Endocrine Regulation of Blood Pressure

Grace M. Kroner, Ph.D.
Clinical Chemistry Fellow

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Learning Objectives

1. List the hormones that regulate blood pressure.

2. Compare the presentation of endocrine diseases that may cause hypertension.

3. Interpret laboratory testing results for primary hyperaldosteronism and diabetes insipidus.
Outline

• Blood pressure
  – Regulation

• Hypertension
  – Primary hyperaldosteronism
  – Laboratory testing
  – Rare causes of apparent mineralocorticoid excess

• Hypotension
  – Diabetes insipidus
  – Laboratory testing
Why is appropriate blood pressure important?

• Needed to ensure nutrient and oxygen delivery to tissues
• Too high blood pressure → hypertension
• Too low blood pressure → hypotension

Blood Pressure Components

Systolic blood pressure (SBP): 120
Diastolic blood pressure (DBP): 80

Systole: contraction
Diastole: relaxation

What factors change blood pressure?

1. Cardiac output
   - Depends on blood volume
   - Average adult has 5 liters of blood

Larger volume $\rightarrow$ ↑ pressure
Smaller volume $\rightarrow$ ↓ pressure
What factors change blood pressure?

1. Cardiac output

2. Vascular resistance
   - Depends on the size of blood vessels
   - Range from 5-10 µm to 2-3 cm!

Vasoconstriction
Smaller size $\rightarrow$ ↑ pressure

Vasodilation
Larger size $\rightarrow$ ↓ pressure

How is blood pressure controlled?

- Sympathetic nervous system
- Endocrine system
  - Hormones affect blood volume and blood vessel size
- Kidney
  - Produce antihypertensive substances

Endocrine Interconnection

Brain

Posterior pituitary

Antidiuretic hormone (ADH)

Atrial natriuretic peptide (ANP)

Brain natriuretic peptide (BNP)

Angiotensin II

Aldosterone

Renin

Catecholamines

Blood-stream

Heart

Adrenal glands

Kidneys

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Hypertension (HTN) is a significant public health concern

- Estimated US prevalence among adults: 46%
- Increases risk of heart attack, heart failure, kidney disease and stroke

Stages of Hypertension

• Change in 2017 to lower cut-off increased prevalence
  
<table>
<thead>
<tr>
<th>Category</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>&lt;120 mmHg</td>
<td>&lt;80 mmHg</td>
</tr>
<tr>
<td>Elevated</td>
<td>120-129 mmHg</td>
<td>&lt;80 mmHg</td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>130-139 mmHg</td>
<td>80-89 mmHg</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>≥140 mmHg</td>
<td>≥90 mmHg</td>
</tr>
</tbody>
</table>

• No perfect cut-off to eliminate risk
  – Often asymptomatic until severe complications develop

Classification of Hypertension

• Primary hypertension
  – Contributing factors:
    • Genetics
    • Stress
    • Obesity
    • Smoking
    • Physical inactivity
    • High-salt diet

• Secondary hypertension
  – Renal or endocrine malfunction

What endocrine disorders may cause hypertension?

- Hyperaldosteronism: 8-20%
- Congenital adrenal hyperplasia: Rare
- Cushing syndrome: 0.1%
- Apparent mineralocorticoid excess: Rare
- Increased catecholamines: 0.1-0.6%
- Acromegaly: Rare
- Hyperthyroidism: <1%
- Hypothyroidism: <1%

What endocrine disorders may cause hypertension?

- Hyperaldosteronism
- Congenital adrenal hyperplasia
- Cushing syndrome
- Apparent mineralocorticoid excess
- Increased catecholamines
- Acromegaly
- Hyperthyroidism
- Hypothyroidism

What other symptoms might patients have?

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperaldosteronism</td>
<td>HTN, hypokalemia, muscle weakness</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Central obesity, facial changes, glucose intolerance, purple striae</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Facial changes, increasing size of hands/feet</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Weight loss, warm skin, heat intolerance, nervousness, diarrhea</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Weight gain, dry skin, cold intolerance, constipation</td>
</tr>
</tbody>
</table>

How do physicians know to consider secondary testing?

