Presentation: A 31-year-old female presented to her family physician 15 years ago with subtle but gradually worsening dyspnea on exertion (DOE) over the previous 5 years. Prior to these symptoms, she had been very active, running 5 miles a day. She felt her running was now limited by this progressive shortness of breath (SOB). She had no significant medical, social, or family history. Her chest radiograph and initial labs were reportedly unremarkable, and she was told her mild DOE was likely secondary to deconditioning. However, 6 months after her initial visit, her dyspnea had progressed to the point where she was SOB with just walking. She did have one presyncopal episode while attempting to exercise. Her physician referred her to a pulmonologist after the screening electrocardiogram revealed right axis deviation.

Assessment: Pertinent physical findings by her pulmonologist included increased jugular venous distension, a loud P2 on auscultation, clear lung fields, and mild bilateral lower extremity pitting edema. Pulmonary function tests (PFTs) showed mild restriction and a diffusion defect of 66% (Table 1). An echocardiogram (ECHO) showed dilated right-sided chambers, moderately reduced right ventricular (RV) function, and an elevated pulmonary artery systolic pressure (PASP) of 80 mm Hg (Figure 1). A complete evaluation for the causes of pulmonary hypertension (PH) was performed. Liver function tests, complete blood count, renal function, hepatitis panel, HIV, and a full autoimmune workup were found to be normal. A chest computed tomography (CT) with pulmonary embolism (PE) protocol was negative for an acute PE; however, it did show an enlarged pulmonary artery (Figure 2). Lower-extremity Dopplers were negative for any peripheral thrombi, and a ventilation-perfusion (V/Q) scan was negative for chronic thromboembolic PH. A right heart catheterization (RHC) revealed no shunts or other signs of congenital heart defects, but showed an elevated mean pulmonary artery pressure (mPAP) with normal wedge pressures (Table 2). The results of the RHC and the entire workup for pulmonary arterial hypertension (PAH) confirmed the diagnosis of idiopathic pulmonary arterial hypertension or IPAH (which at the time was referred to as primary PH). Due to a pending geographic move, no therapy was initiated until she established care with our PH center 4 months later.

Monitoring and Management: When the patient established care at our center, she was initiated on intravenous (IV) epoprostenol. At the time, epoprostenol was the only Food and Drug Administration (FDA)-approved medical treatment available. She experienced significant improvement clinically (World Health Organization [WHO] symptoms improving from class III to II), functionally (improved 6-minute walk test [6MWT] from 240 m to 400 m), and hemodynamically (cardiac ECHO showed improved RV function to mild

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Correspondence: LEVINEDJ@uthscsa.edu
hypokinesis and decreased PASP to 50 mm Hg).

Three years later, she developed worsening DOE despite increasing IV epoprostenol dosage. She declined recommendations to be evaluated for lung transplantation, instead opting to continue with only medical therapy. In 2002, when bosentan (which was an oral endothelial receptor antagonist) approved by the FDA, it was also added to her medical regimen and she experienced significant improvement in her symptoms. Several attempts to titrate down her IV epoprostenol were unsuccessful. She continued to be clinically stable for several years until 2007, when she again developed clinical worsening. Her 6MWT distance decreased to 230 m, and she now desaturated to 85%. Her b-type natriuretic peptide (BNP) level was elevated at 500 ng/L, and a repeat RHC revealed worsening of her hemodynamic parameters (Table 3). She was again offered evaluation for lung transplantation but again declined. Sildenafil 20 mg 3 times a day was started along with 2 L oxygen. This additional therapy improved her symptoms and she remained stable on triple therapy.

In 2010, on maximal therapy, her symptoms dramatically worsened (WHO class IV, 6MWT: 200 m, desaturation to 86% on 2 L nasal cannula), with a rise in BNP level to 800 ng/L. An ECHO showed her PASP to be 90 mm Hg, with worsening of her RV dilation and now with severe RV hypokinesis (Figure 3). She was finally evaluated and listed for lung transplantation. Her lung allocation score (LAS) upon listing was 34, which clearly did not reflect how severe her disease was. Because of her severely elevated right atrial pressure (RAP), decreased cardiac index (CI) (RAP >15 mm Hg and CI <1.8 L/min/m²), and continued clinical decline despite optimal medical therapy, she was granted exception points on the LAS and her score was increased to the 90th percentile.

