Apical Ballooning Syndrome Associated With Isolated Severe Hyponatremia: Case Report and Suggested Pathophysiology

Ofer Sagiv, MD,[1] Sasa Vukelic, MD,[2] Steve Czak, DO,[2] Frank Messineo, MD,[2] Neil L. Coplan, MD[2]
[1]Pat and Jim Calhoun Cardiology Center, University of Connecticut Health Center, Farmington, CT;
[2]Department of Cardiovascular Medicine, Lenox Hill Hospital, New York, NY

An 82-year-old woman who presented to her primary care physician for preoperative evaluation was incidentally found to have severe hyponatremia (sodium = 118 mmol/L). The patient was then admitted for workup and treatment of hyponatremia. On day 2 of the admission, the patient was found to have new T-wave inversions on a telemetry monitor. Further workup, including an electrocardiogram, cardiac markers, echocardiogram, and a cardiac catheterization were consistent with the diagnosis of apical ballooning syndrome (ABS). Mechanisms of how severe hyponatremia may lead to ABS are discussed as well as a possible approach to the management of severe hyponatremia in postmenopausal women.

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KEY WORDS

Takotsubo cardiomyopathy • Apical ballooning syndrome • Broken heart syndrome • Hyponatremia • Mechanism

Takotsubo cardiomyopathy, also known as apical ballooning syndrome (ABS), is characterized by hypokinesis, akinesis, or dyskinesis of the left ventricular (LV) mid segments (with or without apical involvement), new ST-segment elevation and/or T-wave inversion, and elevation in cardiac markers.[1,2] These findings occur in the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.[1,2] ABS was considered a rare entity until recent years, when several case series[1,3-8] estimated that approximately 1% to 2% of patients presenting with an acute coronary syndrome may have ABS. The pathophysiology of ABS is unclear, but in approximately 60% to 80% of patients it is associated with an emotional or physical stress as a trigger.[9] Because approximately 90% of all reported

cases occurred in postmenopausal women, a protective effect of sex hormones has been postulated.[10] Although the long-term prognosis is favorable, ABS is associated with an in-hospital mortality rate ranging from 0% to 8%. Acute complications include cardiogenic shock, arrhythmias, LV rupture, or thrombus.[11] In this report, we describe an unusual case where ABS was associated with severe hyponatremia without an emotional trigger.

Case Report

An 82-year-old woman with a past medical history of diverticulitis, gout, hypertension, and hypercholesterolemia presented to her physician for routine preoperative evaluation prior to a scheduled hip replacement. The patient complained of mild nausea, poor appetite, and weakness, but denied chest pain, shortness of breath, palpitations, loss of consciousness, paroxysmal nocturnal dyspnea, orthopnea, or leg swelling. Her exercise tolerance was limited by hip pain. She denied tobacco use or alcohol consumption. Specifically, the patient denied any recent emotional or physical stresses. Her medications included clonidine (0.3 mg twice daily), simvastatin (20 mg/d), atenolol (25 mg twice daily), and quinapril (40 mg/d). After routine preoperative laboratory values revealed a serum sodium level of 116 mmol/L, the patient was sent to the emergency room for evaluation and management.

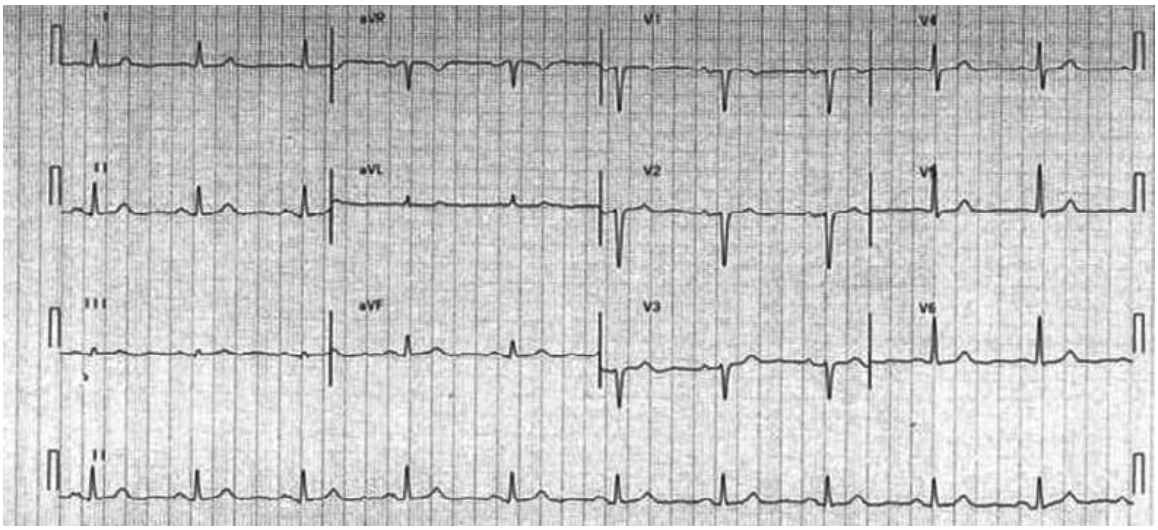
Upon arrival to the emergency room the patient was alert and asymptomatic. Vital signs revealed a blood pressure of 125/68 mm Hg, pulse of 67 beats/min, respiratory rate of 18 breaths/min, and normal oxygen saturation. The cardiovascular and neurologic examination results were normal. Laboratory studies were notable for a leukocyte count of 13,500/uL (with a mild left shift) and serum sodium level of 118 mmol/L. The initial electrocardiogram (ECG) was normal (Figure 1). She was admitted to a telemetry unit for workup and treatment of hyponatremia.

