Hemodynamic Definitions and Updated Classification—Impact on Clinical Practice: A Conversation With Erika Berman Rosenzweig and Nicholas Hill

In this special discussion for PHA, Guest Editor Erika Berman Rosenzweig, MD, sat down with Nicholas Hill, MD, Chief of the Pulmonary, Critical Care and Sleep Division and Professor of Medicine at Tufts University School of Medicine, to cover hemodynamic definitions, updated classification, and implications for clinical practice.

Dr Berman Rosenzweig: As you know, this is part of the *Advances in Pulmonary Hypertension* issue which is a behind-the-scenes look at the World Symposium on Pulmonary Hypertension (WSPH) 2018. We're lucky to have you here to discuss the issues that were raised in the proceedings on hemodynamics, updates and definitions, and the WSPH classification system.

First of all, Nick, thank you for joining us today

Dr Hill: It's my pleasure, Erika.

Dr Berman Rosenzweig: Why don't we kick off with some of the most lively discussions we heard at the symposium—one of which focused on the discussions around proposing a new hemodynamic definition of pulmonary hypertension (PH)? It was suggested that the hemodynamic definition of PH change from a pulmonary arterial (PA) pressure ≥ 25 mm Hg to > 20 mm Hg. I wanted to get your thoughts on that and how you think it might impact the field going forward.

Dr Hill: Well, I did give a presentation at the American Thoracic Society annual meeting in May and I gave some background and also raised some of the issues surrounding this. As I'm sure most people in the field know, this is something that had been percolating for a while. Just by way of very brief background, the ≥ 25 definition dates back to the first World Health Organization meeting of the world symposium back in 1973. At that time, they made some quite prescient observations.

One being that it's unusual to see mean PA pressures over 15 mm Hg in a normal population, so that over 20 mm Hg is really abnormal. They admittedly, at the time, somewhat arbitrarily chose 25 mm Hg or above for a couple of reasons. One being that they were concerned there might be overdiagnosis and overtreatment with a lower threshold.

At the next meeting of the World Symposium in 1998, the panel agreed that 25 mm Hg and over should stay as the definition. They also came up with this idea that if you increase your mean PA pressure over 30 mm Hg during exercise, that was "exercise-induced" PH, which was subsequently thrown out in 2008 when it became clearer that no one could agree on an exercise definition anymore. As people age, many have mean PA pressures that go over 30 who are otherwise normal. So that definition of exercise-induced PH has not been reinstituted.

In 2013, there was a fair amount of discussion about the fact that if you look at a large population of patients, as was done by Gábor Kovács in his analysis and published in *European Respiratory Journal* in 2009, where he looked at something like 50 studies dating back to 1947 on normals who had undergone right heart catheterization—there were over 1,100 patients—the overall average mean PA pressure was 14 mm Hg. The standard deviation was 3, meaning that 2 standard deviations get you up to 20 mm Hg. Therefore, greater than 20 mm Hg would be abnormal in a statistical sense. At the time, they talked about the 21- to 24-mm Hg group as a borderline range. That almost became an official designation, but the committee backed off from that and left it as more of a discussion point. More recently, in the 2018 meeting the committee re-examining the definition decided that there was enough evidence that had accrued to say that pressures between 21 to 24 mm Hg were abnormal and that they should be included as part of the PH definition.

The evidence they were talking about came from a number of studies that showed that if you have PA pressures between 21 and 24 mm Hg, although mean PA pressures of 21 to 24 mm Hg are associated with better outcomes than pressures of 25 or over, they aren't as good as pressures of 20 and below. Some scleroderma studies also showed that the people in this borderline range were more apt to develop PH over a period of years. Of course, the caveat is that this is all based on association and not causality. We don't really know what caused those deaths. Nonetheless, the decision was made to change the definition of PH to a mean PA pressure over 20 mm Hg.

Dr Berman Rosenzweig: I think that's a great background of how this has evolved over the years. The back and forth speaks to the fact that the evidence is not completely clear on what this proposed change in definition means and how it might impact the future of PH. For example, what does it mean for patients who, let's say, have a pressure in a lower range that may have been followed or evaluated for PH and not treated? Does it mean we can go forth and treat patients in that range now, even though our drug studies have not been focused on that group? What are your thoughts on that?

Dr Hill: Virtually all of our therapeutic trials to date have used the definition of 25 mm Hg or over for enrollment. We really don't know what the effect of treatment is on this previously referred

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to as "borderline" group. I don't think we're going to get too many insurance companies jumping up and down enthusiastically about paying for therapy in this group either.

