PLACE DES FACTEURS INTRINSÈQUES DANS LE DÉTERMINISME DE L'HYPERACTIVITÉ VÉSICALE

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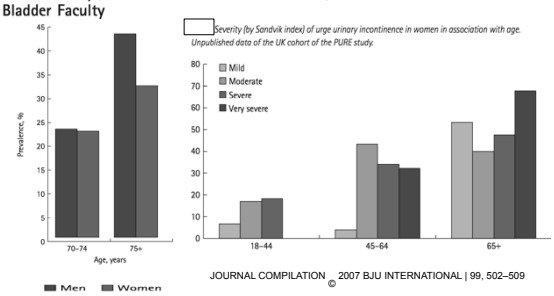
Overactive bladder syndrome in older people

Adrian S. Wagg, Linda Cardozo[1], Christopher Chapple[2], Dirk De Ridder[3], Con Kelleher[4], Michael Kirby[5], Ian Milsom[6] and Mark Vierhout[7], on behalf of the Overactive Bladder Faculty



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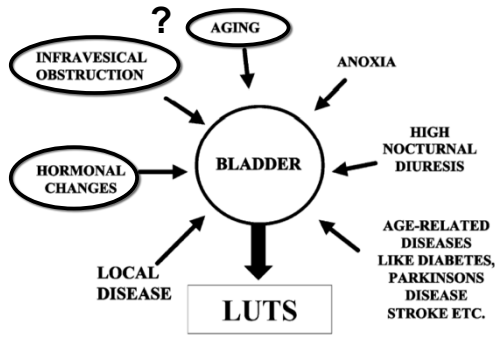
Milsom I, Stewart W, Thuroff J. The prevalence of overactive bladder. Am J Manag Care 2000; 6 (Suppl): S565–73

Perry S, Shaw C, Assassa P et al. An epidemiological study to establish the prevalence of urinary symptoms and felt need in the community: the Leicestershire MRC Incontinence Study. J Public Health Med 2000; 22: 427–34

MULTIFACTORIALITÉ



Effets propres du vieillissement ?

Vulnerable Elderly Patients and Overactive Bladder Syndrome

Stephen R. Kraus,[1] Tamara Bavendam,[2] Tiffany Brake[3] and Tomas L. Griebling[4]

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2 Pfizer Inc, New York, New York, USA
3 Complete Healthcare Communications Inc., Chadds Ford, Pennsylvania, USA
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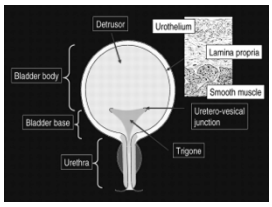
Limites méthodologiques

Modèles animaux
Etudes in vitro
Interactions âge/co-morbidités

Effets de l'âge sur la physiologie détrusorienne



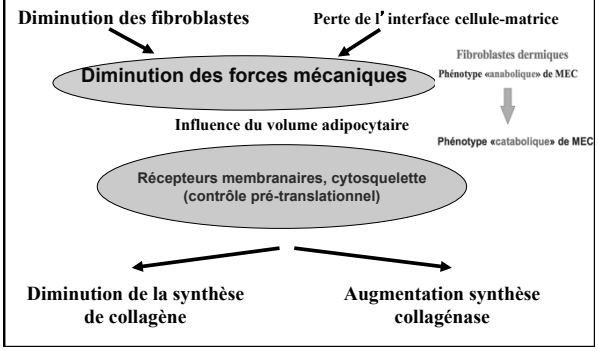
- Vieillissement du tissu musculaire :
  - ***cf sarcopénie***
- Vieillissement de la balance sympatho-vagale :
  - ***cf régulation fréquence/PA***
- Vieillissement vasculaire (artério-capillaire)
- Vieillissement de la matrice extra-cellulaire :
  - ***cf vieillissement intrinsèque du derme***

Fibroblastes dermiques

Phénotype «anabolique» de MEC

Phénotype «catabolique» de MEC

Effets régulateurs des forces mécaniques sur les activités de synthèse et de catabolisme des fibroblastes



