

Other Rare Disorders Associated with Pulmonary Hypertension

While pulmonary hypertension itself is a rare disorder, its association has been identified in conjunction with other rare disorders, which is the theme of this issue of *Advances in Pulmonary Hypertension*. Co-guest editor Sonja Bartolome, MD, facilitated a discussion regarding the experiences and perceptions of leading PH experts—many authors in this issue—on this topic. Participating were co-guest editor Kelly Chin, MD, University of Texas Southwestern Medical Center; Murali Chakinala, MD, Washington University School of Medicine; Richard Channick, MD, Harvard Medical School; Jean Elwing, MD, University of Cincinnati Medical Center; and adding to the comments later, Robert Baughman, MD, University of Cincinnati. Their conversation follows.

Dr. Bartolome: I would like to start the discussion by reviewing pulmonary hypertension (PH) associated with systemic disorders, first focusing on sarcoidosis, and then moving to any experience you may have with PH associated with Langerhans cell histiocytosis or LAM. Murali, PH associated with sarcoidosis certainly occurs, but given the complexities with concomitant pulmonary parenchymal, cardiac, or even pulmonary venous disease, would you talk a bit about how you approach diagnosing PH in this group of patients?

Dr. Chakinala: Thanks, Sonja, happy to. You know, sarcoid nicely fits in Group 5, which of course we all know is titled “PH of unclear and multifactorial mechanisms,” and there is probably no better disease to have in this category because there are so many different ways that sarcoid mechanistically can cause pulmonary hypertension. I first start by quantifying—determining how much parenchymal lung disease is there—because the most common form of pulmonary hypertension in sarcoidosis involves parenchymal lung disease with damaged, destroyed vasculature leading to PH. But then, we certainly see some other unusual cases where the pulmonary hypertension is sort of the dominant problem and the severity of the hemodynamics is discordant with the amount of parenchymal disease. That always makes us think about other causes, including a lot of mediastinal or central fibrosis and compression of central pulmonary arteries and veins, almost like a mediastinal fibrosis picture. You also have to be sure they don’t have significant left heart disease. We certainly have seen some

case series or case reports of a veno-occlusive variant with sarcoid, and then there are also patients whose sarcoid is primarily affecting the pulmonary arteries. Those patients almost act like a Group 1 patient. I also find it hard to know sometimes when you have somebody with severe pulmonary hypertension and it looks like PAH without significant parenchymal findings, and there is a chart diagnosis of sarcoid, if the two even connected at all, given how common sarcoid is. So, I think those are the main subcategories of PH, if you will, and it’s really important to do a thorough diagnostic evaluation to figure out which sort of phenotype.

Dr. Chin: Bob, in your sarcoid-associated pulmonary hypertension (SAPH) review in this issue of *Advances*, you note that SAPH has been classified as a Group 5 condition in the World Symposium Classification, but that “one might debate the appropriateness of this classification”.

Dr. Baughman: I would argue that several conditions have multiple factors which lead to pulmonary hypertension. For example, scleroderma is an example of a Group 1 condition which can lead to pulmonary hypertension by several different pathways, including parenchymal lung disease and left ventricular dysfunction. The allocation of sarcoidosis to Group 5 has sometimes led to patients not to be considered for therapy for their condition. We have recently completed a double-blind placebo controlled trial demonstrating that bosentan was successful in improving hemodynamics in SAPH.

Dr. Bartolome: Rich, are there any particular imaging modalities you do when trying to decide if someone’s PH is discordant to their parenchymal disease or if they perhaps have cardiac involvement?

Dr. Channick: There are a number of imaging techniques that may be useful. I agree with Murali that the goal is to compare the physiology and the hemodynamics with the imaging to see if it “matches up.” Chest imaging is useful in quantifying the degree of parenchymal abnormalities, in looking for nodes, and with a contrast study, evaluating the vasculature—that can be CT scan, or it could be MR where you may get more detailed cardiac morphology and function. I also think that the ventilation perfusion scan can be helpful in these cases, as it is a sensitive indicator for vascular obstruction of large vessels.

Dr. Bartolome: Jean, do you do anything differently when evaluating these patients, and how about treatment? Does the systemic nature of the disease affect your treatment choices?

