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Is It PAH or PH Due to Lung Disease and/or Chronic Hypoxia?

Announcer:
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Dr. Channick:
Thank you very much. It’s a pleasure to be joining you today, and joining my good friend and colleague, Val McLaughlin. We’ve worked together on quite a few of the programs, and we hope you’ll enjoy this one. It’s obviously an interesting topic, as we advanced through pulmonary hypertension, we’re learning more and more about various forms, and so we’ll have a couple interesting cases that will, I think, raise some interesting questions today. So these are our objectives. We’re going to talk a little bit on some background about hemodynamics, and diagnosis, and then we’ll get into a couple cases, go into some treatment issues, and then go from there.

So, this is sort of by way of review. Of course, when we think about pulmonary hypertension, we – the critical point before we treat it is to properly diagnose it. And these classifications, or groups of diagnoses are something that were developed many years ago, and moved on. I participated in the development of the classification system, and I think it works. It’s certainly not perfect, but I think the concept of trying to group pulmonary hypertension into PAH, or what you might think of as more of an intrinsic pulmonary arteriopathy, and you can see the various conditions, on the right, that fall into that category. First is pulmonary hypertension due to another condition, specifically lung disease, left heart disease or thromboembolic disease. And then the usual miscellaneous. So, this – these are clinical classifications, and they’re useful, I – to clinicians, they certainly have their limits, and one of the challenges – and we’ll talk about this in a little while – is, for instance, you know, in a patient who has lung disease and pulmonary hypertension, when can we actually call this what we call “Group 3” pulmonary hypertension, or when is it more, let’s say, “Group 1.” And that’s, you know, I think a topic that we talk about a lot, and I think it’s a very important one, because obviously it relates to how we treat these patients. And again, we’ll get back to that, and one of the cases that I’ll show will, I think, underscore some of those challenges with classifying patients that we have.

And don’t forget that, you know, you need to think about pulmonary hypertension before diagnosing it, and we show data like this, you know, I’ve been doing it even longer than Val has, and showing data that there’s this delay in diagnosis of up to two, and even two and a half years, and so this is a problem, I think, that still exists, and before, you know, we go on with treatment, you need to think about the diagnosis. And we hit that home time and time again. Symptoms are nonspecific, and can be often classified as more common conditions – asthma, other heart diseases, etc. And the diagnostic process really is one of ruling out various conditions. And so the diagnostic algorithm, that you’re probably familiar with, has been pretty well worked out, and it really, again, is to basically check off the boxes. Do they have thromboembolic disease? Do they have significant respiratory or pulmonary disease? Do they have left-sided heart disease? Before you arrive at a diagnosis of PAH, or Group 1 pulmonary hypertension. Not going to go into the, you know, the details or the entire evaluation, except to say that, you know, patients who have pulmonary hypertension can prevent – present with a variety of symptoms, and so, you know, you look at the list of these relatively nonspecific symptoms, and you can see that, you know, many

different conditions share these features. Physical examination, we still stress, and I still use my stethoscope (laughs), but you hopefully can see signs of pulmonary hypertension, and in more severe cases, of right heart failure. Hemodynamic definitions are something worth spending a minute on, because these have really changed a bit, and as Val knows since she runs the Health Around the World Symposium that's every five years or so, that a lot of what was discussed – one of the highlights of this last one – was this re-definition, if you will, of pulmonary hypertension to a mean pulmonary pressure of greater than 20, as opposed to 25, which is how it used to be. Now that, you know, was the result of a lot of discussion and a lot of review of evidence, historical data, what is the normal pulmonary artery pressure. But the consensus was that a mean pulmonary artery pressure, in fact in normal, should average about 12-14 mm of mercury, and so two standard deviations above that would be 20. However, you know, it was felt that we needed to have a little bit more than just a mean pressure over 20, to say you actually have pulmonary vascular disease, i.e. precapillary pulmonary hypertension. And that's where the other criteria, of a wedge less than 16 and a PVR of at least 3 Wood units, comes into play. And then, if you look down the list there at postcapillary PH – also a mean of greater than 20 with a wedge of greater than 15 and a PVR that's normal, or less than 3 – you can now combine pre and postcapillary pulmonary hypertension. Then you can have, what they call, you know, a tripartite definition, and that – I think, in other words, saying that is that you really need to have all of these criteria to say that you have PAH. So, the concept here is that we're not just talking about a number here, we're talking about a disease or a disorder, and that's, I think, the message in this classifica – in this hemodynamic definition of having to have all three of those components present.

Dr. McLaughlin:
Hey Rich, do you think that change in definition has resulted in much of a change to your practice?

Dr. Channick:
It – probably not, surprisingly, and I think, you know, there is even some data that if you use that definition, specifically the PVR/3 part of it, you know, you're not going to add that many patients. And you know, there is a – to be honest, a fear that we would be diagnosing all these people that have this very mild elevation in PA pressure of 21, or something like that, and we'd potentially be overtreating patients, and whatnot. I haven't really found that to be the case. How about you?