ELSEVIER
Experimental Gerontology 37 (2002) 991–999
Experimental Gerontology
www.elsevier.com/locate/expgero

Mini-Review

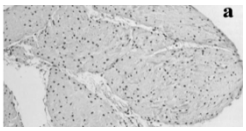
The aging bladder—a significant but underestimated role in the development of lower urinary tract symptoms

Jørgen Nordling*

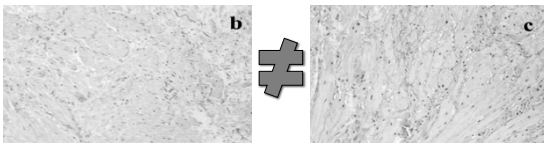
MODIFICATIONS DU DETRUSOR

- **Modèles animaux et humains**
- **Augmentation de la masse musculaire et de la matrice extra-cellulaire**
- **Non spécifique de l'obstruction chronique**
- **Relations avec la baisse de compliance et l'ischémie**

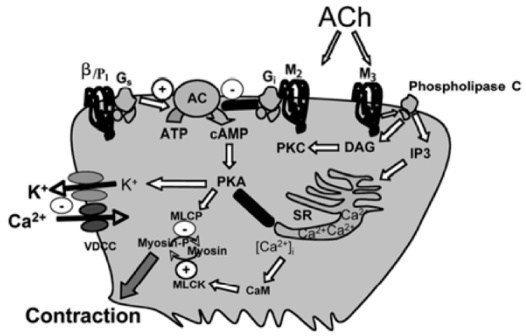
HISTOLOGIE DU DETRUSOR

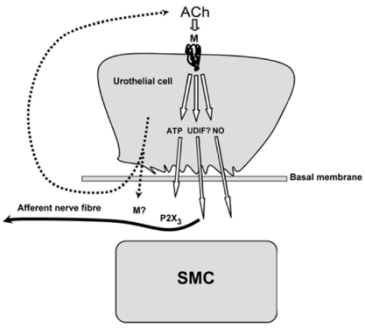


NORMAL



HBP FEMME AGEE SANS LUTS





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Benign Prostatic Hyperplasia

Age and Bladder Outlet Obstruction Are Independently Associated with Detrusor Overactivity in Patients with Benign Prostatic Hyperplasia

Matthias Oelke [a,b,*], *Joyce Baard* [a], *Hessel Wijkstra* [a], *Jean J. de la Rosette* [a], *Udo Jonas* [b], *Klaus Höfner* [b,c]

Table 2 – Median values and 25th–75th percentiles of clinical and urodynamic parameters in groups with or without detrusor overactivity

Parameter	Detrusor overactivity		p value*
	Absent (n = 554)	Present (n = 864)	
	Median (25th–75th percentile)	Median (25th–75th percentile)	
Age (yr)	61 (56–68)	64 (59–70)	<0.001
Body-mass index (kg/m²)	25.9 (23.8–28.4)	25.8 (23.9–28.1)	0.606
IPSS (questions 1–7)	15 (9–21)	17 (11–21)	0.08
IPSS irritative subscore (questions 2, 4, 7)	6 (3–9)	8 (5–11)	<0.001
IPSS obstructive subscore (questions 1, 3, 5, 6)	9 (4–13)	9 (5–12)	0.311
Prostate volume (ml)	33 (25–45)	38 (27–49)	0.014
Q_{max} (ml/s)	11.2 (7.4–16.3)	11.0 (7.4–15.2)	0.588
Voided volume (free uroflowmetry) (ml)	263 (181–376)	217 (166–307)	<0.001
Postvoid residual urine (ml)	64 (20–150)	60 (20–124)	0.574
Cystometric bladder capacity (ml)	409 (299–574)	357 (268–493)	<0.001
Schäfer class (linPURR)	1 (0.75–3)	2 (1–3)	<0.001

IPSS, International Prostate Symptom Score; Q_{max}, maximum urinary flow rate of free uroflowmetry; linPURR, linear passive urethral resistance relation.
* Mann-Whitney test.

