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Pulmonary Hypertension: Diagnosis, Management, and Updates – Chairperson's Perspective

Announcer:
Welcome to CME on ReachMD. This activity, titled "Pulmonary Hypertension: Diagnosis, Management, and Updates – Chairperson's Perspective" is provided by Medtelligence.

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Dr. McLaughlin:
Well, hello, everyone. I'm Dr. Vallerie McLaughlin, director of the Pulmonary Hypertension Program at the University of Michigan, and I had the privilege of participating in a symposium at the AHA with two good friends and colleagues, Dr. Mark Humbert from Paris and Dr. Ryan Tedford from the Medical University of South Carolina. And I'm here to summarize a little bit about what we discussed in that symposium, Pulmonary Hypertension: Diagnosis, Management, and Updates.

So Dr. Humbert started by talking about the hemodynamic definition of pulmonary hypertension. And this has been refined at the 2022 ESC/ERS guidelines. So a mean pulmonary pressure of greater than 20 by right heart catheterization defines pulmonary hypertension. To be considered precapillary pulmonary hypertension, one also has to have a wedge pressure of less than 15 or equal to 15 and a pulmonary vascular resistance of greater than 2 Wood units. So that's Group 1 pulmonary arterial hypertension, although sometimes Groups 3, 4, and 5 can have those criteria as well. And then, isolated postcapillary pulmonary hypertension is when the left heart filling pressures are high, a wedge pressure of greater than 15, and a PVR of less than 2 with a mean pulmonary artery pressure of greater than 20. Combined pre and post includes a wedge pressure that's high, a mean PA pressure that's high, and a pulmonary vascular resistance of greater than 2 Wood units as well.

He then went on to talk a little bit about the clinical classification of pulmonary hypertension, and this was recently updated at the World Symposium in Barcelona in the summer of 2024. So Group 1 is pulmonary arterial hypertension. There were some refinements made with respect to long-term calcium channel blockers, but other than that, this group was left largely unchanged. We have idiopathic, heritable, associated with drugs and toxins, and then associated with a number of other disorders, the most common of which is connective tissue diseases.

There were significant changes made to Group 2 left heart disease-associated PAH and Group 3 lung disease/hypoxemia-related PH, really, to get a bit more specific on the diseases that cause those particular types of pulmonary hypertension.

Dr. Humbert then moved on to discuss the diagnostic algorithm, which was refined and simplified to start with, really, the beginning of the evaluation, the most common symptoms, and then a stepwise evaluation that ultimately concludes with the right heart catheterization. And this diagnostic algorithm also leaves opportunity for, really, a fast track for patients who we're really concerned about.

Now, one of the things that leads to the suspicion is the echocardiogram, and he talked about what we see on echocardiogram, not just the elevated RVSP, but other two-dimensional and Doppler findings consistent with pulmonary hypertension. And he showed this figure

from the ESC/ERS guidelines, which I really love. And I think this is very important to take into consideration as we talk about echocardiograms and screening.

He then spoke a little bit about risk assessment and treatment goals, and this was a whole task force at the World Symposium. And there are a number of different risk calculators which use many of the same variables. Kind of the big 3 are functional class, hall-walk, and biomarkers, but this often needs to be complemented with other information, including right heart catheterization data and imaging data. So he really emphasized that there is a lot of opportunities to do a better job at risk assessment.

We then moved on to Dr. Tedford, and I think it was really important to have Dr. Tedford's talk at the AHA because, really, Group 2 pulmonary hypertension is the most common type of pulmonary hypertension that we see. So differentiating Group 1 from Group 2 is something that's very important in clinical practice.

He talked about 3 steps of evaluating for Group 2. The first step being the overlapping clinical phenotypes, and this is really important because left heart disease is common, and it may also be present in other disorders, for example, chronic thromboembolic pulmonary hypertension or in the connective tissue disease patients or patients with interstitial lung disease who tend to be older and have a lot of risk factors.

He then discussed the pretest probability of the left heart phenotype, and this is something that we're all seeing more and more commonly. There are a number of comorbidities that lead to a higher likelihood of diastolic dysfunction. Things like obesity, hypertension, coronary disease, diabetes, atrial fibrillation, and we need to think about those as we see a patient and develop a pretest probability for left heart disease.

And then the last step is actually the hemodynamic assessment. And if the wedge pressure is high and we thought the patient likely had Group 2 disease, that makes sense, but if the wedge pressure is high and we had a low suspicion for Group 2 disease, then maybe it's not a good wedge pressure and we need to examine it further.

The other thing that's really important is that if the wedge pressure is less than 15, but we had a high likelihood of suspicion, again, maybe that wedge pressure isn't accurate. Or maybe the patient has been really well diuresed, or maybe the heart cath was done at 4:00 PM and they've been NPO all day and we should consider provocative testing in that situation. And the most common type of provocative testing is giving a fluid load in the cath lab.

Now, we talk about this wedge pressure like it's a Holy Grail, like there's this magic number of 15 and above that it's one thing and below that it's another thing. But Dr. Tedford also really highlighted this concept of the zone of uncertainty of the wedge pressure. There are so many things to consider, and perhaps even between that range of 12 to 18, it's not just what the wedge pressure is, it's what that patient's clinical scenario is. So, again, if someone has a wedge pressure of 13 but they have a lot of risk factors for diastolic dysfunction, I'm still worried about Group 2, and that's the sort of patient who should get a fluid challenge.

