Potassium, Aldosterone, and Hypertension: How Physiology Determines Treatment

Jamie Johnston, MD
University of Pittsburgh
School of Medicine
No Disclosures

Acknowledgements: Evan Ray, MD, PhD
Objectives

- Identify patients that should be evaluated for primary aldosteronism
- Recall evaluation for primary aldosteronism
- Describe effect of anti-hypertensive medications on potassium
- Describe benefits of potassium
Hypertension: How common in the US?

- One in three adults Americans have hypertension
  (Hypertension. 2004;44:398–404)
- 76.4 million Americans age 20 or older have HTN
  - NHANES [2005-2008]. NCHS and NHBLI
- Primary hypertension – 85%
Aldosterone

- Release stimulated by
  - Volume depletion
  - Hyperkalemia
- Distal nephron
  - Collecting duct
  - Distal Tubule
Examples of Identifiable Causes of Hypertension

- Renovascular disease
- Renal parenchymal disease
- Polycystic kidneys
- Aortic coarctation
- Sleep apnea
- Pheochromocytoma
- Primary aldosteronism**
- Cushing syndrome
- Hyperparathyroidism
- Hypo/hyperthyroidism
- Exogenous causes
  - Drugs
    - BCPs
    - ES agents
Primary Hyperaldosteronism

- Most common secondary form of hypertension
- Prevalence $\rightarrow$ 5 – 13% of all hypertension
- Higher Risks than Primary hypertension
  - More cardiovascular events
  - Increased prevalence of metabolic syndrome
  - Increased LVH
  - Increased albuminuria

Young WF, Clinical Endocrinology (2007) 66, 607–618
Case Presentation

23 year old woman referred to Hypertension Clinic for difficult-to-treat hypertension.

- History of present illness
  - Diagnosed at 16 years of age
  - Age 24, presented with headache, chest pain
    - Blood pressure 200/114
    - K 2.8
  - Discharged on atenolol, irbesartan, potassium
Case Presentation

- Past Medical History
  - 1st period age 13, irregular periods
  - Chronic sinusitis
  - Overweight
- Meds: Metoprolol, irbesartan, ASA, Ethinyl estradiol/desogestrel OCP
- Social History:
  - Denied tobacco, alcohol, illicit drugs or natural black licorice
  - Little exercise
- Family History: father, grandfather with hypertension
Case Presentation

- **Vital signs:**
  - Wt 196, Height 68.5 inches, BMI 29.4 kg/m²
  - BP 160/104 RUE, 154/100 LUE

- **Physical exam:**
  - Appears comfortable
  - Optic fundus - AV nicking
  - Heart regular, 1/6 SEM entire precordium
    - PMI 6th ICS

Labs: Na 142, K 3.0, Cl 107, CO2 24, sCr 0.7
Primary Hyperaldosteronism

**Normal**
- Aldo upright 4-31
- Upright plasma renin activity 0.5 – 3.3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F/M)</td>
<td>23/31</td>
</tr>
<tr>
<td>Age (years) Mean</td>
<td>52.2 ± 1.3</td>
</tr>
<tr>
<td>Age (years) Range</td>
<td>29–74</td>
</tr>
<tr>
<td>Known duration of hypertension (years) Mean</td>
<td>10.5 ± 1.4</td>
</tr>
<tr>
<td>Known duration of hypertension (years) Range</td>
<td>0.04 (2 weeks) – 33.0</td>
</tr>
<tr>
<td>Antihypertensive medication (No. per patient) Mean</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>Antihypertensive medication (No. per patient) Range</td>
<td>0–4</td>
</tr>
<tr>
<td>Hypertension controlled</td>
<td>11 (20.4)</td>
</tr>
<tr>
<td>Taking three or more antihypertensive medications</td>
<td>29 (53.7)</td>
</tr>
<tr>
<td>Hypokalaemic (plasma potassium &lt; 3.5 mmol/l)</td>
<td>7 (13.0)</td>
</tr>
<tr>
<td>No, with neither hypokalaemia nor hypertension uncontrolled on three or more medications</td>
<td>28 (51.9)</td>
</tr>
<tr>
<td>Upright plasma aldosterone (ng/100 ml)</td>
<td>21.1 ± 1.6</td>
</tr>
<tr>
<td>Upright plasma aldosterone (ng/100 ml) &gt; 15</td>
<td>34 (63.0)</td>
</tr>
<tr>
<td>Upright plasma aldosterone (ng/100 ml) &gt; 40</td>
<td>5 (9.3)</td>
</tr>
<tr>
<td>Upright plasma renin activity (ng/ml per h)</td>
<td>0.39 ± 0.04</td>
</tr>
<tr>
<td>Upright aldosterone:renin ratio</td>
<td>81 ± 10</td>
</tr>
</tbody>
</table>

