Cases from the Pulmonary Hypertension Service

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CASE 1:

A 42-year-old woman with HIV-related pulmonary arterial hypertension (WHO class II) presented to the emergency room with a 2-day history of fever, dysuria, lightheadedness, and increased abdominal girth. Her medications at home included continuous intravenous epoprostenol at a rate of 25 ng/kg/min, furosemide 80 mg po qd, and co-trimoxazole for PCP prophylaxis. Her heart rate (HR) was 140/min regular, blood pressure (BP) was 72/45 mmHg, she had an oxygen saturation of 95% on 3L/min nasal cannula and a temperature of 38 Celsius degrees. Her mucous membranes were moist; she had elevated jugular venous pressure and evidence of ascites. Cardiac examination revealed a right ventricular heave, loud P2, murmur of tricuspid regurgitation, and right-sided gallop. Lungs were clear to auscultation bilaterally, the liver was slightly enlarged, and she had suprapubic tenderness. Hickman line insertion site had no evidence of erythema or discharge. Electrocardiographic examination showed sinus tachycardia at a rate of 138/min, right axis deviation, and incomplete right bundle branch block. Chest radiography demonstrated cardiomegaly, but neither lung parenchymal infiltrates nor pleural effusions. Total white blood cell count was 14.5 x 1000/dL with 95% polymorhphonuclear cells, and urinalysis showed numerous white blood cells, positive leukocyte esterase and nitrite. Blood urea nitrogen (BUN) was 32 mg/dL and serum creatinine (Cr) 1.8 mg/dL (baseline BUN/Cr = 16/0.9). Blood and urine cultures were collected. She was immediately given one liter of crystalloid infusion over 90 minutes, followed by a continuous infusion of normal saline at 100 mL/h and one dose of intravenous Piperacillin-Tazobactam. HR remained elevated at 135/min and BP remained low at 70/45 mmHg; she had minimal urine output and complained of worsening shortness of breath. Her pulmonary hypertension physician was called, the patient was transferred to the CCU, and intravenous fluids were discontinued. Repeat BUN at 4 hours was 38 mg/dL and Cr was 2.2 mg/dL. Urine Na was 25 mEq/L, with a fractional excretion of sodium of 0.22. Bedside echocardiogram showed right ventricular dilatation and severe dysfunction, enlarged right atrium, and a small pericardial effusion without tamponade physiology. She received 80 mg of furosemide intravenously and continuous infusion of dopamine at 2 mcg/kg/min and dobutamine at 3 mcg/kg/min. After 2 hours, BP increased to 85/55 mmHg, and she urinated 250 cc of urine. Dobutamine was increased in 1 mcg/kg/min increments to 5 mcg/kg/min over 3 hours and the patient was initiated on standing dose of intravenous furosemide 80 mg intravenously every 12 hours. Upon urine culture results that showed growth of *Klebsiella pneumoniae* sensitive to fluoroquinolones, the patient was transitioned to oral ciprofloxacin, after receiving 48 hours of intravenous antibiotics. Blood cultures were negative. Over the next 3 days, her BP remained stable at 95-100 mmHg/50-60 mmHg, HR of 95-110/min (sinus tachycardia), she was afebrile, and her respiratory status improved. She had good urine output, her oxygen supplementation requirement decreased and renal function returned to normal. Dopamine and dobutamine were tapered to off, intravenous furosemide converted to oral form, and she was discharged home on oral antibiotics after a 7-day hospital stay.

Discussion:

This case provides an example of acute right heart failure precipitated by an intercurrent urinary tract infection in a patient with pulmonary arterial hypertension who was relatively well controlled with intravenous epoprostenol. Patients with pulmonary arterial hypertension have little tolerance for any comorbidity, which can easily precipitate acutely decompensated right heart failure (ADRVF), particularly in cases with significant baseline right ventricular dysfunction. Even with another obvious source of infection (in this case, a urinary tract infection) patients receiving continuous intravenous prostacyclin through a central catheter who present with fever should have blood cultures done and receive empiric coverage for gram-positive organisms. Patients with ADRVF are usually hypotensive and tachycardic and in a low flow state. Any further increase in the right ventricular preload (such as with intravenous fluid administration) may

