Anesthetic Considerations in Patients Undergoing Orthotopic Lung Transplant for Group 1 Pulmonary Arterial Hypertension

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Case Presentation

A 16-year-old girl with familial pulmonary arterial hypertension (PAH) presented to our institution for consideration of bilateral lung transplant. She was small for her age because of her chronic medical condition and had been taking pulmonary vasodilators for the past several years.

Preoperative Preparation

World Health Organization (WHO) classified Group 1 PAH, formerly known as primary PAH, is a group comprised of diseases with similar pulmonary vascular pathophysiological mechanisms. The subgroups in this class include idiopathic, heritable, or drug and toxin–induced PAH; or PAH associated with certain conditions like connective tissue diseases, congenital heart disease, portal hypertension, and PAH caused by certain infections such as HIV and schistosomiasis.[1] Patients who are admitted for bilateral lung transplant with familial PAH or severe WHO Group 1 PAH present a unique set of considerations. Many of these patients have developed significant right ventricular hypertrophy (RVH) and subsequent right ventricle (RV) failure secondary to persistently elevated pulmonary arterial pressures. In some instances, such as in this case, gas exchange is not the primary problem. Venovenous extracorporeal membrane oxygenation (ECMO) may not be adequate to manage these patients' hemodynamic stability while awaiting

lung transplant, and the use of some variant of veno-arterial ECMO may be necessary.

This patient had profound PAH as well as evident RVH with significant RV systolic dysfunction; therefore, the decision was made to place a preoperative pulmonary artery catheter (PAC). The PAC allowed the pulmonology team to monitor changes in the patient's pulmonary pressures as the team titrated her pulmonary vasodilator regimens. After PAC placement, her pulmonary artery pressures were equal to or greater than her systemic blood pressures. Unfortunately, medication titrations by the primary pulmonology team were ineffective in improving the patient's condition preoperatively.

Pulmonary Vasodilator Selection

In the past two decades, there have been significant advances in the development of pulmonary vasodilators and antiproliferative agents. Many patients presenting for bilateral lung transplant for severe PAH require one or more of these medications, which can have negative side effects. It is vital that anesthesiologists are aware of the potential side effects of the medications outlined below.[2]

- Epoprostenol (Flolan) is the first of the prostanoid class of drugs. The prostanoids are prostacyclin analogues. Epoprostenol was the first drug specifically approved for the treatment of PAH in 2000, and it is the most effective medication for the treatment of advanced disease. A more stable formulation of epoprostenol sold as Veletri was approved in 2010. These medications can be delivered by continuous infusion via an intravenous catheter in the outpatient setting and are nebulized for delivery via inhalation in the inpatient setting. Platelet inhibition and, in some instances, thrombocytopenia are well-known adverse effects of this drug class.[3,4]
- Treprostinil is a prostanoid medication used for the treatment of PAH. It comes in intravenous and subcutaneous (Remodulin), inhaled (Tyvaso), and oral (Orenitram) formulations. Another inhaled prostanoid medication currently approved by the Food and Drug Administration (FDA) for patients with PAH is iloprost (Ventavis). These prostanoid medications have side-effect profiles that are similar to epoprostenol.

- Bosentan (Tracleer) is an endothelin receptor blocker. Bosentan is approved for use in patients with advanced disease due to PAH or connective tissue disease associated with pulmonary hypertension. The adverse effects of this drug differ from those of the prostanoids. Approximately 10% of patients taking bosentan develop elevated transaminases. Other well-known side effects of this drug are anemia and fluid retention. Ambrisentan (Letairis) and macitentan (Opsumit) are drugs in the same class that have been approved by the FDA for the treatment of patients with WHO group 1 PAH. These drugs do not appear to be independently associated with elevated liver transaminases, though case reports exist. This medication class is associated with anemia and fluid retention.[4]
- Sildenafil (Revatio) is a medication approved for patients with New York Heart Association Class II to IV symptoms due to PAH. This drug is a potent vasodilator and acts by inhibiting cGMP-specific phosphodiesterase type-5 (PDE-5) in the smooth muscles of the pulmonary vasculature. The resulting increase in cGMP within pulmonary vascular smooth muscle cells results in relaxation of smooth muscle tone, thereby decreasing pulmonary vascular resistance (PVR). PDE-5 inhibitors are contraindicated in patients using nitrates. This is of particular importance to anesthesiologists because initiation of nitroglycerin for afterload reduction may not be the appropriate first-line therapeutic option for patients taking PDE-5 inhibitors and undergoing bilateral lung transplant. Tadalafil in the form of a once per day dosing (Adcirca) is another drug in the same class that has been approved for the treatment of PAH. These medications can cause hypotension.
- Riociguat (Adempas) is a medication approved for the treatment of PAH. Riociguat is a stimulator of soluble guanylate cyclase (sGC). Riociquat is the first sGC approved for the treatment of PAH; the FDA approved it in 2013. Adverse effects of this medication include gastroesophageal reflux, hypotension, and anemia. This medication is contraindicated for use with PDE-5 inhibitors.
- Selexipag (Uptravi) is an oral prostacyclin IP receptor agonist approved for the treatment of PAH. To date, no significant hematologic side effects have been reported with

