Obesity and Pulmonary Hypertension: A Discussion With Deborah Jo Levine and Anna Hemnes

In this special discussion for the Pulmonary Hypertension Association, Editor-in-Chief Deborah Jo Levine, MD, Professor of Medicine, Pulmonary and Critical Care, Medical Director of Lung Transplantation, and Director of Pulmonary Hypertension at the University of Texas Health Science Center in San Antonio, spoke with Anna Hemnes, MD, Associate Professor in the Division of Allergy, Pulmonary and Critical Care Medicine at Vanderbilt University Medical Center.

Dr Levine: Today, I'm speaking to Dr Anna Hemnes, who is Associate Professor and the Associate Director of Pulmonary Hypertension at Vanderbilt University. Today, we are discussing how obesity affects pulmonary hypertension. I think it will be a really great discussion. I look forward to it. Welcome, Anna.

Dr Hemnes: Thanks so much, Debbie. I'm really excited to be here. Good afternoon to you, too.

Dr Levine: There's so many questions on this topic from all perspectives: from our patients, from our referring docs, as well as our own centers. How these 2 issues are related. The most frequent questions that comes to mind are, "Does obesity cause pulmonary hypertension? How are they associated with each other? Does obesity worsen PH?"

Dr Hemnes: I think that is the most fundamental question that we are trying to answer in our basic science lab, and also, people are trying to approach using epidemiologic studies right now. Certainly, it's clear that in cohorts of patients with pulmonary hypertension, obesity is common, which brought up this question of whether obesity predates pulmonary hypertension and whether obesity might cause it. The average BMI in most American, and even now European, cohorts of pulmonary hypertension patients is about 29 to 31, so it's pretty common.

In our lab, we have done experiments where we took normal mice and just fed them a high-fat diet and made them obese. We found that they do increase their pulmonary artery pressures just being fed a high-fat diet alone,[1] compared to mice that are eating standard chow, but that doesn't really answer the question about the epidemiology in humans. We obviously won't do a similar experiment in people because it would be unethical. There are, though, some large cohort studies that have followed patients over time, using echocardiography, and looking at how BMI might relate to right ventricular changes and estimated PA systolic pressure. There's a nice publication that was, within about the last year, in the CARDIA cohort, and they were able to show in that BMI correlated with higher echo estimated PA systolic pressure at baseline, so people who were at a higher BMI had higher PA systolic pressure, and probably more importantly, the more weight that people put on, the more their BMI went up, the higher their RVSP went, as they measured them echocardiographically over time.[2] Based on this, I would suggest that increasing BMI may very well correlate with rising RVSP on echocardiogram over time.

Then, there's a publication from Evan Britain and colleagues using the deidentified medical record at Vanderbilt that had linked genetic data. They used this genetic data to perform a Mendelian randomization study using a polygenic risk score and were able to find that higher BMI is a modifier of pulmonary hypertension severity on echo.[3]

I do think that there is accumulating evidence that obesity may at least contribute to pulmonary hypertension. I don't think we can say right now what kind of pulmonary hypertension it is, whether it's PAH or Group 3 pulmonary hypertension related to obesity, or whether there's some direct toxicity of some feature of obesity on the pulmonary vasculature.

Dr Levine: That is incredibly fascinating work. I just wonder how we can tease that out, especially in the first trial, about echocardiography and PH. We know there are challenges evaluating the RVSP or PASP in obese patients because of inadequate or difficult windows to assess. Knowing that, how confident can we be on the associations when we know the echo findings may be quite variable in this group of patients?