Values are mean ± SEM and range, or number (%).
Refractory Hypertension

Aldo-renin ratio (ARR)

<25

ARR <25

Primary aldosteronism unlikely

ARR 25-50

Confirmatory Testing

Start Mineralocorticoid receptor blocker

>50 & aldo > 10 ng/dl

Surgical Candidate?
## Confirmatory Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Evaluation</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral NaCl load</td>
<td>&gt;200 mmol/day for 3 d 24 hour urine aldo</td>
<td>Urine aldo &lt; 10 ug/d (-) &gt;12 ug/d (+)</td>
<td>Severe htn, CKD, CHF, hypokalemia</td>
</tr>
<tr>
<td>Saline Infusion Test</td>
<td>2 L NS over 4 hour AM recumbent</td>
<td>Plasma aldo &lt; 5 ng/dl unlikely &gt;10 ng/dl likely</td>
<td>Severe htn, CKD, CHF, hypokalemia</td>
</tr>
<tr>
<td>Fludrocortisone suppression</td>
<td>0.1 q 6 for 4 days +high salt</td>
<td>Plasma Aldo &gt; 4 ng/dl PRA &gt; 1 ng/ml/h</td>
<td>hospitalization</td>
</tr>
<tr>
<td>Captopril challenge</td>
<td>25-50 mg labs immediately before and 1-2 hr post</td>
<td>Plasma aldo decreases by &gt;30%</td>
<td>Greater false positive and negative rate than first 3</td>
</tr>
</tbody>
</table>
Surgical Candidate?

Yes  No

Optimize Mineralocorticoid receptor blocker

Adrenal Imaging CT Scan

Continue Mineralocorticoid receptor blocker

Adrenal Vein Aldo Sampling

Optimize Mineralocorticoid receptor blocker

Good BP response?

Yes

Optimize Mineralocorticoid receptor blocker

No

Unilateral  Bilateral

Laparoscopic adrenalectomy
What causes hypertension?
Na\(^+\) Balance and Blood Pressure

Na\(^+\) balance: Na\(^+_\text{in}\) – Na\(^+_\text{out}\)
# Sodium Consumption and HTN

**Figure 3.** Forest Plots of Changes in Systolic and Diastolic Blood Pressure for Every 1-g Increase in Sodium Excretion. Data are based on multivariable linear regression models with adjustment for covariates and regression dilution bias.

