The regeneration of ureteric function and pathophysiology of ureteric obstruction - what do Hedgehogs and EPO have to do with it?

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Grand Rounds June 2016

Objectives

• To review ureteric functional physiology and the impact of obstruction on ureteric contractile properties

• To review the impact of obstruction on ureteric hemodynamics and pressure profiles

• To discuss functional recovery of the obstructed ureter

• To learn about research into pharmacological intervention to accelerate functional recovery of ureter following obstruction removal
Introduction

- ureteric obstruction affects both pediatric and adult population
- can result in permanent renal damage
- degree of renal injury depends on severity of obstruction, chronicity, baseline renal function, and presence of other mitigating factors (UTI)
- results in multiple histologic and functional derangements in ureteric physiology

Causes of Ureteric Obstruction

- **Congenital**
  - ureterocele
  - obstructing megaureter
  - retrocaval ureter
  - prune belly syndrome

- **Neoplastic**
  - urothelial carcinoma
  - metastases

- **Inflammation**
  - abscess
  - ureteritis cystica
  - endometriosis
  - amyloidosis
  - tuberculosis

- **Miscellaneous**
  - trauma
  - urinoma
  - lymphocele
  - pregnancy
  - RPF
  - pelvic lipomatosis
Clinical Presentation of ureteric obstruction

• acute - classic flank pain, nausea, vomiting due to distension of renal pelvis and visceral nerve activation. Radiates to lower abdomen, testicles, or labia

• chronic - usually relatively painless, can be asymptotic

Ureteric Contractile Physiology
Propulsion of a Urinary Bolus


Obstruction and Ureteric Function
Obstruction and Ureteric Function

- Transient increase in amplitude and frequency in peristaltic contraction, then decreased.
- Peristaltic contraction unable to coapt ureteric wall.
- Urine transport now dependent on hydrostatic forces generated by kidney.
- At 8 days, ureter diameter had increased by 170% and length by 25%.

Obstruction and Ureteric Contraction

- rabbit model, complete ureter obstruction for 2 weeks
  - 250% cross sectional muscle area
  - 24% ureteral length
  - 100% ureteral outer diameter


Obstruction and ureteric contraction

stress = force / unit area muscle

Obstruction and ureteric Contraction

Laplace Equation

\[ P = \text{stress} \times \frac{\text{wall thickness}}{\text{radius}} \]

Pathophysiology of ureteric obstruction - Unilateral vs Bilateral
Pathophysiology of unilateral ureteric obstruction


Obstruction induced increased Rafferent arteriole

- Initially: upregulation of RAAS and increased thromboxane A2 expression, but Vaughan et al (2004) did not reveal a significant effect of these mediators on renal hemodynamic response to obstruction


Obstruction induced increased Rafferent arteriole


Pathophysiology of Bilateral Ureteric Obstruction

Bilateral ureteric obstruction

↑ Intravascular Volume

↑ Atrial Natriuretic Peptide (ANP)
Pathophysiology of Bilateral Ureteric Obstruction

Nitric oxide

Atrial Natriuretic Peptide

Table 1. Renal functional parameters following bilateral ureteral obstruction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (N = 7)</th>
<th>BUO (N = 7)</th>
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</thead>
<tbody>
<tr>
<td>BUN mg/dL</td>
<td>23 ± 3</td>
<td>231 ± 9</td>
</tr>
<tr>
<td>S asymetric g/dL</td>
<td>0.35 ± 0.03</td>
<td>7.78 ± 3.56</td>
</tr>
<tr>
<td>P&lt;sub&gt;N&lt;/sub&gt; mg/ml</td>
<td>124.6 ± 22.8</td>
<td>261.1 ± 32.9</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Abbreviations are: N, number of rats; BUO, bilateral ureteral obstruction; BUN, blood urea nitrogen; S asym, serum asymetric; P<sub>N</sub>, plasma ANP.

*P < 0.05, **P < 0.01 vs. control.

Focus of Stone Centre Research Program is to develop novel approaches to improve the treatment of kidney stone disease.

