Kidney Stress Testing

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Disclosures

• Nxstage Medical, Astute Medical, and Baxter Medical.

• La Jolla Pharmaceutical – Employer (Sabbatical)
Stress Testing

• For acute coronary syndrome (ACS) –
• Severity of disease if often confirmed with stress testing  
  – Does the patient have a critical lesion?  
  – Treadmill? Dobutamine?

• Most common forms of AKI involve tubular injury
GFR versus Time

![Graph showing GFR over 24 hours with peaks at 12p and 7p, and a baseline at 7am.](image-url)
Fig. 1

Normal Conditions | Physiological Stress | Pathological Stress

- Drugs
- Pregnancy
- Exercise
- High altitude
- Stress echo

- Drugs
- Pregnancy
- High protein diet
- Aging
- High CO

- Hypertension
- Sepsis
- Anemia
- Hemorrhage
- Ischemia

- Diabetes
- CKD
- AKI
- C-R Syndrome
- Hyperfiltration

Functional reserve utilization
Protein Consumption (gms/kg)

Baseline GFR

Maximum GFR

Bosch Limit

Renal Functional Reserve
Tubular Reserve?
Stimulation of tubular secretion of creatinine in health and in conditions associated with reduced nephron mass. Evidence for a tubular functional reserve

José Herrera and Bernardo Rodríguez-Iturbe

Renal Service and Laboratory, Hospital Universitario and Instituto de Investigaciones Biomédicas (INBIOMED), Fundación para la Ciencia y Tecnología (FUNDACITE-Zulia), Maracaibo, Venezuela
Fig. 1. Inulin ($C_{in}$, open symbols) and creatinine ($C_{cr}$, closed symbols) clearances in normal individuals (controls) and patients with chronic renal failure (patients) before and after a test meal meal. After the meal, $C_{in}$ increases in controls and patients. In contrast, $C_{cr}$ increases in controls but remains unchanged in the patients. Data of kidney donors (not shown) fall between these two groups.
Tubular stress test detects subclinical reduction in renal functioning mass

Bernardo Rodríguez-Iturbe, José Herrera, Crispín Marín, and Reinaldo Mañalich

Renal Service and Laboratory, Hospital Universitario and Instituto de Investigaciones Biomédicas (INBIOMED), Maracaibo, Venezuela
Fig. 5. GFR (A) and $C_r$ (B) in normals (□, $N = 14$), KDs (○, $N = 7$), and transplant patients (■, $N = 11$) during the tubular stress test. Values are mean ± SD.
Kidney Reserve Testing

• Glomerular Reserve
  – Can be tested with protein loading or i.v. amino acids

• Tubular Reserve
  • Can be tested with protein loading or i.v. creatinine

• Does loss of reserve matter?
  – Reveals vulnerability
  – Opportunity to Intervene
  – Examples: pre-diabetes and diminished FEV$_1$
Furosemide Induced Stress Test

For AKI, aim to test tubular integrity
- specifically PCT
- S1, S2, and S3
- TAL

Stress Testing in AKI?

- Furosemide is not filtered
- Tightly protein bound
- Must be actively secreted by HOAT
- Secreted in S1-S3 segments of PCT
Hypothesis

• Renal tubular integrity can be tested with a functional test
• The response or lack of response to furosemide as measured by urine output may indicate severity of tubular injury before serum creatinine and urine output
• The primary outcome was the progression to AKIN stage III within 14 days of FST.
• The secondary outcome was the composite of achieving stage AKIN III or death within 14 days of the FST.
Furosemide Stress Test Receiver Operation Characteristics for Progression to AKIN Stage III

<table>
<thead>
<tr>
<th>Urine Output</th>
<th>ROC AUC (s.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One Hour</td>
<td>0.82 (0.05)</td>
</tr>
<tr>
<td>Two Hours</td>
<td>0.87 (0.05)</td>
</tr>
<tr>
<td>Three Hours</td>
<td>0.86 (0.05)</td>
</tr>
<tr>
<td>Four Hours</td>
<td>0.86 (0.05)</td>
</tr>
<tr>
<td>Five Hours</td>
<td>0.85 (0.05)</td>
</tr>
<tr>
<td>Six Hours</td>
<td>0.85 (0.05)</td>
</tr>
</tbody>
</table>
## Sensitivity and Specificity of Two Hour Urine Thresholds for Progression to AKIN Stage III

<table>
<thead>
<tr>
<th>Total Urine Output over 2 hours</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 ml</td>
<td>90.2%</td>
<td>60.0%</td>
</tr>
<tr>
<td>&lt;200 ml</td>
<td>87.1%</td>
<td>84.1%</td>
</tr>
<tr>
<td>&lt;300 ml</td>
<td>85.3%</td>
<td>88.0%</td>
</tr>
<tr>
<td>&lt;400 ml</td>
<td>66.7%</td>
<td>88.0%</td>
</tr>
<tr>
<td>&lt;500 ml</td>
<td>50.5%</td>
<td>88.0%</td>
</tr>
</tbody>
</table>
Furosemide Stress Test and Biomarkers for the Prediction of AKI Severity

