What is New in the Diagnosis and Treatment of Benign Prostatic Obstruction

W34, 16 October 2012 09:00 - 12:00

Start	End	Topic	Speakers
09:00	09:05	Introduction	• Carlos D'Ancona
09:05	09:20	Contribution of radiology in the diagnosis of BPO	• Enrico Finazzi Agro
09:20	09:35	What information does urodynamic provide?	• Ervin Kocjancic
09:35	09:50	Clinical treatment of BPO	• Carlos D'Ancona
09:50	10:05	Is it possible to preserve bladder function?	• Peter Rosier
10:05	10:30	Discussion	All
10:30	11:00	Break	
11:00	11:15	TURIS what are the advantages ?	• Ervin Kocjancic
11:15	11:30	Is LASER the gold standard of prostate surgery ?	• Enrico Finazzi Agro
11:30	11:45	New technologies (prostate embolization, botox)	• Peter Rosier
11:45	12:00	Discussion	All

Aims of course/workshop

The treatment of BPO is a public health problem because the augment of life expectancy promoting the increase of the number of patients with these complaints. This workshop aims to explore the contribution of radiology and urodynamics in the diagnosis, drugs in the clinical treatment and the use of new methods in surgical treatment. In addition there will be the opportunity to discuss clinical cases.

Educational Objectives

This workshop intends to provide an update in the diagnosis and treatment of BPO. The guidelines in BPO are well defined, but new research has appeared in the literature providing more information about the contribution of ultrasound in the diagnosis of BPO. It is well known that the urodynamic is the gold standard in the diagnosis of bladder outlet obstruction, but does not have consensus if this should always be performed before surgery. The LASER and TURIS technology will be presented giving support to add this new device in the urological armamentarium. New research like botulin toxin in the prostate and prostate arterial embolization will be presented.

Radiology in the diagnosis of BPO?

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Introduction:

Bladder outlet obstruction due to benign prostatic enlargement (benign prostatic obstruction, BPO) is the term used to describe obstructive voiding, is based on pressure-flow (P-Q) measurement and characterized by increased voiding pressures (Pdet) in combination with low urinary flow (Q). BPO can be detected in approximately 50% of men at initial assessment and before surgical removal of prostatic tissue (e.g. transurethral resection of the prostate). Preoperative determination of BPO and BPO-grade helps to select patients who will most likely profit from the operation; patients with BPO will have a significantly higher postoperative success rate – as determined by symptom reduction or increase of urinary flow - compared to men without BPO.

Many functional or morphological alterations of the lower or upper urinary tract can be found in patients with benign prostatic hyperplasia (BPH) or benign prostatic enlargement (BPE). Alterations of the lower urinary tract are:

- bladder trabeculation,
- bladder wall hypertrophy,
- bladder stones,
- bladder diverticula,
- postvoid residual urine, or
- urinary retention.

Alterations of the upper urinary tract are:

- bilateral hydronephrosis,
- fish-hook sign of the ureter, or
- renal insufficiency.

The frequency of these alterations is higher in patients with BPO compared to those without. However, most of these pathologies have not been proven to be directly or indirectly related to BPO (exceptions: bladder wall hypertrophy, bladder stones or uni- or bilateral fish-hook sign of the ureter).

Until now, only pressure-flow measurements of urodynamic investigation have proven to detect BPO sufficiently (in fact, BPO is defined by pressure-flow measurement). Despite the ability to detect BPO with urodynamics, the investigation is invasive, has a defined morbidity, and is time-consuming, expensive as well as bothersome for the patient. Urodynamics of men are associated with complications in approximately 19% of individuals, mainly due to macroscopic hematuria, urinary tract infection, or (clot) retention. There are also reports about deadly infections after urodynamic investigations. As a result, pressure-flow measurements are only rarely performed in men prior to treatment. Instead, non- or minimally-invasive tests are used to judge BPO.

No symptom or symptom combination is typical for BPO; the patient history is therefore an unreliable tool to detect or estimate obstructive voiding in men (likelihood ratio 1.01-1.04). Furthermore, non- or minimally invasive tests (uroflowmetry, measurement of postvoid residual urine, or ultrasound of the prostate) have also failed to show a sufficient ability to detect BPO in men (likelihood ratios 0.7-2.05). Uroflowmetry and postvoid residual urine, alone or in combination, are unable to distinguish between BPO and detrusor underactivity and can only be used for screening of voiding disorders in general but not for determination of the exact type of voiding disorder. Measurement of total prostate size, by suprapubic or transrectal ultrasound investigation or digito-rectal examination, correlates only weakly with BPO and is not suitable for the judgement of individuals. As a result, all tests used in clinical routine are not useful to detect BPO in the individual man or to stratify patients according to their BPO-grade.

Lately, two tests have been developed to detect BPO non-invasively. These tests use morphological changes of the lower urinary tract to estimate BPO. These tests are based on ultrasound and include:

1. Ultrasound measurement of detrusor (or bladder) wall thickness (DWT or BWT),
2. Ultrasound measurement of intravesical prostatic protrusion (IPP), and

Radiological tests for determination of BPO

1. Ultrasound measurement of DWT or BWT:

Background: This imaging technique is based on preclinical results with experimental animals; these results in animals have later been confirmed in humans. Animal studies demonstrated bladder wall hypertrophy and increased bladder weight following partially induced BOO, within as little as 1-2 weeks. Mean bladder wall thickness (BWT) in control, partially obstructed and severely obstructed rabbits was 1.57 mm, 2.04 mm and 2.77 mm, respectively, with most thickened observed in the detrusor layer. Histological analysis showed smooth muscle cell hypertrophy and hyperplasia, and an increase in collagen deposition, the ratio of type I to III collagen and muscarinic cholinergic receptors. Similar histological patterns were observed in patients with BPO, detrusor overactivity, or augmentation surgery for high intravesical pressures. Furthermore, bladder weight, smooth muscle cell hypertrophy and collagen deposition have been shown to partially reverse following relief of BPO. Beamon et al. demonstrated concurrent development of detrusor hypertrophy and detrusor overactivity with induced BPO in mice at 6 weeks, a well known association in clinical practice. Ultrasonic measurements of BWT and bladder weight were able to distinguish between obstructed and non-obstructed rabbit bladders.

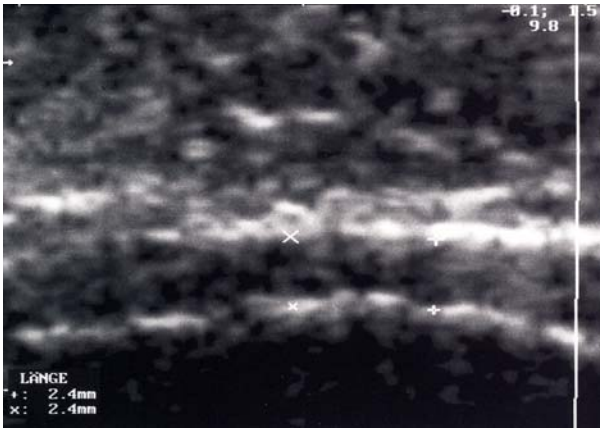
Technique in humans: the investigator has to be aware of some facts concerning the measurement of DWT or BWT in humans:

- Use of high frequency ultrasound probes: the resolution of the ultrasound image is frequency dependent: The higher the ultrasound frequency the better the resolution. High frequency ultrasound probes (e.g. 7.5 MHz) have a resolution of less than 0.13 mm, whereas ultrasound probes with a frequency of 3.5 MHz have a resolution of approximately 0.3 mm. Considering DWTs between 1.1-1.8 mm in filled bladders of healthy male volunteers or non-obstructed bladders and DWTs of 2 mm or higher in patients with obstructed bladders it is important to use frequencies high enough to capture small differences.
- Use of digital ultrasound machines for adequate image enlargement: for precise marker positioning and bladder wall measurements it is necessary to enlarge ultrasound images. Digital ultrasound machines for clinical use can enlarge the image 5 to 15fold. If the image has not been adequately enlarged imprecise placement of the

markers would result in great measurement differences and might suggest bladder wall hypertrophy.

- Ultrasonic appearance of the bladder wall: the outer and inner layers of the bladder wall appear hyperechogenic (white) and represent the adventitia and mucosa together with the submucosal tissue, respectively. The detrusor appears hypoechogenic (black) and is sandwiched between the hyperechogenic lines of the adventitia and mucosa (figure 1). Measurement of all three layers represents bladder wall thickness (BWT) and measurement of the detrusor only represents detrusor wall thickness (DWT). Therefore, BWT values are always greater than DWT values in the same patient and at the same bladder filling; therefore, direct comparison of both values is not possible.

Figure 1:



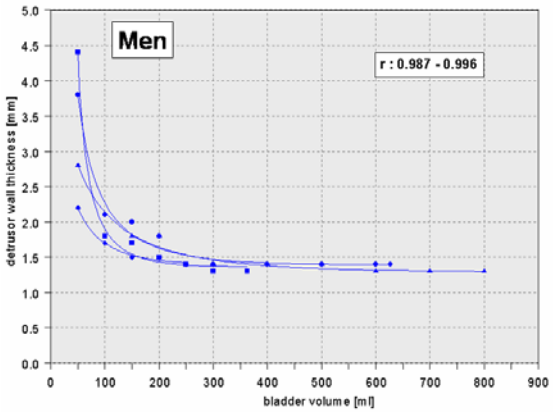
Hyperechogenic (white): adventitia
Hypoechogenic (black): detrusor
Hyperechogenic (white): mucosa

- Perpendicular imaging of the bladder wall: if the bladder wall has been tangentially imaged measurements might suggest bladder wall hypertrophy. Perpendicular imaging is achieved when the hyperechogenic adventitia and mucosa appear as thin and sharp lines.
- Decrease of thickness with increasing bladder filling: BWT and DWT depend on bladder filling in the range of 50 to 250 ml. It was first demonstrated by Khullar et al. that no significant differences of BWT exist in almost empty bladders and those filled until 50 ml. Oelke et al. showed in healthy adult male and female volunteers that DWT decreases rapidly between 50 and 250 ml of bladder filling (or until 50% of bladder capacity) but reaches a plateau thereafter with only minor and insignificant differences between 250 ml and maximum bladder capacity (figure 2). The difference of measurements at 50 and 100% bladder capacity is in the order of image resolution of a 7.5 MHz ultrasound array. This hyperbolic detrusor wall characteristic is identical in both healthy men and women and in line with results obtained in healthy children

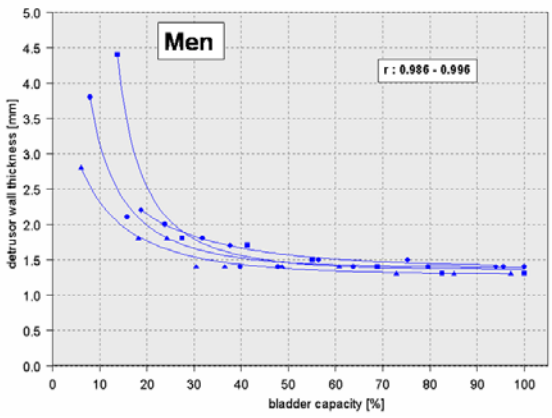
and women with overactive bladder/detrusor overactivity with or without urinary incontinence.

Figure 2:

DWT : bladder filling volume



DWT : bladder capacity in the same volunteers



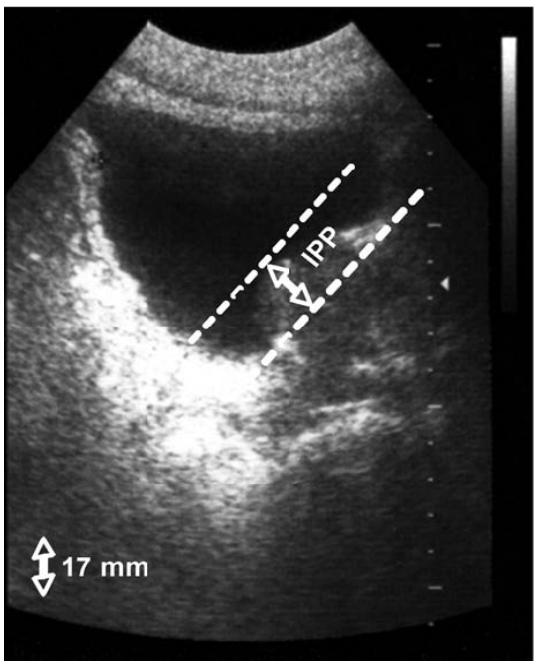
- Similar thicknesses at different parts of the bladder: all parts of the bladder (dome, anterior, posterior, or lateral walls) have the same thickness in the same patient and in the same state of bladder filling. Therefore, any part of the bladder can be imaged to measure BWT or DWT and diagnose bladder wall hypertrophy.
- Gender specificity of measurement values: it was shown in children and adults that females have a significantly lower BWT and DWT than males. Higher BWT and DWT values in males might reflect greater voiding pressures due to the prostate and longer urethra. Therefore, measurement values of females cannot be directly compared to those obtained in males.
- Low intra- and interobserver variabilities: Experienced centres have demonstrated that repeated measurements of BWT or DWT have an intraobserver variability of less than 5% and an interobserver variability of 4-12%.
- DWT/BWT in male patients with BPO is significantly thicker than in patients without BPO (likelihood ratio 2.9-43): a threshold value of 2 mm best distinguished between obstructed or non-obstructed bladders filled ≥250 ml. The technique has been lately confirmed by Kessler et al. from Switzerland although a threshold value of 2.5 mm seemed more appropriate to distinguish obstructed from non-obstructed bladders in order to achieve similar sensitivity and specificity. Compared to the Tubaro approach measuring BWT at a bladder filling volume of 150 ml in all patients, measurement

and threshold values are smaller with the Oelke technique measuring DWT at a bladder filling of ≥250 ml.

DWT in comparison with other tests for BPO detection: One prospective investigation was performed in 160 male patients before treatment and the performance of DWT was compared with pressure-flow measurement and other non-invasive tests (uroflowmetry, postvoid residual urine, and prostate volume). Only DWT measurements were similar to pressure-flow measurements indicating that ultrasound imaging and measurement of the detrusor wall can be used to determine BPO instead (table 1)

2. Ultrasonic measurement of IPP:

A prostate median lobe can increase bladder outlet resistance by causing a "valve ball" type of BOO with incomplete opening and disruption of the funnelling effect of the bladder neck. Ultrasound measurement of intravesical prostatic protrusion (IPP) aims to measure the distance between the tip of the prostate median lobe and bladder neck in the midsagittal plane using a suprapubically positioned ultrasound scanner (figure 3).



