Hypertensive Kidney Injury and the Progression of Chronic Kidney Disease

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Renal Section Chief
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Hypertension in the United States
75 million

< 0.5% ESRD
Susceptibility Patterns of Hypertensive Renal Damage

Bidani and Griffin, *Hypertension* 2004; 44: 595-601
Hypertensive Renal Damage
Susceptibility Patterns in Experimental Models

![Graph showing renal damage score vs. average systolic BP for different groups.](image)

- Sprague-Dawley Control (n=7)
- RK-I (n=16)
- SHR (n=9)
- SHR + NaCl (n=16)
- SHRsp (n=10)
- SHRsp + NaCl (n=18)

$r^2=0.77$
$r^2=0.59$

Loutzenhiser, Griffin, Williamson, Bidani *Am J Physiol* 2006; 90:R1153-R1167
Remnant Kidney Model of CKD (5/6 Ablation)

- Compensatory Hyperfiltration and Hypertrophy
- Hypertension
- Proteinuria
- Progressive GS
Hypertensive Renal Damage
Susceptibility Patterns in Experimental Models

Loutzenhiser, Griffin, Williamson, Bidani *Am J Physiol* 2006; 90:R1153-R1167
Renal Autoregulation and Susceptibility to Hypertensive Damage

Renal Blood Flow (%)

Arterial Pressure, mmHg

60 90 120 150 180 210 240

50 100 150 200

Remnant Kidney Model

Vasodilation

Susceptibility Patterns of Hypertensive Renal Damage

- Malignant Nephrosclerosis
- Diabetic Nephropathy / Chronic Kidney Disease Accelerated GS
- Benign Nephrosclerosis

Bidani and Griffin, *Hypertension* 2004; 44: 595-601
SHRsp Model of Malignant Nephrosclerosis (Prevention)

Griffin KA et al., Hypertension 2014;64:801-7
SHRsp Model of Malignant Nephrosclerosis (Prevention)

- 1% NaCl (n=27)
- 1% NaCl + H&H (n=15)
- 1% NaCl + Enalapril (n=15)
- 1% NaCl + Amlodipine (n=13)

Renal Damage Score

Average SBP (mmHg) - Final 2 Weeks

Griffin KA et al., Hypertension 2014;64:801-7
SHRsp Model of Malignant Nephrosclerosis (Repair)

Griffin KA, et al., Hypertension 2014;64:801-7
SHRsp Model of Malignant Nephrosclerosis (Repair)

Griffin KA, et al., *Hypertension* 2014;64:801-7
Remnant Kidney Model of CKD (5/6 Ablation)

• Compensatory Hyperfiltration and Hypertrophy

• Hypertension

• Hyperfiltration vs. Hypertension

• Progressive GS
Pathogenesis of Glomerulosclerosis in Renal Mass Reduction Models

Griffin et al, JASN 1994; 4: 2023-2031
Pathogenesis of Glomerulosclerosis in Renal Mass Reduction Models

24 Hour Mean Systolic BP (mmHg)

Days

RK-1 5/6 (n=10)
RK-1 2/3 (n=10)
RK-NX 5/6 (n=12)
SHAM (n=8)

Griffin et al, JASN 1994; 4:2023-2031
Pathogenesis of Glomerulosclerosis in Renal Mass Reduction Models

- Sham (n=16)
- RK-1 2/3 (n=22)
- RK-1 5/6 (n=21)
- RK-NX (n=23)

Urine Protein (mg/24 h)

% Glomerular Injury

* P < 0.01 vs sham and RK-NX 5/6
Hyperfiltration in Normotensive States

\[ \uparrow Q_A, \uparrow K_f \text{ (GC Volume)} \]

Minimal glomerulosclerosis


- Normal Pregnancy  (*AJKD* 1989; 290-298)
- Renal Transplant Donors  (*NEJM* 2009; 360:459-469)

