Renal Grand Round, 2016

Role of Uric Acid in Acute Kidney Injury?

A. Ahsan Ejaz, M.D

Division of Nephrology, Hypertension and Transplantation

University of Florida, Gainesville, Florida, U.S.A.

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UNIVERSITY of FLORIDA

Outline

- The crystal-dependent role of uric acid-related diseases
- The crystal-independent role of uric acid-related diseases
  - Acute kidney injury
    - Experimental studies
    - Clinical studies

AKI= acute kidney injury; SUA = serum uric acid

The emergence of the relevancy of uric acid

Scarcity of Vitamin C

Natural selection favored human individuals who could repair arteries with a layer of lipid

Survival benefit?

4th ice age, 20 million years ago

Subsequent million years:

Mutation of L-gulonolactone Oxidase: Loss of ability to synthesize Vit C in humans

Humans can not synthesize Vitamin C, nor degrade uric acid

Adenosine

↓

Inosine

↓

Hypoxanthine

↓ XO

Xanthine

↓ XO

Uric acid

~~↓~~ Urate Oxidase

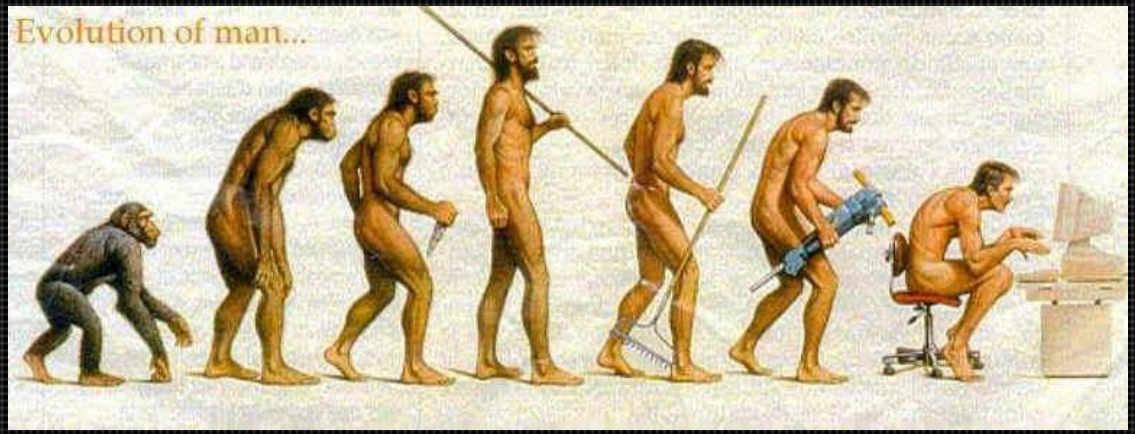
↓

Allantoin

The loss of the ability to synthesize ascorbic acid parallels the loss of the ability to degrade uric acid due to mutation of the gene encoding for uricase / urate oxidase

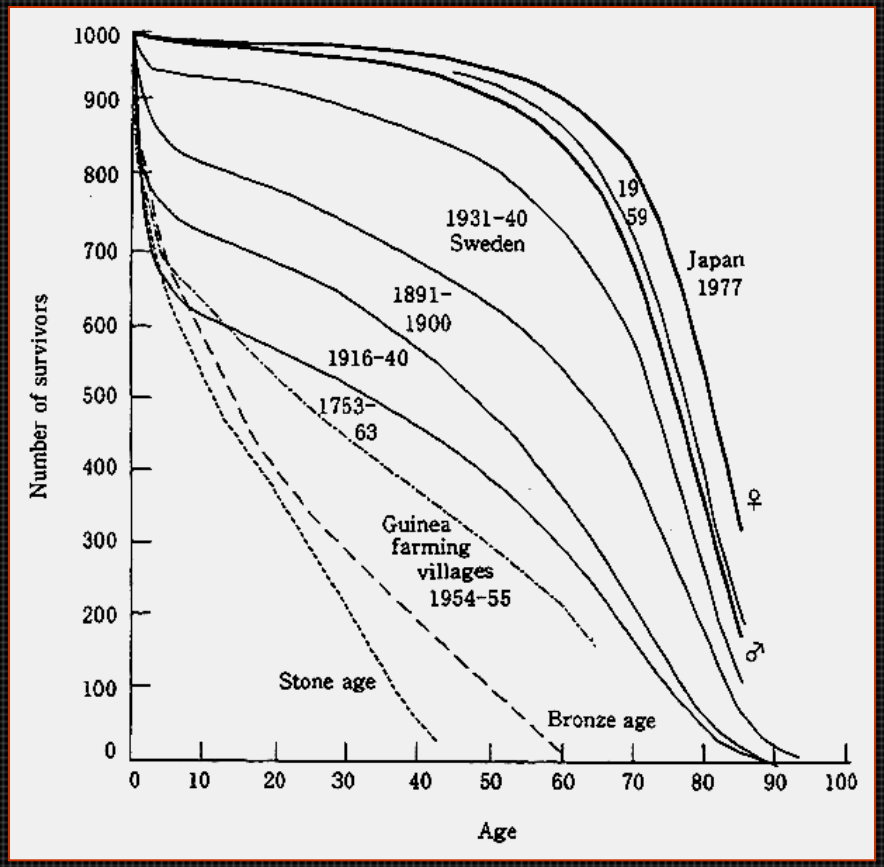
----------20----------15----------10----------5---------MYA

Gibbons Siamang | Orangutan | Gorilla | Human



Uric acid is a protective mechanism against oxidative stress

Survival Curve for Number of Survivors Per 1,000 Births



Plasma uric acid levels have increased during primate evolution

Lengthening of life-span
improved protective mechanisms against oxygen radicals

In 1981, Ames proposed that one of these protective systems is plasma uric acid

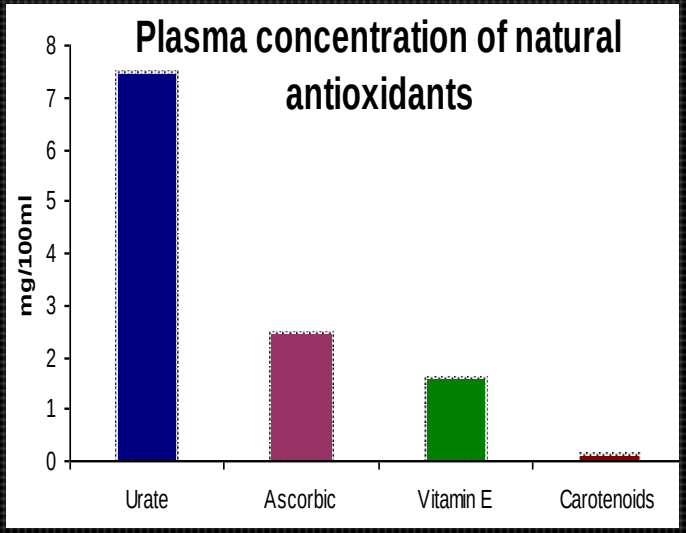
Soluble uric acid may act as an antioxidant that can react with a variety of oxidants including superoxide anion and peroxynitrite

Ames PNAS 1981;78:6858

Uric acid is a powerful antioxidant and scavenger of reactive oxygen radicals

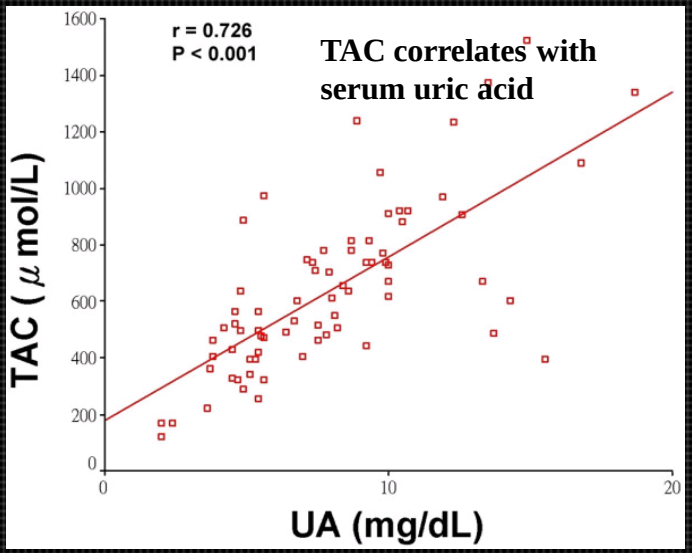
Uric acid is the major antioxidant in humans

Plasma uric acid concentrations are higher than Vit C



Ames PNAS 1981;78:6858

Total antioxidant capacity correlates with increase in plasma uric acid



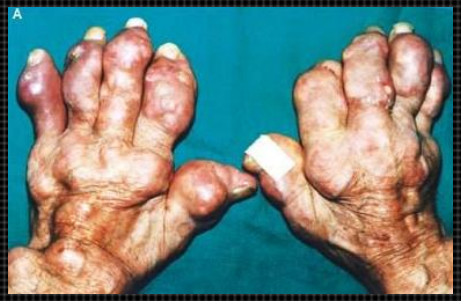
Chuang Crit Care 2006; 10: R36;

A changing role for uric acid in disease states

Crystal dependent mechanism

Known for centuries that the biological significance of uric acid was that it crystallizes in joints to cause gouty arthritis, and in the urinary tract to cause kidney stones

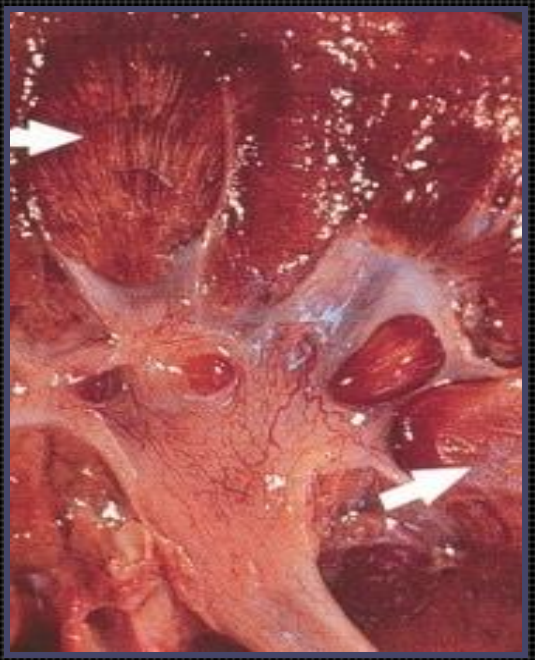
Gouty arthritis



Nephrolithiasis

Urate nephropathy

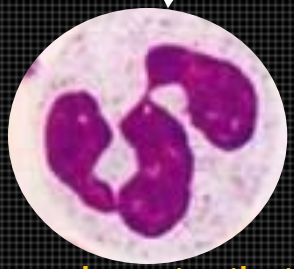
Nephron 1975; 14:88
Mol Med 2000;6:837

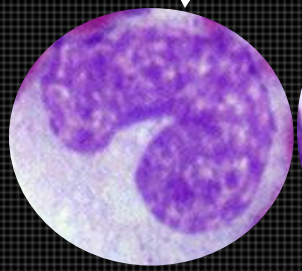


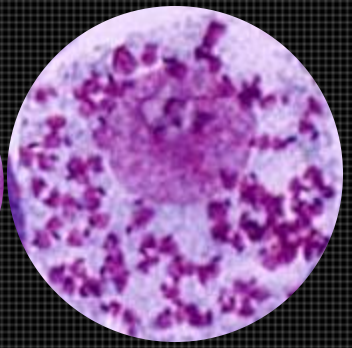
Howard, Childhood Leukemia

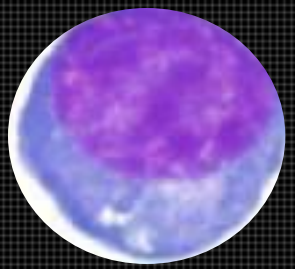
Acute crystallization of uric acid within the kidney during TLS was considered the cause of nephropathy

Uric acid crystals can induce inflammatory response via activation of inflammatory cells









- **via complement activation**
  - Arthritis Rheum 1975;18:765
  - Curr Opinion Rheumatol 1993;5:510
- **Stimulate neutrophil chemotaxis phagocytosis, respiratory burst**
  - Arthritis Rheum 1982; 25:181; 1969:12:189
- **Produce IL-1 and IL-1Ra**
  - J Immunol 1994; 152:5485
- **Releases leukotrienes, kinins, IL-8, PAF**
  - Arthritis Rheum 1975;18:765
  - Curr Opinion Rheumatol 1993;5:510
  - Prostaglandins 1984; 27:563

- **Stimulation of IL-8 thru activation of MAPK and NFκB**
  - Arthritis Rheum 2000; 43:1145
- **Induce production of TNF-α, MCP-1, MIP-2, IL-6**
  - J Clin Invest 1991; 87:1375
  - Arthritis Rheum 2003; 48:2931; 1898; 32:1443

Mo release IL-1B that induce an inflammatory response via IL-1β receptor and MyD88 signaling pathway

Activates T, B and dendritic cells
- Nature 2003; 425:516
- Am J Med Sci 2009; 337:23
- Blood 111:1472

Linking uric acid crystals to the evolution of Chronic Kidney Disease

- In 1975, Bluestone et al demonstrated the link between chronic hyperuricemia and chronic kidney disease.
- Bluestone et al induced and sustained moderately severe hyperuricemia and hyperuricosuria in rats for up to 52 weeks.
- Performed periodic renal biopsies (4, 36 and 52 weeks) to investigate the evolution of urate nephropathy.

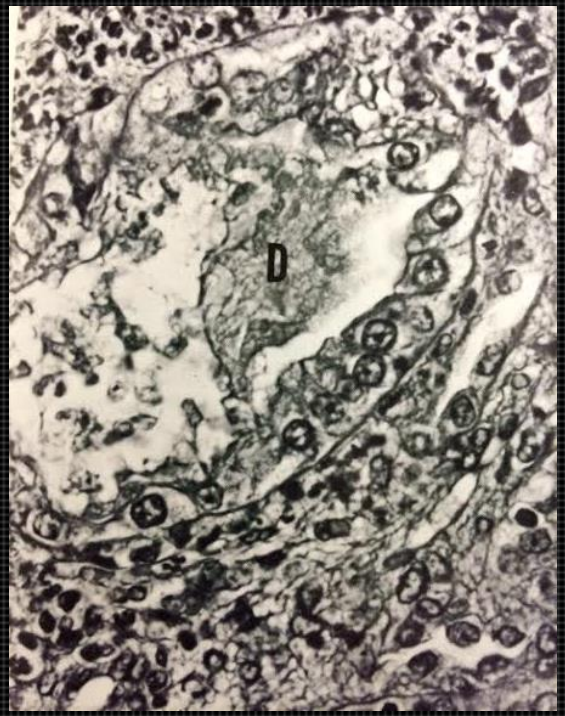
Bluestone Lab Invest. 1975; 33:273.

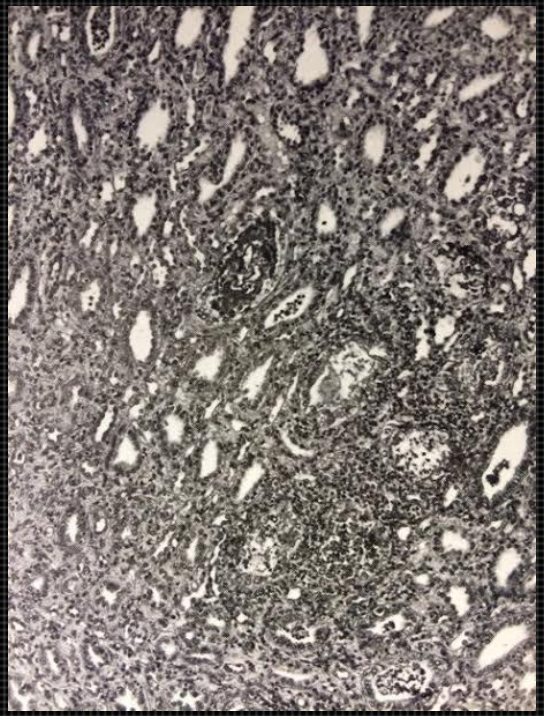
At 4 weeks – the acute phase

Massive intratubular urate deposition

Dilated tubules

Peritubular acute inflammatory response





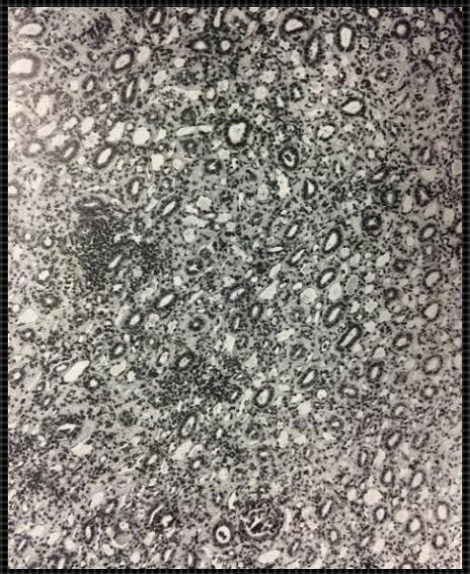
Atrophied and ruptured tubules

Tophi

Bluestone Lab Invest. 1975; 33:273.

At 52 weeks – the chronic phase

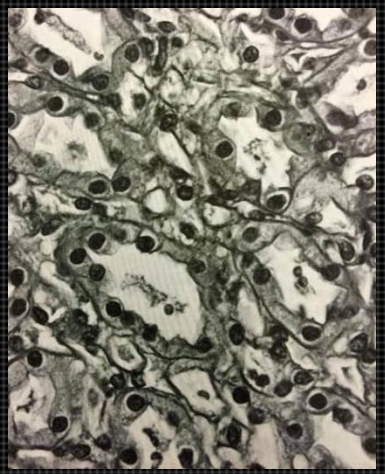
52-week CONTROL

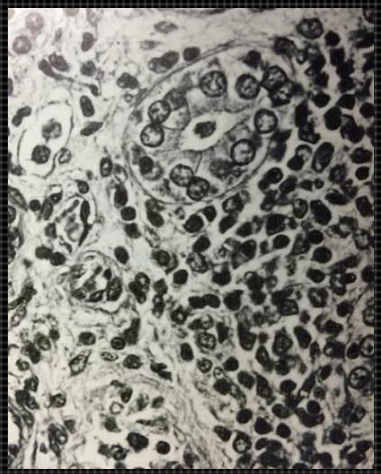


Fibrosis

Chronic hyperuricemia leads to progression to chronic kidney disease via a Crystal-Dependent mechanism

52-week CONTROL





Mononuclear cell infiltrates

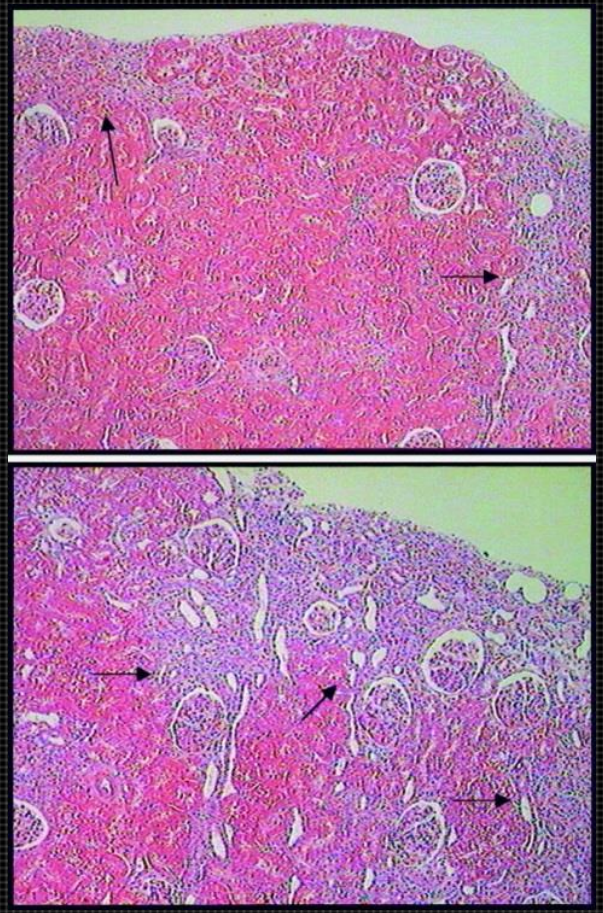
Bluestone Lab Invest. 1975; 33:273.