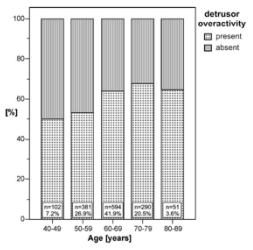

Fig. 1 – Prevalence of detrusor overactivity in relation to different age groups. The y-axis shows the percent of patients with (■) or without (■) detrusor overactivity within the age group. The number of men (%) in each age group is listed at the base of the column. Patients in the older age groups had a significantly higher chance of detrusor overactivity ($p = 0.047$, χ^2-test for trend).

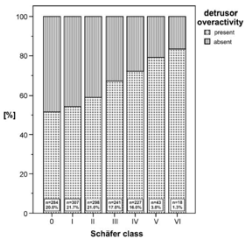

Fig. 2 – Prevalence of detrusor overactivity in relation to the bladder outlet obstruction grade (Schäfer class). The y-axis shows the percent of patients with (■) or without (■) detrusor overactivity within the Schäfer class. The number of men (%) in each Schäfer class is listed at the base of the column. The prevalence of detrusor overactivity increases continuously from 51.4% in Schäfer class 0 to 83.3% in Schäfer class VI ($p < 0.001$, χ^2-test for trend).

Table 3 – Logistic regression analysis of relationship of detrusor overactivity with age and various grades of bladder outlet obstruction compared to Schäfer class 0 (no bladder outlet obstruction)

Parameter	p value	Odds ratio (95% CI)
Age	<0.001	**1.03** (1.01, 1.04)
Bladder outlet obstruction grade		
Schäfer 0		
Schäfer I	0.282	**1.2** (0.86, 1.66)
Schäfer II	0.044	**1.4** (1.01, 1.95)
Schäfer III	<0.001	**1.9** (1.33, 2.71)
Schäfer IV	<0.001	**2.5** (1.74, 3.67)
Schäfer V	0.002	**3.4** (1.58, 7.44)
Schäfer VI	0.016	**4.7** (1.33, 16.8)

Abstract

Background: Detrusor overactivity is one known cause of lower urinary tract symptoms and has been linked to bladder storage symptoms (urgency, frequency, or urge incontinence).

Objective: To determine clinical and urodynamic parameters associated with detrusor overactivity in patients with suspected benign prostatic hyperplasia.

Design, Setting, and Participants: During 1993–2003, urodynamic investigations were performed in patients aged 40 yr or older and with lower urinary tract symptoms, benign prostatic enlargement, and/or suspicion of bladder outlet obstruction (maximum flow rate < 15 ml/s or postvoid residual urine > 50 ml).

Measurements: Detrusor overactivity was defined according to the new International Continence Society classification (2002) as involuntary detrusor contractions during cystometry, which may be spontaneous or provoked, regardless of amplitude. The Schäfer algorithm was used to determine bladder outlet obstruction.

Results: In total, 1418 men were investigated (median age: 63 yr) of whom 864 men (60.9%) had detrusor overactivity. In univariate analysis, men with detrusor overactivity were significantly older, more obstructed, had larger prostates, higher irritative International Prostate Symptoms Score subscores, a lower voiding volume at free uroflowmetry, and a lower bladder capacity at cystometry. The prevalence of detrusor overactivity rose continuously with increasing bladder outlet obstruction grade. Multivariate analysis showed that only age and bladder outlet obstruction grade were independently associated with detrusor overactivity. After age adjustment, the odds ratios of detrusor overactivity compared to Schäfer class 0 were 1.2 for class I, 1.4 for class II, 1.9 for class III, 2.5 for class IV, 3.4 for class V, and 4.7 for class VI.

Conclusions: In patients undergoing clinical therapy for benign prostatic hyperplasia, detrusor overactivity is independently associated with age and bladder outlet obstruction. The probability of detrusor overactivity rises with increasing age and bladder outlet obstruction grade.