exacerbate right ventricular dysfunction, as it did in this case. The systemic hypotension that follows is due to decreased left ventricular filling from interventricular septal shift and decreased right ventricular output. Intravenous fluid administration should be done with great caution in patients with pulmonary hypertension and requires clear evidence of true intravascular fluid depletion, such as a history of recent fluid loss, dry mucous membranes, or drenching sweats with large insensible fluid loss. Patients who present in septic shock, particularly if it is complicated by cardiogenic shock, may be extremely difficult to manage and likely will require pulmonary artery catheterization to guide management. Decreased urinary output and evidence of prerenal azotemia can be due to low cardiac output and cannot be considered evidence enough to begin intravenous fluid administration, as was the case in our patient.

The goal of BP support is to decrease the right ventricular dilatation and to directly improve the right ventricular contractility. Right ventricular dilatation is primarily decreased by administration of intravenous loop diuretics. Because of bowel edema, orally administered diuretics may be ineffective. By decreasing the right atrial size and pressure diuretics improve right ventricular filling and contractility, and in some cases, may be the only intervention required to improve systemic hemodynamics. Most patients, however, will benefit from direct right ventricular inotropic support and vasopressors, as in this case where low-dose dopamine and dobutamine were used. In patients with right ventricular failure dobutamine is the inotropic agent of choice, despite some potential direct pulmonary hypertensive effect. Milrinone may be more beneficial as a pulmonary vasodilator, but the pronounced systemic hypotension induced by this agent has the potential to decrease venous return to the already insufficient right heart, worsening the right ventricular failure. All vasopressors may have a direct pulmonary vasoconstrictor effect, but low-dose dopamine, phenylephrine, norepinephrine, or vasopressin may be used to sustain the systemic blood pressure. Improved systemic hemodynamics are usually translated in improved renal function, increased diuresis, and further increased right ventricular contractility. In conclusion the mainstay of therapy in cases of hypotension from right ventricular failure in pulmonary arterial hypertension is not intravenous fluid administration, but rather inotropic support, diuretics, and vasopressors.

CASE 2:

A 58-year-old man with hepatitis C-cirrhosis (MELD = 32, refractory ascites, recurrent variceal bleeds, episodes of hepatic encephalopathy, and hepato-renal syndrome) and porto-pulmonary hypertension was called for cadaveric orthotopic liver transplantation (OLT). He had been deemed an appropriate candidate for OLT after 9 months of therapy with subcutaneous treprostinil. His initial cardiac catheterization at the time of diagnosis of porto-pulmonary hypertension revealed the following hemodynamics: mean pulmonary artery pressure (mPAP) of 55 mmHg, pulmonary artery occlusion pressure (PAOP) of 10 mmHg, cardiac output (CO) of 6 L/min and pulmonary vascular resistance (PVR) of 600 dynes x s x cm^{-5}. He lived alone, was mildly encephalopathic, and his wife, who had multiple sclerosis, resided in a nursing home. With hemodynamics that posed a prohibitive operative risk for OLT, and an inappropriate social situation for intravenous epoprostenol therapy, treatment was initiated with subcutaneous treprostinil. Six months after initiation a follow-up right heart catheterization on 36 ng/kg/min of treprostinil showed the following hemodynamics: mPAP of 33 mmHg, PAOP of 15 mmHg, CO of 8.7 L/min, and PVR of 166 dynes x s x cm^{-5}. On the basis of these numbers he was listed for liver transplantation and because of rapidly progressing liver disease he received a graft after 3 months.

