Kidney and hypertension
Eberhard Ritz
Heidelberg
(Germany)
Klahr S.
The kidney in hypertension –
villain and victim

Hypertension: The kidney is the culprit even in the absence of kidney disease


Why is World Kidney Day an occasion to raise the issue of whether or not the kidney is involved in the genesis of high blood pressure? High blood pressure affects approximately 30% of the adult population in Western countries,1 tendency rising, and even 80% of people older than 80 years, so that a cynic stated, “The only safeguard against hypertension is to die early.” The burden of high blood pressure is a major, if not the major, public health problem.2

... a polygenic disorder that is dependent on the interaction among several genetic defects, all rare monogenic forms of hereditary hypertension have one common denominator: increased sodium reabsorption by the kidney at different sites and by different mechanisms along the tubules.9

Recently, more insight into the link between a kidney abnormality and hypertension in ‘run-of-the-mill’ essential hypertension has been provided by anatomical studies of the kidney. The number of glomeruli, and, by implication, of tubules, in

Kidney and Hypertension

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2. Hypertension goes with the kidney
3. Antihypertensive treatment in CKD – what do the guidelines say?
4. What is the evidence of the benefit of antihypertensive treatment
5. Treatment targets: beyond blood pressure – lowering of proteinuria
6. Are all antihypertensive agents created equal?
High urinary albumin excretion precedes onset of overt hypertension

- Brantsma A.H. et al
  *Urinary albumin excretion as a predictor of the development of hypertension*

- Wang T.J. et al.
  *Low-grade albuminuria and the risks of hypertension and blood pressure progression*
  Circulation (2005) 111: 1370
Independent of urinary albumin elevated **Cystatin C** precedes onset of **hypertension**

Renal malfunction cause and hypertension consequence?

\[ \Delta 15 \text{ nmol/L Cystatin C} \rightarrow 15\% \text{ greater 3.1 year incidence of hypertension} \]

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   lowering of proteinuria
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Animal experiments: blood pressure “goes with the kidney”

kidney genetically programmed for hypertension, transplanted into a normotensive recipient animal with no immunerejection

persistent hypertension

Persistent normotension after kidney graft from normotensive donor

6 black patients
dialysis dependent because of “essential hypertension”
nephrosclerosis by histology
kidney graft from normotensive donor

after 4.5 years follow-up
all - normotensive
- normal BP response to Na loading / deprivation

<table>
<thead>
<tr>
<th></th>
<th>hypertensive individuals (n=10)</th>
<th>normotensive individuals (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of glomeruli</td>
<td>890,869 ± 158,110</td>
<td>1,666,805 ± 411,690</td>
</tr>
<tr>
<td>volume of glomeruli</td>
<td>5.67 ± 0.85</td>
<td>2.41 ± 0.71</td>
</tr>
</tbody>
</table>

\( p < 0.001 \)

► no evidence of obsolescent glomeruli as evidence of hypertension induced loss of glomeruli

“Oligomeganephrony“

number

volume

hypertension  

normotension  

Low birthweight —
lower blood pressure at birth → more rapid increase during 1st year

Low birth weight – salt sensitivity of blood pressure in healthy adults

![Graph showing the relationship between birth weight and salt sensitivity.](image)

R = -0.60  P = 0.002

de Boer, Hypertension (2008) 51: 928
High salt diet in pregnant rats → high albuminuria in offspring

