

When Pulmonary Arterial Hypertension Is Complicated by Pericardial Disease

Section Editor

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Patients with pulmonary hypertension whose case is complicated by a pericardial effusion pose a management dilemma. These patients are more complex given their unique set of hemodynamics, and the decision to proceed with a pericardial fluid drainage is not straightforward and mortality is potentially high. The current medical literature does not provide strict guidelines or a formal consensus regarding this clinical presentation. It appears management should be tailored to individual cases. We present a case of a patient in whom medical management spared the risk posed by drainage.

Presentation: A 21-year-old female with no significant medical history presented to the emergency department with palpitations, chest discomfort, dyspnea, orthopnea, and fatigue. Symptoms began 1 month prior with intermittent palpitations and fatigue that progressed to the point that she could no longer climb 2 flights of stairs without experiencing dyspnea that required rest. Prior to this, her functional capacity was reportedly normal. She denied diet-medication use, alcohol, tobacco, or illicit drug use. Review of systems was positive for orthopnea.

On physical examination, she was normotensive but tachycardic and

tachypnic. Jugular venous distension of 10 cm H₂O and a right ventricular heave were present, but no murmurs or gallops upon auscultation. Pulmonary examination revealed decreased breath sounds in the lung bases bilaterally. There were no pulsations of the liver, hepatosplenomegaly, rashes, or peripheral edema.

Workup and Therapeutic Interventions:

Electrolytes, troponin, B-type natriuretic peptide, thyroid, creatinine, and hepatic markers were normal. Erythrocyte sedimentation rate (55 mm/h) and C-reactive protein (19.8 mg/dL) were elevated along with a leukocytosis (13.1 K/uL) and microcytic anemia (10.1 g/dL). Urine analysis was unremarkable. Chest x-ray revealed cardiomegaly and small, bilateral pleural effusions. Chest computerized tomography (CT)-angiogram revealed no pulmonary embolus, but an enlarged main pulmonary artery measuring 37 mm along with a large pericardial effusion.

Echocardiogram (ECHO) demonstrated an ejection fraction of 65% with normal valvular function. The right ventricle was mildly dilated with a tricuspid valve lateral annulus systolic velocity of 2.5 m/sec. A moderate pericardial effusion measuring 1.6 cm was present in the absence of pretamponade

or tamponade physiology. Estimated right ventricular systolic pressure was 30 mm Hg. Right heart catheterization demonstrated a right atrial pressure of 9 mm Hg, mildly elevated pulmonary artery wedge pressure of 18 mm Hg, and elevated pulmonary artery pressures of 58/29/42 mm Hg (systolic/mean/diastolic) and right ventricular pressures of 58/7/11 mm Hg. Vasodilator study with nitric oxide revealed a drop in pulmonary vascular resistance from 417 to 350 dynes cm/s², which equated to a decrease by 16%. Hemodynamics were thus consistent with pulmonary arterial hypertension (PAH), but she was not a candidate for calcium channel blocker therapy due to clinical hypotension.

With supportive care, including inhaled nitric oxide, she remained hemodynamically stable and noninvasive conservative management was chosen to address the pericardial effusion. Tadalafil and ambrisentan were initiated despite borderline hypotension with an average systolic blood pressure of 100 mm Hg. Autoimmune workup revealed a positive antinuclear antibody level at a titer of 1:10240 with decreased complement levels. Anti-double stranded DNA and anti-Smith antibodies were positive along with U1 ribonucleic protein (RNP) and SS-A antibodies, consistent with systemic lupus erythematosus (SLE). Intravenous high-dose hydrocortisone was initiated in the intensive care unit with a dramatic improvement

Key Words—connective tissue disease, echocardiogram, idiopathic pulmonary arterial hypertension, pericardial effusion, systemic lupus erythematosus
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within 24 hours. Hydrocortisone was transitioned to oral prednisone. Additional workup for secondary causes of PAH included a negative HIV screen, hepatitis panels, and absence of venous thromboembolism on V/Q scan. Anti-cardiolipin antibodies were negative. A 6-minute walk test was not performed, but she was discharged 1 week later on a prednisone taper, tadalafil, and ambrisentan. She ambulated without need of assistance or supplemental oxygen.