European Association of Urology

Review – Voiding Dysfunction

The Detrusor Muscle: An Innocent Victim of Bladder Outlet Obstruction ?

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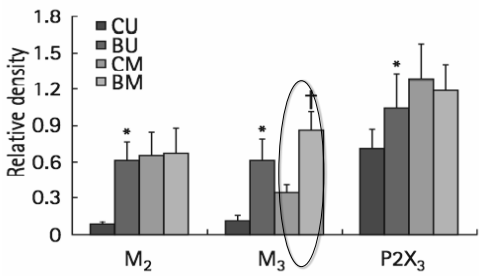
Urologic Clinic, University Federico II of Naples, Naples, Italy

Muscarinic and purinergic receptor expression in the urothelium of rats with detrusor overactivity induced by bladder outlet obstruction

Joon Chul Kim, Jae Suk Yoo, Eun Young Park, Sung Hoo Hong, Seong Il Seo and Tae-Kon Hwang

Department of Urology, College of Medicine, The Catholic University of Korea, Seoul, Korea



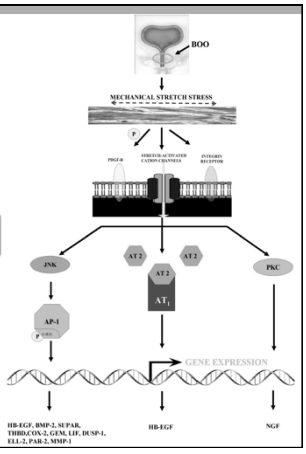
Abstract

Objectives: Benign prostatic hyperplasia (BPH) is considered a frequent cause of bladder outlet obstruction (BOO) and lower urinary tract symptoms (LUTS), although the physiopathologic mechanism through which BPH causes LUTS is not clear. Several morphologic and functional modifications of the bladder detrusor have been described in patients with BPH and could play a direct role in determining symptoms. The opinion is spreading that the enlarged prostates in patients with LUTS is nothing more than a mere bystander. Evidence has accumulated, however, supporting the role of BPH-related BOO as the direct cause determining bladder dysfunction and indirectly causing urinary symptoms. The present review addresses the bladder response to BOO, particularly focusing on the physiopathologic cascade that links obstructive BPH to bladder dysfunction.

Methods: A literature review of peer-reviewed articles has been performed, including both in vivo and in vitro studies on human tissue and animal model experiments.

Results: Epithelial and smooth muscle cells in the bladder wall are mechanosensitive, and in response to mechanical stretch stress caused by BOO, undergo modifications of gene expression and protein synthesis. This process involves several transduction mechanisms and finally alter the ultrastructure and physiology of cell membranes, cytoskeleton, contractile proteins, mitochondria, extracellular matrix, and neuronal networks.

Conclusions: BOO is the initiator of a physiopathologic cascade leading to deep changing of bladder structure and function. Before being a direct cause of storing-phase urinary symptoms, the bladder is the first innocent victim of prostatic obstruction.



Facteurs transcriptionnels identifiés dans culture de CML détrusoriennes humaines sous l'effet d'une stimulation mécanique

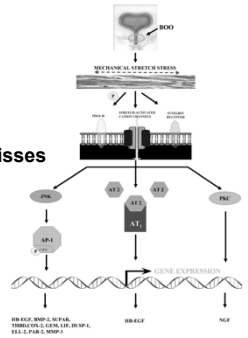
Accession no.	Name	No. of genes regulated	Significance (p)
P05412	c-jun	4	0.011
P15336	CRE-BP1	3	0.029
P05412	AP-1	3	0.045
P21359	NF-1	2	0.02
P01100	c-Fos	2	0.075
P03372	ER-α	1	0.04
P35869	AhR:Arnt	1	0.04
O35410	USF-1	1	0.04
Q15853	USF-2	1	0.04
Q15912	ATBF1-A	1	0.047
Q10586	DBP	1	0.049
P10275	AR	1	0.053

