UAB Phenotyping
-Definition, Symptoms, Etiology-

Naoki Yoshimura, MD, PhD

Department of Urology

University of Pittsburgh

UAB/DU: Underactive Bladder/ Detrusor Underactivity

OAB/DO: Overactive Bladder/ Detrusor Overactivity

DHIC: Detrusor Hyperreflexia with Impaired Contractility

The Other Bladder Syndrome: Underactive Bladder

Minoru Miyazato, MD, PhD,[1,2] Naoki Yoshimura, MD, PhD,[2,3] Michael B. Chancellor, MD[4]

Vol. 15 No. 1 • 2013 • Reviews in Urology

Terminology

- **Underactive Bladder Syndrome**
  - DU is a urodynamically-defined bladder condition underlying incomplete emptying of the bladder
  - UAB may be an appropriate clinical syndromic term that encompasses the symptoms and signs of incomplete emptying of the bladder
  - A syndromic concept of UAB warrants research to determine the true burden of disease, increase awareness among patients and providers, and broaden efforts to investigate therapeutic directions

Detrusor Underactivity (DU)

- A urodynamic diagnosis
- A (detrusor) contraction of reduced strength and/or duration resulting in prolonged bladder emptying and/or incomplete bladder emptying

Abrams, et al,: Neurourol & Urodyn, **21:** 167, 2002

LUTS-Lower Urinary Tract Symptoms

- **Storage symptoms**
  - Daytime urinary frequency
  - Nocturia
  - Urgency
  - Urinary Incontinence

  Overlap with overactive bladder (OAB) symptoms

- **Voiding & Postvoid symptoms**
  - Slow stream
  - Splitting or spraying
  - Intermittency
  - Hesitancy
  - Straining
  - Terminal dribble

  Overlap with Underactive bladder (UAB) symptoms??

UAB phenotyping

- What is the symptom complex of UAB
  - Women with DO + impaired contractility (DU) are older (73 y.o.) than women with DO + preserved detrusor contractility (54 y.o.)
  - Urinary retention and recurrent cystitis are more frequent in women with DU
  - Voiding symptoms (slow stream; 1.6 fold, intermittent stream; 2.8 fold, hesitancy; 1.6 fold, straining; 3.2 fold, terminal dribbling; 1.7 fold and incomplete emptying, 1.4 fold) are more common in women with DU

Comparison of Lower Urinary Tract Symptoms Between Women with Detrusor Overactivity and Impaired Contractility, and Detrusor Overactivity and Preserved Contractility

Kobi Stav,*,† Yaniv Shilo, Amnon Zisman, Arie Lindner and Dan Leibovici

THE JOURNAL OF UROLOGY®
Vol. 189, 2175-2178, June 2013

UAB Working Definition

The underactive bladder is a symptom complex suggestive of detrusor underactivity and is usually characterized by <u>prolonged urination time</u> with or without a sensation of incomplete bladder emptying, <u>usually with hesitancy, reduced sensation on filling, and a slow stream</u>.

Chapple et al., European Urology, 2015 68(3):351-3

Prevalence of DU in LUTS patients

- 40.2% of men and 13.3% of women undergoing a urodynamic study for LUTS were classified as having DU (Jeong et al., Korean J Urol 2012)
- In elderly men with symptoms of difficult bladder emptying, urodynamic pressure flow study revealed 41% of the patients had an obstructive high pressure low flow pattern, 28.2% had an DU pattern, 20.5% had a mixed obstructive and DU type, and 10.3% had a normal pattern (Diokno J Urol 1994)
- In women with impaired bladder emptying (IBE), Gotoh et al. found the pathophysiology of impaired detrusor contraction in 81.9% and BOO in 14.8% of patients (Gotoh et al., Int J Urol 2006)
- In patients with non-neurogenic LUTS, DU was found in 9-48% of men and 12-45% of women (Osman et al., Eur Urol 2014; Review article)

