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Genetic Variants in Combined Pre-/Post-Capillary Pulmonary Hypertension

Dr. McLaughlin:
Hello, I'm Dr. Vallerie McLaughlin from the University of Michigan. And welcome to this MedEd On The Go case. Today, we're going to talk about "Genetic Variants in Combined Pre- and Post-Capillary Pulmonary Hypertension".

So let me introduce a case to you. And this case has been published in the literature and it's a really interesting case. We're going to use it as the basis of our discussion. This patient is a 68-year-old gentleman with heart failure, with reduced ejection fraction and nonischemic, nonvalvular dilated cardiomyopathy. He's of east African origin and really had no close relatives to just support him through this situation. And he was referred because he had refractory heart failure and he was to be evaluated for heart transplantation. He also had a number of other medical problems including the metabolic syndrome and was on continuous positive airway pressure for obstructive sleep apnea. He was not a prior smoker and really had no abnormalities on chest imaging. He had further evaluation, which included PFTs during which a normal diffusing of capacity of carbon monoxide was noted. And his VQ scan did not demonstrate evidence of pulmonary embolism. So as part of his evaluation, he underwent a right heart catheterization.

And here are his hemodynamics. His mean pulmonary artery pressure was 60. His wedge pressure was markedly elevated at 36, really consistent with his heart failure with reduced ejection fraction. But his pulmonary hypertension was much more severe than we'd expect. His diastolic pulmonary gradient, so between pulmonary diastolic pressure and wedge pressure was 12, which is very elevated. He also had a high right atrial pressure and a low cardiac index. Cardiac index of 1.12. So his pulmonary vascular resistance calculated to 11.5 wood units. This is markedly elevated. He also had a markedly elevated NT-proBNP. So based on these hemodynamics, we can see that he has pretty severe pulmonary hypertension with a PVR of over 11, but we can't call it group 1 because his left heart filling pressures are elevated. His wedge pressure is 36.

So we call this combined pre-and post-capillary pulmonary hypertension. So when you have severe pulmonary hypertension and there is a high wedge pressure, you can't call it group 1 because the wedge pressure is high. And so there's some characteristics that we use to say, "Is this combined pre- and post-capillary pulmonary hypertension?" And these include the DPG as well as the pulmonary vascular resistance. So if your mean pulmonary pressure is elevated and your wedge pressure is elevated, and your pulmonary vascular resistance is elevated greater than 3 wood units, we call this combined post- and pre-capillary pulmonary hypertension. Now, it's important to remember that we can see this in lots of different types of heart problems, heart failure, and this case happens to be systolic dysfunction, but I'll tell you in my practice right now, we mostly see this in patients with diastolic dysfunction or heart failure with preserved ejection fraction. So over the course of the year, his condition worsened, and obviously in terms of treatment for this patient, you have guideline-directed medical therapy for his systolic dysfunction, but what he really needs is aggressive diuretics. And so despite all of that therapy, he worsened and so a left ventricular assist device was implanted as a bridge to transplantation. This was not tolerated well by the patient. And you can imagine that in a patient with what such severe pulmonary hypertension, and such severe right ventricular failure, any sort of procedure carries with it inherent risks. So, he did have acute worsening of his pulmonary hypertension during the LVAD implantation. But unfortunately, he really wasn't a candidate for any PAH approved vasodilators because of his high left heart filling pressures, but oftentimes in such patients, when you lower the wedge pressure and you allow the lungs to see normal backfill from the left ventricles, sometimes the pulmonary hypertension improves, sometimes there's pulmonary vascular remodeling. So, he did okay with the LVAD for about a year, and then another right heart catheterization was performed.

And here you see the data from his second right heart catheterization. So I think the most important thing to note is the wedge pressure has declined from 36 to 20. So it's not normal, but that's a pretty impressive improvement. And of course, that's with the aid of the LVAD. So now that the lungs are seeing less back pressure from the left side of the heart, you see the mean pulmonary artery pressure has declined and it's now down to 39. So the diastolic pulmonary artery gradient or pulmonary artery pressure to wedge pressure gradient is now down to four, so that's really great. You can see the cardiac output has gone up and his pulmonary vascular resistance has improved, but it's still not normal. It's still elevated at 4.9. So, there's been an improvement in his hemodynamics, but his hemodynamics are not normal. However, given his severe symptoms that in the LVAD and the systolic dysfunction, at this point, he was still being considered for heart transplantation. And his pulmonary vascular resistance has improved enough to be able to consider that.

