Case 31

Hyperaldosteronism: Conn's Syndrome

Seymour Simon is a 54-year-old college physics professor who maintains a healthy lifestyle. He exercises regularly, doesn’t smoke or drink alcohol, and keeps his weight in the normal range. Recently, however, he experienced generalized muscle weakness and headaches that “just won’t quit.” He attributed the headaches to the stress of preparing his grant renewal. Over-the-counter pain medication did not help. Professor Simon’s wife was very concerned and made an appointment for him to see his primary care physician.

On physical examination, he appeared healthy. However, his blood pressure was significantly elevated at 180/100, both in the lying (supine) and the standing positions. His physician ordered laboratory tests on his blood and urine that yielded the information shown in Table 4-5.

<table>
<thead>
<tr>
<th>Table 4-5</th>
<th>Professor Simon's Laboratory Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.50 (normal, 7.4)</td>
</tr>
<tr>
<td>(P_{CO_2})</td>
<td>48 mm Hg (normal, 40 mm Hg)</td>
</tr>
<tr>
<td>Venous blood</td>
<td></td>
</tr>
<tr>
<td>Na⁺</td>
<td>142 mEq/L (normal, 140 mEq/L)</td>
</tr>
<tr>
<td>K⁺</td>
<td>2.0 mEq/L (normal, 4.5 mEq/L)</td>
</tr>
<tr>
<td>Total (CO_2 (HCO_3^-))</td>
<td>36 mEq/L (normal, 24 mEq/L)</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>98 mEq/L (normal, 105 mEq/L)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.1 mg/dL (normal, 1.2 mg/dL)</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td>Na⁺ excretion</td>
<td>200 mEq/24 hr (normal)</td>
</tr>
<tr>
<td>K⁺ excretion</td>
<td>1350 mEq/24 hr (elevated)</td>
</tr>
<tr>
<td>Creatinine excretion</td>
<td>1980 mg/24 hr</td>
</tr>
<tr>
<td>24-hr urinary catecholamines</td>
<td>Normal</td>
</tr>
</tbody>
</table>

QUESTIONS

1. Professor Simon’s arterial blood pressure was elevated in both the supine and the standing positions. Consider the factors that regulate arterial pressure, and suggest several potential causes for his hypertension. What specific etiology is ruled out by the normal value for 24-hour urinary catecholamine excretion?

2. The physician suspected that Professor Simon’s hypertension was caused by an abnormality in the renin-angiotensin II-aldosterone system. He ordered additional tests, including a plasma renin activity, a serum aldosterone, and a serum cortisol, which yielded the information shown in Table 4-6.
Using your knowledge of the renin-angiotensin II-aldosterone system, suggest a pathophysiologic explanation for Professor Simon's hypertension that is consistent with these findings.

3. The physician suspected that Professor Simon had primary hyperaldosteronism (Conn's syndrome), which means that the primary problem was that his adrenal gland was secreting too much aldosterone. How does an increased aldosterone level cause increased arterial pressure?

4. What effect would you expect primary hyperaldosteronism to have on urinary Na⁺ excretion? In light of your prediction, explain the observation that Professor Simon's urinary Na⁺ excretion was normal.

5. What explanation can you give for Professor Simon's hypokalemia? If the physician had given him an injection of KCl, would the injection have corrected his hypokalemia?

6. Explain Professor Simon's muscle weakness based on his severe hypokalemia. (Hint: Think about the resting membrane potential of skeletal muscle.)

7. What acid–base abnormality did Professor Simon have? What was its etiology? What is the appropriate compensation for this disorder? Did appropriate compensation occur?

8. What was Professor Simon's glomerular filtration rate?

9. What was his fractional Na⁺ excretion?

10. A computed tomographic scan confirmed the presence of a single adenoma on the left adrenal gland. Professor Simon was referred to a surgeon, who wanted to schedule surgery immediately to remove the adenoma. Professor Simon requested a 2-week delay so that he could meet his grant deadline. The surgeon reluctantly agreed on the condition that Professor Simon take a specific diuretic in the meantime. What diuretic did the physician prescribe, and what are its actions? Which abnormalities would be corrected by the diuretic?
1. To answer this question about the etiology of hypertension, recall from cardiovascular physiology the determinants of arterial pressure \((P_a)\). The equation for \(P_a\) is a variation on the pressure, flow, resistance relationship, as follows:

\[
P_a = \text{cardiac output} \times \text{TPR}
\]

In words, arterial pressure depends on the volume ejected from the ventricle per unit time (cardiac output) and the resistance of the arterioles (total peripheral resistance, or TPR). Thus, arterial pressure will increase if there is an increase in cardiac output, an increase in TPR, or an increase in both.