Dr Hemnes: Yes. I think that's a great point. The one nice thing about these studies, like the CARDIA study that I mentioned, is that the patients had highly standardized echocardiography, and that were usually overread by Central readers, so you know that the quality in those studies is pretty high, at least as high as you can get. We do have to acknowledge, as you said that being obese does make echo windows hard to read, sometimes. The studies like the one that I mentioned from Vanderbilt, where there's not a prescribed protocol and overread by a Data Coordinating Center, have a little bit less confidence, I think, in the echo findings. Certainly, in my clinic, we do find, sometimes, patients are referred with obesity, and it's really hard to get a sense of how good quality the echo is. Sometimes there's comments that it's a poor quality window and the RVSP might be elevated, or there might be right ventricular changes, but unfortunately, because of just the quality, technically, it's hard to tell. What is your experience with that?

Dr Levine: It is exactly the same situation you are describing. It makes it difficult to really know how accurate the reading is. I don't know if there's any

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longitudinal studies with serial echoes looking at RVSP/PASP and morphology of the right heart before and after a large amount of weight gain. Have you seen any work of this nature?

Dr Hemnes: Very limited. I think just that CARDIA one is the only one that I can think of off the top of my head. The converse, though, is another interesting question, what about folks who have had massive weight loss, do their echocardiographic changes reverse? Probably the best way to study that would be in the group of patients who have a gastric bypass and have a pretty rapid weight loss? We are working in my lab right now trying to do that study here, and I think the data will be pretty informative, regardless of what we find.

Dr Levine: I think it'll be really important to really elucidate this association between obesity and PH, and really trying to elucidate what that means.

We know now that there is some kind of association, but do we know how obesity impacts the outcomes in PH, whether it be PAH or any of the other groups?

Dr Hemnes: Yes. That is a really interesting question to me. There have been a couple of recent publications that are relevant to that. The first I'll mention came from the Pulmonary Hypertension Association Registry, which is nice to see that that is producing really high quality and meaningful data. Using the PHA Registry, this is PAH patients specifically, Jeff Min and colleagues were able to show that obesity is associated with worse metrics and quality of life.[4] However, it was associated with improved outcomes, so people who were obese tended to live longer, even though they felt worse.

Then there was another study from the Veterans Affair cohort by Aaron Trammell and colleagues, that was recently published, that showed that the people in this Veterans Affair cohort that was essentially an untyped pulmonary hypertension. You couldn't say it was PAH rather it's unspecified pulmonary hypertension. They found that obese patients tended to live longer, and the people with the lowest BMI had the shortest survival.[5] Both of these, together, are pointing to this obesity paradox that has been described in other disease states and suggest that obesity, while it may be linked to development of disease, may actually be associated with better longevity when their disease was established.

I'm not saying that we should advocate for people with PAH or any kind of pulmonary hypertension to go out and gain weight so that they can improve their mortality because I don't think that that's true at all, but it may speak to the role that nutritional status plays in survival in pulmonary hypertension of all causes.

Dr Levine: That is so interesting, When you think about these patients who are obese, whether they have other characteristics of the metabolic syndrome, including heart disease, hypertension, diabetes, it really doesn't correlate to what you would think, in terms of survival.

Dr Hemnes: Yes, I totally agree. To me, I do think, though, certainly, people who have lower body weights sometimes are our sickest patients, but that may be that they're using so many calories to maintain their cardiac output and can't really maintain their nutrition. I don't think we have enough granularity yet to know whether it's these folks that are on the lower end of BMI that are driving the data or whether it truly is a survival benefit related to being obese.

Dr Levine: There is however, a big difference between overweight and obese, so how should we work with our patients in terms of losing weight. What are the expected effects of weight loss on PH? Even if they feel better because they have other improvements in their quality of life, should we be encouraging them to lose weight because of this data?

Dr Hemnes: My practice has been for people who are overweight or obese, to encourage them to lose weight. Probably like you, I did this mental calculation: if they're only able to pump so many liters a minute of blood, based on their fixed cardiac output, then having more body means that you're not able to deliver as much blood per unit weight as they would if they weighed less, and so they'd feel better if they lost weight. In fact, I've had a couple of patients who have lost significant weight, intentionally, and they have told me that they really feel markedly better despite no change in PAH therapy. They can do more, then they're less out of breath.