Jay L. Koyner,* Danielle L. Davison,† Ermira Brasha-Mitchell,† Divya M. Chalikonda,† John M. Arthur,‡ Andrew D. Shaw,§ James A. Tumlin,‖ Sharon A. Trevino,* Michael R. Bennett,¶ Paul L. Kimmel,** Michael G. Seneff,† and Lakhmir S. Chawla††

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ABSTRACT
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC±SEM</th>
<th>P Value for Biomarker Alone</th>
<th>P Value Compared With FST alone</th>
<th>AUC of Biomarker and FST±SEM</th>
<th>P Value for Biomarker and FST Compared With FST Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>FST (2-hr UOP)</td>
<td>0.87±0.05</td>
<td>&lt;0.001</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Urine NGAL</td>
<td>0.65±0.06</td>
<td>0.04</td>
<td>0.002</td>
<td>0.84±0.05</td>
<td>0.10</td>
</tr>
<tr>
<td>Urine IL-18</td>
<td>0.65±0.07</td>
<td>0.04</td>
<td>0.009</td>
<td>0.85±0.05</td>
<td>0.89</td>
</tr>
<tr>
<td>Urine KIM-1</td>
<td>0.63±0.06</td>
<td>0.07</td>
<td>0.007</td>
<td>0.86±0.05</td>
<td>0.79</td>
</tr>
<tr>
<td>Uromodulin</td>
<td>0.54±0.07</td>
<td>0.54</td>
<td>0.002</td>
<td>0.85±0.05</td>
<td>0.94</td>
</tr>
<tr>
<td>Urine IGFBP-7</td>
<td>0.62±0.09</td>
<td>0.20</td>
<td>&lt;0.001</td>
<td>0.88±0.05</td>
<td>0.57</td>
</tr>
<tr>
<td>Urine TIMP-2</td>
<td>0.70±0.08</td>
<td>0.03</td>
<td>0.02</td>
<td>0.83±0.06</td>
<td>0.20</td>
</tr>
<tr>
<td>Urine IGFBP-7×TIMP-2</td>
<td>0.69±0.08</td>
<td>0.04</td>
<td>0.01</td>
<td>0.90±0.06</td>
<td>0.35</td>
</tr>
<tr>
<td>Urine Creatinine</td>
<td>0.48±0.08</td>
<td>0.77</td>
<td>&lt;0.001</td>
<td>0.84±0.06</td>
<td>0.85</td>
</tr>
<tr>
<td>Urine ACR</td>
<td>0.56±0.07</td>
<td>0.45</td>
<td>0.002</td>
<td>0.84±0.06</td>
<td>0.32</td>
</tr>
<tr>
<td>FeNa</td>
<td>0.51±0.07</td>
<td>0.92</td>
<td>&lt;0.001</td>
<td>0.83±0.06</td>
<td>0.47</td>
</tr>
<tr>
<td>Plasma NGAL</td>
<td>0.75±0.08</td>
<td>0.007</td>
<td>0.10</td>
<td>0.86±0.07</td>
<td>0.53</td>
</tr>
</tbody>
</table>

NA, not applicable; ACR, albumin-to-creatinine ratio.
Key Points

• The furosemide stress test (FST) is feasible and well tolerated in critically ill patients with early AKI.

• The performance of the FST to predict the primary outcome was robust and consistent in both cohorts, with a range in ROC AUC of 0.82-0.87.

• Patients should be euvoletic before undertaking any type of furosemide challenge, and that volume replacement is mandatory in patients who are not obviously volume overloaded.

• FST should be conducted in an appropriate clinical setting where UO, heart rate, and blood pressure can be monitored frequently.

• FST is a novel functional assessment of tubular function that appears to have good predictive capacity to identify those patients that will progress to advanced stage AKI. Further validation studies of the FST are warranted.
AKI Diagnostics

• Pre-test Probability Schemes will improve the performance of AKI biomarkers
  – Renal Angina
  – Risk Biomarker

• AKI Stress Testing Provides a Framework for Confirmatory Testing
FST and CKD?
Degree of Fibrosis is one the best predictors of long-term kidney survival
Atubular Glomeruli in CKD

Behzad Najafian et al. JASN 2003;14:908-917

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Fibrosis and Tubular Function

• Hypothesis
  – Furosemide secretion in patients with CKD is a surrogate for tubular functional reserve
  – Tubular Functional Reserve is representative of the degree of fibrosis
Next Steps

• Validation of FST in AKI
• Pilot Studies of FST in patients undergoing kidney biopsy
• Pilot studies of use of AKI in the prediction of DGF in kidney allograft transplantation
• FST in patients with advanced CKD – attempt to predict time RRT initiation
Kidney Stress Testing

• KST may reveal a state of ‘pre-CKD’
• Renal reserve testing in conjunction with biomarkers such as albuminuria and others may allow early intervention
• Tubular stress testing may be on benefit in both AKI and CKD for predicting outcomes and informing clinicians about optimal intervention