Cardiac output is the product of stroke volume and heart rate. Thus, cardiac output increases if there is an increase in either stroke volume or heart rate. An increase in stroke volume is produced by an increase in contractility (e.g., by catecholamines) or by an increase in preload or end-diastolic volume (e.g., by increases in extracellular fluid volume). An increase in heart rate is produced by catecholamines. An increase in TPR is produced by substances that cause vasoconstriction of arterioles (e.g., norepinephrine, angiotensin II, thromboxane, antidiuretic hormone) and by atherosclerotic disease. Thus, hypertension can be caused by an increase in cardiac output (secondary to increased contractility, heart rate, or preload) or an increase in TPR.

One of the potential causes of Professor Simon's hypertension (i.e., increased circulating catecholamines from an adrenal medullary tumor, or pheochromocytoma) was ruled out by the normal value for 24-hour urinary catecholamine excretion.

2. This question asked you to explain how the findings of an increased aldosterone level, a decreased renin level, and a normal level of cortisol could explain Professor Simon's hypertension.

Figure 2-10 (see Case 14) shows the renin-angiotensin II-aldosterone system. This figure shows how aldosterone secretion is increased secondary to a decrease in arterial pressure (e.g., caused by hemorrhage, diarrhea, or vomiting). Decreased arterial pressure leads to decreased renal perfusion pressure, which increases renin secretion. Renin, an enzyme, catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin-converting enzyme then catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II stimulates the secretion of aldosterone by the adrenal cortex. Clearly, Professor Simon's elevated aldosterone level could not have been caused by decreased blood pressure as shown in Figure 2-10; his blood pressure was increased.

Another possibility, also based on the renin-angiotensin II-aldosterone system, is renal artery stenosis (narrowing of the renal artery). Renal artery stenosis leads to decreased renal perfusion pressure, which increases renin secretion, increases aldosterone secretion, and causes hypertension (so-called renovascular hypertension). In that scenario, both renin levels and aldosterone levels are increased, a picture that is also inconsistent with Professor Simon's results: his renin levels were decreased, not increased.

Finally, Professor Simon's aldosterone levels could be increased if his adrenal cortex autonomously secreted too much aldosterone (primary hyperaldosteronism). In that case, high levels of aldosterone would lead to increases in Na⁺ reabsorption, extracellular fluid (ECF) and blood volume, and blood pressure. The increased blood pressure would then cause increased renal perfusion pressure, which would inhibit renin secretion. This picture is entirely consistent with Professor Simon's increased aldosterone level and decreased plasma renin activity.

The normal level of cortisol suggests that an adrenal cortical tumor was selectively secreting aldosterone. If the entire adrenal cortex was oversecreting hormones (e.g., Cushing's disease), then cortisol levels would be elevated as well (see Figure 6–6 in Case 48).

3. Primary hyperaldosteronism (Conn's syndrome) is associated with increased circulating levels of aldosterone, which increases Na⁺ reabsorption in the principal cells of the late distal tubule and collecting ducts. Since the amount of Na⁺ in the ECF determines the ECF volume,
increased Na\(^+\) reabsorption produces an increase in ECF volume and blood volume. Increased blood volume produces an increase in venous return and, through the Frank-Starling mechanism, an increase in cardiac output. As discussed in Question 1, increased cardiac output leads to an increase in arterial pressure (see Figure 4-6 below).

4. In the initial phase of primary hyperaldosteronism, because aldosterone increases renal Na\(^+\) reabsorption, we expect urinary Na\(^+\) excretion to be decreased. However, as a consequence of the Na\(^+\)-retaining action of aldosterone, both the Na\(^+\) content and the volume of ECF are increased (ECF volume expansion). ECF volume expansion then inhibits Na\(^+\) reabsorption in the proximal tubule. In this later phase (when Professor Simon’s urinary Na\(^+\) excretion was measured), urinary Na\(^+\) excretion increases toward normal, although ECF volume remains high.