<table>
<thead>
<tr>
<th>Sodium excretion</th>
<th>No.</th>
<th>Change in Systolic Blood Pressure (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>102,216</td>
<td>-</td>
<td>2.11 (2.00 to 2.22)</td>
</tr>
<tr>
<td>&lt;3 g/day</td>
<td>10,873</td>
<td>-</td>
<td>0.74 (-0.36 to 1.84)</td>
</tr>
<tr>
<td>3 to 5 g/day</td>
<td>46,922</td>
<td>-</td>
<td>1.74 (1.29 to 2.19)</td>
</tr>
<tr>
<td>&gt;5 g/day</td>
<td>44,421</td>
<td>-</td>
<td>2.58 (2.38 to 2.78)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>No.</th>
<th>Change in Systolic Blood Pressure (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>59,238</td>
<td>-</td>
<td>1.30 (1.23 to 1.38)</td>
</tr>
<tr>
<td>Yes</td>
<td>42,978</td>
<td>-</td>
<td>2.49 (2.34 to 2.64)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>No.</th>
<th>Change in Systolic Blood Pressure (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45 yr</td>
<td>30,619</td>
<td>-</td>
<td>1.96 (1.81 to 2.11)</td>
</tr>
<tr>
<td>45–55 yr</td>
<td>33,289</td>
<td>-</td>
<td>2.43 (2.25 to 2.61)</td>
</tr>
<tr>
<td>&gt;55 yr</td>
<td>38,308</td>
<td>-</td>
<td>2.97 (2.78 to 3.17)</td>
</tr>
</tbody>
</table>
What about potassium?
Potassium – Basic Facts

- 98-99% of K is in the cells
- Extracellular fluid - 2% of total body K, 70 mmol
- Necessary for
  - Nerve conduction
  - Cell volume regulation
  - Electrolyte transport
- Hypo or hyperkalemia occurs in 30% of hospitalized patients*. 

Exchange of K$^+$ for Na$^+$ in Westernized diet

And we give drugs that affect potassium

- Diuretics – decrease potassium
- RAAS agents – increase potassium
Blood pressure, sodium and potassium excretion

A

Potassium Excretion (g/day)

Sodium Excretion (g/day)

P<0.001 for interaction

B

Potassium Excretion (g/day)

Sodium Excretion (g/day)

P<0.001 for interaction
All-Cause Mortality and Serum K Levels in Patients with CKD

Multivariable adjusted log hazards (solid line) and 95% confidence intervals (dashed lines) of all-cause predialysis mortality associated with serum potassium levels in the entire study population (n=1,227).

Association of serum potassium, used as a time-varying covariate, with mortality in patients undergoing peritoneal dialysis (n=10,454). Dashed lines represent 95% confidence intervals.

Potassium Supplementation and Blood Pressure

Siani et al. (1987)
- 37 hypertensive subjects, randomized
- Intervention:
  - 48 mEq KCl or placebo daily
  - 15 weeks
- Outcomes
  - Blood pressure
Does $K^+$ reduce the need for anti-hypertensives?

Trial:
- 57 persons with well-controlled HTN
- Intervention:
  - Randomized to high or normal $K^+$ diet
  - Nutritional counseling to increase $K^+$
    - 3 to 6 rations of fruits or vegetables / day
    - Steamed, not boiled
  - Calories held constant
  - Subjects seen monthly by a blinded physician
    - Medications titrated appropriately
  - 1 year