25 Urate nephropathy: crystal-independent pathways

Johnson et al demonstrated that mild hyperuricemia, in concentrations that do not cause crystal precipitation, can cause chronic tubulo-interstitial damage.

Absence of intrarenal urate crystal deposition

Mild hyperuricemia was associated with severe arteriolar hyalinosis and tubulointerstitial damage



Mild hyperuricemia can cause chronic kidney disease via Crystal-independent mechanisms

Mazzali. Transplantation. 2001; 71:900.

Clinical conditions associated with uric acid

Crystal dependent

Gouty arthritis

Urate nephropathy

Soluble uric acid / crystal independent

Hypertension

Israeli Heart Study (Khan, 1972)

Kaiser Permanente (Selby, 1990)

Univ of Utah (Hunt, 1991)

Olivetti Heart Study (Jossa, 1994)

CARDIA study (Dyer, 1999)

Osaka Health Survey (Taniguchi, 2001)

Osaka Factory Study (Masuo, 2003)

Osaka Health Survey (Nakanishi,2003)

Okinawa (Nagahama, 2004)

Bogalusa Heart (Alper, 2005)

Framingham (Sündstrom , 2005)

Normative Aging (Perlstein, 2006)

MRFIT (Krishnan, 2006)

Cardiovascular Disease

Tohoku J Exp Med. 2007;211:369
Am J Hypertens 2007; 20:83
Am J Kidney Dis 2006; 48:761
J Clin Hypertens 2006; 8:510
Stroke 2006; 37:1503
Hypertension 2006; 47:195
Atherosclerosis 2005;183:147

Stroke

EJCPR. 2006;13:193
Atherosclerosis 2006;187:401
J Intern Med. 2005 ;258:435
Stroke 2006;37:1503

Diabetes

Diabetes. 2009
Diabetes Care 2010
Kidney Blood Pressure 2012
AJKD 2006
NDT 2009
CJASN 2010

Chronic kidney disease

Kidney Int. 67:237-47, 2005
Kidney Int 63:994, 2003
Kidney Int 64: s9-s14, 2003
AJN 2003; 23:2

Metabolic Syndrome

Circulation 2007; April epub
Am J Med 2007;120:442
AJP Cell Physiol 2007; April epub
Ann Epidemiol 2007; 17::245
Am J Hypertens 2006; 19:1055
Nat Clin Pract Nephrol 2005; 1:80

Acute Kidney Injury

Clin J Am Soc Nephrol 2007; 2:16
Am J Physiol 2007; 292:F116
Am J Nephrol. 2009;30:425
Am J Med. 2012;125:302.e9
Am J Nephrol 2015;
PLoSOne 2015

Risks of major comorbidities associated with hyperuricemia in the US population

	OR (95% C.I.)
Hypertension	2.60 (2.15-3.14)
Obesity	3.12 (2.43-4.01)
Diabetes	1.63 (1.13-2.34)
Stroke	1.74 (1.16-2.59)
Myocardial Infarction	1.45 (1.12-1.88)
Heart Failure	2.52 (1.58-4.04)
Chronic Kidney Disease	2.33 (1.94- 2.80)

NHANES, N=5707

Zhu *Am J Med* 2012; 125:679

Relationship of allopurinol with improved endothelial function

Study population	Relative improvement	Citation
Congestive heart failure	58%	Doehner, 2002
Congestive heart failure	50%	Farquharson, 2002
Congestive heart failure	30%	George, 2006
Normotensive type 2 diabetes	50%	Dogan , 2010
Obstructive sleep apnea	30%	El Solh, 2006
Metabolic Syndrome	50%	Yiginer, 2008
Type 2 diabetes	30%	Butler, 2000
Asymptomatic hyperuricemia	20%	Kanbay, 2011
Asymptomatic hyperuricemia	30%	Mercuro, 2004
Asymptomatic hyperuricemia	40%	Melendez-Ramirez, 2012
Chronic kidney disease	100%	Yelken, 2012
Chronic kidney disease	25%	Kao, 2011

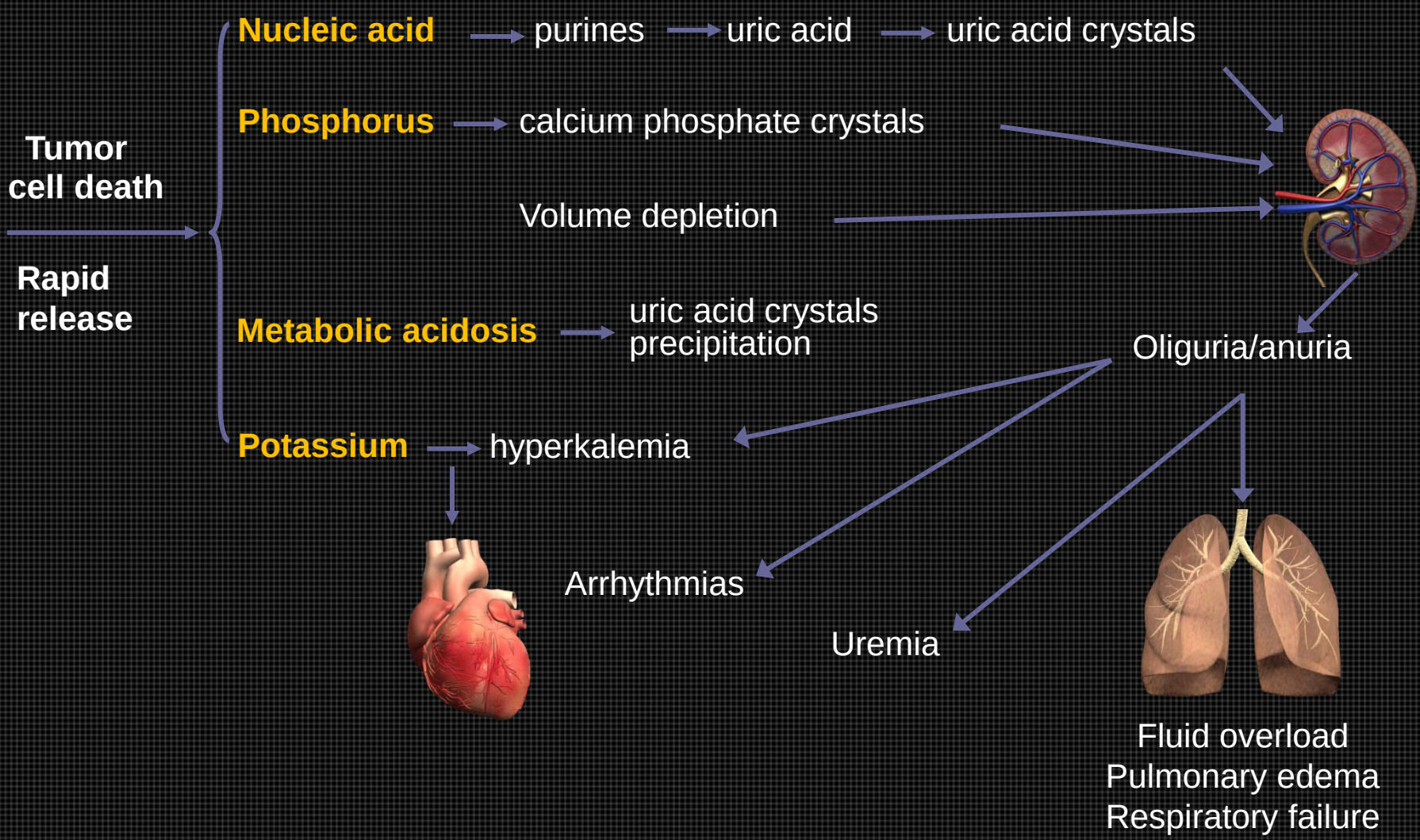
ClinicalTrials.gov

1. **NCT01158911:** Uric Acid and Long-term Outcomes in Chronic Kidney Disease
2. **NCT00978653:** The Effect of Uric Acid Decrement on Endothelial Function in Patients With Chronic Renal Failure
3. **NCT00978653:** The Effect of Uric Acid Decrement on Endothelial Function in Patients With Chronic Renal Failure
4. **NCT01228903:** Uric Acid and the Endothelium is CKD
5. **NCT01350388:** Effects of Febuxostat on Adipokines and Kidney Disease in Diabetic Chronic Kidney Disease
6. **NCT00860366:** Efficacy Study of Combined Treatment With Uric Acid and rtPA in Acute Ischemic Stroke
7. **NCT01368185:** Impact of MK-0954A on Uric Acid in the Management of Hypertension (MK-0954A-366)
8. **NCT02344602:** The Effect of Uric Acid Lowering in Type 1 Diabetes
9. **NCT00793585:** A Controlled Study of Uric Acid on the Progression of IgA Nephropathy
10. **NCT00987415:** Using Allopurinol to Relieve Symptoms in Patients With Heart Failure and High Uric Acid Levels
11. **NCT01082640:** Effect of Febuxostat on Renal Function in Patients With Gout and Moderate to Severe Renal Impairment
12. **NCT00477789:** Effects of Allopurinol on Diastolic Function in Chronic Heart Failure Patients

Interval Summary

Serum uric acid is associated with many chronic diseases via both crystal-dependent and crystal-independent mechanisms

Crystal-dependent AKI associated with Tumor Lysis Syndrome

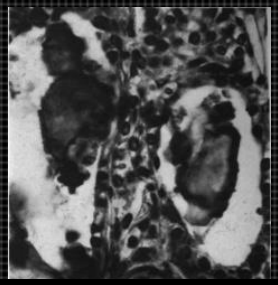


Estimating the role of uric acid in AKI

	All Causes of AKI	Uric Acid Crystal Nephropathy
N	27	5
Serum Creatinine (mg/dL)	6.2 ± 3.1	4.8 ± 3.4
Serum Uric acid (mg/dL)	13.8 ± 5.6	21 ± 20
Urine uric acid to urine creatinine ratio	0.43 ± 0.19 (range 0.12-0.9)	1.68 ± 0.63 (range 1.00-2.60)

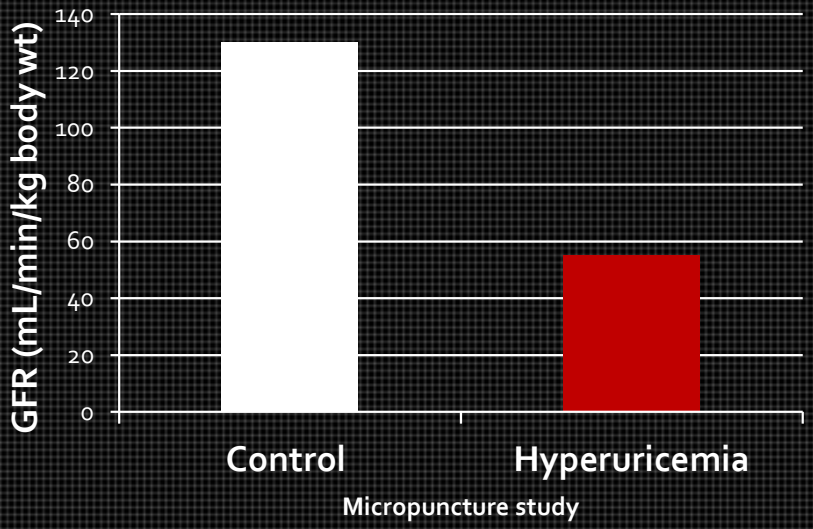
Kelton Arch Intern Med. 1978;138:612

Intraluminal precipitation of uric acid crystals associated with alterations in renal function in experimental urate nephropathy

2.5%UA + 5%OA + Chow → 7 days →  → Micropuncture Clearance

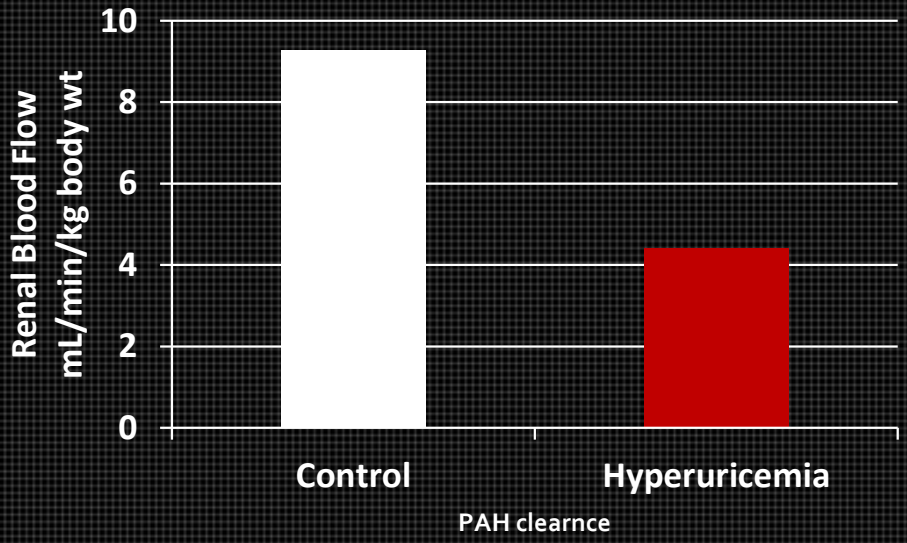
Uric acid crystals

50% decrease in Glomerular Filtration Rate



Micropuncture study

50% decrease in renal blood flow



PAH clearnce

Spencer Kidney Int 1976: 9:489

Soluble uric acid causes renal vasoconstriction via crystal-independent mechanisms

a. Normal
b. Mild hyperuricemia (OA, 750 mg/kg)
c. Mild hyperuricemia (OA) + Allopurinol

5 weeks →

Micropuncture

Model: Experimental

Strain: SD

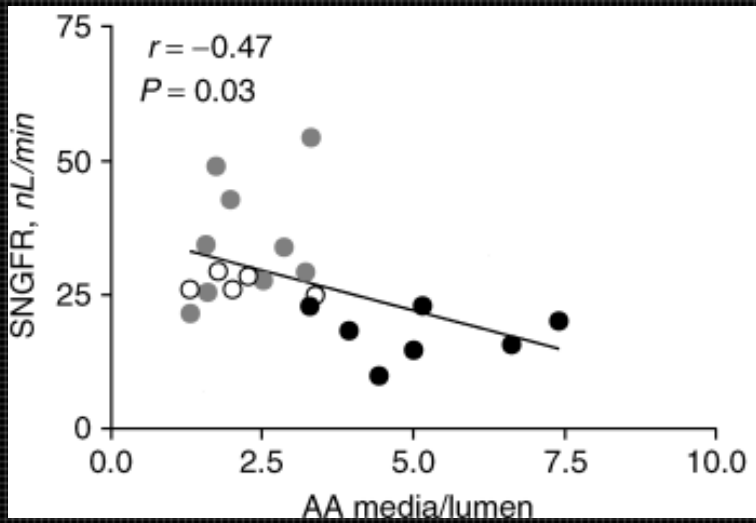
N= 8,9,7

T= 5wks

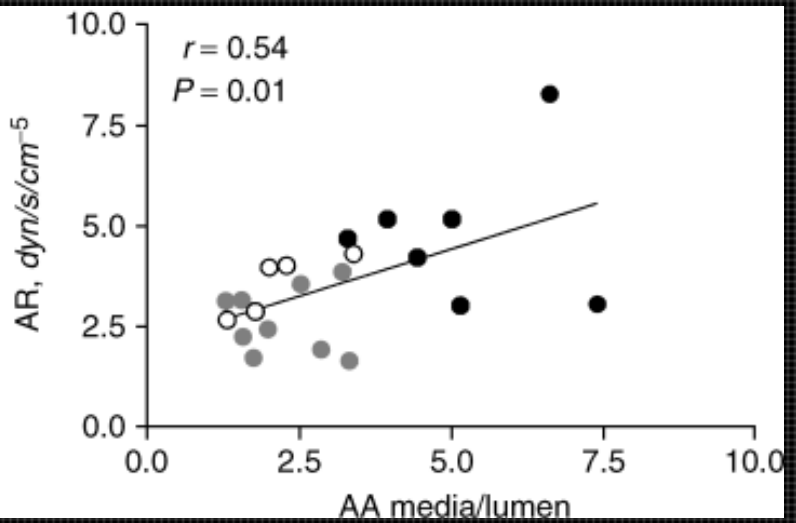
Technique

Microperfusion

Glomerular filtration rate



Vasoconstriction



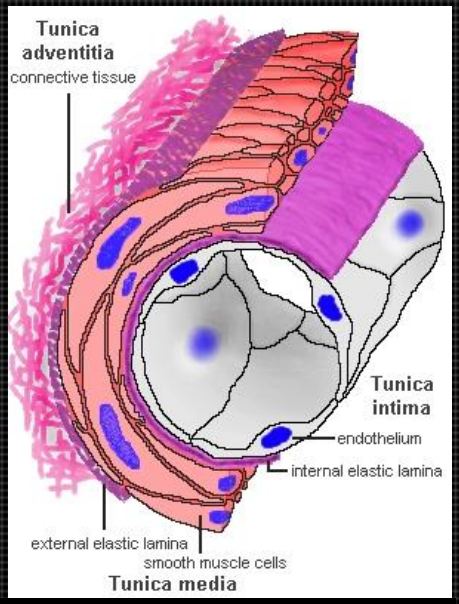
~50% decrease in SNGFR

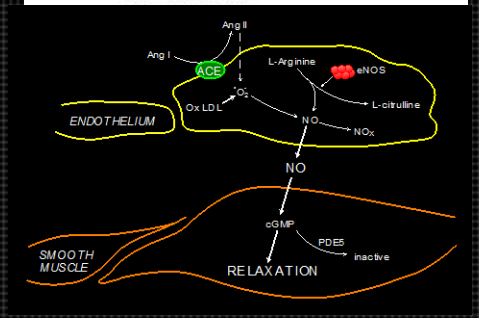
40-60% decrease in renal blood flow

i.e. uric acid in concentrations that do not cause intratubular crystal precipitation was also shown to decrease GFR and renal blood flow, suggesting a crystal independent pathway

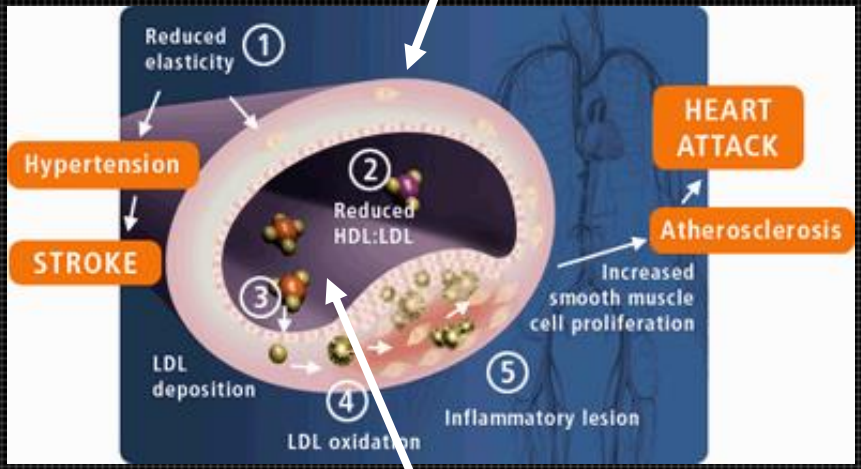
Sanchez-Lozada *Kidney Int.* 2005;67:237

The adverse events associated with uric acid are mediated by endothelial dysfunction and pathologic vascular remodeling





