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The Big Understudied Bucket – ACHD Patients

Dr. McLaughlin:
Hello. Today we're going to talk about underrepresented populations in clinical trials in PAH. I'm Vallerie McLaughlin, from the University of Michigan, and I'm joined by my colleagues, Dr. Sudar Rajagopal from Duke, Ioana Preston from Tufts, and Rich Krasuski from Duke, as well. So, thanks for joining me everyone. We're going to talk a little bit about congenital heart disease to start out with. Sudar, congenital heart disease, repaired, unrepaired, can you give us a little bit of background on that?

Dr. Rajagopal:
Sure. First off, it's important to remember that congenital heart disease is a huge bucket, and there is a lot of different types of diseases that are characterized as simple or complex that fall into this. But in general, these diseases can be associated with the development of pulmonary hypertension. Unfortunately, a lot of these patients have not been enrolled in clinical trials. There are only a couple of clinical trials that have enrolled these patients specifically, and the majority of other trials with repaired congenital heart disease, they represent less than 10% of the population. So it's really an understudied population in pulmonary hypertension.

Dr. McLaughlin:
Ioana, you're a pulmonologist with a big pulmonary hypertension program. How often do you see these patients in your clinical practice?

Dr. Preston:
Not as many as I wish. We collaborate with our congenital cardiologists and heart failure specialists, to give them a comprehensive assessment diagnosis and care, however, there have not been a lot of data to guide us of how to treat these folks. There are a couple of clinical trials enrolling Eisenmenger syndrome patients, but other than those, plus the very few patients enrolled in our typical PH clinical trials with repaired congenital heart diseases, we do not have strong data.

Dr. McLaughlin:
Yeah. So Rich, you're our resident expert here in congenital heart disease. We really appreciate you being the main contributor to this segment. It falls under Group 1, but the pathophysiology, it's really different than the other types of Group 1, it's really over circulation. Do you want to take us a little bit through the pathophysiology of the development of PAH in most of the congenital heart disease patients?

Dr. Krasuski:
Sure, Vall. So first of all, starting, and I appreciate actually Sudar and Ioana's great comments and introduction, but, congenital heart disease is a common problem. It's about almost 2 million patients in the United States with congenital heart disease, and there's really three major complications they develop long-term, arrhythmias, heart failure, pulmonary hypertension. So PH is a big one. And we know if you develop PH your outcomes are considerably worse than if you don't have pulmonary hypertension. So it's really important to recognize, and we believe very important to treat, but as you all correctly identified, it is an area that there's very little data.

We have data in the Eisenmenger population, we have data in the corrected shunt population, we have very minimal data in the uncorrected shunt population. I think those are often the most challenging patients. There are folks that have elevated pulmonary

vascular resistance and an open shunt, and the question is, should you treat them with pharmacologic therapy where you may actually increase their pulmonary blood flow? What's the detrimental effect of that? Is it helpful? Is it harmful? Does the patient feel better? Do they feel worse? That's a very challenging question.I think assessment of pulmonary vascular resistance is critically important in those patients. Obtaining additional information, I think one of the things I try to do, is (inaudible) their defects, or give them vasodilators in the lab just to get a sense of what they're going to do, when we try this on an outpatient basis. It's a lot easier to do this in the cath lab, you can reverse what you do, than if you do it on a longer-term fashion, and have those folks come back.

The other thing to recognize too, we're talking about PAH, but there are a lot of congenital patients with pulmonary venous hypertension, sort of Group 2 disease, and that's a big proportion. And it's still important to differentiate those folks, because treating them like PAH may be doing them a disservice or harm. And there's a group, a large number of patients, who have Group 3 disease as well. So a lot of them actually have evidence of intrinsic pulmonary disease, some of them have restrictive lung disease from their prior heart surgeries, so this is a complex group. Some of them have CTAF, you have Group 4 disease, and they even fit into Group 5 disease as well, so you can really go across all those categories.

Dr. McLaughlin:
So, wow. That's a lot there, and it's very complex. So why don't we chunk it a little bit. Why don't we talk about patients with clear-cut Eisenmengers, right? So, they have an unrepaired defect, they've developed pulmonary vascular disease to the point where they're now shunting through that defect. These patients as we said, have not been included in many trials, there's one specific trial, BREATHE-5, that included them. We've been reluctant to treat them because of concern for worsening their oxygenation. Sudar, you want to go through BREATHE-5, and talk about the safety of that therapy in those patients and why maybe that's not the biggest concern we should have any longer?