The definitions committee used the term, "We propose" this new definition. I have had insurers turn patients down who have borderline pressures and exercise-induced PH (with mean PA pressure >50 mm Hg during exercise) because of the lack of evidence to support therapy. I don't think they'll cover now just because the World Symposium has proposed a change in the definition. Unless we get some evidence, I don't think we're going to be able to use these drugs if we have to rely on getting insurance to cover in this borderline range.

Dr Berman Rosenzweig: Right. As you highlighted, this is just a proposed definition, but I do think it sends the PH community a call to action to start to study these patients and perhaps monitor them a little more closely.

Dr Hill: Absolutely.

Dr Berman Rosenzweig: Would you recommend following them more closely perhaps than we did in the past?

Dr Hill: Yes, absolutely. If I had been on the committee, I would have considered proposing a change, but would have designated the 21 to 24 mm Hg range an official "borderline PH" group and encouraged more study before proposing it as a new definition. Some of the prior studies have been based on echocardiographic findings. We need invasive hemodynamics and it would be reasonable to contemplate doing drug trials targeting these patients now.

Although I think if I were running a pharma company making PH drugs, I'd be reluctant to jump into this pool without careful forethought because the likelihood that they're going to respond like people with greater PH is low in my estimation. I think that because pressures in this "borderline" group aren't as high, it will take more patients over more time to show an effect, which means a lot of expense. Also, this is not a huge population in most PH registries.

Dr Berman Rosenzweig: I think those are excellent points. I think it does raise the question of how will we best study this group of patients if there may not be the commitment by industry to study them for those reasons you just stated. Perhaps we have to just look at prevention of disease progression, but that takes, as you said, a lot of patience and a lot of time to look at. It will be interesting to see how this pans out. What about with respect to other groups, non–Group 1? Is this affecting the other groups like chronic thromboembolic PH, for example?

Dr Hill: Yes. Well, I think I'd first like to bring up a problem I see with all of this that I raised at the symposium. That's what I refer to as the pulmonary vascular resistance (PVR) problem. When they made this proposal about the mean PA pressure, they also proposed that the PVR of 3 Wood units be retained.

The PVR of 3 had been tacked on to the definition in the past, that in addition to having a mean PA pressure over 24, 25 or over, the PVR, if you wanted to have PH, should be over 3 Wood units or 240 $dyn \cdot s^{-1} \cdot cm^{-5}$. We had accepted that, but it really applied only to the patients in Groups 1 and 4, but it had not previously been applied to Groups 2 or 3.

The committee in 2018 decided to retain the PVR of 3 for a couple of reasons. One, it had been established in previous World Symposia, and two, it had been used as a cutoff for eligibility in assessing patients for heart transplant or surgical repair of intracardiac shunts.

The problem is that the rationale for using the mean PA pressure of greater than 20 was based on statistics and epidemiology, which they considered as a scientific approach. Well, if they had taken the same approach to PVR, they would have come up with a very different number. It turns out that in Kovács' study, if you looked at the PVRs and all these normals, the overall mean was 70 dynes/s per cm^{-5} and the standard deviation was 30.

If you convert convert that to Wood units, the overall mean was 0.9 Wood unit. If you add 2 standard deviations to 0.9, you get 1.7 Wood units. That might have made more sense based on the same scientific rationale to select this cutoff rather than 3. If you select 3 as your cutoff, what you're doing is basically saying that either you have a very large transpulmonary gradient—thinking about how we calculate a PVR, the transpulmonary gradient divided by the cardiac output—or you had to have a very small cardiac output. There aren't a lot of patients whose mean PA pressures fall in the borderline range who meet these criteria. There was a pro/con debate on the new definition in the April 4, 2019 issue of the *European Respiratory Journal*. The authors making the Con argument surveyed PH patients at registries at their centers and could identify only 1%-2% of over 3000 patients who had mean PA pressures between 21 and 24 and met the PVR >3 definition. By applying this PVR, you basically don't have a population to study.

Dr Berman Rosenzweig: Obviously, that's a big issue if we really want to study this issue—who are we talking about exactly with the definition as it is? I guess if the PVR was not included, that would be different.

Dr Hill: Right. That would have been more sensible. Even if they had wanted to include PVR and had selected 1.7 based on the scientific rationale they used for PA pressure, it would include substantially more patients. I don't see why you would want to set a PVR limit on the "borderline" group because what you really want to do is cast a broad net to study the borderline group.