Vascular wall thickening

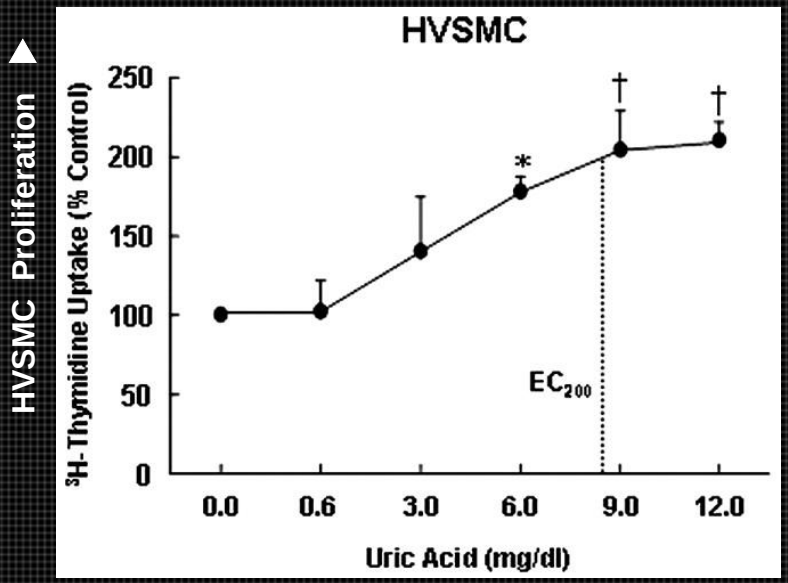


Lumen obliteration

Uric acid has proliferative effect on vascular smooth muscle cells. inhibitory effect on vascular endothelial cells

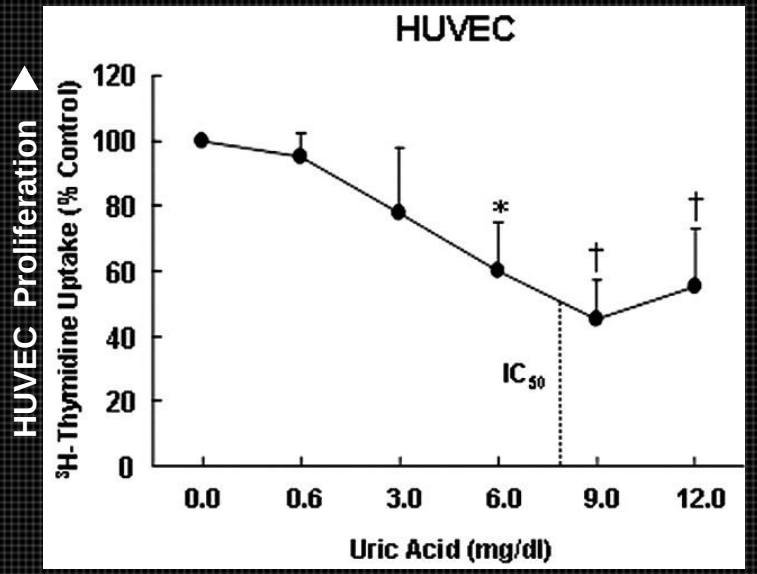
Human Vascular Smooth Muscle Cells

Stimulates proliferation
migration



Human Umbilical Vein Endothelial Cells

Antiangiogenic
inhibits proliferation, migration
Stimulates apoptosis

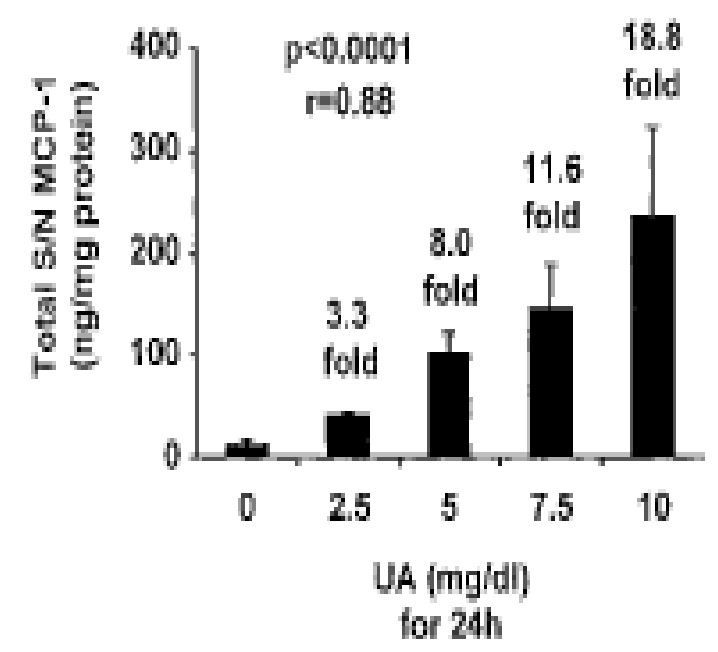


Kang/Johnson JASN 2005;16:3553

Uric acid stimulates proinflammatory chemokine (MCP-1) production in vascular smooth muscle cells

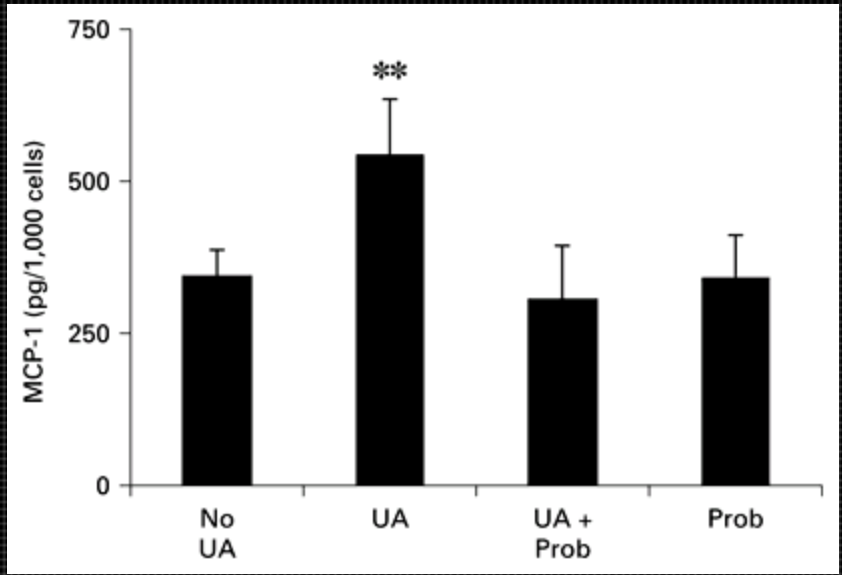
Proinflammatory / Prooxidative

MCP-1 is an inflammatory response



Kanellis/Johnson Hyprtension 2003; 41:1287

Probenecid blocks MCP-1 synthesis



Kang AJN 2005;25:425-433

Uric acid stimulates CRP production in HVSMC and HUVEC

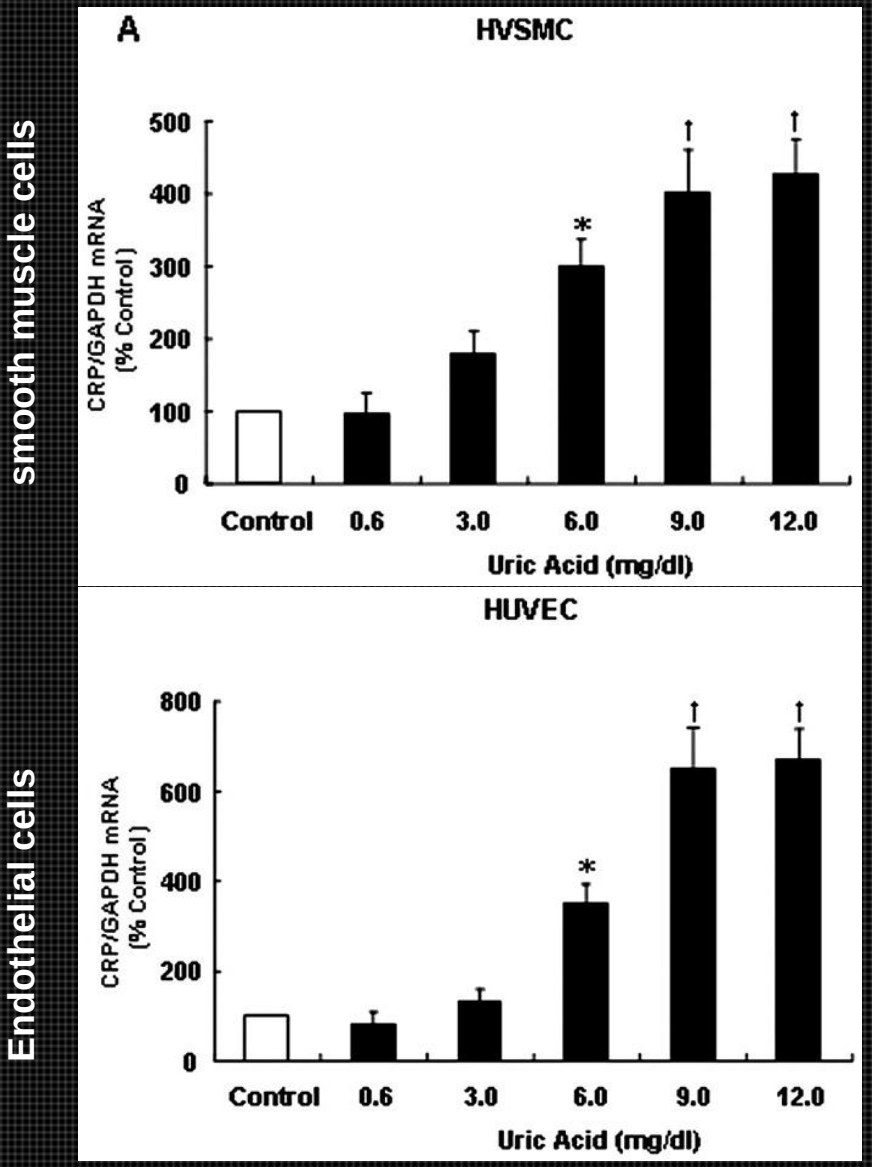
Proinflammatory / Prooxidative

CRP expression in both VSMC and VEC

CRP is an inflammatory protein associated with the secretion of various cytokines, including IL-6, TNF-α, and IL-1

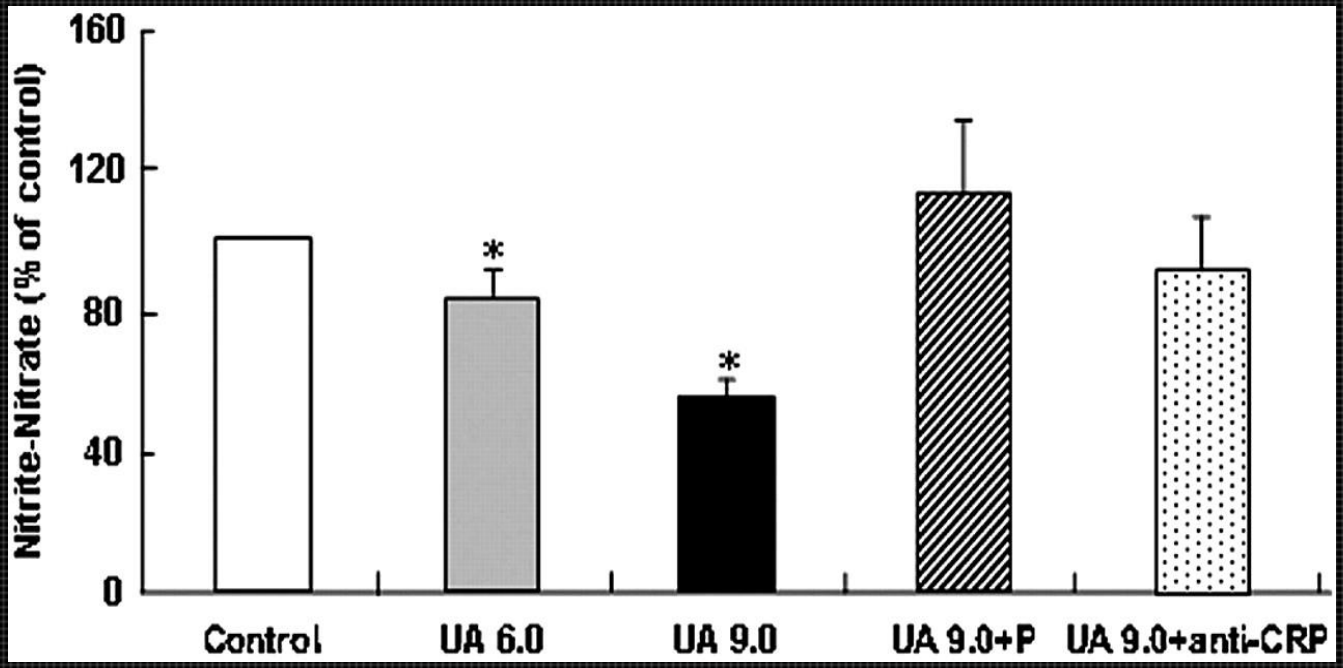
CRP is associated with atherothrombosis

CRP is responsible for uric acid mediated vascular remodeling



Kang/Johnson JASN 2005;16:3553

Uric acid decreases bioavailabily of nitric oxide



Khosla/Johnson KI 2005; 67:1739, Kang JASN 2005;16:3553, Nakagawa Am J Physiol 2006; 290:F625

HUVEC

Uric acid inhibits NO production

NO inhibiting effect of uric acid blocked by
probenecid
anti-CRP antibody

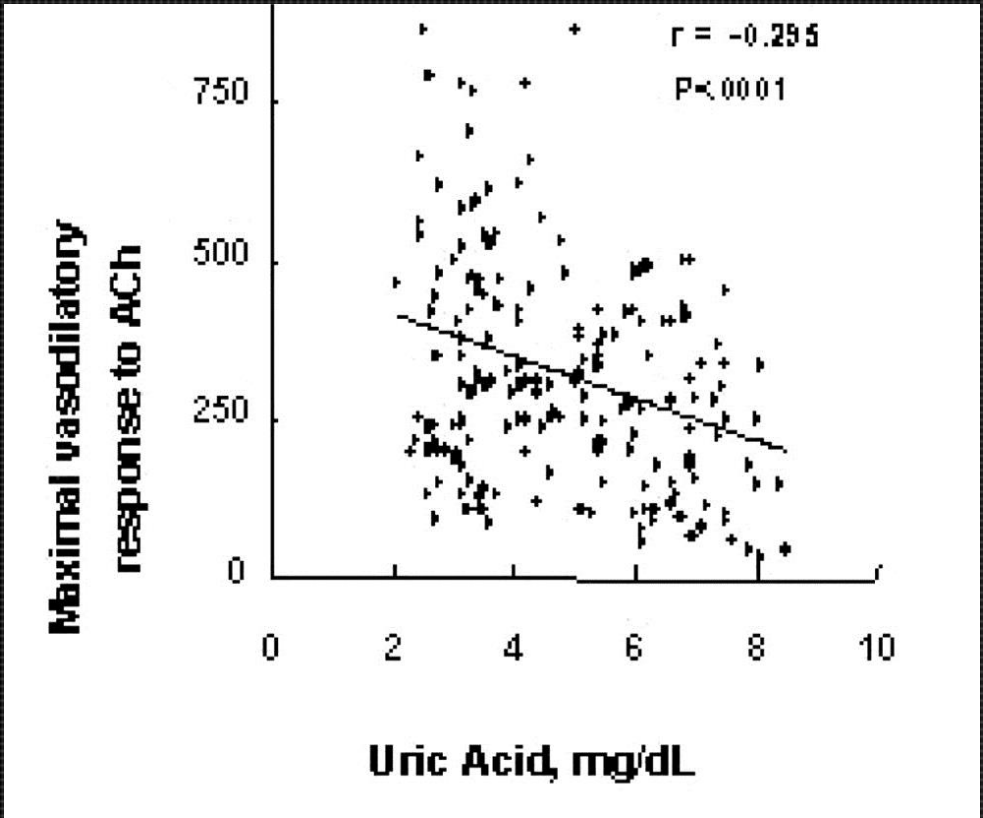
Inverse relationship between plasma uric acid and nitric oxide

- N=217. M108, F109; 48±10.6yrs
  Hypertensive patients
  Untreated

- endothelial function evaluated by vasodilatory response to intra-arterial infusion of ACh

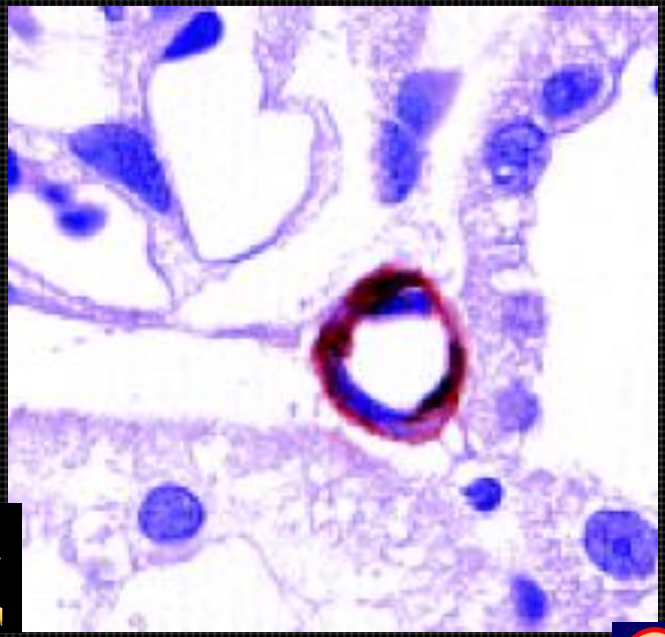
- Forearm blood flow and arterial pressure measured

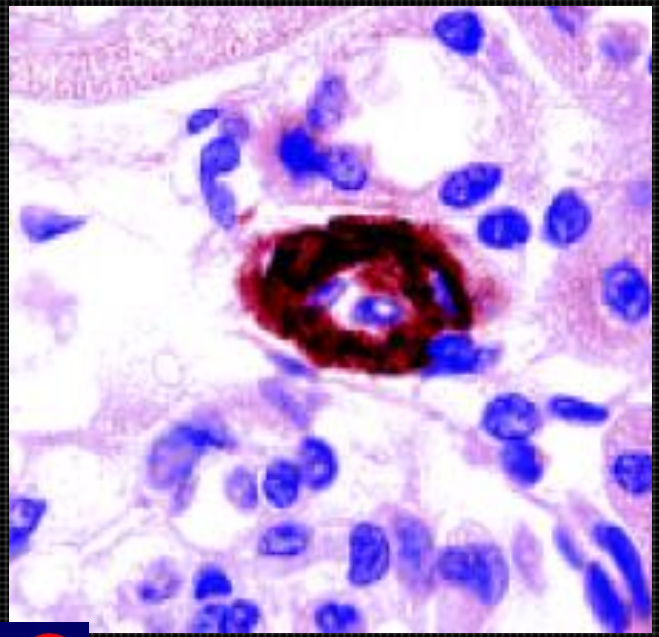
- **Result**
  Uric acid reduces brachial artery flow mediated vasodilation



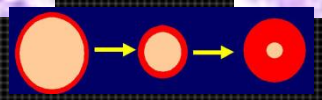
Zoccali JASN 2006;17:1466

Hyperuricemia induces thickening of vascular wall





Control



Hyperuricemia

PAS stain + alpha-actin SM antibody (100X)

Sanchez-Lozada/Johnson KI 2005; 67:237

Summary of the renal effects of uric acid

Preglomerular arterioles

Vasoconstriction

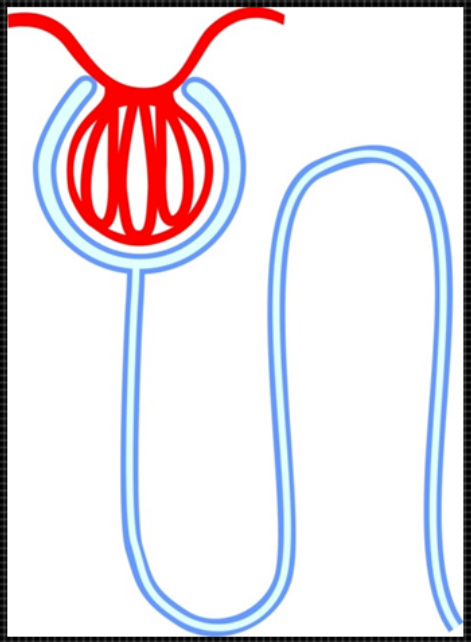
decreases renal blood flow ~40-60%

- ↑ RAS activation
- ↓ NO bioavailability
- ↑ Oxidants
- ↑ inflammatory mediators
- ↑ vascular responsiveness