For IPP measurements, the bladder should be filled with 150-250 ml of fluid since IPP decreases with increasing bladder filling. The IPP distance can be divided into three grades:

Grade I: 0 - 4.9 mm
Grade II: 5 - 10 mm
Grade III: ≥10 mm.

Chia et al. first described IPP as a diagnostic tool to detect BPO in adult male patients. The authors correlated IPP-grades of 200 symptomatic male patients with results of pressure-flow measurements and found that IPP grade III correctly identified 94% of patients as obstructed and IPP grades I-II correctly identified 70% of patients as non-obstructed (table 1). Lim et al.

prospectively evaluated 95 patients with BPH-LUTS and correlated IPP, serum PSA-concentration and prostate volume with results of pressure-flow measurements. All three investigated parameters correlated well with PFS but only IPP was independently associated with BOO (P=0.02, OR 1.21). IPP >10 mm correctly predicted 71% of patients with BOO, whereas IPP ≤10 mm identified only 61% of patients without BOO.

Comparison between ultrasonic DWT/BWT measurements, IPP-measurements and results of pressure-flow studies (reference value):

Test	Ref.	Pat.	Threshold	Positive Predictive Value [%]	Negative Predictive Value [%]	Sens. [%]	Spec. [%]	Likelihood ratio
BWT	Manieri et al. 1998	174	5.0 mm [1]	88	63	54	92	6.8
DWT	Oelke et al. 2002	70	2.0 mm [2]	95	75	64	97	21.3
			2.0 mm [2]	81	85	92	68	2.9
			2.5 mm [2]	89	65	69	88	5.8
			2.9 mm [2]	100	54	43	100	43
	Oelke et al. 2007	160	2.0 mm [2]	94	86	83	95	17.6
IPP	Chia et al. 2003	200	10 mm	94	70	76	92	9.5
	Lim et al. 2006	95	10 mm	71	61	47	81	2.5

Table 1: BWT = bladder wall thickness; DWT = detrusor wall thickness; IPP = intravesical prostatic protrusion. Likelihood ratio of pos. test result: ability to detect BPO independently of the prevalence of BPO in the investigated population: LR >5 indicates a good and LR >10 indicates an excellent ability to detect BPO.

Conclusions:

Ultrasound measurements of BWT, DWT, or IPP are promising non-invasive tools to diagnose BPO in men. All tests have demonstrated an acceptable ability to detect or exclude BPO. One or more of these tests might replace pressure-flow studies in the future if only information in terms of BPO is required. However, invasive urodynamic investigation remains the only test that is able to provide detailed information about bladder function and dysfunction during filling and voiding.

UMC Utrecht

Urodynamic Analysis of Bladder Outlet Obstruction

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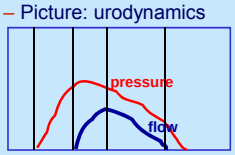
Voiding

- Bladder emptying
  - Elements:
    - Rate: milliliters per second
    - Time (sec) and total volume (ml)
    - Pressure (cmH_2O/energy (M. detrusor)
  - Picture: urodynamics

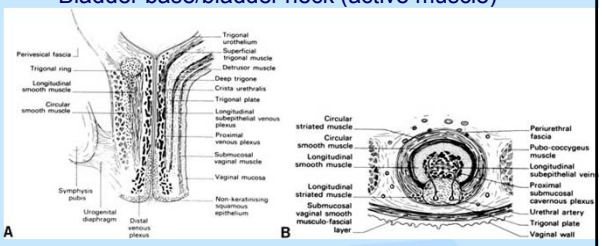


Normal act of voiding (neurologic)

- Pelvic floor initiates (normal and voluntary) voiding
  - (after permission from frontal lobe)
- Detrusor and bladderneck act coordinated
- Detrusor and bladderneck are antagonists
  - *synergic alternating* contraction-relaxation of detrusor and bladderneck.
    - Holding (storage)
      - » pelvic floor is active
      - » bladderneck is contracted and detrusor remains relaxed
    - Voiding (emptying)
      - » pelvic floor relaxes
      - » bladderneck relaxes and detrusor contracts

Funneling

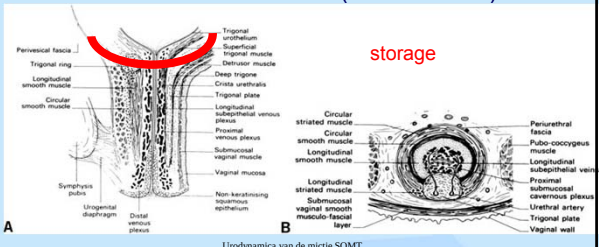
- Bladder base/bladder neck (active muscle)



Urodynamica van de mictie SOMT
Bekkenbodemfysiotherapie

Funneling

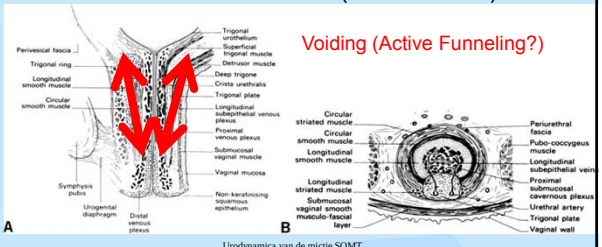
- Bladder base/bladder neck (active muscle)



Urodynamica van de mictie SOMT
Bekkenbodemfysiotherapie

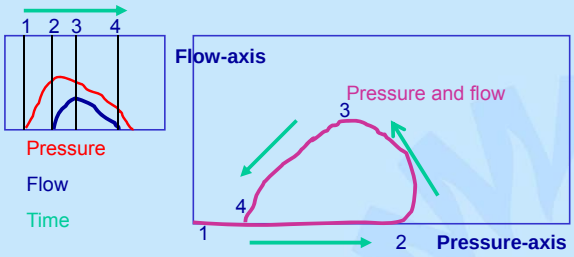
Funneling

- Bladder base/bladder neck (active muscle)



Urodynamica van de mictie SOMT
Bekkenbodemfysiotherapie

Act of voiding (physics)



- Intravesical pressure generates urine-flow

Voiding measuring (Urodynamics)

- Intravesical pressure recording
  - Transurethral (12F ↑ ± 8 cmH_2O $P_{det.max}$)
  - (8F 'no effect')
  - Suprapubic (no static effect)
- (Intra-abdominal pressure)
- Uroflowmeter
  - Close to the meatus!
  - Correct for delay

Good situation for analysis of voiding

- Relaxing surroundings
- Comfortable sitting or…
- Male standing (if preferred by patient)
- Support for feet
- Flowregistration as close to meatus as possible
- Reliable not hindering intravesical pressure recording
- BOO impossible to determine by video
- EMG does not play a role in diagnosis of BOO

BOO: Bladder outlet obstruction

- ≠ 'resistance' / ≠ 'energy loss'

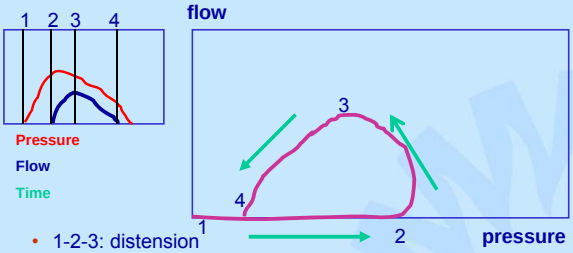
- (hydrodynamics)
- Distensible - collapsible tube
- Flow controlling zone (FCZ)
  Virtual ! by definition

- Boyarski, Bottaccini, Gleason, Zinner
- Derek Griffiths
- Werner Schafer
- Ron van Mastrigt

BOO men = Simple

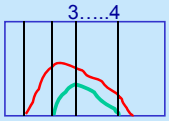
- Man (large prostate)
  - 'Stable' flow controlling zone
  - Simple pressure flow relation
  - 'simple' analysis

Micturition (distension<>collapse)



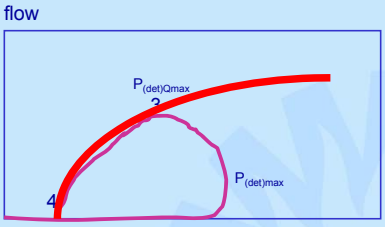
- 1-2-3: distension
- 3-4: steady state
- At 4: collapse

Micturition

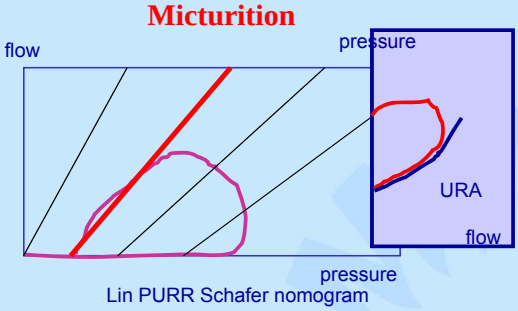


‘Passieve’ phase after Q_{max}

Passive urethral resistance relation PURR

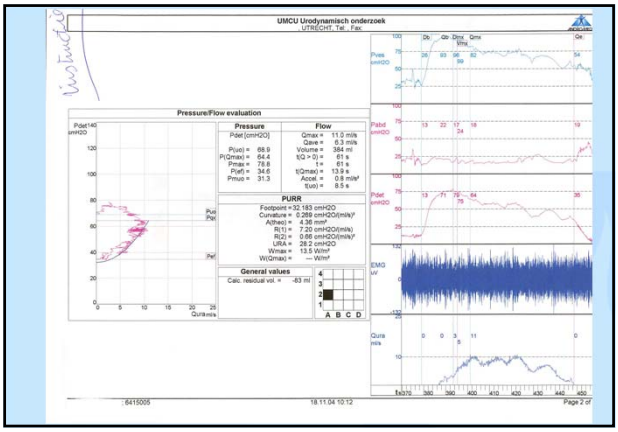


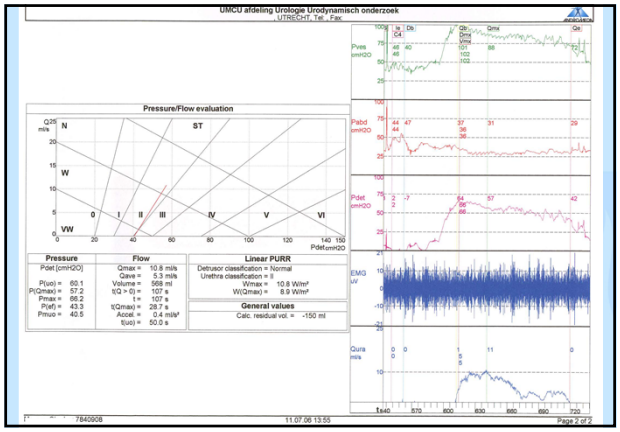
Micturition



Lin PURR Schafer nomogram

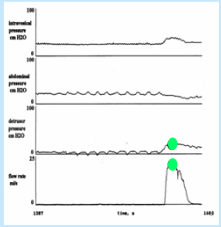
URA: (>30 cmH_2O)

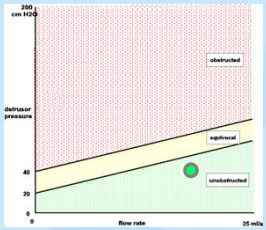




Unobstructed (low pressure normal flow)

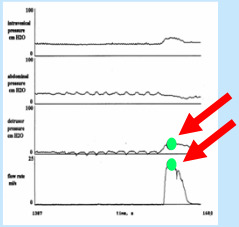
- Low pressure, normal flow

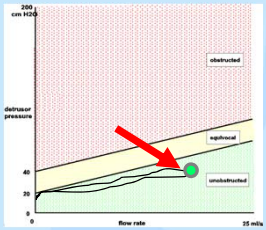




Unobstructed

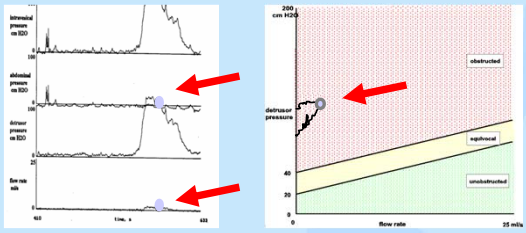
- Low pressure, good maximal flow





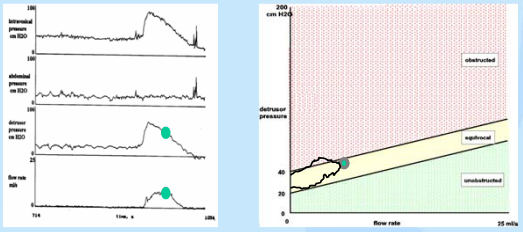
Obstructed

- High pressure, low maximal flow



Intermediate

- Moderate pressure, moderate flow



Analysis BOO

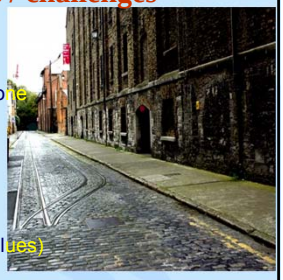
- $P_{det}Q_{max}$
- ICS obstruction index (Abrams Griffiths Number)
  BOOI
- $P_{det}Q_{max} - 2Q_{max}$
  - BOOI ≥ 40 obstruction: desobstruction will help
  - BOOI 20-40 equivocal: result is unpredictable
  - BOOI ≤ 20 no obstruction: 'desobstruction' will not change much

Blaivas Grautz Nomogram

- Female outlet obstruction

Dead end streets / challenges

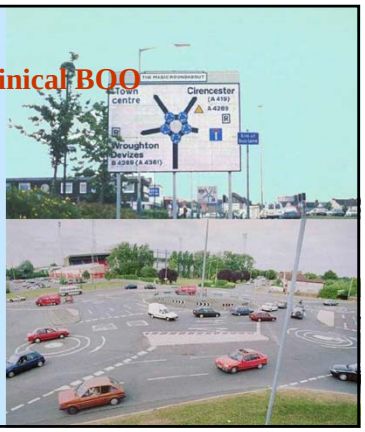
- Female
  - Pelvic floor dynamics
  - Dynamic flow controlling zone
- Young men
  - Dynamic bladderneck
  - Prostate middle lobe
  - Pelvic floor?
- Child (calibration / normal values)
- Neurology
  - Dyssynergia



Clinical BOO

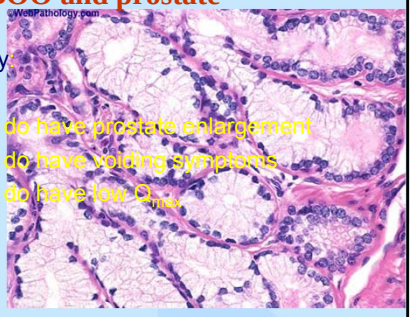
- Symptoms
- Flow
- Prostate
- Volumes voided
- Voiding diary
- Residual urine

- Confusing?



