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Case Reports

Resolution of Severe Portopulmonary Hypertension With Inhaled Treprostinil and Liver Transplantation

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Abstract

Portopulmonary hypertension is a rare condition with a poor prognosis. Prompt management is essential for liver transplantation eligibility, a potentially curative option. This report presents a case of severe portopulmonary hypertension that resolved with a conservative therapeutic regimen of tadalafil, macitentan, and inhaled treprostinil, which ultimately enabled successful liver transplantation. There was no recurrence of pulmonary hypertension after transplantation, and the patient was weaned off most pulmonary arterial hypertension therapies. This case report is the first to provide evidence that inhaled treprostinil is a safe and effective alternative to continuous intravenous prostacyclins in portopulmonary hypertension.

Keywords: Heart failure; hypertension, pulmonary; hypertension, portal; pulmonary arterial hypertension

Case Report

Presentation and Physical Examination

A 41-year-old woman presented to the hospital with fatigue and dyspnea. Her vital signs revealed a blood pressure of 97/70 mm Hg, a respiratory rate of 26/min, and oxygen saturation of 88% on ambient air. Her physical exam was notable for abdominal distention, absent right-sided breath sounds, jugular venous distention to the angle of the mandible, and bilateral pitting edema. Her laboratory values were remarkable for a sodium value of 125 mEq/L, a brain natriuretic peptide value of 192 pg/mL, and a total bilirubin value of 2.2 mg/dL.

Medical History

The patient's medical history included essential thrombocythemia, Budd-Chiari syndrome, and cirrhosis. Her medications included hydroxyurea, warfarin, furosemide, spironolactone, and propranolol.

Investigations

A chest radiograph demonstrated a large, right-sided pleural effusion, and a chest computed tomography scan was notable for a main pulmonary artery dilated to 3.3 cm. The patient's clinical picture was concerning for right heart failure (HF) and pulmonary hypertension, so a transthoracic echocardiogram was obtained. The echocardiogram demonstrated severe pulmonary hypertension, with severe right ventricle enlargement and dysfunction (Fig. 1 and Table I). Subsequent right-heart catheterization demonstrated severe precapillary pulmonary hypertension, with severely reduced cardiac index (Table I). The rest of her pulmonary hypertension workup was unrevealing. She was diagnosed with primarily World Health Organization group 1 pulmonary hypertension from portopulmonary hypertension, with some contribution from group 5 from essential thrombocythemia.

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Technique

This patient's combined disease states of cirrhosis, right HF, and essential thrombocythemia presented several complicated therapeutic challenges. First, the 3 major classes of pulmonary arterial hypertension therapies are all metabolized by the liver, so the careful selection, initiation, and titration of therapies were imperative for this patient with cirrhosis and an impaired hepatic metabolism. Endothelin receptor antagonists in particular have been associated with hepatotoxicity, with bosentan demonstrating the highest risk profile.[1] Second, the combination of right HF and cirrhosis resulted in labile volume status as the patient was prone to both intravascular hypovolemia and hypervolemia from cirrhosis-related extravascular fluid accumulation (ie, ascites), and intravascular hypervolemia from HF-related renin-angiotensin-aldosterone system activation. This lability was complicated by a narrow therapeutic window for diuretics as even small adjustments led to substantial swings in volume status, precipitating symptomatic hypotension, worsening hyponatremia, and worsening HF. The symptomatic hypotension in particular limited initiation and titration of pulmonary arterial hypertension therapies such as phosphodiesterase-5 inhibitors and prostacyclin analogs

Key Points

- Inhaled treprostinil is a safe and effective alternative to continuous IV prostacyclins in portopulmonary hypertension and may be advantageous because of its noninvasive route of administration.
- Orthotopic liver transplantation is a potentially curative option for portopulmonary hypertension and has been associated with improved survival outcomes.
- Clinicians should factor in MELD exception criteria when planning management strategy in patients with portopulmonary hypertension.

