Renovascular hypertension is the most common form of secondary hypertension, and multiple additional symptoms may be associated with the activation of the renin–angiotensin system (RAS) by the renal arterial stenosis, including severe electrolyte disorders and albuminuria. We discuss a case of renovascular hypertension in which severe hypokalemia and hyponatremia also developed.

**Case Report**

A 49-year-old unmarried man was admitted to hospital in November 1994 because of severe hyponatremia, hypokalemia and uncontrolled hypertension. Both of his parents had had hypertension and died from stroke. He smoked 20 cigarettes and drank 700 ml of sake daily. He had had acute pancreatitis at age 42. Five days before admission, the patient presented at the Outpatient Clinic of the hospital complaining of general malaise lasting 1 week. His blood pressure was 220/118 mmHg, and serum sampled at the time of presentation showed the following electrolyte concentrations: K+ 2.2 mmol/L, Na+ 117 mmol/L, Cl– 117 mmol/L. He was hospitalized for further evaluation.

At hospitalization, the patient’s blood pressure was again 220/118 mmHg, the pulse was regular, and no pallor or jaundice was present. The optic fundi showed exudates, focal hemorrhage, and arteriovenous nicking. Otherwise, the head, neck, heart and lungs were normal. No abdominal bruit or peripheral edema was present. The daily urine volume was 4,900 ml.

Renovascular hypertension occasionally manifests clinically as electrolyte disorders and albuminuria in addition to elevated blood pressure. A 49-year-old man who had renovascular hypertension also had severe hypokalemia, hyponatremia, polyuria and polydipsia that were treated by an angiotensin-converting enzyme inhibitor and resection of an atrophic kidney with a compromised blood supply. This is a case of hyponatremic–hypertensive syndrome related to renovascular hypertension and occurring as an additional abnormality. (*Circ J* 2002; 66: 297–301)

**Key Words:** Hypokalemia; Hyponatremia; Polyuria; Renin–angiotensin system
the improvements in blood pressure and electrolytes were insufficient. After the dose of captopril was increased to 75 mg/day, the blood pressure normalized.

Because the ischemic kidney was atrophic and the aortic aneurysm precluded percutaneous transluminal renal angioplasty, a radical right nephrectomy was performed in January 1995. Blood pressure and electrolyte became normal after the operation, and the patient was discharged home.

Pathological Findings
The aneurysm was located at the bifurcation of the right renal artery and histologically consisted of muscular artery. The aneurysmal wall showed sclerotic change without an elastic lamellar structure, and lymphoplasmacytic infiltration was observed in the surrounding adventitia. The right kidney, weighing 120g, had a small extra-artery that perfused a small area of the lower pole. Histologically, this area was normal and clearly demarcated from the adjacent area. The remainder of the right kidney, which was being supplied blood from the renal artery with aneurysmal formation, showed severe interstitial fibrosis (Fig 4A) and diffuse, marked hyperplasia of the juxtaglomerular appara-

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**Table 1 Blood and Urine Electrolytes Values**

<table>
<thead>
<tr>
<th>Variable</th>
<th>On admission</th>
<th>After captoril</th>
<th>19 days after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily urine volume (ml)</td>
<td>4,900</td>
<td>2,200</td>
<td>1,500</td>
</tr>
<tr>
<td>Serum Na (mmol/L)</td>
<td>112</td>
<td>141</td>
<td>143</td>
</tr>
<tr>
<td>Serum K (mmol/L)</td>
<td>2.4</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Serum Cl (mmol/L)</td>
<td>63</td>
<td>101</td>
<td>107</td>
</tr>
<tr>
<td>Urine Na (mmol/L)</td>
<td>33</td>
<td>52</td>
<td>67</td>
</tr>
<tr>
<td>Urine K (mmol/L)</td>
<td>19</td>
<td>19</td>
<td>12.4</td>
</tr>
<tr>
<td>FE sodium (%)</td>
<td>1.50</td>
<td>1.26</td>
<td>1.82</td>
</tr>
<tr>
<td>FE potassium (%)</td>
<td>41.3</td>
<td>17.7</td>
<td>11.8</td>
</tr>
<tr>
<td>Serum osmolarity (mOsm/kg)</td>
<td>245</td>
<td>274</td>
<td>284</td>
</tr>
<tr>
<td>Urine osmolarity (mOsm/kg)</td>
<td>194</td>
<td>259</td>
<td>224</td>
</tr>
</tbody>
</table>

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**Table 2 Endocrinology Tests**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal range</th>
<th>On admission</th>
<th>After captopril (37.5 mg)</th>
<th>5 days after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity (ng·ml⁻¹·h⁻¹)*</td>
<td>0.3–2.9</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>1.2</td>
</tr>
<tr>
<td>Plasma aldosterone concentration (pg/ml)*</td>
<td>29.9–159</td>
<td>1,400</td>
<td>370</td>
<td>23</td>
</tr>
<tr>
<td>Angiotensin I (pg/ml)</td>
<td>≤250</td>
<td>&gt;2,500</td>
<td>&gt;2,500</td>
<td>ND</td>
</tr>
<tr>
<td>Angiotensin II (pg/ml)</td>
<td>≤25</td>
<td>390</td>
<td>60</td>
<td>ND</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>≤100</td>
<td>829</td>
<td>60</td>
<td>ND</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>100–450</td>
<td>102</td>
<td>308</td>
<td>ND</td>
</tr>
<tr>
<td>Cortisol (μg/dl)</td>
<td>4.0–18.3</td>
<td>32.5</td>
<td>23.6</td>
<td>ND</td>
</tr>
<tr>
<td>FreeT4 (ng/dl)</td>
<td>1.01–1.79</td>
<td>1.89</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>9–52</td>
<td>44.0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>ADH (pg/ml)</td>
<td>0.3–3.5</td>
<td>13.7</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

T4, thyroxine; ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; ND, not determined. *Blood sampling were performed in supine position.