At the age of 42, our patient underwent bilateral lung transplantation (BLT) 2 months after being placed on the list. This was 11 years after first being diagnosed with IPAH and after being on a 3-drug regimen for 3 of those 11 years. She had no significant postoperative complications. Her cardiac ECHO 1 month postoperatively showed resolution of her prior RA/RV dilation and hypokinesis, with dramatic improvement in PASP from 90 mm Hg preoperatively to 31 mm Hg postoperatively (Figure 4). She is now back at the gym 5 times per week, has a personal trainer, and runs 2 miles every day with a weight of 120 lbs and a normal 6MWT distance.
only minimal dyspnea—a stark contrast to before her lung transplant.

**DISCUSSION:** Despite being on maximal combination medical therapy including a prostacyclin, our PAH patient had progressive clinical and hemodynamic worsening. For her and many other patients with PAH who fail available medical therapy, lung transplantation is the best therapeutic option. This patient’s long journey with IPAH up to and including lung transplantation demonstrates many key concepts inherent to the management of PAH, including how the assessment and management of PAH has changed over the last 15 years. Before the development of the first approved medical therapy in 1995 (epoprostenol), lung transplantation was the only option available for patients with PAH. At that time, 11% of all lung transplants were performed for patients with PAH. \(^1\) Since that time, 12 medications have been approved in the United States for PAH. The use of these medications has made it possible to delay and in some cases decrease the number of patients actually requiring a lung transplant. This benefit is reflected in the fact that in 2015, and over the last few years, fewer than 3% of all lung transplants performed were for patients with PAH (Figure 5).\(^2\)

Unfortunately, patients with PAH are often referred for lung transplantation when their disease has significantly progressed. At the time of referral, they may already have poor prognostic markers, which may limit their survival and ability to survive long enough on the waiting list to receive an organ. PAH patients can have waitlist mortalities as high as 30%.\(^4\) Thus, education and early referral is key. Historically, referral of PAH patients has been delayed by a lack of awareness on the part of physicians and patients alike regarding how rapidly this condition can progress to hemodynamic instability and irreversible right heart failure. Often, this results in physicians missing a pivotal time window when interventions can actually affect outcomes.

The 2014 International Society of Heart and Lung Transplantation (ISHLT) guidelines recommend referral of the following PAH patients for lung transplant evaluation: a) WHO III or IV symptoms requiring a lung transplant. This benefit is reflected in the fact that in 2015, and over the last few years, fewer than 3% of all lung transplants performed were for patients with PAH (Figure 5).\(^2\)

Unfortu...
the preferred transplant procedure for patients with PAH. However, after it was discovered that the RV could recover after just a lung transplant alone, isolated BLT became the procedure of choice. There is a subset of patients who still require combined heart and bilateral lung transplantation, either because they have intractable right heart failure secondary to permanent cardiac remodeling, dependence on inotropic support, or coexisting left heart disease. Previous studies looking at single lung transplant (SLT) vs BLT revealed that BLT showed superior outcomes, largely because of improved perioperative hemodynamics (Figure 6). Consistent with this, our patient and more than 90% of patients with PAH over the last 15 years have received BLTs. In a recent study, however, Julliard highlighted a single center’s experience showing comparable outcomes between SLTs and BLTs regardless of the severity of the underlying PAH. These results will need to be assessed further in a larger study.

Our patient had worsened clinically prior to transplantation, but did not develop significant hemodynamic instability. Others, however, may not be as fortunate. These patients often may need aggressive therapy for right heart failure as a “bridge to transplantation.” Some of the therapies that may be used are atrial septostomy or extracorporeal membrane oxygenation (ECMO), the latter of which is used more commonly in the United States. When used as a bridge to transplant, ECMO is a life-prolonging therapy until donor organs become available. ECMO can prevent the development of further end-organ damage by maintaining perfusion to the rest of the body. Potential complications of ECMO include vascular access injury, infection at the cannulation sites, hemorrhage, renal failure, neurological complications, and thromboembolic risk. It should only be utilized in well-selected patients and within experienced centers.