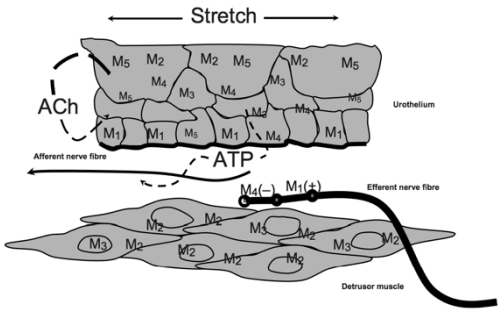
Frequency of transcription factor binding sites in the promoters of genes identified as differentially expressed by microarray analysis. Transcription factors listed are those that achieved statistical significance. AP-1 = activator protein-1; CRE-BP1 = cyclic adenosine monophosphate response element binding protein-1; NF-1 = neurofibromin-1; AhR:ARNT = dimer of aryl hydrocarbon receptor precursor and AhR nuclear translocator; ER-α, estrogen receptor-α; USF = upstream stimulatory factor; ATBF1-A, AT-binding transcription factor 1, isoform A; DBP = D-site binding protein; AR = androgen receptor.
Reproduced with permission from Adam et al. [71].

Effets de l'obstruction vésicale

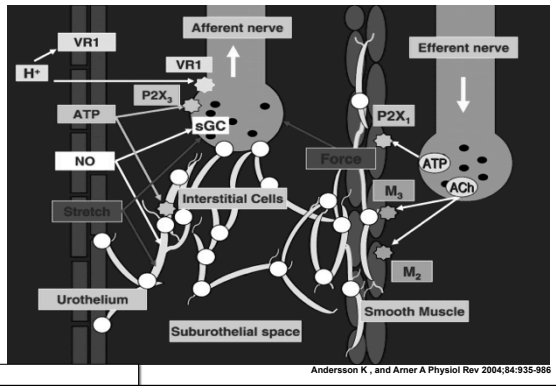
Dysfonctionnement

- **De l'urothélium**
- **Des cellules interstitielles**
- **Des cellules musculaires lisses**



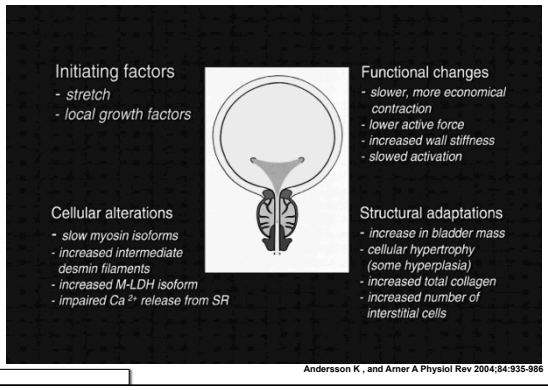


Hypothetical schematic model of urothelial signaling and possible role of interstitial cells for detrusor activity.



Andersson K , and Arner A Physiol Rev 2004;84:935-986

Changes induced in the detrusor by adaptive growth.



Andersson K , and Arner A Physiol Rev 2004;84:935-986

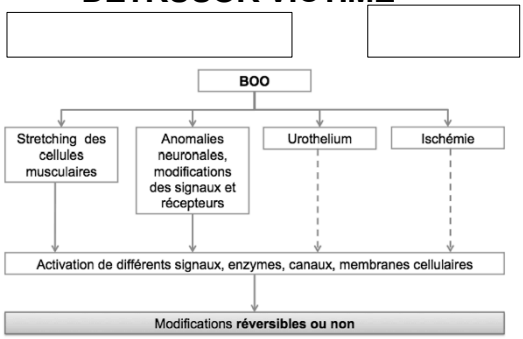
Altérations vasculaires

- Augmentation des marqueurs de l'hypoxie dans le tissu vésical soumis à l'obstruction
- Index de résistance vasculaire élevé en cas d'obstruction, diminuant après résection
- Persistance d'un index de résistance élevé quand persiste une HAV après résection

