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Portopulmonary Hypertension (PoPH): A Case of Complex Physiology and Management

Dr. Elwing:
Welcome, my name is Dr. Jean Elwing, and I'm a professor of medicine and the director of the Pulmonary Hypertension Program at the University of Cincinnati. And I'm going to be talking to you about portopulmonary hypertension, and we're going to go through a case of complex physiology and management.

So I'm going to reintroduce you to Reginald. He has progressive decline in his health with liver disease. Reggie as we'll refer him to him, he's a 53-year-old. He presented to his primary care physician's office for an evaluation of worsening swelling and shortness of breath with his activities of daily living. He has struggled with his weight his entire life even as a teenager, his BMI was more than 45. He was found to have some fatty liver change on an ultrasound when he was 35 and diet and weight management was recommended. He was diagnosed with diabetes at age 40 and started on insulin. And then about six months ago, they noticed he was becoming a little bit jaundiced. He developed a GI bleed and was found to have esophageal varices. At that time, he was diagnosed with NASH cirrhosis and portal hypertension.

So he was seen in the primary care's office and his vitals were 105 over 72, heart rate 92, respiratory rate 14 and saturations of 92% on room air. He was in no distress, but he did have some mild jaundice. His heart was regular rate and rhythm. He had an accentuated P two and a two out of six systolic murmur at the right mid sternal border. Consistent with tricuspid regurgitation. Lungs were clear. Abdomen was distended, and he had some mild ascites and his extremities had two plus edema. So his primary care opted to get some labs and testing, labs were unremarkable other than an INR of two, hemoglobin of 11 platelets of a hundred, bili was elevated at 4.5. Creatine was elevated at 1.3 and B and P was 250, chest x-ray was clear, HRCT chest. No, ILD but in large pulmonary artery and right ventricle. His PFTs had some restriction most likely because of his abdominal distension in ascites and his DLCO was mildly reduced. His six minute walk distance, 234 meters with a low saturation of 90%. And that's when his primary care was concerned and he opted to get an echocardiogram. So what did the echocardiogram show? Well, you can see here in the apical four chamber, the right side is enlarged, the right ventricle is enlarged and the right atrium is enlarged. And if you look at that per sternal short, you can see that significantly enlarged right ventricle and flattening of the septum with a D shaped left ventricle showing pressure and volume overload on the right side. And when they looked at the TR jet velocity it was increased showing us that the pulmonary pressures likely were elevated. So what's next? What is the next step here? Well, it would be referral to a center that can evaluate this patient because there's concern that he has pulmonary hypertension.

So this is a complicated situation. He could have pulmonary hypertension for a number of reasons. Patients with liver disease can have high flow state with increased cardiac output leading to that high pulmonary pressure. They can have extra fluid, so increased wedge pressure driving up all of the other pressures or he could have true pulmonary vascular disease related to that portal hypertension, portopulmonary hypertension where the problem is in the pulmonary vascular bed leading to increased pulmonary pressures. So we need a right heart cath and we need it to tell us what exactly is the pattern? Is it flow, is it volume or is it true PAH? Well, he did have a right heart catheterization and it showed us a mean pulmonary pressure that was clearly more than 20. 58 and it showed us the wedge pressure. The left atrial pressure was normal at 10. So this was not extra volume on the left side. This was pulmonary hypertension. And when you look at the pulmonary vascular resistance, it's elevated at 519. So he was diagnosed with portopulmonary hypertension, high PBR, normal wedge, cardiac output was a little bit on the higher side but that is expected in our liver disease patient but it was not the

cause of pulmonary hypertension.

All right, so we want to know how sick he is. What can we use? We can use REVEAL 2.0 in this patient. And when we calculate his REVEAL score, it's elevated at 14, what does that tell us? He's at high risk of morbidity and mortality in one year, he is a patient we need to treat aggressively.

So let me tell you a little bit about the basics of pulmonary hypertension in the setting of liver disease. You have to have portal hypertension to get portopulmonary hypertension. It's a serious complication of liver disease. And it occurs in about a quarter to 4% of all patients with cirrhosis, depending on the study. There's no longer an absolute contraindication to getting a liver transplant when you have this condition but we have to treat it in order to allow patients to go down that road of liver transplant. It impacts outcomes in liver transplant patients echo is recommended as a screening tool but we need the right heart catheterization to prove the hemodynamics and then allow treatment.

