Updates in primary hyperaldosteronism and the 20-50 rule

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The 20-50 Rule

• Rule:
  ➢ Over a continual cycle of 20 years,
  ➢ 50% of what we think we know in medicine
  ➢ Is shown to be wrong

• Promise:
  ➢ Medical care is better now than in the past, and
  ➢ The future will be even better!

• Implication:
  ➢ We should be humble when we think that we’re doing is the best thing for our patients
Hypertension and the 20-50 Rule

- 40 years ago
  - Hypertension frequently due to aldosterone
- 20 years ago
  - Hypertension rarely due to aldosterone
- Now
  - Hypertension frequently due to aldosterone
Renin-Angiotensin System and BP

↓ BP or Plasma Volume

↑ Renin

Angiotensinogen

Angiotensin I

ACE

Angiotensin II
Relative importance of Ang II vs aldosterone for BP regulation

How does aldosterone increase BP?

- NaCl retention
  - Increased amiloride-sensitive Na⁺ channel expression
  - Increased expression of Cl⁻-absorbing pendrin protein
  - Increased thiazide-sensitive NaCl cotransporter expression
But, NaCl-dependent volume expansion is NOT the only mechanism

Case Report

Primary hyperaldosteronism in a patient with end-stage renal disease

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Keywords: aldosterone; end-stage renal disease; haemodialysis; hypertension to 161/98 mmHg. Measurement of plasma aldosterone and renin revealed a high aldosterone level (12 ng/dl,
Renin-Angiotensin System and BP

- ↓ BP or Plasma Volume
- ↑ Renin
- Angiotensinogen
- Angiotensin I
- ACE
- Angiotensin II
- Aldosterone
- Adrenal Gland

Renal NaCl Retention
- ↑ SNS Tone
- Increased Vasoconstriction
- Decreased Vasodilation
- Increased BP

CNS

↑ Endothelin

↑ SNS Tone

Adrenal Gland

University of Florida
College of Medicine
The Foundation for the Gator Nation
Untreated primary hyperaldosteronism and cardiovascular events

Treating primary aldosteronism reduces CV risk

Combined incidence of MI, CVA, revascularization or sustained arrhythmia

<table>
<thead>
<tr>
<th>Follow-up (y)</th>
<th>Patients, %</th>
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<tbody>
<tr>
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<td>25</td>
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**No. of Patients at Risk**

- Essential Hypertension: 108, 106, 104, 100, 97, 94, 77, 63, 54, 45, 35, 29, 21
- Primary Aldosteronism: 54, 52, 49, 48, 47, 46, 39, 32, 28, 23, 18, 15, 11

Meds vs surgery – no difference

Combined incidence of MI, CVA, revascularization or sustained arrhythmia

No. of Patients at Risk

<table>
<thead>
<tr>
<th>Adrenalectomy</th>
<th>Spironolactone</th>
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<tr>
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<td>8</td>
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<td>5</td>
<td>6</td>
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</table>
Primary hyperaldosteronism - how to define “aldosterone excess?”

- Outside normal limits
  - Plasma aldosterone
    - Random
    - After NaCl loading
  - Urinary aldosterone
- Problem: “Normal limits” don’t consider the current physiologic state of the person

- What are normal physiologic determinants of aldosterone synthesis and release
  - K⁺ and Ang II

- Excessive aldosterone for this person
When is aldosterone “too much?”

- Aldosterone “excessive” for primary endogenous regulators ($K^+$ and AII)
  - Absence of hyperkalemia
  - Renin used as surrogate for AII
  - Aldosterone:Renin Ratio (ARR) measurements
    - > 3x normal ratio
    - Aldosterone “not suppressed”
      - Different investigators use >10, >15 and >20
Hyperaldosteronism prevalence and hypertension severity

Problem – Two renin assays in clinical use

- Normal Aldosterone:Renin Ratio
  - Plasma renin activity, ~10
  - Direct renin assay, ~1
Key Point

- Primary hyperaldosteronism does not require aldosterone levels outside the “normal” range!
Causes of primary hyperaldosteronism

- **Histology**
  - Hyperplasia
    - Bilateral adrenal hyperplasia
    - Unilateral adrenal hyperplasia
  - Adenoma
    - Aldosterone-producing adenoma (APA)
    - Bilateral adrenal adenoma

- **Treatment-defined**
  - Unilateral (surgical)
    - Aldosterone-producing adenoma
    - Unilateral adrenal hyperplasia
  - Bilateral (medical)
    - Bilateral adrenal hyperplasia
    - Bilateral adrenal adenoma
APA is associated with more severe hyperaldosteronism

![Graph showing relationship between Plasma Aldosterone and ARR_PRA](image-url)
Effect of using ARR screening on case identification

Cases diagnosed per year

- Torino: 7 Before ARR, 65 With ARR
- Rochester: 8 Before ARR, 85 With ARR
- Brisbane: 7 Before ARR, 66 With ARR
- Singapore: 6 Before ARR, 25 With ARR
- Santiago: 2 Before ARR, 22 With ARR

Before ARR
With ARR

J Clin Endocrinol Metab 89: 1045-1050, 2004
Hypokalemia is less frequent using ARR screening

![Bar chart showing the percentage of hypokalemic cases before and after ARR screening in different cities.](chart)

- **Torino**
  - Before ARR: 90%
  - After ARR: 25%

- **Rochester**
  - Before ARR: 98%
  - After ARR: 37%

- **Brisbane**
  - Before ARR: 66%
  - After ARR: 22%

- **Singapore**
  - Before ARR: 96%
  - After ARR: 37%

- **Santiago**
  - Before ARR: 100%
  - After ARR: 9%

*Source: J Clin Endocrinol Metab 89: 1045-1050, 2004*
More cases of aldosterone-producing adenoma identified.