Dr. Elwing: Patients affected by sarcoidosis are uniquely challenging to evaluate and manage because of the possible multi-system involvement of this systemic disease. You may begin by caring for a patient with a true pulmonary vascular phenotype resembling a WHO Group 1 patient, but over time the patient may progress and develop more parenchymal lung disease or cardiac involvement. If the person worsens or changes, it is very important to take a step back and reevaluate for other forms of sarcoid involvement that

could be triggering change in symptoms. In terms of treatment of pulmonary vascular disease in the setting of sarcoid, I think it is important to be very clear that we do not have guidelines or large clinical trials to direct treatment strategies. Response to PAH therapy may be variable and could be less robust when compared to individuals without sarcoidosis. PAH therapy choice is often based on patient tolerance and potential side effects rather than data or trials.

Dr. Channick: I would also underscore the importance of recognizing the occurrence of PVOD in the setting of sarcoidosis. We have seen sarcoid patients who clearly worsen on PAH therapy, with increased pulmonary congestion. That response could be due to either concomitant left heart restrictive cardiomyopathy or PVOD. For this reason, we are very careful in treating sarcoid patients with PAH therapies—even those who seem to have a pure arteriopathy.

Dr. Chakinala: Could I just add also that I think that when you do have that sarcoid patient with significant parenchymal disease who also has significant pulmonary hypertension—much like we learned to think about in the ILD population—those are patients that you have to really be worried about because treatment options may be limited, and they really have sort of 2 phenotypes conspiring together in terms of your functional state and oxygenation, and those are patients who, if they are otherwise eligible, should probably be referred for a transplant evaluation sooner than later. If you're going to try to treat carefully with some off-label therapy, that's okay, but I think if they're young enough and comorbidities are not too significant, those are patients I feel better if they are evaluated early for transplant. And then, just one other quick point I would want to make, and I don't know if others on the call want to comment on this, is I always find it a struggle to know what to do about immunosuppression of these patients, especially the ones who don't have so much parenchymal disease, but yet seem to have the arteriopathy, the sarcoid-associated arteriopathy. In addition to

trying the pulmonary vasodilators, how much should we push immunosuppression?

Dr. Baughman: Over the past 10 years, we have developed a fairly wide range of medications beyond prednisone to treat the inflammatory aspects of the sarcoidosis. Recently, the PET scan and soluble IL-2 receptor have been shown to be good predictors of which patients may benefit from more aggressive treatment with anti-tumor necrosis factor agents such as infliximab. We are particularly interested in the patient with no evidence of worsening lung function in terms of vital capacity or HRCT but who has increasing symptoms. This persistently dyspneic patient has a 50/50 chance of having pulmonary hypertension. It is this patient we will study with right heart catheterization. I do agree that this patient may be a candidate for lung transplantation, but their prognosis tends to be better than an IPF patient, since their parenchymal lung disease usually does not progress.

Dr. Bartolome: How about other rare systemic diseases, like Langerhans cell histiocytosis or LAM that have been reported to also perhaps be associated with pulmonary vascular disease. Have any of you cared for these kinds of patients where you really believed the pulmonary hypertension was disproportionate to their parenchymal involvement?

Dr. Elwing: In my experience with working with Dr. Frank McCormack who follows a large number of patients with LAM, the number of individuals affected by significant pulmonary hypertension is quite small. I have only encountered one patient with LAM whose pulmonary hypertension was clearly out of proportion to her parenchymal lung disease. In her case, she was fully evaluated for other contributing causes of pulmonary hypertension and subsequently treated with PDE-5 inhibitor therapy while she awaited lung transplant. Fortunately, she did have symptomatic improvement of her dyspnea and right heart failure with PAH-specific therapy. Though uncommon, significant pulmonary hypertension should be considered if more advanced dyspnea or right heart

failure symptoms than expected with the degree of lung disease.