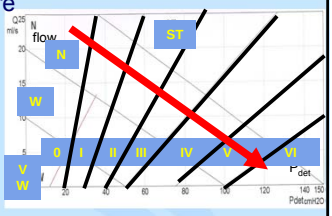
BOO and prostate

- Epidemiology:
- Elderly male do have prostate enlargement
- Elderly male do have voiding symptoms
- Elderly male do have low Q_{max}



BOO and flow

- Pressure and flow are related
- ICS BOO index:
  - $P_{det}Q_{max} - 2Q_{max}$
  - 'Pressure'- '2*flow'
- Free flow has 'some relation with BOO'



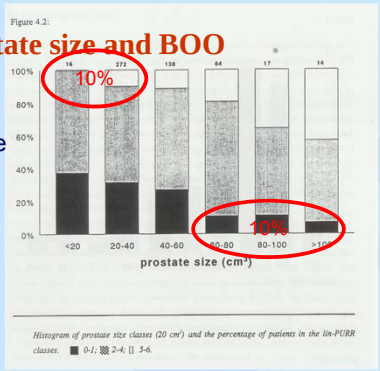
Prostate size and BOO

- World Journal of Urology **13** 9-13-1995: Rosier et al

Schafer	N	Age	Vol cm^3	Void%	IPSS
All	521	64,5	44	82,0	17.4
0	41	63,2	34,2	87,0	17,1
1	99	63,6	38,2	86,4	16,5
2	123	63,2	38,6	86,9	17,2
3	83	65,0	43,6	81,5	17,0
4	111	65,4	52,4	78,2	18,4
5	45	66,9	57,3	73,9	16,9
6	18	65,8	53,4	61,3	22,3

Prostate size and BOO

- Large prostate
- Greater chance to have BOO



BOO and clinical information

- ***Clinical diagnosis of bladder outlet obstruction in patients with benign prosttic enlargement and lower urinary tract symptoms***
  - (J. Urol 1996 Rosier et al)

N: 871	Severe BOO	Moderate BOO	No BOO	P-value
Age	65,6	66	63,3	.0003
IPSS	18,6	17,0	16,4	.0074
Qmax	8,8	11,1	12,6	.00001
Volume	202	272	299	.00001
Residual	89	61	50	.00001
Prost size	54,4	42,1	37,0	.00001

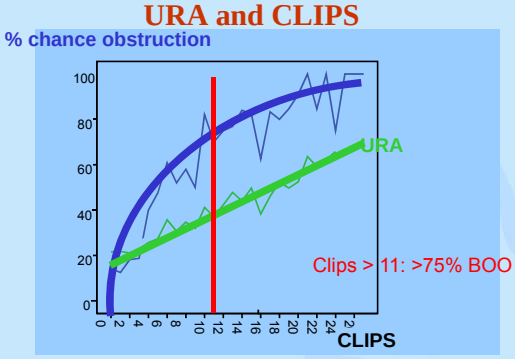
BOO and clinical information

- Prostate size
- Flow maximum
- Residual urine
- Voided volume
- Pieces of the puzzle
- Statistics:
  - (multivariate analysis)

Clinical Prostate Score (CLIPS)

Prostate $<30cm^3$ ***0 points***	Prostate $30\text{-}60cm^3$ ***3 points***		Prostate $>60cm^3$ ***6 points***
Flow >12 ml/s ***0 points***	Flow 8-12 ml/s ***5 points***	Flow 4-8 ml/s ***10 points***	Flow <4 ml/s ***15 points***
Residual <30 ml ***0 points***	Residual 30-100 ***2 points***		Residual >100 ***4 points***
Voided volume >300 ml ***0 points***	Voided volume 200-300 ml ***1 point***		Voided volume <200 ml ***2 points***

URA and CLIPS



CONCLUSIONS

- Symptoms are unrelated to the grade of BOO
- Maximum flow is related to BOO
- Prostate size is related to BOO

- Combine clinical information
- Pressure flow is golden standard

Drugs in the Treatment of BPO

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Male lower urinary tract symptoms (LUTS), benign prostatic hyperplasia, benign enlargement of the prostate (BPO) and bladder outlet obstruction are common among aging men and will increase in socioeconomic and medical importance at a time of increased life expectancy and aging [1]. Approximately 25% of men over 40 suffer from LUTS and the prevalence of this condition rises with age [2]. LUTS are not disease specific and hence diagnostic of BPO. A careful clinical history augmented by the use of validated symptoms score (IPSS) combined with a physical examination including a digital rectal examination and PSA to exclude malignancy.

More than ten years ago, surgery and watchful waiting were the only accepted management option for LUTS suggestive of BPO. Nowadays medications, such as alpha1-adrenoceptor antagonist and 5 alpha reductase inhibitors are the most frequently treatment modality and promote decline number of surgical procedures. Surgery for BPO has decreased by around 60% in the last decade in the USA and Europe [3]. Phytotherapy has become widely used in the USA and in Europe, mostly because of positive comparisons to α-blockers and 5α-reductase inhibitors [4].

Medical therapies include alpha1-adrenoceptor antagonist, which relaxes the smooth muscles in the prostate, 5 alpha reductase inhibitors which shrinks the glandular component and a combination of others drugs such as antimuscarinic, phosphodiesterase 5 inhibitors and desmoressin.

5 alpha reductase inhibitors

A number of compounds have been identified as inhibitors of 5 alpha reductase, including steroidal inhibitors, epristeride, MK-906, finasteride and dutasteride. Only finasteride and dutasteride have reached clinical practice.

Reduction of dehydrotestosterone (DHT) in the serum and prostate tissue is due to the inhibition of the 5 alpha-reductase enzyme [5,6]. Finasteride solely inhibits type 2 whereas dutasteride type 1 and 2 enzymes [7]. The type 2 isoenzyme is the predominant from in genital tissue it is clear that the majority of DHT synthesized in the prostate derives from this enzyme. The same is known for serum DHT. About 80% of serum DHT synthesized from testosterone conversion through type 2, only 20% are synthesized by type 1 [8]. Reduction of serum DHT concentration provided by dutasteride (90-93%) exceeds that of finasteride (70%).

Finasteride – treatment with finasteride induced a significant decrease in symptoms score (-21%) compared to placebo after 1 to 5 years [9]. This treatment is more effective in men with large prostate > 40gms (84) [10]. Finasteride reduces prostate volume by 20% (range 15 – 23%) [11]. The effect on obstructive parameters in pressure flow studies shows: decrease from 76% at baseline to 67% after 1 year and to 60% after 2 years [12]. In general, the urodynamic effect of finsateride are only small or moderate. Finasteride was associated with a lower risk of surgical intervention and increased risk of ejaculation disorder, impotence, and lowered libido, versus placebo [13].

Dutasteride – the efficacy and safety of dutasteride in men with BPO is compared with placebo. Continued improvement in IPSS was noted in the dutasteride group promoting significantly decreased IPSS and improve Qmax compared with placebo. Drug-related sexual function events in the dutasteride group were infrequent and generally were not treatment limiting. Dutasteride improves urinary symptoms and flow rate and reduces prostate volume. Current evidence shows that 5ARIs are effective in treating LUTS and preventing disease progression and represent a recommended option in treatment guidelines for men who have moderate to severe LUTS and enlarged prostate**.** 5-α Reductase inhibitors for BPH treatment reduced PSA and prostate volume significantly when the patients were treated for 1 year. Administration of dutasteride is considered to be more effective in reducing PSA and prostate volume. Therefore, dutasteride should not be considered equivalent to finasteride in the reduction rate of PSA [14].

Adrenoceptor antagonist

The effect on smooth muscle tone is dependent on the release of noradrenaline (NA) from adrenergic nerves, the amine stimulating alpha 1 –ARs on smooth muscle of the prostatic stroma, bladder neck and urethra. Prostatic and urethral alpha ARs are considered to mediate the dynamic component of obstruction and since a direct relationship between the amount of prostatic smooth muscle and dynamic obstruction (as assessed by the response to alpha1 – AR blockade) has been demonstrate [15]. It has been clear that the effects of alpha-blockers on BOO are moderate at best, and are insufficient to explain improvement in symptoms, particularly storage symptoms. Newer concepts highlight a possible involvement of alpha1-ARs in the bladder and/or spinal cord as possible mediators of alpha-blocker induced symptom relief [16].

The efficacy of alpha-blockers in relieving LUTS has primarily been assessed by their ability to reduce IPSS and by their ability to increase maximum flow rate. The aggregate data of studies, presents level 1 evidence to support the efficacy of alpha-blockers as a class in relieving both storage and voiding symptoms associated with BPO. Multiple direct studies have confirmed that similar efficacy of the various alpha-blockers.

Early α-blockers that were nonselective for adrenoceptor subtypes have been associated with blood pressure-related adverse effects, such as orthostatic hypotension, that may be attributed at least in part to the blockade of α(1B)-adrenoceptors in arterial vessels. Silodosin, a novel α-blocker with exceptionally high selectivity for α(1A-) versus α(1B)-adrenoceptors, possesses an excellent cardiac- and blood pressure-related safety profile, and data have demonstrated that it does not promote QT-interval prolongation [17]. It is clear that there appears to be a discrepancy between the ability for alpha1-AR antagonist to relieve symptoms when compared to the relief of BOO and consequent improvement in urodynamic parameters.

Patients with ejaculation disorder may be caused by selective alpha(1A)-blockers. Results suggest that ejaculation disorder caused by selective alpha(1A)-blockers is associated with very large improvements in lower urinary tract symptoms without incremental risk for adverse events [18].

At the initial diagnosis of BPO, patients with a larger prostate volume and severe IPSS have a higher risk of alpha-blocker monotherapy failure. In this case, combined therapy with 5-ARI or surgical treatment may be useful [19].

Phytotherapy

Phytotherapy have a great appeal in the treatment of BPO due to of lack of side effects. During the last few years high quality trials comparing Serenoa repens to placebo were done. This therapy does not improve LUTS or Qmax compared to placebo in men with BPO, even at double or triple the usual dose.

These agents are a heterogeneous group of plant extracts used to improve BPH-LUTS. Phytotherapy remains problematic to use because of different concentrations of the active ingredients in different brands of the same phytotherapeutic agent.

Combine treatment

Alpha-blocker + antimuscarinic – the presence of storage symptoms is extremely common in patients with BOO. There is statistical significant advantage of combine treatment in patients with BOO and overactive bladder (OAB) symptoms.

The safe use of antimuscarinic drugs mainly acting by decreasing urgency and increasing bladder capacity during storage phase, when there is no activity in the efferent parasimpatic nerves. The action of these drugs may be reduced during the voiding phase, when there is a massive release of acetylcholine [20].

Incidence of acute urinary retention (AUR) in men receiving antimuscarinics with or without an α-blocker was ≤3%; changes in postvoid residual volume and maximum flow rate did not appear clinically meaningful. Post hoc analyses from

double-blind, placebo-controlled trials and prospective studies of fesoterodine, oxybutynin, propiverine, solifenacin and tolterodine also suggest that antimuscarinics are generally safe and efficacious in men. A retrospective database study found that risk of AUR in men was the highest in the first month of treatment and decreased considerably thereafter. Antimuscarinics, alone or with an α-blocker, appear to be efficacious and safe in many men with predominant OAB symptoms or persistent OAB symptoms despite α-blocker or 5-α-reductase inhibitor treatment. Monitoring men for AUR is recommended, especially those at increased risk, and particularly within 30 days after starting antimuscarinic treatment [21].

5 alpha reductase inhibitors + Alpha-blocker - combination therapy is considered an option for men in whom baseline risk of progression is significantly higher in patients with larger glands and higher PSA values [22]. In men with symptomatic BPO and an enlarged prostate (>30 cm3), combination therapy was more effective than tamsulosin or dutasteride mono-therapies alone in improving IPSS and Qmax after 2 years (Fig. 1). This must be balanced against the increased rate of adverse events observed with combination medical therapy as well as against pharmacoeconomic considerations. BPO is a progressive disease that is commonly associated with LUTS and might result in complications, such as acute urinary retention and BPO-related surgery. Therefore, the goals of therapy for BPO are not only to improve LUTS in terms of symptoms and urinary flow, but also to identify those patients at a risk of unfavorable disease progression and to optimize their management.

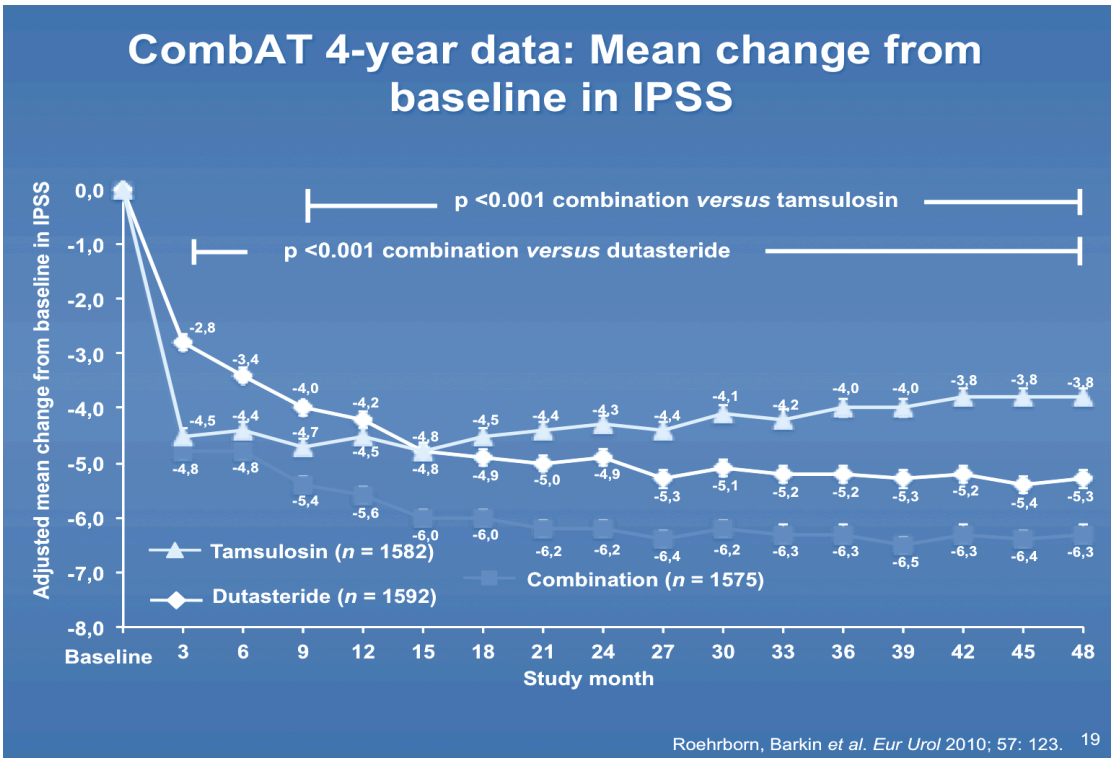


Figure 1 – improving IPSS in tansulosin, dutasteride and combination treatment.