Dr. McLaughlin:
Yeah, I agree. I haven't at all, and in fact, we reviewed our historic database on the scleroderma patients, which I think is our greatest opportunity to find early disease. And, I can't remember the exact numbers, but out of the right heart caths we've done on the scleroderma patients over the past, you know, X number of years, there was maybe one or two additional patients that met that criteria, that didn't previously get categorized as PAH.

Dr. Channick:
Yeah. Yeah, that's in our experience as well, and so I think, you know, this is accepted in the community and I think it is important, and again, the concept is that you're really trying to diagnose a disease, not a number. We don't have time to get into the details of all the evaluations that are done. I think these are, you know, all familiar with you. There's nothing super fancy about the evaluation of pulmonary hypertension, except that you need to do it. And we still feel that ventilation profusion scan remains the best test, to exclude chronic thromboembolic pulmonary hypertension. In other words, the normal or near normal VQ scan excludes the diagnosis of CTEPH. An abnormal one, on the other hand, doesn't make the diagnosis of CTEPH. Of course, you need confirmatory testing, but we're talking about excluding it. Echocardiography, which is, you know, almost always done, because that's often the first test, but you know, I think we're starting to appreciate the use of echocardiography in ways way beyond, let's say just estimating the PA pressure, but to really get some detailed evaluations of right heart function, as well as obviously looking for left heart disease. And I think that we're, you know, learning more and advancing more with echocardiography as I've said, as the non-cardiologists.

Dr. McLaughlin:
So, as the non-pulmonologist, Rich, let me ask you a question about the VQ scan. Many institutions are really having a hard time doing the V part of it, in the era of COVID. Can you tell folks how you approach that when you, perhaps, just have the Q part of it?

Dr. Channick:
Yeah, no, that's exac – that's a very reasonable issue, and a very topical issue, becau – exactly for the reasons you said. And a lot of hospitals are just not doing ventilation scans. We've been able to do okay with that. I think my general experience is if the chest imaging is normal, and really doesn't show significant pulmonary disease, the ventilation scan probably doesn't add that much to the study. On the other hand, if they do have, let's say, extensive emphysema, or fibrosis, the same defect, especially smaller defects in the profusion scan, you don't know if that's due to the underlying lung disease or not, so that can be a bit of an issue, but I think if you couple a CT angiogram along with a perfusion scan, for most patients, it's okay. All right.

Dr. McLaughlin:
Yeah, I agree. I mean, you know, we've been able to do them, you know, just with COVID testing in advance, and all that stuff, but you

know, when patients have them done locally, there have been some challenges, so you need to kind of customize it, exactly as you said.

Dr. Channick:
Exactly. Okay. And then, we get pulmonary function testing, of course, looking for lung disease. So, the right heart catheterization, we still feel is critical, and as I tell patients, we would never make a diagnosis of pulmonary hypertension without confirmation with right heart catheterization. It helps us confirm a diagnosis, helps determine the cause of the PH by looking at left-sided or wedge pressure, helps us determine severity of pulmonary hypertension by measuring things like right atrial pressure, cardiac index, which are the best hemodynamic indications of seve – indicators of severity. And then we can look for other, you know, intracardiac lesions, left-to-right shunt – those kind of things.

So, on the right there is the laundry list, and what I always say, and you know, my own cast and you know, what I always teach is that, you know, doing the procedure is the easy part. It's knowing what to do with the information – interpreting the wave form, knowing what's an accurate wedge pressure, for instance, is really critical. And I mean, Val, when you – I mean, I do my own, and I know you've still got your – you're probably too busy now, and so you have other people doing it… (Laughter) for you. But I mean, do you – what do you tell people, you know, like who say… I mean, do you have like one particular person you recommend, you know, one person? I mean, I – again, I'm not – I don't want to put down our – my cardiology friends, but you know, some cardiologists are very busy, and, you know, getting good hemodynamics isn't necessarily a high priority, let's say.

Dr. McLaughlin:
Yeah, so, I mean, I'm a cardiologist, so I can say that, I guess, and be less defensive than you, Rich. I mean, most cardiologists who spend their time in the cath lab are, you know, interested in other things. They're interested in coronaries, or they're interested in structural heart, or what have you. So, you know, in many institutions, the art of a good right heart cath is – has been lost. So I think it's a really valid point, and I can't tell you how many outside caths I get that there's no cardiac output, or they, you know, the, you know, PA pressure tracing changes a little bit, but it's not quite wedged, and you get a wedge of 35 reported, in a 22-year-old woman with no other medical history, right? So these things all happen. So, you know, I think that trying to control as much as you can is important, so you're right, Rich. I used to do them. I no longer do my own right heart caths, but we have one other person in our PH group who tends to do most of our right heart caths. We have one interventional cardiologist that works with us in the CTEPH area, who also does some, and then we have kind of a heart failure doc with an interest in hemodynamics, who kind of is our back-up in the event that our other PH faculty is not available, on vacation, on service, what have you. So we try to control it. I think one other thing that we do is, you know, when we order our first right heart cath, we always prep it for an LVEDP as well, and so if the wedge pressure isn't good, if they can't get a good tracing, then, you know, then that's an option, too, to directly measure the left ventricular and diastolic pressure. But having someone who's interested is really important, and I think the other thing is, for that person that kind of knows the patient, right? You know, like if it's someone who we go into the lab, expecting or having a high likelihood of diastolic heart failure, we, you know, we think of that as a little bit different than, you know, that 21-year-old who's got a family history, that we think is, you know, most certainly idio – or, heritable disease. And so, those things can help you make decisions about fluid challenges and that sort of stuff as well.