Dr. Chakinala: Yeah, I haven't actually seen anybody myself, but like many other advanced parenchymal lung diseases, it's not uncommon certainly in LAM patients that are being evaluated for lung transplantation. One case series says even as much as 45%, but I think most of those patients are going to be Group 3 type patients and if there is a more profound arteriopathy associated, I think it's going to be pretty rare, otherwise all of us would have seen it more. The only other interesting thing I would comment about that is, as you guys know, there's so much interest in the sex hormone pathways and estrogen paradox, and since LAM is also affected by those pathways we think, is there potentially a subset of patients who have a second hit or a problem whereby they get LAM, but it also may lead to a more significant pulmonary vasculopathy? Obviously, I am speculating here, but I think it's worth mentioning.

Dr. Chin: I wanted to comment on the Langerhans cell histiocytosis, because we've seen a handful of these patients that seem to have markedly higher pulmonary pressures than you could account for from their parenchymal disease, though I would say they did tend to be on the hypoxic side - kind of like what you can see in combined pulmonary fibrosis and emphysema patients. I am not sure if we're just getting a mostly hypoxic response, or if we're really truly seeing more of a pulmonary vasculopathy associated with it, above and beyond what occurs in anyone with hypoxia. A few patients we see have had fairly significant RV failure, and we know in this setting patients can be more "cardiac limited" with exertion, rather than being limited by oxygenation or their parenchymal limited disease.

Dr. Channick: I would echo that. We've seen several cases where the PH does seem to be disproportionate to the lung disease, so LCH does seem to stand out as a diffuse lung disease with a higher prevalence of pulmonary hypertension; but, I agree, we don't totally understand the mechanism.

Dr. Bartolome: Another systemic disorder which may be complicated by PH which I'd like to talk a little bit about is hereditary hemorrhagic telangiectasia (HHT). Murali, I know you have a large center there at Barnes-Jewish and there must be quite a few of these patients. We do have a review article in this issue discussing the diagnosis of PH in this group and that the vast majority of them will be high-output heart failure. I was wondering, when you do encounter the rare patient who you believe has true PH, perhaps due to the genetic defect, do they often also have the clinical manifestations of HHT and if so, do you think that treatment with PH-specific drugs has any effect on those shunts or bleeding from their telangiectasias?

Dr. Chakinala: Yeah, I think this is a really fascinating area, just partly because of the phenotype and the evaluation, and because that the management can be challenging. So for folks who are going to be reading this who don't know much about HHT, we tend to think of 2 main types of mutations, although there are more. There are mutations in endoglin and ALK-1, or now it's called ACVR1. Richard Trembath and the folks in Britain over 10 years ago did beautiful work that showed how ALK-1 mutations can lead to a PAH phenotype, and others have shown since then in the literature that PAH in families with ALK-1 mutations are what we call HHT2. So to get to your question, Sonja, a lot of these patients actually will not have been diagnosed with HHT at the time they present with their pulmonary arterial hypertension. In other words, they look and act like one of our WHO Group I patients and will be classified as idiopathic PAH patient unless you find something in the family history or the patient has other clues. This includes most commonly spontaneous recurrent epistaxis or skin telangiectasias, or possibly they have a characteristic visceral AVM. Most of us don't do genetic testing on new patients with pulmonary arterial hypertension. So the HHT part of the diagnosis can be silent, if you will, and only come up in the diagnosis later, after PAH has already been diagnosed and treated. Based on recent data coming out of the

Netherlands that was presented at the HHT meeting in June 2015, it appears that about 11% of patients with HHT will have a PA systolic pressure of at least 35 or more on a screening echo. And as you alluded to, the vast majority of those patients are going to have PH from high output related to liver AVMs and severe anemia. And in this large series of almost 400 patients, only 1% of patients wound up having PAH as we would think of in a Group 1 category, and they were all patients with ALK-1. So I think the most important thing really for people to understand is that PH in general is not that uncommon in HHT, but the vast majority of the time it's related to high output where patients have a normal or low pulmonary vascular resistance. Then there's the rare patient, probably no more than maybe 1% of HHT population, that has PAH. And in those patients, management can be difficult because they do have lesions in other parts of their body, particularly in their nose and GI tract, that are prone to bleeding. And as we know, our PAH drugs—all of them to some extent—have some antiplatelet or anti-aggregatory effects of platelets. In my limited experience, as has been noted by others, I think that these lesions can bleed more when they're on our therapy. So we really have to be vigilant in terms of hemostatic procedures to try to minimize the bleeding as we carefully introduce these therapies, as we don't want to aggravate other problems as we treat the pulmonary hypertension.