Khosla/Johnson KI 2005; 67:1739,
Kang JASN 2005;16:3553,
Nakagawa Am J Physiol 2006; 290:F625

Impaired autoregulation

- ↑ VSMC proliferation & migration
- ↓ VEC proliferation & migration
- ↑ preglomerular arteriolar thickening



Glomerulus

↓ **Glomerular filtration rate ~40-50%**

Sanchez-Lozada AJP 2002
Sanchez-Lozada KI 2005

Proximal Tubules

Oxidative stress

Inflammation

↑ MCP-1, ICAM-1
KHK dependent
Cirillo AJP 2009

Innate and adaptive immunity

↑ complement, TLR activation
Burne-Taney AJP 2003
Rabb AJP 2000

Inhibition of PTC proliferation

↑ MAPK, NFκB
Sautin AJP 2007

Mitochondrial dysfunction

Distal Tubules

Intratubular crystal deposition

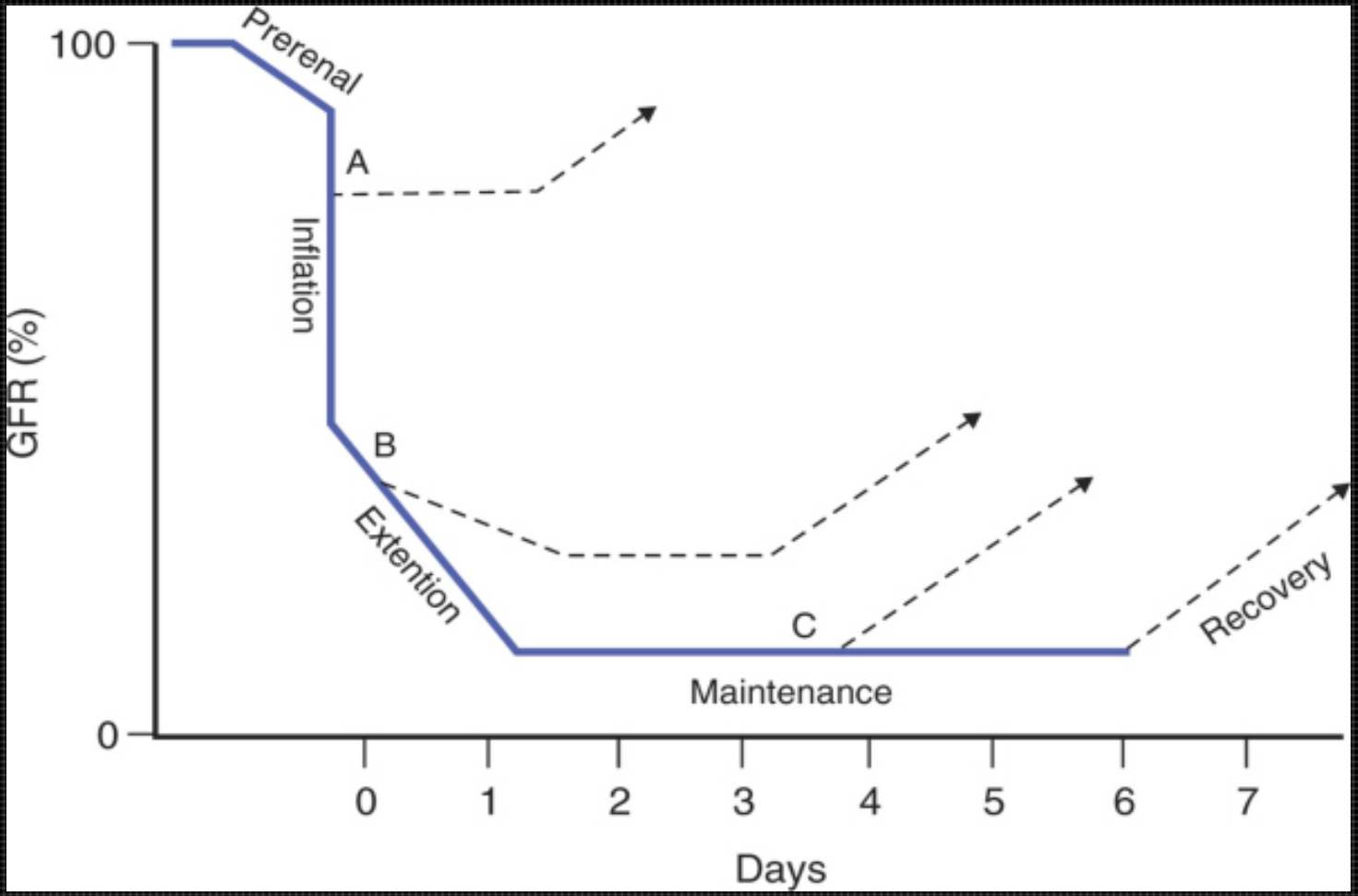
tubular obstruction
Kjellstrand Arch Intern Med 1974
Riesalbach Am J Med 1964

Crystal-induced inflammation

RAS: renin angiotensin sysytem; VSMC: vascular smooth muscle cells; VEC: vascular endothelial cells; KHK: keto-hexokinase; PTC: proximal tubular cells;

Ejaz/Johnson CJASN 2007;2:16
Shimada/Ejaz NDT 2009; 24:2960
Ejaz/Johnson AJN 2009; 30:425
Shimada/Ejaz Seminar Nephrol 2011; 31:543

Renal vasoconstriction: potential initiator of ischemic AKI



Kidney Int 2002;62:1539

Hypothesis of the mechanism of ischemic AKI

Reduction in outer medullary oxygen tension

Vasoconstrictors
Ang II
Catechol
ET-1
ROS
Cytokines

Vasodilators
NO
PGI_2
Bradykinin
EDHF

Vasoconstriction

Impaired Autoregulation

↓ RBF
↓PO_2

↓ATP → ↑Ca^{++}

↑Calpain → Cytoskeletal changes

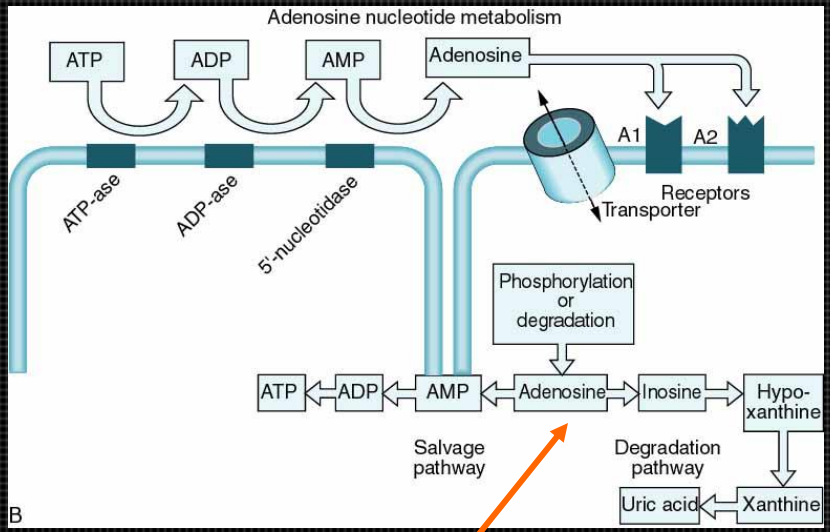
↑NOS → ↑NO → ↑$OONO^-$

↑ PL → Membrane PL hydrolysis

Tight junction / Apical-basolater / Microfilament polarity

Hemodynamic changes / tubular injury

TG Feedback activation vasodilates the efferent arteriole by an adenosine-dependent mechanism



TG Feedback

AA vasoconstriction
A1 –AR

EA vasodilatation
A2a – AR
↓
↓ P_{GC}
↓
↓GFR

\+ −

↓RBF
↓PO_2

↓ATP

↓
↓NO

Vasoconstriction

Impaired autoregulation

Vasoconstriction

The Inflammatory cascade

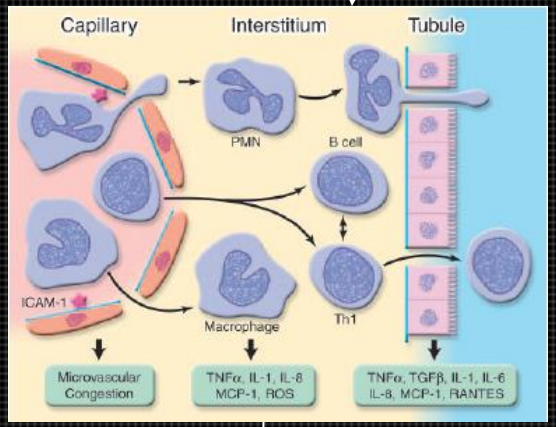
OM vasa recta congestion

Neurophil Sequestration

Entrapment of leukocytes, Platelets, T, others

Enhanced EC-Leukocyte adhesion

↑ ROS, cytokines, chemokines, complements



JASN 2006; 17:1503

Ischemia-reperfusion injury
VASCULAR INJURY
TUBULAR INJURY

↓Nitric Oxide
↑ Renin-Angiotensin

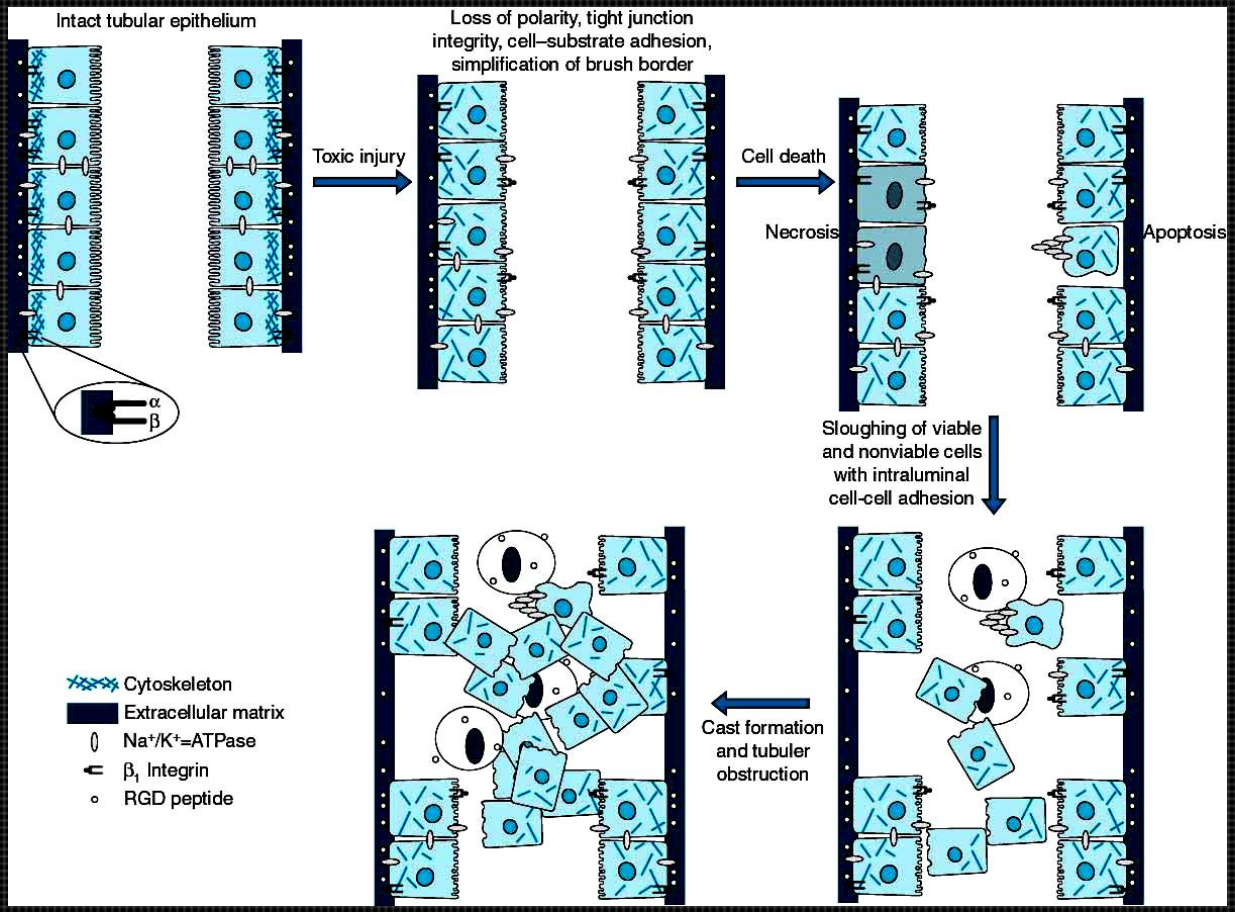
↓RBF
↓PO_2

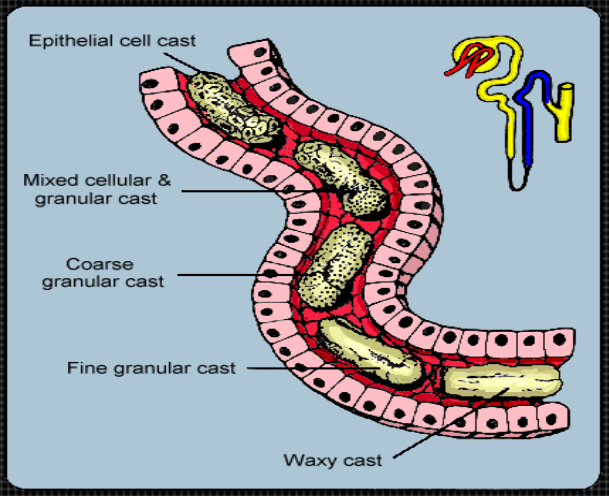
Microvessels dropout
↓
↑Tubuloiinterstitial fibrosis
↓Concentration capacity

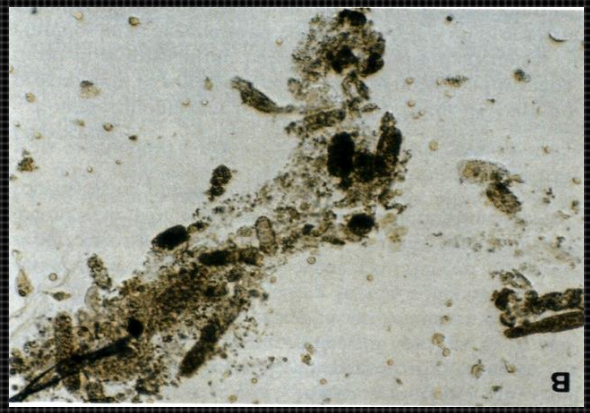
Vasoconstriction

Impaired Autoregulation

Mechanism of acute kidney injury







Interval Summary

- Serum uric acid associated with many disease conditions via crystal-independent mechanisms
- SUA causes renal vasoconstriction
- SUA is proinflammatory and anti-angiogenic
- SUA causes thickening of preglomerular arteriolar thickening
- SUA appears to affect many of the hypothetical mechanisms of acute kidney injury

Experimental Evidence

Am J Physiol Renal Physiol 292: F116–F122, 2007;
doi:10.1152/ajprenal.00160.2006.

Effect of elevated serum uric acid on cisplatin-induced acute renal failure

Carlos A. Roncal,[1*] Wei Mu,[1*] Byron Croker,[2] Sirirat Reungjui,[1] Xiaosen Ouyang,[1]
Isabelle Tabah-Fisch,[3] Richard J. Johnson,[1] and A. Ahsan Ejaz[1]

Hypothesis: hyperuricemia might exacerbates AKI in CP-induced AKI

S-D rats
N=6 each group

1 wk

Control (C)
(0.25% methyl cellulose gavage x5days)

Cisplatin (CP)
(5mg/kg, NS x1 dose)

Cisplatin-Hyperuricemia (OA/CP)

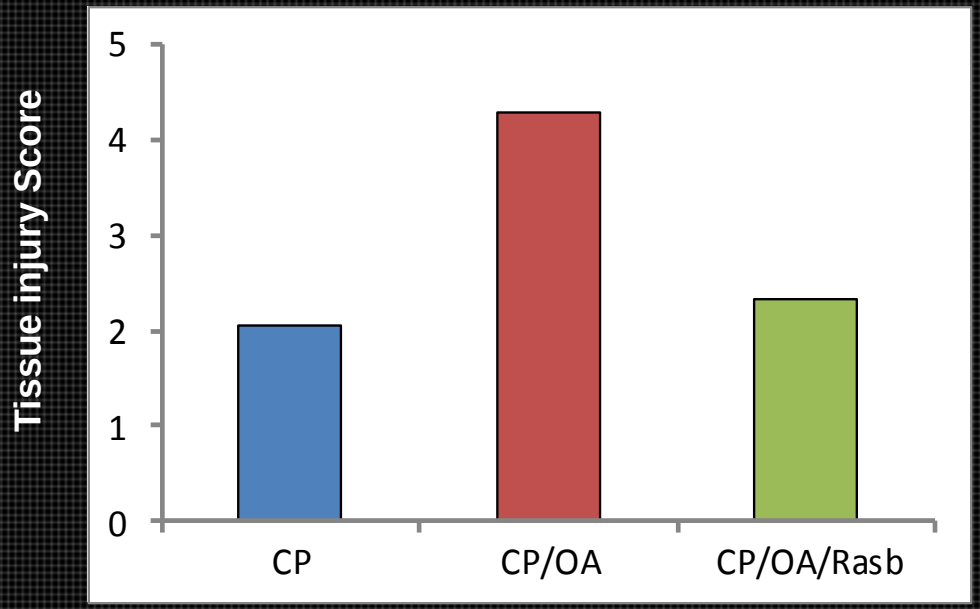
Cisplatin-Hyperuricemia-Rasburicase (OA/CP/Rasburicase)
(+ 25mg/kg IP x 5days)

Day 5 Sacrifice

Roncal AJP Renal Physiology 2007; 292:116

Tissue injury scores were highest in the hyperuricemia /cisplatin group

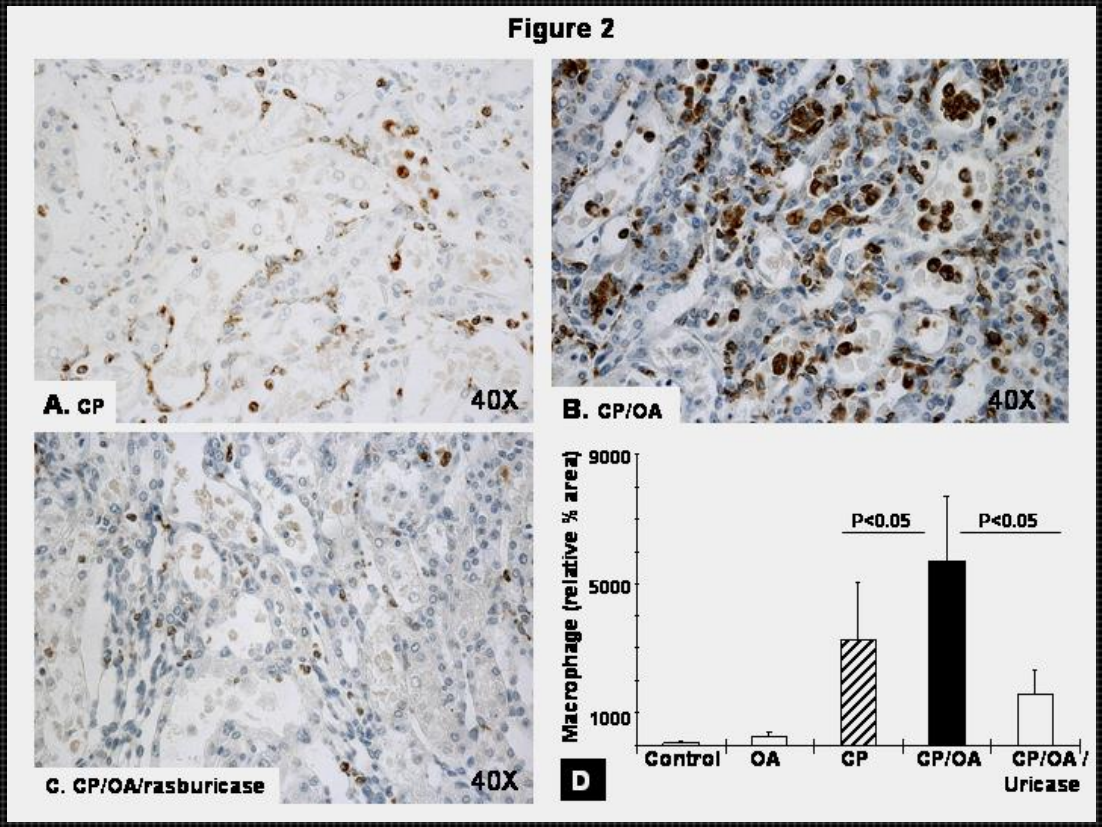
Loss of brush border
Karyolysis
Tubular swelling
Nuclear condensation