This so-called “escape” from aldosterone (or mineralocorticoid escape) is a safety mechanism that limits the extent to which hyperaldosteronism can cause ECF volume expansion. Three physiologic mechanisms underlie mineralocorticoid escape, and all of them lead to an increase in Na\(^+\) excretion. (1) ECF volume expansion inhibits renal sympathetic nerve activity. This decreased sympathetic nerve activity inhibits Na\(^+\) reabsorption in the proximal tubule. (2) ECF volume expansion causes dilution of the peritubular capillary protein concentration. The resulting decrease in peritubular capillary oncotic pressure causes a decrease in Na\(^+\) reabsorption in the proximal tubule (by decreasing the Starling forces that drive reabsorption). (3) ECF volume expansion stimulates the secretion of atrial natriuretic peptide (ANP, or atrialpeptin). ANP simultaneously causes dilation of renal afferent arterioles and constriction of renal efferent arterioles. The combined effect on the two sets of arterioles is to increase the glomerular filtration rate (GFR). As the GFR increases, more Na\(^+\) is filtered; the more Na\(^+\) that is filtered, the more Na\(^+\) that is excreted. ANP may also directly inhibit Na\(^+\) reabsorption in the collecting ducts.

5. Professor Simon’s hypokalemia was another consequence of his primary hyperaldosteronism. In addition to increasing Na\(^+\) reabsorption, aldosterone stimulates K\(^+\) secretion by the principal cells of the late distal tubule and collecting ducts. Increased K\(^+\) secretion leads to excessive urinary K\(^+\) loss, negative K\(^+\) balance, and hypokalemia. If Professor Simon’s physician had given him an injection of KCl, it would not have effectively corrected his hypokalemia. Because of his high aldosterone level, the injected K\(^+\) would simply have been excreted in the urine (Figure 4-5, and see Figure 4-6).
6. Hypokalemia was responsible for Professor Simon’s generalized skeletal muscle weakness. Remember that, at rest, excitable cells (e.g., nerve, skeletal muscle) are very permeable to K⁺. In fact, the resting membrane potential is close to the K⁺ equilibrium potential, as described by the Nernst equation. (Intracellular K⁺ concentration is high, and extracellular K⁺ concentration is low; K⁺ diffuses down this concentration gradient, creating an inside-negative membrane potential.) When the extracellular K⁺ concentration is lower than normal (i.e., hypokalemia), as in Professor Simon’s case, the resting membrane potential becomes even more negative (hyperpolarized). When the resting potential is hyperpolarized, it is further from threshold, and it is more difficult to fire action potentials in the muscle (see Case 4).

7. The alkaline arterial pH of 7.50 and the elevated HCO₃⁻ concentration of 36 mEq/L are consistent with metabolic alkalosis. The elevated PCO₂ of 48 mm Hg is the result of hypoventilation, which is the respiratory compensation for metabolic alkalosis. Decreased ventilation caused CO₂ retention, which decreased (compensated) the pH toward normal.

We can apply the Henderson-Hasselbalch equation to the HCO₃⁻/CO₂ buffer pair to demonstrate why hypoventilation is a compensation for metabolic alkalosis:

\[
\text{pH} = pK + \log \frac{\text{HCO}_3^-}{\text{PCO}_2}
\]

In metabolic alkalosis, the primary disturbance is an increase in HCO₃⁻ concentration. By itself, this change would profoundly increase blood pH. However, the respiratory compensation (hypoventilation) elevates PCO₂, which tends to normalize the ratio of HCO₃⁻ to CO₂ and decrease the pH toward normal. Respiratory compensation never corrects the pH perfectly and, as you can see, Professor Simon’s pH was still alkaline (7.5).

The “renal rules” shown in the Appendix provide a method for determining whether the degree of respiratory compensation for metabolic alkalosis is appropriate. According to the rules, in simple metabolic alkalosis, PCO₂ should increase by 0.7 mm Hg for every 1 mEq/L increase in HCO₃⁻. Therefore, in Professor Simon’s case:

Increase in HCO₃⁻ (above normal value of 24 mEq/L) = +12 mEq/L
Predicted increase in PCO₂ = 0.7 \times 12 \text{ mEq/L}
= +8.4 \text{ mm Hg}

Predicted PCO₂ = 40 \text{ mm Hg} + 8.4 \text{ mm Hg}
= 48.4 \text{ mm Hg}

Based on this renal rules calculation, the predicted PCO₂ is 48.4 mm Hg, which is virtually identical to Professor Simon’s actual PCO₂ of 48 mm Hg. Thus, he had simple metabolic alkalosis with appropriate respiratory compensation.