Dr. Channick:
Yeah, yeah, those are really great points. Okay, so we do the cath, and we may do vasodilator testing for certain patients, to help us define vasoactivity. There's then a number of other miscellaneous blood tests we get, and most of these are looking for some of these associated conditions, in PAH patients. Is there evidence for a connective tissue disease, HIV, liver – you know, portopulmonary hypertension, thyroid disorders which are commonly associated with PAH, hemoglobinopathy, even? So, we do get, you know, a variety of blood tests as part of the workup, and we don't want to exclude that. So again, very brief of a review of the diagnosis, so the basic diagnosis. And now we'll get into a little bit of detail with case one, and I'll turn it over to Val, to take it from there.

Dr. McLaughlin:
Yeah, thanks Rich. I think, if you don't mind, Rich, I'm going to just address one question while the discussion about hemodynamics is fresh in our minds.

Dr. Channick:
Sure.

Dr. McLaughlin:
And our dear friend and colleague, Carrie Trout (15:23) asked if a PVR of three is too high. And I think it's a really good question, right? Because just how you said, Rich, that, you know, the mean pulmonary pressure is 14, two standard deviations is 20. They pulled 25 out of the sky way back when, because it seemed like you needed to have a little bit more than, you know, upper normal to be called this disease. It's kind of the same thing with pulmonary vascular resistance, and, you know, honestly, if I had a pulmonary vascular

resistance of 2.9, I probably would be a little nervous. I do think this is something that's going to be addressed in the next World Symposium. I think it may even be addressed currently, as they're writing the next iteration of the ERS/ESC guidelines. And I personally will not be surprised if we see that drop to two. What about you, Rich?

Dr. Channick:
Yeah, again, it's, you know, with any number, cutoffs, you know, are not perfect, and, you know, this is a continuum, and so, yeah. I tend to agree. I mean, does that mean I would treat everybody who had a PVR of 2.9? No. I mean, if I have a 75-year-old patient, who's, you know, has multiple comorbidities, and is not particularly limited by pulmonary hypertension and they have 2.9, I'm not going to necessarily put them on PAH therapy, even if the definition changes. So I think definitions don't, you know, get you off the hook from actually thinking about each patient individually, and when you're making these kinds of decisions.

Dr. McLaughlin:
That's a really great point. Okay, so let me tell you about this case. This is a 49-year-old woman with scleroderma, and I first met her in May of 2015, because she had an abnormal echocardiogram. You know, in retrospect, she said that she had progressive dyspnea over the past six months, and at the point where I met her, she was able to do some simple activities of daily living, some light household chores, without dyspnea, but she needed to kind of pace herself walking longer distances, such as walk – when she was going – doing her weekly grocery shopping, or up a flight of stairs. She was short of breath at the top of a flight of stairs. She had some lightheadedness with very extreme exertion, but denied syncope. And really, the rest of her cardiac review of systems was negative.

This is her physical exam. 5'2", 160 pounds. Her blood pressure was kind of on the high end of normal. She was a little tachycardic when I first met her, but she was saturating just fine. On physical examination, her carotid upstrokes were reduced. Her JBP was a little bit elevated, at 10, and her lungs were clear. Her cardiac exam was really pathognomonic for pulmonary hypertension. She had this palpable right ventricular heave, this loud, booming P2 that you heard well, even at the apex, and she had a tricuspid regurgitant murmur.

Her abdomen was soft. She didn't have lower extremity edema, and she had some of the other peripheral findings of scleroderma, including sclerodactyly and telangiectasia.

So the echo that was eventually done that led her to my office demonstrated severe right ventricular enlargement, moderate right ventricular dysfunction, severe right atrial enlargement, normal EF. The septum was flat in the short axis and RV pressure overload pattern. She had moderate tricuspid regurgitation and then her estimated RVSP was 87. We completed the evaluation. We did a hall walk, during which she walked 372 meters, which is low, and you know, particularly in light of the predicted, for her young age, and her Borg score was not high, and she saturated well throughout. She had normal perfusion. Her PFT showed relatively normal volumes and flows, but her diffused incapacity was 48%, which is something that we typically see in scleroderma patients as they start to develop pulmonary hypertension. Her HIV was negative, her LFTs were normal, and her BNP was elevated at 247. So we took her to the cath lab, and did a right heart catheterization on her. Her right atrial pressure was 11. Her pulmonary artery pressure was forty – 92/42, with a mean of 62. And that mean declined to 51 with inhaled nitric oxide, so a bit of a reduction – a reduction, in fact, of over ten millimeters of mercury, but not to our goal of less than 40, and I think it's better if it's even lower than that to consider her a responder to nitric oxide, and a candidate for calcium channel blockers. Her left heart-filling pressures were normal. Her wedge was nine. Her blood pressure was a little bit lower there, as you can see. We tend to do cardiac outputs by both thermodilution and by an assumed Fick, and so sometimes there is a bit of a variation there. Her thermodilution cardiac output was 4.6, with an index of 2.7, and her pulmonary vascular resistance calculated to 14.8 Wood units.