DHIC

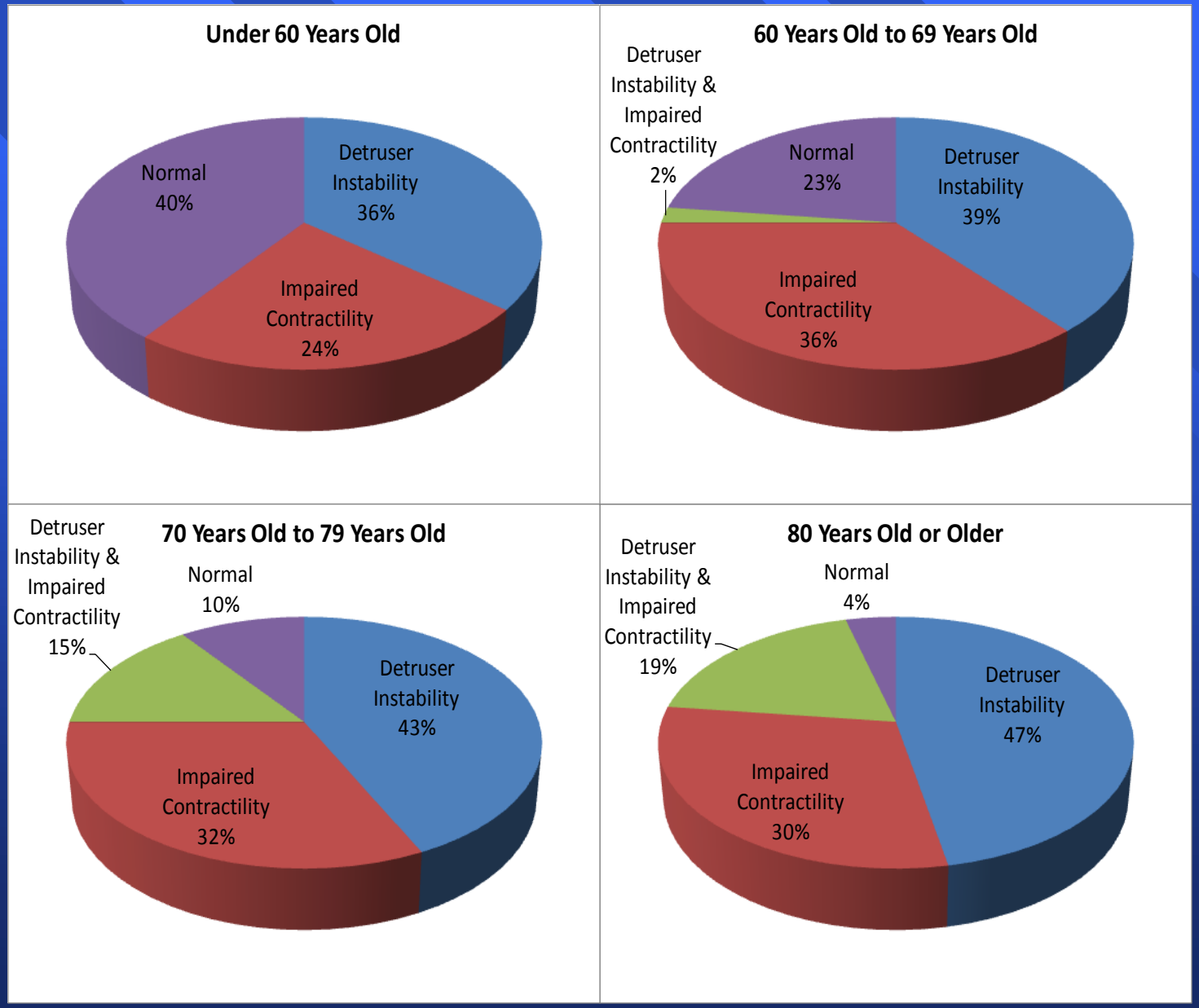
- Combination of DO/OAB and DU/UAB
- The urodynamic study of UAB/DU is characterized by a non-contractile detrusor, a low pressure, or poorly sustained detrusor contraction in association with a poor flow rate with or without a large post-void residual (PVR) volume (Thomas et al., BJU Int 2004)
- A part of UAB/DU patients have both detrusor hyperactivity and inadequate contractility (DHIC), resulting in urgency incontinence and large PVR (Smith, Neurourol Urodyn 2010)

Prevalence of UAB/DU/DHIC (Dr. Kuo, Taiwan)

- The videourodynamic characteristics in men and women with LUTS refractory to conventional medication
- Among 2831 men with LUTS, DU was noted in 146 (5.2%) and DHIC in 150 (5.3%) patients
- In 1333 female patients with LUTS, the incidence of DU was 11.4% and DHIC was noted in 4.3%

- The incidence of DHIC increased with ageing, however, the incidence of DU with age was not significantly different from that in the other vesicourethral dysfunction such as DO, BND or BPO
- Among the 299 patients with PVR>250ml, DU was noted in 108 (36.1%) and DHIC in 44 (14.7%) patients
- The bladder sensation of filling and fullness was significantly reduced in male DU patients compared to that in the patients with bladder outlet obstruction

Detrusor Instability (DO)/Impaired Contractility (DU) Urodynamic Construct of 193 men with LUTS w/o BOO



Ameda et al.
J Urology
162:142,1999
.

Summary- DU prevalence

- DU (DU + DHIC) is found in both men (10-40%) and women (15-45%) with LUTS, and increased as age progresses
- When difficult bladder emptying is a dominant condition, DU is found in 50% of male patients who had decreased filling sensation more often than BOO patients
- When difficult bladder emptying is a dominant condition, the majority (80%) of female patients have DU
- The prevalence of DU increases when patients have PVR larger than 250ml

Diagnosis of UAB

Symptoms +"Residual urine volume"?

Volume (150ml, 250ml) or Ratio (1/3 Capacity)?

How to measure it?

- **The prevalence of DU and DHIC is increased from 7.1% to 36.1% and from 5.0% to 14.7%, respectively (12% to 50% in total) when the patients have PVR>250ml (Kuo HC, 2015)**

- **Obvious DU is defined with the urodynamic findings of:**
  (1) low maximum detrusor contraction velocity
  (2) low isovolumetric detrusor pressure
  (3) bladder emptying efficiency less than 67%

(Cucchi et al., J Urol 2009)

Etiology of DU/UAB

- Detrusor areflexia or impaired detrusor muscle contractility
  - Motor:

    A) Neurological dysfunction

    B) Detrusor muscle damage

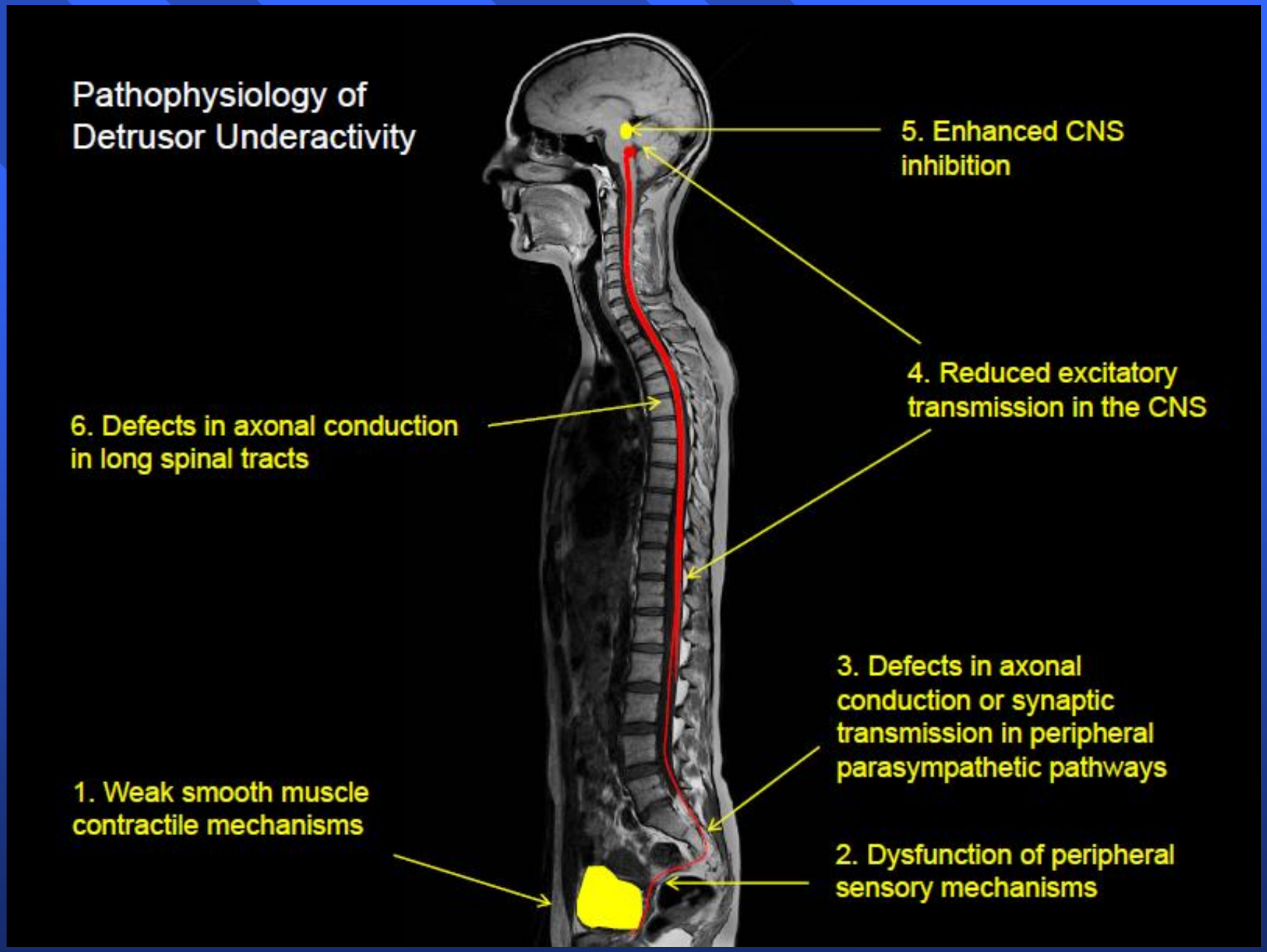
    C) Anticholinergic drug

  - Sensory: Sensory deficit

Causes of Detrusor Underactivity

- Aging
- Diabetes mellitus (diabetic cystopathy)
- Bladder Outlet Obstruction (BOO)
- Neurological disorders
  - Acute cerebrovascular accidents
  - Multiple sclerosis
  - Parkinson's disease
- Injury to the spinal cord, cauda equina, and pelvic plexus
  - Pelvic surgery
  - Pelvic and sacral fractures
  - Herniated disc
  - Lesions of the pudendal nerve
- Infectious neurologic problems
  - Acquired immune deficiency syndrome (AIDS)
  - Neurosyphilis (tabes dorsalis)
  - Herpes zoster and herpes simplex
  - Guillain-Barré syndrome

Miyazato et al;., Rev Urol, 2013



Prepared by Fowler CJ & de Groat WC

Pathophysiology of DU/UAB

1. Aging

Aging Bladder - Human

Aging is associated with:

- **Decrease in axonal content in the bladder**
- **Decline in bladder and urethral sensations**
- **Increase in bladder volume at first desire to void**
- **Decreased responses to bladder filling in areas of the brain (insula) responsible for mapping visceral sensations**

✓ Aging-related Neural Dysfunction ➔ UAB/DU

✓ Aged people also often exhibit both OAB and UAB conditions (=DHIC)

DHIC in Older Patients

- Clinical urodynamic studies
  - First identified by Resnick and Yalla in 1987
  - Griffiths et al, 2002: coincidental occurrence of two conditions with different etiological factors
  - Abarbanel and Marcus, 2006 – overlap IDC and DO
- Histological studies
  - Electron microscopy “signatures” of both DO and Impaired contractility found in DHIC
  - Age-related changes

Age-related Bladder Dysfunction -Animal studies-

- Aged rats exhibit increased volume and pressure thresholds for voiding (Chun et al. 1988, Chai et al. 2000)
- Aged rats exhibit a reduction in the maximal bladder pressure generated during pelvic nerve stimulation (Hotta et al. 1995)

- Aged rats exhibit decreased responses to intravesical capsaicin (Chai et al. 2000)
- CGRP and SP in lumbosacral DRG neurons is decreased with age (Mohammed and Santer 2002)
- The density of PACAP innervation of the bladder base is decreased in old rats (Mohammed et al. 2002).