The etiology of Professor Simon’s metabolic alkalosis was hyperaldosteronism. Recall that, in addition to its actions to increase Na⁺ reabsorption and K⁺ secretion, aldosterone stimulates H⁺ secretion by the α-intercalated cells of the late distal tubule and collecting ducts. This
H+ secretion is linked to the synthesis and reabsorption of new HCO3−, which elevates the blood HCO3− concentration and produces metabolic alkalosis (Figure 4–6).

![Diagram of primary hyperaldosteronism (aldosterone-secreting tumor)](image)

**Figure 4–6** Consequences of primary hyperaldosteronism (aldosterone-secreting tumor). ECF, extracellular fluid volume.

8. **GFR** is calculated from the inulin clearance or the creatinine clearance. Because creatinine is an endogenous substance and inulin is not, the creatinine clearance is often preferred.

\[
GFR = \frac{C_{\text{creatinine}}}{P_{\text{creatinine}}}
\]

The plasma creatinine concentration is provided in the laboratory data, although the urine creatinine concentration and urine flow rate are not provided. Are we stuck? Not at all. To perform the calculation, you must realize that the numerator of the clearance equation, \( U \times V \), is equal to excretion rate. The 24-hour excretion rate of creatinine is provided in the laboratory data. Thus, the calculation is as follows:

\[
GFR = \frac{C_{\text{creatinine}}}{P_{\text{creatinine}}}
= \frac{U_{\text{creatinine}} \times V}{P_{\text{creatinine}}}
= \frac{\text{Creatine excretion rate}}{P_{\text{creatinine}}}
= \frac{1980 \text{ mg/24 hr}}{1.1 \text{ mg/dL}}
= \frac{1980 \text{ mg/24 hr}}{11 \text{ mg/L}}
= 180 \text{ L/24 hr, or 180 L/day}
\]
9. In words, fractional \( \text{Na}^+ \) excretion is the fraction of the filtered load of \( \text{Na}^+ \) that is excreted in urine. It is calculated as follows:

\[
\text{Fractional Na}^+ \text{excretion} = \frac{\text{Na}^+ \text{excretion}}{\text{Filtered load of Na}^+} = \frac{\text{Na}^+ \text{excretion}}{\text{GFR} \times P_{\text{Na}}} = \frac{200 \text{ mEq/24 hr}}{180 \text{ L/24 hr} \times 142 \text{ mEq/L}} = \frac{200 \text{ mEq/24 hr}}{25,560 \text{ mEq/24 hr}} = 0.0078, \text{ or 0.78%}
\]

10. While Professor Simon awaited surgery for removal of the aldosterone-secreting tumor, he was treated with spironolactone, an aldosterone antagonist. Spironolactone blocks the actions of aldosterone by preventing aldosterone from entering the nucleus of its target cells in the late distal tubule and collecting ducts. (Normally, aldosterone enters the nucleus and directs the synthesis of messenger ribonucleic acids that encode specific transport proteins.) Thus, spironolactone inhibits all of the actions of aldosterone: \( \text{Na}^+ \) reabsorption, \( \text{K}^+ \) secretion, and \( \text{H}^+ \) secretion. The drug was expected to decrease Professor Simon's ECF volume and arterial pressure and to correct his hypokalemia and metabolic alkalosis.
Key topics

Aldosterone
Angiotensin II
Arterial blood pressure (P_a)
Atrial natriuretic peptide, or atrialpeptin (ANP)
Cardiac output
Conn's syndrome
Cortisol
Creatinine clearance
Equilibrium potential
Fractional excretion
Frank-Starling mechanism
Glomerular filtration rate (GFR)
Henderson-Hasselbalch equation
Hyperaldosteronism
Hyperpolarization
Hypokalemia
α-Intercalated cells
K^+ balance
Metabolic alkalosis
Mineralocorticoid escape (escape from aldosterone)
Na^+ excretion
Nernst equation
Pheochromocytoma
Plasma renin activity
Principal cells
Renal artery stenosis
Renin
Renin-angiotensin II-aldosterone system
Renovascular hypertension
Respiratory compensation
Resting membrane potential
Spironolactone
Starling forces
Total peripheral resistance (TPR)