Abbreviations and Acronyms

HF	heart failure
IV	intravenous
MELD	Model for End-Stage Liver Disease
PVR	pulmonary vascular resistance

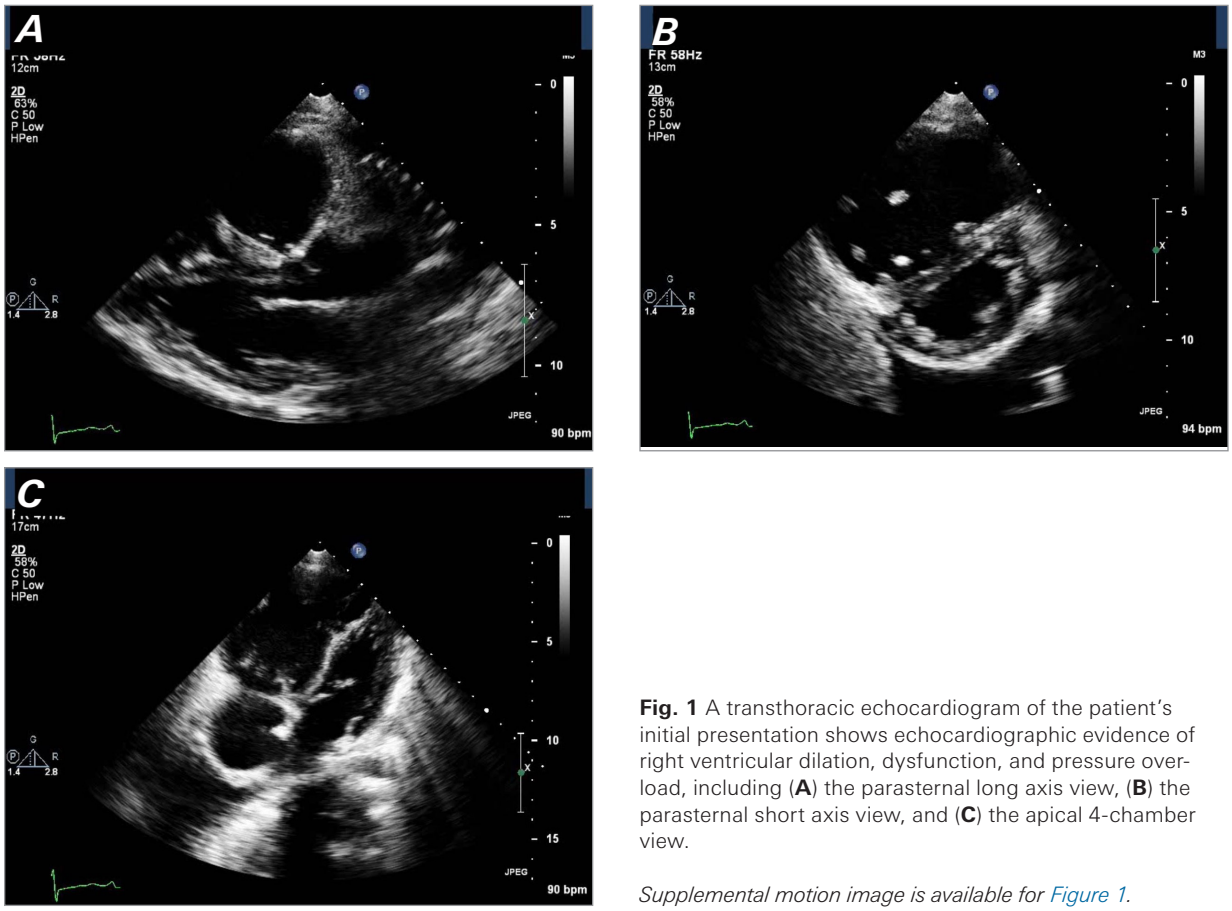

Fig. 1 A transthoracic echocardiogram of the patient's initial presentation shows echocardiographic evidence of right ventricular dilation, dysfunction, and pressure overload, including (**A**) the parasternal long axis view, (**B**) the parasternal short axis view, and (**C**) the apical 4-chamber view.

Supplemental motion image is available for Figure 1.