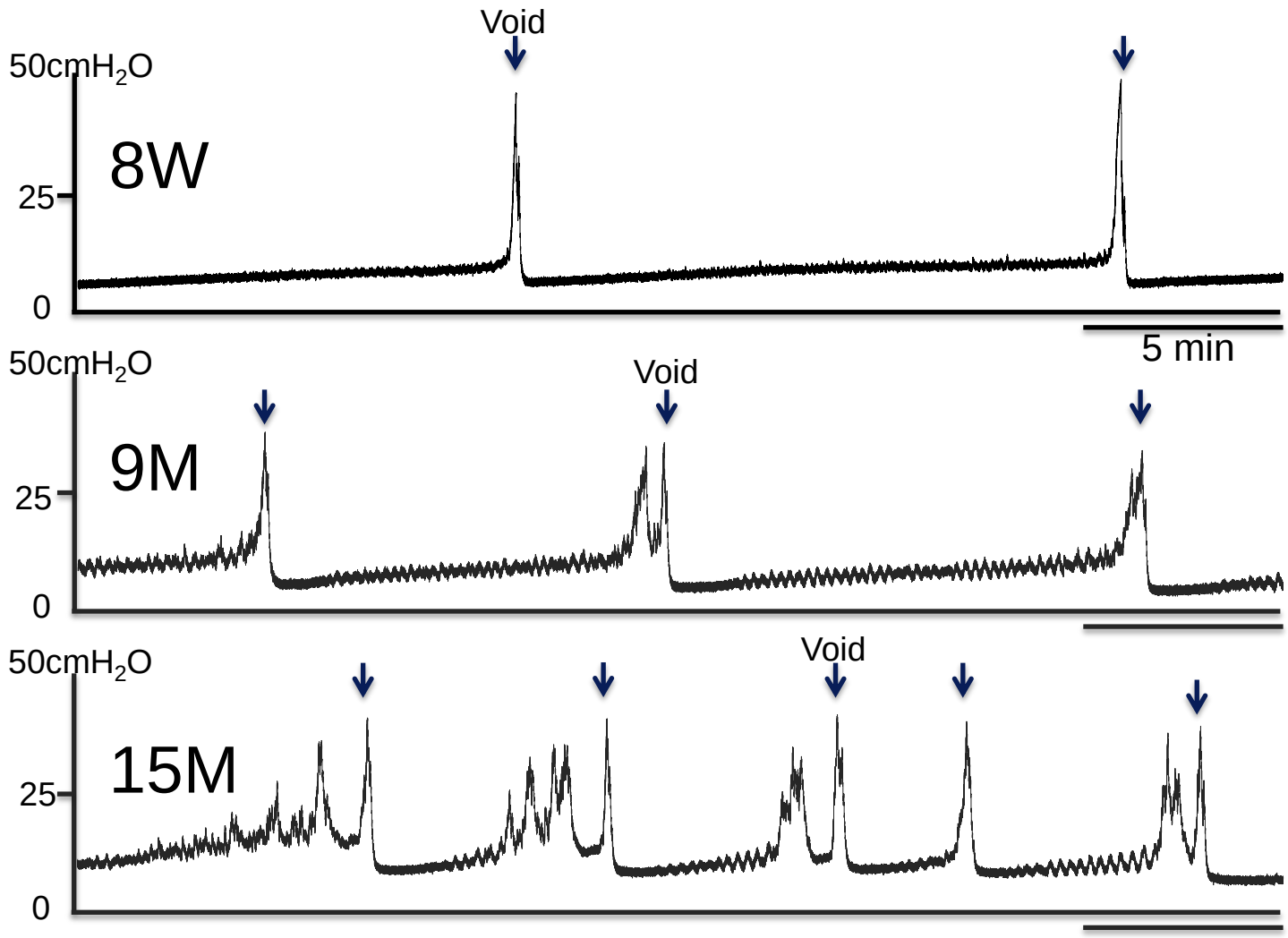
Efferent and Afferent Nerve Impairment ➔ UAB/DU

