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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Screening, Diagnosis, and Treatment of PH-ILD

Announcer:
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Dr. Moles:
So, first of all, thank you for the organizing committee for inviting me. I've been tasked with talking about screening, diagnosis, and treatment of PH-ILD. And I'm going to start by saying that pulmonary hypertension is a common and usually unrecognized complication of interstitial lung disease. The prevalence of PH associated with ILD can range anywhere from 8 to over 60%. And that prevalence is determined a lot by the severity of the underlying ILD, with more severe ILD forms of having a higher prevalence of PH. The mechanisms leading to PH in this population is poorly understood, although there may be molecular and genetic pathways that are altered. The destruction of the lung parenchyma certainly plays a role. But I think hypoxia leading to vasoconstriction is also a very significant contributor to this condition. And what we know about PH-ILD is that it is associated with a reduced functional capacity, impaired quality of life, and a greater oxygen requirement, and also increased mortality. And until recently, we did not have an evidence-proved – evidence-based medication that can alter these patient's symptoms.

So when we're talking about screening, I always want to start with a noninvasive testing first, and I think that pulmonary function test and CT of the chest are two tests that are routinely done for patients with ILD, but it can give us a pretty good idea of the physiological and morphological severity of patients with ILD. So, patients who may have mild lung disease, may have an FVC over 70% and the CT showing mild parenchymal changes, whereas patients with severe lung disease may have an FVC that is less than 70% and more extensive parenchymal changes on CT. So the question is, is there a mismatch between the severity of the lung disease and the patient's symptoms? And if there is, I would encourage you to think about pulmonary hypertension as potentially contributing to the patient's symptoms.

The other noninvasive testing that we can easily do in clinic is ordering a BNP and NT-proBNP levels. BNP levels have been – in a previous study now in the early 2000s, been linked to the presence of pulmonary hypertension in patients with chronic lung disease. And particularly, BNP levels were associated with the presence of a mean PA pressure over 35 in this population, and they also predicted 1-year mortality. The issue that I found is that a normal BNP level may not completely exclude patients with milder forms of pulmonary hypertension. And it also is confounded in patients who have other comorbidities, such as left heart disease, including heart failure, which is a very prevalent disease.

If you continue to suspect pulmonary hypertension, you should always do an echocardiogram. And as Val was mentioning before, I think that the European guidelines in 2022 did a phenomenal job I do in a very didactic figure and also explaining to us the very important concept that there is so much more to an echocardiogram than RVSP, and that includes looking at the right ventricular dilation, looking at the presence of RV pressure overload or septal flattening during systole, looking at the IVC, whether it's dilated and non-collapsible with respiration, suggesting elevated right atrial pressures. Something that I find very, very useful when I'm looking at these patients' echocardiograms is looking at RVOT Doppler notching and the acceleration time. If there is a presence of a midsystolic notch, or an exhalation time that is short, less than 105 milliseconds, this is highly suggestive that the PVR is above usually 4 to 5 Wood

units. But of course, it doesn't rule out when they're not there, though they now may be milder increasing in PVR. Right ventricular function is very important when assessing these patients. I will urge you, if you can, to look at the images and calculate right ventricular fractional area change, which speaks of a global RV function compared to TAPSE or S prime that speaks more of a regional right ventricular function and can have some nuances whether they don't accurately predict right ventricular function. Right atrial area, when the right atrium is dilated, where it's suggesting that the right-sided filling pressures have been elevated for some time. And of course, the presence of pericardial effusion which is usually a sign that pulmonary hypertension has been there for some time, and probably is quite severe.

So these are some examples that I have to show you. So on the top image, what you're seeing is a very large right ventricle that is compressing the left ventricle, which is on the right side of the image. It's pretty dysfunctional. You're seeing that those tricuspid leaflets just touching at the bare tips and, probably if I put color there, there would be a lot of tricuspid regurgitation. The right atrium is massively dilated. The interatrial septum is bowing into the left atrium, suggesting that the RA pressure is much higher than the LA pressure. On the bottom image, you will see that there is a presence of a pericardial effusion right there. And that interventricular septum is flat in both in systole and diastole, but more pronounced in diastole, you will see that the right ventricle is as the dominant chamber in the heart. This is the RVOT Doppler envelope. And what you will see is that the acceleration time is very short. The time from onset of systole to peak of systole is very short. And also, there's presence of these notch in the middle of the RVOT Doppler which is suggestive of elevated pulmonary vascular resistance.

And the other thing that I'll always encourage you to do is to try to look at the echocardiograms with your own eyes as much as you can. This is an example of a very poor TR jet signal that should not be used to calculate RVSP. And a lot of times, you know, this ended up being reported in the echocardiogram report in the conclusions, and this is something that we should try to avoid you do.