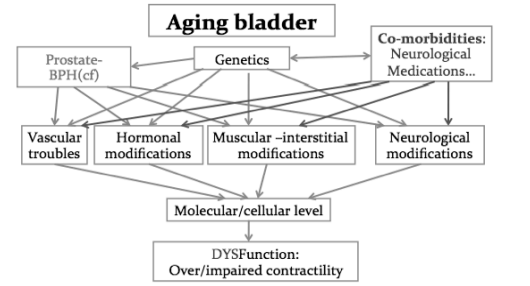
CONSEQUENCES DE L'OBSTRUCTION VESICALE

- Modifications vésicales
  - Musculaires et matricielles
    - Augmentation de l'épaisseur et du poids du détrusor
    - Corrélation entre poids et degré de l'obstruction
    - Hypertrophie résultant du muscle et de la matrice (collagène)
  - Neuronales : fibres C +++ (impliquées dans l'HAV)
  - Vasculaires : ischémie
- A l'échelon cellulaire : nombreuses voies de signalisation impliquées

DETRUSOR VICTIME



MECANISMES MULTIPLES



Human Bladder as a Novel Target for Vitamin D Receptor Ligands

Clara Crescioli,* Annamaria Morelli,* Luciano Adorini, Pietro Ferruzzi, Michaela Luconi, Gabriella Barbara Vannelli, Mirca Marini, Stefania Gelmini, Benedetta Fibbi, Silvia Donati, Donata Villari, Gianni Forti, Enrico Colli, Karl-Erik Andersson, and Mario Maggi

Department of Clinical Physiopathology, Center of Research, Transfer and High Education (C.C., A.M., P.F., M.L., S.G., B.F., S.D., G.F., M.Mag.), Departments of Anatomy, Histology, and Forensic Medicine (G.B.V., M.Mar.) and Surgical and Medical Critical Care (D.V.), Urology Unit, University of Florence, 50139 Florence, Italy; BioXell (L.A., E.C.), Milan, Italy; and Institute of Laboratory Medicine, Department of Clinical Pharmacology, Lund University Hospital (K.-E.A.), 22185 Lund, Sweden

Human prostate is now considered a target for vitamin D receptor (VDR) ligands, such as BXL-628. Because BXL-628 inhibited prostate growth without interfering with androgen signaling, it represents a new option for benign prostate hyperplasia (BPH) therapy. However, BPH symptoms are related not only to prostate size, but also to compensatory bladder hypertrophy and eventual overactivity. We now report that human bladder expresses VDR (determined by real-time PCR immunohistochemistry and Western blot) and responds to VDR agonists, such as the natural ligand, calcitriol, and its synthetic and less hypercalcemic derivative, BXL-628. Experiments were conducted with stromal cells derived from human bladder neck obtained at surgery from BPH patients. BXL-628 counteracted keratinocyte growth factor (KGF) and androgen-induced cell proliferation and stimulated apoptosis with a parallel reduced expression of the survival oncoprotein Bcl-2. Prolonged serum starvation time-dependently pushed bladder stromal cells to express activated myofibroblast markers, such as desmin and smoothelin, without changing other contractile-related proteins and intermediate filaments, such as vimentin. Chronic exposure to BXL-628 prevented starvation-induced cell phenotype modification. Because hypertrophy and starvation-induced bladder remodeling are supposed to underlie bladder overactivity, it is possible that BXL-628 might be helpful in reducing not only cumbersome symptoms related to prostate overgrowth, but also those related to bladder irritation. *J Clin Endocrinol Metab* 90: 962–972, 2005)

HAV = multifactorielle

- Vieillissement vésical
  - Hyperactivité détrusorienne fréquente même en l'absence d'obstruction vésicale
  - Fibrose et altérations neurologiques identiques à celles observées dans l'obstruction vésicale
- Pathologies associées
  - Neurologiques
  - Non neurologiques
- Iatrogénie médicamenteuse