The Kidney in Hypertension

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Outline

• Pathophysiology of hypertension in chronic kidney disease (CKD)
  — Renin-Angiotensin-Aldosterone System

• Case Study #1
  — Hypertension in Proteinuric Hypertensive Nephrosclerosis

• Case Study #2
  — Hypertension in Chronic Kidney Disease and Fluid Overload

• Case Study #3
  — Hypertension in Diabetic Nephropathy

• New potential therapies on the horizon
Components of the Normal Nephron

Angiotensin II (Ang II) generated in the afferent arteriole interacts with AT1 receptors on cellular components of the nephron.
Stimuli to Increase Renin Production

- Mechanical
  - Decrease stretch/low blood pressure

- Chemical
  - Decrease sodium delivery to macula densa

- Neuronal
  - Increase in sympathetic tone

Renin-Angiotensin-Aldosterone System
Angiotensin II

**Meta Analysis: Lower Systolic BP**

Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics

![Graph showing the relationship between SBP and GFR](image)

- Untreated HTN


www.hypertensiononline.org
Case Study #1

- 63 yo woman with hypertension and hypertensive nephrosclerosis presents for follow up

- Medications:
  - Lisinopril 20mg qd
  - Amlodipine 5mg qd

- VS: 154/84, 74

Case Study #1

- Labs: Creat 1.3(baseline), normal electrolytes, spot urine protein/spot urine creatinine = 1.5g

- You increase lisinopril to 40mg qd and recheck basic metabolic panel in 1 week

- Creat now 1.6, normal electrolytes
Case Study #1: Question #1

- What do you do?
  - A. Stop lisinopril and instead increase amlodipine
  - B. Decrease lisinopril back to 20mg and increase amlodipine instead
  - C. Make no change in medications and repeat basic metabolic panel in 1 week
  - D. Panic

Answer

- C
- Make no change in medications and repeat basic metabolic panel in 1 week
Why Do We Tolerate an Increase in Creatinine?

- Answer: There is an initial decrease in GFR which is reversible. Ultimately there is a slower decline in kidney function over time.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mm Hg)</td>
<td>140/82 (2/1)</td>
<td>151/89 (2/1)</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>101 (1)</td>
<td>109 (1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>76 (4)</td>
<td>81 (4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Albuminuria (mg/24 hr)</td>
<td>764 (1.2)</td>
<td>1122 (1.2)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>


Importance of Proteinuria in CKD Progression

Case Study #2

- 77 yo man with hypertensive nephrosclerosis, CHF, chronic LE edema with recurrent cellulitis presents for routine follow-up

- Medications
  - Aspirin
  - Coreg 80mg qd
  - Benazepril 40mg bid
  - Furosemide 60mg qd

- PE
  - 179/83, 56, 317 lbs (nl 300 lbs)
  - Neck – elevated JVP
  - Lung – clear
  - CV – RRR
  - Ext – marked edema

- Labs
  - Creat 1.6 (baseline 1.9), nl electrolytes, Hgb 9.6 (baseline 11.2)
Case Study #2: Question #1

- His creatinine is better (1.6 vs 1.9). Is his kidney function
  - A. Better
  - B. Worse
  - C. The Same
  - D. Can’t tell

ANSWER

- D
- Can’t tell
Creatinine Is a Concentration

• Our patient has a decrease in serum creatinine in setting of severe fluid overload

• The creatinine can be falsely lower in this situation secondary to a dilutional effect

Case Study #2

• Patient advised to increase furosemide to 100mg a day and recheck basic metabolic panel in a week.

• Repeat lab shows creatinine up to 2.3 from 1.6
Case Study #2: Question #2

What do you do?
A. Advise patient to stop diuretic and repeat lab in a week
B. Advise patient to stop diuretic and ace-inhibitor and repeat lab in 1 week
C. Advise patient to continue current medications and repeat lab in 1 week
D. Panic

ANSWER

• C
• Advise patient to continue current medications and repeat lab in 1 week
Importance of fluid control

• Cardiac function
• Blood pressure management
• Decrease risk of recurrent cellulitis
• Patient comfort/mobility

• Treat the patient, not the number (creatinine)

Case Study #2

• Patient returns after 1 month

• PE
• 114/65, weight 305lbs
• Improved LE edema

• Hgb up to 10.7, creatinine steady at 2.3
Case Study #2: Question #1 - Revisited