Sometimes, people tell me they also feel better for other reasons, like their osteoarthritis doesn't hurt as bad, or there are other disease comorbidities, so diabetes doesn't require as much intervention as it would otherwise. I have generally told people to lose weight if they're overweight or obese. I don't think these data are going to change my practice. I generally think we should aim for patients to have a normal weight. The same way, if I have people who were underweight, I try to encourage them to eat and maintain a normal BMI. It does call into question whether that advice is good advice, but I guess that's a personal decision about this issue of quality of life being worse for people who are overweight. What do you tell your patients?

Dr Levine: It's hard because I think we both live in states where there is a high proportion of overweight people. Sometimes, it is difficult to say what is a normal weight. It's hard because it is a spectrum. For our patients, it is hard because what's normal in terms of some populations is not normal for others. We know that obesity is a BMI greater than 30 or morbid obesity over 35. These are the patients that weight loss should help their quality of life and hopefully mortality.

If someone is just mildly overweight, I would say, just make sure you're still doing your physical rehab, trying to eat right. We already all counsel our patients on using a low salt diet, it is important we continue to talk to them about healthy eating in other realms as well.

I feel it's a patient-to-patient basis and, really, a spectrum. Where I do think it's important, is when a patient is obese and needs to be evaluated for lung transplantation. I think if we're thinking

one step ahead in this population, that's another thing to look at.

Dr Hemnes: Yes, that's a really good point. I often encounter that as well because, like you, we live in a state that has a lot of obesity, and it's particularly sad when you have people who are medically capable of having a lung transplant, but really, the only thing that keeps them from that is their BMI. It's an important concern.

Dr Levine: It is. If patients do have problems losing weight, and you feel like it's important, either for lung transplantation or just quality of life or decreasing other comorbidities, would you offer these patients, or do you have any experience with bariatric surgery in PH patients?

Dr Hemnes: I had a patient, probably about 10 years ago, who had a BMI of about 54, who, unbeknownst to me got to the point where she was getting ready to have bariatric surgery and came to me wanting medical clearance. I told her that I didn't think that was a great idea, and we generally didn't recommend elective surgery in our patients. She basically told me that she didn't care what I said, and she was going to have the surgery no matter what. We decided to support her and try to get her through surgery, which occurred without complications. We got a right heart catheterization and echo on her pre-op and also repeated these post-op. Within about a month of her gastric bypass surgery, before her weight loss had really occurred, she had rapid improvement of RV function on echo. Her PVR actually, over time, fell, while her cardiac output went up, which is the opposite of what you'd expect with weight loss.

Based on this, I have not become somebody who recommended gastric bypass surgery to my patients because I still think that there's risk associated with any surgery, but when patients come to me and say, "This is something that I feel like I need to do for my quality of life. I'm miserable being as overweight as I am," I no longer say, "I think that's a terrible idea." In our practice, we've probably had about 5 or 6 people who have had bariatric surgery, mostly by doing a gastric bypass. Some of them have had improvements in their pulmonary hypertension, but most of them have had improvements in their symptoms and their ability to walk further on the 6-minute walk test. I don't feel like the science is such that we would advocate for doing this as a treatment for pulmonary hypertension at all. I do think patients who do not have severe right heart failure or a lot of risk for poor outcomes associated with surgery may be candidates for a gastric bypass if they feel like that's appropriate for their own quality of life. Have you had any patients that have done this?

Dr Levine: Yes. Again, like you, they haven't been patients who are severe. They've been patients with more mild PH, some with moderate and none with severe. On this topic, there are so many different types of procedures performed on for weight loss now. Do we look towards the least invasive? Obviously, the severe patients, you're not going to advocate for that, but at what point would you start to discourage that type of procedure, in terms of their severity?

Dr Hemnes: That's a hard question. People who have more-than-moderate RV dysfunction, hospitalizations for heart failure, use of parenteral prostacyclins would make me nervous.

