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Epidemiology and Management of Left Heart Disease Associated PH

Announcer:
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Dr. Cascino:
Thank you, Dr. Patel. I am excited to be here to talk about the epidemiology and management of left heart disease associated pulmonary hypertension. We have had the opportunity to learn about how we diagnose HFpEF. We've talked a little bit about some novel trials in heart failure in HFpEF specifically. And we'll conclude by talking about the most feared complication of HFpEF, PH-associated left heart disease - or PH associated with left heart disease. So an overview over the next 10 minutes we'll review the classification and epidemiology of PH associated with left heart disease. We'll then spend the remaining time discussing treatment strategies for PH associated with left heart disease in 2023.

Starting with the classification epidemiology. So we have to have our hemodynamic definitions. When we look at PH associated with left heart disease, we either have isolated post-capillary PH, this is when the mean PA pressure is greater than 20, or wedge is greater than 15, and our PVR is less than 2. This is by far and away the most common hemodynamic pattern that we see. We also see combined pre- and post-capillary pulmonary hypertension. This is when the mean PA pressure is greater than 20, the wedge is greater than 15, and the PVR is greater than 2. And this increase in PVR is really representative of a pulmonary vasculopathy that's forming.

When we look at the clinical definitions and the causes or etiologies of this hemodynamic pattern, we have heart failure across the spectrum of ejection fractions, heart failure preserved to reduced ejection fraction, any kind of left-sided valvular disease, and then any congenital abnormality that's associated with an elevated left atrial pressure.

Looking at the epidemiology and the prevalence of pulmonary hypertension, and this figure from the recent guidelines, the global prevalence is estimated to be 1%.

When we look at the bottom, the causes of the pulmonary hypertension, the only one that's very common is PH associated with left heart disease. It's hard to know exactly how many patients or how many people worldwide have this. If we look at a screening study of echocardiograms from Australia, this was 10,000 people who had an echo done, 9.1% had an elevated RVSP that they defined as greater than 40 mmHg. of the patients who had an elevated RVSP, 68% were thought to have group II pulmonary hypertension. This puts us at 250 cases per 100,000 people.

When we start to think about how common it is within patients who have heart failure, this is a study from Olmsted county, 244 HFpEF patients who had a screening echocardiogram, they also had hypertension patients who did not have HFpEF. Of the patients who had HFpEF, 83% had an elevated RVSP on echo. When we look at general screening studies around the world, somewhere between 50% and 80% of patients with heart failure are thought to have elevated pulmonary pressures.

And then we look at the global prevalence of heart failure worldwide. This is a recent review that was done that tried to estimate it

throughout the world, estimated 64 million people have heart failure. If we do some back-of-the-napkin calculations, we can use that conservative estimate of 50% of patients with heart failure having elevated pulmonary pressures, estimated that 30 million people worldwide have PH associated with left heart disease. This is truly an epidemic.

PH with left heart disease is really a spectrum. It starts with an elevated left atrial pressure and congestion. This is where most people fall; they have an increase in their wedge, their mean PA pressures go up in a similar amount. For some people, it's unclear why and it's unclear if there's a genetic susceptibility, if there's comorbidities, or inflammatory milieu that cause it, they get vascular remodeling. This vascular remodeling involves both the arteries and the veins. These patients have mild increases in their wedge, 15 to 20. They have mean PA pressures in their 40s to 60s. And they have PVRs rather than 1 to 2, upwards of 5, 6 and 7.

We've shown this data earlier. I think it's important to highlight one final time, or at least one final time. We know that this matters because patients do worse. Patients who develop a pulmonary vasculopathy die more. This is that same screening study from the VA with the increase in mortality as the PVR goes up. Showing that data again from Olmsted County, 244 patients with HFpEF to get a sense of how they actually do, when we look at patients with an elevated RVSP or PASP greater than 48, 50% will die within 3 years. So half the patients we see who have this condition die within 3 years currently.

So to summarize, PH with left heart disease is common and its associated increased mortality. I want to spend the remaining time talking about what treatment looks like in 2023.