Age-related Bladder Dysfunction

- Assessment of bladder function in 15 months-old female rats

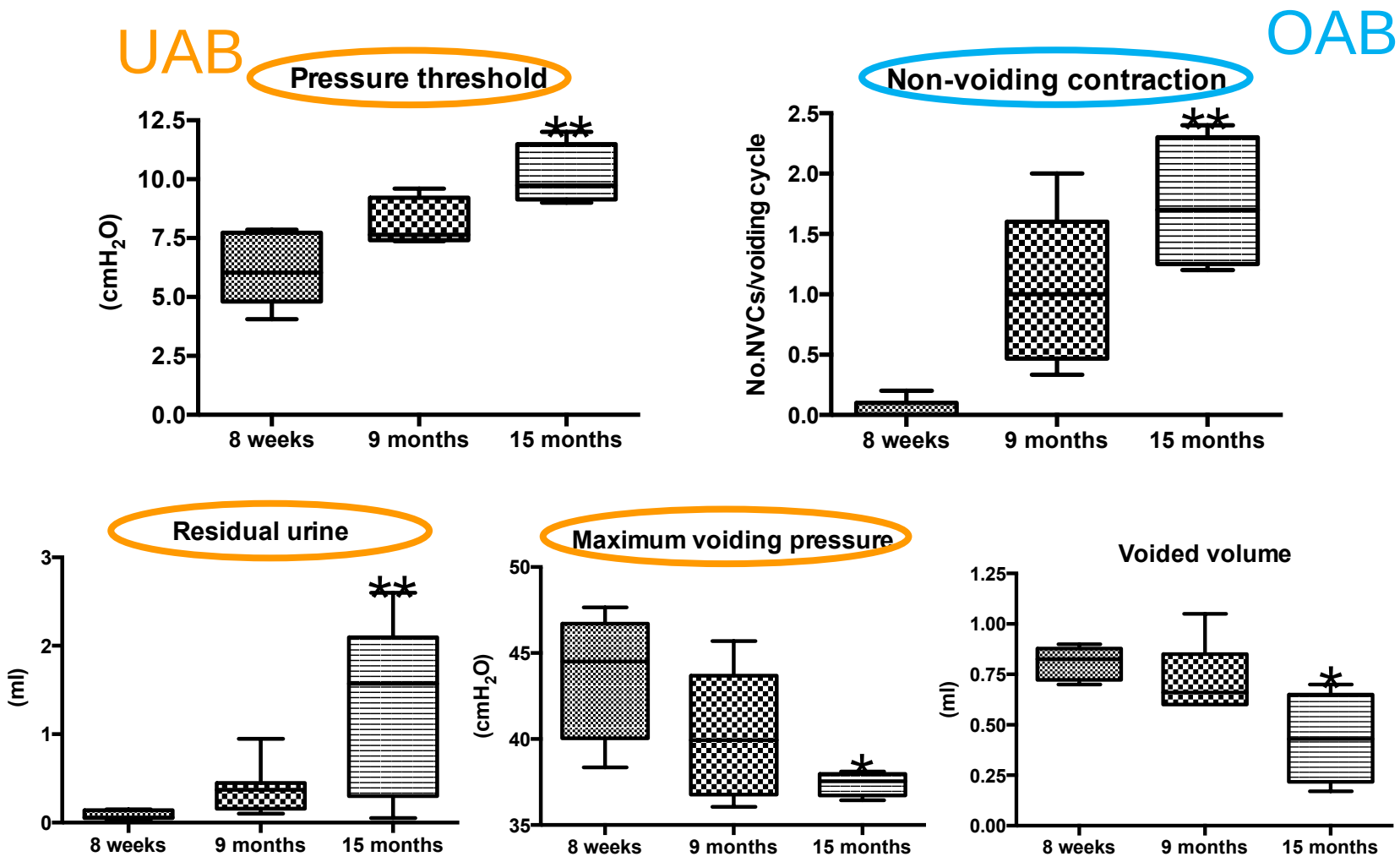
Mori et al., Neurourol & Urodyn 2015, in press

Cystometrogram



8W:8 weeks old, 9M:9 months old & 15M:15 months old

Cystometric parameters (UAB+OAB)



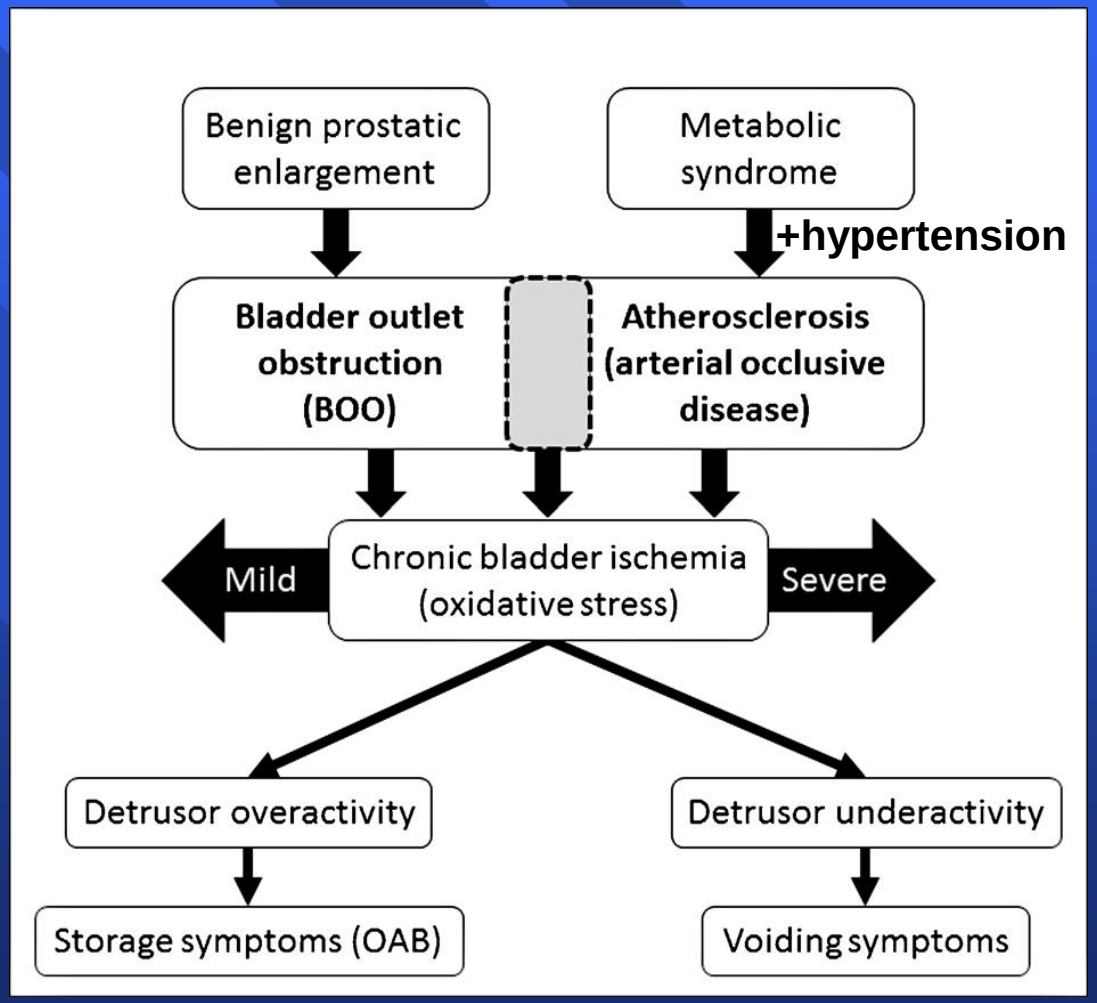
Dunn's Multiple Comparison Test, 15M vs. 8W; *P<0.05, **P<0.01