Long-term treatment (4 years) with combination therapy (dutasteride plus tamsulosin) is significantly superior to tamsulosin but not dutasteride at reducing the relative risk of AUR or BPH-related surgery. Furthermore, combination therapy is significantly superior to both monotherapies at reducing the relative risk of BPH clinical progression, and provides significantly greater reductions in IPSS. In another study, the patients were followed for 10 years, compared an α-blocker with a combination therapy: the AUR incidence was 13.6% and 2.8%, respectively, and the incidence of BPH-related surgeries was 8.4% and 3.2%, respectively. There were no significant differences in the length of AUR incidence between the two treatments when PV was 35 g or lower and serum PSA level was 2.0 ng/ml or lower [23].

In addition, combination therapy significantly improved patient-reported, disease specific QoL and treatment satisfaction compared with monotherapy [24].

Phosphodiesterase 5 inhibitors and alfa bloqcker

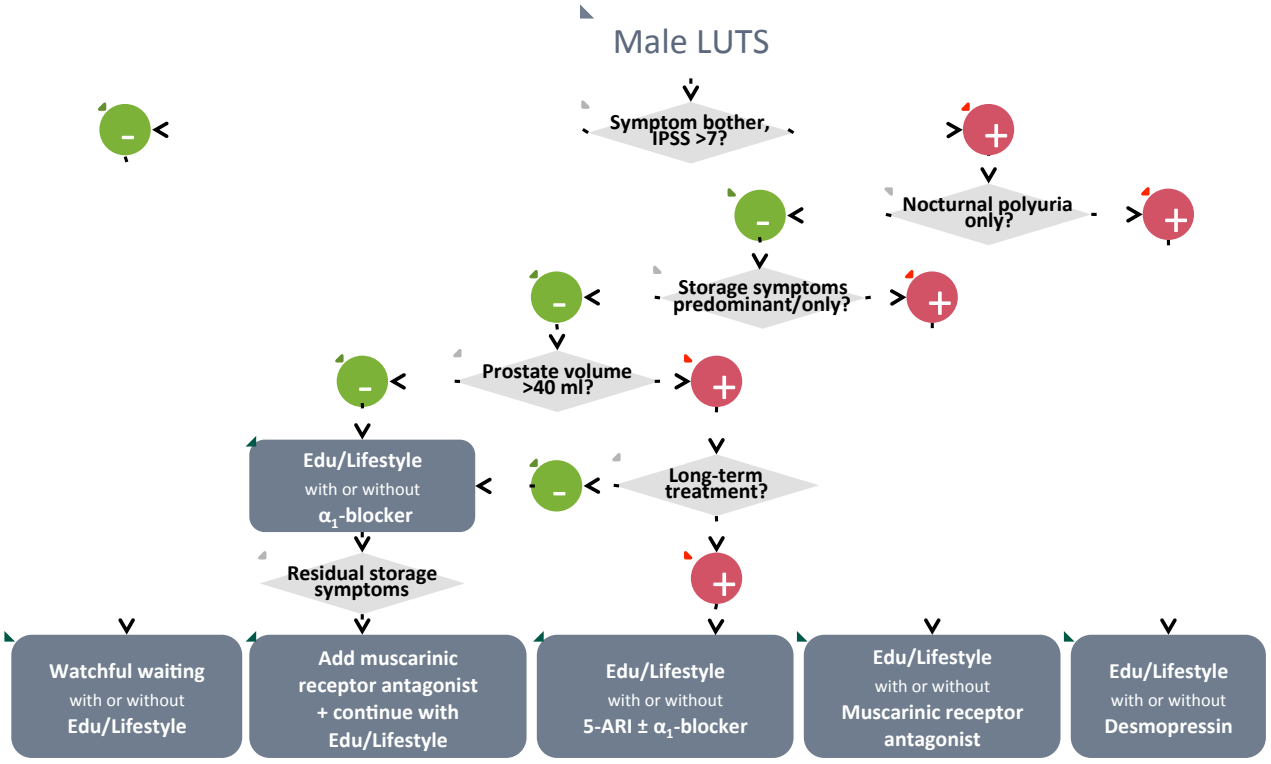
The phosphodiesterase 5 inhibitors are used in the treatment of erectile dysfunction (ED) and there are increasing data of effects of these drugs on bladder and urethral relaxation as well as of prostatic smooth muscles that may relief the symptoms of BPH. Preliminary data have suggested that treatment with PDE-5 inhibitors, such as sildenafil, improves LUTS in men with ED possibly as the result of smooth muscle relaxation of the lower urinary tract [25]. However, the results are inconsistent.

A systematic review and meta-analysis suggests that PDE5-Is can significantly improve LUTS and erectile function in men with BPH. PDE5-Is seem to be a promising treatment option for patients with LUTS secondary to BPH with or without ED [26].

Alpha-blocker and or 5 alpha reductase inhibitors + desmopressin

Desmopressin has no effect on the prostate, however, some patients have decreased voiding symptoms with alpha-blocker and/or 5AR and are bothered by nocturia. In these cases desmopressin is indicated. The antidiuretic hormone plays a key role in body water homeostasis and the control of urine production. The drug should be titrated from 0.1 to 0.4 mg, according to the individual's clinical response. Desmopressin significantly reduces nocturnal diuresis by approximately 0.6-0.8mL/min (-40%), decreases the number of nocturnal voids by approximately 0.8-1.3 (-40%), and extends the time until the first nocturnal void by approximately 1.6 hours [27].

Education/lifestyle with or without medical treatments is usually the first choice of therapy. A conservative and medical treatment choice according to evidence-based medicine and patients' profiles is provided in Figure 2 [27].



Oelke M et al. EAU Guideline on Male LUTS, update 2012; http://www.uroweb.org/gls/pdf/12_Male_LUTS_LR.pdf

Figure 2 – Flowchart of male lower urinary tract symptoms recommended by the EAU Guideline 2012.

Conclusion

The efficacy of new selective α-blockers: combination therapy of α-blocker and 5α-reductase inhibitor results in great benefit for symptom improvement as well as risk reduction of disease progression and complications. The use of selective antimuscarinic agents in patients with moderate-to-severe symptoms and nonobstructive pattern recognized as overactive bladder type has also been successfully evaluated. PDE5 inhibitors have been officially licensed only for the treatment of erectile dysfunction and pulmonary arterial hypertension. Treatment beyond this indication, LUTS, is still experimental and should not be used routinely in the clinical setting. Otherwise, as many as 30% of patients fail to achieve sufficient symptom improvement with medication, lifestyle adjustment, and fluid management, and may require more invasive or surgical treatment options.

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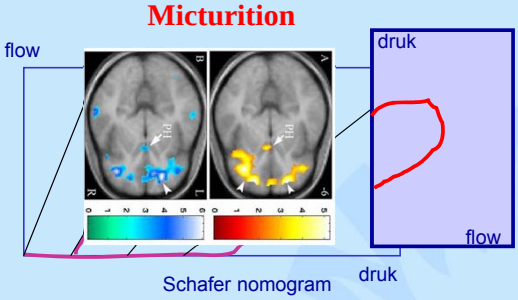
UMC Utrecht

Urodynamic analysis

Dr. Peter F.W.M. Rosier

Detrusor contraction and contractility

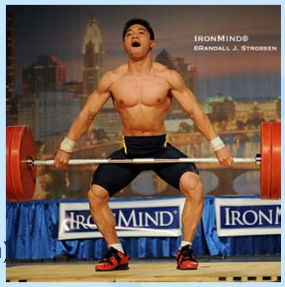
Micturition



(Detrusor)muscle (function)

- Strength (power)
- Velocity
- Duration /endurance

- Volume
- Innervation
- Oxygenation (circulation)



(Detrusor)muscle (function)

Confusion!!!
- Contraction
- Contractility
- Maximal contraction
- Maxmal contractility
  - Voiding phase
  - Filling phase
- tone hypertonia atonia hyperreflexia

(Detrusor)muscle (function)

Confusion!!!
- Contraction
- ~~Contractility~~
- Maximal contraction
- M~~axmal contra~~ctility
  - V~~oiding phase~~
  - ~~Filling phase~~
- ton~~e hypertonia~~ ~~atonia hyperreflexia~~

(Detrusor)muscle (function)

- Detrusor and bladder-neck are antagonists

- Pelvic floor: ‘switch’ between bladderneck ‘dominance’ and ‘detrusor dominance’

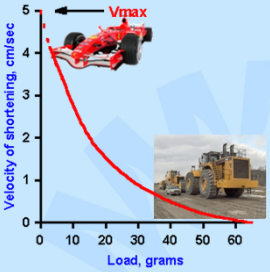
Velocity & Speed

Muscle function:

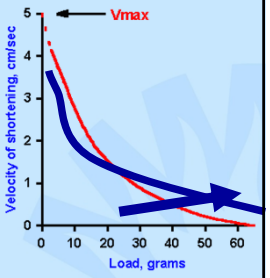
- Speed (velocity)

  OR

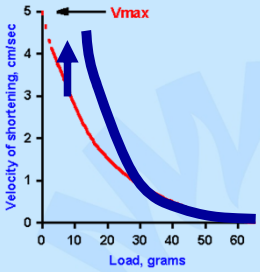
- Power (load)



Velocity and power



Power and velocity



Power & velocity: detrusor

- Velocity= Muscle shortening speed
  - Detrusor = Hollow muscle >
  - Volume reduction /time
    - is relative to shortening velocity
  - Volume reduction / time = milliliters / second = flow
- Flowrate is a measure of shortening velocity

Power & velocity: detrusor

- Detrusor energy > force; directed to the center of the bladder
- Force of muscle >> pressure inside the bladder
  - Maximum or force / maximum of muscle generated 'power' (≈ maximum of pressure)
    - Isovolumic contraction > Isometric contraction

Power and velocity

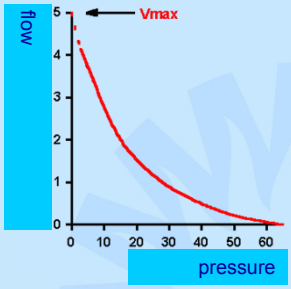
- Speed (velocity)

Shortening >>>

- ≈ flow
- Power (load)

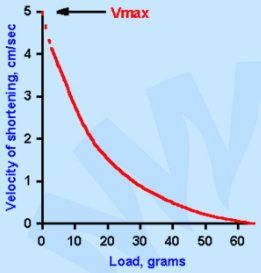
>>>

- ≈ pressure

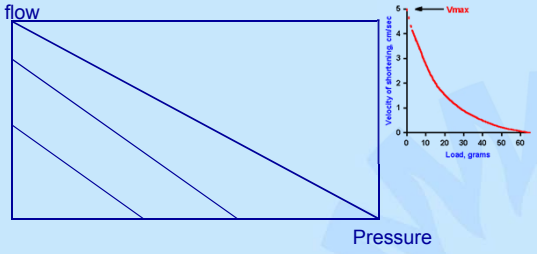


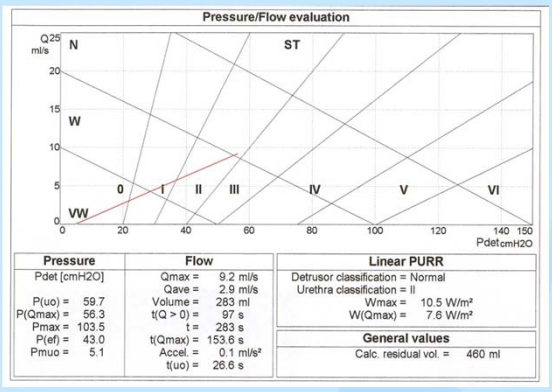
Detrusor contraction

- At every point in the voiding: pressure/flow
- Therfore power/velocity
  - (over time): work
    - formula
- Calculate: Detrusor-work
  >W/m^2
  W_{max}



Detrusocontraction (nomogram)





Detrusor contraction

- Pressure > Power (load)
- High pressure is high 'load'
  - ***Therfore 'obstruction'***
- Low pressure indicates
  - No obstruction
  - Or weak contraction
  - Not effective voiding

Effective voiding

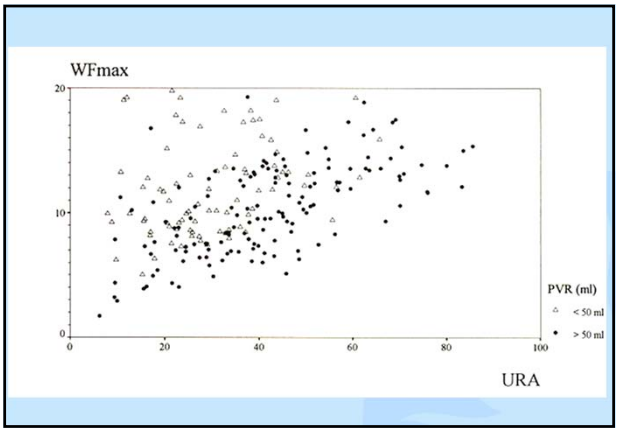
- 'Clinically'
  - Good max flow
  - Uninterrupted voiding
  - No residual urine
  - Fast and complete emptying
- Muscle activity:
  - Small muscle load
  - (Adequate duration of the contraction)

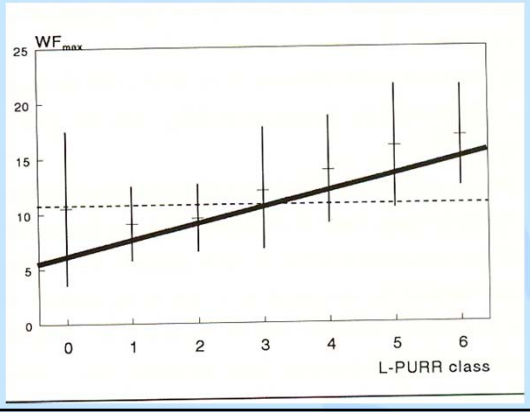
Not effective voiding

- Too much load (contraction duration)
  - Good contraction that fades away
  - residual urine
- (Too) weak contration
  - Mechanically (e.g. diverticula, reflux)
  - Energy consumption (vascularisation)
  - Innervation / stimulation
  - 'myogenic diseases'
- BOO > because of growing prostate: detrusor training!