In the first 24 hours of admission, despite being treated conservatively with fluid restriction and normal saline, the patient's sodium level remained less than 120 mmol/L. The patient was subsequently treated with an intravenous infusion of 3% saline at a rate of 50 mL/h. At that time, the serum sodium was 119 mmol/L. The sodium level then improved to 122 mmol/L, 126 mmol/L, and 131 mmol/L, at 6 hours, 12 hours, and 36 hours after the initiation of the 3% saline, respectively.

On day 2 of the admission, T-wave inversions were noted on the telemetry monitor. Repeat ECG (Figure 2) showed diffuse symmetric T-wave inversions consistent with ongoing myocardial injury or central nervous system (CNS) pathology. The patient was asymptomatic during this period and the serum sodium level at that time was 126 mmol/L. Cardiac enzymes on day 2 were notable for a troponin-I of 1.8 ng/mL (normal, $<$ .05 ng/mL) and creatine phosphokinase of 822 U/L (normal, $<$ 200 U/L). An echocardiogram demonstrated apical akinesis and a hyperdynamic base, with an estimated LV ejection fraction of 40%. The patient was started on aspirin (325 mg/d), clopidogrel (75 mg/d), rosuvastatin (5 mg/d), metoprolol (50 mg twice daily), and a continuous infusion of intravenous unfractionated heparin, and was scheduled for cardiac catheterization.

On day 3, cardiac catheterization revealed nonobstructive coronary

Figure 1. Patient's presenting electrocardiogram (ECG) on day 1 of admission. The ECG shows normal sinus rhythm, with no evidence of prior infarct or ST abnormality.



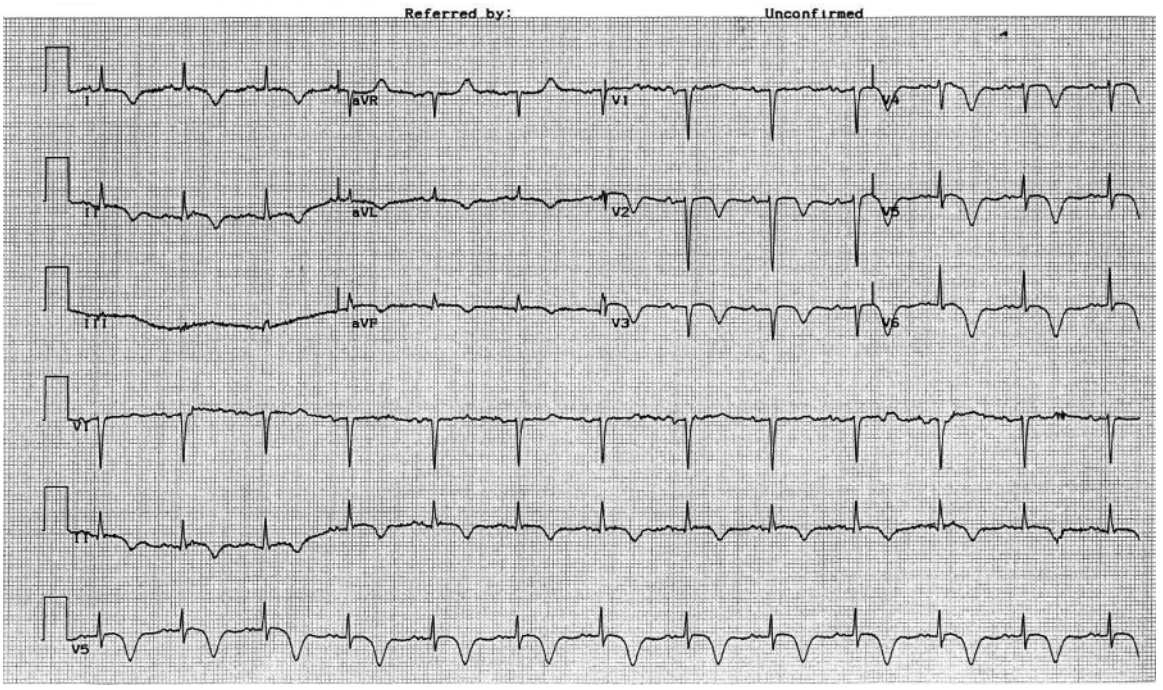


Figure 2. Electrocardiogram of the patient on hospital day 2. Significant diffuse deep T-wave inversions are now seen.

