The "Aldosterone Renaissance"

Bench to bedside evidence for the expanding role of aldosterone excess as a cause of hypertension and cardiovascular disease, and importance of detection and management

Michael Stowasser¹,², James Sharman², Richard Gordon¹, Diane Cowley¹,² and Thomas Marwick²

¹Endocrine Hypertension Research Centre and ²CCRE in Cardiovascular and Metabolic Diseases, University of Qld School of Medicine, Princess Alexandra Hospital, Brisbane, Australia

SUBTYPES OF PRIMARY ALDOSTERONISM

BILATERAL ADRENAL HYPERPLASIA (BAH) ~70%

ALDOSTERONE-PRODUCING ADENOMA (APA) ~30%

ALDOSTERONE-PRODUCING CARCINOMA

FAMILIAL HYPERALDOSTERONISM TYPE I - rare, genetic form of PAL that runs in families (glucocorticoid suppressible hyperaldosteronism)

Harrison's Principles of Internal Medicine, 1991

"...primary aldosteronism accounts for less than 1% of all patients with hypertension…"

Clinical Hypertension, 1994

"...the search for primary aldosteronism need only be undertaken in those with hypokalemia…"

PRIMARY ALDOSTERONISM - Greenslopes Hospital (1970-)

Out of 199 normokalemic patients referred to the HT Unit without the diagnosis of PAL in mind:

- 19 had PAL (9.5%)


Out of 52 patients with HT who volunteered for antihypertensive drug trials:

- 6 had PAL (12%)

PREVALENCE OF PAL - SINCE 1997

- Units reporting increased prevalence:
  - Fardella, et al (Chile)
  - Widimsky, et al (Czech Rep)
  - Douma, et al (Greece)
  - Benchetrit, et al (Israel)
  - Rossi, et al (Italy)
  - Mulatero, et al (Italy)
  - Nishikawa, et al (Japan)
  - Loh, et al (Singapore)
  - Davy, et al (UK)
  - Young, et al (USA)
  - Galloy, et al (USA)
  - Calhoun, et al (USA)
  - Schwartz, et al (USA)

- Prevalence rates: mostly 5 - 15%

- Proportion normokalemic: 59 - 100%

TREATMENT OF PRIMARY ALDOSTERONISM DUE TO ALDO-PRODUCING ADENOMA

UNILATERAL LAPAROSCOPIC ADRENALECTOMY

- HT cured in 50-60%, improved in all the remainder
- Marked improvement in quality of life

TREATMENT OF PRIMARY ALDOSTERONISM DUE TO BILATERAL ADRENAL HYPERPLASIA

SPECIFIC MEDICAL TREATMENT

- Aldosterone receptor blockers - spironolactone, eplerenone
- Epithelial sodium channel inhibitors - amiloride
- Improved control of hypertension (often marked)

ALDO + SALT = INFLAMMATION & FIBROSIS

- 1990 Karl Weber aldo+salt, rats, myocard fibrosis
- 2002 Ricardo Rocha aldo+salt, rats, coronary vasculitis

CARDIOVASC ABNORMALITIES IN PRIMARY ALDOSTERONISM

Compared with matched essential hypertensives:

- ↓ myocardial perfusion at rest on thallium-201 scanning
- ↑ exercise-induced myocardial ischemia on MIBI-SPECT and echocardiography
- ↑ LVMI, ↓ Diastolic function
- ↑ Myocardial backscatter
- ↓ Flow-mediated vasodilatation
- ↑ Strokes, AMIs, AF

CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 1

Relationship of aldo levels to cardiac abnormalities in primary aldosteronism

Subjects

- 60 patients with primary aldosteronism (PAL)
  - mean age 54 ± 12 y SD; 48% males
- 33 normotensive controls (CTRL)
  - mean age 47 ± 13 y SD; 58% males
CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 1

<table>
<thead>
<tr>
<th>Function</th>
<th>PAL (n=60)</th>
<th>CTRL (n=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Aldo (ng/dL)</td>
<td>23.3 ± 14.2</td>
<td>11.8 ± 7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24h Amb SBP (mmHg)</td>
<td>148 ± 19</td>
<td>125 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24h Amb DBP (mmHg)</td>
<td>87 ± 11</td>
<td>75 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>14.3 ± 4.1</td>
<td>12.4 ± 3.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>113 ± 28</td>
<td>81 ± 14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results expressed as means ± SD