• Abrupt onset of HTN
• New onset of HTN at early or late age
• Initial presentation with stage 2 HTN
• Clinical clue(s) suggesting specific cause
• Drug resistant HTN
  – Occurs when goal BP is not obtained with 3 different classes of medications, or is obtained with ≥ 4 medications
  – Up to 14.8% of treated hypertensive patients

Renin-Aldosterone System

1. Blood pressure falls
2. Renin
3. Angiotensin-converting enzyme (ACE)
4. Angiotensin II
5. Aldosterone

Sodium, Water, Potassium, Hydrogen ions

“Chapter 66,” Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 6th edition, 2018; Image from Chemistry Class Slides, Horbachevsky Ternopil State Medical University, Ukraine.
Renin-Aldosterone System

1. Renin
2. Angiotensin I
3. Angiotensin-converting enzyme
4. Angiotensin II

Blood pressure rises → Salt retention → Aldosterone

Blood pressure falls
What is primary hyperaldosteronism?

- High blood pressure due to uncontrolled excretion of aldosterone
  - Most common:
    - Aldosterone-producing adenoma
    - Bilateral idiopathic hyperaldosteronism
  - Relatively rare:
    - Familial hyperaldosteronism
    - Unilateral adrenal hyperplasia
    - Adrenal carcinoma
    - Ectopic aldosterone-producing tumor
- Increased risk for cardiovascular complications

One or both adrenal glands?

What is primary hyperaldosteronism?

- One adrenal gland affected → aldosterone producing adenoma (~30% of cases)
What is primary hyperaldosteronism?

- Both adrenal glands affected → bilateral adrenal hyperplasia (~60% of cases)
Testing for primary hyperaldosteronism

• Screening hypertensive patients
• Confirming primary hyperaldosteronism
• Classifying disease as unilateral or bilateral

Diagnosis of primary aldosteronism, *Up To Date*, July 2018.
Testing for primary hyperaldosteronism

• Screening hypertensive patients
  – Prevalence may be up to 5-10% of hypertensive patients
  – Plasma aldosterone: renin ratio
  – Expect: high aldosterone, low renin → elevated ratio
    • Normal ratio is between 4 and 10
    • Abnormal ratio can be > 30-50

Testing for primary hyperaldosteronism

• Screening hypertensive patients
  – Pre-analytical concerns:
    • Unrestricted salt intake
    • Normal potassium
    • No mineralocorticoid antagonists within 4 weeks

Testing for primary hyperaldosteronism

- Screening hypertensive patients

- Confirming primary hyperaldosteronism
  - Sodium loading to test aldosterone suppression
  - Urine or plasma aldosterone

Testing for primary hyperaldosteronism

- Screening hypertensive patients
- Confirming primary hyperaldosteronism
- Classifying disease as unilateral or bilateral
  - CT (computed tomography) imaging and/or adrenal venous sampling
  - *Critical* for making treatment decisions

Why is classification so important?

• Treatment depends on classification:
  – One adrenal affected → surgery to remove it
  – Both adrenals affected → treat with drugs

Image from Diagnosis of primary aldosteronism, *Up To Date*, July 2018.
Why can’t we just look at it?

- CT imaging not always accurate or sensitive
- Incidentalomas more likely in individuals >40 years
- Adenoma >4cm suggests carcinoma

How does adrenal venous sampling (AVS) work?

• Is more aldosterone produced from one adrenal gland or another?

• May use cosyntropin stimulation
  – Minimize stress-induced changes
  – Maximize aldosterone and cortisol production

• Use fluoroscopy to help image catheter

AVS Procedure Overview

Goals
1. Right adrenal vein
2. Left adrenal vein
3. Inferior vena cava

Measure aldosterone and cortisol

Image from Diagnosis of primary aldosteronism, *Up To Date*, July 2018.
AVS Procedure Overview

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AVS Procedure Overview

Goals
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Measure aldosterone and cortisol
How are the results interpreted?