So the diagnosis of pulmonary hypertension requires a right heart catheterization. I will emphasize over and over and over that zeroing is the most critical part of a right heart catheterization. I always tell the fellas that rotate with me through the cath lab to do it yourself, because that way, you know that it's been done consistently on every patient. The other point of debate with heart catheterizations in patients with significant parenchymal disease is how to acquire that those measurements. There's a school of thought that suggests that we should measure always at end expiration. The problem is that patients with interstitial lung disease have increased variation in the intrathoracic pressures. And that can lead to an underestimation of an average pressure. In the 6th World Symposium at least suggested that we should try to use the average approach. But this is a topic that I have not seen much research about and maybe this is something that will be investigated in the near future.

So these are some of the definitions that we use to diagnose patients with ILD. Patients without pulmonary hypertensions or those who have a mean PA pressure less than 21, or a pressure within between 21 and 24 with a PVR that is below 3 Wood. ILD with mild PH is those patients who have a mean PA between 21 and 24 with a PVR over 3, or a mean PA pressure between 25 and 34. In patients with severe ILD and severe pulmonary hypertensions are those who have a mean PA pressure over 35, or a mean PA pressure over 25 with a cardiac index is less than 2, or a PVR more than 5 Wood units. And I put that PVR comment there in red, because this is not from the 6th World Symposium, which initially suggested these definitions, but rather from the European guidelines from last year, who are incentivizing us to use PVRs, a cutoff for severity of PH in ILD patients.

So I want to also put into perspective that pulmonary hypertension and parenchymal lung disease, they occur in a wide variety, across a wide variety of a spectrum. And we need to be very sure about who are the patients that we're treating. We ,in 2023, at least at this point, I think that patients whose predominant feature is emphysema and they have pulmonary hypertension, this should not be the target or the focus of our treatment efforts. And I think we should definitely focus on those patients who have fibrosis and in some degree of pulmonary vasculopathy. Patients who have ILD and they don't have PH, which are in general, the majority of patients, they're not going to be our focus. This is I think, where we should focus our effort because these are probably the underrecognized patients, those who have nonsevere PH, they represent about 20% of the patients who have ILD and they should be treated as PH-ILD patients, as I will show in a little bit. And the severe PH patients, and I will suggest those who have very advanced hemodynamics in a right ventricle, which is the dilated and dysfunctional, as I showed you before, we should be thinking that the predominant feature here is a pulmonary vascular disease and not a parenchymal lung disease. And we should be treating them a little bit different, and I'll show you in a second.

So, if I want to summarize a little bit how to screen for patient – for pulmonary hypertension in ILD patients, I'll show you this figure which I think it nicely reflects the effort of a recent consensus by 16 pulmonologists and pulmonary hypertension experts who had to sit down and, through various surveys, have to agree on what would be a reasonable way of screening these patients, there's not a lot of evidence on how we should proceed. And some of the testing that you should consider is using pulmonary function test. A very dramatically decreased DLCO should catch your attention, especially those patients who have an FVC over a DLCO ratio above 1.6,

indicating that the DLCO is disproportionately low compared to the FVC. When you order a CT scan, you can also look at right ventricular dilation, especially if you have contrast and pulmonary artery dilation as indirect signs of pulmonary hypertension. When you assess your oxygenations, those patients who have oxygen requirements should raise your suspicion. And those patients who have symptoms or a 6-minute walk test that is disproportionately low to the degree of parenchymal lung disease. And of course, looking at your BNP and NT-proBNP, all those tests should generate some degree of suspicion, whether it's high, low, or no suspicion at all. And if you have any degree of suspicion, you should always proceed to an echocardiogram, which again, by looking at all the variables that we reviewed recently, should create another degree of suspicion and lead you to a right heart catheterization.

So I have an example here I have two patients to show to you and I think in a way, they're very similar, but in some other ways, they're very different. So Patient A and Patient B have both WHO functional class III symptoms. Patient A has an FVC of 30%. And as you can see very extensive parenchymal changes, including interstitial lung disease and fibrosis. Patient B has an FVC of 75%, with more subtle changes on the CT scan. The echocardiogram, so Patient A has a more normal right ventricle, maybe mildly dilated and maybe mildly dysfunctional. But Patient B has some more significant degree of our right ventricular dilation and dysfunction, which is out of proportion to the degree of parenchymal lung disease. Patient A has a mean PA pressure of 30, a PVR of 4, and a cardiac index of 2.6. Whereas Patient B has a mean PA pressure 45, a PVR of 9, and a cardiac index of 1.9. So I think that the diagnosis that I would give each one of these patients, to Patient A, I would call this a PH-ILD. And Patient B, I will probably call this patient pulmonary arterial hypertension, because the predominant feature here is the pulmonary vascular disease.