selexipag; however, hyperthyroidism has been observed at higher frequencies in patients taking this medication.[5]

Our patient was on triple therapy for severe PAH prior to bilateral lung transplant. Before arriving at our hospital, she was taking intravenous treprostinil through a tunneled central venous line, 2.5 mg of riociguat three times daily, and 10 mg of macitentan daily. The patient was also taking 0.125 mg of digoxin daily as well as 60 mg of furosemide and 60 mg of spironolactone. The pulmonary service transitioned her intravenous treprostinil to inhaled Flolan shortly after she arrived at our hospital. Her platelet counts were around 40000/μl with a hemoglobin of 12.8 g/dL and she was experiencing gastroesophageal reflux.

Before lung transplant, the patient's thrombocytopenia had slightly improved while on inhaled Flolan and her platelet count had increased to 74000/μl. All of her other medications were continued to prevent rebound PAH. Her preoperative transthoracic echocardiogram (see linked video clips)revealed a moderately dilated right atrium, severe tricuspid regurgitation, and a severely dilated RV with severe RV systolic dysfunction, as well as flattening of the interventricular septum during systole and diastole consistent with RV pressure and volume overload. By using transthoracic echocardiography, we estimated that her RV systolic pressures were 124 ± 5 mmHg.

Induction Considerations

In patients with advanced PAH with significant RV failure, as in this patient, balancing the pulmonary arterial pressure as well as systemic blood pressure is paramount. If induction drops systemic blood pressure below the pulmonary arterial pressure, these patients are at risk of myocardial ischemia, particularly reduced flow to the right coronary artery. This situation can lead to catastrophic circulatory collapse and worsening RV failure; thus, it is imperative to ensure right coronary artery perfusion during induction by maintaining a high systemic afterload as well as by reducing PVR. Typical considerations involve preferential use of vasopressin as a vasopressor given that it has a minimal effect on PVR while it increases systemic vascular

resistance (SVR). Physiologic factors that increase PVR, which include hypoxia, hypercarbia, acidosis, agitation, pain, and hypothermia, should also be considered.[6]

Because lung isolation is necessary for this procedure, an appropriately sized double-lumen endotracheal tube (ETT) should be selected. Hypoxia, hypercarbia, and acidosis are very poorly tolerated because they will further increase the patient's PVR; thus, if there is a potential for airway difficulty, it may be necessary to place a single-lumen tube to facilitate rapid securing of the airway. An exchange catheter to transition to a double-lumen ETT may then be used.

Intraoperative Management

Given the severely elevated RV pressures and RV failure in our patient, as shown by transthoracic echocardiography (Figure 1), we chose to initiate inhaled nitric oxide during induction while continuing inhaled Flolan. We ensured that pulmonary arterial pressures were transduced and monitored during induction. Induction was performed with midazolam, fentanyl, and small boluses of propofol titrated to effect. A paralytic agent was subsequently administered. Small boluses of vasopressin (to increase SVR without affecting PVR) were administered, as was epinephrine during induction to ensure that the induction agents were not significantly dropping her systemic afterload relative to her pulmonary afterload. After induction, we placed a double-lumen ETT without incident. We made sure to hyperventilate the patient with high inspired oxygen before checking the tube position by using a fiberoptic bronchoscope. After the double-lumen tube position was verified, the patient was prepared in the normal fashion and we proceeded to a clamshell incision. This patient would not have tolerated pulmonary arterial clamping; therefore, we opted for central cannulation for cardiopulmonary bypass. Dilution from the cardiopulmonary bypass circuit in the setting of the patient's pre-existing anemia necessitated transfusion of packed red blood cells shortly after initiation of cardiopulmonary bypass. With the reduction of flow through the pulmonary circulation, her pulmonary arterial pressures dropped significantly after initiation of full cardiopulmonary bypass (Figure 2 see linked video clips). The operative portion of the procedure went well and we weaned the patient from cardiopulmonary bypass without