Findings
- Urinary $K^+$ increased 46%
- No change in urinary $Na^+$

## Potassium Intake and Blood Pressure

**Table: Mean (SD) Total No of Participants**

<table>
<thead>
<tr>
<th>Study</th>
<th>Increased potassium intake</th>
<th>Control</th>
<th>Mean difference (inverse variance, random) (95% CI)</th>
<th>Weight (%)</th>
<th>Mean difference (inverse variance, random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure status (normotensive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barden BPAA 1996</td>
<td>113.67 (8.87)/43</td>
<td>113.69 (9.44)/43</td>
<td>6.90 (3.89 to 9.85)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Trial Hyp C/A BPA 1992</td>
<td>-0.78 (5.86)/278</td>
<td>-0.86 (5.82)/273</td>
<td>10.59 (-1.34 to 1.28)</td>
<td>10.00</td>
<td>0.13 (1.15 to 1.41)</td>
</tr>
<tr>
<td>Whelton BPA 1995</td>
<td>-0.37 (5.94)/161</td>
<td>1.00 (5.69)/157</td>
<td>10.40 (9.87 to 9.95)</td>
<td>27.80</td>
<td>0.09 (2.77 to 0.95)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>382</td>
<td>375</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: χ²=4.00, p=0.05, df=2, P=0.01, I²=40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: χ²=0.20, P=0.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure status (hypertensive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulpitt BPA 1985</td>
<td>-5.30 (7.50)/19</td>
<td>-7.50 (25.80)/24</td>
<td>0.00 (15.30 to 15.90)</td>
<td>5.10</td>
<td>0.10 (6.32 to 6.62)</td>
</tr>
<tr>
<td>Chalmers BPA 1986</td>
<td>-8.90 (7.00)/29</td>
<td>-8.90 (7.00)/29</td>
<td>6.60 (7.35 to 7.29)</td>
<td>5.10</td>
<td>0.10 (6.32 to 6.62)</td>
</tr>
<tr>
<td>Forrester BPA 1988</td>
<td>130.80 (13.50)/25</td>
<td>133.20 (13.70)/23</td>
<td>3.40 (10.87 to 6.17)</td>
<td>5.10</td>
<td>0.10 (6.32 to 6.62)</td>
</tr>
<tr>
<td>Forrester BPA 1992</td>
<td>176.00 (24.00)/18</td>
<td>166.00 (24.00)/18</td>
<td>1.20 (36.43 to 4.43)</td>
<td>5.10</td>
<td>0.10 (6.32 to 6.62)</td>
</tr>
<tr>
<td>Grobbee BPA 1987</td>
<td>125.00 (12.50)/40</td>
<td>125.00 (12.50)/40</td>
<td>5.10 (6.32 to 6.62)</td>
<td>5.10</td>
<td>0.10 (6.32 to 6.62)</td>
</tr>
<tr>
<td>He BPA 2000</td>
<td>142.00 (21.00)/41</td>
<td>145.00 (15.00)/42</td>
<td>4.90 (8.63 to 2.63)</td>
<td>5.10</td>
<td>0.10 (6.32 to 6.62)</td>
</tr>
<tr>
<td>Kaslani BPA 1995</td>
<td>127.00 (11.00)/16</td>
<td>133.20 (16.00)/16</td>
<td>2.20 (36.43 to 4.43)</td>
<td>5.10</td>
<td>0.10 (6.32 to 6.62)</td>
</tr>
</tbody>
</table>

### Total (95% CI)

| 947                | 945                | 100.00 | -3.49 (-5.15 to -1.82) |

22 randomized, controlled trials

Aburto et al (2013) BMJ
# How Does $K^+$ Reduce BP?

**Table 2.** Data for rats subjected to potassium loading and studied for a 4 hour period

<table>
<thead>
<tr>
<th>Load*</th>
<th>n</th>
<th>Potassium balance**</th>
<th>Plasma potassium meq/l</th>
<th>Plasma protein g/l</th>
<th>$U_{NaV}$ µeq/100 g/4 h</th>
<th>PRC† ng Angiotensin I /ml/2 h</th>
<th>Urinary free aldosterone ng/4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>171 µeq Potassium</td>
<td>7</td>
<td>50.6 ± 24.7</td>
<td>4.07 ± 0.27</td>
<td>59.71 ± 2.29</td>
<td>52.6 ± 30.8</td>
<td>88 ± 39</td>
<td>2.70 ± 0.72</td>
</tr>
<tr>
<td>513 µeq Potassium</td>
<td>7</td>
<td>123.4 ± 77.9</td>
<td>4.23 ± 0.25</td>
<td>66.43 ± 0.98</td>
<td>234.3 ± 92.4</td>
<td>156 ± 55</td>
<td>6.67 ± 1.59</td>
</tr>
<tr>
<td>769 µeq Potassium</td>
<td>6</td>
<td>162.0 ± 62.1</td>
<td>5.01 ± 0.29</td>
<td>66.67 ± 3.44</td>
<td>343.8 ± 51.6</td>
<td>168 ± 40</td>
<td>10.25 ± 2.53</td>
</tr>
<tr>
<td>769 µeq Potassium + 513 µeq Sodium</td>
<td>7</td>
<td>176.9 ± 41.5</td>
<td>4.30 ± 0.25</td>
<td>63.71 ± 1.50</td>
<td>538.1 ± 45.2</td>
<td>64.4 ± 40.3</td>
<td>11.27 ± 3.79</td>
</tr>
</tbody>
</table>

* Potassium (KCl) and sodium (NaCl) loading are expressed in µeq/100 g body weight.