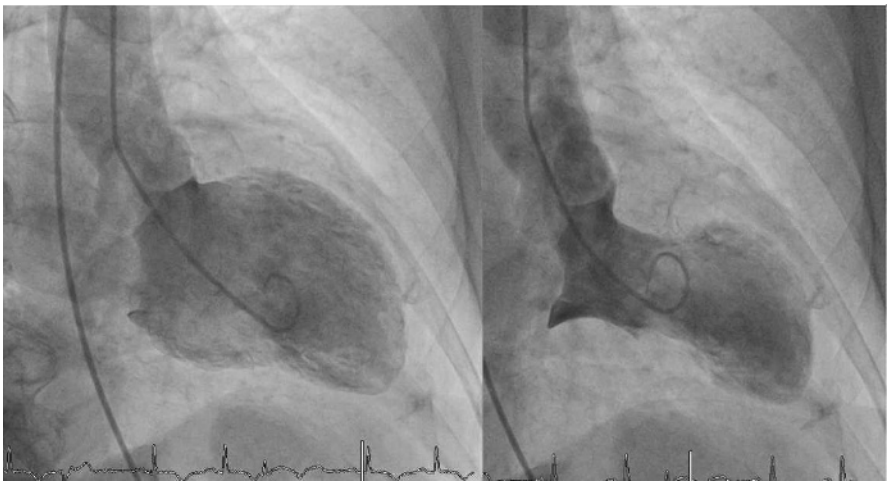


Figure 3. Still images from the initial cardiac catheterization. The ventriculogram in systole (*right*) shows the typical "apical ballooning" that characterizes apical ballooning syndrome.

artery disease and a typical wall motion abnormality consistent with ABS (Figure 3). At the time of the catheterization her serum sodium was 131 mmol/L. The patient had an uneventful hospital course and was discharged on aspirin (81 mg/d), atenolol (25 mg twice daily), rosuvastatin (5 mg/d), and lisinopril (2.5 mg/d). The etiology of the hyponatremia was never elucidated.

Three months later, the patient was referred for a nuclear perfusion stress test at an outside institution as part of another preoperative evaluation. Because the test result was abnormal, the patient had a repeat cardiac catheterization that showed complete resolution of the LV wall motion abnormality and unchanged coronary arteries (Figure 4).

Discussion

This case reports a patient with transient severe hyponatremia who developed a clinical syndrome consistent with ABS. There are previous reports of ABS in the setting of hyponatremia, but in contrast to the current case, hyponatremia was associated with vomiting,[12] endocrine disorders,[13] or significant nervous system dysfunction (including seizures[9,14] and confusion[15]). Although the T-wave abnormalities seen on the patient's ECG could reflect a primary CNS event, the rapid improvement of the patient's mild symptoms upon arrival to the emergency department, the absence of residual neurological deficits, and the classic ballooning abnormality seen on the ventriculogram make a primary CNS event an unlikely reason for the ECG changes seen in this case.

Although the mechanism underlying ABS is not clear, a centrally mediated sympathetic discharge leading to myocardial stunning

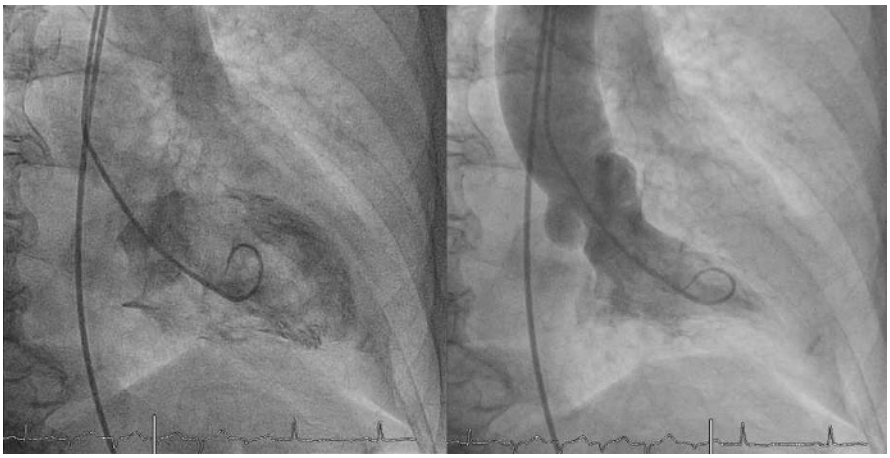


Figure 4. Still images from the follow-up cardiac catheterization 3 months after discharge. Diastolic (*left*) and systolic (*right*) ventriculogram frames are shown above. The wall motion abnormality seen on the prior catheterization has resolved.

