Kidney Stress Testing

Lakhmir S. Chawla, MD
Professor of Medicine
Veterans Affairs Medical Center
Washington DC

Disclosures

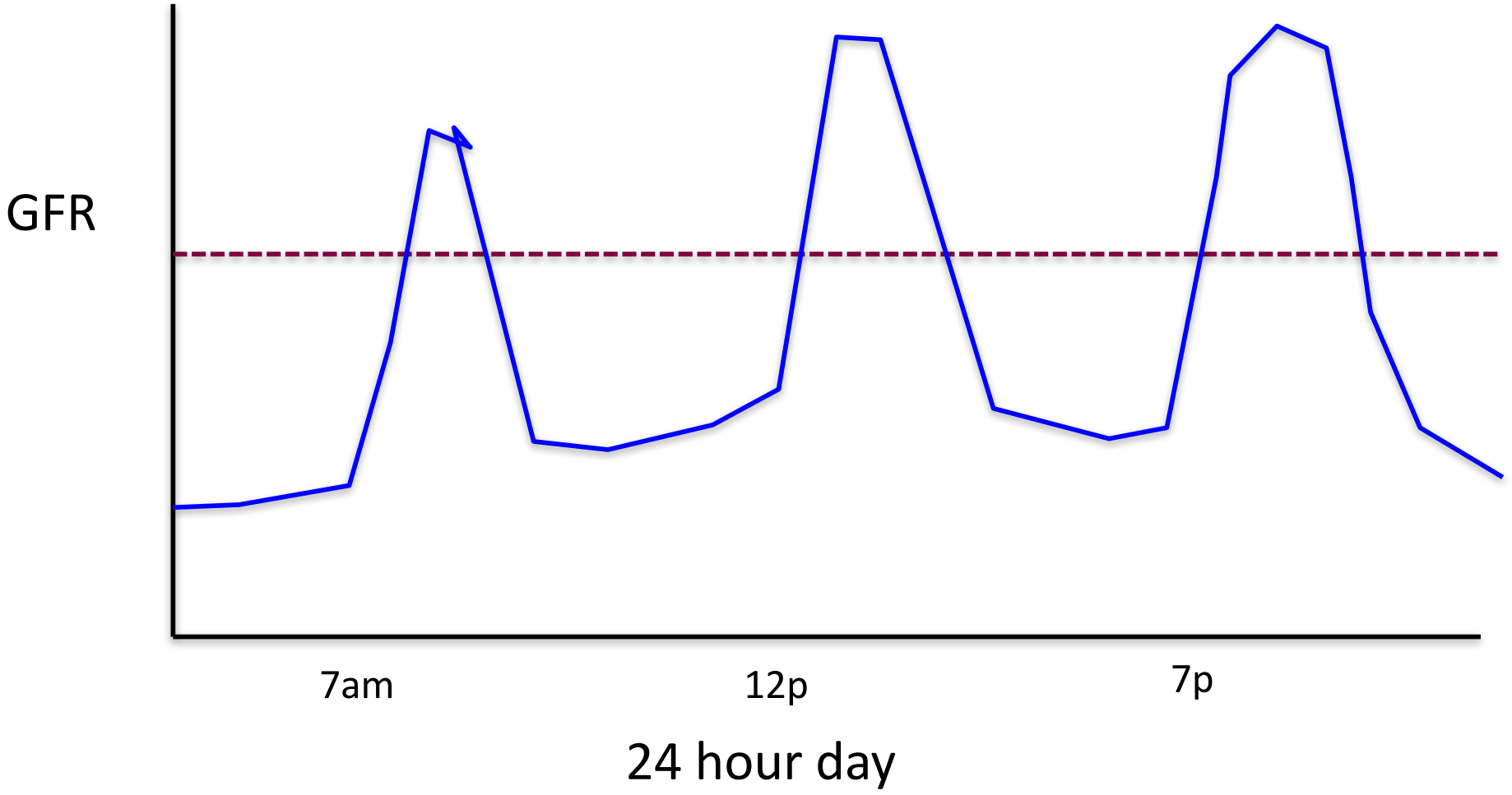
- Nxstage Medical, Astute Medical, and Baxter Medical.
- La Jolla Pharmaceutical – Employer (Sabbatical)