Dr. Rajagopal:
Sure, Vall. So, I think in many ways, these patients with Eisenmenger syndrome can be treated like a PAH patient. BREATHE-5, showed that it was safe to use these drugs in patients with Eisenmenger syndrome, and we didn't see hypoxemia systemically with that. Indeed, many patients with Eisenmenger syndrome can respond very well to PAH therapies. And we see that their right ventricle can improve and their functional status improves. I think it is important to remember that these types of patients can present in a different way than your typical PAH patient, who will get a lot of right heart failure with edema.

A lot of the time with the Eisenmenger's patient, what you see is worsening functional status, which sometimes they're not aware of, because these patients for their whole lives, they've been very limited, in terms of their exercise capacity. But what you can also see, is worsening hypoxemia with exertion. And so, we have to keep in mind, it's important as a PAH specialist, I rely on someone like Rich, with his adult congenital heart disease expertise, who has a lot of insight into that. And there are other things that we have to look at in those Eisenmenger patients, such as making sure they don't develop iron deficiency anemia and have other problems like that.

Dr. McLaughlin:
Right. Absolutely. So Rich, I think, let's talk about the repaired congenital first, and let's keep it to the simple shunts, cause as you alluded to earlier, this can be very complex. Tell me a little bit about how you approach a repaired simple shunt, simple ASD/VSD, and are they really like an IPH patient? Or how do you think of them differently?

Dr. Krasuski:
Yeah, Vall, that's a fascinating area because we've known about this for a long time, people do develop pulmonary hypertension even if they're repaired. What's shocking to know, is actually, when you look back at large registries and identify those patients, the ones who actually develop pulmonary hypertension with close shunts, appear to actually do worse than patients who develop it with open shunts. And so this has brought up a lot of questions about what we ought to be doing for patients with shunts and PH. But just talking about the close shunts, this is somebody you have to treat very aggressively, this is somebody just like your IPH patient.

In fact, the therapies are going to be pretty close to identical. I think there's ample evidence now, when these patients have been included in clinical trials, that their outcomes look very, very similar. That in fact, they achieve benefit, their pulmonary vascular resistance drops with medical therapy, their function class improves, they get better six-minute walk distances and maybe even better survivability. I think there's now three large registries, this is in Eisenmenger specifically, that actually have shown improved survival with these therapies. We haven't seen that same thing with the patients who've been repaired, but again, it is a high-risk group of patients that really need to be identified and treated.

Dr. McLaughlin:
Do you think some of that risk has to do with patients who maybe shouldn't have been repaired or who were borderline? I mean, repairing is so easy these days for some simple ASDs, for example. Sometimes I wonder if too many people are getting repaired.

Dr. Krasuski:
I think that's a difficult question to answer. I think it's easy to kind of play Monday morning quarterback and point back. One of the things we note, is that if you have late repairs as opposed to early repairs in life, your outcomes tend to be worse. Again, identifying patients early in their disease process and treating those people with surgical or even transcatheter interventions, we've done some work looking at transcatheter closure of ASDs, and PH is a tremendous predictor of worse and long-term outcome. But whether or not that patient would've done better if the defect had not been closed, is not entirely clear. I think we have reasonable data that suggest that if they have a defect close, they do better long term, but PH, I think, is the real bugaboo there. So if they have PH, maybe some of those patients as you mentioned shouldn't have been closed or shouldn't be closed.

Dr. McLaughlin:
Or should be treated before being closed

Dr. Krasuski:
Before the closure or treated after they're closed too. I think people sometimes think, I'm going to treat, I'll close, I'll stop treatment, and then they come back with recurrent PH and that can be bad.

Dr. McLaughlin:
Ioana, take the last comment.

Dr. Preston:
Yes. On the other hand, there are patients who had the shunt repaired and they develop PH many years after the repaired shunt. So that tells me that there may be a genetic susceptibility in those particular subgroup of patients who will develop PAH in the future, and those we treat like idiopathics, right?

Dr. McLaughlin:
Well, this was a very complex topic, I feel like we just scratched the surface. But Sudar, Ioana, Rich, thanks for joining me, and thank you, for joining us in this very interesting discussion of PAH related to congenital heart disease.