Lowering uric acid reduced tissue injury

Roncal/Ejaz AJP 2007; 292:F116

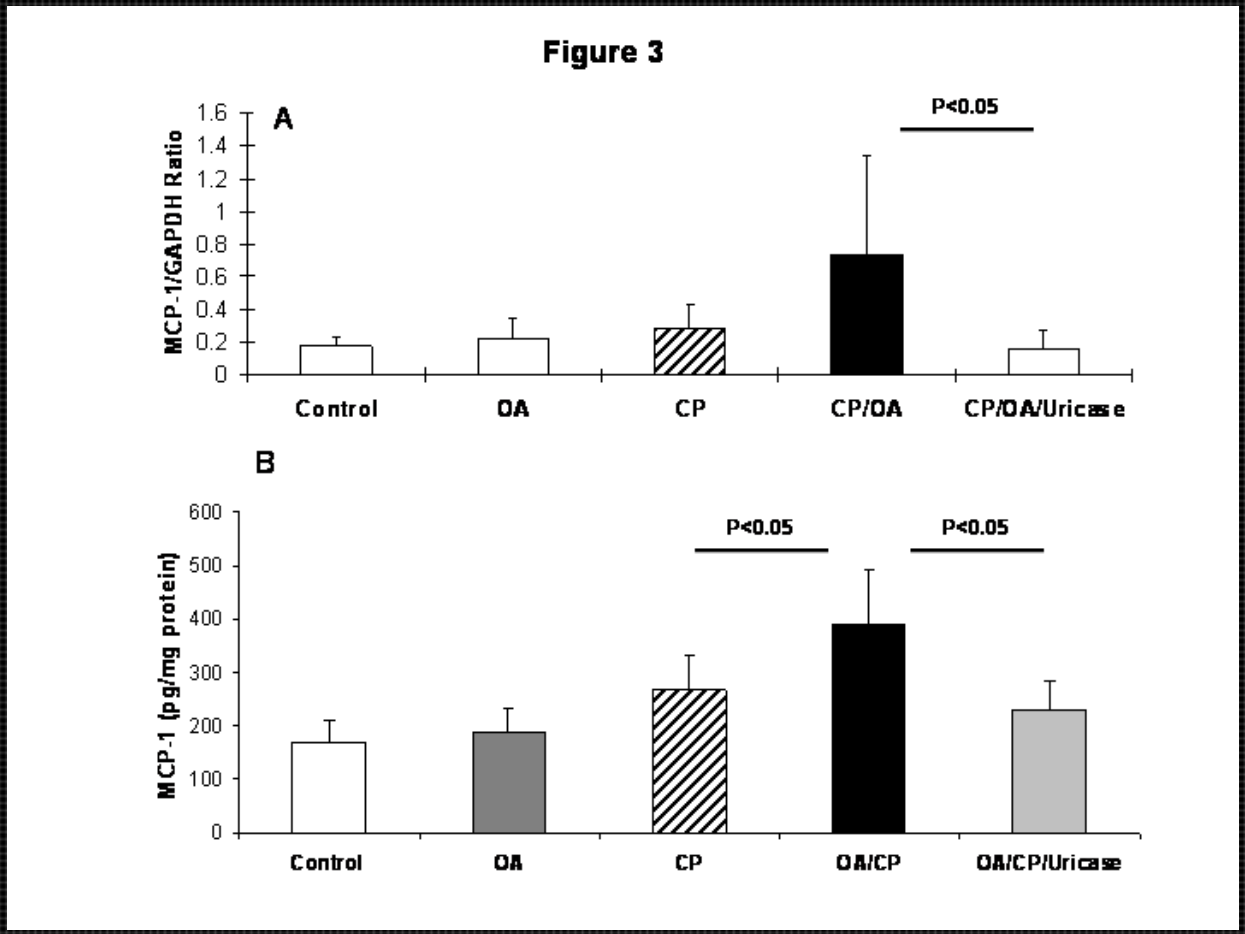
Hyperuricemic rats with CP injury displayed significantly more monocytes and macrophages in the cortex and inner stripe.



MCP-1 mRNA and protein was significantly increased hyperuricemic rats that received CP

Results of inflammatory cytokines

MCP-1 mRNA and protein was significantly increased hyperuricemic rats that received CP

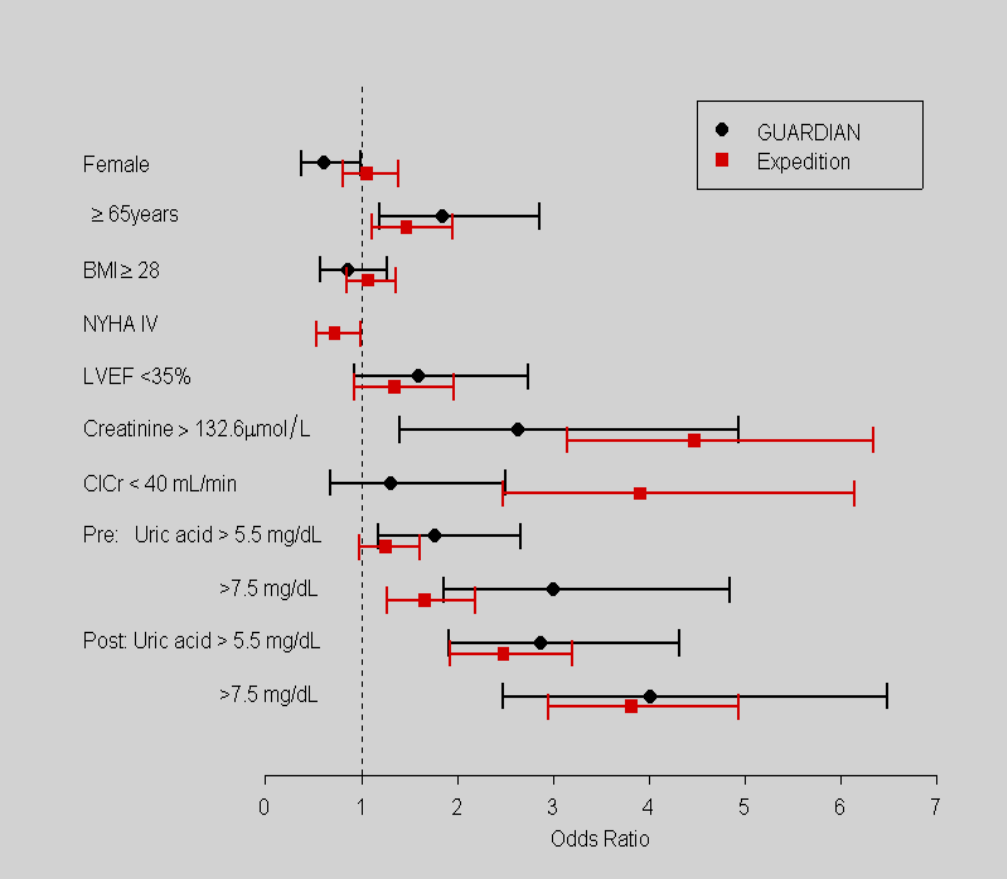


Roncal AJP Renal Physiology 2007; 292:116

Epidemiological evidence

Could Uric Acid Have a Role in Acute Renal Failure?

A. Ahsan Ejaz,* Wei Mu,* Duk-Hee Kang,† Carlos Roncal,* Yuri Y. Sautin,* George Henderson,* Isabelle Tabah-Fisch,‡ Birgit Keller,§ Thomas M. Beaver,‖ Takahiko Nakagawa,* and Richard J. Johnson*



865 and 2832 patients who were in the placebo arm qualified for the study

Preoperative uric acid increases the risk for AKI in cardiac surgery

GUARDIAN/EXPEDITION Trials

SUA > 5.5mg/dL: 2 - 3 x risk for AKI
SUA > 7.5mg/dL: 3 - 4 x risk for AKI

GUARDIAN / EXPLORER
NHE inhibitors (cariporide) to prevent reperfusion injury during cardiac surgery

Ejaz/Johnson CJASN 2007; 1:16

Epidemiological evidence

American Journal of Nephrology

Original Report: Patient-Oriented, Translational Research

Am J Nephrol 2009;30:425–429
DOI: 10.1159/000238824

Received: June 4, 2009
Accepted: August 4, 2009
Published online: September 11, 2009

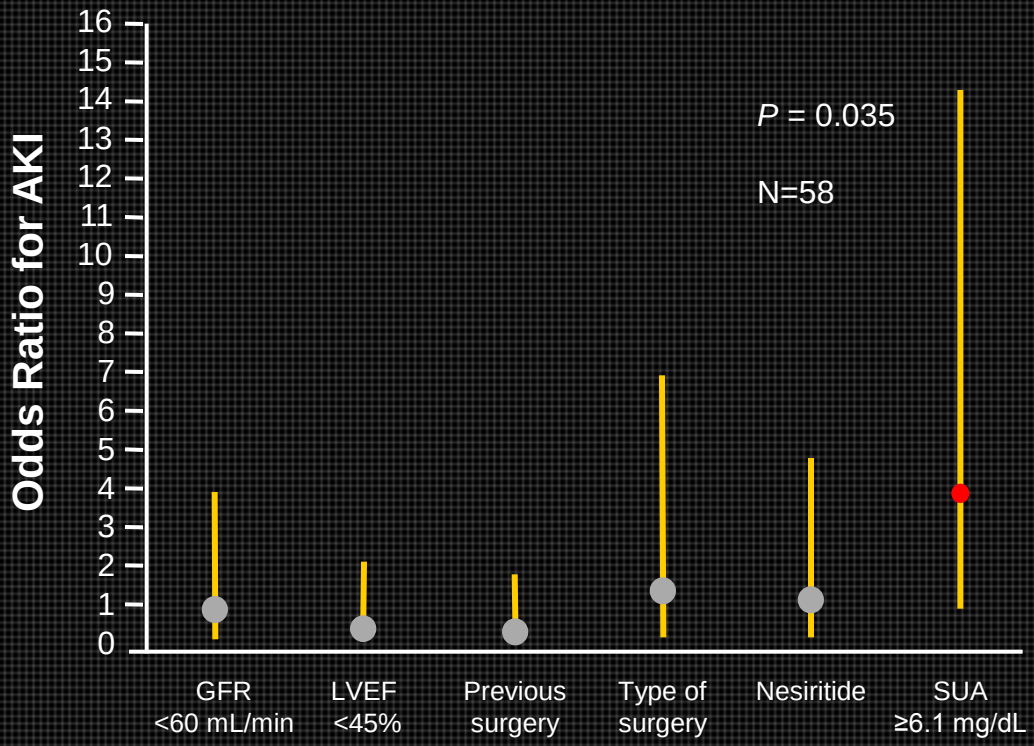
Uric Acid: A Novel Risk Factor for Acute Kidney Injury in High-Risk Cardiac Surgery Patients?

A. Ahsan Ejaz[a] Thomas M. Beaver[b] Michiko Shimada[a, c] Puneet Sood[a]
Vijaykumar Lingegowda[a] Jesse D. Schold[a] Tad Kim[b] Richard J. Johnson[a, c]

SUA is a novel, independent predictor of postoperative AKI in CV surgery

Preoperative serum uric acid >6.1mg/dL confers a 4-fold increased risk for AKI

Hyperuricemia is associated with increased risk for AKI, longer hospital stay, and more severe decrease in postoperative GFR



SUA >6.1 mg/dL increases the risk of AKI by 4-fold

Ejaz Am J Nephrology 2009; 30:425

Epidemiological evidence

The American Journal of Medicine

Volume 125, Issue 3, March 2012, Pages 302.e9–302.e17

AJM online

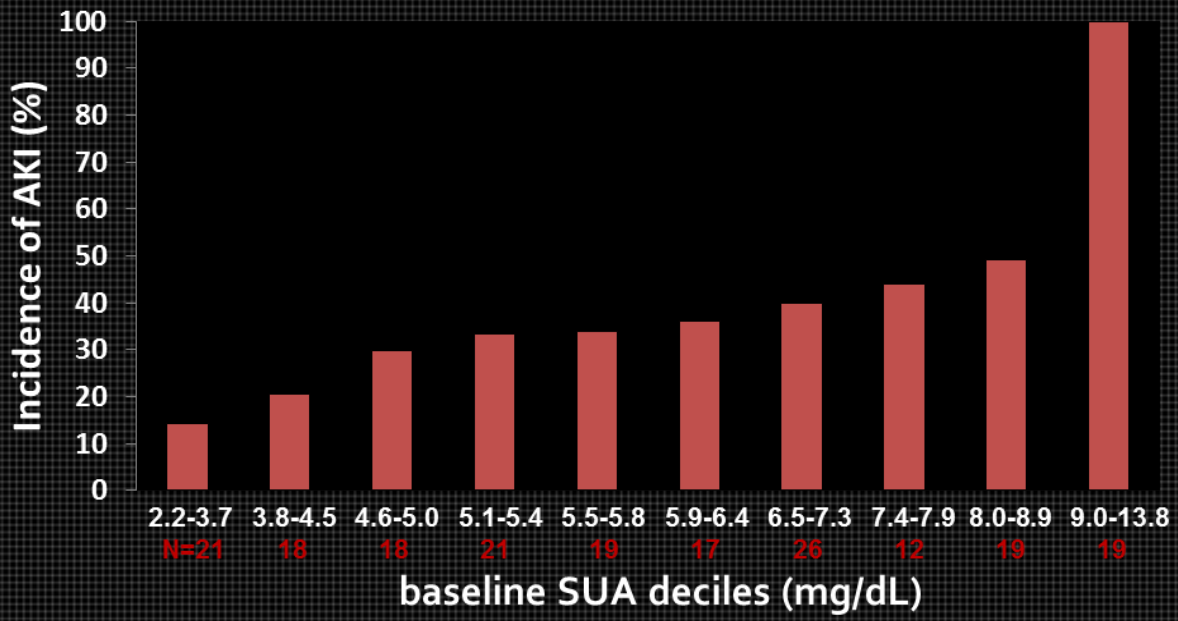
Elevated Uric Acid Increases the Risk for Acute Kidney Injury

Vijay Lapsia, MD[a], Richard J. Johnson, MD[b, c], Bhagwan Dass, MD[c], Michiko Shimada, MD, PhD[d], Ganesh Kambhampati, MD[c], Noel I. Ejaz[c], Amir A. Arif[c], A. Ahsan Ejaz, MD[c,]

Investigated the potential influence of preoperative serum uric acid (SUA) on acute kidney injury in patients undergoing cardiovascular

Lapsia Am J Med 2012 Mar;125(3):302.e9

Incidence of acute kidney injury

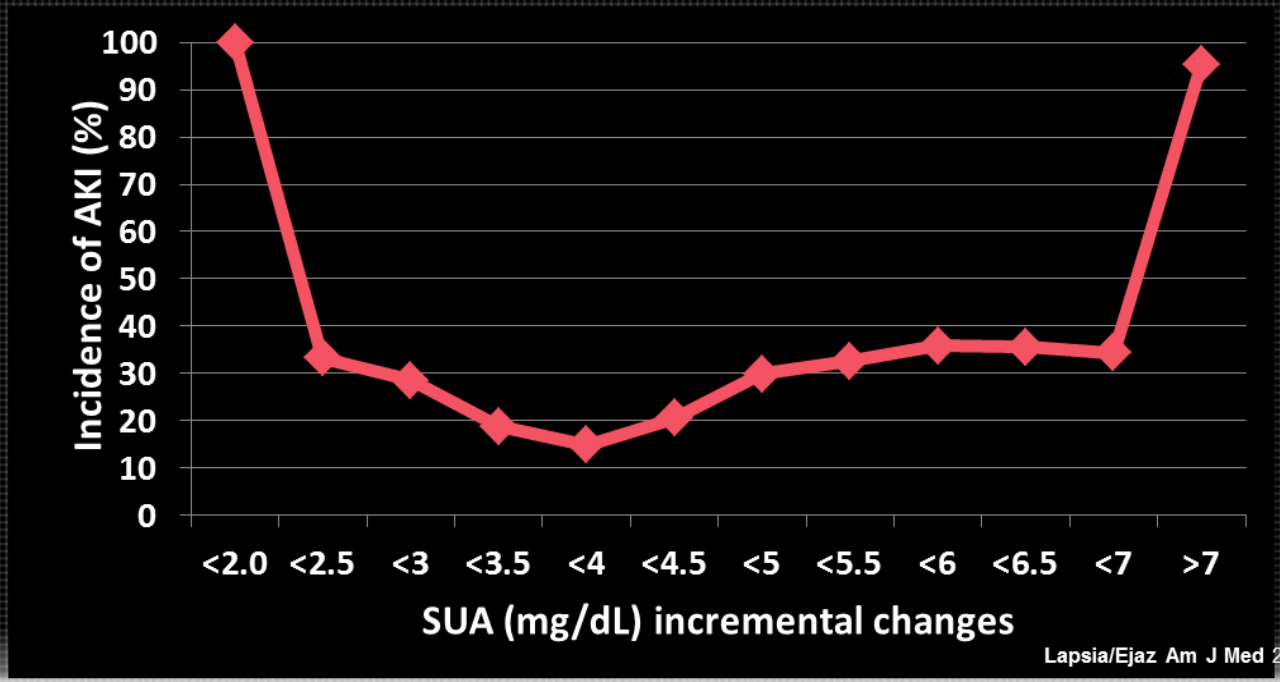


Baseline SUA was divided into deciles

The higher the SUA, the higher the incidences of AKI

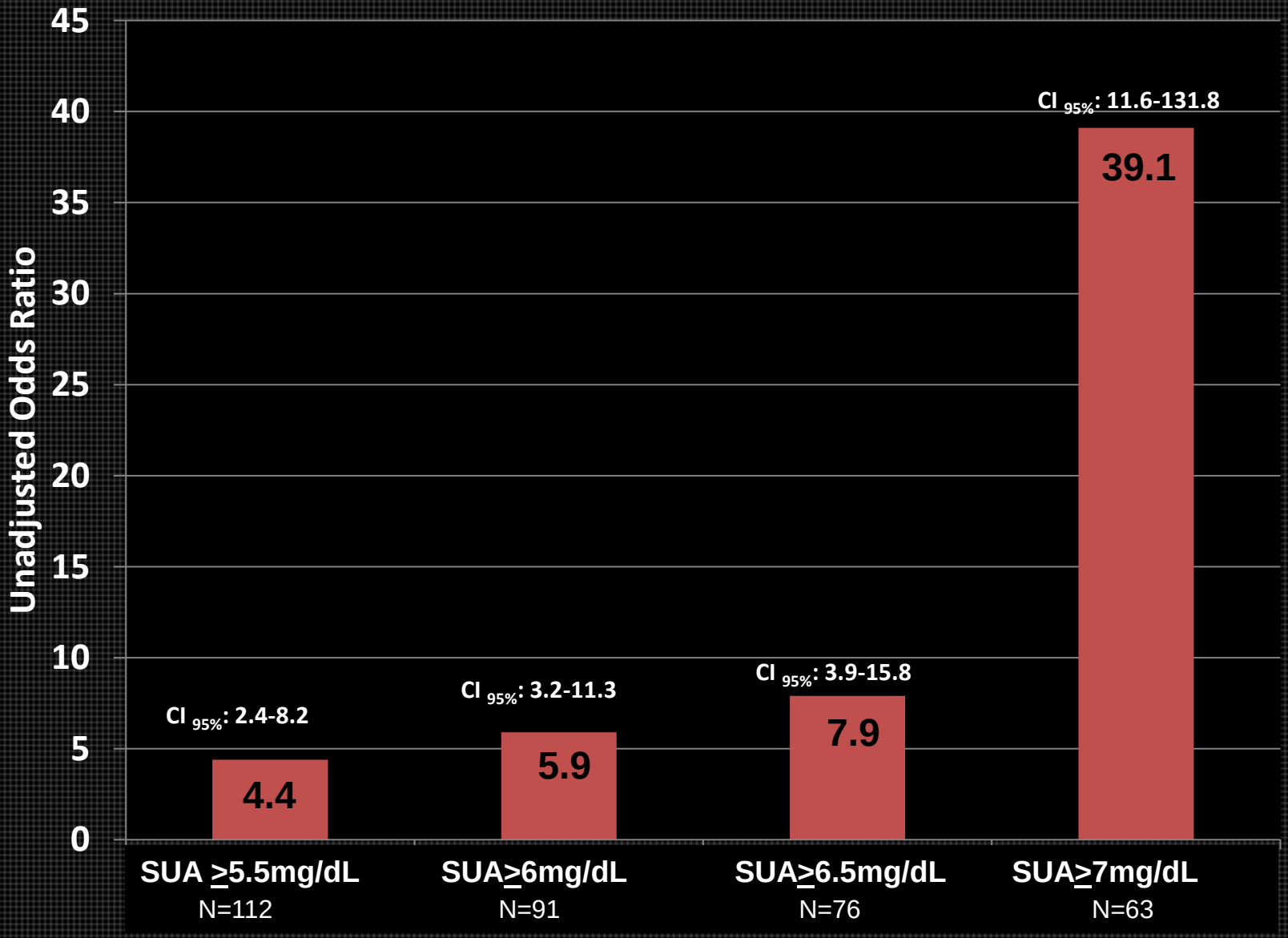
Plotted incidence of AKI against all the available values of SUA at increments of 0.5mg/dL

