Urodynamic studies in animals: techniques and interpretations

Workshop 24

Monday 23 August 2010, 14:00 – 15:30

Time	Time	Topic	Speaker
14.00	14.05	Introduction	Matthew Fraser
14.05	14.30	Lower urinary tract anatomy and physiology	Matthew Fraser
14.30	14.55	Cystometric evaluation of lower urinary tract function	Matthew Fraser
14.55	15.20	Clinical urodynamics	Derek Griffiths
15.20	15.30	Discussion	

Aims of course/workshop

This workshop will review and explore underlying assumptions that are important in the proper design and interpretation of animal urodynamic experiments. Methodological and model specific considerations will be discussed in the context of the information obtainable from each. Basic physiological principles will be applied to the interpretation of data, and common misconceptions and misinterpretations will be discussed. Clinical correlates and translation of animal data will be described and discussed. Attendees of this workshop will be further empowered to interpret basic science results in the context of their scientific and clinical interests.

Educational Objectives

Basic science research of the lower urinary tract depends to a large degree on the use of animal models. In many cases, methods are employed and/or conclusions made from results obtained without full consideration of the basic physiology of the system or the unique physiology of the utilised species. A common mistake, for example, is the use of maximal bladder pressure attained during a voiding event with continuous open-outlet cystometry as a measure of bladder contractile strength, while it more correctly represents the pressures at which the bladder outlet opens or closes. Additionally, ignoring the effects of treatments on phasic external urethral sphincter activity in the rat, important for efficient voiding in this species, may result in improper interpretation of results. This workshop will educate the delegates in both proper methodological design and subsequent interpretation of results, with emphasis on clinical correlates and translation.

Urodynamic studies in animals
techniques and interpretations

Matthew O. Fraser, Ph.D.
Derek J. Griffiths, Ph.D.

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Outline of Major Topics

- Lower urinary tract anatomy and physiology
- Cystometric evaluation of lower urinary tract function
- Clinical urodynamics

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Lower urinary tract anatomy and physiology:

• Evolution and ontogeny
• Anatomy
• Function

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Lower Urinary Tract
Anatomy and Physiology

- Evolution and ontogeny
- Anatomy
  - Musculature
  - Innervation
- Function
  - Normal physiology
  - Pathophysiology

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Lower Urinary Tract
Anatomy and Physiology

- Evolution and ontogeny
  - From cloaca to LUT

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Lower Urinary Tract
Anatomy and Physiology

- Anatomy
  - Musculature
    - Smooth muscle
    - Striated muscle
  - Innervation
    - Autonomic
      - Parasympathetic
      - Sympathetic
    - Somatic

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Lower Urinary Tract
Anatomy and Physiology

- Function
  - Normal Physiology
    - Storage
      - Ureteric filling
      - Sympathetic nervous system influences
      - Somatic nervous system influences
    - Voiding
      - Parasympathetic nervous system influences

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Lower Urinary Tract
Anatomy and Physiology

- Pathophysiology
  - Storage
    - Sensory
      - » Overactive bladder (OAB Dry)
      - » Painful bladder syndrome
  - Motor
    - Hypermotility
      - » Overactive bladder (OAB wet, a.k.a urge incontinence)
      - » Detrusor hyper-reflexia (neurogenic bladder)
    - Hypomotility
      - » Overflow incontinence (bladder hypomotility)
      - » Stress urinary incontinence (urethral hypomotility)

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Cystometric evaluation of lower urinary tract function:

- Cystometric techniques in animals
- Methodological details can make all the difference
- Summary of Conditions and Measurables in Experimental Animal Studies

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Cystometric Evaluation
of Lower Urinary Tract Function

- Cystometric techniques in animals
- Methodological details can make all the difference
- Summary of Conditions and Measurables in Experimental Animal Studies

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Cystometric Evaluation
of Lower Urinary Tract Function

- Cystometric techniques in animals
  - Open cystometry
  - Closed outlet cystometry
    - Traditional
    - Simultaneous bladder and urethral recording
  - External urethral sphincter activity
    - Direct measurement
    - Indirect measurement

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Cystometric Evaluation
of Lower Urinary Tract Function

- Cystometric techniques in animals
  - Open cystometry
    - Single filling cystometrograms
    - Continuous cystometry
    - Combined open methods

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Cystometric Evaluation
of Lower Urinary Tract Function

- Cystometric techniques in animals
  - Closed outlet cystometry
    - Traditional
      - Single filling cystometrograms
      - Isovolumetric recordings
      - Combined closed methods
    - Simultaneous bladder and urethral recording
      - Open cystometry with urethral pressure measurement
      - Isolated bladder-urethra preparations
        - » Closed cystometry
        - » Open cystometry with vent catheter

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Cystometric Evaluation
of Lower Urinary Tract Function

- Cystometric techniques in animals
  - External urethral sphincter activity
    - Direct measurement
      - Electromyography
    - Indirect measurement
      - Anal sphincter pressure
      - HFOs
      - Subtraction by neuromuscular blockade
        - » Closed vs. open abdomen interpretation

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Cystometric Evaluation
of Lower Urinary Tract Function