Hypertensive States: \( \uparrow P_{GC}, \text{ but } \downarrow K_f \text{ due to a reciprocal relationship} \)

*JCI* 1986; 77:1993-2000

EFFECTS OF HYPERTENSION AND IMPAIRED AUTOREGULATION ON CKD PROGRESSION
(8 WEEKS – Hematoxylin/Eosin)

Renal Autoregulation and Susceptibility to Hypertensive Damage


Average Systolic BP, mmHg

- RK-I (n=16)
- SHRsp (n=27)

P < 0.01 maximum vs RK-I

Quantitative Relationship Between BP and Renal Injury

BP – RBF Relationships in Conscious Angiotensin II vs. Phenylephrine-induced Hypertensive Rats

Angiotensin II

10 seconds


BP – RBF Relationships in Conscious Angiotensin II vs. Phenylephrine-induced Hypertensive Rats

Susceptibility to Hypertensive Renal Damage

BP | Pre-glomerular resistance | Glomerular Capillary Pressure (45-50 mmHg) | Post-glomerular resistance | Efferent Arteriole
NOS Expression in the Renal Microvasculature


Kriz and Bachmann J Cardiovasc Pharm 1985; 7: S24-30;

- nNOS
- eNOS
Ang II vs. L-NAME-induced Hypertension

- Ang II-induced hypertension exhibits a diminished susceptibility to renal injury as compared to L-NAME-induced hypertension.

- BP – RBF relationships in conscious Ang II-infused rats suggests this is likely due to reduced transmission of elevated systemic BP to the renal microvasculature.

Hypertensive Renal Damage (Impact of Susceptibility and BP Differences)

Collaborators

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University of Calgary

Manjeri Venkatachalam, M.D.
Univ. of Texas, San Antonio

Geoffrey Williamson, Ph.D.
Illinois Institute of Technology

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Department of Veterans Affairs Merit Review Award
Renal Circulation: Pressure Profiles

# Pathogenesis of Glomerulosclerosis in Renal Mass Reduction Models

## MICROPUNCTURE AND MORPHOMETRIC DATA AT 3 WEEKS

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Modification of the Relationship Between Blood Pressure and Renal Albumin Permeability by Impaired Excretory Function and Diabetes

James Fotheringham, Aghogho Odudu, William McKane, Timothy Ellam

Abstract—In animal models, reduced nephron mass impairs renal arteriolar autoregulation, increasing vulnerability of the remaining nephrons to elevated systemic blood pressure (BP). A feature of the resulting glomerular capillary hypertension is an increase in glomerular permeability. We sought evidence of a similar remnant nephron effect in human chronic kidney disease. In participants from the United States National Health and Nutrition Examination Surveys 1999 to 2010 (N=23710), we examined the effect of reduced estimated glomerular filtration rate (eGFR) on the relationship between brachial artery BP and albumin permeability. Renal albumin permeability increased exponentially with systolic BP >110 mmHg, and this association was modified by independent interactions with both excretory impairment and diabetes mellitus. Each 10 mmHg increase in systolic BP was accompanied by an increase in fractional albumin excretion of 1.10-, 1.11-, 1.17-, 1.22-, and 1.38-fold for participants with eGFR≥90, 90>eGFR≥60, 60>eGFR≥45, 45>eGFR≥30, and eGFR<30 mL/min/1.73 m², respectively, adjusted for age, sex, race, antihypertensive use, eGFR category, diabetes mellitus, smoking, history of cardiovascular disease, body mass index, and C-reactive protein. A 10 mmHg systolic BP increment was associated with increases in fractional albumin excretion of 1.10- and 1.21-fold in nondiabetic and diabetic participants, respectively. Using urine albumin creatinine ratio as an alternative measure of albumin leak in eGFR-adjusted analyses gave the same conclusions. Our findings are consistent with the presence of a remnant nephron effect in human kidney disease. Future trials should consider the nephroprotective benefits of systolic BP lowering in kidney disease populations stratified by eGFR.