What is the Role of Plasma Renin Activity Levels in the Management of Hypertension?

Ilya Danelich, PharmD, BCPS
Cardiology Clinical Pharmacist

Pharmacy Grand Rounds
Mayo Clinic Hospital - Rochester
July 19, 2016
Objectives

• Describe the role of PRA levels in the management of hypertension
• Review the differences between using PRA levels and traditional methods of managing hypertension
• Outline a treatment care plan using PRA levels to manage hypertension
Epidemiology of Hypertension

• Affects nearly 78 million people ≥ 20 years in the US
• 47.5% have uncontrolled hypertension
• Hypertension related mortality: 18.5%
• Estimated Cost: $51 billion

Percent of patients with hypertension at first event

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>69%</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>74%</td>
</tr>
<tr>
<td>Stroke</td>
<td>77%</td>
</tr>
</tbody>
</table>

JNC 8 Guidelines

Implement Lifestyle Interventions

- General Population (no diabetes or CKD)
- Diabetes or CKD present

Select a drug treatment titration strategy
A. Maximize first medication before adding second or
B. Add second medication before reaching maximum dose of first medication or
C. Start with 2 medication classes separately or as fixed-dose combination

- Thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination
- Thiazide-type diuretic or CCB, alone or in combination
- ACEI or ARB, alone or in combination with other drug class

ACEI - angiotensin-converting enzyme inhibitor
ARB - angiotensin receptor blocker
BP - blood pressure
CCB - calcium channel blocker
CKD - chronic kidney disease
JNC 8 - Eighth Joint National Committee

PRA Levels: Laragh Method

John H. Laragh, MD

Jean E. Sealey, D.Sc.

http://www.laraghmethod.org/
Volume – Vasoconstriction Concept to Blood Pressure Control

Blood Pressure is sustained by:

✓ Body sodium-volume content (V)
✓ Plasma renin-angiotensin vasoconstrictor activity (R)

The V and R interacting control system sustains all normotension and all forms of hypertension

Interaction between Body Sodium and Circulating Renin-Angiotensin

Blood Pressure

BP = V x R

Arterial Volume (V)

Vasoconstriction (R)

Renal Sodium Retention

Diuretic

Sodium

Renin

Angiotensinogen

Angiotensin I

Angiotensin II

ARB

ACEI

DRI

RENIN

Feedback suppression of renin secretion

β-blocker

DRI - direct renin inhibitor

## PRA Definitions

### For Patients Not Taking ACEI or ARB

<table>
<thead>
<tr>
<th>Type of Hypertension</th>
<th>PRA Level (ng/mL/hr)</th>
<th>Low renin</th>
<th>Medium renin</th>
<th>High Renin</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>&lt; 0.65</td>
<td>&lt; 0.65</td>
<td>0.65-6.5</td>
<td>&gt; 6.5</td>
</tr>
<tr>
<td>R</td>
<td>6.5-6.5</td>
<td>0.65-6.5</td>
<td>6.5</td>
<td>R</td>
</tr>
</tbody>
</table>

### For Patients Taking ACEI or ARB

<table>
<thead>
<tr>
<th>Type of Hypertension</th>
<th>PRA Level (ng/mL/hr)</th>
<th>ePRA Level (ng/mL/hr)</th>
<th>Low renin</th>
<th>Medium renin</th>
<th>High Renin</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>&lt; 6.5</td>
<td>&lt; 0.65</td>
<td>&lt; 6.5</td>
<td>0.65-6.5</td>
<td>&gt; 6.5</td>
</tr>
<tr>
<td>R</td>
<td>6.5-65</td>
<td>0.65-6.5</td>
<td>6.5</td>
<td>6.5</td>
<td>R</td>
</tr>
</tbody>
</table>

\[ \text{ePRA} = 0.1 \times \text{PRA} \]

## Drug Types

### Anti-V Drugs
- Diuretics
- Aldosterone receptor antagonists
- Calcium channel blockers
- Alpha-1 blockers

### Anti-R Drugs
- ACEI
- ARB
- Direct renin inhibitors
- Beta-blockers
- Central α2-agonists
Untreated Hypertensive Patient

**Step 1:** Measure PRA

- Low PRA: \(< 0.65 \)  
  - V Patient
  - **Steps 2 & 3:** Give anti-V drug

- Medium to high PRA: \(\geq 0.65\)  
  - R Patient
  - **Steps 2 & 3:** Give anti-R drug

**Step 4:** If BP elevated, measure PRA

- **Steps 5 & 6:** If PRA \(< 0.65\) = V+V patient  
  - Add 2nd anti-V Drug

- **Steps 5 & 6:** If PRA \(\geq 0.65\) = V+R patient  
  - Add anti-R Drug

- **Steps 5 & 6:** If PRA (or ePRA) \(< 0.65\) = R+V patient  
  - Add anti-V drug