Dr. Bartolome: You mentioned the subset of folks who do have high-output heart failure due to liver AVMs, and I was wondering, for those that are undergoing a liver transplant evaluation as treatment for their liver AVMs and who also have high-output heart failure, does the presence of this alter your pre-surgical risk assessment or recommendations for anesthesia?

Dr. Chakinala: Well, I think it depends on the degree of cardiac compensation. If you have somebody who's in a high-output state but compensated, I think the risk profile is probably fairly low, of course, accounting for any other issues; but certainly as these patients

evolve into a more decompensated state where you have significant ventricular enlargement and dysfunction and elevated filling pressures and maybe even pulmonary hypertension, there again we're talking about more of a Group 2 type pulmonary hypertension. I think their anesthetic risks, with anybody with heart disease, is going to be a little higher. It's hard to be more specific or dogmatic on that, but I think it comes down to just the degree of compensation that patients' ventricles have.

Dr. Channick: Murali, do you think that some of these people have pathophysiology similar to portopulmonary hypertension? I'm thinking of an HHT patient I just saw last week who has large liver AVMs and a high cardiac output, but also has an elevated pulmonary vascular resistance in the 8-9 Wood units range. She seems to have more than one mechanism causing PH.

Dr. Chakinala: You know, it's possible, Rich. There are 2 things I would think about in that lady. That is that these folks who get high output from liver AVMs can live decades like this, and if it's missed or not treated appropriately in terms of managing the left-sided components, they can go on to develop some pulmonary vascular remodeling, and they can even start getting elevations in their pulmonary vascular resistance. However, you're describing somebody with a PVR of around 9 Wood units if I heard you right, so that's pretty darn high, and so you wonder, if they have an ALK-1 mutation in particular, do they also have the potential to have pulmonary arteriopathy, and to your point, is there a portal pulmonary component? I think that really depends then on what the actual abnormal plumbing, if you will, in the liver is. Most of the time when you have liver AVMs it's hepatic artery to hepatic vein shunt, so it's kind of a left-to-left shunt, if you will, but you can also see portal vein to hepatic vein shunts, and hepatic artery to portal vein, so you can see a combination of all 3 in some people, but if they have sort of that physiology that we're used to thinking about with portal pulmonary hypertension or essentially

portal flow is bypassing the liver, then I think it's possible they could have an arteriopathy, much like portopulmonary hypertension patients do. I think it's very rare, and unfortunately the kind of patient you describe—and I've seen just a couple in my career—they are very difficult to manage for the reasons that we were talking about. They have multisystem involvement, they have micro probably and certainly macrovascular disease; and some of the therapies for the pulmonary hypertension component can really sort of aggravate the underlying physiology and the propensity for bleeding.

Dr. Channick: The other mechanism could be high-output-induced PAH; Eisenmenger's-like.

Dr. Bartolome: We're going to transition a bit to one of the other topics we're talking about in this issue, and that is pulmonary veno-occlusive disease. We often discuss this disease as a footnote in many of our conferences due to the potentially detrimental effect of PH-specific therapy. Rich, would you talk about how you recognize this rare disorder and how you evaluate them if you suspect it, and then how you proceed with caring for this patient?

Dr. Channick: Great topic, Sonja. My first comment is that it may not be such a rare disease. As is the case with many conditions, what's often considered rare is only true with severe or extreme forms, but I think for every severe disease, there are milder subforms that may go unrecognized. I believe this to be the case with PVOD. PVOD is a progressive narrowing obstruction of the microvenular circulation, either idiopathic or associated with certain conditions, like connective tissue disease, hematologic malignance, or chemotherapy regimens. In the severe "textbook" form, PVOD is rapidly progressive. It may also involve the pulmonary capillaries in the interstitium, a condition called pulmonary capillary hemangiomatosis. The presentation of PVOD/PCH includes severe hypoxemia, predisposition to pulmonary edema, and varying degrees of pulmonary hypertension. It is very