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



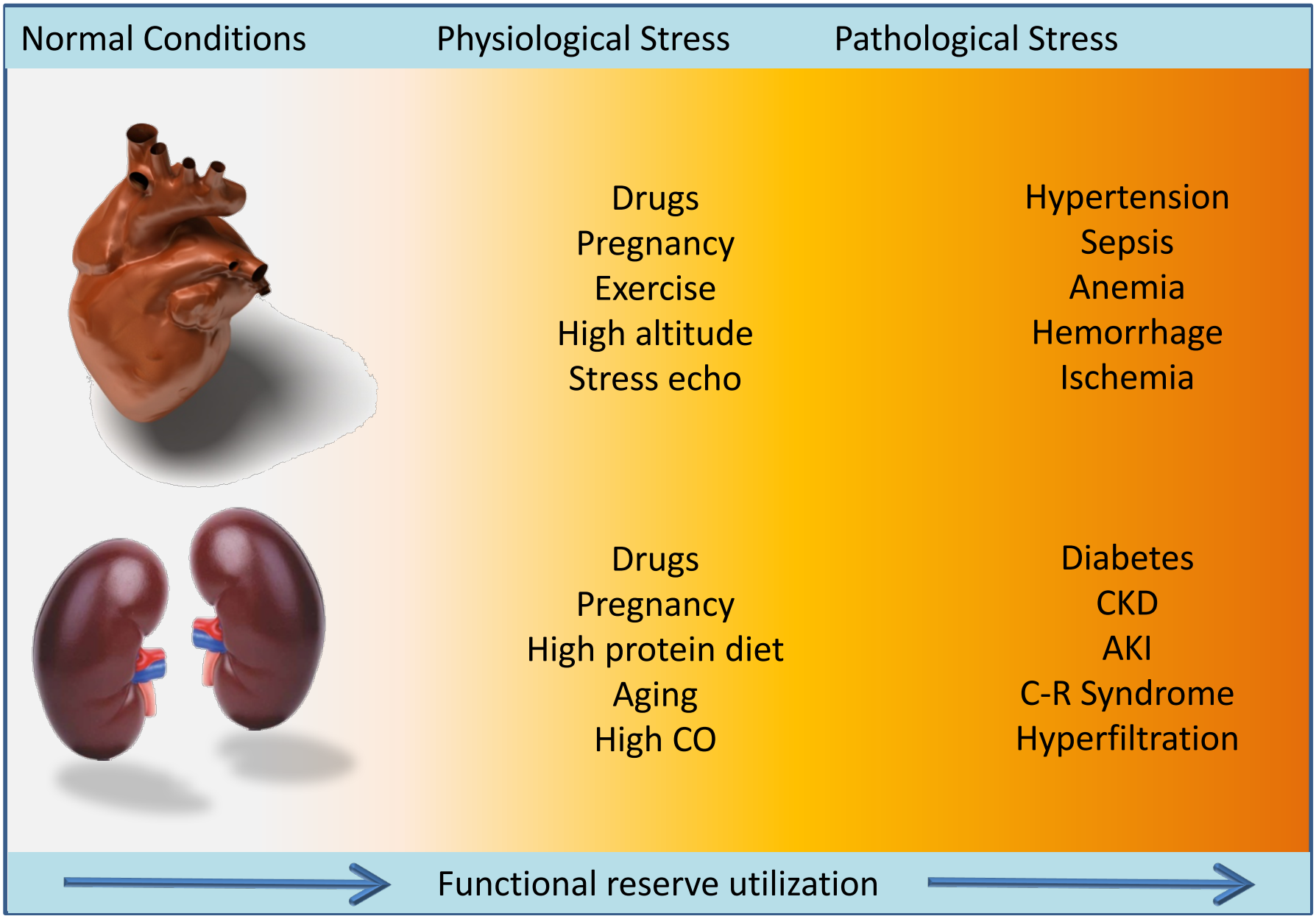