We could put a registry together to track them and get more rich data on them and then you learn more. It's worth mentioning that the Pulmonary Vascular Disease Phenomics (PVDOMICS) network to which we both belong decided to include a "comparator" group consisting of subjects who fit into different PH groups based on clinical criteria, but whose mean PA pressures were <25 mm Hg. These patients have been carefully phenotyped and are undergoing sophisticated omics analyses, and findings on this group, that contains mainly patients

with "borderline" pressures, should be very informative. In retrospect, it was fortuitous that we decided to retain this group.

Dr Berman Rosenzweig: Right. I think that will be fascinating to see how that shakes out, and certainly timely as well. Well, it sounds like this proposed definition, if you will, has raised as many questions as answers. I think it just opens the dialogue as you say to perhaps refine it, and figure out better ways to study these patients so that we know more in terms of what this all means with respect to outcomes.

Dr Hill: I think it's healthy to raise questions like this and generate a lot of discussion and controversy. It makes people think. A lot of people think and you get good creative thoughts. In the end, it will move the field forward, but it certainly needs to be refined. As I said before, I think it would have made more sense just to say, "Let's make this borderline category official and let's study it rather than redefine just yet."

Dr Berman Rosenzweig: Now, that's a great overview of the history of how this evolved and, hopefully, the future and how we can further study, learn, and maybe apply this proposed definition of PH. With that, I'm just going to shift to the second part of this conversation, which is yet another topic that I would say was a hot topic at the WSPH meetings and that always is, which is the update of the diagnostic group classification system for PH.

We know that's been a work in progress from the very beginning, when you either had primary or secondary PH. Now, we've got a 5-group classification system, which keeps getting tweaked. I was hoping we could talk about some of the changes from the most recent meeting. I guess the first one that I thought was very interesting, of course, is that there's now another specific subgroup under Group 1. That is for patients who are vasoreactive. That is a move that I'd like your opinion about in terms of what you think of this proposed change and that as a separate entity within Group 1 PH?

Dr Hill: Well, we've been aware of this group for a long time. Of course, we've routinely been doing vasoreactive testing. We also have the insurance companies who generally want us to sign off on some attestation that we've considered using calcium channel blockers first rather than move on to these much more expensive drugs.

It's been out there for a long time. It's a subgroup that we have sought ever since the work of Stuart Rich, MD, almost 20 years ago on calcium channel blockers. The Rich criteria defined it as a decrease in mean PA pressure and in PVR ≥20%. Of course, in 2005, Olivier Sitbon et al. came up with the definition we currently use for a positive acute vasodilator response, characterized by a drop in mean PA pressure by ≥10 mm Hg or ≥20%, reaching a mean PA pressure of <40 mm Hg and increased/unchanged cardiac output.

That predicted that about 50% of people meeting those criteria who were put on calcium channel blockers would manifest a long-term response. We all have a few of these patients in our practices. They do very well, a lot of them, in the long term. I think it's important to identify it as a separate subgroup because I think there are going to be characteristics of this subpopulation that will enlighten us if we study it as a separate subgroup.

Once again, I think the work of the PVDOMICS is relevant here because we also are interested in looking at this separately, as you know. I would predict that there are going to be genetic differences among these vasoreactive patients compared to nonvasoreactive and also probably other omic differences that will enable us to practice more precision medicine and have more effective targeted therapies for them.

Dr Berman Rosenzweig: Yes, I agree. I think this kind of robustly vasoreactive phenotype is almost a different disease entity. I also agree with putting it as a separate group. We have the opportunity to really hone in and learn a lot about these patients and why they respond the way they do. I'm kind of excited about that, that it's got its own designation. I guess in a similar vein because I often find, I don't know if you've had the same experience, that some folks—particularly the more junior folks—have never seen one of these patients in their practice. And even though someone's vasoreactive, they might not start a calcium channel blocker because somehow they think maybe one of the newer agents will be even more effective. I know you've seen robust responders. You said that, and I've had the same experience, they can go on for many years with calcium channel blockers alone.

Dr Hill: I had one of them die last year, but he had been on treatment for 40 years.

Dr Berman Rosenzweig: Wow, that's impressive.

Dr Hill: I have another calcium channel blocker responder who has been stable on CCB therapy for more than 20 years. She's a physician whom I met when she was in her residency and was having trouble keeping up with her friends climbing Rainier. That was kind of the canary in the mine experience where we picked her up early. She had moderate PAH initially, but has had normal estimated PASP by echo since starting calcium channel blockers and walks 700 m in 6 minutes.

That's the kind of response you really want. You don't see it all the time. Like I said, about half of the people who meet the definition for positive response have a favorable long-term response. I also think that we are going to rethink the definition because we not only have the calcium channel blocker responders, but we have superresponders to other drugs. I think each of these kinds of hyperresponders are of interest and are going to enlighten us about the pathophysiology of the disease.