- **Steps 5 & 6:** If PRA (or ePRA) \(\geq 0.65\) = R+R patient  
  - Add 2nd anti-R drug

Treated Hypertensive Patient

BP not controlled on full doses of 1 anti-V & 1 anti-R drug (ACEI or ARB)

**Step 1:** Measure PRA

**Step 2:** If PRA < 0.65, there is no renin to block. Anti-R drug may be pressor. Subtract anti-R drug

**Steps 2 & 3:**
- If PRA 0.65-6.5 (ePRA < 0.65), renin is effectively blocked.
  - Add 2nd anti-V drug

**Steps 3 & 4:**
- If BP not controlled on monotherapy, Add 2nd anti-V drug

**Step 2:** If PRA > 6.5 (ePRA > 0.65) patient may be volume depleted
- Subtract anti-V drug

**Steps 3 & 4:**
- If BP not controlled on monotherapy, Add 2nd anti-R drug

**Steps 4:** If BP controlled, Test subtracting anti-R drug

Audience Response #1

Using PRA levels in the management of hypertension helps determine which of the following?

a. Whether the patient would benefit most from ACE inhibitor vs. beta-blocker

b. Whether the patient has R mediated hypertension vs. V mediated hypertension, thereby guiding treatment

c. Which blood pressure goal to target

d. Whether the patient would benefit most from spironolactone vs. amlodipine
Audience Response #2

Which of the following statements between using PRA levels and traditional methods of managing hypertension is true?

a. JNC8 recommends thiazide-type diuretic as initial therapy for all patients whereas using PRA levels allows for individualized care

b. JNC8 provides the ability to individualize the pharmacotherapy plan whereas using PRA levels consists of stepped care with progressive addition of medications

c. JNC8 recommends stepped care with progressive addition of medications whereas using PRA levels focuses on individualizing the pharmacotherapy plan

d. JNC8 provides guidance for patients with treated and untreated hypertension whereas PRA levels only provide guidance for untreated hypertension
Plasma Renin Test–Guided Drug Treatment Algorithm for Correcting Patients With Treated but Uncontrolled Hypertension: A Randomized Controlled Trial

**Study Design**

- Randomized, unblinded \( (n = 77) \)

- **Treated, uncontrolled hypertension**
- **Uncontrolled**: \( \geq 140/90 \) mm Hg or \( \geq 130/80 \) mm Hg in patients with DM and/or nephropathy

- **Primary Outcome**
  - Difference in BP

- **Exclusion Criteria**
  - Uncontrolled DM or hyperlipidemia
  - Alcohol or drug abuse in the past 5 years
  - ESRD and CKD with SCr > 2.5
  - Intolerance to \( \geq 2 \) classes of anti-hypertensive medications

---

DM - diabetes mellitus
ESRD - end stage renal disease
SCr - serum creatinine

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RTGT (n = 38)</th>
<th>CHSC (n = 39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.9</td>
<td>58.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Men, %</td>
<td>84</td>
<td>74</td>
<td>0.29</td>
</tr>
<tr>
<td>Race, % Caucasian</td>
<td>68</td>
<td>41</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.6</td>
<td>28.9</td>
<td>0.44</td>
</tr>
<tr>
<td>Diabetic, %</td>
<td>24</td>
<td>36</td>
<td>0.24</td>
</tr>
<tr>
<td>CKD, %</td>
<td>13</td>
<td>5</td>
<td>0.21</td>
</tr>
<tr>
<td>PRA, ng/mL/h</td>
<td>5.8</td>
<td>4.6</td>
<td>0.52</td>
</tr>
<tr>
<td>SCr, mg/dL</td>
<td>1.09</td>
<td>1.09</td>
<td>0.93</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>77</td>
<td>92</td>
<td>0.02</td>
</tr>
</tbody>
</table>

BMI – body mass index

eGFR - estimated glomerular filtration rate
Blood Pressure Effect

<table>
<thead>
<tr>
<th></th>
<th>Baseline SBP</th>
<th>Baseline DBP</th>
<th>Last Visit SBP</th>
<th>Last Visit DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RTGT</strong></td>
<td>157</td>
<td>87.1</td>
<td>127.9</td>
<td>73.1</td>
</tr>
<tr>
<td><strong>CHSC</strong></td>
<td>153.2</td>
<td>91.1</td>
<td>134</td>
<td>79.8</td>
</tr>
</tbody>
</table>

SBP - systolic blood pressure
DBP - diastolic blood pressure

P = 0.27
P = 0.17
P = 0.10
P = 0.01

Changes in Blood Pressure

<table>
<thead>
<tr>
<th>SBP Change</th>
<th>DBP Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>-29.1 mm Hg</td>
<td>-14.1 mm Hg</td>
</tr>
</tbody>
</table>