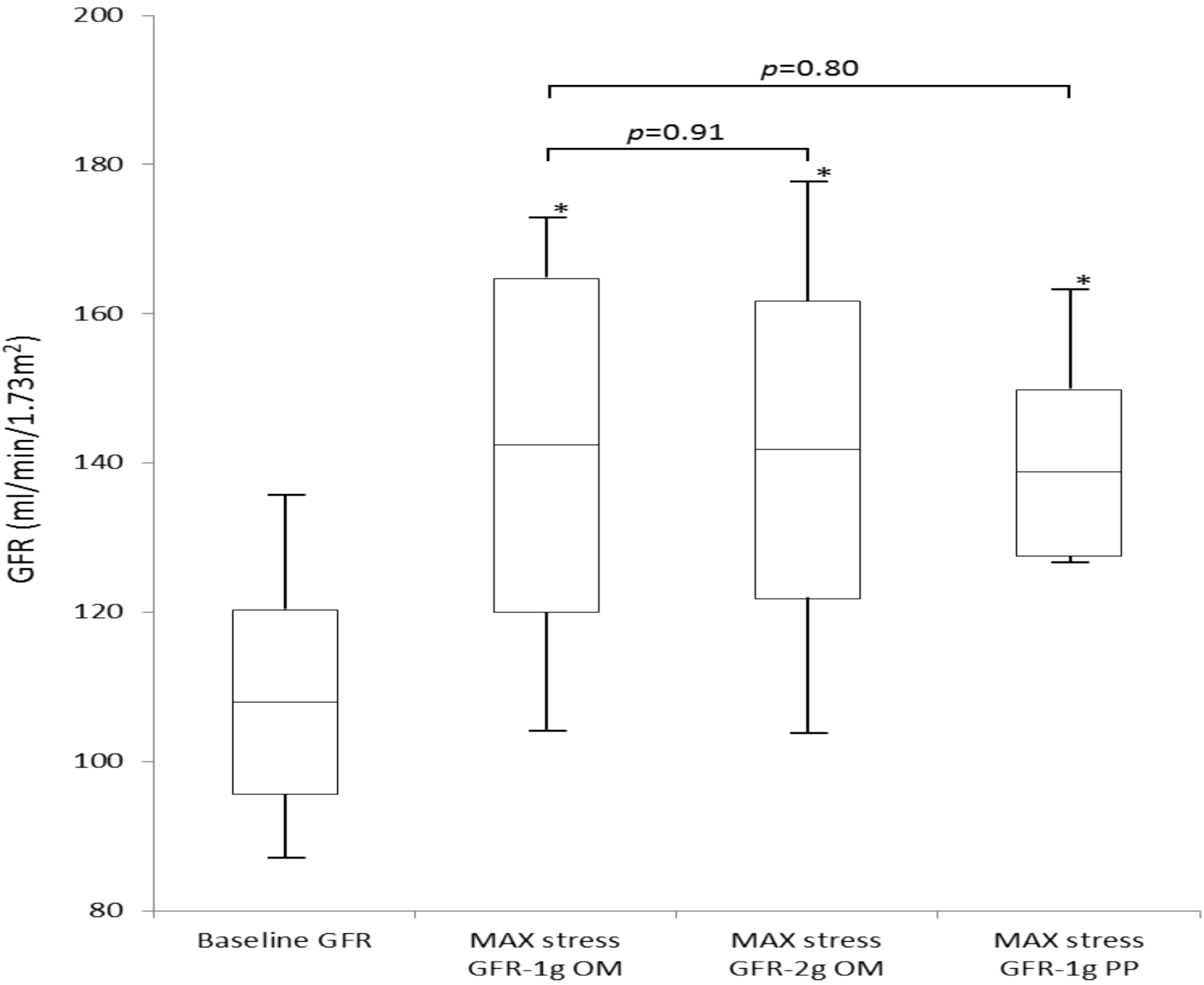
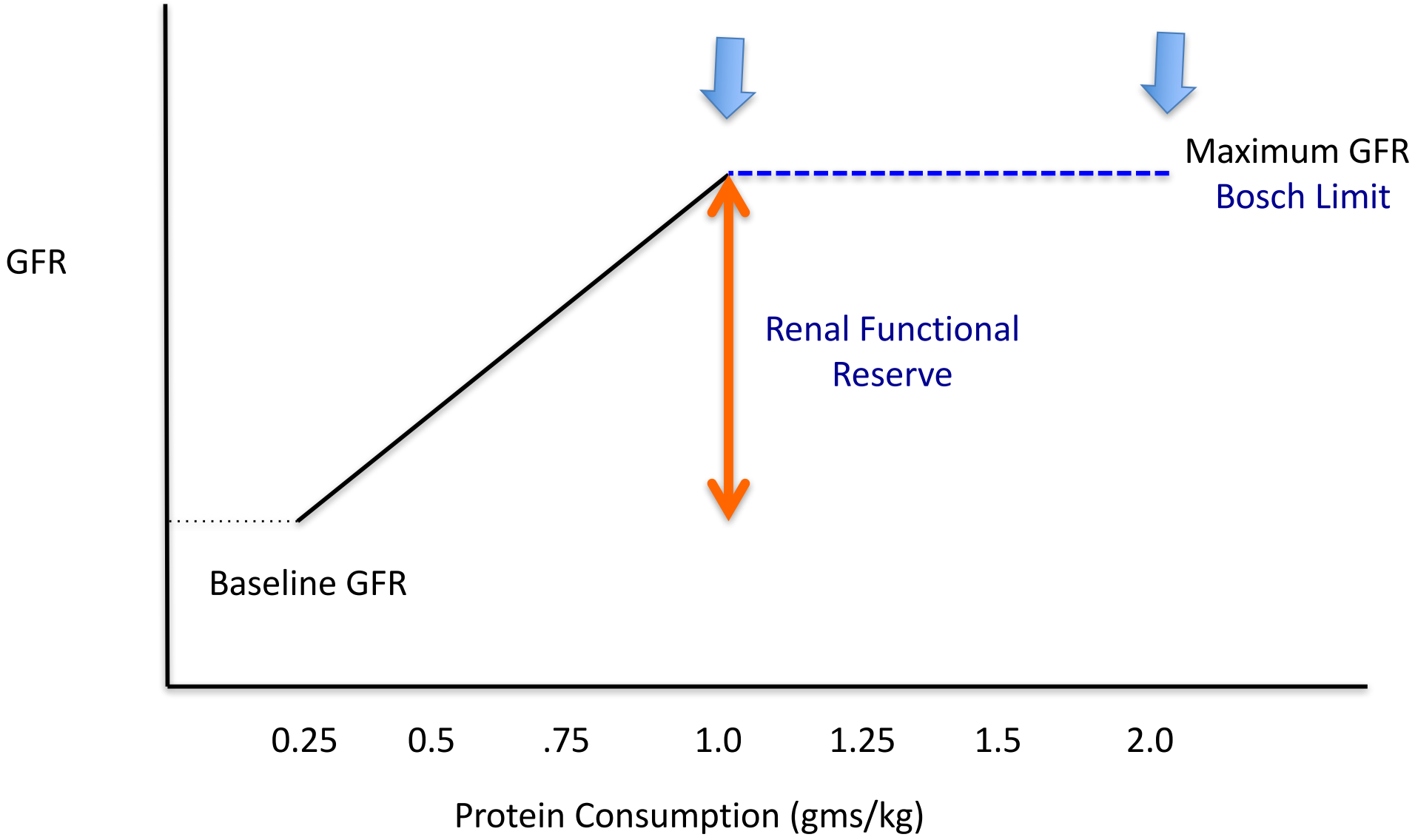
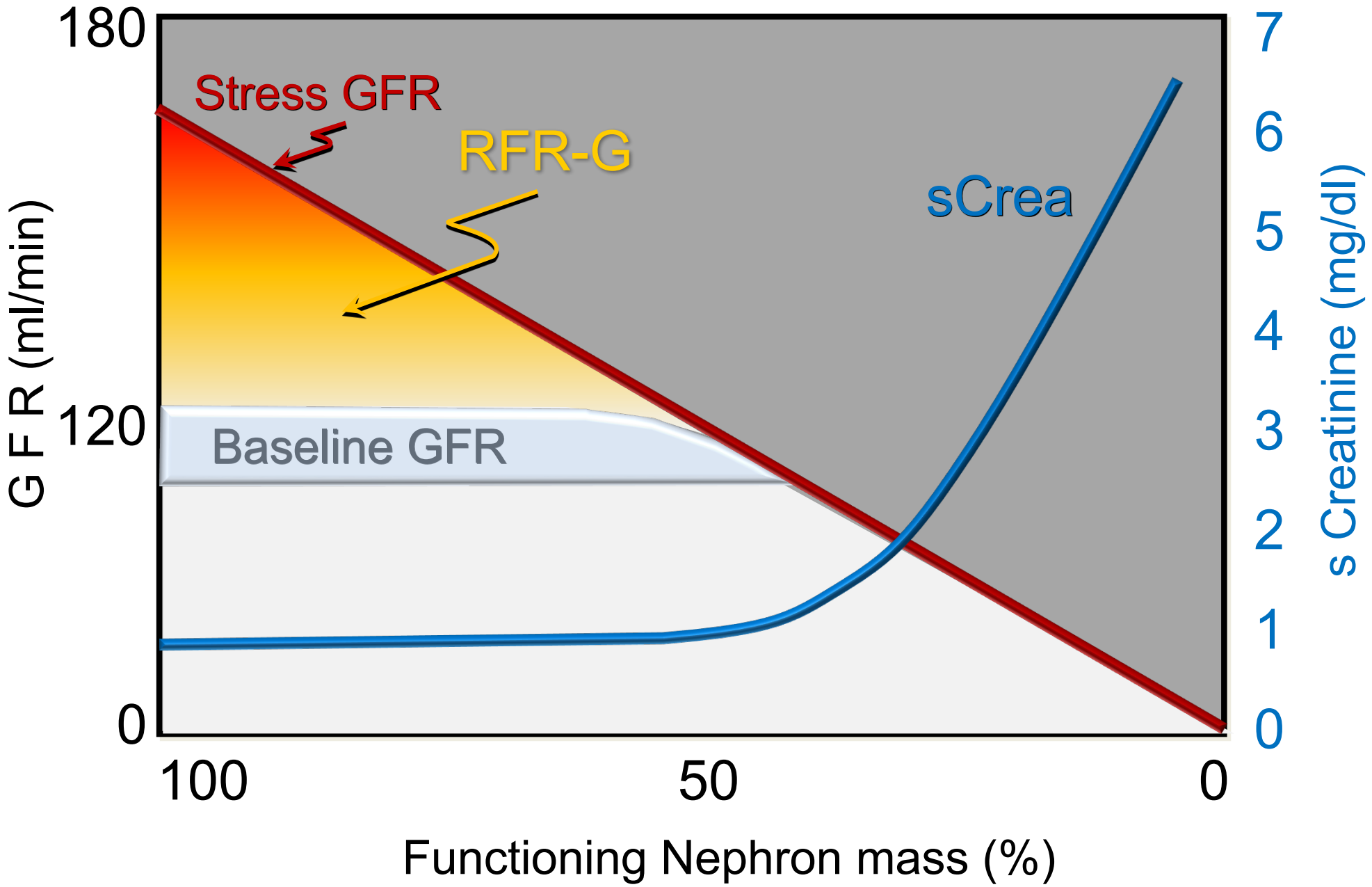