Follow-Up: As an outpatient, azathioprine and plaquenil were added as the prednisone was tapered. At 6 weeks, she was asymptomatic and able to walk long distances and climb stairs without significant dyspnea. Repeat ECHO revealed complete resolution of her pericardial effusion 8 weeks after discharge.

Discussion: The pericardium of the heart is an avascular fibrous sac composed of 2 layers. The visceral pericardium is adherent to the epicardium, while the pleural pericardium is a more fibrous structure composed of collagen and elastin. The 2 layers comprise the pericardium, but are separated by a potential space that normally contains 15 to 35 mL of serous fluid.¹ During periods of long-standing stress, the elasticity of the pericardium permits the pericardial space to dilate, which allows for slowly developing pericardial effusions to develop without cardiac chamber compression or limiting ventricular function. However, if fluid accumulates rapidly or a large volume of fluid accumulates, then cardiac tamponade may occur with minimal development of a pericardial effusion. This medical emergency can be diagnosed clinically and assisted with echocardiography. Right atrial and ventricular diastolic chamber collapse is a sensitive finding on ECHO, and pericardiocentesis is often performed to relieve extracardiac pressure and restore normal hemodynamics. With that said, drainage of large pericardial effusions resulting in cardiac tamponade is common medical practice, but management of large pericardial effusions in the absence of cardiac tamponade is controversial due to its dependence on underlying eti-

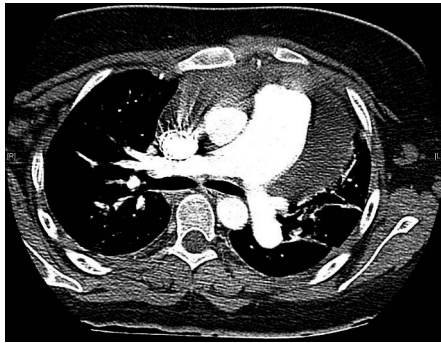
ologies.² Furthermore, the management of large pericardial effusions in PAH can be challenging with a paucity of data to guide treatment decisions.

Pulmonary arterial hypertension is defined as a mean pulmonary arterial pressure >25 mm Hg at rest associated with a pulmonary artery wedge pressure <15 mm Hg and pulmonary vascular resistance >3 Wood units.³ The Fourth World Symposium has subdivided PAH into 5 subcategories. Group 1 includes idiopathic pulmonary arterial hypertension (IPAH) or PAH associated with connective tissue disease (CTD), portopulmonary hypertension, HIV or congenital heart disease with left-to-right shunts, among other etiologies. Certain factors are associated with a worse prognosis including older age, male sex, elevated brain natriuretic peptide, high right atrial pressure, low cardiac index, and pericardial effusion.⁴ Data from the Registry to Evaluate Early and Long-Term PAH Disease Management demonstrate a high mortality in the setting of pericardial effusion with a hazard ratio of 2.9 (95% CI, 1.91-4.29).³ Pericardial effusion size also has prognostic value, with moderate or larger pericardial effusions demonstrating a median survival of 11.3 months compared to 42.3 months with a small pericardial effusion.⁵

In the setting of PAH, the development of a pericardial effusion signifies an element of right heart failure secondary to high right atrial pressure and/or myocardial edema. Furthermore, those with a pericardial effusion have a higher right atrial pressure when compared to PAH patients without a pericardial effusion.⁶ High right atrial pressure compromises the pericardial fluid drainage via venous and lymphatic channels into the right atrium, resulting in pericardial effusion development. According to the Chinese PAH registry, PAH associated with CTD has a higher prevalence of pericardial effusion than patients with IPAH (21% vs 13%).³ Studies have demonstrated the presence of immunoglobulin, complement, macrophages, and lymphocytes within the pulmonary artery walls when CTD is present,⁷ which highlights the role for anti-inflammatory and immunosuppressive

therapy in patients with PAH associated with CTD.