Dr Berman Rosenzweig: That's a great point. There are these different phenotypes for drug responsiveness and probably the pathways. I think just having this as a separate group raises a lot of really interesting, good questions. I hope that we'll learn more from this group. I think we will.

Another change, which I thought was interesting, was the addition to—or I would say sort of a refinement in terms of how we look at patients with pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH). It really is a spectrum of disease with pulmonary arterial hypertension (PAH). There were good conversations about this especially now that we have an associated genetic mutation as a potential clinical marker and better imaging techniques. What are your thoughts in terms of that change?

Dr Hill: Well, I think we've been moving in this direction for a while because pathologists were the ones who first clued us in. It's hard to draw clear distinctions between those who are diagnosed with PVOD and the people who were diagnosed with PCH. A lot of these patients manifest features of both. Now that we have the *EIF2AK4* gene and it is occurring in both, I think it's much clearer that they really are different parts of the spectrum of the same condition. Anyway, I think we're just scratching the surface now. It was like the discovery of the BMPR2 receptor where we're just now starting to see treatments that are actually going after that mechanism entering the clinical space. I think we're now going to see a lot of work on what is the mechanism that links this gene with this pathology. I think it'll be very exciting to see this evolve.

Dr Berman Rosenzweig: Again, I think our radiologists have gotten better at imaging in terms of noninvasive ways to diagnose these patients as well. Nobody wants to do a lung biopsy for a patient with severe PH and potentially PVOD anymore. It is interesting because sometimes you'll treat a patient with what you think is PAH and then, obviously, they don't do well when you start titrating up your intravenous prostanoid. They might do well for a little while, a honeymoon period.

Dr Hill: I found that I'm really not very good at making a preclinical diagnosis of PVOD or PCH. Many patients don't manifest the typical features you read about in textbooks; what looks like left heart failure with septal lines with a normal-sized heart and with significant PH, but a lot of people don't manifest that.

We've all seen people who really don't have much on their CT scan imaging, who we would pass on having PVOD. And we see people who have nonspecific abnormalities but are behaving like they have PVOD in terms of getting into trouble when we start drugs. When we get the path eventually, it's not PVOD. I think having a genetic marker is going to help us a lot.

Dr Berman Rosenzweig: I agree. I think including leading to potentially new therapies?

Dr Hill: Yes.

Dr Berman Rosenzweig: Getting turnaround on a genetic marker is not always the quickest. If we can put it into clinical practice because the treatment pathways are so different where you might do early transplantation for these patients, I think that would be an amazing advance. I want to ask one final question because, again, I know the role that you have in the omics program—

Dr Hill: We could go on and talk about it for a long time. [chuckles]

Dr Berman Rosenzweig: Forever, I know. This is my last question. Maybe to put you on the spot a little bit. With regard to the classification system, there are these 5 groups. We're learning from our omics experience that not everybody fits nicely into one group. Can you maybe just speak for a minute about what we've observed in terms of mixed phenotypes and the complexity of what we're seeing?

Dr Hill: This, of course, is something we knew about. Your work along with Evelyn Horn has illustrated this for the field. It comes out loud and clear in the PVDOMICS findings, which is that about a little more than a third of our patients fit into more than one WSPH group. The most common ones we're seeing are Groups 2 and 3; Groups 1 and 2; Groups 1 and 3; and Groups 1, 2, and 3. There is a lot of overlap.

Dr Berman Rosenzweig: I think it's been sort of amazing to watch that across the board. Back, I think, when the field was just in its early phases, the focus was on these pure Group 1 patients specifically, idiopathic PAH. We're seeing so many of these mixed phenotypes. That'll raise, I guess, the next set of questions about what to do with them and what's driving their disease and certainly I hope we will get some of these answers out of the omics work.

Dr Hill: As you know, we've done some preliminary work. So far with very small numbers, we're seeing a pretty high percentage of genetic abnormalities that we would expect to pick up in Group 1 patients in our Group 3s—25%, 30% of patients had some identifiable genetic abnormality.

Dr Berman Rosenzweig: Again, who knows what will evolve before the next symposium? I'm hoping there'll be some more updates to the classification system based on some of the findings from the omics work and hopefully a better understanding of these mixed phenotypes.

I think we're going to wrap it up. This has been awesome. I really appreciate your wisdom and experience in the field and being able to participate in this interview. Thank you so much.

Dr Hill: Thank you so much, Erika. I've really enjoyed speaking to you about it. Thanks for inviting me.

Dr Berman Rosenzweig: My pleasure. Again, thanks on behalf of PHA.