TABLE I. Echocardiographic and Hemodynamic Findings at Initial Presentation and After Maximal Pulmonary Arterial Hypertension Therapies

	Initial presentation	After maximal pulmonary arterial hypertension therapies
Pulmonary arterial hypertension therapies	None	Tadalafil 20 mg once daily Macitentan 10 mg once daily Inhaled treprostinil 90 μg 4 times daily
Transthoracic echocardiogram		
Right ventricle		
Size	Severely enlarged	Mildly enlarged
Tricuspid annular plane systolic excursion, cm	1.0	2.1
Right ventricular systolic pressure, mm Hg	117	Incomplete tricuspid regurgitation jet
Right atrium		
Size	Severely enlarged	Normal
Right atrial pressure, mm Hg	15	3
Left ventricle		
Size and shape	Small and D-shaped	Normal
Left ventricular ejection fraction, %	65	65
Septal flattening	Present	Not present
Valves	Severe tricuspid regurgitation	Trace tricuspid regurgitation
Right heart catheterization		
Right atrial pressure, mm Hg	16	6
Pulmonary arterial pressure (mean), mm Hg	79/37 (51)	30/12 (18)
Pulmonary capillary wedge pressure, mm Hg	21	7
PVR, Woods unit	23.7	2.6
Transpulmonary gradient, mm Hg	30	11
Cardiac output, L/min	Fick: 2.2 Thermodilution: 2.1	Fick: 4.3 Thermodilution: 5.4
Cardiac index, L/min/m^2	Fick: 1.3 Thermodilution: 1.2	Fick: 2.6 Thermodilution: 3.2
Left ventricular end-diastolic pressure, mm Hg	2	Not obtained

PVR, pulmonary vascular resistance.

SI conversion factor: To convert mm Hg to kPa, multiply by 0.133.

as the patient could not tolerate their hypotensive side effects. Finally, her essential thrombocythemia prohibited intravenous (IV) prostacyclin analogs as her immunocompromised and hypercoagulable state was not amenable to long-term central venous access.

The general management approach to this patient's portopulmonary hypertension was to introduce pulmonary arterial hypertension therapies at low doses in succession and slowly increase doses as tolerated and as dictated by symptoms and hemodynamic goals. She tolerated initiation and up-titration of pulmonary arterial hypertension therapies, with the main, rate-limiting side effect being symptomatic hypotension, which was generally limited to episodes of volume status fluctuations and would resolve when euvolemia was achieved. She eventually was placed on maximal triple pulmonary arterial hypertension therapy of tadalafil, macitentan, and inhaled treprostinil, and a repeat echocardiogram