Normal Conditions
Physiological Stress
Pathological Stress
Drugs
Pregnancy
Exercise
High altitude
Stress echo
Hypertension
Sepsis
Anemia
Hemorrhage
Ischemia
Drugs
Pregnancy
High protein diet
Aging
High CO
Diabetes
CKD
AKI
C-R Syndrome
Hyperfiltration
Functional reserve utilization

Fig. 1


200
180
160
140
120
100
80
GFR (ml/min/1.73m²)
p=0.80
p=0.91
*
*
*
Baseline GFR
MAX stress GFR-1g OM
MAX stress GFR-2g OM
MAX stress GFR-1g PP


GFR
Maximum GFR
Bosch Limit
Renal Functional
Reserve
Baseline GFR
0.25
0.5
.75
1.0
1.25
1.5
2.0
Protein Consumption (gms/kg)


180
120
0
G F R (ml/min)
Stress GFR
RFR-G
Baseline GFR
sCrea
7
6
5
4
3
2
1
0
s Creatinine (mg/dl)
100
50
0
Functioning Nephron mass (%)

Tubular Reserve?

Nephrol Dial Transplant (1998) 13: 623–629

Nephrology
Dialysis
Transplantation

Original Article

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

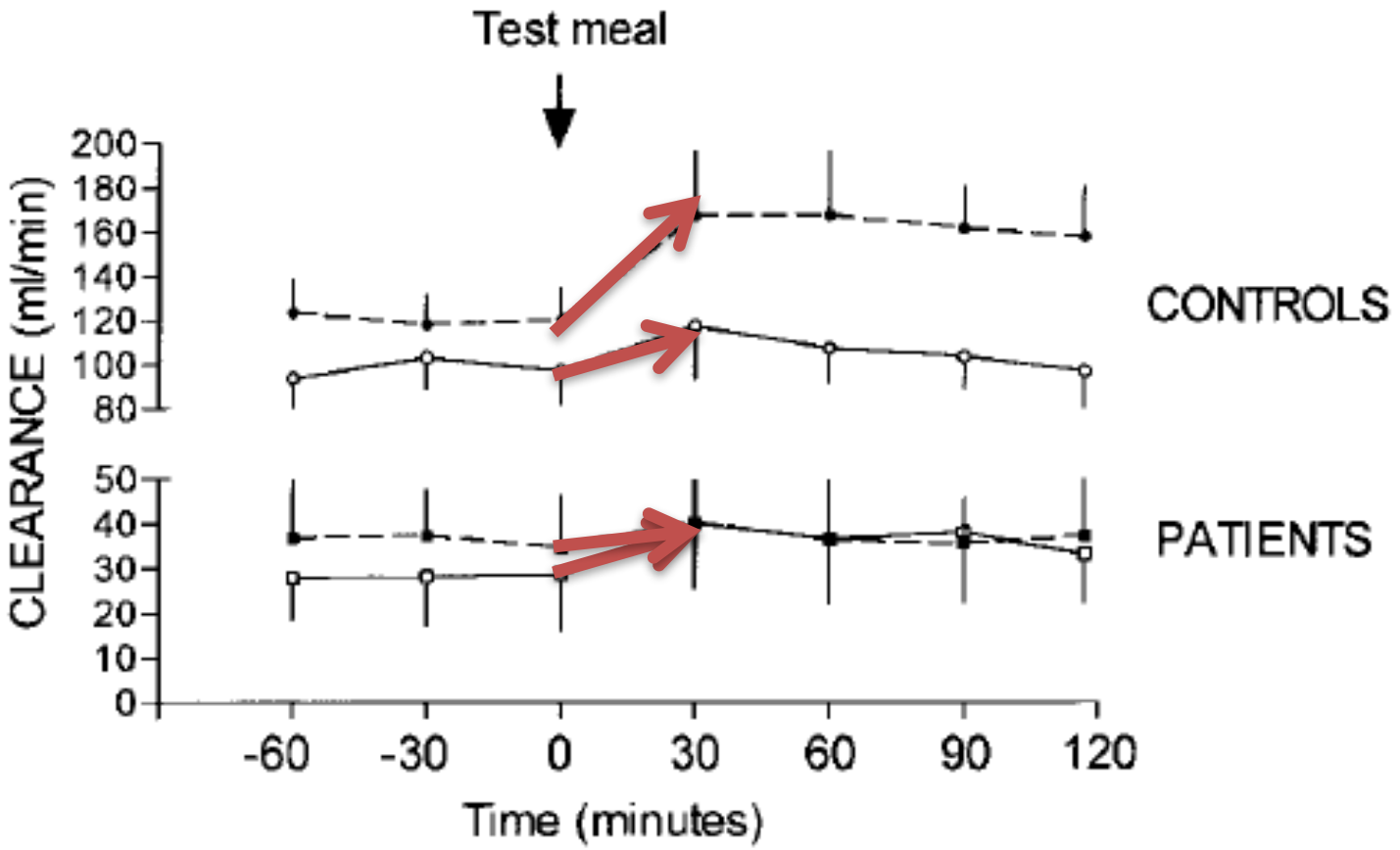


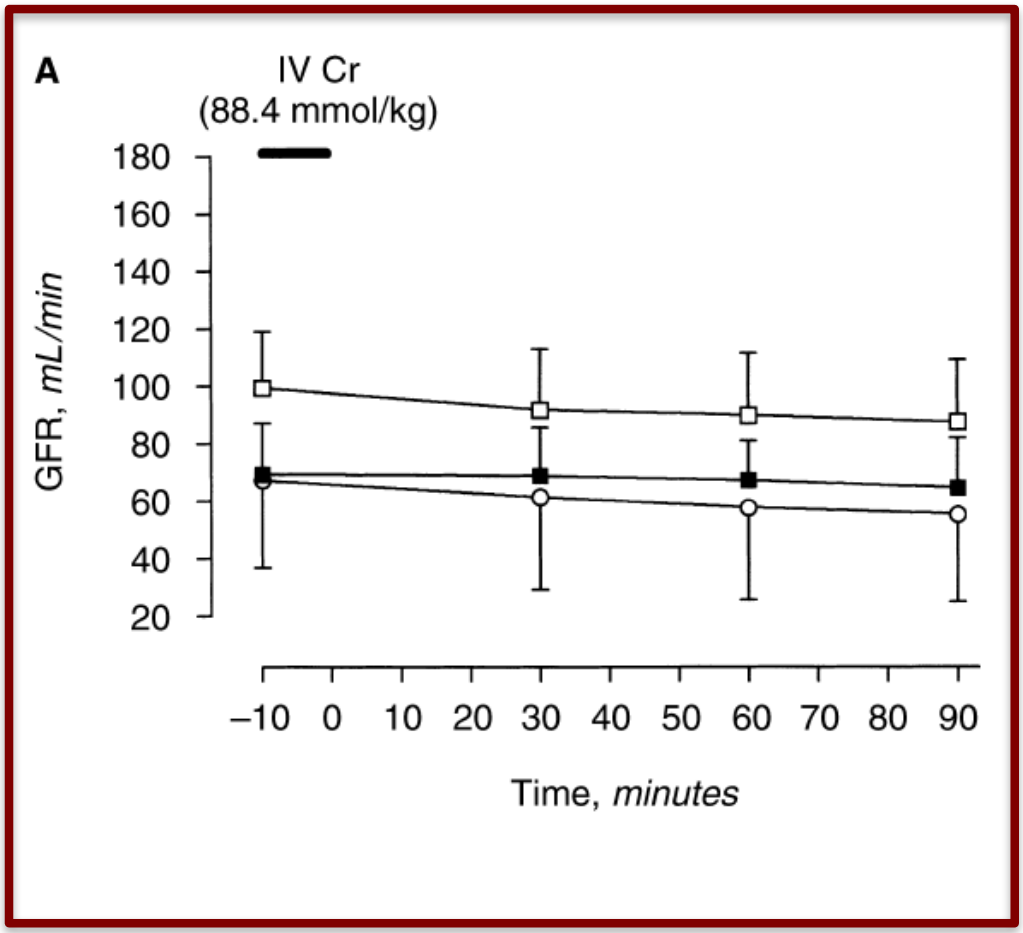
Fig. 1. Inulin (C_{in}, open symbols) and creatinine (C_{cr}, closed symbols) clearances in normal individuals (controls) and patients with chronic renal failure (patients) before and after a test meat meal. After the meal, C_{in} increases in controls and patients. In contrast, C_{cr} increases in controls but remains unchanged in the patients. Data of kidney donors (not shown) fall between these two groups.