** Potassium balance is the difference between input and output.

† PRC: Plasma renin concentration.
How Does K⁺ Reduce BP?

- 11 male subjects (24-31 yo) Overnight fast
- Bolus of either 500 cc NSS (control) or 500 cc NSS + 32 mEq KCl

<table>
<thead>
<tr>
<th>Results</th>
<th>Compared to control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K⁺</td>
<td>Increased 0.64 ± 0.04 mmol/L</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine K⁺</td>
<td>Increased 13.8 ± 1.9 mEq</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine Volume</td>
<td>Increased 138.6 ± 33.6 mL</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Urine Na⁺</td>
<td>Increased 18.6 ± 5.8 mEq</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Aldosterone</td>
<td><strong>Increased</strong> 3.6 ± 8.9 ng/dL</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*K⁺ affects aldosterone signaling.*

Barnes et al. (1984) Clinical Science
K\(^+\) Loading, Na\(^+\) Excretion, and Aldosterone

- Healthy volunteers 22-26 yo
- Metabolic ward
  - Baseline diet
    - 100 mmol K\(^+\) / day
    - 100 mmol Na\(^+\) / day
  - Supplement started:
    - Total K\(^+\) 400 mEq/day
- Electrolytes measured hourly over 8 hours
  - Baseline
  - After 1\(^{st}\) K\(^+\) load
  - 72 hrs
    - Discharged home
  - 20 days

Conclusions: K\(^+\) loading
- 400 mEq/day was safe
- *Increased* aldosterone
- *Increased* Na\(^+\) excretion

Rabelink *et al.* (1990) *Kidney Intl*
Hypertension Clinic K⁺ Recommendations
(Matt Muldoon, MD; Kelly Junker, PharmD, Mark Dinga RD)

- **Patients**
  - eGFR ≥ 45
  - Serum K⁺ ≤ 4.6 mEq/L
  - Not recently started on
    - ACEi / ARB
    - K⁺-sparing diuretic

- **Dietary recommendations**
  - Na⁺ 2000 mg/day
  - Increase consumption of K⁺-rich food (DASH Diet)
    - E.g. un-boiled root vegetables, fruits

- **For patients who cannot increase K⁺-rich foods**
  - Over-the-counter KCl Powder ($5/month)
    - Patients ≤ 130 lbs: 1 tsp (75 mEq)
    - Patients > 130 lbs 1½ tsp (125 mEq)
  - Monitoring of serum K⁺
Why Does K do this?

- Distal nephron
  - Collecting duct
  - Distal Tubule
RAAS Inhibition and CKD

- ACEis and ARBs
  - Hypertension Rx
  - Rx of CKD, heart failure, and diabetic nephropathy
  - But impair renal potassium secretion, increasing the risk of hyperkalemia
- This can raise a dilemma in treating patients with CKD or other conditions

Adverse Outcomes or Mortality by Prior RAAS Inhibitor Dose

In Patients at Risk for Hyperkalemia due to RAAS Inhibition

- Monitor kidney function (eGFR, ACR)
- Monitor serum potassium levels
- Discontinue drugs that increase hyperkalemia risk, if possible
- Prescribe low-potassium diet
- Prescribe diuretics (loop diuretics when eGFR <30 mL/min)
- Correct metabolic acidosis in patients with CKD
- If required, initiate therapy with low-dose ACEi or ARB and monitor
- Newer potassium binders may offer a potential option to continue RAAS inhibition in patients who need these therapies

GFR, glomerular filtration rate; ACR, albumin-to-creatinine ratio; RAAS, Renin-Angiotensin-Aldosterone System