Dr Levine: I agree. I definitely agree.

Dr Hemnes: Those would be the main ones that I think.

Dr Levine: It's almost like you would want to recommend it early on in their progression, but you still want to see if they can lose weight on their own, but maybe sooner rather than later. These procedures seem to be improving, with less risk than they were even 5, 10 years ago, but it's still a procedure, it's still a surgery, and I still worry about it. I discourage it, probably, more than not, because, obviously, the people that you see, the people I see, are not going to be these people with a mean PAP of 22. These are people who've progressed farther. It is a difficult decision, and I think it comes up a lot.

Dr Hemnes: I think it comes up a lot in our clinic. I can think of several patients, off the top of my head, who I think their main limitation to their quality of life is their obesity, and yet, I don't recommend or bring up bariatric surgery because of my concerns about their operative mortality.

Dr Levine: How often, and not for a conditioning activity, but more for weight loss, how often are you prescribing or recommending pulmonary rehab for weight loss, specifically?

Dr Hemnes: I have not had success with getting people into pulmonary rehab for weight loss. I do recommend increased activity, joining SilverSneakers at the YMCA, getting outside and taking walks, being more active, and that sort of behavior change. I usually just recommend pulmonary rehab for getting people more active with pulmonary hypertension. Have you recommended pulmonary rehab for obesity?

Dr Levine: I don't know if it's always a pulmonary rehab program, but I do try to get them to do as much activity as they are able. If we can get them into a pulmonary rehab, because of their heart or lung disease, then I think it's almost like a really good jump-off point for them to do it on their own. Sometimes, that's what it takes. Some kind of organized course or class or monitored setting where they feel, "Okay. It's fun and I can do it," and then they maybe continue it when the course is over.

For pretransplant patients, whether it be PH or ILD or a different lung disease, the people who do pulmonary rehab once they go to it, they seem to carry on better after they've done it, than before trying to start it on their own. The big questions are "can you always get it paid for?", number 2, "will they go?" and number 3, "is there a facility convenient to their home?"

Dr Hemnes: I agree, though. The folks that have engaged in pulmonary rehab, almost universally, found it to be

tremendously helpful and set up a habit for them that they were able to continue and oftentimes have lost weight and feel a lot better. I recommend it pretty much to everybody. Not everybody feels like they have the time or the resources to be able to do it, but I really think it's beneficial.

Dr Levine: I think that's, nationwide, a big problem for our patients and other patients with end-stage lung disease, especially in smaller towns and places where there's not as many resources, not as many big hospitals or centers. Sometimes, trying to get them in cardiac rehab, something is so important but very difficult. Maybe we're putting our money in the wrong places.

Dr Hemnes: We just did a trial that was published in Chest, within the last few months, that looked at a mobile health intervention in patients with PH.[6] People were given Fitbits and randomized either to a text-based intervention to increase their step counts per day or just the usual care where we said essentially, "Walking is good for you." It looks like the text-based intervention did improve step counts by about 1500 steps per day in the intervention group compared to the placebo. There was a reduction in visceral fat in the intervention group.

I think we, as a country, and particularly our field, need to think creatively about how we can get rehab more accessible to people, and whether it's a telehealth delivery model or a text-based intervention. I think we need to recognize that it's hard for people to travel to rehab centers, or they don't have time, even if they lived in a big city and it's close to them. We need to think more creatively about how to deliver exercise to our patients.

Dr Levine: I agree, and I think that a lot of it comes down to motivation and how we motivate them. There's one patient I had who is 68 years old. Her daughter says, "You have to get 10 000 steps a day." She never likes to go outside, and she'd walk around her kitchen island, and she would not go to sleep until she had her 10 000 steps every day. Now that is motivation. I think it comes down to, how do we, not only find different tools, but how do we motivate them that this is really the right thing to do, and probably the best thing they could do for themselves to be able to use whatever oxygen they do have more efficiently? We've got to figure out a way too, to make that believable to them.