BOO and training and failure

- Analysis of contraction
- In relation to increased BOO



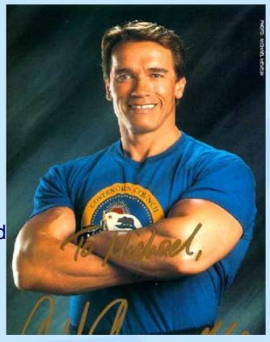


Detrusor underactivity (clinical)

- Ten years follow –up 200 men detrusor underactivity > No significant change in contractility
- Not in patients with TURP
  - Surgery did not improve contracility
- Not in patients without TURP
- No treatment for detrusor underactivity

BOO

- Men (large prostate)
  - Flow controlling zone
  - Stable outlet
  - Simple pressure flow relation
  - Increased load > increased power
  - ‘simple’ analysis



What is yet unknown?

- Why does the bladder stop contracting?
  - End of voiding
    - residual
  - Premature
  - Contraction time
- Pelvic floor as switch

Highlights

- Pressure-flow equals velocity-force
- High pressure ≈ obstruction
- High pressure ≈ good contraction
- (Maximal contraction) depends on load (compensating)
- Residual urine
  - Prematurely stopped contration
- Low pressure
  - No obstruction
  - Or …?

Conclusions

- Diagnosis of contraction and contractility
  - Helps somewhat to undestand the patients problem
- BOO is the predominant reason for therapy
- NoBOO and week contraction is a benign (however chronic) condition

TURIS (Trans Urethral Resection in Saline): what are the advantages

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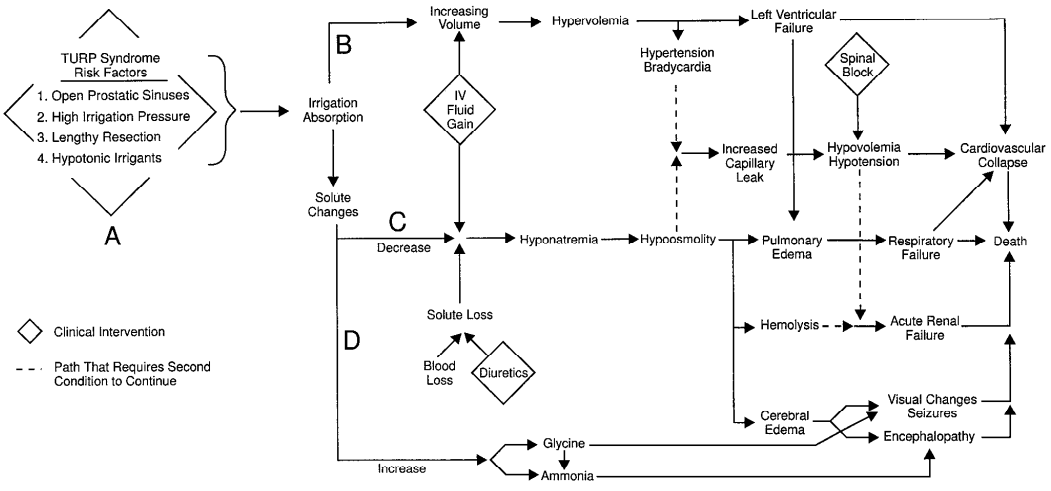
Despite the availability of medical treatment a significant proportion of patients require surgical intervention for BPH.
TURP (Trans urethral resection of Prostate) remains the gold standard however many less invasive alternatives have been proposed in order to reduce the complications and hospital stay.

Despite many technical advances in TURP technique, the morbidity has remained in the range of 15 to 18%
The most frequently reported complications are:

- Blood loss
- Fluid absorption with dilutional hyponatremia and TURP syndrome)
- Glycine toxicity
- Perforation

Conventional TURP is performed with nonelectrolyte irrigation fluid and monopolar current and this represent the major risk to develop a TUR syndrome.

TURP Syndrome



Signs and symptoms of TURP syndrome

Cardiopulmonary	Hematologic and renal	Central nervous system
Hypertension Bradycardia Dysrithmia Respiratory distress Cyanosis Hypotension Shock Death	Hyperglicynemia Hyperammonemia Hyponatremia Hypoosmolality Hemolysis/anemia Acute renal failure Death	Nause/vomiting Cnfusion/restlessness Blindness Seizures Lethargy/paralysis Midriasis Coma Death

Major role in the genesis of TURP syndrome have acute hyponatremia caused by the rapid absorption of a large volume of sodium-free irrigation fluid. This is one form of acute water intoxication which can trigger the central nervous system (CNS) complications. It is clear from the decreasing incidence of TURP syndrome over the, past 40 years that progress has been made in its prevention and treatment. In the 1989 American Urological Association (AUA) Cooperative Study, the risk of TURP syndrome was reported to be higher with a resection time exceeding 90 minutes and a gland greater than 45 grams.
Data on current frequency of TURP Syndrome vary considerably in the literature , ranging from 0.18 to 10.9%.

The use of bipolar energy for transurethral resection of tissue allows the use of saline instead of a nonconductive fluid such as glycine for intraoperative irrigation.
In the bipolar resection the current flows from the resection loop through the tissue and returns via the sheath of the resectoscope loop to complete the electrical loop.

Advantages of TURP in saline:

- more time to perform the resection
- better visualizatioin and coagulation of bleeding vessels
- more time for teaching/training residents without compromising patient's safety.

The teaching advantage is specially advantagouse considering the smaller number of TURP procedure currently available for residency training.

The first TURIS system was describer in an animal study by Schiozawa in 2002. The authors developed an innovative transurethral resection system (TURis) consisting of a uniquely-designed generator and a resectscope. The goal was protecting the obturator nerve induced ccperforation or other complications. In the article the authors observed that the obturator nerve was protected from troublesome reflexes during TURis because the high frequency current delivery route is via the resection loop to the sheath of the resectscope and not via a patient plate. After extensive

preclinical evaluation and verification of the system using an animal model to ensure efficacy as well as operational safety, TURis was conducted for treatment of superficial bladder cancer and benign prostatic hyperplasia.

In the first sizable clinical series of patient in they're pilot study published in J. endourol in 2006 Ho and coworkers presented a prospective evaluation done on 45 patients with clinically significant BPH and treated with trans urethral resection of the prostate using the TURIS system. Authors described a negligible reduction in the hemoglobin and serum sodium concentration. The IPSS decreased from 22.6 pre op to 6.5 at 1 year and q max increase in flowmetry from 6.5 ml/ec to 18.3 ml/sec.
In a prospective randomized comparative study by the same author in Eur.Urol 2007 (Ho and coworkers) a monopolar resectioin was compared in a randomize fashion with a TURIS resection. Mean resection time and mean weight of resected prostate tissue were comparable for both groups. Declines in the mean postoperative serum Na+ for TURIS and monopolar TURP groups were 3.2 and 10.7 mmol/l, respectively ($p < 0.01$). However, there was no statistical difference in the decline in post-operative Hb between the two groups. This series of patient only smaller glands were treated. There were two cases of clinically significant transurethral resection syn- drome in the monopolar group. Urethral strictures were observed in three cases of TURIS and one patient in the monopolar group. The IPSS and Qmax improve- ments were comparable between the two groups at 12 mo of follow-up.

	Monopolar	TURIS	*p* value
Clot retention	2	3	NS
Blood transfusion	1	1	NS
TUR syndrome	2	0	<0.05
UTI	2	2	NS
Failed TWOC	4	5	NS
Stricture	1	3	NS

TURIS = transurethral resection in saline; NS = nonsignificant; TUR = transurethral resection; UTI = urinary tract infection with positive urine culture; TWOC = trial of voiding without catheter; NS = nonsignificant.

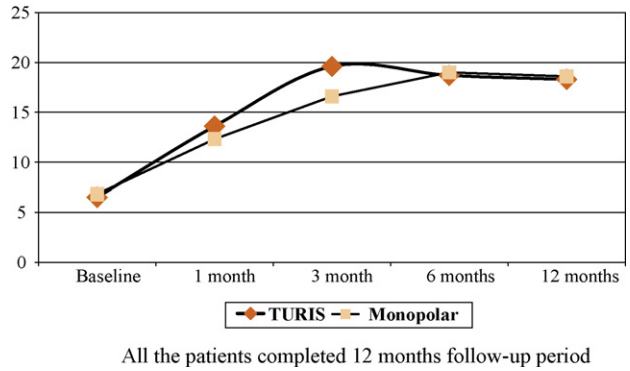


Fig. 2 – Efficacy profile: mean maximum urinary flow rate (Q_{max}). TURIS = transurethral resection in saline.

They're conclusion was that bipolar TURP using the TURIS system is clinically comparable to monopolar TURP at 1 yr with an improved safety profile.

The increased safety profile, specially related with the serum Na concentration has been confirmed by several other authors.
QiChen and coworkers published in Urologia internationalis 2009 a prospective series of patients with large volume BPH (> 50g). Patients were randomized in 2 groups (TURP and TURIS).

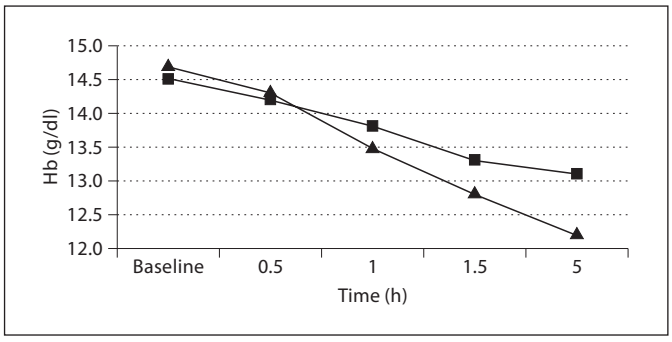


Fig. 2. Mean change in Hb in the TURP (▲) and TURIS (■) groups.

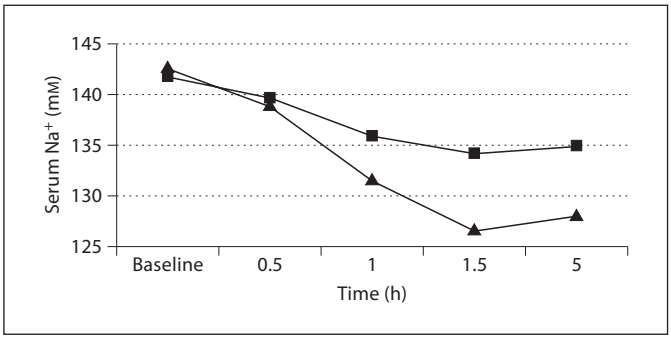


Fig. 1. Mean change in serum Na^+ in the TURP (▲) and TURIS (■) groups.

As expected there was a statistically significant difference in drop of serum sodium concentration, but interestingly a difference in Hb concentration was noticed starting at 1.5h of resection. There was a nonsignificant difference in the alteration of Hb between the two groups at baseline, 0.5 and 1 h. However, the difference was found at 1.5 h (TURIS = 13.3 8 0.3 vs. TURP = 12.8 8 0.4 g/dl, p = 0.001). Postop- eratively, the mean Hb only dropped by 1.4 g/dl in the TURIS group, whereas it fell by 2.5 g/dl in the TURP group (p = 0.001).
The authors conclude that TURIS system has less influence on serum sodium and more protective effect on blood loss in case of large volume BPH.

In a larger series of patients (550 consecutive patients with symptomatic BPH published in Scandinavian J of Urol and Nephrol, Michelsen and coworkers

Table I. Characteristics of the two groups.

Variable	Monopolar TURP	Bipolar TURIS	*p*
Age (years)	72.4 ± 9.0	72.1 ± 9.4	0.722
Operative time (min)	50.2 ± 22.2	52.0 ± 22.5	0.357
Resection weight (g)	19.2 ± 15.0	17.6 ± 11.5	0.173
Resection speed (g/min)	0.40 ± 0.32	0.36 ± 0.22	0.100

No difference in terms of operative time, resection weight and speed was observed between the two groups. As noticed the amount of resected tissue was limited to less than 20 grams and not surprisingly no statistically significant difference in Hb conentration was observed. There were 2 cases of TURP syndrome in TUR group and non-in the TURIS. The difference in serum sodium concentration was statistically significant in favor of TURIS group of patients.
The conclusion was that bipolar TURP with saline is safe technique and obviates the risk of TURP syndrome, thus repeated serum analysis of electrolytes after TURIS can be safely omitted.
In a larger study on bigger prostate (>60g) the difference in blood loss was again showed to be statistically significant. Bhansali and coworkers published in J. of endourology in 2009 they're series of 70 patients randomized in TURP or TURIS resectioin and with a power calculation based on level of significance 5% and power analysis of 79.45%. The difference in blood loss was statistically

significant. In the TURP group of patients the average blood loss was 361.51 ml while in the TURIS group was only 197.97 with a p value <0.001.
They also noticed a relatively high incidence of postoperative stricture in both groups (5 pts in TURIS and 4 in TURP). The difference was non statistically significant and it has bean attributed to a longer operative time required to remove larger prostate (around 80 minutes in both groups.)

In a recently published paper (J. of endourology2011) Fagerstrom and coworkers compared the complication rates and clinical outcomes 18 months after bipolar and monopolar TURP.

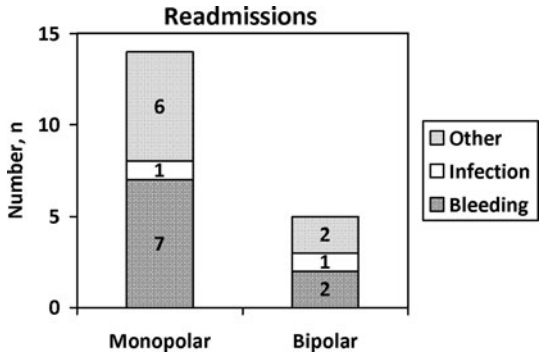
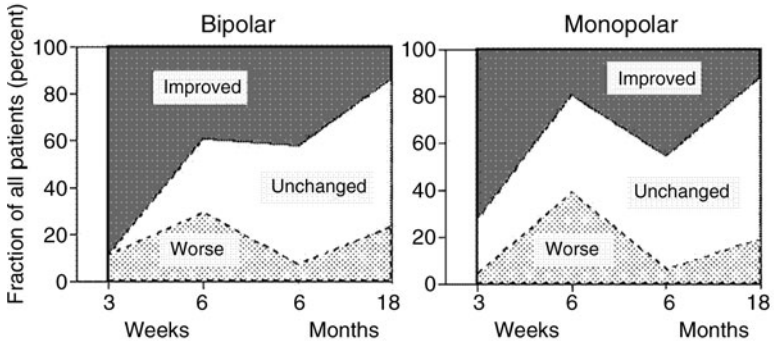


FIG. 3. The incidence of readmissions and their causes after transurethral resection of the prostate (TURP) using two different surgical techniques. "Others" comprised catheter problems, urge, and urinary retention.