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Fig 1. Magnetic resonance imaging of the abdomen shows an atrophic kidney.

Fig 2. Renal scintigram showing reduced uptake on the right and delayed excretion on the left.
Discussion

Renovascular hypertension is the most common type of secondary hypertension and a variety of symptoms are caused by activation of renin secretion by the ischemic kidney. In the 1950s some cases of severe hypertension that included polydipsia, polyuria, weight loss, hypokalemia and hyponatremia were reported and in 1965, Brown et al named this combination the hyponatremic–hypertensive syndrome (HHS). A small number of cases of HHS have been reported since the 1960s, and only 2 cases have been reported from Japan.

In a study of the clinical features of renovascular hypertension, 16% of cases had hypokalemia although the serum Na+ concentration showed no difference between a group with renovascular hypertension and a group with essential hypertension. We believe that HHS represents a special type of renovascular hypertension.

Our proposed mechanism of pathogenesis is shown in Fig. 5. On physical examination, this present case was thought to be hyponatremia with normal extracellular fluid volume; thirst and the subsequent polydipsia are believed to be the initial factors leading to hyponatremia. The serum concentrations of antidiuretic hormone (ADH) and angiotensin-II were elevated (Table 2). Intraventricular injection or intravenous infusion of angiotensin-II provokes a moderate increase in plasma ADH. ADH acts on the septal area, which is the neural substrate for thirst and the salt–water balance in the brain, and has a dipso-genic effect. The precise site and mechanism of ADH release have not been defined, but the central angiotensin receptors, which were located in the circumventricular organs such as the subfornical organ (SFO), are the likely candidates because angiotensin is most effective when injected directly into the dorsal third and lateral ventricles and within the SFO in a rat model. Moreover, intravenous...
tricular administration of angiotensin antagonists inhibit the dipsogenic and vasopressin secretory responses to intra-cerebroventricular infusion of hypertonic saline. Angiotensin also acts directly at the SFO and anteroventral region of the third ventricles to elicit drinking behavior. Therefore, angiotensin leads to polydipsia and the excessive intake of water causes expansion and dilution of body fluids, which is believed to lead to hyponatremia. The daily urinary volume in the present patient exceeded 4,000 ml, reflecting a high intake of water, and as a result, daily urinary Na+ excretion (161 mmol) was high, causing hyponatremia even though the urinary Na+ concentration was normal (33 mmol/L). As a consequence, the rate of water excretion rises to balance the intake and the osmolality of body water stabilizes at a new, slightly lower level that approximates the osmotic threshold for ADH secretion.

On the other hand, decreased sensitivity of the collecting tubules to ADH was apparent, and resulted in hypotonicity of the urine, associated with a urine concentration disturbance (abnormal Fishberg test) and polyuria. We believe that the severe hypokalemia blocked the action of ADH in this case. Prolonged hypokalemia causes a vasopressin resistant urinary concentrating ability, but the mechanism by which hypokalemia decreases urinary concentrating ability is not well established. In the rat, there may be a decrease in adenylyl cyclase sensitivity in response to vasopressin, thus reducing the production of cAMP, the second messenger for vasopressin action. Hypokalemia also results in decreased NaCl reabsorption in the thick ascending limb of the loop of Henle, and this will reduce medullary osmolality and hence the driving force for water reabsorption. Angiotensin-II moderates Na+ depletion, but promotes K+ loss via aldosterone secretion. Renin secretion is stimulated further by K+ deficiency resulting in a vicious cycle while only modestly reducing aldosterone secretion. Therefore, polyuria persists because free water is not reabsorbed in the collecting ducts, and both water and electrolytes are lost in the urine.

Secondarily, a direct action of angiotensin upon the renal tubular sodium transport in the presence of hypertension is likely. Angiotensin-II reportedly has a biphasic dose-dependent action on water and electrolyte metabolism in vivo and in vitro. At physiologic concentrations (10^-12 to 10^-9 mol/L), angiotensin-II stimulates Na+ and water reabsorption, but at elevated concentrations it can inhibit reabsorption. Angiotensin-II probably promoted Na+ excretion in the present case, even though its concentration was not as high as in those experiments.

In addition, pressure natriuresis caused by severe hypertension is a suspected contributor, especially in infant cases. The pathogenesis in the present case most probably was the outcome of a number of different factors acting together, rather than any one single factor.

Many cases of renovascular hypertension do not present with the symptoms described here. Because urinary Na+ loss resulting from the polyuria was a principal factor, the function of the contralateral kidney was necessarily normal. If serious hypertension had progressed and resulted in retention of fluid, this syndrome would not have developed. Therefore, the underlying condition causing unilateral renal artery obstruction was of relatively recent onset, with the other kidney functioning normally. Polyuria, the main cause of HHS, does not occur often in patients with renovascular hypertension, because treatment with antihypertensive agents is usually initiated at an early stage of the disease.

Therefore, HHS has become rare. However, this does not negate the importance of careful differential diagnosis for severe hypertension accompanied by electrolyte abnormality.

References