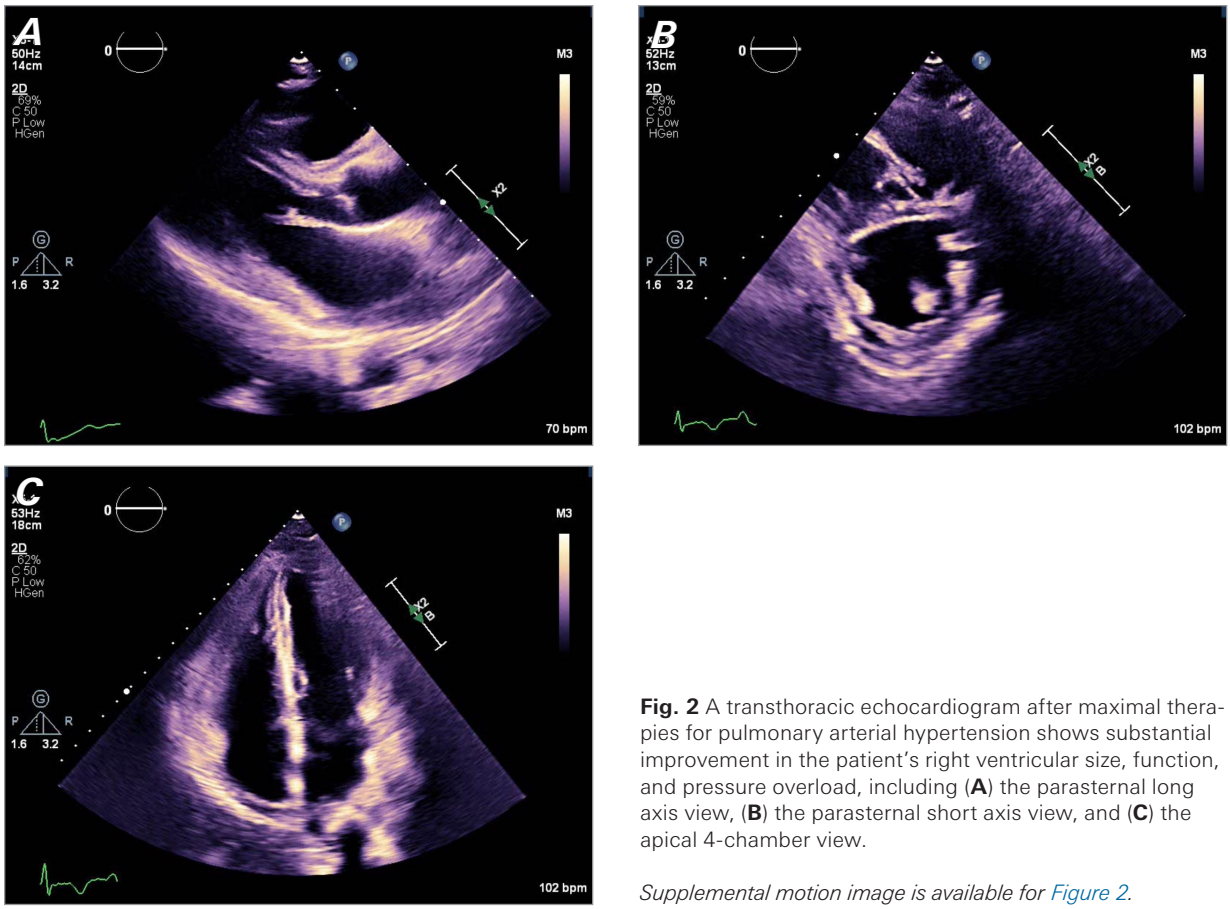

Fig. 2 A transthoracic echocardiogram after maximal therapies for pulmonary arterial hypertension shows substantial improvement in the patient's right ventricular size, function, and pressure overload, including (**A**) the parasternal long axis view, (**B**) the parasternal short axis view, and (**C**) the apical 4-chamber view.

Supplemental motion image is available for Figure 2.

and right heart catheterization demonstrated complete normalization of hemodynamic markers (Fig. 2 and Table I). She underwent successful orthotopic liver transplantation and continued on triple pulmonary arterial hypertension therapy without any need for dose adjustments in the immediate postoperative period. In subsequent months, she was weaned off pulmonary arterial hypertension therapy and is now on a minimal dose of tadalafil without recurrence of pulmonary hypertension.

Discussion

Portopulmonary hypertension is a form of pulmonary arterial hypertension that occurs in the setting of portal hypertension with or without hepatic cirrhosis. The pathogenesis of portopulmonary hypertension is not fully understood, but it is thought to involve a complex interplay of factors, with the main driving force being portal hypertension. Portal hypertension leads to splanchnic vasodilation and the formation of portosystemic shunts, which in turn manifest as high cardiac output and hyperdynamic circulation.[2] This hyperdynamic circulation is transmitted to the pulmonary vasculature and exposes pulmonary blood vessels to increased shear stress, which initiates a process of endothelial cell injury and vascular remodeling.[3] The proinflammatory state of cirrhosis likely contributes to further pulmonary vessel damage and vascular remodeling.[4] This process of hyperdynamic circulation and pulmonary vessel damage occurs in an imbalanced biochemical background that favors vasoconstrictive substances such as endothelin, norepinephrine, and angiotensin II, which is propagated by portosystemic shunts that allow these substances to bypass hepatic clearance and reach the pulmonary vascular bed.[5,6] The cumulative effect involves pulmonary vasoconstriction, pulmonary vessel smooth muscle proliferation, and pulmonary vessel wall thickening, which lead to high pulmonary artery pressures, high pulmonary vascular resistance (PVR), and eventually right HF.