Preoperatively his mPAP was 40 mmHg, his central venous pressure (CVP) was 18 mmHg, PAWP was 20 mmHg, and CO was 8.5 L/min, with a PVR of 188 dynes x s x cm^{-5}. During abdominal preparation the subcutaneous treprostinil administration was discontinued. Systemic blood pressure was 85/55 mmHg before induction of general anesthesia and decreased to 70/35 mmHg after induction. This fall in blood pressure responded to a phenylephrine bolus of 0.2 mg. Approximately half an hour after treprostinil discontinuation a continuous intravenous epoprostenol infusion was started at 2 ng/kg/min and adjusted to keep mPAP = 30-40 mmHg, with up-titration in 1-2 ng/kg/min increments every 30 to 60 minutes. Cardiac output was constantly monitored and remained at 6.5-8.5 L/min. Inhaled nitric oxide (NO) was kept on stand-by for potential rebound pulmonary hypertensive episodes, but was not used. After removal of ascites, mPAP, PAOP, and CVP decreased by 10 mmHg. Intermittent boluses of phenylephrine (0.2 mg) and vasopressin (2-4 U) were used to maintain the mean systolic BP above 45-50 mmHg. During the procedure the patient received a total of 6 L crystalloid infusion, 10 U of fresh frozen plasma, and 5 units of packed red blood and he was placed on continuous veno-venous hemofiltration (CVVH). He remained stable hemodynamically throughout the transplant, including during the anhepatic phase. Upon graft revascularization during a 2 minute hypotensive episode (with a decrease in the mean systemic BP to 30 mmHg and a rebound mPAP to 45 mmHg) he received 4 U of vasopressin and this increased the mean systemic BP to 50 mmHg, without significant change in mPAP. On completion of the transplant operation he was receiving 15 ng/kg/min of continuous intravenous epoprostenol. He was transferred to the surgical intensive care unit, where he remained hemodynamically stable. The next day subcutaneous treprostinil was reinitiated and up-titrated in 3-4 ng/kg/min increments, with simultaneous down-titration of intravenous epoprostenol in 1-2 ng/kg/min decrements, until a dose of 30 ng/kg/min of treprostinil were reached. Prior to discontinuation of the pulmonary artery catheter the mPAP was 32 mmHg, the CO was 7.5 L/min, the PAOP was 12 mmHg, and the calculated PVR was 213 dynes.

Discussion:

This case illustrates the strategy that may be employed for the perioperative hemodynamic management of patients with porto-pulmonary hypertension who require OLT. Porto-

pulmonary hypertension is a type of pulmonary arterial hypertension that develops in patients with end-stage liver disease, characterized by the presence of a true pulmonary arteriopathy (elevated PVR) and (potential for) right ventricular dysfunction. Perioperative mortality is significantly increased in the presence of moderate to severe pulmonary hypertension. These patients require chronic therapy for pulmonary hypertension for hemodynamic optimization prior to OLT, and case series in the literature support the use of continuous intravenous epoprostenol in these circumstances. This patient was treated with subcutaneous treprostinil instead because of the lack of social support and his own inability to manage the complexities of intravenous epoprostenol therapy. With the advent of alternative therapeutic options for pulmonary arterial hypertension, it is likely that physicians will use other forms of chronic prostacyclin therapy, ideally in the setting of organized clinical trials. This patient had a good hemodynamic response to treprostinil, rendering him an OLT candidate, but the particular challenge in his case was the timing of transition from subcutaneous to intravenous prostacyclin during the surgical procedure. Given the relative unpredictability of the time of OLT, it is not possible to transition these patients in advance. Liver transplantation surgery is associated with hemodynamic instability, rebound pulmonary hypertension, and precipitation of right ventricular failure, particularly after induction of general anesthesia, after graft revascularization, and during the first postoperative days. Transitioning from one to another form of prostacyclin therapy during OLT may increase the risk of hemodynamic instability. In this case, transition from subcutaneous treprostinil to prostacyclin infusion was successfully achieved with guidance from pulmonary artery catheterization.

As a general rule, prostacyclin deficiency may be associated with rebound pulmonary hypertension and prostacyclin excess with systemic hypotension. There is a difference in half-lives between epoprostenol and treprostinil (2 to 3 minutes and 2 to 4 hours, respectively) and anecdotal evidence suggests that approximately two to three times more treprostinil (in nanograms) is required for an equivalent effect. Inhaled NO may be used for the pulmonary vasodilator effect, particularly in cases with systemic hypotension, because of its selectivity for the pulmonary vasculature. Inotropic agents and vasopressors, as well as volume replacement or volume removal, may be used as needed for the hemodynamic management during liver transplantation.