Aldosterone, Hypertension and Cardiovascular Risk

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Conflicts of Interest in Last 12 Months

- Grant Support: Novartis, NHLBI
- Consultant: Novartis, CVRx
- Off-label Use: None
Conn’s Syndrome

“...a new clinical syndrome which is designated temporarily as primary aldosteronism. In its fully developed state it is characterized by the presence in the urine of excessive amounts of a sodium-retaining corticoid, by severe hypokalemia, hypernatremia, alkalosis...”

Conn JW. Primary aldosteronism, a clinical syndrome. J Lab Clin Med 1955;45:3-17.
Historical Prevalence of Primary Aldosteronism: 1-2% of General Hypertensive Population

*Hypokalemia in the Hypertensive Patient: With Observations on the Incidence of Primary Aldosteronism*

Kaplan NM. Annals Internal Med 1967;66:1079-1089

*The Incidence Rate of Phaeochromocytoma and Conn’s Syndrome in Denmark, 1977-1981*

Contemporary Prevalence of Primary Aldosteronism: 10-12% of General Hypertensive Population

Evidence that Primary Aldosteronism May Not Be Uncommon: 12% Incidence Among Antihypertensive Drug Trial Volunteers


High Incidence of Primary Aldosteronism in 199 Patients Referred with Hypertension.

A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients


JACC 2006;48:2293-3000
Prevalence of Primary Aldosteronism in Subjects With Resistant Hypertension

<table>
<thead>
<tr>
<th>City</th>
<th>Prevalence of PA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle</td>
<td>17%</td>
</tr>
<tr>
<td>Birmingham</td>
<td>20%</td>
</tr>
<tr>
<td>Oslo</td>
<td>22%</td>
</tr>
<tr>
<td>Prague</td>
<td>19%</td>
</tr>
</tbody>
</table>

PA = Primary aldosteronism.

Age- and sex-adjusted incidence rates for incident hypertension a mean of 3 years across tertiles of aldosterone (A1 to A3) and renin (R1 to R3).

Newton-Cheh et al, Hypertension 2007
Primary Aldosteronism: Current Considerations

• More common than that though historically with an estimated prevalence of approximately 10%

• Prevalence increases with increasing severity of hypertension and in patients with resistant hypertension (approximately 20%)

• Risk of aldosterone-producing-adenoma increased with higher aldosterone levels, occurrence of hypokalemia, and more severe/resistant hypertension
BP Response with Eplerenone or Spironolactone in Patients with Mild-Moderate Hypertension

Weinberger et al, Am J Hypertens 2002
Blood Pressure Response to Spironolactone in Subjects With Resistant Hypertension

BP Response to Spironolactone in PA and Non-PA Subjects

SBP = Systolic blood pressure; DBP = Diastolic blood pressure.
ASCOT: BP Response to Spironolactone

Δ SBP = 21.9
(95% CI 20.8, 23.0)

Δ DBP = 9.5
(95% CI 9.0, 10.1)

Chapman et al, Hypertension 2007
Primary Aldosteronism and Rates of Cardiovascular Events

<table>
<thead>
<tr>
<th></th>
<th>Primary Aldo</th>
<th>Essential HTN</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (%)</td>
<td>12.9</td>
<td>3.4</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI (%)</td>
<td>4.0</td>
<td>0.6</td>
<td>6.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Atrial fib (%)</td>
<td>7.3</td>
<td>0.6</td>
<td>12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Echo LVH (%)</td>
<td>34</td>
<td>24</td>
<td>1.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ECH LVH (%)</td>
<td>32</td>
<td>14</td>
<td>2.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Melliez et al., JACC 2005
Renal Damage in Primary Aldosteronism
Results of the PAPY Study