Kidney International, Vol. 59 (2001), pp. 1094–1102

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



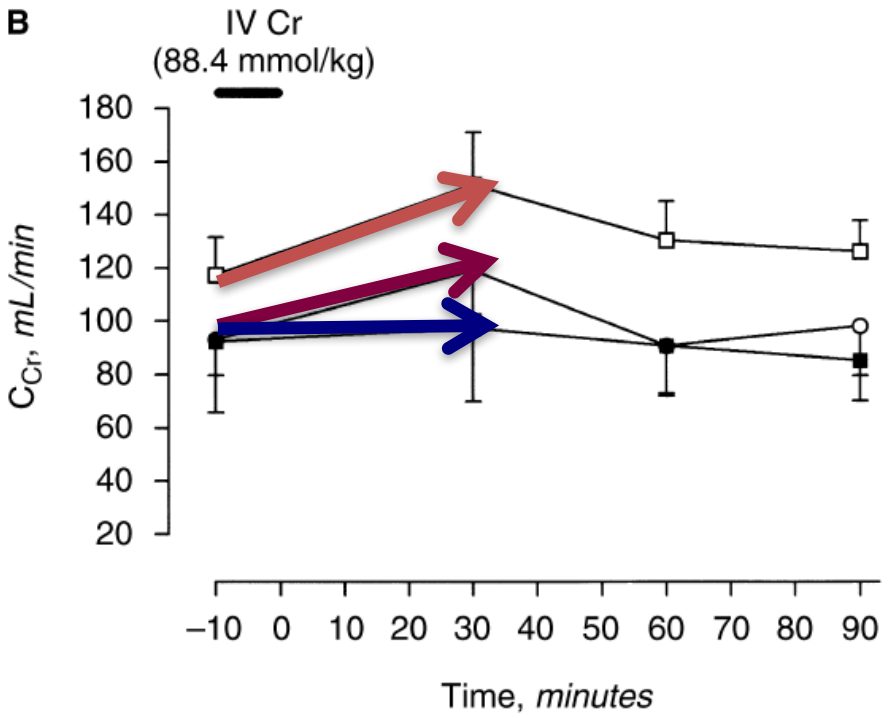


Fig. 5. GFR (*A*) and C_{Cr} (*B*) in normals (□, *N* = 14), KDs (○, *N* = 7), and transplant patients (■, *N* = 11) during the tubular stress test. Values are mean ± SD.