So this is an article that I found very interesting and thought-provoking, and also kind of increased my awareness about how important it is to diagnose and treat pulmonary hypertension patients with interstitial lung disease. This retrospective analysis of 317 patients from 12 centers in Europe. And they took patients with chronic lung disease that were classified as having no pulmonary hypertension, borderline pulmonary hypertension, mild to moderate pulmonary hypertension, or severe pulmonary hypertension. And on the left, you're going to see patients with COPD. You will see that most patients, which are these three bars here, have a relatively good overall survival. But this line, which has a very dramatically different prognosis, and these are the patients who have severe pulmonary hypertension. Whereas when you look at patients on the right graph, you will see that the overall survival is very different in ILD patients compared to COPD. And this blue line here, which are the patients who have a better prognosis, are those who have no pulmonary hypertension at all. Compared to even patients who have borderline pulmonary hypertension, their survival is dramatically affected and impacted by pulmonary vascular disease.

So the treatment of pulmonary hypertension associated with ILD should include treating the ILD and treating the pulmonary hypertension. And treating the ILD, you should always think about assessing and correcting low oxygenation, you should use non-invasive ventilation if that's needed, enrollment in pulmonary rehabilitation, and now with the advancement of anti-fibrotic medications that should we also highly considered. And when you treat pulmonary hypertension, I would suggest that we should try to use inhaled treprostinil in all the patients that meet criteria for the use of it. And I will even venture to say that we should consider the use of phosphodiesterase inhibitors in this group.

You may all be familiar with the data from the INCREASE trial, which was phase 3 clinical trial assessing inhaled treprostinil versus placebo within 16 weeks. And the primary endpoint was the change in 6-minute walk distance. And as you can see on the graph, the curve here in red is the group that was on inhaled treprostinil. There was a very early increase in the 6-minute walk distance that was sustained over those 16 weeks, compared to placebo patients who very early on started to have a decline in functional capacity.

This is the data of the secondary endpoints, and both secondary endpoints were met. The change in NT-proBNP levels at 16 week was significantly lower in the PH-ILD group that was treated with inhaled treprostinil. And the occurrence of a clinical worsening event which included hospitalizations, decrease in 6-minute walk distance by 15%. Death or lung transplantation was also significantly lower in patients with who were receiving inhaled treprostinil.

So what I find more interesting is that in the data from the open-label extension portion of INCREASE, there's a really nice graph about the occurrence of a worsening – clinical worsening event. And I'll show you here in green, you have patients who were initially on inhaled treprostinil, and then continued during the open-label extension period, on increased inhaled treprostinil. The initial slope is very steep, but very early on, it kind of stabilizes and it's a little bit more flat. Whereas patients who were on placebo initially, that slope is very steep and continued to be very steep. And it starts to get a little bit more flat, only when they transition to inhaled treprostinil.

So sildenafil, or no sildenafil? That is the question. My argument is that we should be using these medications when clinically indicated, especially in those who have a higher pulmonary vascular resistance, who have a higher degree of pulmonary hypertension. This is data from the STEP-IPF trial. That was a randomized, double-blinded clinical trial using sildenafil versus placebo in 180 patients who have ILD. Please note that there was no inclusion criteria for the presence of pulmonary hypertension. And what they showed is that there was no difference in the primary endpoint between placebo and sildenafil. But there was an improvement in secondary endpoints such

as dyspnea and quality of life, and there was no signal of harm. So I think that being this is a medication that probably doesn't have a deleterious effect in ILD patients, we should be considering using it in selected patients.

On the contrary, I think we should be very careful when prescribing riociguat in patients who have PH-ILD, since this medication in a phase 2 clinical trial shows significant harm and increased mortality in patients who were receiving real sick work compared to placebo.

So conclusions, PH is a serious comorbidity complicating interstitial lung disease and it's associated with worsened prognosis. The screening of PH in patients with ILD is very reasonable, and should include testing such as pulmonary function tests, CT scans, oxygenation, and 6-minute walk distance, BNP or NT-proBNP levels, and an echocardiogram. A right heart catheterization is needed to make the right diagnosis and risk stratify these patients. And inhaled treprostinil is the only current FDA approved medication and we should consider using it in patients who have pulmonary hypertension with ILD. I will also add that methodical follow-up is crucial in understanding how these patients progress and how we titrate the medications, which is a very crucial part of the treatment of these patients.

So, thank you very much.

Announcer:
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