Rossi et al. Hypertension 2006
# Resistant Hypertension and Proteinuria

**Biochemical evaluation**

<table>
<thead>
<tr>
<th></th>
<th>All Patients n = 84</th>
<th>High-UALDO n = 38</th>
<th>Normal-UALDO n = 46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>4.0±0.4</td>
<td>4.0±0.5</td>
<td>4.0±0.3</td>
</tr>
<tr>
<td>PAC (ng/dL)</td>
<td>11.1±7.6</td>
<td>14.4±9.0</td>
<td>8.3±4.8**</td>
</tr>
<tr>
<td>PRA (ng/mL/h)</td>
<td>3.4±6.5</td>
<td>2.2±3.5</td>
<td>4.4±8.1</td>
</tr>
<tr>
<td>ARR</td>
<td>14.1±17.1</td>
<td>15.7±13.6</td>
<td>8.3±8.7*</td>
</tr>
<tr>
<td>UNa (mEq/24-hr)</td>
<td>172.3±74.8</td>
<td>177.3±70.2</td>
<td>168.2±78.8</td>
</tr>
<tr>
<td>ClCr (ml/min)</td>
<td>110.3±31.5</td>
<td>123.4±32.6</td>
<td>100.1±26.8**</td>
</tr>
</tbody>
</table>

*p<0.01 compared to high-Ualdo; **p<0.001 compared to high-Ualdo.

Pimenta et al, HYPERTENSION 2007
Results

Urinary protein excretion according aldosterone status

![Bar chart showing urinary protein excretion](chart.png)

- All patients
- High Aldo
- Normal Aldo

*p < 0.05*
Results

Urinary protein excretion according aldosterone and salt status

* p< 0.05

Pimenta et al HYPERTENSION 2007
Spironolactone Reduces Proteinuria in Patients with CKD

Patients (n=42) with mean eGFR of 57 mL/min treated for 8 weeks with spironolactone 25 mg/day in addition to ACEi or ARB.

No change in BP.

Fig 1. Line graphs show proteinuria levels in all 42 patients at baseline; during treatment with spironolactone, 25 mg/d; and 4 weeks after discontinuation of the drug.

Bianchi et al 2005
Spironolactone and Intracardiac Volumes

Resistant Hypertension
Baseline MRI and Biochemical Evaluation

Spironolactone 25-50 mg

3 and 6 Months Follow-Up
Repeat MRI and Biochemical Evaluation
## MRI Changes in High and Normal Aldo Patients after Treatment with Spironolactone 50 mg Daily

<table>
<thead>
<tr>
<th></th>
<th>High Aldo (n=19)</th>
<th>Normal Aldo (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>3 Mo</td>
</tr>
<tr>
<td><strong>BNP</strong></td>
<td>47</td>
<td>-62%*</td>
</tr>
<tr>
<td><strong>LVEDVI</strong></td>
<td>77</td>
<td>-9%*</td>
</tr>
<tr>
<td><strong>RVEDVI</strong></td>
<td>83</td>
<td>-12%*</td>
</tr>
<tr>
<td><strong>LAVI</strong></td>
<td>40</td>
<td>-15%*</td>
</tr>
<tr>
<td><strong>LVMI</strong></td>
<td>80</td>
<td>-16%*</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>67</td>
<td>-3%</td>
</tr>
</tbody>
</table>

* <0.05  Gaddam et al.  Hypertension 2010, in press.
High Prevalence of Unrecognized Sleep Apnoea* in Drug-Resistant Hypertension