Dr Hemnes: Yes, I totally agree. To do a better job of conveying the benefits of exercise, like how much better people feel and the motivating features to do it.

Dr Levine: Exactly. That will be a great addition to the literature. I think all of those new tools, which all of us learned more about during the pandemic, are going to be useful for all of our patients, especially those that do live out in rural areas and don't have these opportunities that people who live in town do.

I'd like to ask you a couple of questions at the end of our session about trials of metabolic interventions, whether it'd be fatty acid oxidation inhibitors or metformin. Can you expand a little bit about that?

Dr Hemnes: Yes. Since we know that metabolism is important to the development of PAH, specifically, people that thought, "Well, there's metabolic therapies that are well-tolerated, that we could then give to patients with PAH and repurpose them and see if they could work. The first one that was published was a trial of dichloroacetate from Evangelos Michelakis' group.[7] They were able to show a benefit in about half of the patients. It seemed like it was mediated by different genetic polymorphisms related to metabolism, but there was a lot of side effects of DCA, like neuropathy in the patients. It seems like that drug probably won't move forward as a therapy for PAH.

We got interested in metformin as a treatment for PAH because of our interest in insulin resistance, how it could promote pulmonary vascular disease, and right heart failure. We just completed a pilot study of metformin in 20 PAH patients,[8] and we were able to show that it was well-tolerated and safe, which wasn't known before. Secondly, it showed that there was an improvement in RV function, as measured by the fractional area change on echo, and a reduction in RV lipid content, which we have previously shown was common in PAH potentially bad for their right heart.

Based on that, we are now enrolling in a multicenter trial of metformin that's funded by the NHLBI. After these data, we will know more definitively if metformin improves relevant endpoints like functional class and 6-minute walk distance. metformin, has many effects, and one is that it increases mitochondrial fatty acid oxidation. So we are looking at the effects of metformin on heart lipid content and other markers of fatty acid oxidation. There've been other groups that say metabolism of RV fatty acid oxidation is low in PAH, and glucose oxidation is impaired as well, so what we should do is further impair fatty acid oxidation to try to rev up the glucose metabolic pathway. There have been some trials using drugs like ranolazine in PAH patients, that have mixed results in their publications.[9-11] Those have not been widely adopted, and I'm not aware of those drugs moving forward into any phase 3 trials, presently.

The other question that comes up sometimes, is whether drugs like liraglutide, the GLP-1 class of antidiabetics, that have shown major impact in cardiovascular disease, whether they may have a role in treating pulmonary hypertension. We presently don't know the answer to that, but it's a really interesting question.

Dr Levine: Are you all planning to look at that in your cohort?

Dr Hemnes: Yes. We're looking at it in our basic science lab using mouse models, presently. I think we can, hopefully, in the future, translate that to patients with PAH pretty rapidly, given how well tolerated the drugs are in other populations.

Dr Levine: Well, that is fascinating, and I've been looking forward to seeing your results.

Dr Hemnes: Thanks. It makes me feel better that there might be some benefit

to these studies—that other people read them or are interested in the questions!

Dr Levine: What do you think about the genomics of obesity and PH?

Dr Hemnes: That's a good question. We don't know very much, right now, about whether genetic mutations that have been associated with PAH or pulmonary veno-occlusive disease are also associated with alterations in metabolism that could predispose to obesity. I also have not seen any publications on whether patients with PAH, like idiopathic PH, without a genetic mutation, have lower BMIs than those that do have genetic mutations, which is a really interesting question, and I've not seen anybody ask that yet. Good question, but little knowledge right now.

Dr Levine: It's another study for you to do.

Dr Hemnes: Yes. Thank you, that you feel that way.

Dr Levine: Anna, thank you so much for talking today, and I look forward to your continued work in this area.

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