So, he did undergo heart transplantation about a year post the LVAD placement. And again, he suffered from acute right heart failure requiring temporary VA ECMO, so this was a rocky course. And you can imagine that's the case in someone who has a high pulmonary vascular resistance, cause when you do a heart transplant on this sort of a patient, you're putting a normal heart in. And so you have a right ventricle that's not used to pumping against that high pulmonary vascular resistance, that high pulmonary artery pressure. So we did have some heart failure, some right heart failure symptoms. He received standard immunosuppressives including prednisolone, mycophenolate mofetil, and cyclosporin. And clinically, he improved after his heart transplantation. However, he continued to have pulmonary hypertension. It persisted despite the heart transplant, despite the chronic immunosuppressive therapy. So a number of years later, he had a repeat echo which now shows a normal left ventricle which is great. That's the result you want from a heart transplant for LV systolic dysfunction, no valvular disease, but there was still evidence of pulmonary hypertension with septal dyskinesia and biatrial dilatation. And then, he had another right heart catheterization.

And again, he still has pulmonary hypertension. So his mean pulmonary artery pressure is 41. His wedge pressure is down to just mildly elevated at 16. He still has a high DPG and a high PVR of 4.5 wood units. However, his pulmonary hypertension is less severe. His pulmonary vascular resistance is only 4.5, got a normal cardiac index. So this patient still has pulmonary hypertension, years after his heart transplantation. And so why do you think this is? It's a really interesting case and what this group did was a genetic analysis looking for eight genes that are known to cause pulmonary hypertension. And there was a defect identified in two genes, the BMPR2 receptor and in the ENG receptor. So this patient must have some genetic predisposition to the pulmonary hypertension. And we've thought about this for a long time. We've for many, many years, have seen patients with pulmonary hypertension that was related to group 2 etiologies that was much more severe than we expected. In fact, the literature on this goes back into the 1950s and 60s, the days of mitral stenosis. When we know that there was a subgroup of patients with mitral stenosis who presented primarily with RV symptoms and severe pulmonary hypertension, high pulmonary vascular resistance, and in fact, back in the days when we were doing mitral valve surgery on these patients, there were patients who underwent lung biopsy and you look at their vessels, and they look very much like the patients who have idiopathic pulmonary arterial hypertension. And why that happens to some patients with chronically elevated left heart filling pressures and not others, we never really understood, but we always wondered if there could be some sort of a genetic basis to that. Same thing happens today with HFpEF patients. So it's really interesting that this group did this genetic series and found these defects. Maybe we should be thinking about that more often when we see patients with left heart disease and this out-of-proportion pulmonary hypertension.

So to sum up, the patients with pulmonary hypertension due to left heart disease, it's really a heterogeneous population. The vast majority of patients are going to have modest pulmonary hypertension with a normal DPG, a normal transpulmonary gradient, and a normal pulmonary vascular resistance. But every once in a while, we're going to see a patient like this who has very severe pulmonary hypertension and a high pulmonary vascular resistance. And the factors that lead to this development of the precapillary component or the disproportionate component are incompletely understood. Probably, these patients have some sort of predisposition and a genetic predisposition could be the etiology in some patients. The hemodynamic definition of the precapillary component has been debated over time. We have thought about this DPG of greater than 7. The most recent WORLD Symposium really lists PVR as the discerning factor. A PVR of greater than 3, defines that combined post- and pre-capillary disease. And perhaps we should be more cognizant of the genetic predisposition. We have all these genetic panels that we now consider in patients with idiopathic disease, but maybe we should start thinking about that more frequently in our patients with combined pre- and post-, those patients who have a much more elevated mean pulmonary pressure and pulmonary vascular resistance than we expect for their left heart disease. And as in this case we might identify some genes that might serve as the rationale for treating the underlying pulmonary hypertension.

So thank you for joining me for this case of "Combined Pre- and Post-Capillary Pulmonary Hypertension" and a discussion of the potential genetic variants that might predispose to this.