refractory to pulmonary hypertension therapy, and the patient may actually get worse or even die from a pulmonary artery vasodilator. The treatment is early lung transplantation. If you have a patient with pulmonary hypertension who has marked impairment of gas exchange and a very low diffusing capacity and they don't have much of interstitial lung disease, or they have signs of fluid in the lungs, including pleural effusion, reactive lymph nodes, ground-glass, etc., then you really want to think about it. And the other big clue—and often people don't realize this—is that the wedge pressure which measures the large pulmonary venous pressure is typically normal in PVOD. The other point though, is that I believe that veno-occlusive disease may occur as a reaction to a number of other much more common triggers. We talked about sarcoidosis, but even very common conditions like chronic left-sided heart disease, I believe, can lead to remodelling of the pulmonary venules. I see features of PVOD in a lot of patients with some of the secondary forms of pulmonary hypertension, and a clue may be the disproportionate hypoxia or the low diffusing capacity, as well as chest imaging suggesting excess pulmonary congestion, but with a normal wedge pressure on right heart catheterization. In summary, in the absence of lung tissue, PVOD is diagnosed by a constellation of clinical, radiographic, and physiologic findings.

Dr. Bartolome: Would you comment a little bit on the radiographic findings in a patient with PVOD?

Dr. Channick: The classic radiographic findings are similar to what one sees in congestive heart failure or pulmonary edema: interlobular septal thickening, ground-glass opacities, mosaic patterns, pleural effusions, and nonspecific mediastinal lymphadenopathy. However, in contrast to a CHF patient, as discussed earlier, right heart catheterization will show a normal wedge pressure.

Dr. Chin: So when you see a patient with these findings clinically, what do you do as far as therapy?

Dr. Channick: As I mentioned, in general, pulmonary arterial hypertension therapies do not help such patients and may hurt them. But having said that, there are always exceptions, and for patients in whom we feel the predominant feature is right heart failure and severe elevation of pulmonary vascular resistance, with lesser degrees of gas exchange abnormalities, I would consider therapy. Anecdotally, I have seen some beneficial responses with PDE-5 inhibitors in those carefully selected PVOD patients, but we certainly watch them closely. Although there are cases in the literature of acute flash pulmonary edema and death in PVOD patients receiving IV prostacyclins, I have not seen this dramatic adverse effect from PDE-5 inhibitor. However, the bottom line is early referral for lung transplantation.

Dr. Elwing: I echo Rich's comments regarding PVOD. Patients affected by this condition are extremely challenging to manage because the associated hypoxia can be severe and may markedly worsen with pulmonary vasodilators. As Rich mentioned, PAH therapy can be cautiously trialed, but pulmonary transplant is the only recommended intervention. Early referral is key. Isolated PVOD accounts for only a very small fraction of the PAH patients seen and followed in PAH centers; however, it is increasingly being recognized to complicate other conditions that are known to affect the small pulmonary arteries. Scleroderma and sarcoidosis are 2 conditions that we frequently think about where there can be a mixed picture of PAH and PVOD. This coexisting pulmonary arterial and venous disease may account for the blunted responsiveness to PAH therapy occasionally seen in scleroderma patients. Clues regarding pulmonary venule involvement can sometimes be gleaned from careful review of HRCT imaging. It has been reported that scleroderma patients frequently have HRCT changes that raise suspicion for pulmonary venous involvement with ground-glass opacities and lymphadenopathy in addition to the expected cardiomegaly and pulmonary artery enlargement we typically see in PAH patients. PVOD is something to consider when patients

with classic PAH hemodynamics do not respond well to PAH therapy and have worsening oxygenation.

Dr. Bartolome: The final topic we would like to touch on this afternoon is PH related to myeloproliferative disorders. Specifically, I would like to talk a little bit about dasatinib, which is used to treat CML and has been associated with PH that appears to be reversible with discontinuation of the drug in the majority of patients. Does anyone on the panel have any experience with PH related to dasatinib and how does this potential reversibility affect your evaluation and follow up?