So I think, of course, we have to start with the elephant in the room. There's no FDA approved PH-specific medications for the treatment of group II associated pulmonary hypertension. And this makes sense mechanistically when you look at the cause; for most patients with isolated post-capillary PH, you get this increase in left atrial pressure, it passively transmits. Pulmonary vasodilators are going to increase the pressure in the left atrium. For patients who have combined pre- and post-capillary PH who have vascular remodeling, the pulmonary vasodilators primarily address the arteries, and you still have a pulmonary vasculopathy. And the greatest fear of giving patients medications that increase cardiac output and dilate the arteries is pulmonary edema.

And so, when we look at clinical trials in this space, this is a high-level overview that just summarizes kind of what's been done. PDE5 inhibitors have had the most promising data, it's been really mixed results; we'll talk about that more shortly. endothelial receptor antagonists, multiple studies have failed to show benefit. Many studies have shown increased fluid retention. And then with prostacyclins, the first trial that was done showed, and this was done in patients with heart failure with reduced ejection fraction and IV Flolan, increased mortality.

And so looking at PDE5 inhibitors specifically, two trials that I wanted to highlight. So the first was a small-center, two-center study of 44 patients, they had to have pulmonary hypertension on echo prior to enrollment. Mean PA pressure was 53. The second is the RELAX study on the right. It's a larger trial, multicenter trial, patients had to have HFpEF, they did not have to have pulmonary hypertension, although many of them did. The trial that required pulmonary hypertension on screen echoed, did heart catheterizations, the other did not. The first trial was positive. The second trial in which patients did not have to implement hypertension was a negative trial. Intuitively, it would make sense that if patients don't have probably hypertension, the medications we use to treat it won't be of benefit. But this is the kind of mixed results we've had with PDE5s.

This is a summary table from the recent World Symposium that shows an overview of the results of many trials. I would just draw in on the last line in the table in which we really have mixed results; there's no clear benefit for our meds.

And so then the question becomes what do we do? So I think first and foremost, we need to make sure we have an accurate diagnosis of what's causing it. Shortness of breath, the symptoms of fatigue are all very, very common. We want to make sure we know what we're treating. We want to make sure that we don't miss zebras in particular. We want to make sure that we treat the underlying heart disease, this is going to be to treat valve disease by the valve guidelines. We now have heart failure therapies across the spectrum of ejection fractions. We want to make sure that we - that all our patients are on an optimal guideline-directed medical therapy. We want to make sure we use diuretics to optimize volume and lower that left atrial pressure. The best evidence that we have that lowering left atrial pressure matters is from LVAD patients. This was almost 1,600 patients in the Intermacs Registry who all received an LVAD and had PVRs measured before and after LVAD. After LVAD, we see a really nice decrease in PVRs. It went down 1.5 Wood units per month for the first 3 months. Key point, we need to lower left atrial pressure.

We want to treat comorbidities aggressively, and we'll talk about this I think shortly, things like atrial fibrillation and obesity that we just heard about, hypertension. We want to get patients involved in chronic disease management programs. Exercise training, has had some positive results. And then as Ravi hinted at, we want to make sure that we enroll patients in clinical trials.

This is a nice summary from Dr. Tedford's group about the current state of treatment for pulmonary hypertension in HFpEF. So patients

who have isolated post-capillary pulmonary hypertension, meds that should be a benefit SGLT2s for all loop diuretics as needed. Exercise and weight loss for all, may be of benefit, MRAs and ARNi's. Not of benefit are any of our pulmonary hypertension-specific medications. This tells us that if we're going to think about using any of these medications in someone who has a HFpEF phenotype, we want to make sure that we do a right heart catheterization. In patients who have combined pre- and post-capillary PH, meds that should be of benefit of the same, meds that may be of benefit of the same. We still need more studies for PDE5 inhibitors and soluble guanylate cyclase stimulators. ERAs and prostacyclins should not be used.

This here highlights the recent guidelines and the current recommendations as it relates to the treatment. We want to make sure we optimize the underlying conditions. In patients who have severe combined pre and post which they define as a PVR greater than 5 Woods units, we can take an individualized approach. And then the only class III recommendation is that drugs approved for PH are not recommended for PH associated with left heart disease. Certainly not for anyone who has isolated post-capillary pulmonary hypertension.

And so to highlight the final conclusions, PH left heart disease is common, it's associated with increased mortality, we want to treat the underlying cause, we want to optimize left atrial pressure, and we want to enroll in clinical trials.

Announcer:
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