So we have a woman with scleroderma, six months of dyspnea, functional Class 3, hall walk in the high 300's, moderate RV dysfunction on echo and PVR of 14.8, kind of to sum it up. Rich, how worried are you about this patient?

Dr. Channick:
I'm worried. I mean, she, you know, we can sort of – and I think we'll get into, sort of how we risk-stratify patients, for determining the degree of severity. But just looking at everything you've told me, and especially the hemodynamics, I mean, you have a scleroderma patient, so by – you know, they're going to – we're more worried about them, in a lot of ways. She's got a somewhat elevated right atrial pressure. She's got a cardiac index, you know, at least by Fick that puts her sort of in the low intermediate, or, you know, intermediate to severe hemodynamics, with the index, you know, two to 2.5 or so, and a very high pulmonary vascular resistance. So, you know, those are concerning numbers to me, that she, you know, is in tough shape.

Dr. McLaughlin:
Yeah. They're concerning to me, too, and I was really worried, and I – you know, whenever we have our new patients, whenever we talk to them after their first right heart catheterization, we really talk to them about all the therapies. We want to introduce everything even if we're not going to start with everything. But she was sick enough that I was really worried about her, and tried to talk to her in great

length about parenteral prostacyclin therapy. And she was one of those people that, you know, was just overwhelmed by it. She just couldn't absorb it at that point in time, and asked if there was possibly anything else. And so, we made the decision to start dual oral therapy, with ERA and PDE5 inhibitor, with close follow-up, and I think this is something that is really, really important. We'll talk about risk stratification. Whatever decision you make following the patient and reassessing them is really very important. So we did that, and she actually perked up nicely. Her symptoms improved. When I saw her about four months later, she really claimed to be about 90% back to normal. I characterized her as functional Class 2. Her hall walk was better – it's now over that magic 440 number, at 450. She is nicely saturating. Her BNP is better, but not normal, at 125. Her echo, to me, was still a little bit worrisome. Her right ventricle looked a little bit better, but it was still enlarged with moderate right ventricular dysfunction and evidence of right ventricular pressure overload. So, I wasn't happy with her. I didn't think she was a fool. I honestly didn't think she was to the point where she needed a parenteral prostacyclin – she had improved enough. But I was still really worried about that right ventricle, and so we had a conversation about all of the prostacyclin pathway agents, and she started therapy on an IP receptor agonist, in addition to her ERA and PDE5 inhibitor. And she did well. We recath patients within the first year, and here you can see her hemodynamics. Her right atrial pressure is down to nine. Her mean pulmonary artery pressure is down to 39. Her cardiac index is now at about three and a half – same by both methods, actually, and her PVR declines from 14.8 to 4.8. And that right heart cath was done in January of '16, and I still follow this woman, and she is still doing well, minimal symptoms, hall walk probably high-500s, low-600s now. And interestingly, her RV function's absolutely normal on her echo.

Dr. Channick:
Hm.

Dr. McLaughlin:
So, she continues to do really well on triple oral therapy. So, a nice success story, but there's a lot there to kind of talk about, and discuss risk assessment with. So, this is the table from the 2015 ERS/ESC guidelines on risk assessment. On the far left, you see the parameters that we believe are important determinants of prognosis – loosely based on historical or observational registries. And so, the things we know are bad are right heart failure, we all sense rapid progression of symptoms as bad, although there's very little data on that.

Syncope is a very poor prognostic indicator, really signifies inadequate cerebral perfusion. You can't mount a cardiac output to do exertion. Functional class, as crude as it is, as crude as it is, is highly prognostic in all of the studies and registries in pulmonary arterial hypertension, and the thing with six-minute hall walks – you know, we all say, gosh that six-minute hall walk is so crude, not very sensitive. But it's highly prognostic. Some institutions use a bit more cardiopulmonary exercise testing and peak CO2 and VE/VCO2 are important prognostic indicators on that. Over the recent, I don't know, maybe decade or so, we've learned a great amount about natriuretic peptides – very, very highly prognostic. They really reflect the stress that the right ventricle is under, in pulmonary arterial hypertension. I think probably the most disappointing thing on this table is imaging, and the truth of the matter is, it's really difficult to quantitate RV function, that, you know, there's different standards. You know, most of our patients have echo's at various places, and there's not a uniform reporting system for right ventricular function on echo. Cardiac MR is great, but, you know, they don't get done very frequently. There's just not that much data in all the registries, upon which tables like this are built, that have precise RV function data. So it's really not in there, although to me, a picture is worth a thousand words, and going to look at that echo is something that's really important, and something I do every single time that my patient has an echo. And then the hemodynamics that are important – really not what the pulmonary artery pressure is. Really, the hemodynamics that reflect function of the right ventricle, so high right atrial pressure, low cardiac index, low SCO2 output are prognostic indicators. And so, you can see this table comes up with cut points, that they consider to be low-risk, which is a less than 5% 12-month mortality, intermediate risk which is a 5-10% one-year mortality, and high risk, which is a greater than 10% one-year mortality.