U-shaped curve emerged



Lapsia/Ejaz Am J Med 2012 Mar;125(3):302.e9

Univariate analysis: Risk for AKI by threshold SUA levels

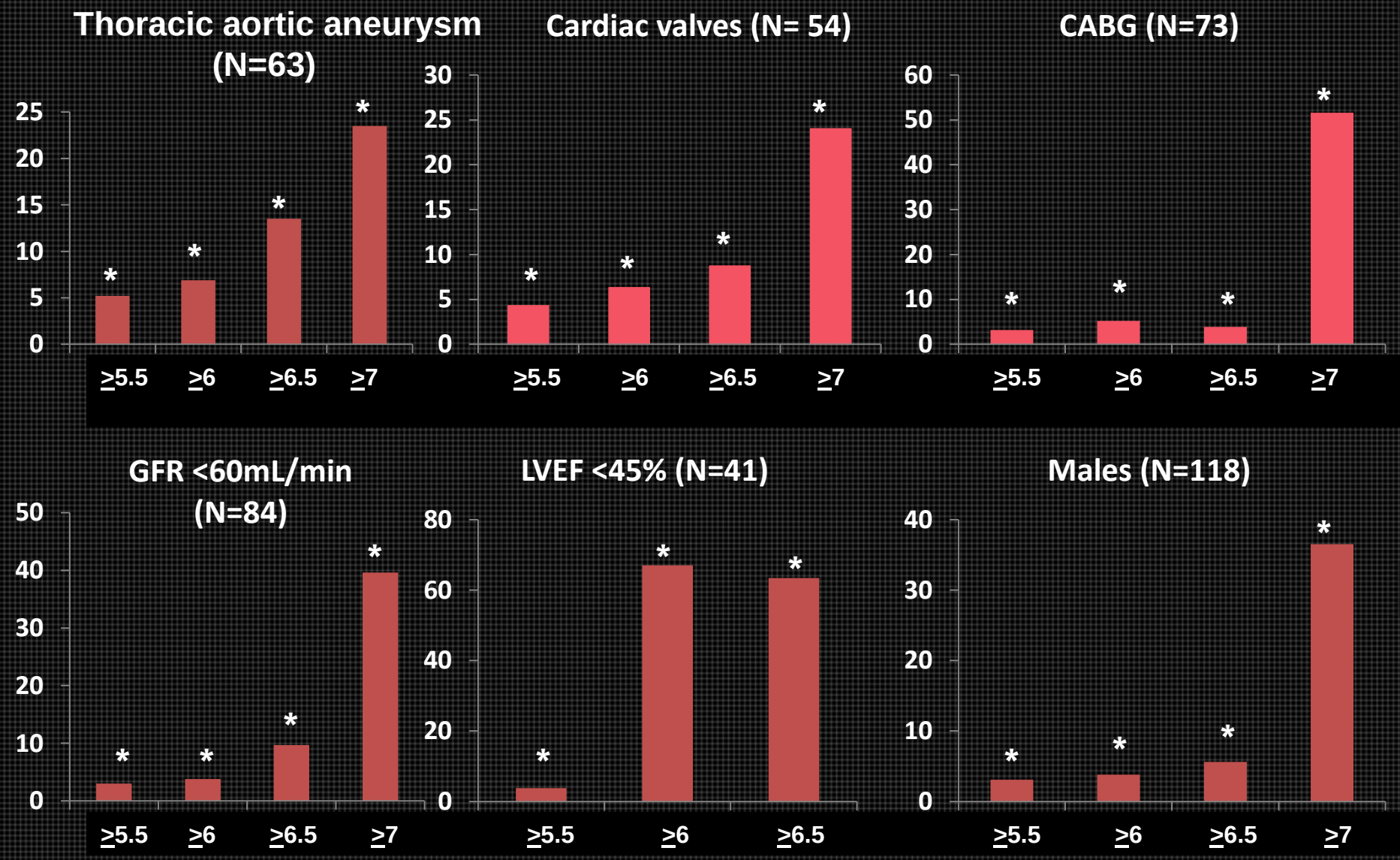


Lapsia/Ejaz Am J Med 2012 Mar;125(3):302.e9

Multivariate analysis: Substitution of SUA≥7mg/dL with other SUA values

SUA ≥5.5mg/dL:	OR for AKI:	3.83	$CI_{95\%}$ 1.93-7.63	p<0.001
SUA ≥ 6mg/dL:	OR for AKI	5.15	$CI_{95\%}$ 2.56-10.35	p<0.001
SUA ≥6.5mg/dL:	OR for AKI	6.79	$CI_{95\%}$ 3.23-14.23	p<0.001
For reference SUA ≥7mg/dL:	OR for AKI	39.68	$CI_{95\%}$ 11.1-141.9	p<0.001

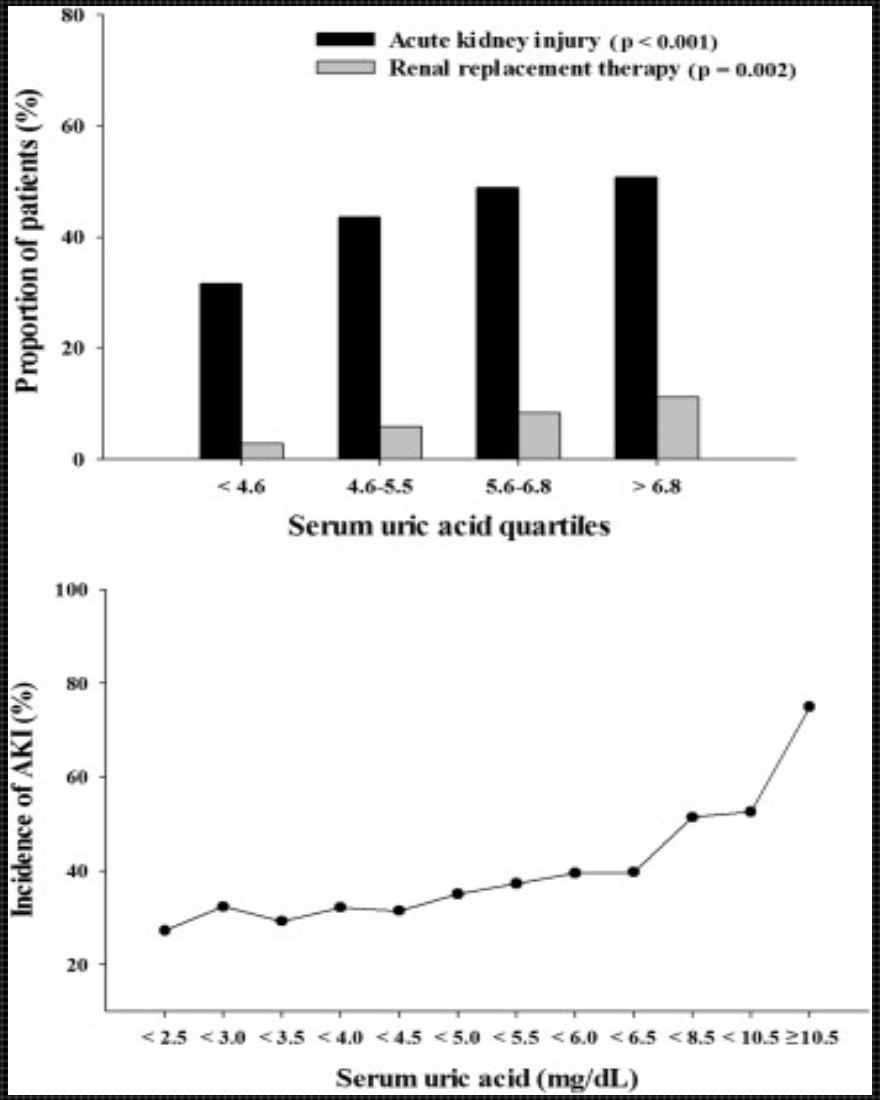
Multivariate analysis in subgroups at high risk for AKI



Lapsia/Ejaz Am J Med 2012 Mar;125(3):302.e9

Epidemiological evidence

Association of Preoperative Uric Acid and Acute Kidney Injury Following CV Surgery.



Preoperative elevated uric acid (≥6.5 mg/dL) was associated independently with AKI after CV surgery
OR 1.46;
95%CI 1.04–2.06, p = 0.030).

N=1019

J Cardiothorac Vasc Anesth. 2014, S1053-0770:00178

Epidemiological evidence

Investigation of the relationship between post-op serum uric acid and AKI and comparison with conventional and novel biomarkers of AKI.

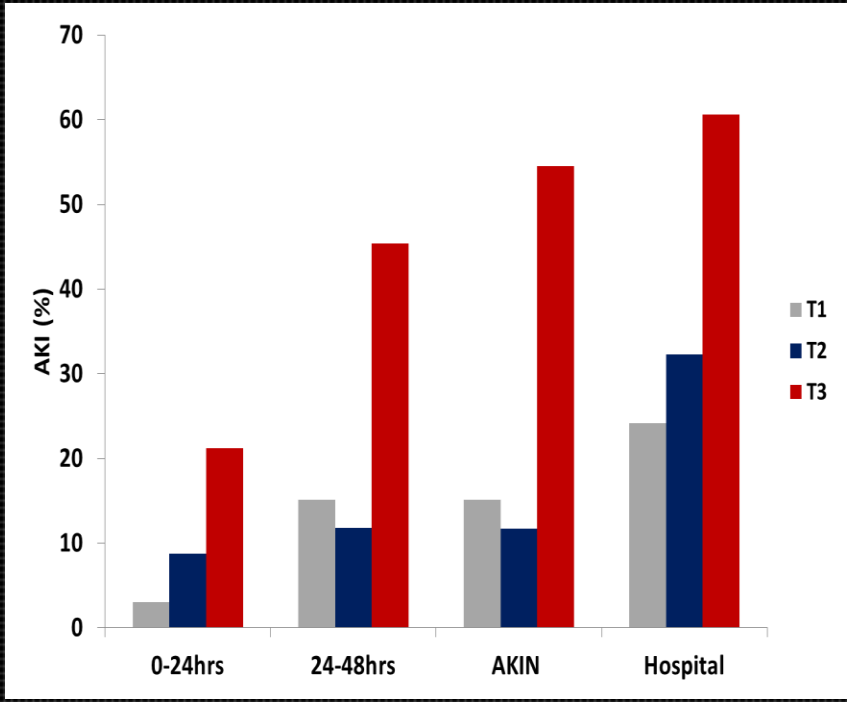
Full cohort SUA: 5.3±0.1mg/dL.
Mean SUA with AKI :6.4±0.3mg/dL
no AKI:4.9±0.1mg/dL, p<0.001

OR for AKI: 0.49, $CI_{95\%}$ 0.35-0.71, p<0.001)

SUA has a graded relationship with AKI, therefore we divided SUA into tertiles

1st tertile SUA≤ 4.53mg/dL
2nd tertile SUA> 4.53mg/dL and ≤ 5.77mg/dL
3rd tertile SUA> 5.77mg/dL.

N=100



T1= 1st SUA tertile, T2= 2nd SUA tertile, T3= 3rd SUA tertile, AKIN: 0-48hours

Major finding: postoperative SUA was associated with an increased incidence of AKI and graded risk for AKI.

The 1st, 2nd, and 3rd SUA tertiles were associated with 15.1%, 11.7%, and 54.5% incidence of AKI, respectively.

Ejaz, J Nephrology 2012; 25:497

- **The 3rd SUA tertile: OR 8.38, CI95% 2.13-33.05, p=0.002) risk for AKI.**

  Compared to referent 1st tertile

- 3rd tertile vs. referrent 1st SUA tertile:

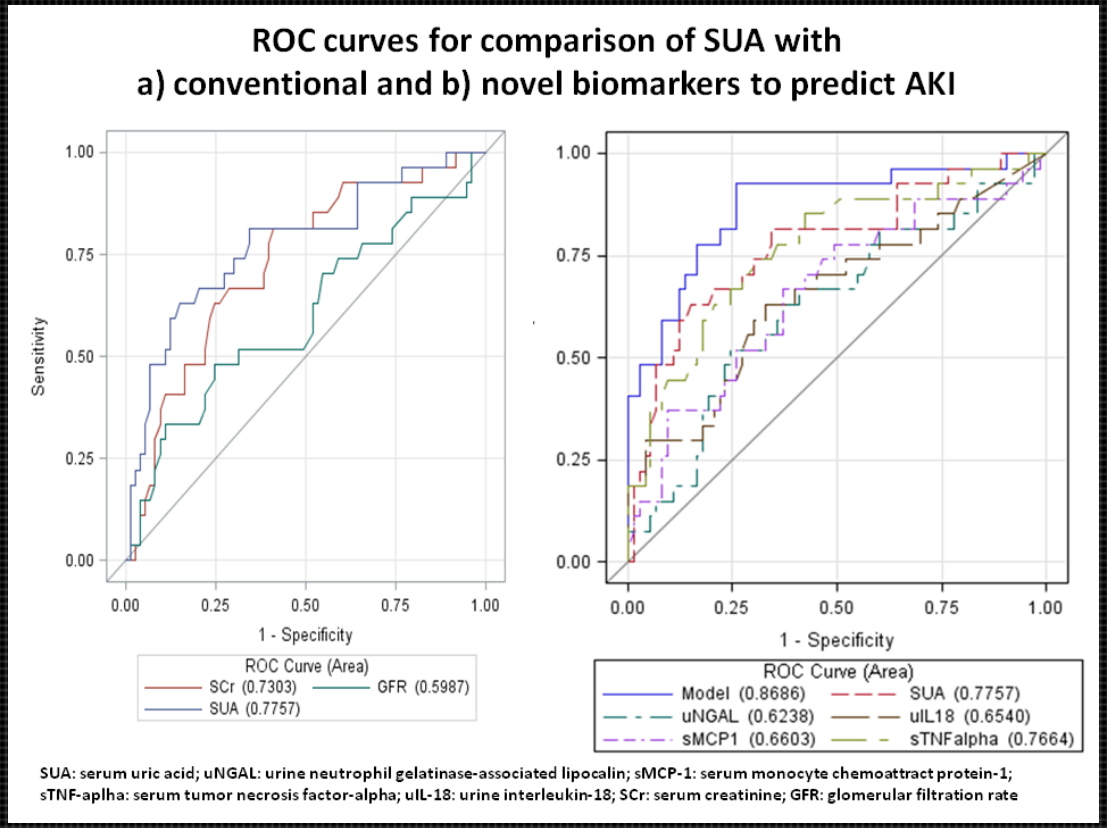
  AKI on day 2: **adjusted OR 7.94, $CI_{95\%}$ 1.50-42.08, p=0.015**

  AKI during hospital stay: **adjusted OR 4.83, $CI_{95\%}$ 1.21-19.20, p=0.025**

- **Since the prooxidant effect of SUA manifests at levels ≥5.5mg/dL, we also calculated that the incidence of AKI for**

  SUA<5.5mg/dL 13.1% vs.
  SUA≥5.5mg/dL 48.7%, p<0.001.

•**Important finding:** was that SUA had comparable predictive values as the *conventional preoperative* biomarker SCr and *novel* biomarkers at 24 hours from start of surgery, and was superior to preoperative GFR.



•The observations that pre- and postoperative SUA are associated with AKI offers the potential to predict AKI at any perioperative time-point.

Epidemiological evidence

PLOS | ONE

RESEARCH ARTICLE

Uric Acid and the Prediction Models of Tumor Lysis Syndrome in AML

A. Ahsan Ejaz[1]*, Negiin Pourafshar[1], Rajesh Mohandas[1,2], Bryan A. Smallwood[3], Richard J. Johnson[4], Jack W. Hsu[5]

- Prediction of TLS and institution of prophylactic and therapeutic options are paramount to the favorable clinical outcomes for patients undergoing cancer treatment.
- The current prediction models of laboratory TLS (LTLS) in acute myeloid leukemia (AML) are based on white blood cell count (WBC), with or without lactate dehydrogenase (LDH), and specific cytogenetic abnormalities and karyotype complexity.
- None of the prediction models include SUA.
- We have demonstrated that SUA is an independent predictor of acute kidney injury (AKI).
- Given our findings, we wanted to **investigate the discrimination ability of baseline SUA to predict TLS and also to compare it to common laboratory variables, cytogenetic profiles, tumor markers and prediction models in acute myeloid leukemia patients.**

Ejaz/Hsu PLoS One. 2015; 10(3):e0119497

Retrospective study of 183 AML patients between 2000-2012

- ***Cairo-Bishop* definition of LTLS**
  - **Uric acid ≥8 mg/dL or 25% increase from baseline**
  - **Potassium ≥6 mEq/L or 25% increase from baseline**
  - **Phosphorus ≥6.5 mg/dL (children) or ≥4.5 mg/dL (adults) or 25% increase from baseline**
  - **Calcium ≤7 mg/dL or 25% decrease from baseline**

Cairo prediction model
Low: WBC <25x10^9/L and LDH <2x ULN
Intermediate: WBC ≥25x10^9/L and LDH ≥2x ULN
High: WBC≥100x10^9/L

SUA prediction model
Low: SUA <5.5mg/dL
Intermediate: SUA >5.5mg/dL and <7mg/dL
High: SUA > 7mg/dL

NHS prediction model
Low: WBC <10x109/L
Intermediate: WBC 10-50x109/L
High: WBC >50x109/L
Does not include LDH

CALGB prediction model
Favorable
Intermediate
Adverse groups
based on remission outcomes for specific cytogenetic abnormalities and karyotype complexity.