Another interesting observation is shown in the above figure. More patients operated with the bipolar technique reported early improvement in IPSS and QoL scores than those having monopolar surgery, and thus recovered faster. Bipolar TURP was followed by fewer readmissions, especially when caused by late hematuria.

In 2009 Mamoulakis, Ubbink and de la Rosette published in European Urology a systematic review and Meta analysis of randomized controlled trials on bipolar versus monopolar transurethral resection of the prostate. In this paper no difference were evident regarding operation time, rates of adverse events such as transfusion, retention, stricutre. Authors recognize that the main limitation of thee meta-analysis were low trial quality and relatively limited follow up. They're conclusion was that the data on TURIS are not yet mature enough to permit safe conclusioins, however bipolar TURP is preferable due to it's more favorable profile, defined by the clinically relevant differences regarding the incidence of TURP syndrome and clot retention.

Conlcusion:
Bipolar resection with saline a promising treatment modality in the management of large prostate glands, has all the features of gold-standard monopolar TURP, along with added safety and efficacy. It is probably ready to be included in the urologist's armamentarium. As will lessen stress on the patient and hospital as well as the surgeon.

Recommended reading:

1. Complications and Clinical Outcome 18 Months After Bipolar and Monopolar Transurethral Resection of the Prostate. Fagerström T, Nyman CR, Hahn RG. J Endourol. 2011 May 13.
2. Urethral strictures and bipolar transurethral resection in saline of the prostate: fact or fiction? Michielsen DP, Coomans D, . J Endourol. 2010 Aug;24(8):1333-7.
3. Bipolar transurethral resection of the prostate causes less bleeding than the monopolar technique: a single-centre randomized trial of 202 patients. Fagerström T, Nyman CR, Hahn RG. BJU Int. 2010 Jun;105(11):1560-4.
4. Bipolar transurethral resection in saline system versus traditional monopolar resection system in treating large-volume benign prostatic hyperplasia. Chen Q, Zhang L, Liu YJ, Lu JD, Wang GM. Urol Int. 2009;83(1):55-9.
5. Bipolar versus monopolar transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. Mamoulakis C, Ubbink DT, de la Rosette JJ. Eur Urol. 2009 Nov;56(5):798-809.
6. Bipolar transurethral resection in saline (TURis): outcome and complication rates after the first 1000 cases. Puppo P, Bertolotto F, Introini C, Germinale F, Timossi L, Naselli A. J Endourol. 2009 Jul;23(7):1145-9.
7. A prospective randomized study comparing monopolar and bipolar transurethral resection of prostate using transurethral resection in saline (TURIS) system. Ho HS, Yip SK, Lim KB, Fook S, Foo KT, Cheng CW. Eur

Urol. 2007 Aug;52(2):517-22.

8. Bipolar transurethral resection of prostate in saline: preliminary report on clinical efficacy and safety at 1 year. Ho H, Yip SK, Cheng CW, Foo KT. J Endourol. 2006 Apr;20(4):244-6;

Is the LASER the new gold standard of prostate surgery?

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Introduction

Transurethral resection of the prostate (TURP) is regarded as the gold standard of treatment of benign prostatic obstruction (BPO). TURP is the oldest endoscopic surgical treatment modality that has been modified numerous times since the early descriptions approximately 80 years ago in order to make the procedure faster and safer. However, TURP is considered to be a difficult procedure with a considerable learning curve and associated with potentially serious complications. The latest observational study (2008) including more than 10,000 patients treated by TURP during a two-year period reported about prevalences of TUR-syndrome in 1.4%, blood transfusions in 2.9%, and surgical revisions due to bleeding in 5.6% of patients. As a consequence, alternative techniques are desirable to combine efficacy of TURP with a lower level and amount of morbidity. These techniques, summarized as minimal-invasive procedures, aim to eradicate BPO and, secondarily, LUTS without causing bothersome, dangerous, and legally relevant side-effects, such as intraoperative bleeding, blood transfusions, TUR-syndrome, bladder neck or urethral stenoses, urinary incontinence, retrograde ejaculation, or erectile dysfunction.

Minimally invasive procedures aim to treat BPO and LUTS by reducing prostate volume either by vaporization, resection, or enucleation leading to immediate tissue ablation, or application of heat causing thermal damage of prostatic tissue and leading to necrosis and delayed tissue ablation. Numerous minimally invasive procedures have been described in the literature including various laser treatments. Lately, laser treatments have regained attention because of new laser devices using higher energies or new laser probes. These laser operations are:

- Greenlight-Laser-Vaporization
- Holmium laser enucleation
- Thulium laser techniques

Figure 1 shows currently available laser devices, wave lengths, absorption coefficients, and depths of penetration in media:

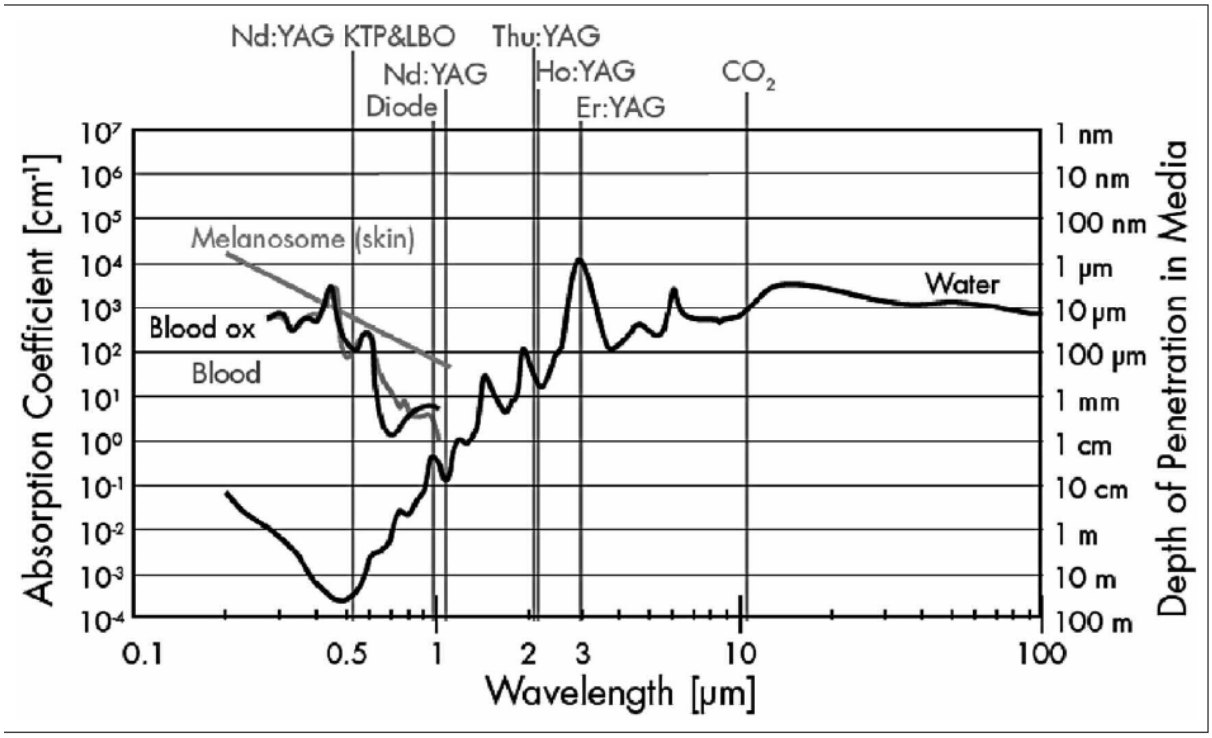

Figure 1.—Various lasers, their wave lengths, and depth of penetration in media. Blood ox: oxygenized hemoglobin; Blood: hemoglobin; Nd: neodym; YAG: yttrium-alluminium-garnet; KTP: kalium-titanyl-phosphat; LBO: lithium-borat; Thu: thulium; Er: erbium; Diode: diode laser.

From: Herrmann TRW, Georgiou A, Bach T, Gross A, Oelke M (2009) Laser treatments of the prostate vs. TURP/open prostatectomy: systematic review of urodynamic data. Minerva Urol Nefrol 61: 309-24

Potential advantages of laser procedures are reduced morbidity and shorter postoperative recovery time resulting in reduced hospitalization time. Furthermore, laser operations of the prostate can also be applied to sick patients who would otherwise be unsuitable candidates for surgical BPO treatments. However, laser treatments in BPH patients would only be useful if BPO treatment is as efficient as TURP or open prostatectomy in order to avoid persistence of BPO and long-term damage of the lower or upper urinary tract.

1. Greenlight-Laser Vaporization

Mode of action and surgical technique: Potassium-titanyl-phosphate (KTP) is a 532 nm wavelength laser that was created by doubling the frequency of pulsed Nd:YAG laser energy with a KTP crystal for 80 Watts lasers; for the 120 Watt laser device, lithium-borat (LBO) instead of KTP is used. The latest modification uses energies up to 180 Watts. The 532 nm

wavelength beam of the KTP laser is located in the visible green region of the electromagnetic spectrum and, therefore, the system was also named “Greenlight laser”. KTP or LBO laser beams are minimally absorbed by water (such as irrigation fluid or urine) but highly absorbed by hemoglobin. This leads to fast removal of prostatic tissue by rapid photothermal vaporization (PVP). The depth of penetration of the KTP laser is approximately 0.8 mm in tissues containing hemoglobin. However, in tissues without hemoglobin the depth of penetration becomes much deeper and is even higher than Nd:YAG (figure 1). The resulting coagulation zone is limited in depth (1 - 2 mm) resulting in a focused and efficient vaporization.

Clinical data: Several trials using the 80 and 120 Watt laser devices demonstrated the ability to improve symptoms, urinary flow and postvoid residuals in patients with BPH-LUTS or urinary retention. However, only 4 RCTs have been published in which the results of KTP laser treatment (80 Watt) were compared with TURP after a maximum follow-up time of 12 months (level 1b evidence, table 1). No RCT using the 120 or 180 Watt device has been published yet. Three trials showed comparable results with a significant mean Q_{max} increase ranging from 8.5 ml/s preoperatively to 20.6 ml/s postoperatively in the KTP group (increase of 167%) compared to the TURP arm in which mean Q_{max} changed from 8.7 ml/s to 17.9 ml/s (increase of 149%) [Bachmann et al. 2005 and Bouchier-Hayes et al. 2006 + 2008]. In contrast, 1 RCT showed highly significant results in favor of TURP; IPSS, Q_{max} or postvoid residuals were significantly lower in the 80 Watt Greenlight laser group [Horasanli et al. 2008].

In one large cohort study with 285 patients, improvement of voiding parameters at one year after the operation remained stable after two years. However, the New York Presbyterian–Cornell KTP laser vaporization report dealing with the first 265 patients describes a gradual decrease in Q_{max}, which initially increased from 8.5 ml/s preoperatively to 19.6 ml/s at six months but decreased to 15.7 ml/s after two years (overall improvement of 85%). The same happened with postvoid residual urine two years after the operation which was reduced to 55% compared to baseline (105.5 vs. 192 ml).

2. Holmium Enucleation of the Prostate (HoLEP)

Mode of action and surgical technique: The holmium/yttrium-aluminium-garnet (Ho:YAG) laser is a pulsed solid-state laser with a wavelength of 2140 nm that is strongly absorbed by water (figure 1). In prostatic tissue, the depth of penetration of holmium is approximately 0.4 mm resulting in an energy density high enough to vaporize prostatic tissue, which creates tissue ablation without deep coagulation. All holmium laser techniques (vaporization-resection-enucleation) are based on the principle of vaporization. The energy is delivered to the prostate through an end-firing 0.55 mm laser fiber. During the HoLEP procedure, the surgical capsule of the prostate is exposed by incision and vaporization of the periurethral prostatic tissue. After identifying the plane at the surgical capsule, the prostatic adenoma is separated from the capsule by disruption similar to suprapubic prostatectomy. Mimicking open prostatectomy, the prostatic lobes are completely enucleated and pushed into the bladder before being fragmented and aspirated afterwards by a morcellator.

Clinical data: Six RCTs have dealt with HoLEP in comparison to TURP and one study in comparison to open prostatectomy (table 1). In total, 794 patients between 64 and 71 years of age were randomized. Mean IPSS value varied between 20 and 26 and mean prostate volumes ranged between 50 and 114 g. There was a tendency of Q_{max} improvement in favor of HoLEP but the differences in the individual studies were not statically significant. This tendency was obvious during the entire follow-up period of up to 30 months. Beside those RCTs, other studies without randomization found that HoLEP has a low morbidity and is also effective in patients with urinary retention. HoLEP was equieffective to TURP/prostatectomy in terms of symptom improvement (both filling and voiding) and quality of life. Only hospitalization time (one day shorter for HoLEP vs. TURP and 3-7 days vs. prostatectomy) and catheterization time (one day shorter for the HoLEP vs. TURP) were the only significant differences.

One RCT dealt with changes of urodynamic parameters of HoLEP vs. TURP using computer urodynamic investigation. This is the only urodynamic study of all laser treatments of the prostate with pressure-flow data. Pressure-flow studies before and 6 months after the operation indicated that $Pdet_{qmax}$ after HoLEP (76.2 vs. 20.8 cm H_2O) decreased significantly more compared to TURP (70 vs. 40.7 cm H_2O; $p<0.001$). Furthermore, Schaefer BOO grade before and 6 months after the operation decreased significantly more after HoLEP (3.5 vs. 0.2) compared to TURP (3.7 to 1.2; $p<0.001$).

Gilling et al. (2008) reported long-term data with a mean follow-up of 6.1 years, indicating that HoLEP results were durable and most patients remained satisfied with their procedure. Two meta-analyses, which analyzed available RCTs comparing HoLEP and TURP [Tan 2007, Lourenco 2008], reported about a significantly longer operation time with HoLEP but lower blood transfusion rate (RR 0.27, p=0.04), shorter catheterization time and shorter inpatient time. The experience of the surgeon was the most relevant factor of intra- or postoperative complications; prostate size has no significant impact on complications if experience surgeons perform the operation [Shah et al. 2008]. Symptom improvements were comparable, but Q_{max} at 12 months was significantly better with HoLEP. In prostates >100 ml, HoLEP proved to be as effective as open prostatectomy for improving micturition, with equally low re-operation rates at 5-years' follow-up [Kuntz 2008].