M Stowasser & T Marwick, et al

CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 1

<table>
<thead>
<tr>
<th>Function</th>
<th>PAL (n=60)</th>
<th>CTRL (n=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain Rate b value</td>
<td>-0.30</td>
<td>-0.35</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P value</td>
<td>n.s.</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Results expressed as means ± SD

M Stowasser & T Marwick, et al

CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 2

Assessment of cardiac structure and function in normotensive subjects with primary aldosteronism

- 8 subjects with an inherited form of primary aldosteronism (Familial Hyperaldosteronism Type I, FH-I) detected by genetic testing, whose blood pressure levels were still normal, compared with 24 normotensive age- and sex-matched controls (3 for each subject with FH-I):
  - 24h ABPM
  - Aldo, renin, ARR levels
  - Echo

<table>
<thead>
<tr>
<th>Function</th>
<th>FH-I (n=8)</th>
<th>CTRL (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall thicknesses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>9.4 ± 1.2</td>
<td>7.9 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PW (mm)</td>
<td>9.2 ± 1.7</td>
<td>7.7 ± 1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RWT</td>
<td>0.29 ± 0.03</td>
<td>0.24 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>82 ± 21</td>
<td>70 ± 14</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E wave (ms)</td>
<td>0.74 ± 0.10</td>
<td>0.90 ± 0.16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.8 ± 0.2</td>
<td>2.1 ± 0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Em (cm/s)</td>
<td>8.3 ± 1.8</td>
<td>10.3 ± 2.6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Results expressed as means ± SD

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Assessment of cardiac response to surgical and medical treatment of primary aldosteronism

- Comparison of pre-treatment versus at least 6 months post-treatment (lap adrenalectomy or commencement of spironolactone):
  - 24h ABPM, No. of Drugs
  - Echo

**CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 3**

**CV EFFECTS OF ADRENALECTOMY VS SPIRONOLACTONE**

**CHANGES DURING FOLLOW UP (mean 17 mo)**

<table>
<thead>
<tr>
<th></th>
<th>ADX-treated (P = PTI)</th>
<th>Spiro-treated (P = PTI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ 24h SBP (mmHg)</td>
<td>-16.3 ± 14.1***</td>
<td>-11.6 ± 18.8*</td>
<td>NS</td>
</tr>
<tr>
<td>Δ 24h DBP (mmHg)</td>
<td>-8.9 ± 10.2**</td>
<td>-6.4 ± 10.0*</td>
<td>NS</td>
</tr>
<tr>
<td>Δ No. Drugs</td>
<td>-0.8 ± 1.2*</td>
<td>0.3 ± 0.9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Δ IVS (mm)</td>
<td>-0.17 ± 1.3***</td>
<td>0.12 ± 0.2**</td>
<td>NS</td>
</tr>
<tr>
<td>Δ PW (mm)</td>
<td>-0.17 ± 7.0.1***</td>
<td>0.09 ± 0.18</td>
<td>NS</td>
</tr>
<tr>
<td>Δ LVM (g)</td>
<td>-87.1 ± 56.8***</td>
<td>44.3 ± 58.1**</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Δ LVMi (g/m²)</td>
<td>-43.2 ± 26.4***</td>
<td>-23.8 ± 32.6**</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Δ ESV (mL)</td>
<td>-7.8 ± 10.2***</td>
<td>-5.1 ± 12.6</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Δ EDV (mL)</td>
<td>-44.3 ± 18.6***</td>
<td>-15.6 ± 24.3*</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01 and ***P<0.001 for pre- vs post-treatment

**CONCLUSIONS**

1) PAL is much more common than previously thought, accounts for 5-10% of HTIves, with most patients normokalemic, and is the commonest potentially curable/specifically treatable form of HT

2) Among patients with PAL, ald levels predict impaired LV systolic function independently of BP. Furthermore, compared with matched normotensive controls, normotensive subjects with PAL (due to FH-I) and raised ald levels demonstrate thicker LV walls and evidence of reduced diastolic LV function. These findings are consistent with ald excess having direct adverse effects on the heart independently of, and possibly even predating, its effects on raising BP

3) Unilateral adrenalectomy (in APA) and, to a lesser extent, spironolactone (in BAH), leads to marked reductions in LV dimensions

These findings highlight the importance of detecting patients with PAL who may then benefit not only from the BP-lowering effects, but also from reversal of non-BP dependent adverse effects of ald excess, by the institution of specific surgical or medical treatment.