For our case, the decision to noninvasively treat the large pericardial effusion is a reflection of current medical literature and absence of definitive data. The European executive summary on the diagnosis and management of pericardial diseases, in 2004, suggested that PAH patients with small pericardial effusions should not have them drained, but cardiac tamponade was a clear indication for drainage.⁸ In recent updates to the guidelines for the treatment of PAH, pericardial effusions and their management are not mentioned.⁹ Additionally, in 2013, Sahay and Tonelli summarized the available evidence on pericardial effusion in PAH and concluded that small pericardial effusions can be managed medically, but the treatment of larger pericardial effusion remains controversial.³ The largest study to date involved 577 patients with PAH, including 150 (26%) with pericardial effusion.⁵ Twenty-two patients had moderate or greater pericardial effusions, with 82% of those occurring in patients with connective tissue-associated PAH. Only 7 patients with an initial pericardial effusion required ECHO-guided pericardiocentesis. In all, 14 PAH patients required ECHO-guided pericardiocentesis over a follow-up period of 5 or more years at a major PAH referral center with zero periprocedural mortality. In contrast, a small case series of 6 patients with PAH and large pericardial effusions who underwent pericardiocentesis or pericardial window demonstrated high periprocedural mortality.¹⁰ This may be a reflection of ECHO-guided pericardiocentesis expertise, but demonstrates that pericardiocentesis can be performed safely in the setting of PAH and pretamponade/tamponade and should not be taken lightly. Multiple case reports and retrospective studies have demonstrated resolution of moderate-to-large pericardial effusions with medical therapy alone.¹¹⁻¹³ Patients treated with nonsurgical interventions did not demonstrate medical instability or pretamponade/tamponade on imaging. Treatment regimens encompassed oral vasodilators, prostaglandin analogues, diuretics, phosphodiesterase inhibitors, warfarin, and

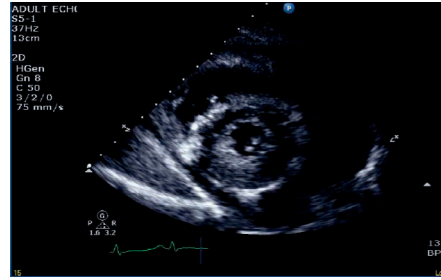


CT-Angiography of Chest

No large, acute pulmonary embolus, but enlarged pulmonary artery measuring 37 mm (top left). Moderate-to-large pericardial effusion noted.

Transthoracic Echocardiogram; Parasternal Short-Axis View

Moderate-to-large pericardial effusion (top right). No ventricular collapse of right or left chambers.



inhaled oxygen. Although most of these patients did not have underlying CTD, therapy was directed toward reversing the underlying PAH etiology.

In our patient, immunosuppressive therapy was initiated given our patient's underlying SLE. In contrast to the most recent retrospective studies with cyclophosphamide,⁷ azathioprine, plaquenil, and prednisone were initiated given the potential of an improved side effect profile and absence of SLE-related renal disease. Given the subsequent clinical response and complete resolution of the pericardial effusion, it is feasible that high-intensity anti-inflammatory medication along with a form of long-term immunosuppression and close monitoring is a reasonable alternative to pericardiocentesis if pretamponade/tamponade physiology are not present. Randomized controlled studies of this topic are not amendable to study given the complexities of the disease and infrequent presentation of pretamponade/tamponade with moderate-to-large pericardial effusions. However, recent studies report performing echocardiographic-guided pericardiocentesis on patients with PAH and moderate-to-large pericardial effusions with low immediate morbidity and mortality.⁵ Pericardiocentesis were performed at high-volume referral centers, reflecting an element of procedural experience and skill that may limit complications and improve survival. Given the current literature as a whole, the general approach to a large pericardial effusion in patients with PAH and absence of cardiac tamponade

should be conservative, but, if chosen, pericardiocentesis should be performed only under echocardiography and in experienced hands.

Teaching Points

1. SLE- and autoimmune disease-related PAH is an uncommon disorder.
2. The incidence of pericardial effusion in autoimmune disease-related PAH is higher than that seen in IPAH, reflecting myocardial edema and/or high right atrial pressure.
3. Anti-U1 RNP has proven to be a predictor in the development of a pericardial effusion for patients with PAH related to autoimmune disease.
4. Guidelines on the management of large pericardial effusions in the setting of PAH do not exist. While it is reasonable to manage pericardial effusions conservatively, pericardial effusions with pretamponade/tamponade physiology may be managed with ECHO-guided pericardiocentesis with low periprocedural mortality in high-volume centers.
5. If tamponade is absent, targeting the underlying etiology of PAH is of highest importance.
6. The anti-inflammatory properties of steroids and long-term immunomodulatory agents make them a feasible alternative in the treatment of pericardial effusions related to autoimmune-induced PAH.

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