So there've been a lot of risk scores that have been developed over the years. We certainly don't have time to review them all, but I want to highlight some. One is the REVEAL Risk Calculator, which was based on a U.S. registry of well over 2,000 patients, that included all types of PAH, not just the idiopathic types, and it came out with this calculator that was then modified. REVEAL 2.0 is this modified version, and this includes both modifiable and non-modifiable variables. So, Dr. Channick mentioned earlier, he's worried about this patient because she has scleroderma. So we know patients with scleroderma don't do as well. We know patients with portal hypertension don't do as well. We know men don't do as well. We know older people don't do as well. So, those non-modifiable variables are included in the REVEAL Risk Score, which is highly prognostic.

The REVEAL 2 Lite Calculator is something that was more recently published, and this is really honed down to six variables, which are all modifiable. It's taken the non-modifiable variables out. They're given a weighted score based on their prognosis, or their prognostic impact.

And honestly, this is something that you can do every time you see a patient in clinic. We do everything on the REVEAL 2 Lite Calculator every time we see a patient in clinic. We talk to them, we assess their functional class, we examine them, we get their vital signs, we draw blood, we have a BNP, we have renal function, we get a six-minute hall walk. So you can really do everything here, at the time of a clinic visit, and again, it's highly prognostic.

There are, of course, other methods as well, based on the ERS/ESC table, based on the French. So, the key with risk stratification is it doesn't matter which technique you use, you just have to do it every time that you see a patient. And remember, the goal is getting the patient to the low-risk status, really trying to have them in the green zone, or having a low REVEAL score, or having a high proportion of the French criteria. And as much as there are these different ways to calculate risk, they really have many of these things in common. They all look at biomarkers, at clinical assessment, some sort of exercise assessment, hemodynamics. The only one that really includes the echo is the REVEAL score has a – the full REVEAL has the pericardial effusion in it. So that's a little bit about PAH, but you know, sometimes that overlaps with lung disease, especially in the scleroderma patient, like I presented. Rich, don't you think a lot of the scleroderma patients, even if you think their PAH has some interstitial lung disease as well. Sometimes it's difficult to tease those out.

Dr. Channick:
Yeah, that's the challenge. I mean, this is – that's the classic, you know, case where, you know, there's several potential mechanisms for developing pulmonary hypertension, as you say, including, you know, primary arteriopathy, PAH, lung disease, and you know, in fact, they often have restrictive heart disease from scleroderma involvement. So, it gets complicated, and you really – we really need to think about some of the nuances for how you classify these patients, because that's going to, you know, affect how they respond to therapy, to be honest. And I can, you know, get to that a little bit further. There's a lot of interest in that. I'm a pulmonologist, so specific interest in lung disease, and its role in pulmonary hypertension is, I think, evolving. I think if we were to look at it, and I'll show you a case in a minute, but, you know, if we're talking about basic concepts, I think, you know, at the extremes it's pretty easy. If a patient has, you know, and this is shown here in this nice algorithm – visual algorithm. So obviously, you're doing the usual workup for pulmonary hypertension. Let's say this algorithm, and then you're trying to separate out, let's say, Group 1 vs 3. So the patient has some degree of lung disease, whether it's COPD, pulmonary fibrosis, etc. And then you can – you look at the severity, so the concept here, of course, is that, you know, the less severe the lung disease is, the less likely it is to cause pulmonary hypertension. Now that's not always true, I can tell you, and there are certain lung diseases that are more highly associated with more severe PH – things like sarcoidosis, or things like Langerhans cell histiocytosis. Those conditions may cause more pulmonary hypertension, or, you know, connective tissue disease associated.

But in general, if a patient has relatively mild lung disease, and here you use these cutoffs of FEV1 of greater than 60%, or an FVC of greater than 70%. And relatively modest degree of parenchymal changes. It's probably more appropriate to put that patient into Group 1. As things get worse with the lungs, then obviously, you're thinking changes, and so if you have a patient who has poor pulmonary function – and I should tell you that, and Val knows this very well, since she also helped design a lot of the inclusion criteria for the big trials – is that if you have FVC less than 70%, in some cases 60%, you know, you would not have qualified for a PAH trial. So if we want to use that as a definition of non-PAH, pulmonary hypertension, that may explain some of the rationale. But, the concept, of course, is as parenchymal disease is more extensive, the likelihood that, you know, with PAH, is less and the likelihood that it's PH due to lung disease is more. And that's why this pretty simple algorithm says Group 3 PH if you have these more severe changes, and at that point, you want to look at the severity of the pulmonary hypertension. So, if you have a patient that has only modest degree of PH, with extensive lung disease, then this algorithm would simply say you would never consider that patient for PAH therapy. On the other hand, if they also have severe PH, then each case is different, and certainly, you know, we go through this a lot. We have a patient with pretty severe PH, right ventricular failure, but also has fairly extensive lung disease. Then we have to try to dissect out, or flesh out, whether it's the lung disease for instance, or the right heart issues, that's leading to this patient's symptoms. And that's, you know, can be a challenge at times, but this is, you know, what we're – what we're very interested in.