So as I mentioned you have to have portal hypertension to be able to have portal pulmonary hypertension. You have to have that right clinical setting. So how do we diagnose it? Well, the criteria are just the same as other forms of pulmonary arterial hypertension with the mean of more than 20 in the mean pulmonary artery pressure, a wedge of 15 or less and a PBR that's three or greater. In addition to that portal hypertension, which in Reggie was based on a clinical finding of esophageal varices, but other patients it could be the hepatic venous pressure gradient of more than five and you'll see that here.

So what about the epidemiology of this disease? It is something that's frequently missed because these patients have other medical conditions. So we know based on a series of hundred or 502 consecutive patients the incidence in those cirrhotic patients was about 2%. When patients have more advanced symptoms that they're presenting for liver transplant, it could be up to 6%. In the REVEAL registry, about 5% of the patients in that registry were portopulmonary hypertension patients and in the French registry, nearly 15%. Most of the patients we treat in the US with portopulmonary hypertension are in centers awaiting liver transplant. So there's many patients out there that are unrecognized, untreated that are not being evaluated for liver transplant.

So how does this happen? So we have multiple things that are happening in our cirrhotic patient with pulmonary hypertension. We have portosystemic shunts that cause this imbalance of the pro and anti angiogenic factors. We have systemic endotoxemia and that causes inflammation, we have this high flow state that's causing sheer stress. This all leads to endothelial dysfunction and in the right setting, with the right genetic factors and in certain patients that are more prone like females and autoimmune liver disease we then develop pulmonary vascular disease, remodeling and pulmonary hypertension. So what are some risk factors?

Well, as I told you, you have to have liver disease with portal hypertension to be able to develop this. But some other things that we need to be aware of is women are more commonly develop this condition and patients with autoimmune liver disease more commonly developed portal pulmonary hypertension. It is less common in patients with Hep C related cirrhosis. And it's important to differentiate from our idiopathic patients because these patients have poor outcomes. We need to recognize and treat as early as we can to see if we can impact that. And if you look care over a five year period, the idiopathic patients have 65% survival as compared to 40% in the portopulmonary hypertension patients.

So what are some treatments? Well, there are a few things we shouldn't do. And some that we should think about. So let's start with general measures. Anticoagulation, we don't use that routinely. Our patients are at high risk when they have liver disease they have low platelets and coagulopathy and increased risk of bleeding. We do however, treat volume overload to euvolemia and we use oxygen to make sure we maintain those saturations of 90% or better. We try to avoid things like beta blockers. These are things we use frequently in portal hypertension patients, but in patients who develop portal pulmonary hypertension, it's associated with worse outcomes worse hemodynamics and lower exercise tolerance. We try to avoid tips if at all possible because that can cause worsening right heart failure. And we don't use calcium channel blockers because it's associated with worsening portal hypertension. So things that are unique to this disease.

So what about PAH specific therapies? What do we know about that population and how our PAH therapies apply to our portopulmonary patients? Okay, we usually use our standard PAH targeted therapies based on the existing data for other PAH. In general, patients with liver disease have been excluded from most randomized clinical trials. It's important for us as clinicians to look at those patients as individuals and understand the severity of liver disease when we're choosing medications. And we need to understand what medications are cleared through the liver so we can adjust dosing. Treatments may be initiated through many different avenues, but we really recommend that patients be seen, assessed and followed in an expert pH center because these patients are very complex.

So, what do we know about specific medications? I'll tell you what we do know. A little bit but at least it gives us a hint of response. The Bosentan study that looked at a very small group of patients with Child Pugh A cirrhosis was published by Dr. Hopper looking at 11

patients and they found that there was a trend towards improvement in pulmonary pressures but statistically significant improvement in cardiac index, PBR and walk distance without sending liver disease so that gave us a hint that maybe Bosentan, an endothelial receptor antagonist may be helpful in these patients.

Now this was looked at further in patients with child B and A cirrhosis, and they found that child B patients in this study had improvement in their cardiac index and distance much like we see in other patients with pulmonary arterial hypertension without other worsening in terms of liver disease. So again, supporting possibly safe use of an endothelian receptor antagonist in this patient population. This was followed later by a Macitentan study. The PORTICO study that patients were given either Macitentan or placebo for 12 weeks and then reevaluated. And we found a 35% reduction in PBR in those patients but no other statistically significant changes in outcomes.

So what about other classes of medications? Well, we really don't have any other randomized clinical trials in PDE5 therapy or prostacyclin therapy in these patients. We extrapolate data as safely as we can. There's no data on riociguat or selexipag, there's small case series in PDE5s and prostanoids showing us in hemodynamic and exercise tolerance improvement. And we use that to help guide our management of these patients.