- Methodological details can make all the difference
  - Recording instrumentation
  - States of Consciousness
  - Species differences

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Cystometric Evaluation
of Lower Urinary Tract Function

- Methodological details can make all the difference
  - Recording instrumentation
    - LUT filling
    - EUS EMG recording
    - Video recording

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Cystometric Evaluation
of Lower Urinary Tract Function

- Recording instrumentation
  - LUT filling
    - Catheter placement
    - Infusion rate
      - » Initial response is spurious compared to natural flow rate
      - » Accommodation, even with natural filling via diuresis
    - Infusate composition
      - » Distilled water vs. saline vs. urine
      - » Drug solutions and vehicles

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Cystometric Evaluation
of Lower Urinary Tract Function

- Recording instrumentation
  - EUS EMG recording
    - Placement of electrodes
    - Effect of electrode placement
  - Video recording

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Cystometric Evaluation
of Lower Urinary Tract Function

- Methodological details can make all the difference
  - States of Consciousness
    - Anesthesia
      - Urethane in the rat
        - » Interruption of descending control
        - » Sympathetic response
      - Chloralose in the cat
        - » Reduces/eliminates EUS activity
        - » Causes urethral smooth muscle dysfunction

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Cystometric Evaluation
of Lower Urinary Tract Function

- States of Consciousness
  - Awake
    - Stress response
    - Chronic catheter issues
  - Decerebrate
    - Cleanest, but difficult prep
    - Spasticity

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Cystometric Evaluation
of Lower Urinary Tract Function

- Species differences
  - Pharmacology
    - Substance P story
    - Others
  - Physiology
    - Scala naturae vs. genetic relatability
    - Ecological niche concerns
      - » Toileting vs. "Peemail"
    - EUS participation
      - » Muriform rodents – obligate phasic firing
      - » Guinea pig, cat – conditional phasic firing
      - » Dog – interrupted voiding – related to marking behavior?

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Cystometric Evaluation
of Lower Urinary Tract Function

- Summary of Conditions and Measurables in Experimental Animal Studies

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Clinical urodynamics:

- What it shows
- How it compares and contrasts with animal experiments

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Typical clinical urodynamics

- One fill via catheter followed by voiding
- Measuring:
  - abdominal pressure p_{abd}
  - intravesical pressure p_{ves}
  - volumes (infused and voided/leaked)
  - voiding flow rate Q
  - possibly, anal sphincter EMG

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Pressures 1

- Closed abdomen
- So, abdominal pressure p_{abd} is not zero
  - especially in sitting or standing positions
- Can be large (up to 50 cm H_2O)
- Changes with cough, strain, position
- So p_{ves} doesn't show what bladder (detrusor) is doing

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Pressures 2

- What bladder does = p_{ves} - p_{abd}
  = p_{det} (detrusor pressure)
- Straining (etc) and detrusor contraction
  - both raise p_{ves},
  - but mechanism and effect on urine flow and leakage are completely different

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Central control

- Clinical urodynamics
  - no anesthetic
- Main observations during filling are sensations
  - subjective, subject to cerebral control
- Even bladder capacity is usually limited by sensation
  - not a mechanical parameter
  - depends on cerebral control
  - maximum anesthetic bladder capacity is larger than cystometric bladder capacity
- Normal voiding is voluntary by definition
  - depends on decisions made in brain
  - involuntary voiding is abnormal = leakage, incontinence

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Lack of central control

- High spinal cord injury
  - bladder works automatically
  - reproducible
    - no variable central control
  - fill/void sequences can be repeated many times
    - like animal experiments

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Abnormalities: DO

- During bladder filling, detrusor pressure normally hardly changes
- Detrusor overactivity (DO):
  - involuntary detrusor contraction – elevations of P_{det}
  - therefore depends on communication with subject
  - impossible with animals
  - "nonvoiding detrusor contractions" may be equivalent (see Matt Fraser's part) but certainly not identical
  - believed abnormal

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Abnormalities 2:

- DO
  - usually accompanied by sensation - urgency
  - may limit bladder capacity
  - usually isometric (no leakage)
  - sometimes leads to leakage – urge/reflex incontinence
  - If so, not a "non-voiding contraction"
- Low compliance
  - seems to be mechanical
  - similar in animals and man

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Voiding: interpretation of pressures

- Obstruction
  - during flow detrusor pressure measures
    - urethral properties (obstruction)
    - not detrusor contractility
    - this may not be true in all animals
      - needs research
- Contractility
  - If flow stops, detrusor pressure measures isovolumetric pressure
    - contraction strength
- Importance of flow recording to distinguish these

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Filling route and voiding flow rates

- Matt Fraser suggests natural filling via ureter may differ from per catheter filling in animals
  - Not much researched in man
  - But flow rates through catheterized urethra are lower than natural free flows
- Some studies suggest this is due to prior filling via catheter (bypassing ureter)
  - not obstruction by catheter

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Geometrical considerations

- Strips versus whole bladders
  - conversion of length/extension to volume
  - conversion of force to pressure
- Normalization of forces generated by strips of different size

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Summary Comments and Discussion

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