32.3 (36.7)	22.07 (26.9)
Physical mobility *	12.1 (17.7)	5.1 (12.7)
Emotions *	19.7 (24.8)	12.8 (18.4)

CONCLUSION

It is clear that colposuspension is a successful treatment for women with genuine stress incontinence, associated with few side effects and considerable improvement in urinary symptoms and quality of life. Although new innovative techniques may well have financial incentives, and a reduction in early postoperative morbidity, these factors and their long term efficacy demand close scrutiny before considering than an alternative to the highly successful coplosuspension.

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BURCH COLPOSUSPENSION - HOW LONG DOES IT CURE STRESS INCONTINENCE ?

AIMS OF STUDY

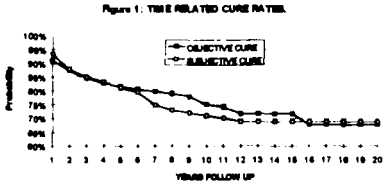
Burch colposuspension remains one of the most widely used and successful operations for genuine stress incontinence (GSI). Reported cure rates range from 71% to 98% with a follow up range of 8 months to 10 years (1-3). The only report in the literature of a 10 year post colposuspension follow up reported a cure rate of 90% (3), however, no distinction was made between primary and secondary surgery. The aim of this longitudinal study was to review the long term clinical and urodynamic data of patients who underwent colposuspension 10 to 20 years ago performed by the senior author.

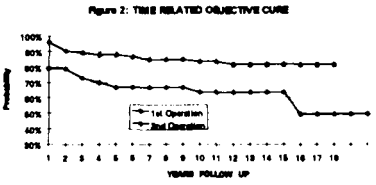
METHODS

Of 366 patients who underwent colposuspension operation between 1974-83, 25 deceased, 148 did not reply, 71 had changed address, 13 could not attend and 109 patients attended for follow up at the beginning of 1994. Their mean age at follow up was 60.3 (SD 8.91, range: 44-85). Mean parity was 2.8 (SD: 1.4, range: 0-7). At the time of the operation 68.2% were premenopausal. The mean long term follow up was 13.8 years (10-20 years). Subjective and urodynamic evaluation were performed preoperatively and 2 months postoperatively (cystometry), and then repeated annually for 5 years and at final follow up (pad test and uroflowmetry). Subjective and objective cure rates were calculated and a life table analysis was constructed. Logrank test was used to compare independent groups for continence cure. Numeric parameters were compared using paired t-test, and sign test was used for nonparametic data.

RESULTS

76 (69.7%) underwent colposuspension as a primary operation and 33 (30.3%) had at least one prior continence operation (Mean: 1.5, range:1-4). The most common previous continence operation was anterior repair (78%). Time related subjective and objective cure rates are shown in the figure 1. Subjective and objective (figure 2) cure rates were significantly reduced in patients undergoing secondary operations compared to primary procedures ($p<0.05$). Detrusor instability (DI) was demonstrated in 5 (4.6%) patients preoperatively and in 22 (20.2) as new postoperative finding. However, the prevalence of significant urgency (29.6%) and urge incontinence (22.9%) at final follow up was unchanged from preoperative prevalence (urgency-38.1%, urge incontinence 26.7%).





The prevalence of poor stream was increased significantly in 2 months follow up ($p<0.001$) and did not change significantly in the final follow up. However, mean peak flow rate returned to preoperative values at the long term follow up (29.1 vs 29.9 ml/s) after a significant decrease at the 2 month follow up (29.1 vs 18.8 ml/s, $p<0.01$). Eleven (10.1%) patients with failed colposuspension underwent 14 further continence procedures with 10/11 (91%) objective cure and 9/11 (82%) subjective cure (follow up range: 2-13 years).

CONCLUSIONS

Cure rates after colposuspension decline time dependently for 10 years and then a plateau is reached. The subjective cure rate is higher than objective cure rates for the first 5 years after which this is reversed. The differences between cure rates for primary and secondary surgery indicates that they should be reported separately. Although there are high incidences of DI (20.2%) and voiding difficulties in the immediate postoperative period, these improve by 10 years. Patients whose colposuspension fails may benefit from another continence procedure, as the success rate of repeat opeation is high.

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A RANDOMISED COMPARISON OF LAPAROSCOPIC AND OPEN COLPOSUSPENSION.

AIMS OF STUDY:
Laparoscopic surgery has generally been introduced into medical practice with little objective analysis and little objective comparison to "Gold Standards". To date, there have been no large trials reporting urodynamic follow-up of laparoscopic Colposuspension against Open Colposuspension. However, many surgeons are performing the laparoscopic procedure without any evidence of medium or long term efficacy, knowing that (unlike operations when tissue is removed) if the procedure fails then the chance of a cure with the next operation is greatly reduced. The aim of this study is therefore to compare the outcome of Laparoscopic Colposuspension with Open Colposuspension.

PATIENTS AND METHODS:
Sixty women with Urodynamically proven moderate to severe GSI were randomised to laparoscopic or open Colposuspension over a period of 14 months. Ten previous laparoscopic Colposuspensions were performed to familarise and standardise technique. An intra-peritoneal technique using 4 x 1-0 polyglycholic sutures was used in both types of operations. The women were analysed before the operation and then 6 months and 12 months after the operation by Videocystourethrography, Urethral Pressure Profile, 1 hr ICS pad weighing test, urinary diary and a visual analogue symptoms analysis. A cost analysis was undertaken as well.