British J Haematol 2010; 149:578
http://www.royalsurrey.nhs.uk/Default.aspx?DN=45ce893f-8494-413f-9dc6-b3c7a6e21a51

CALGB prediction model

Cytogenetic risk group	Induction success	Cumulative incidence of relapse	Overall survival
Favorable	t(8;21) inv(16) or t(16;16)	t(8;21) inv(16) or t(16;16)	t(8;21) inv(16) or t(16;16) del(9q)
Intermediate	Normal karyotype −Y del(5q) t(6;9) t(6;11) −7 Loss of 7q +8 sole +8 with 1 other abnormality del(9q) t(9;11) +11 del(11q) t(11;19)(q23;p13.1) +13 del(20q) +21	Normal karyotype −Y t(9;11) del(9q) +8 sole +8 with 1 other abnormality +11 +13	Normal karyotype −Y del(5q) Loss of 7q t(9;11) +11 del(11q) abn(12p) +13 del(20q) +21
Adverse	Complex karyotype (≥ 3 abnormalities) inv(3) or t(3;3) abn(12p)	Complex karyotype (≥ 3 abnormalities) −7 +21	Complex karyotype (≥ 3 abnormalities) inv(3) or t(3;3) t(6;9) t(6;11) −7 +8 sole +8 with 1 other abnormality t(11;19)(q23;p13.1)

Univariate analysis of risk factor for LTLS in AML

Variables	LTLS		
	OR	$CI_{95\%}$	p-value
Pretreatment laboratory			
WBC (full cohort), N=183	1.00	0.9-1.0	0.390
WBC <10x10^9/L, N=95	0.94	0.7-1.2	0.603
WBC 10-50x10^9/L, N=43	0.98	0.9-1.0	0.477
WBC >50x10^9/L, N=15	1.00	0.9-1.0	0.449
WBC >100x10^9/L, N=6	0.99	0.9-1.0	0.943
SUA (full cohort), N=183	1.12	1.0-1.2	0.042
SUA low risk, N=113	0.33	0.2-0.6	<0.001
SUA intermediate risk, N=38	1.22	0.5-3.1	0.663
SUA high risk, N=32	7.26	3.2-16.6	<0.001
LDH, N=145	1.00	1.0-1.0	0.930
LDH, 2xULN, N=65	1.00	1.0-1.0	0.486
Tumor markers			
CD34, N=99	0.32	0.1-0.6	<0.001
Cytogenetics			
CALGB (full cohort)=169	1.83	1.1-3.2	0.031
CALGB adverse, N=48	0.56	0.2-1.3	0.169
CALGB intermediate, N=96	0.89	0.4-1.8	0.755
CALGB favorable, N=25	2.62	1.1-6.3	0.032
Gene mutations			
NPM1, N=33	1.00	0.1-5.1	1.000
FLT3, N=35	0.87	0.2-3.4	0.322

Adjusted model

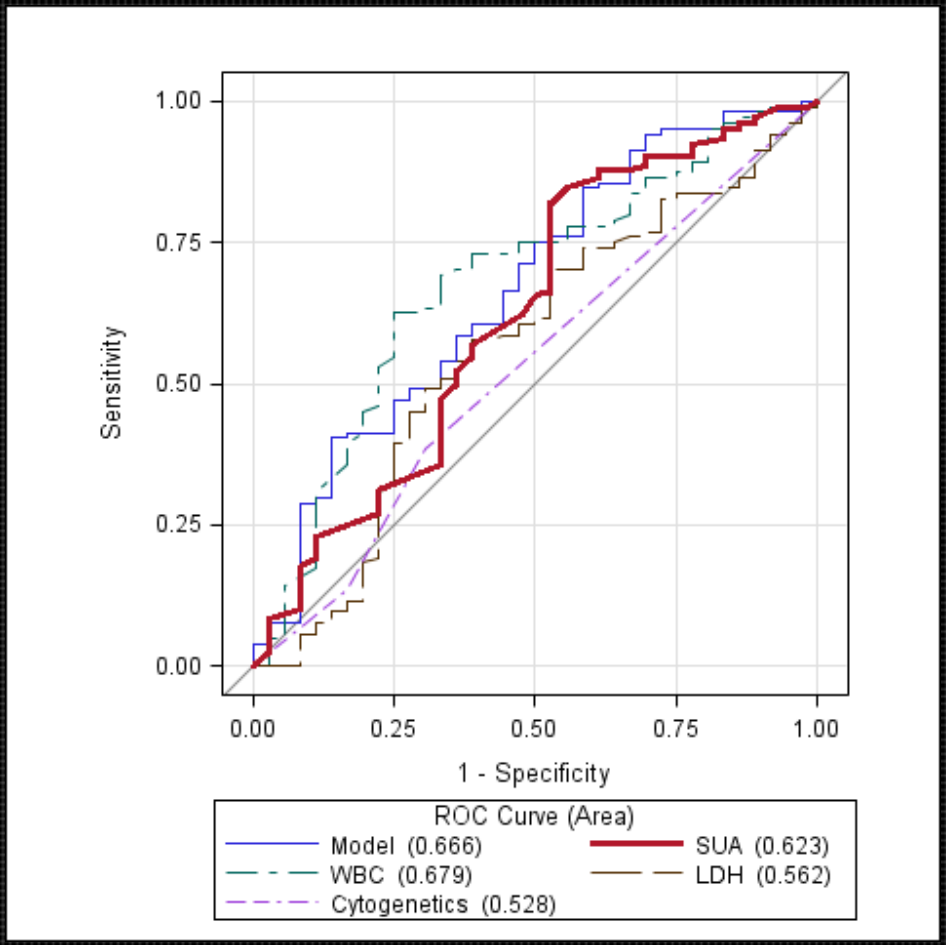
CALGB favorable:
OR 2.7, CI95% 1.1-6.5, p=031

baseline SUA
OR 1.12, CI95% 1.0-1.3, p=0.048)

SUA high-risk
OR 6.6, CI95% 2.4-17.9, p<0.001

$LTLS_{modified}$
baseline SUA
OR 2.8, CI95% 1.1-7.1, p=0.033.

Comparison of clinical parameters to predict LTLS

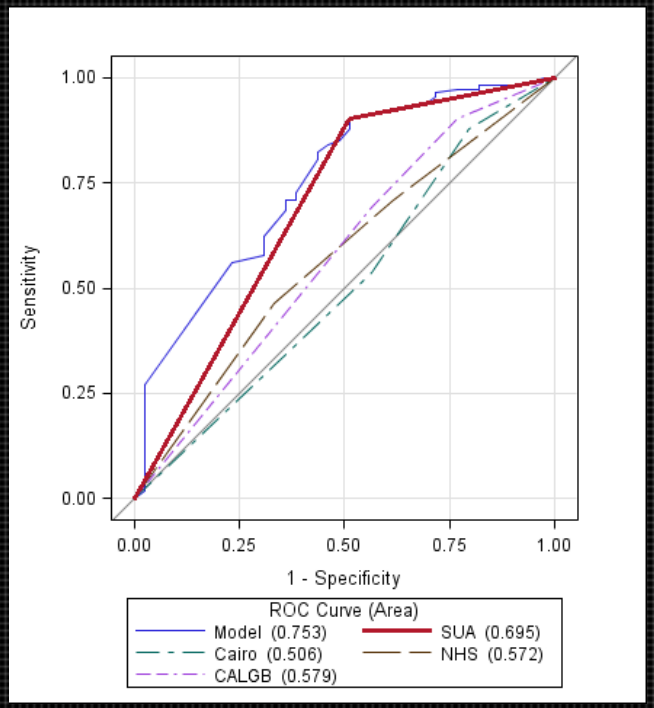


The discriminatory ability of SUA was superior to LDH, cytogenetic profile and tumor markers *but not to WBC (AUC_{WBC} 0.679).*

However in comparisons between high-risk SUA and high-risk WBC, SUA had superior distinguishing capability (AUC_{SUA} 0.664 vs. AUC_{WBC} 0.520; p <0.001) to predict LTLS.

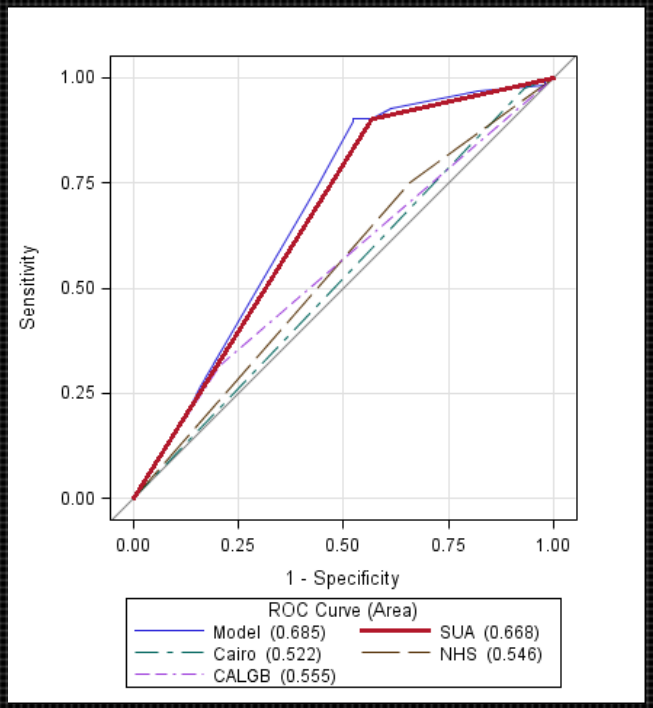
Major finding: SUA had comparable predictive value as conventional prediction models and the combined model.

Prediction models



SUA demonstrated better performance than the prediction models ($AUC_{\text{high-risk SUA}}$ 0.695, p<0.001)

High-risk groups



In direct comparison of high-risk groups of each prediction model, SUA again demonstrated superior performance than the prediction models ($AUC_{\text{high-risk SUA}}$ 0.668, p=0.001) in predicting LTLS, approaching that of the combined model (AUC 0.685, p<0.001

Interventional data

Int Urol Nephrol (2013) 45:449–458
DOI 10.1007/s11255-012-0192-2

NEPHROLOGY - ORIGINAL PAPER

Effect of uric acid lowering therapy on the prevention of acute kidney injury in cardiovascular surgery

A. Ahsan Ejaz · Bhagwan Dass · Vijaykumar Lingegowda · Michiko Shimada · Thomas M. Beaver · Noel I. Ejaz · Amer S. Abouhamze · Richard J. Johnson

Pilot Study

Inclusion
1. Age > 18 years
2. CABG, Valves, TAA
3. Serum Uric Acid > 6.5mg/dL
4. MDRD GFR >30 - <60ml/min

Exclusion:
1. adverse reaction to Rasburicase
2. Study drug cannot be administered at least 2 hours prior to CPB
3. Organ transplant recipient
4. On IABP

Eligible patient → **Randomization** → **Placebo control** / **Rasburicase**

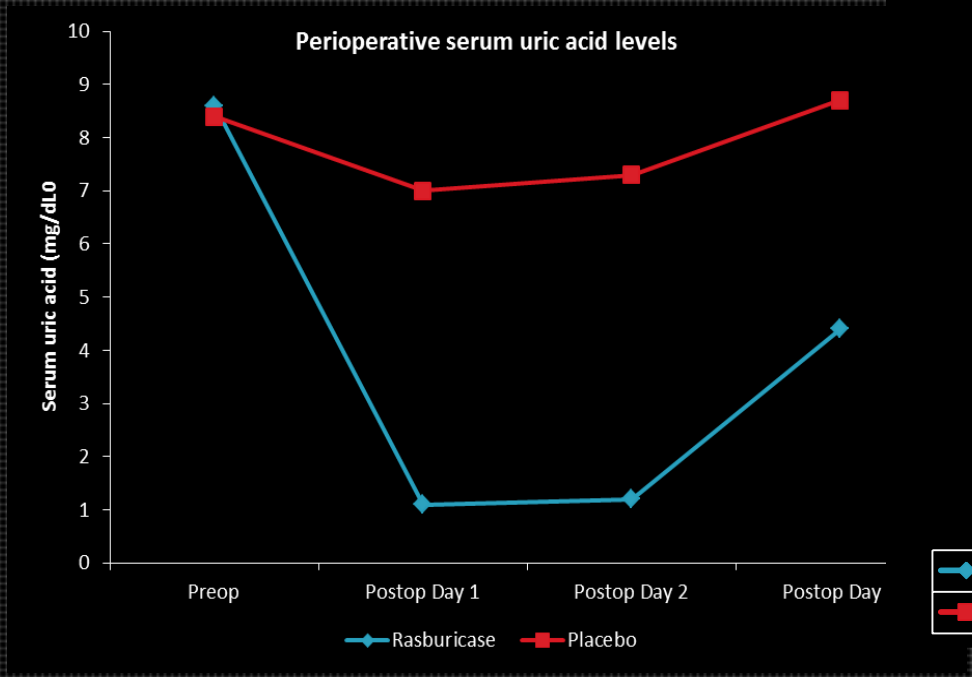
Study Drug 2-4 hours prior to CPB

SUA
>5mg/dL : Study drug
<5mg/dL : No study drug

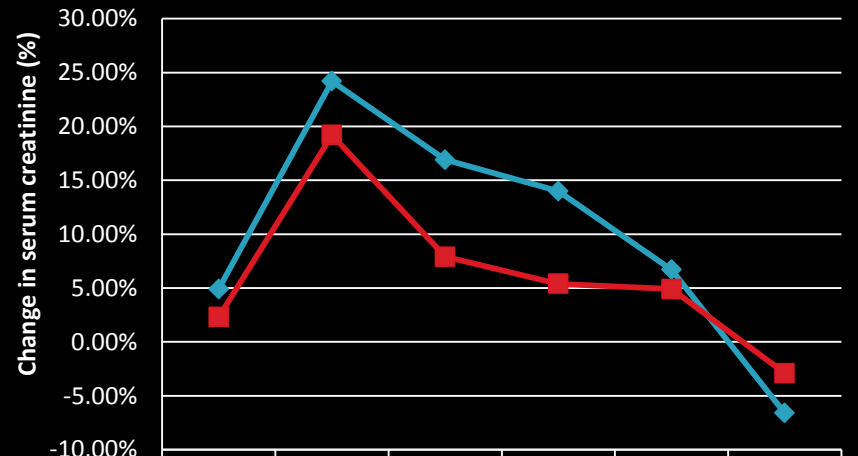
OR / CPB → ***Post-op 24hr*** → ***Post-op 48hr*** → ***Post-op 120hr*** → ***Dialysis /+ Death 28-day***

Ejaz Int J Urol Nephrol 2013; 45:449

Effect of rasburicase on Screat

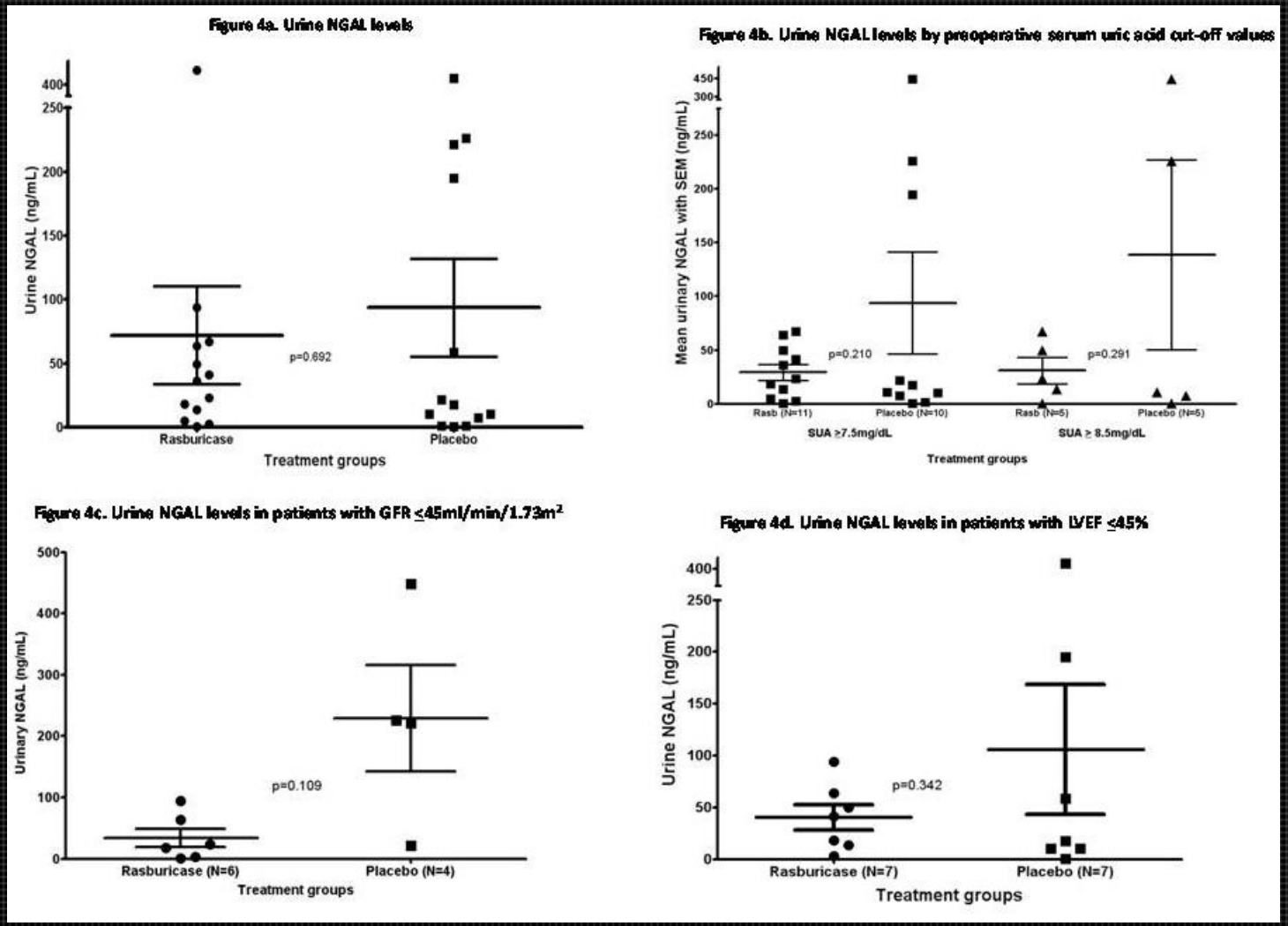


No benefits on SCreat were observed



	Day1	Day2	Day3	Day4	Day5	Discharge
Rasburicase	4.90%	24.20%	16.90%	14%	6.70%	-6.60%
Placebo	2.30%	19.20%	7.90%	5.40%	4.90%	-2.90%

Lowering hyperuricemia resulted in less renal structural injury as measured by the AKI biomarker NGAL



Epidemiological evidence

American Journal of Nephrology

Original Report: Patient-Oriented, Translational Research

Am J Nephrol 2015;42:402–409
DOI: 10.1159/000443283

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Effects of Serum Uric Acid on Estimated GFR in Cardiac Surgery Patients: A Pilot Study

A. Ahsan Ejaz[a] Kawther F. Alquadan[a] Bhagwan Dass[a] Michiko Shimada[b]
Mehmet Kanbay[c] Richard J. Johnson[d]

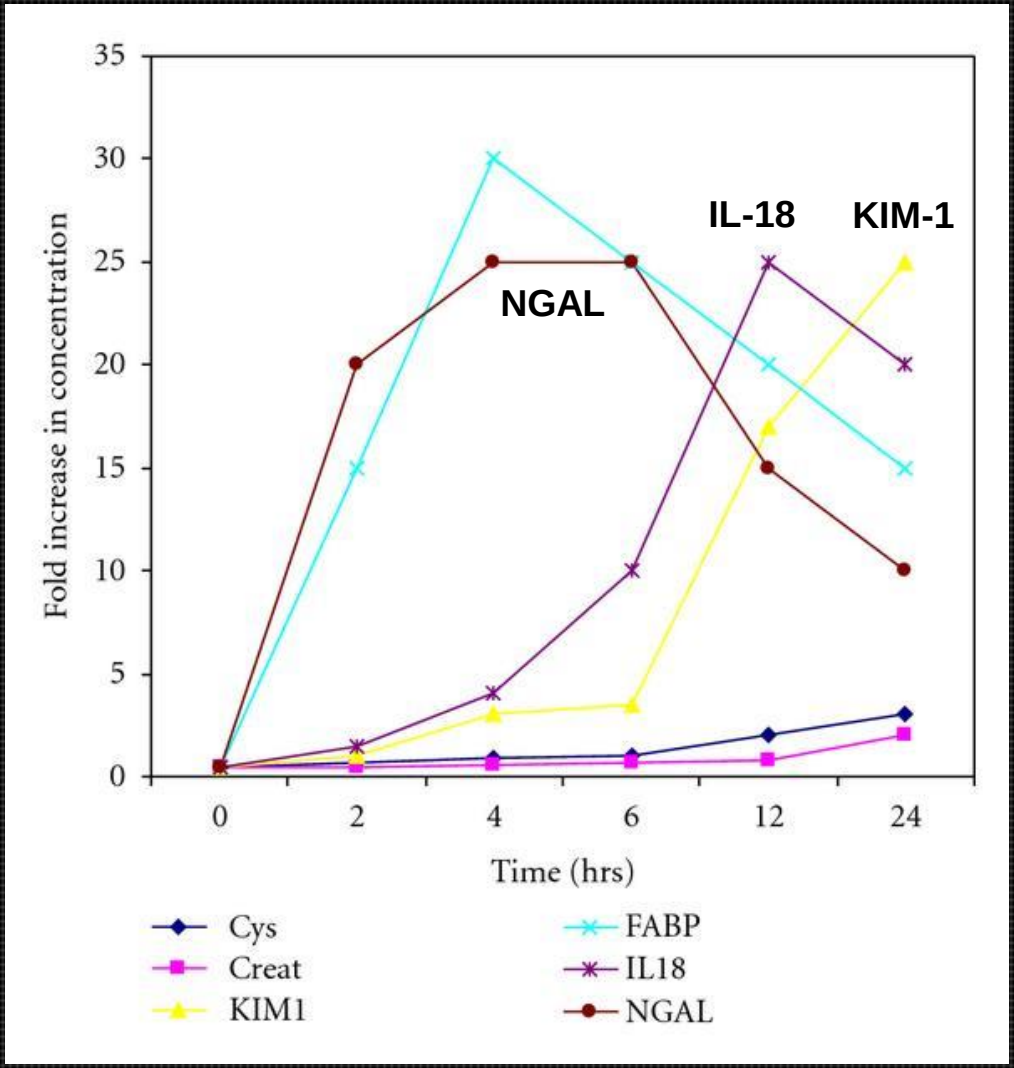
The effect of SUA on GFR) in the non-steady state is uncertain, calculations of which have been hindered by the technical complexities and the lack of broad consensus on guidelines about estimating GFR.