Kolegenova, in press
**High salt** diet in pregnant rats

→ *lower number and greater volume of* glomeruli *in offspring*

<table>
<thead>
<tr>
<th>NaCl content of maternal diet (%)</th>
<th>0.15%</th>
<th>1.3%</th>
<th>8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>17,159</td>
<td>22,760</td>
<td>14,310</td>
</tr>
<tr>
<td>±2,632</td>
<td>±8,8270</td>
<td>±2,573</td>
<td></td>
</tr>
<tr>
<td>Glomeruli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>volume (µ³x10⁶)</td>
<td>2.59</td>
<td>4.10</td>
<td>4.83↑</td>
</tr>
<tr>
<td>±0.43</td>
<td>±1.62</td>
<td>±1.19</td>
<td></td>
</tr>
<tr>
<td>kidney weight (g)</td>
<td>2.34</td>
<td>2.33</td>
<td>2.66↑</td>
</tr>
<tr>
<td>±0.22</td>
<td>±0.24</td>
<td>±0.45</td>
<td></td>
</tr>
</tbody>
</table>

*Koleganova, in press*
High salt diet in pregnant rats (8%) → despite low salt diet for offspring after weaning and independent of blood pressure (telemetry) in offspring

Cardiovascular abnormalities in offspring

increased wall thickness:
- aorta
- carotis
- mesenteric
- intrapulmonary

- eNOS ↓
- ADMA ↑
- oxidative stress (8-isoprostane ↑)
- endothelial cell proliferation ↑

....
Loss of nephrons prenatal vs adult life

No excess hypertension in kidney donors

402 alive kidney donors 1964-1995:

- **proteinuria** 12%
- **hypertension** 38%

not exceeding rate in matched Swedish background population

_Fehrman-Ekholm, Transplantation(2001) 72:444_
Hypothesis

• high blood pressure not result of low glomerular number per se
  (less, but bigger glomeruli $\rightarrow$ normal filtration surface)

• but result of developmental changes in postglomerular segments
  (higher sodium reabsorption $\rightarrow$ sodium sensitive blood pressure)
Main mechanisms contributing to hypertension from prenatal programming

- upregulation of sodium channels
- upregulation of renin-angiotensin system (AT1-R)
- cortisol (11βHSD2↓) → mineralocorticoid receptor
- sympathetic overactivity
- ....
Low birth weight – salt sensitivity of blood pressure in healthy adults

\[ R = -0.60 \quad P = 0.002 \]

*de Boer, Hypertension (2008) 51: 928*
The kidney is involved in the genesis of any type of hypertension.

All forms of hypertension are ultimately the consequence of resetting of the pressure natriuresis relationship.
Monogenic (Mendelian) forms of human hypertension
→ increased renal sodium reabsorption
→ salt-sensitivity

Glucocorticoid remediable aldosteronism -
excess production of aldosterone under ACTH control

Apparent mineralocorticoid excess
(11 β-hydroxysteroid dehydrogenase-2 deficiency)

Gain of function mutations of mineralocorticoid receptors

Excess ENaC activity (e.g. Liddle’s syndrome)
Heterozygous carriers of Gitelman mutation (~ thiazide therapy) lower blood pressure

Mendelian randomization

Variation of blood pressure in Chimpanzees with changes in salt intake corresponding to human intakes

Elliott, Circulation (2007) 116:1563
Causes of salt-sensitive blood pressure

- low birth weight (nephron underdosing)
- primary glomerular diseases
- aging
- obesity
- diabetes mellitus
- consequence of hypertension
Blood pressure and prevalence of hypertension increase stepwise with **S-aldosterone** concentration

*Framingham study*

Decreased nephron number shifts pressure natriuresis relationship to the right

Normal

Intake

Urinary Sodium Output (x normal)

High Intake

Normal Intake

Mean Arterial Pressure (mmHg)

Salt-sensitive

nephron loss
Development of salt-sensitive hypertension in rats after exposure to angiotensin II

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Patients with renal dysfunction

- Renal dysfunction is associated with a very high CV risk
- Protection against progression to renal dysfunction has two main goals
  - a.) strict blood pressure control
    - (<130/80 mmHg and even lower if proteinuria is > 1g/day)
  - b.) lowering proteinuria to values as low as possible

To achieve the blood pressure goal, combination of several antihypertensive agents (including loop diuretics) is required