Pathophysiology of DU/UAB

2. Ischemia→Oxidative stress

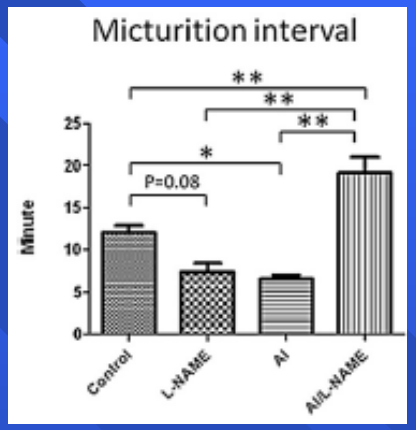
Male
Bladder outlet obstruction (BPH)

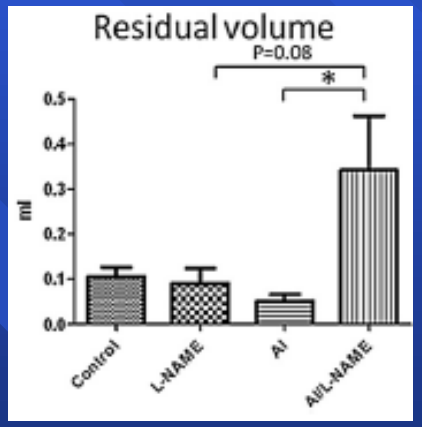
Male & Female
Atherosclerosis



Yamaguchi et al, Neurourol Urodyn, 2014

Detrsusor underactivity in a rat model of chronic ischemia and vascular dysfunction





Combination of arterial balloon endothelial injury (AI) and L-NAME (NOS inhibition) induces DU whereas either treatment alone induces bladder overactivity

(Nomiya et al, J Urol, 2014)