Compared to other diagnostic groups, patients with PAH have a higher mortality rate early after lung transplantation due to the increased requirement for cardiopulmonary bypass, preoperative RV dysfunction, and increased risk of ischemic-reperfusion injury during the perioperative period. In fact, 3-month survival for PAH patients is 78%, compared to 86% for idiopathic pulmonary fibrosis (IPF) and 91% for cystic fibrosis and chronic obstructive pulmonary disease (COPD). These outcomes highlight the importance of providing PAH patients with aggressive hemodynamic support and close surveillance in the early postoperative period. However, if patients survive the first year, they will have similar outcomes to the other diagnostic groups up to 5 years post-transplant. In the long term, PAH patients actually have among the highest 10-year survival rates at 45%, compared to 28% for COPD and IPF (Figure 7). This patient is now more than 5 years post-transplant and is currently running marathons and traveling the world with her family. She is showing every indication that her outcomes will be just as promising if not more.

**Teaching Points**

1. PAH patient with escalating therapy should be followed closely with fre-
quent follow-up visits because of the rapidly progressive nature of this disease, requiring frequent therapeutic adjustments.

2. The following patients with PAH should be placed on the transplant list:
   a. WHO functional class III or IV symptoms despite a trial of at least 3 months of combination therapy including prostanooids
   b. CI of <2 L/min/m²
   c. Mean RAP >15 mm Hg
   d. 6MWT <350 m
   e. Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure (renal insufficiency, increasing bilirubin, BNP, or recurrent ascites)

3. After listing, lung transplant centers may apply for exception points to the LAS if the following criteria are met:
   a. Deterioration on optimal medical therapy
   b. RAP >15 mm Hg or CI <1.8 L/min/m²

4. Bilateral lung transplantation is currently the preferred and most commonly used operation for patients with PAH. However, for a subset of patients with intractable right or left heart failure dependent on inotropic support, combined heart-lung transplantation is still performed.

5. If life-threatening RV failure develops before lung transplant, bridging with aggressive therapies such as ECMO can be used to prevent the occurrence of secondary organ injury.5,6

References
8. McLaughlin VV, Archer SL, Badesch DB, et al; American College of Cardiology Foundation...

a pulmonary vascular tumor endarterectomy will result in tissue acquisition for diagnostic purposes, tumor debulking, and some survival benefit, albeit variably dependent on the extent of resection and the type of tumor present. Rarely is the tissue type such that a cure is obtained with surgery. Often surgical resection is simply the first step in the management of this rare and clinically challenging neoplasm. Consultation with radiation and medical oncology is required to provide the essential multidisciplinary treatment plan to achieve the best possible outcome.

*William R. Auger, MD
University of California, San Diego

**Teaching Points**

1. Pulmonary artery sarcomas are relatively rare intravascular tumors that may present with signs and symptoms that mimic acute or chronic thromboembolic disease.

2. Pulmonary artery sarcomas should be considered in patients who fail to respond to appropriate anticoagulation therapy.

3. The diagnosis is primarily based on imaging studies to include CTPA, chest MRI, and PET scans.

4. No single imaging study is sufficiently sensitive to exclude the presence of a pulmonary artery sarcoma.

5. Surgical debulking is the mainstay of therapy and may provide a survival advantage in this patient population. Consequently, early referral to a center of excellence should be strongly considered.

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**References**


**ERRATUM**

The Volume 15, No 1 issue of *Advances in Pulmonary Hypertension* contained an error in the PH Grand Rounds column, “Pulmonary Arterial Hypertension: ‘A Journey to Lung Transplant.” The PVR values in Tables 2 and 3 reflect an incorrect calculation from the original outside medical records. The editors thank Michael Slack, MD, Professor, Department of Pediatrics, University of Maryland School of Medicine; Director, Pediatric and Adult Congenital Interventional Cardiac Catheterization Laboratory, University of Maryland Medical Center, Baltimore, for pointing out this oversight. Dr Slack reinforces that PVR is the basis for many critical clinical decisions and provides the following 3 different ways to express PVR:

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>Pulmonary vascular resistance (PVR)</td>
<td>dyn.s/cm², MPa.s/m³, mmHg/min/l or HRU/Wood units</td>
</tr>
<tr>
<td></td>
<td>20-130, 2-13, 0.25-1.6</td>
</tr>
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</table>

In cardiac ICUs, the units of dyn.s/cm² are often used and the conversion factor between this value and Wood units is, conveniently, 80. During cardiac catheterization, the convention is to use the Cardiac Index (not cardiac output) and express the PVR in Wood units, which are indexed to body surface area.