3. Thulium laser techniques of the prostate

Mode of action and surgical techniques: A new device, a 2 micron continuous wave (cw) thulium laser (Tm:YAG) has recently been introduced into clinical practice. Together with the holmium laser, thulium laser is the only continuous wave laser that offers complete absorption of laser energy in water (figure 1). Therefore, the thulium laser only penetrates superficially in any media and is independent of chromophore concentration of the tissue. Based on standardized *ex vivo* investigations, the 2 micron cw thulium laser offers higher tissue ablation capacity and similar haemostatic properties compared to the KTP laser. In comparison to TURP, tissue ablation rate was slightly less with Thulium vaporization but bleeding rates were significantly reduced. 4 distinct thulium laser techniques for prostate tissue removal have been described:

1. Thulium vaporization of the prostate
2. Thulium vaporesection of the prostate
3. Thulium vapoenucleation
4. Thulium laser enucleation of the prostate. The surgical technique of ThuLEP is similar to HoLEP. A modified technique described by Herrmann et al. (2010) uses the laser only for coagulation of vessels but uses the cystoscope for disruption of the prostatic adenoma similar to open prostatectomy.

Clinical data: Several open label trials have documented the efficacy of thulium lasers for prostate tissue ablation in patients with or without anticoagulants. One trial compared thulium laser resection with TURP and documented equivalent results [Xia et al. 2008]. Another trial compared the results of thulium vapoenucleation with holmium enucleation and, again, no differences were seen [Shao et al. 2009]. No reports have been published on TUR-syndrome with the thulium lasers. Bleeding occurred in 0-3.4% and blood transfusions in 0-4% of patients who were treated with the thulium laser. In contrast, the RCT with thulium laser resection and TURP reported about a blood transfusion rate in thulium laser patients in 4% compared to 9.5% in those with TURP. The TUR-syndrome occurred in 2.1% of patients with TURP, whereas there was no TUR-syndrome in patients with thulium resection.

Conclusions

TURP and TURP modifications are currently still the gold standard for the treatment of BPE and BPO, mainly because of the universal availability of this technique and long-term results. However, the latest laser techniques (e.g. Greenlight laser vaporization, holmium enucleation, and thulium techniques) have shown to have similar efficacy compared to TURP with significantly lower morbidity as well as catheterization and hospitalization time. In patients with bleeding disorders or anticoagulants, laser techniques are already now the first choice of treatment. It is likely that laser techniques will reduce the number of TURPs in the future and will become the first choice of treatment once more hospitals will have lasers and long-term data will be available.

Table 1: Efficacy of laser treatments with or without comparison with TURP, adapted from the EAU Guidelines on Male LUTS (Oelke et al. 2011)

Trials	Duration (months)	Patients (n)	Surgery	Change symptoms (IPSS)		Change Q_{max} (mL/s)		Change PVR (mL)		Change prostate volume (mL)		Level of Evidence
				absolute	[%]	absolute	[%]	absolute	[%]	absolute	[%]	
Le Duc et al. (1999)	6	42	HoLRP	-18.4	-84	+15.1	+170					1b
		43	TURP	-17.9	-78	+13.2	+145					
Westenberg et al. (2004)	48	43	HoLRP	-14.7 [a]	-67 [a]	+13.4 [a]	+151 [a]	- 61.1 [a] †	-70 [a] †	- 15 [a] †	-34 [a] †	1b
		30	TURP	-16.4 [a]	-71 [a]	+9.4 [a]	+103 [a]	- 50.4 [a] †	-60 [a] †	- 17 [a]	-39 [a] †	
Fraundorfer et al. (1998)	1	14	HoLEP	-14.0	-66	+18.2	+260					3
Gilling et al. (2008)	72	38	HoLEP	-17.2	-67	+10.9	+135	-71.7 †	-68 †	- 31.3 †	-54 †	3
Tan et al. (2007)	12	232	HoLRP	-17.5 to -21.7	-81 to -83	+13.4 to +23.0	+160 to +470	-232.7	-98			1a
		228	TURP	-17.7 to -18.0	-76 to -82	+10.1 to +21.8	+122 to +370	- 189.4	-88			
Lourenco et al. (2008)	12	277	HoLRP	-17.7 to -21.7	-82 to -92	+13.4 to +23.0 [b]	+160 to +470 [b]					1a
		270	TURP	-17.5 to -18.7	-81 to -82	+10.1 to +21.8	+122 to +370 [a]					
Kuntz et al. (2008)	60	42	HoLEP	-19.1	-86	+ 20.5	+540	-269.4	-96			1b
		32	Open prostatectomy	-18.0	-86	+ 20.8	+578	-286.7	-98			
Heinrich et al. (2007)	6	140	KTP (80 W)	-10.9 [a]	-55	+ 5.6	+ 43	-65 [a]	-74 [a]			3
Ruszat et al. (2008)	12	302	KTP (80 W)	-11.9 [a]	-65 [a]	+ 10.2 [a]	+121 [a]	-173 [a]	-83 [a]			3
	48	88	KTP (80 W)	-10.9 [a]	-60 [a]	+ 10.2 [a]	+121 [a]	-179 [a]	-86 [a]			
Hamann et al. (2008)	12	157	KTP (80 W)	-13.4 [a]	-65 [a]	+ 10.7 [a]	+135 [a]	-103.4 [a]	-78 [a]			3
Reich et al. (2005)	12	51	KTP (80 W) OA	-13.7 [a]	-68 [a]	+ 14.9 [a]	+222 [a]	-122 [a]	-83 [a]			3
Ruszat et al. (2007)	24	116	KTP (80 W) OA	-13.0	-70	+ 11.3	+140	-103	-80			3
		92	KTP (80 W) CG	-12.7	-71	+12.0	+168	-160	-78			

Ruszat et al. (2006)	24	16	KTP RUR	-11.1	-72			-280	-88			3
		19	KTP NUR	-12.1	-65	+16.2	+228	-131	-85			
Rajbabu et al. (2007)	24	38	KTP (80 W)	-17.2 [a]	-75 [a]	+11.3 [a]	+141 [a]	-85 [a]	-63 [a]			3
Bouchier-Hayes et al. (2006)	12	38	KTP (80 W)	-14.0 [a]	-50 [a]	+12.0 [a]	+167 [a]	-120 [a]	-82 [a]			1b
		38	TURP	-12.9 [a]	-50 [a]	+8.6 [a]	+149 [a]	-82 [a]	-69 [a]			
Bachmann et al. (2005)	6	55	KTP (80 W)	-12.9 [a]	-71 [a]	+11.2 [a]	+162 [a]	-133 [a]	-91 [a]			3
		31	TURP	-12.5 [a]	-72 [a]	+12.2 [a]	+177 [a]	-106 [a]	-88 [a]	-21	-45	
Bouchier-Hayes et al. (2008)	12	46	KTP (80 W)	-16.4 [a]	-65 [a]	+9.8 [a]	+111 [a]	-107 [a]	-83 [a]	-30	-63	1b
		39	TURP	-14.5 [a]	-57 [a]	+10.5 [a]	+118 [a]	-93 [a]	-84 [a]	-27	-44	
Horasanli et al. (2008)	6	39	KTP (80 W)	-5.8	-31	+4.7	+156	-104	-57			1b
		37	TURP	-13.8 [b]	-68 [b]	+11.5 [b]	+225 [b]	-154 [b]	-87 [b]			

† 6-month data; CG = control group; RUR = refractory urinary retention; OA = oral anticoagulation; NUR = no urinary retention
[a] significant compared to baseline (indexed whenever evaluated)
[b] significant difference in favour of indicated treatment

The use of Botulinum Neurotoxin A in the Treatmant of Prostatic Hyperplasia associated Lower Urinary Tract Symptoms

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Introduction

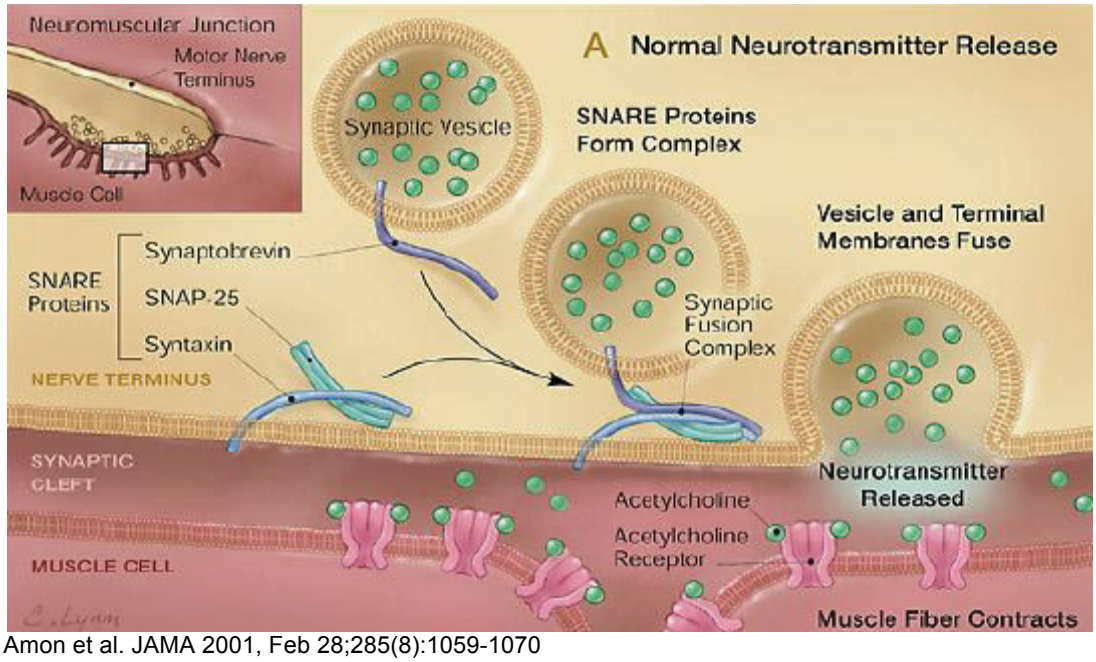
The use of botulinum neurotoxins (BoNTs) in the treatment of lower urinary tract symptoms (LUTS) associated with neurogenic voiding dysfunction started over 20 years. Since 2003 there is an increasing number of evidence for potential indications for the use of BoTNs in the treatment of intractable LUTS due to prostatic hyperplasia.

Mechanism of action

Botulinum toxin is produced by Clostridium botulinum and is regarded as the most potent biological toxin known to men. Seven immunologically distinct neurotoxins are designated A to G and to date only BoTN-A in BoTN-B are in clinical use. There are two commercially available BonT-A. Botox® and Dysport® have similarities between the products but they have different doses, efficacy and safety profiles and it needs to be borne in mind that different preparations are not interchangeable. LD50 units are not equivalent since manufacturers use different methods of purification, formulation, and unit determination. Clinically, Dysport® units are not equivalent to Botox® units. Botox® vial contains 100 U/5 ng toxin and Dysport® contains 500 U/12,5 ng toxin.

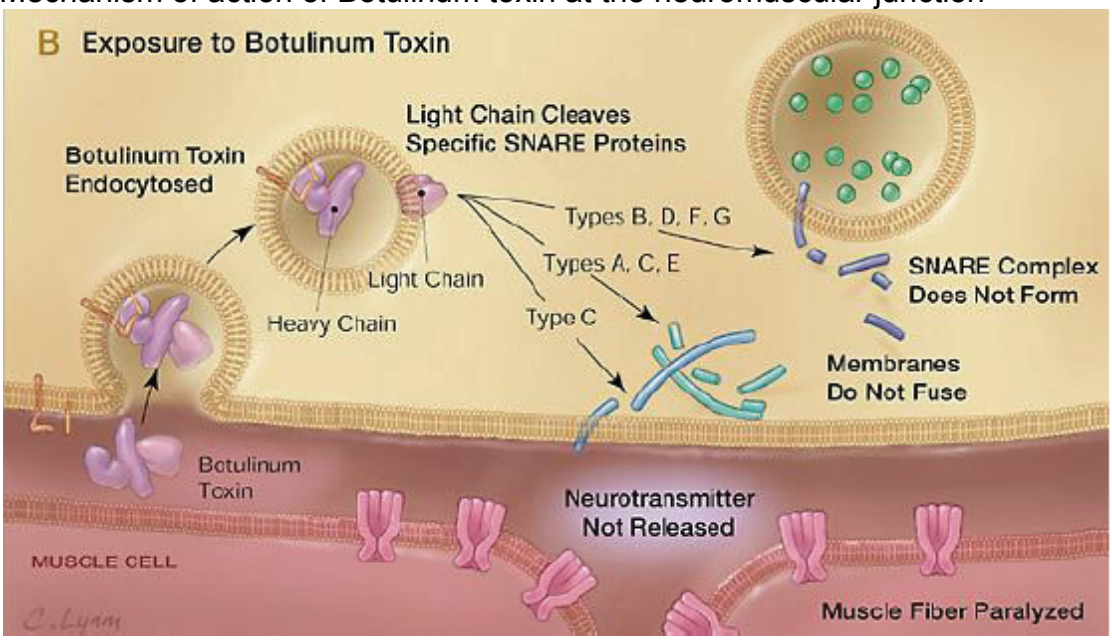
BoTN-A exerts paralyzing effects by inhibiting ACh release from the motor nerve into the neuromuscular junction with inhibitory effect on autonomic and somatic neurotransmission. After intramuscular injection of BoTN-A a temporary chemodenervation and relaxation of skeletal and smooth muscle can be achieved.

Normal neurotransmitter release



Amon et al. JAMA 2001, Feb 28;285(8):1059-1070

Mechanism of action of Botulinum toxin at the neuromuscular junction



Amon et al. JAMA 2001, Feb 28;285(8):1059-1070

Animal studies have also demonstrated diffuse atrophy and apoptosis of prostate gland after local BoTN-A application. Thus causing reduction of prostate volume and downregulation of the expression of α-adrenoreceptors within prostate. It also inhibits norepinephrine release and therefore modulating sympathetic nerve hyperactivity, especially in conditions such as internal sphincter dyssynergia and possibly benign prostatic obstruction. During recent years there has been increasing evidence that BoTN-A also inhibits afferent neurotransmission and have analgesic properties. Inhibitory effects of BoTN on sensory function may therefore relieve irritative symptoms. With all it's actions BoTN-A can influence both static and dynamic component of prostatic hyperplasia related LUTS.

Benign prostatic enlargement (BPE) or prostatic hyperplasia (histological diagnosis) with bladder outlet obstruction and bladder dysfunction results in LUTS, including storage and voiding symptoms and decreased QoL in these patients.