has been proposed.[16,17] However, in the present case, ABS occurred in a mildly symptomatic patient who was incidentally found to have hyponatremia. Given the course of events and the absence of usual triggers for ABS (eg, stressful event, endocrine disorder), the patient's severe hyponatremia or correction of the hyponatremia may have served as a physiological trigger for ABS. The fact that hyponatremia was not associated with seizure, confusion, or any other coexistent stressor precipitating a catecholamine surge suggests that the presence of hyponatremia or the correction of hyponatremia may either provoke myocardial injury independently or increase cardiac adrenergic stimulation.

Catecholamine-mediated stunning of the myocardium is believed to be the leading mechanism underlying ABS, but evidence is limited.

Catecholamine-mediated stunning of the myocardium is believed to be the leading mechanism underlying ABS, but evidence is limited.[17] Overwhelming adrenergic stimulation may shift the beta receptor from its stimulatory G protein-mediated pathway to an inhibitory G protein pathway, thereby decreasing cyclic adenosine monophosphate levels, calcium load, and myocardial contractility.[18] Almost 90% of reported ABS cases occur in postmenopausal women,[10] and it has been proposed that the absence of estrogen sensitizes the heart to the effect of circulating catecholamines.[9,19] In the current case, it may be that the combination of hyponatremia or the correction of hyponatremia in a postmenopausal woman created a situation in which even baseline catecholamine levels led to transient myocardial dysfunction.

Although catecholamine effects may explain the majority of cases of ABS associated with a stressful trigger, it may not provide an explanation when significant adrenergic stimulation cannot be identified. Hyponatremia or its correction may induce cardiac dysfunction in a mechanism independent of catecholamines. Goldenberg and colleagues[20] described a patient free of cardiac symptoms with a sodium level of 123 mmol/L who developed repeated episodes of creatine kinase-MB elevation without ECG changes or LV dysfunction. The authors suggested that cell swelling attributed to hyponatremia-induced subclinical myocyte damage.[20] It is possible that more extensive myocardial injury associated with severe hyponatremia or its correction may have induced ABS in this case. Moreover, in a recent case series characterizing ABS, cardiac magnetic imaging suggested myocardial edema was present in 81% of ABS patients.[21] Others suggest that low sodium concentration can induce, through changing activity of sodium-calcium transporter, persistent calcium overload of myocardial cells leading to dysfunction.[15] Ex vivo experiments in rat hearts have shown that a change in sodium concentration has profound effects on cardiac contractility and relaxation, but this has not been investigated in vivo.[22,23] In addition, the decrease in contractile force by calcium overload appears to be associated with a decrease in high-energy phosphates, which may contribute to depressed contraction.[24]

In the absence of stressors that could cause catecholamine levels to rise, the above mechanisms may explain why ABS in the setting of hyponatremia can occur even without a classical trigger. Regardless of the mechanism, this case suggests that hyponatremia may have had a central role in the development of ABS.

Conclusions

Our case illustrates that isolated hyponatremia may be a rare cause of ABS in the absence of a classical trigger. Limited evidence suggests that hyponatremia or its correction may induce myocardial dysfunction through a catecholamine-dependent or -independent mechanism. Because ABS may be associated with life-threatening complications, prompt recognition is important. In postmenopausal

women with marked hyponatremia, an initial ECG and an ECG after correction of serum sodium level are crucial in making the diagnosis. Assessment of markers for myocardial injury and LV function may also be warranted. ■

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MAIN POINTS

- Takotsubo cardiomyopathy, also known as apical ballooning syndrome (ABS), is characterized by hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments (with or without apical involvement), new ST-segment elevation and/or T-wave inversion, and elevation in cardiac markers.
- Because approximately 90% of all reported cases occurred in postmenopausal women, a protective effect of sex hormones has been postulated.
- Although the mechanism underlying ABS is not clear, a centrally mediated sympathetic discharge leading to myocardial stunning has been proposed.
- Limited evidence suggests that hyponatremia or its correction may induce myocardial dysfunction through a catecholamine-dependent or -independent mechanism.