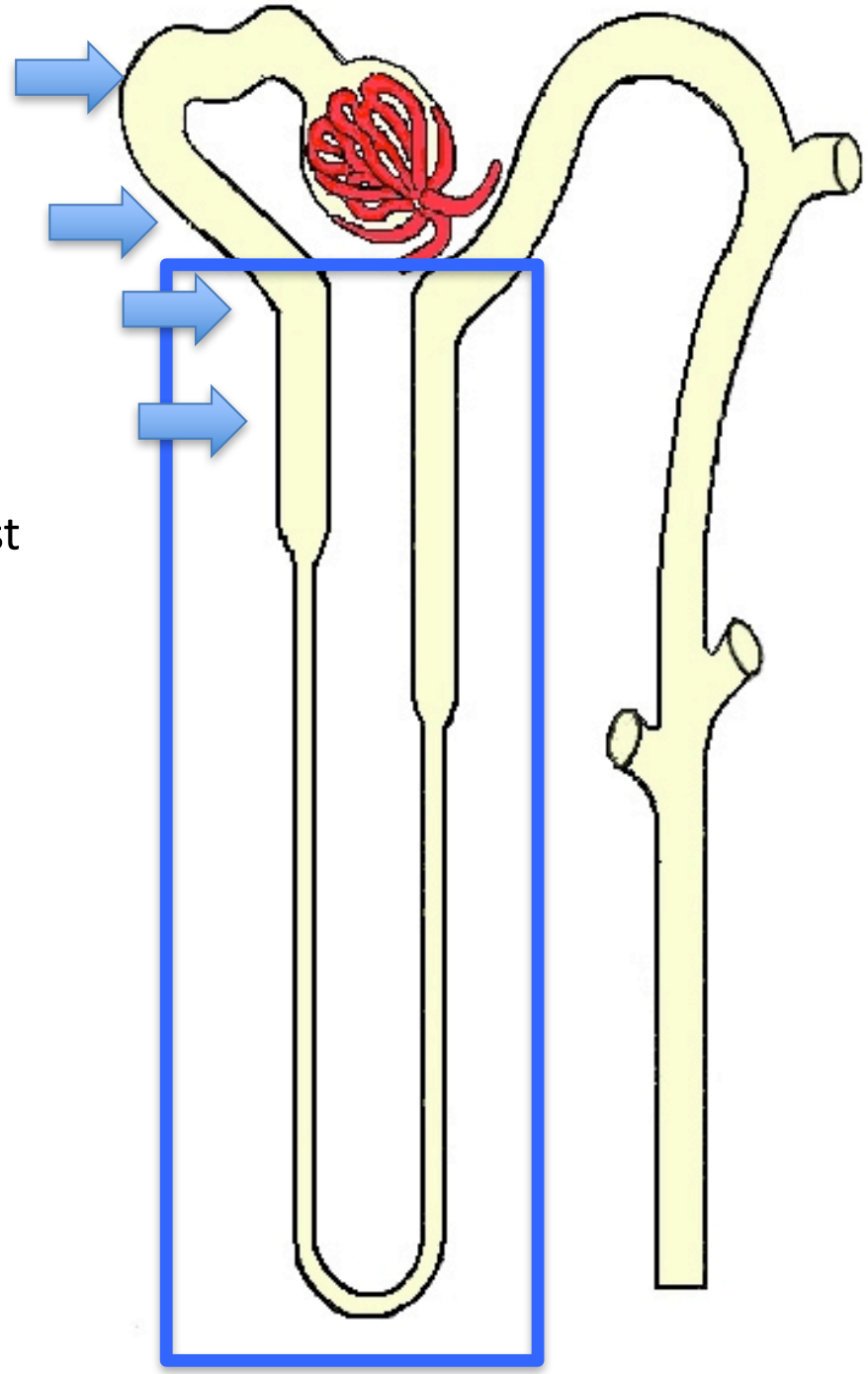
Kidney Reserve Testing

- 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

Stress Testing in AKI?

Furosemide Induced Stress Test



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

For AKI, aim to test tubular integrity

-specifically PCT
-S1, S2, and S3
-TAL

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

Chawla *et al. Critical Care* 2013, **17**:R207
http://ccforum.com/content/17/5/R207

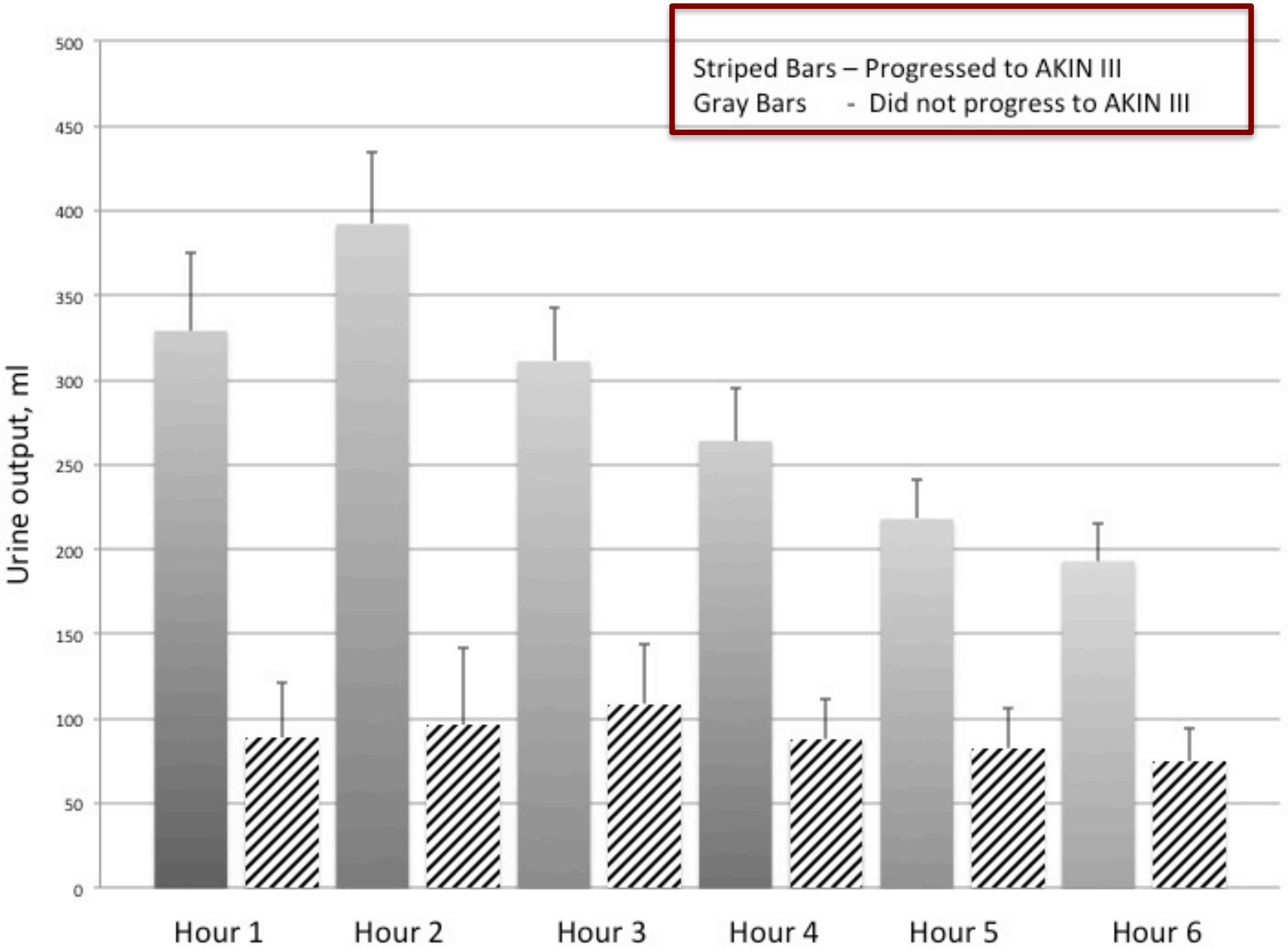
CRITICAL CARE

RESEARCH Open Access

Development and Standardization of a Furosemide Stress Test to Predict the Severity of Acute Kidney Injury

Lakhmir S Chawla[1,2*], Danielle L Davison[1], Ermira Brasha-Mitchell[1], Jay L Koyner[3], John M Arthur[4], Andrew D Shaw[5], James A Tumlin[6], Sharon A Trevino[3], Paul L Kimmel[7] and Michael G Seneff[1]

- 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.