Dr. Elwing: I have encountered 2 patients that were felt to have dasatinib-related pulmonary hypertension. Unfortunately, the first individual was detected in late stages of disease with advanced pulmonary hypertension and associated right heart failure. The second individual was referred for an evaluation of dyspnea while on dasatinib. He underwent an expedited assessment for pulmonary hypertension and his dasatinib was discontinued. He was followed closely as an outpatient to ensure resolution of his pulmonary hypertension. His symptoms of dyspnea did resolve over the next several months and it was recommended that dasatinib not be reinitiated at that time. Because of the significant and potentially reversible pulmonary vascular disease that can be related to dasatinib use, I think that is very important to work closely with our hematology/oncology colleagues to increase awareness of the potential adverse effects of this medication. Patients receiving dasatinib should be monitored for increased shortness of breath or decreased exercise capacity. If this occurs, early referral for pulmonary hypertension assessment is key.

Dr. Chakinala: You know, I've only seen 1 patient myself, and as Jean pointed out in her first case, unfortunately, it was somebody that was picked up too late. I think Jean's point is an excellent one. This is somebody that was followed primarily by oncology, outside of our institution, and she

actually, from piecing the history, described increased dyspnea for a while. I think it just went under the radar because this hasn't been well publicized. In her case, even though the drug was stopped, she was presenting in very dire straits. And as you alluded to, Sonja, although the PAH can be reversible, this takes time—on the order of weeks, if not months. In this case we treated her like anybody else with pulmonary arterial hypertension, but unfortunately she succumbed to the disease and the right heart failure. I think that probably the right approach is that if you've got somebody who is fairly mild and then maybe, just like Jean described, stop the drug and watch closely as they may completely reverse; but there are clearly going to be others that I think we ultimately have to treat like a drug-induced or a toxin-induced PAH and hope that by, with time, their vasculopathy may regress back to normal or be a minimal problem.

Dr. Channick: I think the dasatinib story really points to the complexity of these tyrosine kinase inhibitors. Some TKIs may actually be beneficial for PAH, and then you have dasatinib, which certainly seems to lead to the development of PAH. I think the other point is that association and causation are not the same and that epidemiologists are fairly stringent when it comes to proving an association. One could make an argument that myeloproliferative conditions could be included in Group 1, as Murali said, or is it still in Group 5? We have typically made this decision based on the strength of the association, ie., is there a well-designed case-control study showing a significant association, is there biological plausibility, etc.

Dr. Chakinala: You know, I think this has sort of come up in several of our answers today so far. It just goes to show you how, as comfortable as we all get and as large as our centers get—and I think this point is important because more and more people are treating PH—it's still so important when you first meet a PH patient that a very thorough and comprehensive medical history and

examination are done. It is important to ask about drug use in the past or even medications they may be still getting that can cause PH. I mentioned how HHT can be missed in initial evaluation. I've talked about some other parenchymal lung diseases; it's so important that the patients get an extremely thorough evaluation, and that we shouldn't just immediately focus on the echo and getting the heart cath.

Dr. Bartolome: We all agree that a methodical history and physical are the cornerstone of a PAH evaluation and essential in finding and diagnosing these rare diseases. Take myeloproliferative disorders for example. Not just PAH, but also chronic thromboembolic pulmonary hypertension, has been reported in patients with myeloproliferative disorders. Rich, what's your experience with CTEPH in this group, and does myeloproliferative disorder alter either your workup or treatment algorithm?

Dr. Channick: I agree that myeloproliferative diseases can cause pulmonary hypertension through many different mechanisms, from deposition of white cells in the lung or extramedullary hematopoiesis, including the lungs. Certainly, this group of patients is hypercoagulable, and we've seen patients with true CTEPH, as well as those who have microthrombosis. In addition, many of these patients are receiving chemotherapeutic regimens known to cause PVOD and pulmonary arterial hypertension; and they may have had splenectomies, which we know is associated with both CTEPH and PAH. So patients with myeloproliferative conditions require a full workup looking for thrombotic sequelae or evidence of intrapulmonary hematopoiesis, and should otherwise undergo a standard PH workup.

Dr. Bartolome: I would like to thank the group today for a lively discussion of some of the lesser discussed topics within pulmonary hypertension. I'd like to thank the PHA for organizing the discussion and Drs. Baughman, Chakinala, Channick, and Elwing for their expertise and my co-editor, Dr Chin.