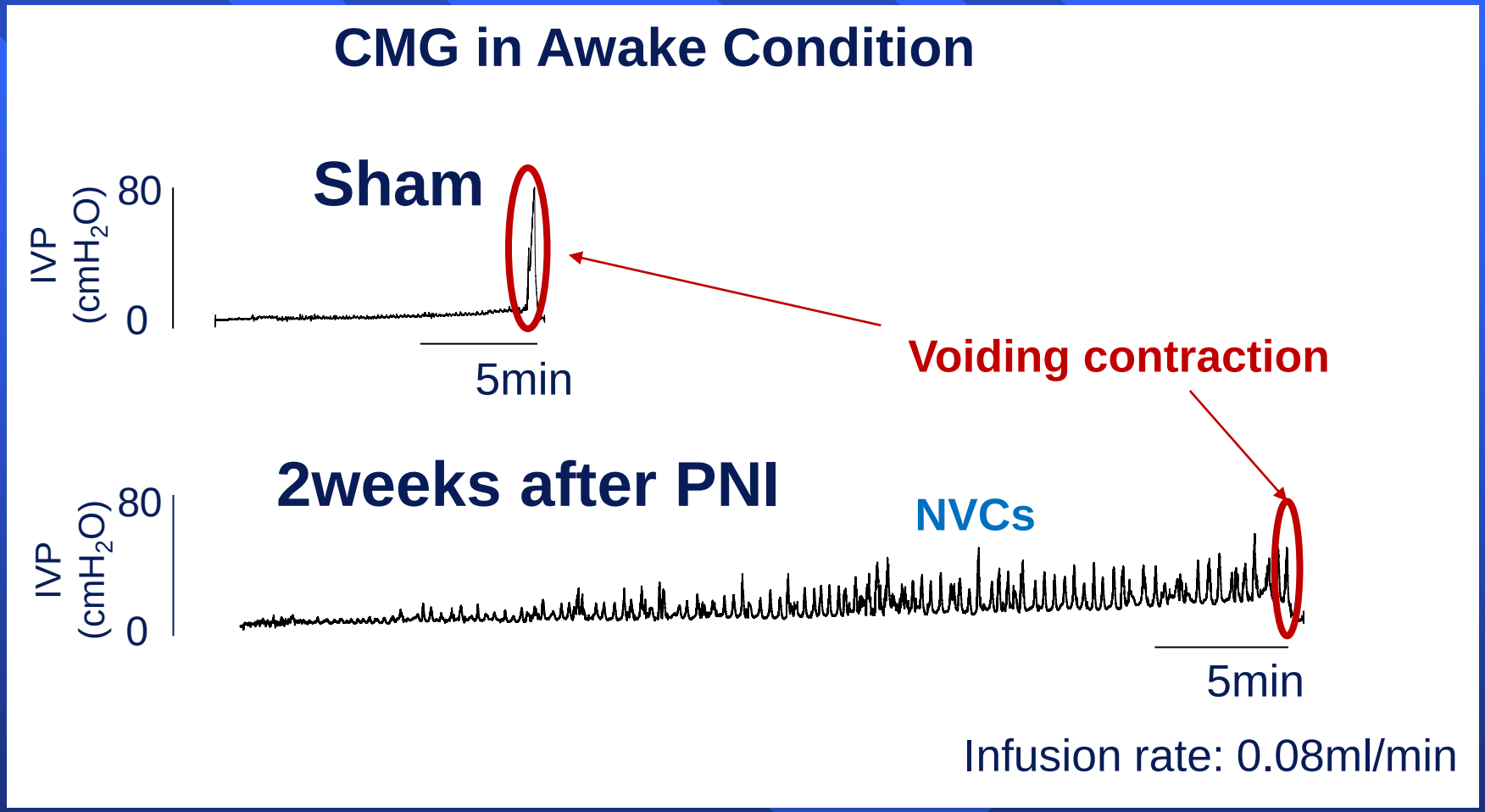
Pathophysiology of DU/UAB

3. Nerve injury

Pelvic nerve injury (PNI) model (Rat)

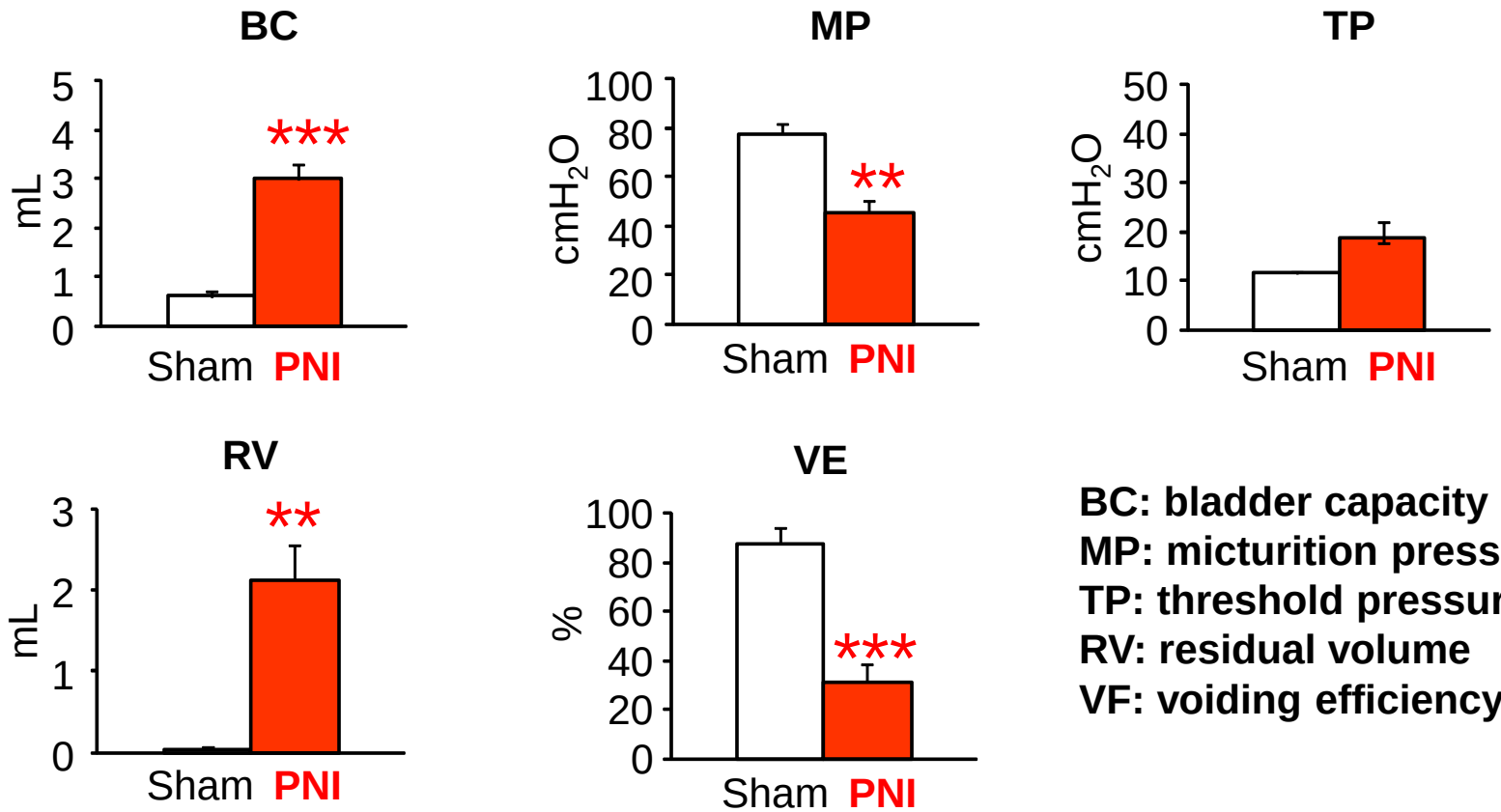
- Efferent and afferent nerve dysfunction is involved in UAB/DU
- Modeling #1- Cryoinjury (dry ice) of bilateral pelvic nerves in female rats
- Modeling #2- Crush injury of bilateral pelvic nerves in female rats