So, what about liver transplant? People think, oh man, that may be the solution for our portopulmonary hypertension patients. We replace the liver. We replace the nites for the portopulmonary hypertension but it's not always that easy. They are mutually interactive and outcomes in our portopulmonary hypertension patients are unpredictable. Transplant evaluation is pursued based on their liver disease. And it's not only indicated based on portopulmonary hypertension, that's different than our hepatopulmonary syndrome patients. So we need to see patients assess them, diagnose them with portopulmonary hypertension, control that disease before they may be a candidate for liver transplant.

So let's talk about that a little bit more. Okay, you have your patient like Reggie. He has severe pulmonary hypertension, high risk. We look at him, we evaluate and we treat. If our first go on our cath, the mean pressure is less than 35, we can go straight to transplant but if the mean pressure's greater than 35, we need to treat aggressively and we need to pull that pressure mean pulmonary artery pressure less than 35 or between 35 and 50 with a normal more pulmonary vascular resistance. And then we can safely look at transplant as an option but we're not out of the woods. These patients require very intensive management, pre, intra and postoperatively.

So let's go back to Reggie talk a little bit more about him. So we diagnosed him with portopulmonary hypertension. He has severe disease, very high pressures and we treat him aggressively. He was started on a PDE5 and IV epoprostenol with plans to add macitentan in the future. And we talked about liver transplant. He was aware, yes, we would like to entertain this but he was too severe in terms of his portopulmonary hypertension to safely go down that route.

So we looked, we watched, we followed, we up titrated medications, and then he underwent a repeat right, heart catheterization. And he now meets criteria. His port of pulmonary hypertension has improved, the mean pulmonary artery pressure is now down to 33 meeting that criteria with preserved cardiac output and PBR is in the normal range. So he is now eligible for liver transplant.

So where do we get this information to guide us? Well, this is a Krowka publication from 2000 from the Mayo Clinic showing us that patients in their center with mean PA pressure is less than 35 did well with liver transplant with no mortality intraoperatively. The patients who had pulmonary pressures, 35 to 50 with normal PBR also did well. Once that PVR was creeping up above 250, there was a 50% mortality. And those patients who had pressures greater than 50, a hundred percent mortality with liver transplant. So this is where we get our framework on guidance to the approach of the portopulmonary hypertension patient who would like to pursue liver transplant.

So, is it over after we get the transplant? Actually, we would love for it to be automatically improving their pressures, but it is not. As you can see here, there are two groups of patients those exposed to pulmonary arterial hypertension therapies and those who are not, both have actual is in their pulmonary vascular resistance in that three months after transplant and then improvement. In this series of 35 patients, those who survived on IV epoprostenol all weaned off their infusion therapy but about 50% remained on PAH therapies going forward. So yes, we think we can stabilize patients frequently with liver transplant when they have portopulmonary hypertension, but it is possible they will remain on PAH therapies long term.

So in summary, portal hypertension is a frequent sequel of cirrhosis and complicates the medical management of the liver transplant candidate. Portal hypertension and cirrhosis lead to an imbalance of that pro and anti-angiogenic factors. They cause systemic endotoxemia, inflammation, hyperdynamic circulation which causes sheer stress, all leading to endothelial dysfunction. And they contribute to that vaso regulatory imbalance in our patients leading to pulmonary vascular resistance increases in pulmonary hypertension. Aside from portal hypertension, the clinical manifestations of portopulmonary hypertension are very similar to group one PAH, but have worse outcomes. Screening for liver transplant candidates includes an echocardiogram. If it's abnormal, we need to onto the right heart catheterization with detailed assessments. So we can understand the hemodynamics. There are currently no approved

medications specifically for portopulmonary hypertension but we use general measures and medications for PAH including ERAs to treat and improve hemodynamics in our patients. To date, there have been limited randomized clinical trials specifically targeting the efficacy and safety of all the PAH therapies, but we need to use what we have in terms of information about those medications to treat our current patients. portopulmonary hypertension and liver transplant have interactive effects. We know portopulmonary hypertension limits liver transplant and liver transplant may indeed help the outcomes of our portopulmonary hypertension patients but we may have persistent elevated pressures after liver transplant and transiently they can even worsen. So we need to be aware of that. All liver transplant patients with a mean pulmonary artery pressure of more than 35 need treatment for their portopulmonary hypertension before they undergo surgery. Management of PAH hemodynamics improve outcomes after liver transplant. And it's been proposed that a mean PA pressure, less than 35 with normal PVR portends better prognosis short term and long term in our patients undergoing liver transplant.

So thank you so much for joining me and learning about Reggie and his course of management with his portopulmonary hypertension.