Dr. McLaughlin:
Hey Rich, can I ask a question?

Dr. Channick:
Yeah.

Dr. McLaughlin:
On that – so, you know, so at what point are PFTs enough versus needing a CT? I mean, there are some different lung disease where you can get fooled by the PFTs that have, you know, relatively normal volumes and flows, but there is something going on, and you know, how do you incorporate the CT into that decision-making that you just reviewed?

Dr. Channick:

Yeah, the CT is critical. The CT is really, in my thinking, is really important, and you said it exactly right, Val, that, you know, and there's a condition called – pulmonologists are familiar with – called CPFE, or combined pulmonary fibrosis and emphysema, in which you may have relatively well-preserved volumes and flows because you have both restrictive and obstructive processes. The – but when you look at the CT, you'll see extensive emphysema, in the upper lobes typically, and fibrotic changes in the lower lobes, from you know, a variety of causes.

Those patients will often have severe hypoxemia, and very low DLCO, and that raises another, kind of, general teaching point I make, is that, you know, in patients with lung disease, usually the degree of PH correlates with the gas exchange, and patients who have more severe PH lung disease tend to be patients who are more hypoxic, have very low diffusing capacities. And you may – you're exactly right. The CPFE may be one of those reasons. And then there's other things. Even the sarcoid patients, Langerhans cell patients, you know, may have this mixed obstructive/restrictive pattern.

So, very good question. So then we have, you know, you still need the full workup, for patients who have, you know, suspected lung disease, looking for other things. So you can also have thromboembolic disease. Very briefly, I want to show you this patient here. This is a 58-year-old gentleman, some comorbidity. He's getting short of breath over nine months. Also had a cough, mild chest pain. Had a detailed history, that we take with our lung disease patients looking for exposures, or other risk factors for PH. He's pretty symptomatic, but, you know, a block on flat ground, lifting packages, and he also has a SAT monitor at home, and he notes that he's desaturating to 83%, with relatively modest exertion. So, when we look at him he's, you know, borderline O2 SATs on room air at rest. He's got pretty clear basilar crackles, some evidence for PH on cardiac exam, and pretty prominent clubbing in both upper and lower extremity – hands and feet. No peripheral edema is noted. So, I think, you know, we kind of already – obviously suspected this guy was going to have interstitial lung disease. We got an echo, and it did show some degree of right ventricular enlargement, but relatively mild, and an RVSP estimated in the 56 range. You can see here his FEV1 was relatively well-preserved. His FVC was quite reduced, at 59%, so he has an elevated FEV1 FVC ratio, and a very low DLCO of 48%. Just to, you know, complete it, we have imaging here, and Val, I want to ask you to interpret the chest CT, although it – you probably are smart enough.

Dr. McLaughlin:
I just assessed as normal, believe me, I (laughter) few of these in my day.

Dr. Channick:
I'm sure you have. Yes. You're a – just like I'm an honorary cardiologist, you're an honorary pulmonologist. And…

Dr. Mclaughlin:
Well, I don't know about that, but…

Dr. Channick:
And so yes, one can see obviously extensive fibrotic lung disease is what we see. There's obvious honeycombing, more in the lower lobes and the periphery. This is a classic UIP pattern, where you have this peripheral traction bronchiectasis, where he dilated airways (38:30) as well as honeycombing seen in the lungs, which is typical of a UIP, usually interstitial pneumonitis. The patient didn't have any other cause, so we felt pretty confident that this was a patient who likely had, you know, idiopathic pulmonary fibrosis. Other work-up was negative for, you know, again, associated causes of interstitial lung disease, and it is all work-up that we do. Very briefly, he was cathed, and it showed you this hemodynamic – Val, I mean, what do you think of these – these numbers for this particular guy?

Dr. McLaughlin:
Yeah, and so he's got, I would say, moderate pulmonary hypertension. His mean pulmonary refresher is 38. You know, I guess, like I think of up to the mid-30's as something that you expect for many, kind of Group 3 patients. You know, much higher than that, I, you know, I don't like to use the term "out of proportion" but like you worry that there's something else going on, as cardiac output is preserved, which, you know, in my experience, we see frequently in patients with parenchymal lung disease or Group 3 PH, and his PVR is modestly elevated. So, yeah, I think this is a pretty straightforward Group 3 PH patient.

Dr. Channick:
Yeah. Yeah, I think – I absolutely agree. Right on. Yeah. And, you know, the question, you know, obviously is what are we going to do about this guy? But, you know, we say as you exactly said – extensive lung disease, moderate degree of PH, no obvious overt RV failure. This is likely a Group 3 patient, in our opinion, and we agree. We still have a question of how much shortness of breath is due to the PH versus the lung disease? And, as you are well aware, you know, treatment options are very limited for Group 3 PH. There's – and this is more recently – one approved therapy for Group 3 PH that was recently shown in a large study to be beneficial for some patients with Group 3 PH – only not all patients. But I think, you know…

Dr. McLaughlin:

Yeah, I think it's really important to temper the expectations when we have this conversation, because just like you said, you know, the – they have dyspnea due to both, right? And PH therapies are not likely to have the dyspnea that's related to the underlying – or not to help the dyspnea related to the underlying fibrotic disease. So, I, you know, we definitely treat a lot of these patients, but I think it's really important to temper the expectations.