Awake cystometry in pelvic nerve injured rats



Non-voiding contractions (NVCs) in the storage phase in PNI rats →<u>OAB/DO</u>

Changes in voiding parameters in PNI rats



BC: bladder capacity
MP: micturition pressure
TP: threshold pressure
RV: residual volume
VF: voiding efficiency

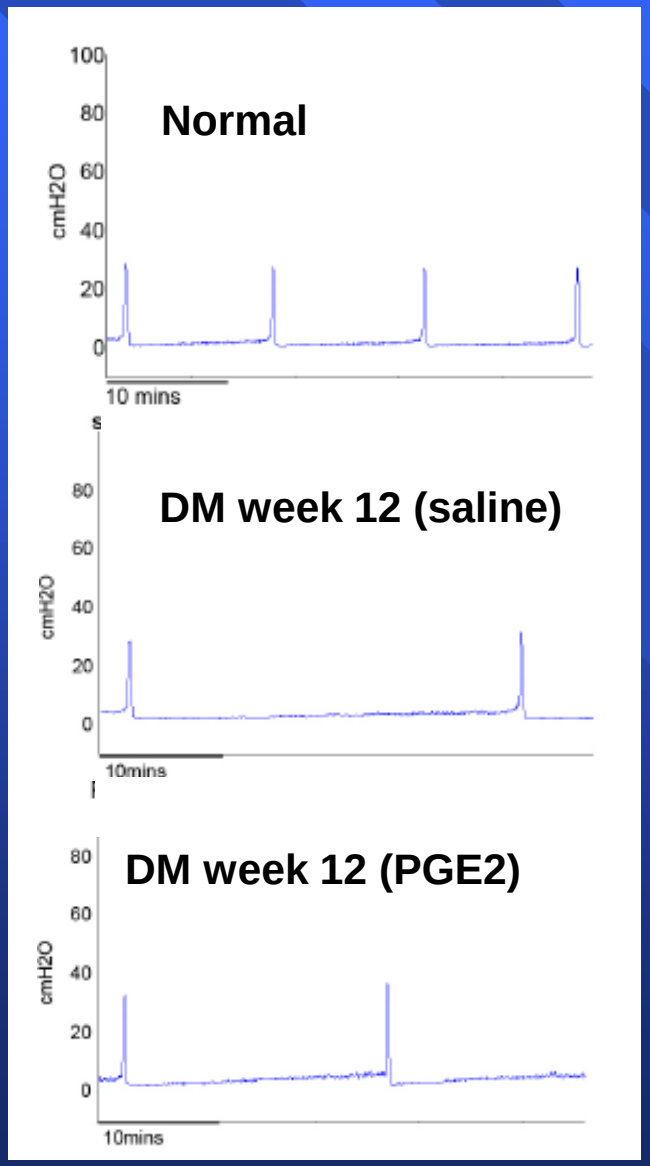
*N=5. *p<0.05; **p<0.01; ***P<0.001 (unpaired t test).*

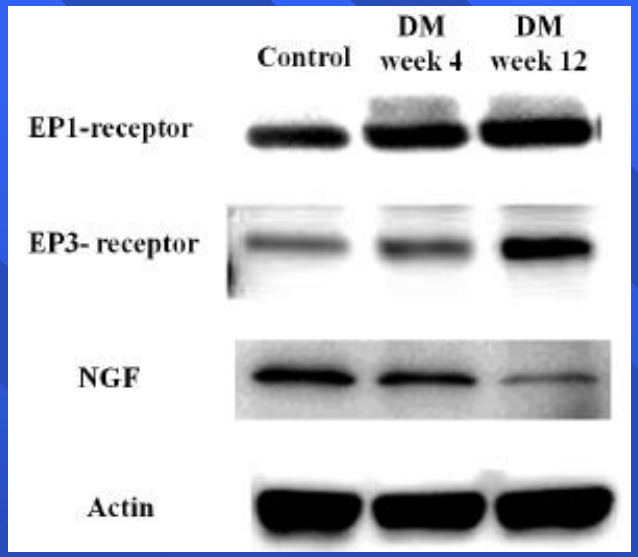
PNI rats showed significant increases in BC and RV and decreases in MVP and VE in cystometry→ **UAB/DU**

Pathophysiology of DU/UAB

4. Diabetes Mellitus (DM)

Underactive bladder in streptozotocin-induced diabetic rats





- DM rats showed:
  1. Increased intercontraction interval (ICI) and residual urine volume
  2. Upregulation of prostanoid EP1 and EP3 receptors
  3. Downregulation of bladder NGF expression

Nirmal et al., PLOS One 2014

Hypothesis for LUTS Progression OAB to UAB

Primary (Idiopathic, Aging)

Secondary (BOO, NB, DM)

Bladder Dysfunction

Decompensation

Bladder Remodeling

Aging
Denervation
Ischemia
Inflammation

DO, Hypertrophy, Low Compliance, Fibrosis

Non-OAB → OAB → OAB+UAB (DHIC) → UAB/DU

DHIC: Detrusor Hyperactivity with Impaired Contractility

Conclusion: Key Steps Moving Forward

- Consensus definition and classification
  - ✓ What is the suitable symptom complex (subjective and objective) for detection of patients with UAB/DU?
  - ✓ Is UAB phenotyping possible based on its pathophysiology?
  - ✓ Are PVR measurement and/or urodynamics needed?
- Detailed epidemiologic surveys
- Health economics
- Advance the understanding in basic pathophysiology
- Develop new and better treatment
- Develop prevention strategies to halt UAB progression

Chancellor and Diokno: Int Urol Nephrol, 46 Suppl 1: S1, 2014