RESULTS:

Symptoms Analysis: A visual analogue score of symptoms was done pre operatively, at 6 months and 12 months after the operation. Median values:

* = Open # = Laparoscopy

Urgency	Pre-op	0 ——— #_* ——— 10	
	6 mths	0 ——— #* ——— 10	
	12 mths	0 ——— *# ——— 10	No sig. diff.
Urge Incont	Pre-op	0 —— #* ——— 10	
	6 mths	0 — # — * ——— 10	
	12 mths	0 —— #* ——— 10	No sig. diff.
Stress Incont	Pre-op	0 ——— #* ——— 10	
	6 mths	0* — # ——— 10	
	12 mths	0* ——— # ——— 10	p < 0.05
Frequency	Pre-op	0 —— #* ——— 10	
	6 mths	0 — #* ——— 10	
	12 mths	0 — • — # ——— 10	p = 0.06

Pad Weighing Test: Pre-operatively the mean pad weight for one hour testing was 22 g for the open colposuspension and 24 g for the laparoscopic colposuspension. At 6 months it was 1 g (open) and 5 g (lap). At 12 months it was 2 g (open) and 12 g (lap). The difference was significant ($p < 0.05$).

Urinary Diary: Pre-operatively the mean number of leakages per 24 hrs was 12 for the open colposuspension and 13 for the laparoscopic colposuspension. At 6 months the mean number of leakages was 0 (open) and 2 (laparoscopic) and at 12 months it was 2 (open) and 6 (lap). The difference was significant ($p < 0.05$).

Videocystourethrography:

	Pre-op	6 months	12 months
Residual (Open)	24mls	42mls	40mls
Residual (Lap)	21mls	33mls	30mls
Peak Flow Rate (Open)	34mls/sec	24mls/sec	28mls/sec
Peak Flow Rate (Lap)	33mls/sec	29mls/sec	31mls/sec
Max P Det (Open)	5 cm/H_2O	7 cm/H_2O	6 cm/H_2O
Max P Det (Lap)	5 cm/H_2O	5 cm/H_2O	5 cm/H_2O
Proven GSI (Open)	30	1	1
Proven GSI (Lap)	30	4	8 *
MUCP (Open)	31 cm/H_2O	64 cm/H_2O	59 cm/H_2O
MUCP (Lap)	31 cm/H_2O	51 cm/H_2O	41 cm/H_2O *

* $p < 0.05$ (All other values not sig. diff.)

CONCLUSIONS:

After one year the outcome of Laparoscopic Colposuspension appears to be considerably worse than Open Colposuspension both on subjective and objective testing. Proper assessment will take 5 years. Until longer term data is available perhaps laparoscopic colposuspensions should only be done if they are part of an ongoing trial involving pre and post operative urodynamic assessment.

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PROSPECTIVE RANDOMIZED COMPARISON OF THREE SURGICAL PROCEDURES FOR STRESS URINARY INCONTINENCE: FIVE YEAR FOLLOW-UP

AIMS OF STUDY

There are mainly three groups of surgical procedures for the treatment of stress urinary incontinence (SUI): 1) vaginal plication of the bladder neck (1); 2) needle suspension (2); 3) retropubic urethropexy (3). Only few studies compared the success rate of these procedures (4-5). The purpose of this study was to evaluate and compare the long-term results of the Kelly plication, modified Pereyra needle suspension and Burch urethropexy for the treatment of SUI in women.

PATIENTS AND METHODS

One hundred twenty-seven consecutive women were operated between January 1986 and June 1987. The only indication for surgery was SUI. Women with previously failed anti-incontinence procedures were excluded. Mean age 55 years (29-77); mean parity 3 (1-12). Fifty-three patients were premenopausal, 74 postmenopausal. History, physical exam, urethrocystoscopy, cotton swab test, filling cystometry, urethral pressure profile at rest and on cough, and uroflometry were performed preoperatively, three months, one year and five years post-operatively. The subjects and surgeons were randomly allocated to one of three surgical procedures: Group I had anterior colporrhaphy with Kelly plication; Group II had modified Pereyra needle urethropexy; Group III had Burch urethropexy. One hundred seven women were available after one year, 93 were the subjects of a 5-year evaluation. Fisher exact test, X^2, t-test, and paired t-test were used for the statistical analysis.

RESULTS

The objective success rate for Group I, II, and III after five years was 37%, 43%, and 82% respectively, and the difference was statistically significant. The drop of success rate between 1 year and 5 year follow-up was 41.2%, 33.8% and 7.8% for Group I, II, and III respectively. Urodynamically all three procedures increased significantly the abdominal pressure transmission to the urethra when successful. Ninety-one percent of women after Burch had a negative Q-tip after five years as compared with 46% for the Pereyra, and 30% for the Kelly.

CONCLUSIONS

In our hands the Burch urethropexy has a higher cure rate that holds over time when compared with the modified Pereyra needle suspension and the Kelly plication. The lower incidence of positive Q-tip test in women after Burch may be a proof of better anatomical suspension of the bladder neck.

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