Dr. Channick:
Yeah. Yeah, absolutely agree. I'd like to finish this saying, you know, we can look at overall things that help us – may help separate Group 1 versus Group PH, and, you know, a lot of it comes down to severity of disease, and the echo, I think, underscores that. So it still remains a challenge separating these patients, but you know, again, that's what PH experts are about, and understanding some of the nuances. So, I'm going to turn it over to Val, who will just kind of give us a little bit of an overview, run-through quickly of, you know, where we are at with therapy, overall for PH.

Dr. McLaughlin:
Yeah, thanks, Rich. So – and that was a really interesting case and, you know, we are all seeing a lot of these sorts of patients right now. So, medical therapies for PAH have really evolved over the past couple of decades. You know, when Rich and I started doing this, I'm not even going to tell you how many years ago, like we were privileged to be around when the first therapy got approved, and we had that only one therapy for a long time. And now there are many others – 14 FDA-approved therapies for Group 1 PAH in the United States. And they fall into the mechanism of action based on these three different pathways. On the left, you see the endothelin pathway – patients with PAH make too much endothelin 1, which works on the smooth muscle cells, the endothelin A and B receptors, that you can see on the bottom – smooth muscle cells, to induce basal constriction, and chronically this causes cellular proliferation and you can block these receptors with oral agents called endothelin receptor antagonists. In the middle, you see the nitric oxide pathway, where the deficiency is the inadequate production of nitric oxide synthase, which is required to convert L-arginine to nitric oxide, which works via the cyclic GM key pathway, to result in vasorelaxation and inhibition of cellular proliferation. And we can attack this pathway two ways. We can block PDE5 inhibitors and inhibit the degradation of SGC, or we can directly stimulate SGC – so two oral agents to work on that pathway. And then on the far right, you see the prostacyclin pathway, the very first pathway we were able to target the deficiency here is in prostacyclin synthase, which is required to convert prostacyclin I2 to arachodo – or, convert arachidonic acid to prostacyclin I2, which then works via the cyclic AMP pathway. And we have a number of prostacyclin analogs that can be given intravenously, subcutaneously, intermittent inhaled, and orally. And we also have an IP receptor agonist that directly binds to that IP receptor, to stimulate the cyclic AMP pathway. So, really thrilled to have agents to work in all of these different mechanisms, but what I always say when I show a slide like this is this is just the tip of the iceberg. There are many other pathologic pathways in pulmonary hypertension, and in fact, we're in a very rich trial period now, where we have agents – novel agents that look at other pathways, that are being studied. So, really a thorough overview of all of the agents is beyond what we can do. This is a listing of them – three commercially available: endothelin receptor antagonist, two TD5 inhibitors, and one SGC stimulator that work on the nitric oxide pathway, a number of prostacyclin analogs and one prostacyclin receptor agonist.

The ERAs have been studied in clinical trials, that have demonstrated improvements in hall walk. One – macitentan – was an M&M trial, long-term benefit. Ambrisentan – hall walk, and also was an important part of the ENVISION trial. These are all effective agents that do need some monitoring because of the REMS particularly associated with a pregnancy risk and LFT monitoring for bosentan. These are the PDE5 inhibitors and SGC, so both sildenafil and tadalafil have indications for PAH. Both have been demonstrated to improve hall walk, as has riociguat. Riociguat also has REMS and monitoring because it is pregnancy category X, and REMS monitoring is important for these agents. It's an important part of the FDA approval. There are some steps you need to go through to enroll in the REMS program, and these have a limited distribution because of that.

A number of prostacyclin pathway agents – epoprostenol the very first therapy we had. Treprostinil, which can be delivered four different ways: IV, subcu, inhaled and orally. Iloprost is another oral – I'm sorry, another inhaled prostacyclin analog, which we don't use very much in the U.S., and it's given more frequently than inhaled Treprostinil, which is already given four times a day, so it's not as much used here. And then the receptor agonist – the IP receptor agonist, selexipag. And, you know, our treatment strategy has really evolved over the recent decades, from that of the sequential looking back to that of an upfront combination therapy, the induction therapy, shall we say. And it's important to follow these patients. These are some consensus statements from the ACC/AHA, that kind of gives some guidelines on how frequently you should follow patients and what tests you should do, and it varies based on how sick the patient is. I think it's been a really rich year for some publications, with respect to risk assessment, in PAH. This is from a French paper that looked at initial therapy strategies, so initial triple combination therapy had better improvements in risk status. The bar on the right, you can see the change in risk status was much more dramatic in patients who received triple combination therapy, than either mono or dual therapy, despite the fact that those patients were sicker to start out with.