• Did the sample come from the correct spot?
• Are one or both adrenals secreting too much aldosterone?
• If only one is affected, does the other adrenal have suppressed aldosterone secretion levels?

• Aldosterone: cortisol ratios employed
Identifying unilateral or bilateral disease

Sensitivity: 95.2%
Specificity: 100%

Aldosterone_{high-side}
Cortisol_{high-side}
Aldosterone_{low-side}
Cortisol_{low-side}

One adrenal affected (unilateral) Both adrenals affected (bilateral)

Diagnosis confirmed surgically

Is there suppression of the unaffected adrenal gland?

\[
\begin{align*}
\text{Aldosterone}_{\text{low-side}} & < 1 \\
\text{Cortisol}_{\text{low-side}} & < 1 \\
\text{Aldosterone}_{\text{inferior vena cava}} & \geq 1 \\
\text{Cortisol}_{\text{inferior vena cava}} & \geq 1
\end{align*}
\]

<1 suggests suppression

Diagnosis confirmed surgically

Why might elevated cortisol cause HTN?

- **Mineralocorticoids**
  - Also able to bind the mineralocorticoid receptor
  - Usually inactivated by 11β-HSD
Apparent mineralocorticoid excess

- Inherited defect (very rare)
- Inhibition by glycyrrhizic acid metabolites

Eating too much black licorice can be dangerous. Should you be worried this Halloween?

N'dea Yancey-Bragg USA TODAY
Published 5:28 a.m. ET Oct. 31, 2019 | Updated 12:30 p.m. ET Oct. 31, 2019

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Hypotension

• Absolute hypotension
  – SBP <90 mmHg
• Relative hypotension
  – SBP drop >20-40 mmHg
• Causes inadequate tissue perfusion
• May manifest with fainting
• When severe, will cause shock

What is osmolality?

- Concentration of dissolved particles in blood

High osmolality = concentrated

Low osmolality = dilute

Definition from https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=osmolality_blood
Antidiuretic hormone (ADH)/Vasopressin

Increased osmolality → Low blood pressure → Posterior pituitary → ADH → Kidneys → Increase water reabsorption → Production of ↓ volume, concentrated urine

Diuretic: substance that increases urine production


What is diabetes insipidus?

• Symptoms: polyuria and polydipsia
  – Lab testing often shows hypernatremia
  – Without water intake → dehydration, hypotension

• Central diabetes insipidus: ADH deficiency
  – Hypothalamic lesion

What is diabetes insipidus?

- **Symptoms:** polyuria and polydipsia
  - Lab testing often shows hypernatremia
  - Without water intake → dehydration, hypotension
- **Central diabetes insipidus:** ADH deficiency
  - Hypothalamic lesion
- **Nephrogenic diabetes insipidus:** problem with ADH action
  - Congenital mutations
  - Kidney disease or drug-induced kidney damage

What testing is performed for diabetes insipidus?

• ADH testing not usually required

<table>
<thead>
<tr>
<th>Assay</th>
<th>Expected result in diabetes insipidus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume</td>
<td>&gt;2.5 L/day</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>↓</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>↑ or ≈</td>
</tr>
</tbody>
</table>
How is osmolality measured?

- Performed by freezing point depression

What dynamic lab testing may be done?

- Water deprivation test
- Monitor urine output, serum osmolality and urine osmolality

**Central:** deficiency of ADH
**Nephrogenic:** ADH not able to act on kidneys

What dynamic lab testing may be done?

- Water deprivation test
- Monitor urine output, serum osmolality and urine osmolality

**Central:** deficiency of ADH  
**Nephrogenic:** ADH not able to act on kidneys

Summary

• Blood pressure regulation is complex
• Critical to investigate secondary endocrine causes of HTN
  – Most common endocrine cause is primary hyperaldosteronism
• Diabetes insipidus may cause hypotension
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