Striped Bars – Progressed to AKIN III
Gray Bars - Did not progress to AKIN III
Urine output, ml
500
450
400
350
300
250
200
150
100
50
0
Hour 1
Hour 2
Hour 3
Hour 4
Hour 5
Hour 6

Furosemide Stress Test Receiver Operation Characteristics for Progression to AKIN Stage III

Urine Output		ROC AUC (s.e.)
One Hour		0.82 (0.05)
Two Hours		0.87 (0.05)
Three Hours		0.86 (0.05)
Four Hours		0.86 (0.05)
Five Hours		0.85 (0.05)
Six Hours		0.85 (0.05)

Sensitivity and Specificity of Two Hour Urine Thresholds for Progression to AKIN Stage III

Total Urine Output over 2 hours	Sensitivity	Specificity
≤100 ml	90.2%	60.0%
<200 ml	87.1%	84.1%
<300 ml	85.3%	88.0%
<400 ml	66.7%	88.0%
<500 ml	50.5%	88.0%

CLINICAL RESEARCH www.jasn.org

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††

*Section of Nephrology, Department of Medicine, University of Chicago, Chicago, Illinois; †Department of Anesthesiology and Critical Care Medicine and **Department of Medicine, George Washington University Medical Center, Washington DC; ‡Division of Nephrology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; §Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee; ‖Renal Division, University of Tennessee College of Medicine at Chattanooga, Chattanooga, Tennessee; ¶Division of Nephrology and Hypertension, Cincinnati Children's Hospital, Cincinnati, Ohio; and ††Department of Medicine, Division of Intensive Care Medicine and Division of Nephrology, Washington DC Veterans Affairs Medical Center, Washington, DC

ABSTRACT

Table 2. AUCs for prediction of progression to AKI stage 3

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

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 euvolemic 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.