Includes ureteral stent biomaterial design and most recently how the ureter responds to indwelling stents and obstruction.

Primary Focus On Indwelling Stents

Purpose of ureteral stents is to drain the kidney in the presence of an obstruction or post-op following stone removal.

Stents associated with significant patient discomfort/severe pain.

Known Causes: Irritation of urothelium as stent moves inside ureter and bladder.

Unknown Causes: ?
**Stent-Induced Hydronephrosis and Peristalsis**

- despite stents maintaining drainage past an obstruction they themselves trigger hydronephrosis

**Targeting Hedgehog Signaling**

Sonic hedgehog regulates proliferation and differentiation of mesenchymal cells in the mouse metanephric kidney

- Inactivation of Hedgehog results in hydrometer and hydronephrosis
- Caused by ureteral aperistalsis
Specific Research Questions

- Considering that stents are supposed to facilitate urinary flow, why do they stop peristalsis?
- What are the molecular mechanisms that regulate ureteral peristalsis?

Studied Gli-1 Expression in Stented and Unstented Ureters

- Gli-1 expression in ureteral smooth muscle decreases with stent indwelling time
- Recovers following Removal of stent
### Functional Consequences

- **Unstented**
- **48 hr stented**
- **7 day stented**

### Summary of Findings

- Indwelling stents dilate the ureter (desirable)
- Stretches ureteral smooth muscle resulting in overall dysfunction and peristalsis (undesirable)
- Decreased peristalsis = lower urine flow and increased reflux resulting in hydronephrosis
- Can we target molecular pathways (i.e. Gli-1) to maintain peristalsis with a stent in place = improved urine flow and less patient discomfort
How Does Ureter Respond To Ureteral Obstruction?

- Disruption of ureteral peristalsis
- Reduction and/or cessation of urine flow from kidney to bladder
- Increased pressure on the kidneys and hydroureteronephrosis
- Renal injury, dysfunction and eventual failure

Common Research Focus:
Effect of ureteral obstruction on kidney function

What we don’t know:
- How does the ureter respond to obstruction?
- How does the ureter recover following obstruction?

Ureteral Recovery Following Obstruction Reversal

- obstructed ureters of mice for 24 hrs, 48 hrs, and 72 hrs, followed hydronephrosis via ultrasound and quantified peristalsis
Summary of Findings

- Refutes hypothesis that resolution of hydronephrosis normal ureteral function
- Ureteral dysfunction = decreased urine flow
- Potentially prolonged negative effects on kidney function
- CAN WE ACCELERATE RECOVERY FOLLOWING OBSTRUCTION REVERSAL?

Can Recovery Be Enhanced Via Pharmacological Intervention?

Erythropoietin (EPO): Protective Effects in other organs

Erythropoietin restores bowel damage and hyperperistalsis in gastroschisis

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EPO Treatment Accelerates Resolution of Hydronephrosis

- Gave 20IU EPO to mice on 4 consecutive days pre-obstruction and obstructed for 24 hrs, 48 hrs, and 72 hrs.
- Followed recovery using ultrasound and quantifying peristalsis

EPO Accelerates Recovery of Ureteral Function

- Time for ureteral peristalsis to return to normal levels accelerated in EPO treated animals
Continued Research

• Intention is not to promote use of EPO for patients with obstruction (significant side-effect profile and costly)

• Studying EPO-induced molecular mechanisms that regulate ureteral protection and accelerated recovery

• Potential targets for less expensive, safer and more effective future therapeutic agents

• Current studies in the lab aimed at understanding molecular mechanisms regulating ureteral dysfunction following obstruction (including members of Hedgehog pathway) and how they are changed by EPO.

• Also obtaining ethics for human ureteral tissue from transplant donors (unused tissue) to study EPO treatment on peristaltic activity using tissue baths

Acknowledgements

• Dr. Ben Chew

• Dr. Chun Seow (Pathology & Laboratory Medicine)

• Stone Centre Research Lab:
  • Joey Lo
  • Elliya Park
  • David Choy
  • Dr. Claudia Janssen (now in Mainz, Germany)