But risk is really what the algorithm is based on, and so, the salient points of the algorithm here are making the correct diagnosis, which

is what Rich went through very nicely, making the initial treatment decision based on risk, and using an objective score to do that. But probably the most important part of this algorithm is that last part, is reassessing the patient, no matter what treatment decision you made to start out with, reassessing the patient and seeing if the patient got to the low-risk status. And if they did, that's great. You just continue to reassess them. And if they didn't, you need to do something else, whether it's add another therapy or escalate to a more potent prostacyclin. You need to try to get that patient into the low-risk status.

And while we're all very excited about upfront combination therapy, which is what the majority of patients get – upfront oral combination therapy, which is what the majority of patients get after correct diagnosis, you know, it doesn't work for everyone. I mean, Rich, you remember all the enthusiasm everyone had about the AMBITION trial – very, very important trial – but I really found this Italian paper interesting, because what you see – let's just look at the left. It's using the ERS/ESC, kind of composite score, and on the bottom, you see low, intermediate, or high at the time of diagnosis. And in the colors, you see where they got at the time of first follow-up. So you can see, only less than half of the patients who had intermediate risk status at baseline got to low risk with dual combination therapy, with ERA/PDE5. And none of the patients at high risk got to low risk, with dual combination therapy with PDE5. Now, not to say it's not appropriate to try it, in intermediate-risk patients at the time of diagnosis, but the key is following them, because not everyone is going to have that response that you want them to have. Did you – what did you think about this paper, Rich?

Dr. Channick:
Yeah, no, absolutely. It's the, you know, 100% correct. I mean, statistics is one thing from a study, showing significant benefit of the approach, but, you know, it just underscores the need for the individual assessment and reassessment, and the importance of serial risk scores, not just initial risk scores.

Dr. McLaughlin:
Yeah. And on the right, you see the data using the real risk calculator, and it's essentially the same thing. You know, half of the patients at intermediate risk get to low risk, and none of the patients at high risk get to low risk.

You know, lung transplant, you know, back in the day, we thought of medical therapy as a bridge to transplant, but we do so well with medical therapy these days, that we don't do as many transplants. It's now reserved, at least in the U.S. for patients who fail maximal medical therapy, and Rich, being a pulmonologist, you could speak better to the challenges of, you know, trading one disease for another, with transplant, but I could probably count the number of my patients who get transplanted each year on one, maybe two hands.

Dr. Channick:
Mm-hmm. Yeah, no, absolutely. It's still a challenge because, you know, the timing of it, and I think we agree, if a patient's doing well on medical therapy for PAH, and they're low risk, we wouldn't transplant them. And we have many patients, and you have many, many patients who've been on intravenous prostacyclin for, in some cases, decades, who are doing great, right? And…

Dr. McLaughlin:
Yeah.

Dr. Channick:
They never needed a lung transplant. They're used to the therapy, etc. Yeah.

Dr. McLaughlin:
Yeah. And we spend so much time talking about all of our fancy new treatments, that sometimes we don't emphasize the supportive therapies enough. And some patients need oxygen, if they're hypoxic, that causes further pulmonary vasoconstriction, so we don't want them to be hypoxic, and you have to think about supplementing oxygen, not just at rest, but with exercise, and altitude. A lot of our patients need diuretics, right? You want to move that right ventricle to a better place on the Frank-Starling curve, so many of them need diuretics. And I think exercise is really important. Once they're on therapy, getting them into a pulmonary rehab program, and getting them conditioned and exercising regularly is important. Of course, it's a very difficult conversation to have, that, you know, the risks of pregnancy in a woman who's been diagnosed with PAH, but it's a critical one to have, and you know, it's a devastating disease, for both the patient and their family, so psychologic support and comforting are always very important. And patient support groups help with that a lot.

Dr. Channick:
Yeah, absolutely.

Dr. McLaughlin:
And, you know, we always say, kind of, it takes a village, right? Like it takes a whole group of folks to take care of our PAH patients, and I say frequently, I could not do what I do without my nursing staff. Like they are really the backbone of our center, and there's

collaboration. Rich and I are making jokes with each other about the cardiology/pulmonary thing, but they're both – they're very important as well as many other subspecialists that you see here.

Dr. Channick:
Thanks, Val. Yep.

Dr. McLaughlin:
Yeah.

Dr. Channick:
Great overview of treatments, and where we're at. So, just a way to include, and I'll get your final remarks as well, you know, it all starts with understanding risk factors, signs and symptoms, making a proper diagnosis, understanding some of the nuances of the classification system. For instance, as it relates to lung versus, you know, PA – Group 1 versus Group 3.

Val talked about modes of therapy, and this emphasis on risk – getting patients to low risk, which we think is very, very important, both because patients want to feel better, and it's also prognostic as well. And using these tools that are widely available now at every follow-up visit – I think a very consistent, systematic approach, and that – the concept of combination therapy, aggressive combination therapy, add-on therapies, you know, is getting more and more attraction, and really is currently the standard of care. So, with that, that concludes our presentation. Any last words, Val?

Dr. McLaughlin:
No, Rich, I always enjoy working with you. I think this is a conundrum that we get into a lot. Like I face it all the time, particularly in the scleroderma patients. You know, are they Group 1? Are they Group 3? Are they some of both? So, it's a really important topic.

Dr. Channick:
Great. Well thanks everybody, for joining, and have a great rest of your day.

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