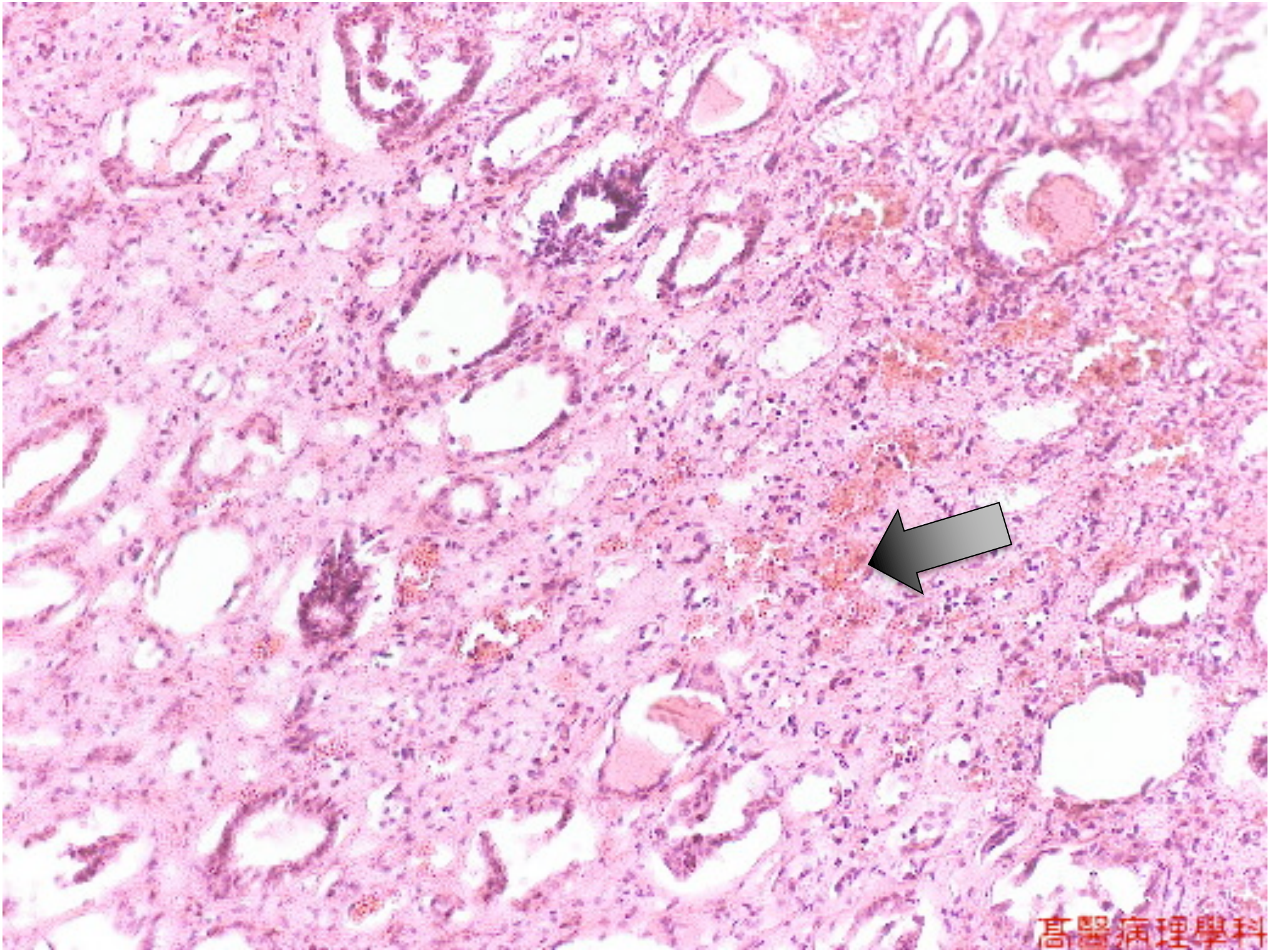
AKI Diagnostics

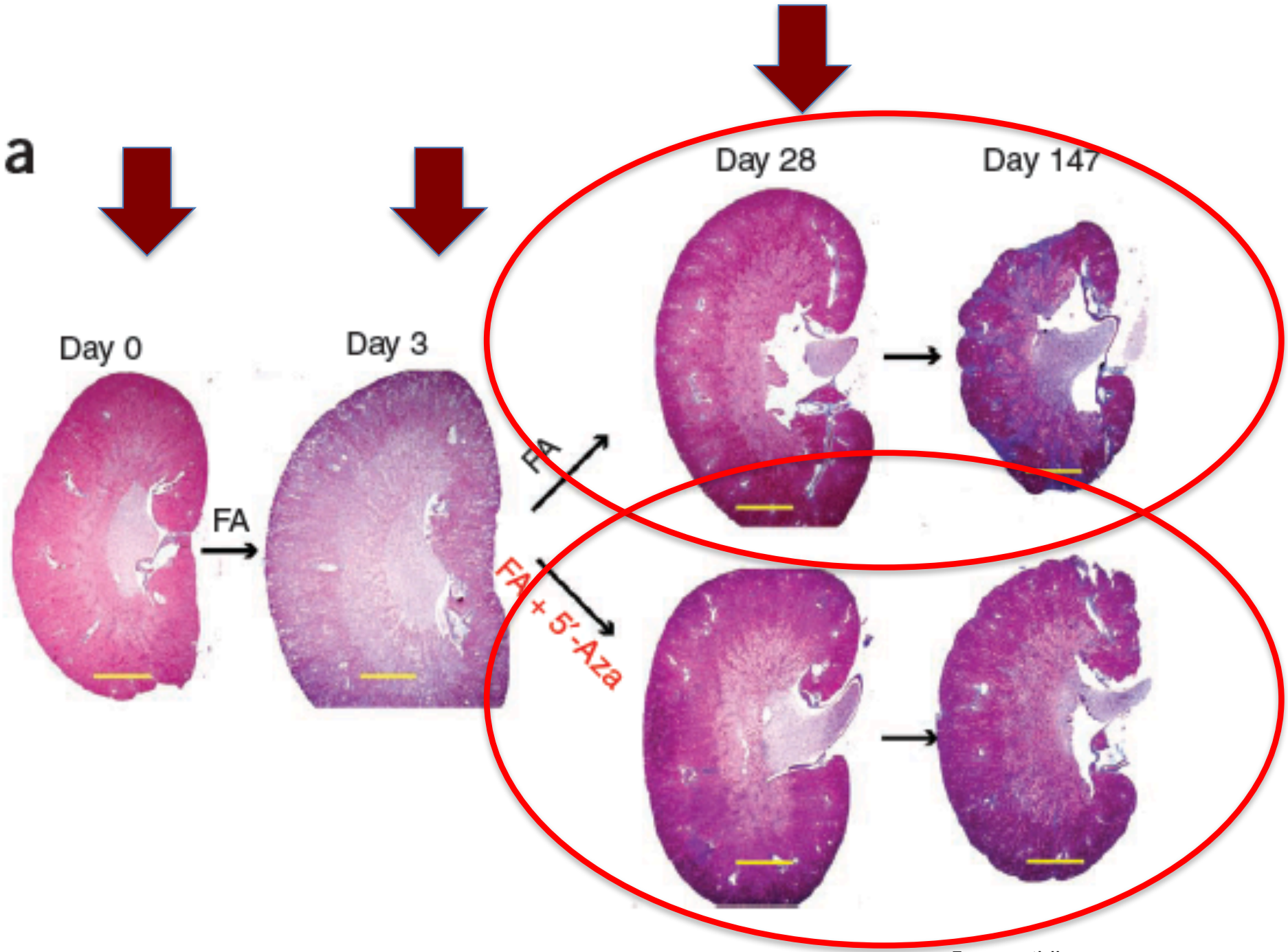
- Pre-test Probability Schemes will improve the performance of AKI biomarkers
  - Renal Angina
  - Risk Biomarker
- AKI Stress Testing Provides a Framework for Confirmatory Testing

FST and CKD?

Fibrosis and and Tubular Function

- Degree of Fibrosis is one the best predictors of long-term kidney survival

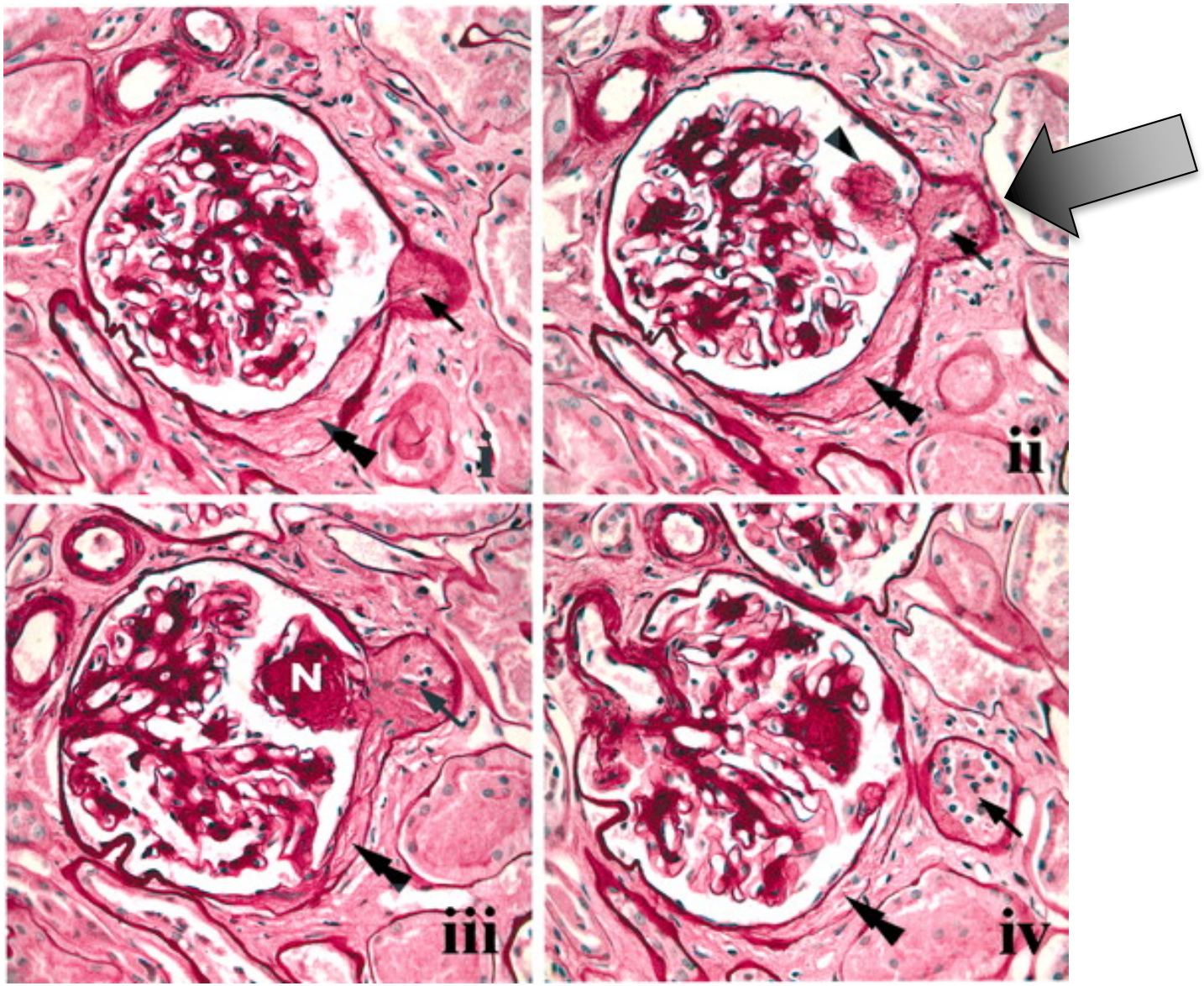

高醫病理學科



Bechtel, Nature Medicine 16, 544–550 (2010)

5 azacytidine

Atubular Glomeruli in CKD



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

JASN

Fibrosis and 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 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