

# Hyponatremia Associated with Pulmonary Arterial Hypertension: Syndrome of Inappropriate Antidiuresis Versus Right Heart Failure

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Because it is associated with mortality, hyponatremia is an important feature of pulmonary arterial hypertension. Its mechanisms remain unclear, although right heart failure resulting from pulmonary arterial hypertension may lead to systemic congestion and arterial underfilling. However, most patients with pulmonary arterial hypertension are clinically euvolemic and have no peripheral edema. Unlike patients with underlying heart disease, neurohumoral activation is not demonstrated in hyponatremic patients with pulmonary arterial hypertension, who show features of congestive heart failure only at later stages in their disease. Here, a case vignette is introduced, and the pathophysiology of hyponatremia in pulmonary arterial hypertension will be discussed. Syndrome of inappropriate antidiuresis (SIAD) appears to underlie hyponatremia in the initial phase of pulmonary arterial hypertension. The mechanisms by which various lung diseases can lead to SIAD remain an enigma.

**Key Words:** Hyponatremia, Pulmonary arterial hypertension, Right heart failure, Syndrome of inappropriate antidiuresis

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## Case Vignette

A 70-year-old female was admitted for evaluation of hyponatremia. She was previously well until a skin rash appeared five years prior to admission. Two years thereafter, she visited a hospital because of exertional dyspnea and recurrent skin rash and was diagnosed with pulmonary arterial hypertension (PAH) and systemic lupus erythematosus (SLE) by cardiac catheterization (mean pulmonary arterial pressure, 50 mmHg) and serologic tests, respectively. Echocardiography revealed an enlarged right atrium and ventricle, moderate tricuspid regurgitation, and an estimated systolic pulmonary arterial pressure of 71 mmHg. However, left ventricular systolic function was normal.

At presentation, she complained of general weakness and

nausea. Hypocomplementemia (C3, 26 mg/dL; C4, 2 mg/dL) was noted, but erythrocyte sedimentation rate was normal (18 mm/h). Her serum sodium was 125 mmol/L, and she was euvolemic on physical examination. Serum osmolality was 260 mOsm/kg H<sub>2</sub>O, urine osmolality 326 mOsm/kg H<sub>2</sub>O, urine sodium 66 mmol/L, blood urea nitrogen 8.6 mg/dL, serum creatinine 0.72 mg/dL, and serum uric acid 3.1 mg/dL. Hypothyroidism and adrenal insufficiency were excluded. The level of brain natriuretic peptide (BNP) was 27 pg/mL. Arterial blood gas analysis showed pH 7.43, PaCO<sub>2</sub> 29.7 mmHg, PaO<sub>2</sub> 97.6 mm Hg, and HCO<sub>3</sub><sup>-</sup> 19.1 mmol/L.

## Pathogenesis and Differential Diagnosis of Hyponatremia

Hyponatremia occurs when water is primarily or secondarily

daily retained in the body. The primary causes of water retention are pure water balance disorders such as primary polydipsia and syndrome of inappropriate antidiuresis (SIAD). On the other hand, the secondary causes of water retention accompany sodium balance disorders. When sodium is depleted (e.g., vomiting), neurohumoral activation stimulates vasopressin release and induces renal water retention. When extracellular fluid sodium is excessive (e.g., congestive heart failure), decreased effective arterial blood volume also enhances vasopressin release and leads to dilutional hyponatremia. Thus, a patient's volume status, whether hypovolemic or hypervolemic, is an important clue in the differential diagnosis of hyponatremia. When the patient appears euvoletic, the differential diagnosis is more challenging.

SIAD is the prototype of euvoletic hyponatremia and includes the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), reset osmostat, and nephrogenic syndrome of inappropriate antidiuresis (NSIAD). Whereas reset osmostat has a subnormal threshold for antidiuretic hormone secretion, NSIAD is characterized by suppressed levels of plasma vasopressin irrespective of plasma sodium concentrations. In clinical practice, however, it is very difficult to differentiate between SIADH and NSIAD because correct routine measurement of plasma vasopressin is not feasible. Thus, "SIAD" is frequently diagnosed based on its diagnostic criteria<sup>1</sup>.

### **Causes of Syndrome of Inappropriate Antidiuresis (SIAD)**

From the viewpoint of channelopathy, NSIAD is the mirror image of nephrogenic diabetes insipidus (NDI). Loss-of-function vasopressin-2 receptor mutations cause NDI, whereas gain-of-function mutations cause NSIAD<sup>2</sup>. Activity of the vasopressin-2 receptor is connected to trafficking of aquaporin-2 water channel to the apical membrane and increasing the abundance of aquaporin-2 mRNA and protein. Thus, the activity of either vasopressin-2 receptor or aquaporin is enhanced in NSIAD.

The causes of SIAD are largely divided into enhanced vasopressin release and potentiation of the renal action of vasopressin<sup>1</sup>. The latter may be interpreted as spontaneous

aquaporin-2 hyperactivity. However, the detailed etiology remains unclear. Vasopressin hypersecretion was demonstrated in only a few cases of neoplasm, lung or central nervous system disorders, and drug-induced hyponatremia. Notably, drugs are an important cause of NSIAD by upregulating the vasopressin-2 receptor mRNA<sup>3</sup>.