Office blood pressure vs. # home blood pressure and # ambulatory blood pressure measurement (ABPM)

average blood pressure (mmHg)

<table>
<thead>
<tr>
<th></th>
<th>Office</th>
<th>Home</th>
<th>ABPM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>142/82</td>
<td>136/77</td>
<td>124/76</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>130/70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night</td>
<td>119/67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

correlation to target organ damage:
[heart(ECG,echo); carotis (echo); albuminuria]
→ worst for office BP; equally good for home measurement and ABPM

Gaborieau, J.Hypertens.(2008) 26:1919

Renal disease and Diabetes → nighttime decrease of blood pressure attenuated
How often does office BP yield wrong data?

Lack of agreement between office BP and home BP

Sessa, Circulation (2001) 104:1385
Blood pressure measured by patient – better predictor of cardiovascular events, the higher blood pressure → the greater superiority of home BP and ABPM

Seega, Circulation (2005) 111:1777
Advantages if patient measures his blood pressure

- more data points
- no white coat effect
- better correlation to cardiovascular risk
- better assessment of treatment efficacy
- improved compliance
Kidney and Hypertension

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4. What is the evidence of the benefit of antihypertensive treatment (observational data, controlled data)
5. Treatment targets: beyond blood pressure – lowering of proteinuria
6. Are all antihypertensive agents created equal?
Even modest blood pressure within “normal” range predict future ESRD.

Tozawa, Hypertension (2003) 41:1341
Blood pressure predicts future endstage renal disease in diabetic and nondiabetic individuals without renal disease at baseline

(Kaiser Permanente cohort)
Cumulative incidence of endstage kidney disease according to baseline blood pressure

Systolic > diastolic pressure for prediction of endstage renal disease

1-Year Systolic Blood Pressure
Cadaver Kidney Transplants 1985-2005

% Graft Survival

<table>
<thead>
<tr>
<th>Systolic Blood Pressure</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>120-129</td>
<td>9,968</td>
</tr>
<tr>
<td>&lt; 120</td>
<td>6,318</td>
</tr>
<tr>
<td>130-139</td>
<td>12,571</td>
</tr>
<tr>
<td>140-149</td>
<td>12,783</td>
</tr>
<tr>
<td>150-159</td>
<td>7,612</td>
</tr>
<tr>
<td>160-169</td>
<td>5,046</td>
</tr>
<tr>
<td>170-179</td>
<td>2,051</td>
</tr>
<tr>
<td>≥ 180</td>
<td>2,027</td>
</tr>
</tbody>
</table>

Years

CTS Collaborative Transplant Study

K-61101-0207
## Blood pressure in parents of patients with IgA-GN

<table>
<thead>
<tr>
<th>parents of:</th>
<th>percent hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA-GN</td>
<td>57%</td>
</tr>
<tr>
<td>(n=63)</td>
<td></td>
</tr>
<tr>
<td>traffic accident victims</td>
<td>32.6%</td>
</tr>
<tr>
<td>(n=138)</td>
<td></td>
</tr>
</tbody>
</table>

*Schmid, J Hypert (1990) 8: 573*
Type 1 diabetics with / without nephropathy: how is blood pressure of parents?

Parents: percent hypertensive

\( (ABPM>135/85\text{mmHg}) \)

- Offspring diabetic nephropathy (n=73) 57%
- Offspring no diabetic nephropathy (n=73) 41%

Fagerudd, Diabetes (1998) 47: 439
Is there evidence that blood pressure lowering attenuates progression of chronic kidney disease?
## MDRD - study
*(modification of diet and renal disease)*

<table>
<thead>
<tr>
<th>Blood Pressure Control</th>
<th>Loss of GFR (ml/min/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ordinary</td>
<td>107 mmHg MAP</td>
</tr>
<tr>
<td>Intensified</td>
<td>91 mmHg MAP</td>
</tr>
</tbody>
</table>