- **J Clin Endocrinol Metab**: 89: 1045-1050, 2004

The diagram shows the number of APA cases per year before and with ARR for different cities:

- **Torino**
  - Before ARR: 20
  - With ARR: 23

- **Rochester**
  - Before ARR: 5
  - With ARR: 20

- **Brisbane**
  - Before ARR: 5
  - With ARR: 20

- **Singapore**
  - Before ARR: 5
  - With ARR: 13

- **Santiago**
  - Before ARR: 2
  - With ARR: 2

The bars represent the number of APA cases per year before and with ARR, with the yellow bars indicating cases with ARR.
Likelihood of a patient with primary hyperaldosteronism having APA is lower.
Causes of primary hyperaldosteronism

- **Histology**
  - Hyperplasia
    - Bilateral adrenal hyperplasia
    - Unilateral adrenal hyperplasia
  - Adenoma
    - Aldosterone-producing adenoma (APA)
    - Bilateral adrenal adenoma

- **Treatment-defined**
  - Unilateral
    - Aldosterone-producing adenoma
    - Unilateral adrenal hyperplasia
  - Bilateral
    - Bilateral adrenal hyperplasia
    - Bilateral adrenal adenoma
Differentiating unilateral vs bilateral aldosterone release

- **Indirect assessment**
  - Imaging
    - CT scan – adrenal imaging protocol
  - Angiotensin II regulation of aldosterone
    - Saline suppression test
    - Postural stimulation test
  - Steroid metabolites

- **Direct assessment**
  - Adrenal vein aldosterone measurement
Limitation of adrenal vein sampling

Limitation of adrenal vein sampling

Modified from C Clemente. *Human Anatomy*, 1975
Treatment of primary hyperaldosteronism

- Unilateral
  - Laparoscopic adrenalectomy
Response to adrenalectomy

- Cure, 50%
- Improved
  - 100%
  - 1.2 ± 1.3 medications per day
- Predictor
  - Age < 50
Response to adrenalectomy

- Predictors of cure
  - Family history in multiple individuals
  - Number of medications

Treatment of primary hyperaldosteronism

- Unilateral
  - Laparoscopic adrenalectomy

- Bilateral
  - Aldosterone receptor antagonist
    - Spironolactone
    - Eplerenone
Aldosterone receptor antagonists

- Spironolactone
  - 25 – 400 mg qd
  - Limitations
    - Gynecomastia, gynecodynia, menstrual irregularities
  - Cost $0.10-0.30 per day

- Eplerenone
  - 25 - 100 mg qd
  - Limitations
    - Cost, $1-2 per day
Which is better, spironolactone or eplerenone?

A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism

Which is better, spironolactone or eplerenone?

- 4 entry criteria – patients must meet ALL criteria
  - Serum aldosterone
    - > 20 ng/dl while on 150 mmol d⁻¹ NaCl diet, or
    - > 5 ng/dl after 2 L NS infused over 4 hr
  - Renin
    - AM plasma renin activity < 1.0 ng/ml/hr, or
    - Upright immunoreactive renin < 15 pg/ml
  - ARR
    - > 23
  - Urine aldosterone
    - > 20 µg d⁻¹ with urine Na⁺ > 150 mmol d⁻¹

Which is better, spironolactone or eplerenone?

