Updates in primary hyperaldosteronism and the 20-50 rule

I. David Weiner, M.D.

C. Craig and Audrae Tisher Chair in Nephrology
Professor of Medicine and Physiology and Functional Genomics

University of Florida College of Medicine
Changes in health-care and the 20-50 rule

- Patient with ACS
  - 20 years ago, ASA absolutely contraindicated
- Patient with COPD exacerbation
  - 20 years ago, steroids absolutely contraindicated
- Patient with peptic ulcer disease
  - 20 years ago, antibiotics are useless
- Patient with hypertension
  - 20 years, BP 160/90 is the target
The 20-50 Rule

- **Rule:**
  - Over a continual cycle of 20 years,
  - 50% of what we think we know in medicine
  - Is found 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, even when we think we know what we’re doing
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
Severity of hypertension and the prevalence of primary aldosteronism

- Hypertension >180/110: 13.2%
- 160-179/100-109: 8.0%
- 140-59/90-99: 2.0%
- <130/85: 1.6%

Why should we care?

- Identifying and treating primary aldosteronism makes a difference!
  - Better blood pressure control
    - Holy grail of hypertension management
    - Identify the etiology
    - Treat the etiology
  - Better outcomes
Untreated primary aldosteronism increases cardiovascular events

- MI or reversible ischemia: 8% Essential hypertension, 20% Primary Aldosteronism
- CVA or TIA: 3% Essential hypertension, 11% Primary Aldosteronism
- Sustained arrhythmia: 3% Essential hypertension, 15% Primary Aldosteronism
- PAD: 2% Essential hypertension, 6% Primary Aldosteronism

Treating primary aldosteronism reduces CV risk

Combined incidence of MI, CVA, revascularization or sustained arrhythmia

Blood pressure is regulated by the renin-angiotensin system

↓ BP or Plasma Volume

↑ Renin

Angiotensinogen

Angiotensin I

ACE

Angiotensin II
How important is aldosterone: relative importance of Ang II vs aldosterone

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, if this was all
  - Thiazide diuretic plus amiloride would be enough
Primary hyperaldosteronism in a patient with end-stage renal disease

Amir Kazory\textsuperscript{1} and I. David Weiner\textsuperscript{1,2}

\textsuperscript{1}Division of Nephrology, Hypertension and Transplantation, University of Florida and \textsuperscript{2}Nephrology and Hypertension Section, North Florida/South Georgia Veterans Health System, Gainesville, FL 32610, USA

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

- Decrease in BP or Plasma Volume
- Increase in Renin
- Conversion of Angiotensinogen to Angiotensin I
- Conversion of Angiotensin I to Angiotensin II by ACE
- Production of Aldosterone
- Increased SNS Tone
- Increased Renal NaCl Retention
- Increased Endothelin
- Increased Vasoconstriction
- Decreased Vasodilation
- Adrenal Gland
- CNS
Primary aldosteronism - how to define “aldosterone excess?”

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

- 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
    - > 2.5x normal ratio (300:1 in SI units)
  - Aldosterone “not suppressed”
    - Different investigators use >300, 450 and 600
When is aldosterone “too much?”

- ARR has difficulties due to variability because of low renin values
  - Plasma renin activity change from 0.1 → 0.2 ng/ml/hr
    - Not physiologically significant
    - Causes 2x-fold change in ARR (50% reduction)

- My preference:
  - Plasma renin activity is suppressed
    - Typically 0.1-0.3 ng/ml/hr;
  - Plasma aldosterone is not
    - I use plasma aldosterone > 300 pmol/L
Key Point

- Primary aldosteronism does not require aldosterone levels outside the “normal” range!
Use of ARR leads to more cases of primary aldosteronism being identified

Cases diagnosed per year

- Torino: 7 cases/year before ARR, 65 cases/year with ARR
- Rochester: 8 cases/year before ARR, 85 cases/year with ARR
- Brisbane: 7 cases/year before ARR, 66 cases/year with ARR
- Singapore: 6 cases/year before ARR, 25 cases/year with ARR
- Santiago: 2 cases/year before ARR, 22 cases/year with ARR
Hypokalemia is less frequent using ARR screening

- **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%

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

<table>
<thead>
<tr>
<th>Location</th>
<th>Before ARR</th>
<th>With ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torino</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Rochester</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Brisbane</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Singapore</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Santiago</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Source: J Clin Endocrinol Metab 89: 1045-1050, 2004
Likelihood of bilateral adrenal hyperplasia is higher

Before ARR

With ARR

<table>
<thead>
<tr>
<th>City</th>
<th>Before ARR</th>
<th>With ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torino</td>
<td>30%</td>
<td>70%</td>
</tr>
<tr>
<td>Rochester</td>
<td>32%</td>
<td>72%</td>
</tr>
<tr>
<td>Brisbane</td>
<td>25%</td>
<td>70%</td>
</tr>
<tr>
<td>Singapore</td>
<td>14%</td>
<td>50%</td>
</tr>
<tr>
<td>Santiago</td>
<td>17%</td>
<td>91%</td>
</tr>
</tbody>
</table>

J Clin Endocrinol Metab 89: 1045-1050, 2004
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
    - 20-30% incorrect assignment risk
  - MUST use “adrenal protocol”

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

Modified from C Clemente. *Human Anatomy*, 1975
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
  – ACTH/Cortrosyn-stimulated adrenal vein cortisol
    • Also increases aldosterone production
      – As much as 40-fold
      – Possible differential effects on hyperplastic and adenomatous glands
      – Can lead to incorrect assignment of aldosterone site
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 antagonists
    - Spironolactone
    - Eplerenone
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

SBP response to eplerenone vs spironolactone

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

*Statistically significant difference versus spironolactone at P = 0.11, **P < 0.001.
Likelihood of response – DBP < 90 or $\Delta \geq 10$

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Spironolactone</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>45%</td>
<td>30%</td>
</tr>
<tr>
<td>8</td>
<td>71%</td>
<td>35%</td>
</tr>
<tr>
<td>12</td>
<td>75%</td>
<td>46%</td>
</tr>
<tr>
<td>16</td>
<td>68%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Study withdrawals

Study withdrawals

Why does spironolactone appear more effective?

- **Eplerenone**
  - Half-life, ~4 hrs
  - Metabolites
    - Biologically inactive

- **Spironolactone**
  - Half-life 1-2 hrs
  - Metabolites,
    - Biologically active
    - Half-life, ~15 hrs
  - Effectively is a “pro-drug” of a variety of compounds with long half-lives
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

Refractory Hypertension

ARR and Plasma Aldosterone

- Aldosterone suppressed; Plasma renin activity suppressed
  - Primary Aldosteronism unlikely
- ARR 300-750
- ARR > 750 and [Aldo] > 300; Renin suppressed; Aldosterone not!

Plasma aldosterone after oral NaCl loading

- Suppressed
  - Primary Aldosteronism unlikely
- Non-suppressed
  - Adrenal Protocol CT Scan
    - Positive
      - Adrenal Vein Aldosterone Sampling
        - Unilateral Aldosterone Release
          - Laparoscopic Adrenalectomy
        - Bilateral Aldosterone Release
          - Optimize MR Blocker
    - Negative
      - Optimize MR Blocker

Surgical Candidate?

- Yes
  - Begin MR Blocker
- No
  - Optimize MR Blocker

Adequate BP Response?

- Yes
  - Continue Therapy
- No
  - Optimize MR Blocker