Logan et al. J Hypertens 2001;19:2271

* >10 events/hr
Prevalence of OSA

1 Young et al. NEJM 1993. AHI ≥5 events/hr.
Aldosterone Levels and Risk of OSA in Subjects with Resistant Hypertension

Calhoun et al. CHEST 2003
Biochemical and polysomnography results of evaluated subjects with resistant hypertension (n=71)* and without resistant hypertension (n=29)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Resistant Hypertension</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC, ng/dL</td>
<td>12.4±7.9</td>
<td>7.3±3.6</td>
</tr>
<tr>
<td>PDR, µUnits/mL</td>
<td>21.4 ± 36.0</td>
<td>27.6±29.7</td>
</tr>
<tr>
<td>Serum Cr, mg/dL</td>
<td>1.1 ± 0.3</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>Serum K, mEq/L</td>
<td>3.8 ± 0.4</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>AHI, events/hr</td>
<td>24.1±24.7</td>
<td>29.0±32.3</td>
</tr>
<tr>
<td>HI, %</td>
<td>7.4±10.9</td>
<td>2.9±3.8</td>
</tr>
<tr>
<td>OSA Prevalence</td>
<td>85%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.
†Different from resistant hypertension subjects (p<0.05).

Pratt et al., CHEST 2004
Apnea-hypopnea index and hypoxic index correlates with plasma aldosterone in resistant hypertension subjects

Figure 1

Rho = 0.44, p = 0.0002

Rho = 0.38, p = 0.001
Apnea-hypopnea index and hypoxic index does not correlate with plasma aldosterone in control subjects

Figure 2

Rho = 0.12, p = 0.52

Rho = 0.002, p = 0.99
Results

AHI, Apnea-Hypopnea Index; HI, Hypoxic Index; REM, Rapid eye movement sleep; * p<0.05.

Gaddam et al, J Human Hypertens 2009, Epub ahead of publication
Meta-analysis of Salt Restriction Trials

Mean change in BP with 100 meq/day reduction in salt intake

Midgley et al, JAMA 996
Resistant Hypertension
High/Low Dietary Salt Cross-Over Evaluation

12 patients

6 patients low-salt diet 1 week

6 patients high-salt diet 1 week

wash-out 2 weeks

6 patients low-salt diet 1 week

6 patients high-salt diet 1 week
## Results: High-Low Salt Cross-Over

<table>
<thead>
<tr>
<th></th>
<th>High-salt (n=12)</th>
<th>Low-salt (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>94.3 ± 18.6</td>
<td>92.7 ± 17.6*</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>35.1 ± 32.1</td>
<td>12.5 ± 10.8*</td>
</tr>
<tr>
<td>Serum K (mEq/L)</td>
<td>3.8 ± 0.3</td>
<td>4.1 ± 0.5</td>
</tr>
<tr>
<td>PAC (ng/dL)</td>
<td>11.1 ± 4.8</td>
<td>15.5 ± 9.3*</td>
</tr>
<tr>
<td>PRA (ng/mL/h)</td>
<td>0.9 ± 0.5</td>
<td>14.3 ± 32.6</td>
</tr>
<tr>
<td>Ualdo (mcg/24-hr)</td>
<td>11.7 ± 5.1</td>
<td>18.6 ± 11.2*</td>
</tr>
<tr>
<td>UK (mEq/24-hr)</td>
<td>56.9 ± 21.8</td>
<td>69.2 ± 27.7*</td>
</tr>
<tr>
<td>UNa (mEq/24-hr)</td>
<td>261.5 ± 70.4</td>
<td>48.6 ± 27.2*</td>
</tr>
<tr>
<td>TFC (kohms⁻¹)</td>
<td>29.3 ± 3.7</td>
<td>26.5 ± 3.5</td>
</tr>
</tbody>
</table>

* Different from high-salt, p<0.05
Reduction in Blood Pressure High to Low Salt Ingestion

Blood pressure reduction (mmHg)

- Office: Systolic -23, Diastolic -9
- Daytime: Systolic -21, Diastolic -9
- Nighttime: Systolic -20, Diastolic -10

Systolic
Diastolic
Conclusion

• Aldosterone excess contributes importantly to development and severity of hypertension, particularly resistant hypertension

• MRA’s broadly effective in treating mild-moderate hypertension and resistant hypertension

• Aldosterone excess contributes importantly to target organ complications including CKD, LVH, and OSA

• Excess dietary salt ingestion is an essential component of these effects