Chen has recently retooled the fundamental creatinine clearance equation with the power and versatility to estimate renal function under non-steady conditions.

We therefore utilized this novel kinetic estimated GFR (KeGFR) method, along with traditional (serum creatinine, SCr) and non-traditional biomarkers (NGAL) to investigate the effects of SUA on renal function in patients undergoing cardiac surgery.

Ejaz Am J Nephrol. 2015; 42:402

Tmax for NGAL, IL-18 and Screat following ischemia-reperfusion injury



SCR

Methods and Materials

N=37

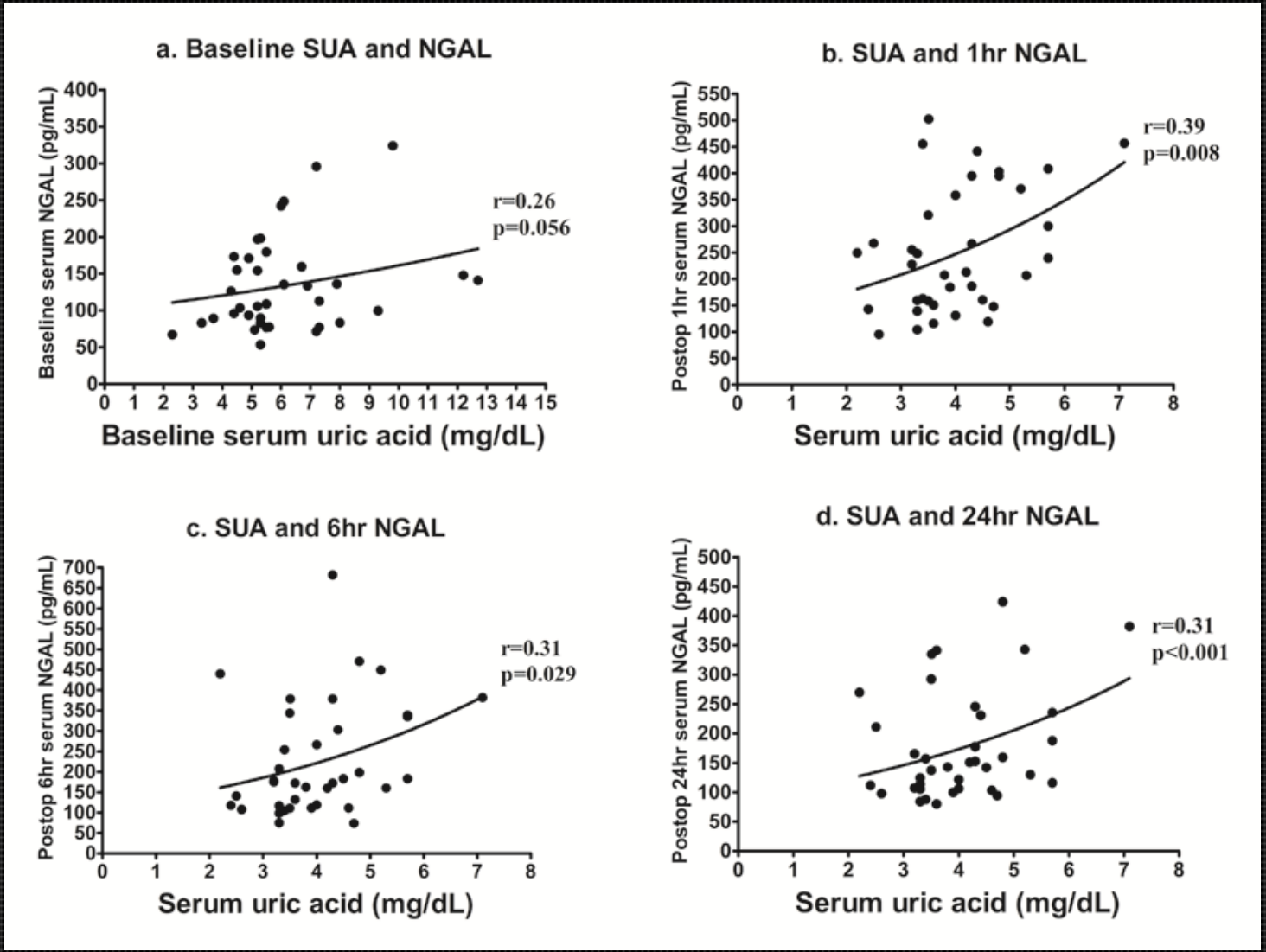
Adjusted for dilution effect of intraoperative fluid administration on SCr adjusted according to the following equation (Macedo)

SCr adjustments were performed for postoperative SCr values. Daily cumulative fluid balance was calculated according to the following formula: (sum of daily fluid received (L) - total amount of fluid eliminated (L)/preoperative weight (kg) × 100).

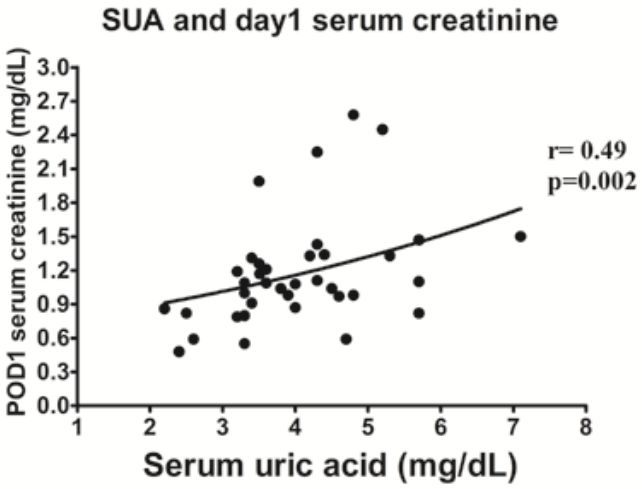
KeGFR: kinetic estimated GFR

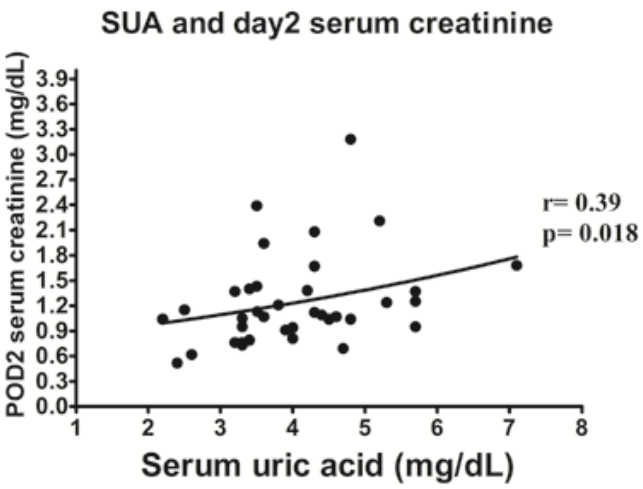
Since there is no broad consensus method to correct for dilution effect on SUA, we used the absolute value of SUA measured at 1hr (SUA1h) post aortic cross-clamp (ACC) release, the time of maximum dilution based on our previous studies.

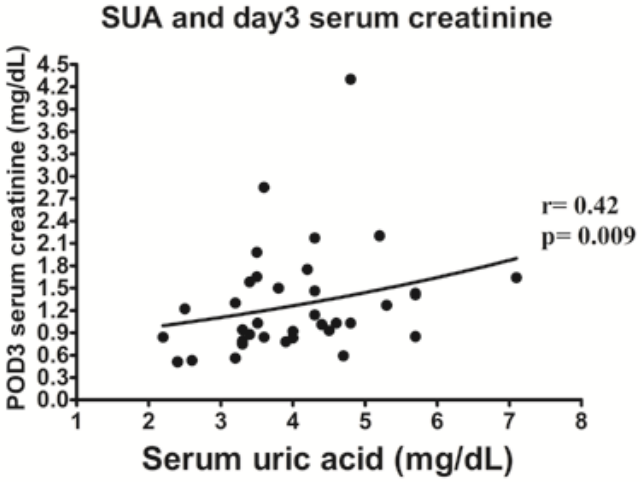
Early biomarkers as a function of SUA concentration.

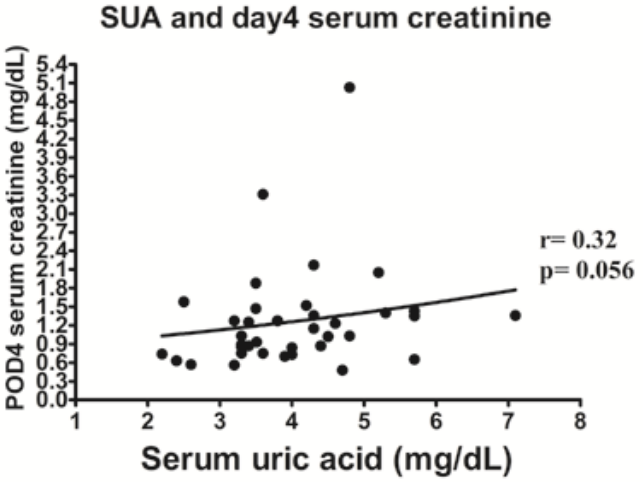


Conventional biomarkers as a function of SUA concentration.



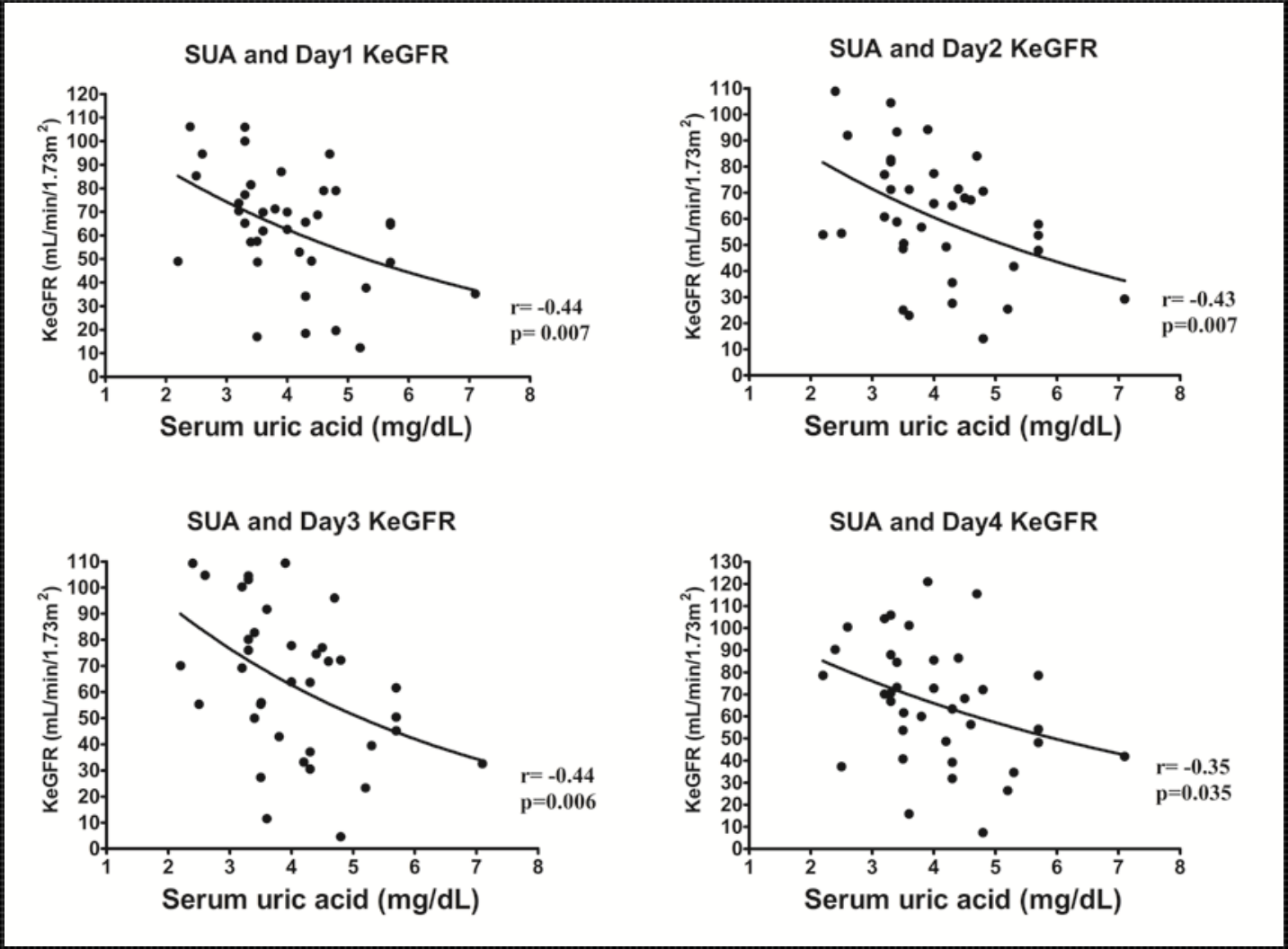




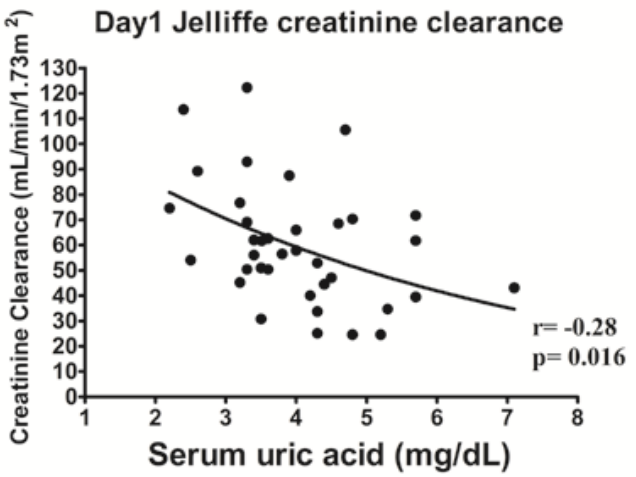


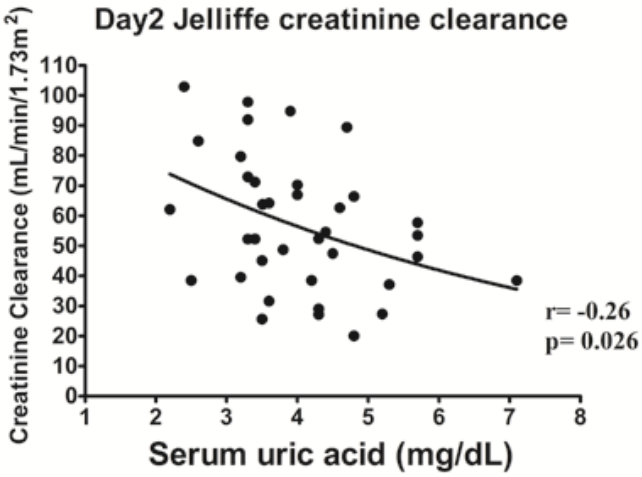
POD: postoperative day

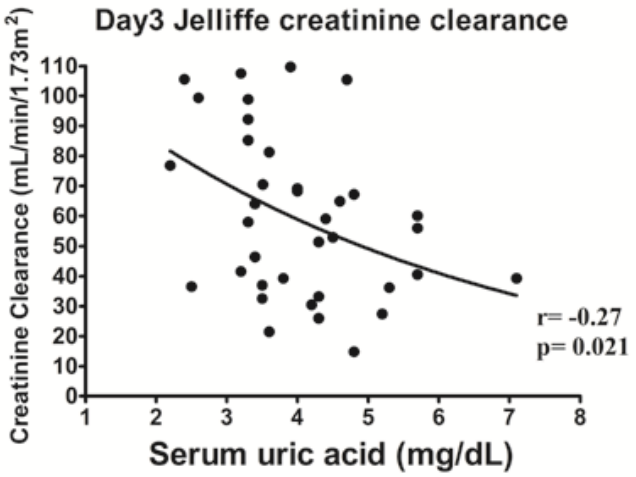
Kinetic eGFR as a function of SUA concentration.

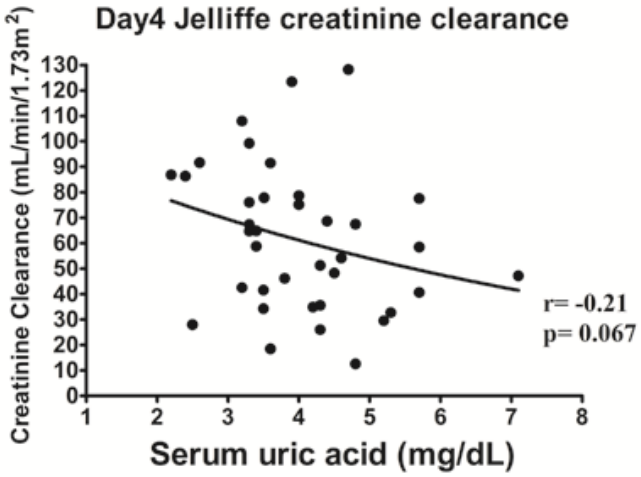


Confirmation with Jeliffe creatinine clearance









Major findings

The major findings of the study were the demonstration of significant correlations of SUA_{1h} with early biomarkers (NGAL) and traditional biomarkers (SCr) of kidney injury and inverse correlations with KeGFRs measured by two independent method developed especially for use in non-steady states.

Furthermore, the highest tertile of SUA_{1h} was associated with more severe renal injury as measured by NGAL in comparison to that associated with the lowest SUA_{1h} tertile.

The results provide further evidence that SUA_{1h} is a predictor of acute kidney injury in the early, intermediate and late phases of injury and also that higher SUA_{1h} concentrations are associated with lower KeGFRs.

These findings suggest that uric acid precedes and predicts acute changes in renal function and cannot be ascribed to a simple relationship in which a reduced GFR raises serum uric acid.

Conclusion

Provided experimental, epidemiological and interventional data of the role of uric acid in AKI

Uric acid contributes to acute kidney injury
- impairs renal blood flow autoregulation, causes severe cortical vasoconstriction and decreases renal flow and GFR, stimulates inflammatory response

Serum uric acid is an intriguing risk factor and target for treatment



Thank you

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UNIVERSITY of FLORIDA