Human prostate is innervated by sympathetic and parasymphatetic efferents and also sensory afferents. Prostatic epithelium has cholinergic innervation, while the stroma predominantly noradrenergic innervation. Cholinergic innervation has an important role in the regulation of prostate epithelium function with effects on growth and secretion. Noradrenergic innervention is responsible for smooth muscle contraction and possible outflow obstruction related to BPE.

Injection technique

Successful BoNT injection into the prostate can be performed using transperineal, transurethral or transrectal routes. In most studies transperineal injection route with transrectal ultrasound guidance has been described. Usually a 20-22 G needle is used to perform one to three injections per lobe either without or under local anesthesia. A total of 100-300U (most frequently 200U) of BoTN-A in different dilutions (4-20 ml of saline) are used, although there is no rationale for this since dose finding studies are still missing.

Results

The clinical studies demonstrated that BoNT-A intraprostaic injection therapy brings significant improvements in terms of maximum flow rate, IPSS, QoL, prostate volume, post void residual and also PSA serum levels.

Maria et al. in 2003 investigated 30 patients, 50-80 year old, with moderate to sever LUTS do to BPE. Patients were received 4 ml of solution injected in prostate gland (2 ml into each lobe) either with 200U of Botox or plain saline. BoTN-A injection group demonstrated a significant improvement in IPSS, Qmax., prostate volume, serum PSA level and PVR at 1 and 2 months post-treatment. Follow-up after up to 12 months demonstrated efficacy in all parameters. Interestingly no local or systemic complications were observed in any patient. Some studies reported very few generally mild and self limiting adverse events, mainly as gross hematuria, urinary retention and acute prostatitis. On the base of results of this first human study similar results in similar study populations were reported by other authors. Brisida et al. in 2009 reported that 71 % of patients had significant improvement and that also retreatments with 200 U are possible, if patients reported no improvements. The results remained stable up to 30 months. First results using Dysport were reported by Nikoobakht et al. in 2010. All parameters significantly improved from 1 up to 12 months in the study population with results that are comparable to the one observed by Maria et al. in 2003.

Other studies investigated the use and effect of BoTN-A for LUTS due to BPE in prostate size related BoTN-A dosing, in patients who failed treatment with 5-ARI or/and α-blocker, in patients with small and large prostates and in poor surgical candidates for prostatic hyperplasia surgery. All studies demonstrated significant improvement in Qmax., IPSS, prostate volume and PVR with follo-up from 6 to 18 months. It is of great value that in patients who are not surgical candidates because of their poor general condition indwelling catheters could be omitted in most of the patients after treatment.

Treatment results – table 1

	Patients improved (patients treated)	Reduction in IPSS	Increase in Q_{max}	Reduction in PVR
Chuang *et al.* [26]				
1st month	8 (8)	From 19 ± 1.8 to 5 ± 2 (73.1%, $P < 0.05$)	From 7.5 ± 1.8 to 12.9 ± 0.5 ml/s (72%, $P < 0.05$)	From 177.6 ± 71.7 to 24.5 ± 4.5 ml (86.2%, $P = 0.064$)
Maria *et al.* [36]				
1st month	11 (15)	From 23.2 ± 4.1 to 10.6 ± 1.7 (54%, $P = 0.00001$)	From 8.1 to 14.9 ml/s ($P < 0.00001$)	From 126.3 ± 38.3 to 49.6 ± 13.4 ml (60%, $P = 0.00001$)
2nd month	13 (15)	From 23.2 ± 4.1 to 8 ± 1.6 (65%, $P = 0.00001$)	From 8.1 to 15.4 ml/s ($P < 0.00001$)	From 126.3 ± 38.3 to 21 ± 16.2 ml (83%, $P = 0.00001$)
Placebo group	2 (15) 1st month; 3 (15) 2nd month; 4 (BoNT-A)	NS ($P = 0.9$)	NS ($P = 0.9$)	NS ($P = 0.9$)
Chuang *et al.* [37]				
1st month	16 (16)	From 18.8 ± 1.6 to 8.9 ± 1.9 (52.6%, $P = 0.0001$)	From 7.3 ± 0.7 to 11.8 ± 0.8 ml/s (39.8%, $P < 0.001$)	From 67.7 ± 30 to 25.1 ± 4 ml (63%, NS)
Chuang *et al.* [38][a]				
100 U BoNT-A	31 (41)	From 18.7 to 9.8 (48%, $P < 0.001$)	From 7.9 to 12 ml/s (62%, $P < 0.001$)	From 64.2 to 35.7 ml (44%, $P = 0.3$)
200 U BoNT-A		From 19.3 to 9.5 51% ($P < 0.001$)	From 7 to 10.3 ml/s (47%, $P < 0.001$)	From 161.7 to 45.2 ml (72%, $P = 0.02$)
Kuo [39]				
6 months	10 (10)	–	From 7.6 ± 3.9 to 11.6 ± 3.5 ml/s ($P = 0.05$)	From 243.5 ± 133.9 to 36.8 ± 34.1 ml ($P = 0.005$)
Park *et al.* [40]				
3 months	39 (52)	From 24.3 ± 7.8 to 16.9 ± 6.4 (30.3%, $P < 0.05$)	From 9.6 ± 6.5 to 11.1 ± 5.9 ml/s (15.5%, $P < 0.05$)	From 122.7 ± 141.2 to 84.7 ± 40.9 ml (34.3%, $P < 0.05$)
Larson *et al.* [41]				
3 months	10 (10)	From 21.2 to 11.4	From 10.4 to 13.3 ml/s	–
Guercini *et al.* [42]				
6 months	16 (16)	From 24 to 9 ($P = 0.002$)	From 8.2 to 18.1 ml/s ($P < 0.05$)	From 295 to 85 ml ($P = 0.05$)
Silva *et al.* [27•]				
3 months	17 (21)	–	From retention to 10.3 ± 1.4 ml/s	From retention to 92 ± 24 ml
Kuo [43]	–	47%	By 2.9 ml/s	–
Silva *et al.* [28•]				
6 months	17 (21)	10.6	From retention to 12 ± 1.8 ml/s	From retention to 55 ± 17 ml
Kuo and Liu [29]				
12 months	27 (30 BoNT-A) 28 (30 medical therapy)	From 18.2 ± 6.8 to 8.9 ± 5.2 ($P < 0.05$)	From 8.4 ± 5.8 to 10.7 ± 5.3 ml/s ($P < 0.05$)	From 92.7 ± 111.6 to 113.7 ± 100.1 ml (NS)
Brisinda *et al.* [30•]	41 (77) at first month; 77 (77) after repeated injections	From 24.1 ± 4.6 to 8.7 ± 1.6 (63.9%, $P = 0.00001$)	From 8.6 ± 2.9 to 16.5 ± 1.8 ml/s ($P = 0.00001$)	From 92.1 ± 42 to 40.6 ± 16.2 ml ($P = 0.005$)
Crawford *et al.* [31••]	96 (125)	From 19.2 to 11.8	From 9.9 to 12.3 ml/s	–
Yokohama *et al.* [33•]				
3 months	7 (10)	From 23.8 ± 2.2 to 14.9 ± 2.6 ($P = 0.0074$)	–	–
De Kort *et al.* [34]	10 (11)	From 24 ± 5.7 to 16.6 ± 6.9 ($P < 0.05$)	From 7.1 ± 3.5 to 10.1 ± 4.9 ml/s ($P < 0.05$)	From 242 ± 180 to 105 ± 119 ml ($P < 0.05$)

BoNT-A, botulinum neurotoxin A; IPSS, International Prostate Symptoms Score; NS, not significant; PVR, postvoid residual volume; Q_{max}, maximum urinary flow rate.

[a] All values reported in this study are during month 1.

Oeconomou A, Madersbacher H. Botulinum neurotoxin A for benign prostatic hyperplasia. Curr Opin Urol 2010; 20:28-36.

Treatment results – table 2

	Reduction of PV	QoL	PSA	Safety	Biopsy
Chuang *et al.* [26]					
1st month	From 61.6 ± 8.7 to 50 ± 5.9 ml (18.8%, $P < 0.05$)	From 3.9 ± 0.3 to 2.1 ± 0.3 (61.5%, $P < 0.05$)	–	No side-effects	–
Maria *et al.* [36]					
1st month	From 52.6 ± 10.6 to 23.8 ± 6.2 ml (54%, $P = 0.00001$)	–	From 3.7 ± 0.9 to 2.1 ± 0.7 ng/ml (42%, $P = 0.00006$)	No side-effects	–
2nd month	From 52.6 ± 10.6 to 16.8 ± 7.8 ml (68%, $P = 0.00001$)	–	From 3.7 ± 0.9 to 1.8 ± 0.7 ng/ml (51%, $P = 0.00001$)		
Placebo	NS ($P = 0.6$)	–	NS ($P = 0.8$)		
Chuang *et al.* [37]					
1st month	From 19.6 ± 1.2 to 17 ± 1.1 ml (13.3%, $P < 0.0014$)	From 3.8 ± 0.3 to 2.1 ± 0.3 (44.7%, $P < 0.0001$)	From 0.8 ± 0.23 to 0.72 ± 0.14 ng/ml (NS)	Dysuria and minor hematuria ($n = 3$)	Increased apoptosis
Chuang *et al.* [38][a]					
100 U BoNT-A	From 21.1 to 18 ml (15%, $P < 0.001$)	From 3.9 to 2.1 (46%, $P < 0.001$)	–	No side-effects	–
200 U BoNT-A	From 54.3 to 46.3 ml (15%, $P < 0.001$)	From 4.1 to 2 (51%, $P < 0.001$)			
Kuo [39]					
6 months	From 65.5 ± 19 to 49.6 ± 17.6 ml ($P = 0.009$)	From 4.5 ± 2.7 to 2.1 ± 1.9 ($P = 0.0000$)	–	No side-effects	–
Park *et al.* [40]					
3 months	From 47.2 ± 23.9 to 42 ± 19 ml (13.1%, $P < 0.05$)	–	From 2.6 ± 3.2 to 2.4 ± 3.1 ng/ml (NS)	No side-effects	–
Larson *et al.* [41]					
3 months	–	From 4.1 to 1.7	–	Acute epidydimitis ($n = 1$); urinary retention ($n = 1$)	–
Guercini *et al.* [42]					
6 months	From 106 to 53 ml ($P < 0.0001$)	–	From 9.5 to 2.5 ng/ml ($P < 0.05$)	No side effects	–
Silva *et al.* [27•]					
3 months	From 70 ± 10 to 47 ± 7 ml ($P < 0.001$)	–	From 6 ± 1.1 to 5 ± 0.9 ng/ml ($P = 0.04$)	No side-effects	–
Kuo [43]	23.5% ($P < 0.05$)	–	35.4% ($P < 0.05$)	–	–
Silva *et al.* [28•]	From 82.2 ± 16.2 to 49 ± 9.5 ml ($P = 0.002$)	–	From 6.7 ± 2.1 to 5.1 ± 1.4 ng/ml 51.6% ($P = 0.16$)	–	–
Kuo and Liu [29] (12 months)	From 89.7 ± 33.5 to 76.8 ± 32.9 ml ($P < 0.05$)	From 4.11 ± 1.05 to 2.04 ± 0.82 ($P < 0.05$)	From 5.94 ± 7.05 to 3.87 ± 2.22 ng/ml (NS)	Urinary retention ($n = 3$); gross hematuria ($n = 7$); acute prostatitis ($n = 1$)	–
Brisinda *et al.* [30•]	From 54.1 ± 10.8 to 30.9 ± 7.8 ml (42.8%, $P = 0.0001$)		From 6.2 ± 1.7 to 3 ± 0.6 ng/ml (51.6%, $P = 0.00001$)	No side effects	–
Crawford *et al.* [31••]	–	–	–	17–18% severity grade 2–3	–
Yokohama *et al.* [33•] (1 month)	From 47.8 ± 6.7 to 40.2 ± 5.8 ml ($P = 0.0169$)	–	–	–	–
De Kort *et al.* [34]	From 41 ± 7 to 40.4 ± 11.6 ml (NS)	From 4.6 ± 1.1 to 2.4 ± 0.5 ($P < 0.05$)	From 2.3 ± 1.5 to 2.3 ± 1.4 ng/ml (NS)	Prostatitis ($n = 2$)	No change in proliferation

NS, not significant; PSA, prostate-specific antigen; PV, prostate volume; QoL, quality of life.
[a] All values reported in this study are during month 1.
Oeconomou A, Madersbacher H. Botulinum neurotoxin A for benign prostatic hyperplasia. Curr Opin Urol 2010; 20:28-36.

Conclusion

There is an increasing number of evidence derived from animal and human studies that gives us a rationale for potential use of BoTNs in the treatment of intractable LUTS due to prostatic hyperplasia. Clinical studies show good results with significant symptom relief and improvement of QoL in majority of treated patients. Intraprostatic injection technique is easy to learn and has only rare and mild adverse events. There is still very little known on exact onset and duration of effect, on the dose-effect relation and dose-effect relation to prostate volume. What is the potential effects of BoNT-A on erectile function, on risk of retrograde ejaculation or sperm abnoramlities, the potential

role in treatment of chronic prostatitis, chronic pelvic pain syndrome and prostate cancer remains to be answered. At present this therapy is still experimental but future studies should address this questions.

Recommended reading

1. Maria G, et al. Relief by botulinum toxin of voiding dysfunction duo to benign prostatic hyperplasia: results of a randomized, placebo – controlled study. Urology 2003; 62:259-264.
2. Chuang YC, et al. Botulinum toxin type A improves benign prostatic hyperplasia symptoms in patients with small prostate. Urology 2005; 66:775-779.
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8. Kuo HC, Liu HT. Therapeutic effects of add-on botulinum toxin A on patients with large benign prostatic hyperplasia and unsatisfactory response to combined medical therapy. Scand J Urol Nephrol 2009; 43:206–211.
9. Brisinda G, et al. Relief by botulinum toxin of lower urinary tract symptoms owing to benign prostatic hyperplasia: early and longterm results. Urology 2009; 73:90–94.
10. Silva J, et al. Mechanisms of prostate atrophy after glandular botulinum neurotoxin type A injection: an experimental study in the rat. Eur Urol 2009; 56:134–141.
11. Oeconomou A, Madersbacher H. Botulinum neurotoxin A for benign prostatic hyperplasia. Curr Opin Urol 2010; 20:28-36.
12. Nikoobakht M, et al. Intraprostatic botulinum toxin type A injection for the treatment of benign prostatic hyperplasia: Initial experience with Dysport. Scand J Urol Nephrol 2010; 44:151–157.
13. Chartrier-Kastler E, et al. Botulinum neurotoxin A for male lower urinary tract symptoms. Curr Opin Urol 2011; 21:13-21.

Notes

Record your notes from the workshop here