• His creatinine is better (1.6 vs 1.9). *This is in a setting of fluid overload.* Is his kidney function
  — A. Better
  — B. Worse
  — C. The Same
  — D. Can’t tell

• Answer – B. worse – new creatinine is 2.3

Case Study #3

• 67 yo woman with poorly controlled diabetes, diabetic retinopathy, diabetic nephropathy presents for routine follow up

• Medications
  — Lisinopril 20mg qd
  — Insulin
  — Amlodipine 5mg qd
  — Simvastatin 10mg
Case Study #3

• PE
• 165/95, 71, BMI 36
• Ext – trace edema

• Labs
• Creat 1.2, K 5.5, albuminuria 3500mg

Case Study #3: Question #1

How do you treat her HTN?
A. Advise her to exercise, watch sodium, and lose weight
B. Increase lisinopril, add thiazide diuretic, and check basic metabolic panel in 1 week
C. Stop Ace-inhibitor and increase amlodipine/start another agent
D. A&B
E. A&C
ANSWER

- D

- Advise her to exercise, watch sodium and lose weight
- Increase lisinopril, start thiazide diuretic and check basic metabolic panel in 1 week

Lifestyle Modifications - JNC7

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP Reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Reduction</td>
<td>5-10 mmHg/10kg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>2-4 mmHg</td>
</tr>
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Issues
Decrease Progression of Diabetic Nephropathy
Control Hypertension
Decrease Proteinuria (RAAS blockers)
Control of Potassium

ACE Inhibitors Lessen Chance of Progression to Overt Nephropathy

Diabetologia 1996;39: 587
Captopril Retards Progression of Diabetic Nephropathy in Type I Diabetes

\[
\text{RENAAL: Rate of Progression of Renal Disease} \\
\text{(median 1/sCr slope)}
\]

18% reduction P = 0.01

Hyperkalemia in Diabetes

- Type 4 renal tubular acidosis (hyporeninemic hypoaldosteronism)
- Medications induce hyperkalemia – all RAAS blockers (Ace-Inhibitors, ARBs, Renin-inhibitors, aldosterone antagonists)

Control of Hyperkalemia

- Need to monitor patients
- Dietary potassium restriction (less than 2000-3000mg/day)
- Use of diuretics (thiazides and loop diuretics)
Potential Treatments on the Horizon

- Hypertension Vaccine
- Renal Denervation
- Vasopeptidase Inhibitors

Vaccine Against Angiotensin II

Hypertension Vaccine

<table>
<thead>
<tr>
<th></th>
<th>100 µg Placebo (n=12)</th>
<th>300 µg Placebo (n=12)</th>
<th>100 µg AngQb (n=22)</th>
<th>300 µg AngQb (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic bp</strong></td>
<td>-3.4 (2.3)</td>
<td>3.4 (2.8)</td>
<td>-3.5 (1.7)</td>
<td>-5.5 (2.1)*</td>
</tr>
<tr>
<td><strong>Diastolic bp</strong></td>
<td>-1.6 (1.8)</td>
<td>1.1 (1.7)</td>
<td>0.0 (1.3)</td>
<td>-2.9 (1.2)*</td>
</tr>
<tr>
<td><strong>Systolic bp</strong></td>
<td>-2.6 (3.2)</td>
<td>-2.5 (4.0)</td>
<td>1.1 (2.3)</td>
<td>-1.2 (3.0)</td>
</tr>
<tr>
<td><strong>Diastolic bp</strong></td>
<td>1.7 (2.0)</td>
<td>-1.8 (2.3)</td>
<td>1.3 (1.5)</td>
<td>-0.8 (1.7)</td>
</tr>
</tbody>
</table>

Data are mean (SE). *p<0.012 compared with baseline. †p=0.024 compared with baseline.

*Table 5: Change from baseline in ambulatory blood pressure for treatment groups.*

Renal Denervation
Symplicity HTN-2 Trial

*Figure showing change in blood pressure from baseline to month 1, 3, and 6 for Renal Denervation group and Control group. Two-way repeated measures ANOVA, p<0.001. Primary endpoint.*

*Lancet 2010;376:1903-09.*
Vasopeptidase Inhibitors

- Inhibit angiotensin converting enzyme

- Inhibit neutral endopeptidase
  - Prolongs activation of natriuretic peptides

OCTAVE Trial

Summary

• Kidney disease and hypertension go hand in hand
• Importance of blood pressure control (<130/80)
• Importance of decreasing proteinuria
• Watch for hyperkalemia