Pulmonary arterial hypertension therapies, including the 3 major classes of phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and prostacyclin analogs, play a pivotal role in the management of portopulmonary hypertension. The overall goals of these therapies are to improve symptoms, functional class, and cardiopulmonary hemodynamics. Pulmonary arterial hypertension therapies also enable orthotopic liver transplantation; a meta-analysis demonstrated that almost 50% of patients with portopulmonary hypertension became eligible for orthotopic liver transplantation with pulmonary arterial hypertension therapy.[7] The available evidence behind pulmonary arterial hypertension therapies is mostly limited to small, observational case series and retrospective cohort studies as these patients have traditionally been excluded from randomized controlled trials of pulmonary arterial hypertension therapies. Several studies on phosphodiesterase-5 inhibitors have demonstrated improvements in exercise tolerance and hemodynamics with sildenafil in patients with portopulmonary hypertension.[8,9] Instead of sildenafil, this patient was on tadalafil 20 mg once daily, which proved advantageous with regard to ease of dosing compared with sildenafil's thrice-daily dosage. No studies to date have evaluated the efficacy and safety of tadalafil in patients with portopulmonary hypertension, and this report provides anecdotal evidence that it is a reasonable alternative to sildenafil in this patient population. Several studies on endothelin receptor antagonists have demonstrated improvements in World Health Organization functional class, exercise tolerance, and hemodynamics with bosentan and ambrisentan.[10,11] The endothelin receptor antagonist class is also the only form of pulmonary arterial hypertension therapy to have been studied in a randomized controlled trial in patients with portopulmonary hypertension. The PORTICO study, a multicenter randomized controlled trial of 85 patients, found that macitentan was associated with a 35% reduction in PVR compared with placebo.[12] Macitentan was also well tolerated, with no severe adverse hepatic events. This report corroborates the investigators' findings as this patient quickly reached the target dose of macitentan 10 mg once daily with no notable side effects. For prostacyclin analogs, several studies have reported hemodynamic and survival benefits with continuous IV epoprostenol.[13,14] A limitation of epoprostenol is its administration route, with patients requiring long-term central venous access and an IV pump for continuous drug infusion. In addition to carrying a high risk for catheter-related infections and thrombosis, these devices require high levels of patient and family engagement, which can be problematic in patients with cirrhosis who are at risk for hepatic encephalopathy. Prostacyclin analogs are also widely known to cause thrombocytopenia, which must be considered when initiating this medication in patients with cirrhosis.[15] Thrombocytopenia was not a major issue for this patient with essential thrombocythemia and thrombocytosis. As a result of patient preference, high infection risk, and high thrombotic risk, this patient was not treated with IV prostacyclin therapy. She was instead treated with inhaled treprostinil at a dose of 90 μg 4 times daily via nebulization. Though reports have described the successful use of inhaled iloprost in patients with portopulmonary hypertension, this is the first report of successful treatment of patients with portopulmonary hypertension with inhaled treprostinil.[16] This patient had striking improvement in her hemodynamics with a relatively conservative regimen, providing evidence that inhaled treprostinil can be a reasonable alternative to IV prostacyclins in patients with portopulmonary hypertension.

Orthotopic liver transplantation is the only potentially curative therapy for patients with portopulmonary hypertension and has been associated with improved survival.[7] Portopulmonary hypertension, however, is not an absolute indication for orthotopic liver transplantation and is guideline recommended only for highly select patients with acceptable hemodynamics.[17] A mean pulmonary arterial pressure of at least 35 mm Hg is associated with increased morbidity and mortality, and a mean pulmonary arterial pressure of at least 50 mm Hg is associated with a 100% mortality rate and is an absolute contraindication to orthotopic liver transplantation.[18] If orthotopic liver transplantation is indicated, patients with portopulmonary hypertension can receive Model for End-Stage Liver Disease (MELD) exception points. The MELD exception system was created for cirrhosis-related diseases such as portopulmonary hypertension that impair survival but are not directly accounted for in the standard MELD scoring system. Portopulmonary hypertension MELD exception criteria include a pretreatment mean pulmonary arterial pressure of at least 35 mm Hg and a PVR of at least 3 Wood units, with posttreatment improvement to a mean pulmonary arterial pressure less than 35 mm Hg and a PVR less than 5 Wood units or a mean pulmonary arterial pressure of 35 to 45 mm Hg and a PVR less than 3 Wood units.[19] Patients who meet criteria receive additional MELD points and are prioritized on

the transplantation waiting list. Combined liver-lung transplantation is occasionally performed in patients with portopulmonary hypertension, with 1 single-center study reporting its feasibility and acceptable long-term outcomes.[20] The available evidence is limited, however, because of the rarity of the procedure and immense variability in patient selection, surgical technique, and intraoperative and postoperative management.

This case of severe portopulmonary hypertension was successfully treated with conservative pulmonary arterial hypertension therapies, which enabled successful orthotopic liver transplantation without the recurrence of pulmonary hypertension after transplantation. In addition to adding to the growing body of evidence that orthotopic liver transplantation leads to improved outcomes and mortality rates in patients with portopulmonary hypertension, this case report is the first to provide evidence that tadalafil and inhaled treprostinil are safe and effective alternatives to traditional portopulmonary hypertension therapies.

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