Table 1  Demographics and other baseline characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Eplerenone (N = 70)</th>
<th>Spironolactone (N = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (37.1%)</td>
<td>19 (26.8%)</td>
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<tr>
<td>Male</td>
<td>44 (62.9%)</td>
<td>52 (73.2%)</td>
</tr>
<tr>
<td>Age mean (SD)</td>
<td>53.9 (10.89)</td>
<td>53.2 (10.92)</td>
</tr>
<tr>
<td>Number in each age group</td>
<td></td>
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<tr>
<td>&lt;55</td>
<td>36</td>
<td>37</td>
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<td>55–64</td>
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<td>66–74</td>
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<tr>
<td>75+</td>
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<tr>
<td>Ethnicity</td>
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<tr>
<td>White</td>
<td>60 (85.7%)</td>
<td>65 (91.5%)</td>
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<tr>
<td>Black</td>
<td>9 (12.9%)</td>
<td>5 (7.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.4%)</td>
<td>1 (1.4%)</td>
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<tr>
<td>Weight (kg) mean (SD)</td>
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<tr>
<td>Women</td>
<td>73.0 (12.95)</td>
<td>83.9 (15.09)</td>
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<tr>
<td>Men</td>
<td>93.7 (21.55)</td>
<td>88.3 (13.85)</td>
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<tr>
<td>Height (cm) mean (SD)</td>
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</tr>
<tr>
<td>Women</td>
<td>160.0 (5.36)</td>
<td>161.8 (6.78)</td>
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<tr>
<td>Men</td>
<td>174.2 (7.60)</td>
<td>173.6 (9.02)</td>
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<td>BMI (kg/m²) mean (SD)</td>
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<tr>
<td>Women</td>
<td>28.6 (5.2)</td>
<td>31.8 (5.2)</td>
</tr>
<tr>
<td>Men</td>
<td>30.7 (6.0)</td>
<td>29.3 (3.6)</td>
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<tr>
<td>Blood pressure (mmHg)</td>
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<tr>
<td>Mean seSBP (SD)</td>
<td>166.4 (13.91)</td>
<td>162.6 (17.12)</td>
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<tr>
<td>Mean seDBP (SD)</td>
<td>101.8 (7.92)</td>
<td>101.8 (7.82)</td>
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<td>Median SBP</td>
<td>167.0</td>
<td>162.5</td>
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<td>Range SBP</td>
<td>138.0–197.5</td>
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<td>Median DBP</td>
<td>100.3</td>
<td>101.8</td>
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<tr>
<td>Range DBP</td>
<td>90.0–118.5</td>
<td>89.5–118.0</td>
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<td>Serum sodium (mmol/l)*</td>
<td>143.9 (2.42)</td>
<td>142.6 (2.49)</td>
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<tr>
<td>Serum potassium (mmol/l)*</td>
<td>3.48 (0.40)</td>
<td>3.34 (0.57)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)*</td>
<td>74.1 (8.86)</td>
<td>68.3 (8.31)</td>
</tr>
</tbody>
</table>

se, seated.
SBP response to eplerenone vs spironolactone


**Statistically significant difference versus spironolactone (P<0.001).
**DBP response to eplerenone vs spironolactone**

![Graph showing the adjusted mean change from baseline in seDBP (mmHg) over weeks 4, 8, 12, and 16 for Eplerenone (N = 68) and Spironolactone (N = 69).](image)

- **Baseline**
- **Week 4**
- **Week 8**
- **Week 12**
- **Week 16**

*Statistically significant difference versus spironolactone at *P* = 0.11, **P < 0.001.*

Likelihood of response – DBP < 90 or Δ ≥ 10

Study withdrawals

Study withdrawals

- Total withdrawals: 37%
- Treatment failure: 20%
- Adverse event: 10%
- Other: 7%

Why does spironolactone appear more effective?

- **Spironolactone**
  - Higher affinity for MR
  - Highly protein bound, >90%
  - Rapid first-pass metabolism (half-life 1-2 hrs)
  - Metabolites, 
    - Biologically active
    - Long half-life, ~15 hrs
  - Effectively is a “pro-drug” of a variety of compounds with long half-lives

- **Eplerenone**
  - Less protein binding, ~50%
  - Half-life, ~4 hrs
  - Metabolites
    - Biologically inactive
Major adverse effects

- Spironolactone
  - Gynaecomastia, 21%*
  - Headache, 21%
  - Female breast pain, 21%*
  - Menstrual disorder, 10%
  - Impotence, 6%

- Eplerenone
  - Headache, 17%
  - URI, 6%
  - Gynaecomastia, 4%

Tolerability differences

- Favoring eplerenone
  - Breast discomfort (M&F)
  - Breast tenderness (M&F)

- Favoring spironolactone
  - Feeling out of touch with reality
  - Difficulty thinking
  - Feeling lost, disoriented
  - Unawareness of what is going on
  - General weakness
  - Difficulty planning, organizing
  - Tiredness, feeling weary

Confirmation of successful adrenal vein sampling

- Anatomic confirmation is NOT adequate
- Biochemical confirmation is NECESSARY
  - Adrenal vein aldosterone
    - Inadequate to differentiate APA from unsuccessful cannulation
  - Adrenal vein cortisol
    - If ACTH levels low, adrenal cortisol production low
  - Cortrosyn-stimulated adrenal vein cortisol
    - ~10-fold greater than IVC cortisol
Refractory Hypertension

ARR and Plasma Aldosterone

ARR <25

ARR 25-50

ARR >50 and [Aldo] > 10

Primary hyperaldosteronism unlikely

Plasma aldosterone after oral NaCl loading

Suppressed

Non-suppressed

Primary hyperaldosteronism

Adrenal Protocol CT Scan

Negative

Optimize MR Blocker

Positive

Surgical Candidate?

Yes

Bilateral Aldosterone Release

Optimize MR Blocker

No

Unilateral Aldosterone Release

Laparoscopic Adrenalectomy

Adequate BP Response?

Yes

Continue Therapy

No

Optimize MR Blocker

Plasma aldosterone after oral NaCl loading

Suppress

Non-suppressed

Begin MR Blocker