He also talked a lot about the issues with measuring a wedge pressure, making sure that you're zeroed, making sure you're looking at the right point in the respiratory cycle, making sure it's a good tracing, making sure that the pulmonary artery is occluded the way we want, and if the waveform isn't great, then maybe that should be checked with a wedge saturation. There are all these details that need to be evaluated when we are measuring hemodynamics. So he gave a really lovely talk on right heart catheterization.

We then concluded with a talk that I did on treatment of PAH, and it's a very exciting time. We've had a number of therapies for pulmonary hypertension for decades, which really focus on 3 pathways: the endothelin pathway, the nitric oxide pathway and the prostacyclin pathway. Many therapies that target those pathways, which we've talked about many times. But we now have a new pathway, the activin pathway, and this pathway represents the imbalance between the anti-proliferative effects of BMPR2, which is downregulated in pulmonary hypertension, and the pro-proliferative effects of the activin ActRIIA/B, which is pro-proliferative. So those are out of balance in pulmonary hypertension. And the new ASIs bind that activin and essentially reduce the activity of the activin and thereby improve the balance and the activity of BMPR2 that helps rebalance that pro-proliferative and anti-proliferative signaling.

Then we talked about the new treatment algorithm that was decided upon at the 7th World Symposium. And I think it's very important to highlight a number of factors in the treatment algorithm. Really, that this applies to Group 1 PAH, that is primarily idiopathic, heritable, drug and toxin-induced, and CTD-related, because that is the population that these clinical trials were performed in. It also emphasizes that almost all of those trials included patients with a PVR of greater than 3, so the old hemodynamic criteria, and some of them even required a PVR of greater than 5. The treatment algorithm emphasizes risk assessment. The first step is whether the patient's at high risk or not high risk, and those at very high risk should get combination therapy that includes a parenteral prostacyclin, and those who are at not high risk should get combination therapy with an ERA and PDE5. But it really allows for some judgment. There may be some patients that are not high risk technically when you do a risk score on them, but have some features that really concern us, like RV

dysfunction or low cardiac index, and those patients might be treated with aggressive triple therapy as well.

And then the next step is repeat risk assessment after 3 to 4 months and continuing to repeat the risk assessment. And the second risk assessment is done using the 4-strata approach, and there are a number of options depending on where the patient falls.

I just want to spend a couple minutes talking about some of the newer clinical trial data that has been available since the last World Symposium. This study, the A DUE study, looked at a combination tablet of macitentan and tadalafil in a single pill compared to either macitentan alone or tadalafil alone and demonstrated really impressive improvements in PVR and 6-minute hall walk, and certainly this is an added convenience for patients to reduce their pill burden and copays and the like. So I think that is a very important study to discuss.

And then I just want to show the figure from the World Symposium looking at the add-on trials. So if a patient gets their initial therapy and then you do the next step of risk assessment, what are the options? And there are a number of options. And here's some of the clinical trial data behind that. This table really points out that the GRIPHON and STELLAR studies were studies that took place in patients that were on a number of background therapies, whereas some of the other prostacyclin pathway agents were studied in patients on just one background therapy.

To highlight that, this is the primary endpoint from the GRIPHON study, looking at selexipag on top of background therapy. Again, a high proportion of patients on combination therapy, demonstrating improvement in first morbidity and mortality event in patients randomized to selexipag versus placebo.

And then I also want to highlight the new agent sotatercept, the activin signaling inhibitor. Again, the patients in this study were a highly pretreated patient population, 35% were on double therapy, 61% were on triple therapy, so that really reflects the patient population that we see today. And the patients who were randomized to the activin signaling inhibitor sotatercept had an improvement of about 40 meters in the primary endpoint of 6-minute hallwalk, and this drug also improved 8 of 9 of the secondary endpoints, including the very important time to clinical worsening. So less events over the course of the trial.

There have also been subsequent analyses, post hoc analyses, in more detail of the hemodynamic effects and the impacts on echo from the STELLAR trial published in a separate paper. And again, very impressive effects, about a reduction of 14 mm in mean pulmonary artery pressure, improvement in pulmonary artery compliance, improvement in NT-ProBNP, improvement in echo parameters of right ventricular function as well. So very reassuring that this drug has significant impact on the cardiopulmonary system.

So as we look at the treatment algorithm, we make that first choice, either combination therapy, ERA, PDE5, or, in the high-risk patients, triple therapy, and then we reassess. The data would suggest that if you're at low risk with that first treatment option, that your prognosis is good and you can continue that. If you're at intermediate-low risk, there are a number of options, including the activin signaling inhibitor and oral and inhaled prostacyclin pathway agents, and potentially consider switching the PDE5 to an SGC.

If you're at intermediate-high risk, then we're still worried about you. If you're not already on a parenteral prostacyclin, that should be considered, or one can think about the activin signaling inhibitor. And if you're still at high risk, then we really need to do something more urgently. Again, if you're not on a parenteral prostacyclin, that should be an option, or the activin signaling inhibitor. And if you have persistent intermediate-high or high risk despite all of the therapies that we have available, then, really, lung transplant evaluation is the only option.

So I wanted to just sum up by thanking Drs. Humbert and Tedford. They both did wonderful jobs at presenting this very important topic at the AHA and it was a pleasure for me to summarize that for you today as well. Thank you.

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