difficulty. Notably, pulmonary arterial systolic pressures after lung transplant and cardiopulmonary bypass did not exceed 50 mmHg. The patient required 3 additional units of packed red blood cells, 2 pooled units of cryoprecipitate for a fibrinogen of 100 mg/dL, and 3 units of platelets for a platelet count of 28000/μl. After the bilateral lung transplant, we discontinued the patient's pulmonary arterial vasodilators and her platelet count remained above 139000/μl without further platelet transfusions until discharge.

Conclusion

Concomitant severe PAH and RV systolic dysfunction present a significant clinical challenge for cardiothoracic anesthesiologists, who should be aware of the potential side effects of various PAH treatment options. A balanced anesthetic technique and appropriate vasoactive selection are essential to the success of lung transplant in this patient population.

References

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Figure Legends

Figure 1. Transthoracic echocardiogram showing collapse of the left ventricle and increased right ventricle size during ventricular systole, which is suggestive of right ventricle pressure overload.

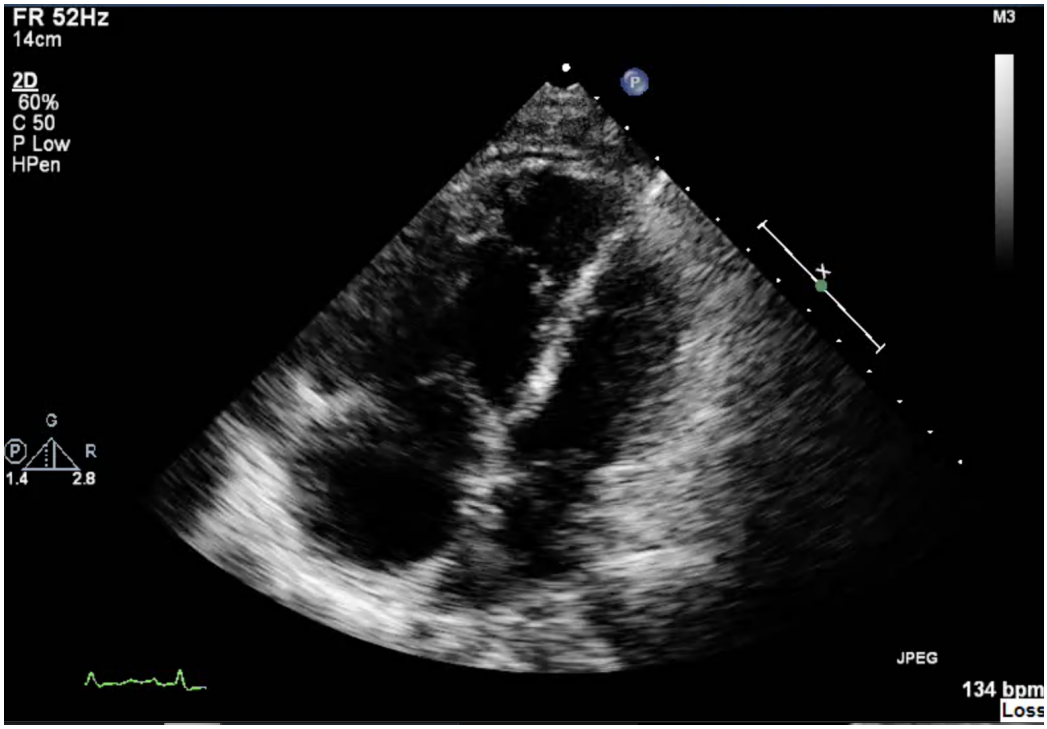

Figure 2. Transesophageal echocardigram showing an underfilled right ventricle after the initiation of cardiopulmonary bypass. The right ventricle free wall and septum are hypertrophic.