P = 0.03

P = 0.32

Number of Medications

<table>
<thead>
<tr>
<th></th>
<th>RTGT</th>
<th>CHSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Last Visit</td>
<td>2.7</td>
<td>3</td>
</tr>
<tr>
<td>Change</td>
<td>0</td>
<td>0.3</td>
</tr>
</tbody>
</table>

P = 0.21

P = 0.73

P = 0.25

Conclusions & Limitations

Conclusions
Using PRA levels may provide better BP control without a net increase in the number of medications

Limitations
✓ RTGT group older, more Caucasians, worse kidney function
✓ Unblinded
✓ Small sample size
✓ Hypertension specialist group may not mimic general practice

Pressor Responses To Antihypertensive Drug Types

Study Design

• Retrospective analysis \((n = 945)\)

  ✓ Untreated hypertension
  ✓ SBP \(\geq 140\) mm Hg

  Anti-V Drug: Diuretic or CCB  
  \(n = 537\)
  Anti-R Drug: \(\beta\)-blocker or ACEI  
  \(n = 408\)

• Primary Endpoint
  Incidence of pressor responses, and influence of PRA status

• Pressor Response – SBP rise \(\geq 10\) mm Hg

# Blood Pressure Response

<table>
<thead>
<tr>
<th>Categories of SBP Change (%)</th>
<th>V Drug ( (n = 537) )</th>
<th>R Drug ( (n = 408) )</th>
<th>( P \text{ Value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 10 mm Hg rise</td>
<td>5.2</td>
<td>11.0</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 10 mm Hg fall</td>
<td>62.0</td>
<td>54.9</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categories of DBP Change (%)</th>
<th>V Drug ( (n = 537) )</th>
<th>R Drug ( (n = 408) )</th>
<th>( P \text{ Value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 5 mm Hg rise</td>
<td>6.3</td>
<td>7.8</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 5 mm Hg fall</td>
<td>63.1</td>
<td>63</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS - not significant
Pressor Response by PRA Status

- Low PRA: 6, 17 (P < 0.001)
- Middle PRA: 4, 10 (P = 0.02)
- High PRA: 6, 9 (P = 0.08)

V Drug: 6, 4, 6
R Drug: 17, 10, 9

Percent with Treatment SBP ≥ 160 mm Hg

- Low PRA: V Drug, P < 0.01
- Middle PRA: R Drug, P = 0.16
- High PRA: V Drug, R Drug, P = 0.90

Percent with Treatment SBP ≤ 130 mm Hg

- Low PRA: $P \leq 0.003$
- Middle PRA: $P = 0.72$
- High PRA: $P = 0.002$

Conclusions

• Overall, anti-R drugs were associated with a greater incidence of pressor response than anti-V drugs

• Pressor responses were most likely when anti-R drugs were given to patients in the low-renin tertile

• To increase likelihood of achieving BP control with monotherapy
  ✓ Avoid anti-R drugs in the lowest PRA but use them in the highest PRA
  ✓ Avoid anti-V drugs in the highest PRA but use them in the lowest PRA

57 yo African American male with a past medical history of dyslipidemia is diagnosed with new-onset hypertension. After a trial of therapeutic lifestyle changes, the decision is made to initiate pharmacotherapy to manage hypertension. The blood pressure in clinic is 152/93 mmHg, HR 64 BPM. SCr – 0.9 mg/dL, K 4.3 mmol/L. PRA level: 7.1 ng/mL/hr. Which of the following is an appropriate first line therapy?

a. Spironolactone
b. Hydrochlorothiazide
c. Amlodipine
d. Lisinopril

BPM - beats per minute
# Proposed Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Guiding initial and follow-up treatment strategies in untreated hypertensive patients</td>
</tr>
<tr>
<td>II</td>
<td>Guiding drug subtractions and additions in patients whose BP is <em>uncontrolled</em> on an anti-V and anti-R drug combination</td>
</tr>
<tr>
<td>III</td>
<td>Guiding drug subtractions and additions in patients whose BP is <em>uncontrolled</em> on ≥ 3 drugs</td>
</tr>
<tr>
<td>IV</td>
<td>Reducing medication burden in hypertensive patients whose BP is <em>controlled</em> on ≥ 4 drugs</td>
</tr>
</tbody>
</table>
Conclusions

• PRA levels provide an individualized approach to managing hypertension

• Using PRA levels may provide better BP control without a net increase in medications

• Further clinical trials are necessary to assess hypertension control and impact on cardiovascular outcomes
Questions & Discussion
What is the Role of Plasma Renin Activity Levels in the Management of Hypertension?

Ilya Danelich, PharmD, BCPS
Cardiology Clinical Pharmacist
Pharmacy Grand Rounds
Mayo Clinic Hospital - Rochester
July 19, 2016