### **PAH, SLE, and Hyponatremia**

PAH is caused by diffuse pulmonary artery vasculopathy, leading to progressive narrowing of the vessel lumen<sup>4</sup>. PAH belongs to World Health Organization (WHO) group 1 pulmonary hypertension (PH), which includes idiopathic PAH, heritable PAH, connective tissue disease-associated PAH (CTD-PAH), congenital heart disease-associated PAH (CHD-PAH), portopulmonary hypertension (PoPH), and PH associated with HIV, schistosomiasis, anorexic drugs, and toxins<sup>5</sup>.

Systemic sclerosis is the leading cause of CTD-PAH, followed by SLE, mixed connective tissue disease, idiopathic inflammatory myositis, rheumatoid arthritis, and Sjogren's syndrome<sup>6</sup>. However, PAH is a rare complication of SLE. Prabu et al. reported that the point prevalence of PAH was 4.2% in their British cohort of patients with SLE, and most of their PAH cases were found to be of mild severity (systemic pulmonary artery pressure <40 mmHg)<sup>7</sup>.

Hyponatremia may be a poor prognostic marker in PAH. Rudkovskaia et al. reported that 31 patients had severe hyponatremia (<130 mmol/L) in two different cohorts (n=1,611 total) and that severe hyponatremia was associated with higher overall mortality<sup>8</sup>. According to Forfia et al., hyponatremia was strongly associated with right heart failure and poor survival in PAH<sup>9</sup>. However, right heart failure is only an advanced feature of PAH.

### **Right Heart Failure Versus SIAD**

The mechanism of hyponatremia in PAH has not been established. Patients with PAH are typically euvoletic and may be edematous at late stages. In patients with cor pulmonale (group 3 PH), the renin-angiotensin-aldosterone axis is stimulated in response to right ventricular failure<sup>10</sup>. This effect may relate to arterial underfilling associated with a decrease in systemic vascular resistance<sup>11</sup>.

However, neurohumoral activation appears different between right and left ventricular failure. Arterial underfilling, as a result of either a decrease in cardiac output or systemic arterial vasodilation, may not be present with PAH<sup>11</sup>. The neurohumoral axis has rarely been studied in PAH with right ventricular failure in humans. Nootens et al. reported that patients with PAH showed increases in plasma endothelin, atrial natriuretic peptide, and norepinephrine concentrations but not in plasma renin activity. Plasma aldosterone and vasopressin levels were not assessed<sup>12</sup>.

Thus, we postulate that a different mechanism induces hyponatremia during the early phase of PAH (group 1 PH) because the BNP level was normal in our case. Additionally, our case showed the following findings compatible with SIAD: (1) decreased serum osmolality, (2) urine osmolality >100 mOsm/kg H<sub>2</sub>O, (3) clinical euolemia, (4) urine sodium >40 mmol/L, (5) serum uric acid <4 mg/dL, and (6) absence of renal failure, hypothyroidism, and adrenal insufficiency. Because pulmonary artery vasculopathy is a lung disease, it might cause SIAD via inducing vasopressin hypersecretion or aquaporin-2 hyperactivity.

### Can PAH Cause SIAD?

Pulmonary infection and malignancy are the major causes of SIAD among various lung disorders. However, other pulmonary disorders can induce SIAD, including asthma, cystic fibrosis, and respiratory failure associated with positive pressure breathing<sup>1</sup>. We found no case reports of SIAD or SIADH in patients with PAH. Right heart failure has been regarded as a cause of renal sodium and water retention. However, whether the early stages of PAH and right heart failure are associated with neurohumoral activation remains unclear<sup>11</sup>. Considering the possibility of SIAD in PAH, the use of vasopressin-2 receptor antagonists would be warranted.

On the other hand, previous studies reported that disease activity was associated with hyponatremia in SLE<sup>13,14</sup>. Active SLE frequently involves the kidneys, lungs, and central nervous system. Stressful conditions may also stimulate vasopressin release. Although the excessive unsuppressible release of vasopressin was not clearly demonstrated, SIADH was reported in the patients with SLE<sup>15,16</sup>.

The mechanism by which SIAD is induced in pulmonary disorders other than ectopic vasopressin production is poorly understood. Hypoxia, hypercapnia, and decreased vascular volume have been attributed<sup>1,17,18</sup>, but these factors were not compatible with our case. Can NSIAD be induced by pulmonary disorders? The lung may be an important endocrine organ in disease<sup>19</sup>, and a certain signaling cascade may reach the kidney and act as a ligand to the vasopressin-2 receptor, thereby stimulating aquaporin-2 trafficking and production<sup>20</sup>. Further studies are required to elucidate the mechanisms by which various pulmonary disorders cause SIAD.

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### Conflict of interest

The authors have no conflicts of interest to declare.

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