Less progression by reducing blood pressure within the range of “normotensive” values – but only in proteinuric patients

Proteinuria < 1g/24h

Proteinuria > 1g/24h

Transition from microalbuminuria to proteinuria in type 2 diabetes conventional vs intensified blood pressure lowering (ABCD trial)

Reaching targets is difficult
Blood pressure reaching target (<130/80 mmHg) in type 1 diabetics with nephropathy

Fagerudd, Diabetes Care (2004) 27:803
Communist Ideal

One blood pressure fits all
Primary endpoint in ON TARGET study:
adjusted risk according to tertiles of systolic blood pressure at baseline

<table>
<thead>
<tr>
<th>Changes SBP</th>
<th>Reduced Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: baseline SBP &lt;= 130</td>
<td>HR (95%CI) p-value (changes SBP as continuous)</td>
<td></td>
</tr>
<tr>
<td>T1: &lt;= -9.17</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T2: &gt; -9.17 &amp; &lt;= 0.22</td>
<td>1.2 (1.04, 1.4)</td>
<td></td>
</tr>
<tr>
<td>T3: &gt; 0.22</td>
<td>1.19 (1.02, 1.38)</td>
<td></td>
</tr>
<tr>
<td>Q2: baseline SBP &gt; 130 &amp; &lt;= 142</td>
<td>p=0.0004</td>
<td></td>
</tr>
<tr>
<td>T1: &lt;= 0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T2: &gt; 0 &amp; &lt;= 8.36</td>
<td>0.89 (0.76, 1.04)</td>
<td></td>
</tr>
<tr>
<td>T3: &gt; 8.36</td>
<td>0.81 (0.69, 0.95)</td>
<td></td>
</tr>
<tr>
<td>Q3: baseline SBP &gt; 142 &amp; &lt;= 154</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>T1: &lt;= 5.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T2: &gt; 5.5 &amp; &lt;= 14</td>
<td>0.77 (0.67, 0.89)</td>
<td></td>
</tr>
<tr>
<td>T3: &gt; 14</td>
<td>0.59 (0.5, 0.69)</td>
<td></td>
</tr>
<tr>
<td>Q4: baseline SBP &gt; 154</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>T1: &lt;= 11.92</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T2: &gt; 11.92 &amp; &lt;= 21.71</td>
<td>0.72 (0.63, 0.82)</td>
<td></td>
</tr>
<tr>
<td>T3: &gt; 21.71</td>
<td>0.57 (0.5, 0.66)</td>
<td></td>
</tr>
</tbody>
</table>
Blood pressure and CV events in high risk survivors of MI (VALIANT study)

14,703 pat. LV dysfunction (EF<35%) or heart failure after acute MI
Rx Valsartan, Captopril or both

Signorovitch, Hypertension (2008) 51:48
When is less aggressive blood pressure lowering indicated?

- diastolic blood pressure < 70mmHg
- known target organ damage (ON TARGET)
Diastolic BP < 70mmHg:
more frequently de novo MI, but not stroke

Increase of serum creatinine after blood pressure lowering

2 possibilities

- **Reversal of hyperfiltration**
  (particularly diabetic nephropathy)
  
or
- **Consequence of hypertension-induced renal damage**
  (vascular sclerosis with narrowing and increased resistance)
  
  ➤ reduced kidney perfusion (often reversible in the long run)
  
or
- **extremely rarely bilateral renal artery stenosis**

➤ don‘t stop antihypertensive medication!
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Proteinuria at baseline:
Predictor of renal prognosis (ESRD)
(type 2 diabetes; nephropathy; RENAAL study)

Reduction of proteinuria during study
Additional predictor of renal prognosis (ESRD)
(type 2 diabetes, nephropathy; RENAAL study)

Reduction of proteinuria by:

Measuring proteinuria during treatment indispensable

DeZeeuw, Kidn.Intern.(2004) 65:2309
Metaanalysis of cardiovascular events in controlled studies - relative importance of eGFR and proteinuria

eGFR plus albuminuria – superior prediction of cardiovascular mortality

**SMART study**

**CV death**

![Graph showing cumulative fraction with event over follow-up (year)]

- eGFR > 60 and ACR < 3
- eGFR < 60 and ACR < 3
- eGFR > 60 and ACR > 3
- eGFR < 60 and ACR > 3

ACR albumin/creatinine ratio

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Discussion whether RAS inhibition superior – purely academic

- to reach target blood pressure > 4 different classes of antihypertensive agents necessary


- greater difficulty to lower BP in absence of RAS inhibition:
  
  in most studies despite a protocol aiming for identical blood pressure in the two arms blood pressure was actually lower in the arm with RAS blockade

# ACE inhibitors vs conventional antihypertensive agents

**Metaanalysis**

<table>
<thead>
<tr>
<th></th>
<th>ACEi</th>
<th>controls</th>
<th>RRR (reduction of rel.risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD</td>
<td>7.4%</td>
<td>11.6%</td>
<td>37%</td>
</tr>
<tr>
<td>doubling of S-creatinine</td>
<td>9.5%</td>
<td>14.7%</td>
<td>35%</td>
</tr>
</tbody>
</table>

NNT 24 pat./2 years to avoid 1 case of dialysis dependency

Relative risk of enstage renal failure:

**ACE-inhibitors vs alternative antihypertensive agents**

The higher proteinuria, the greater superiority of ACE inhibitors.

*N=1860*

---

Blood pressure lowering vs RAS Blockade

RENAAL study

Untreated
i.e. BP lowering
without RAS blockade

Placebo
BP lowering
with RAS blockade

GFR loss
(ml/min/year)

12
4.4
- 56%

5.2
- 6%

~ 10:1

without consideration of:
- antiproteinuric effect
- easier achievement of target blood pressure

not fire and forget!
Lowering of BP vs RAS Inhibition
Effect on renal endpoints
(IDNT study)

at the end –
thank you for your attention

prof.e.ritz@t-online.de
Decrease of GFR greater in patients with higher proteinuria
(MDRD study)

Bakris, Arch.Int.med.(2000) 160: 685
Proteinuria prognostic „marker“ for mortality in patients with PTCA

EXCITE study

Long-term observation of renal function in MDRD study – “usual vs lower blood pressure”

The lower blood pressure during treatment →
the more marked reduction of cardiovascular events
independent of age <65 or >=65 years

Reduction in risk for each 5 mm Hg reduction in systolic blood pressure:
- Age <65: 11.9% (5.3% to 18.0%)
- Age ≥65: 9.1% (3.6% to 14.3%)

P for heterogeneity of slopes = 0.38
Kidney graft survival – with and without ACE inhibition

In nonproteinuric CKD patients (ADPKD) - no additional renal benefit from intensified BP lowering ($\Delta C_{cr}$)

standard $R_x$ MAP 101±4 mmHg; intensified $R_x$ MAP 90±mmHg

In nonproteinuric CKD patients (ADPKD)-
but additional **cardiac benefit** from intensified BP lowering

\(\Delta \text{LVMI}\)

standard Rx MAP 101±4 mmHg; intensified Rx MAP 90±mmHg

Serum creatinine predictor of mortality

Hypertension Detection and Follow-up Program

Cumulative Mortality Per 100

Creatinine stratum limits (mg/dL)
- 2.50
  - n = 72
- 2.00–2.49
  - n = 78
- 1.70–1.99
  - n = 147
- 1.50–1.69
  - n = 326
- 1.20–1.49
  - n = 2,142
- < 1.20
  - n = 8,003

Months of Follow Up

PEACE study
Trandolapril (vs Placebo)

Reduction of mortality in pat. with stable coronary heart disease:
eGFR higher or lower than 60 ml/Min/1.73m²