PH in Patients with Lung Disease and Hypoxia


Nicholas Hill, MD


Omar A. Minai, MD


Steven Nathan, MD

Global experts in pulmonary hypertension attended the 2009 American College of Chest Physicians meeting in San Diego. While there, Dr Nicholas Hill, Chief of the Pulmonary, Critical Care and Sleep Division, Tufts Medical Center, and Professor of Medicine, Tufts University, Boston; and Dr Steven Nathan, Medical Director, Lung Transplant and Advanced Lung Disease Program, Inova Fairfax Hospital, Falls Church, Virginia, talked with guest editor Dr Omar A. Minai to share their perspectives on current diagnosis, management, and future outlook for pulmonary hypertension patients with existing lung disease and hypoxia.

Dr Minai: Thank you for taking the time to discuss this very interesting topic regarding pulmonary hypertension in patients with lung disease and hypoxia. We will have a discussion around three broad areas; firstly, epidemiology and pathophysiology of pulmonary hypertension in patients with lung disease; secondly, the diagnostic strategy; and finish with treatment options and a look to the future. To begin, can you tell me if you think this is an important topic that we should be discussing and focusing on and what are the reasons for its importance.

Dr Hill: Well, I'm going to let Steve do most of the talking here. But my answer is an unhesitating yes, an emphatic yes, because this is a problem that we all encounter quite frequently in our practices: patients with underlying lung disease or chronic hypoxia associated with pulmonary hypertension. Yet we have very little evidence to guide our management or treatment, and we need more information. It would be very helpful if we had additional studies addressing the questions that we face almost daily in our practices, and so this is an extremely important topic.

Dr Nathan: I agree with Nick, Omar. I think it is very important. I think it's very much an emerging area of interest. The one thing that we are developing a growing appreciation for is the incidence of pulmonary hypertension in these patients as they develop advancing lung disease, be it COPD or any form of ILD, like IPF. What we also know, and there have been a number of studies now attesting to it, is the impact that this has on patients' functional ability and survival, In conditions like IPF and COPD, it's a strong predictor of survival. In fact, there is data in the COPD population attesting to PH having greater prognostic implications than the FEV1. So I think the reason that there has been so much emerging interest in this is because we have all these therapies available now for WHO Group I pulmonary arterial hypertension, and the big unanswered question is whether or not these therapies would be any good in WHO Group III pulmonary hypertension.

Dr Minai: What I hear from both of you is that pulmonary hypertension in patients with WHO Group III diagnoses has clinical relevance, in the sense that it impacts functional capacity and survival. If we were to define it further, are there any other relevant parameters that indicate its significance? As you know, pulmonary arterial hypertension has more significant hemodynamic alterations and progresses very rapidly, which may not be the case with pulmonary hypertension in WHO Group III patients in some instances.

Dr Nathan: Well, I agree with what you're saying. I think that the pulmonary hypertension in lung disease is a different animal to pulmonary arterial hypertension tend to have mild to perhaps moderate pulmonary hypertension. In the one study that we did of patients with IPF, we found pulmonary hypertension in about 40% of them. In half of the PH group, the mean PA pressures was between 25 mm Hg and 30 mm Hg, and that's not what we see in pulmonary arterial hypertension. So a lot of times it's there, it's underappreciated; and you can't detect it clinically because it's mild. Yet it still has significant ramifications in terms of patients' functional ability and prognosis.

Dr Hill: Yes, I think these forms of pulmonary hypertension differ from Group 1 PAH; not only ILD, but also COPD and OSA. The vast majority of these patients have relatively mild PH and a minority have severe PH.

Dr Minai: One thing that we should discuss right off the bat is how we define pulmonary hypertension, because much of the older literature in this population defines pulmonary hypertension as a mean PA pressure greater that 20 mm Hg at rest; however, the accepted definition of PH is a mean PA greater than 25 mm Hg at rest. Clearly, there is a large population of patients with this disease who would have mean PA pressure between 20 and 25 mm Hg. So should PH in

this category be defined as mean PA pressure above 25 mm Hg, or should we be looking at patients in that 20 to 25 mm Hg range, as well?

Dr Hill: Well, I don't think we really know the answer, because our definition of PH is based on consensus and not on statistics or outcomes. If you define pulmonary hypertension as more than 2 standard deviations above the mean, we don't have enough data to know what the mean is in a large population of these patients. And from as far as prognostic implications are concerned, we know that higher PA pressures are bad, but we don't know what the threshold should be. From a practical point of view, if you define PH as levels of 20 mm Hg or above, you end up with very high prevalences, as have been reported in the older literature; but we don't really know if pressures between 20 and 25 have any prognostic or therapeutic significance. So although it's arbitrary, I think the cutoff of 25 mm Hg or higher makes more sense; but until we have more outcome data, we don't really know the answer.

Dr Nathan: I think for standardization purposes, 25 mm Hg is reasonable to use in the context of Group III pulmonary hypertension. I think if we start to lower the threshold for different diseases, it will just be very confusing for the community out there. But your point is very well-taken in terms of what are the implications if you have a mean PA pressure of 21 or 22 mm Hg versus16 or 17 mm Hg. It makes intuitive sense that if we did those kinds of studies, we would show that patient outcomes in terms of functional ability and mortality would worsen as their mean PA pressure increases. It would really take large population-based studies to see what the optimal cut-point is. However, I still think at this time, even though conceptually it might be a lower PA pressure in the context of parenchymal lung disease that determines outcomes, for standardization purposes, we should keep it the same.

Dr Hill: Right. And we do have some of that data in COPD patients, where it's clear that the higher the mean PA pressure, the worse the prognosis and the greater the effect on functional capacity.

Dr Nathan: It does raise another point, though, and I'm sure we'll get on to talk about therapies. But if we talk about therapies and we talk about trials of therapy, which patients should we enroll? Should we use the 25 mm Hg cutoff, should we use a higher threshold, or should we use a lower threshold?

Dr Minai: Now, let's draw our attention to the pathophysiology of pulmonary hypertension in these patients. Most of us agree that hypoxia plays a role of critical importance in this, but is hypoxia the main driving mechanism or are other mechanisms such as inflammation, smoke exposure, and diastolic dysfunction relevant as well?

Dr Nathan: I think it's multi-factorial and certainly hypoxia does play a role in this. However, there are likely many other factors involved. If you look at most forms of diffuse parenchymal lung disease, be it COPD or interstitial lung disease, you have fibrotic or emphysematous destruction of the lung with lots of the pulmonary capillary bed that is destroyed.That certainly plays a role and contributes to the pulmonary hypertension. You raised the issue of co-morbidities, which I think are extremely important contributors in some patients. For example, if you look at any of the patient populations we're talking about, be it COPD or IPF, about 15-20% of the patients will have elevated pulmonary capillary wedge pressures suggestive of diastolic dysfunction. The other co-morbidity that requires attention is obstructive sleep apnea; the prevalence of obstructive sleep apnea has recently been looked at in patients with IPF and it was very high, in excess of 80%. So I think co-morbidities certainly play a role, and if nothing else, pulmonary hypertension might be a signal or a clue to the existence of some of these co-morbidities. I think other factors that might play a role include the cytokine milieu, for example; some of the same cytokines that are up-regulated in IPF play an important role in pulmonary hypertension, for example TGF-beta and PDGF are up-regulated in both conditions. It is therefore conceivable that there is cytokine "cross-talk" in terms of the parenchyma and the vasculature. Those are some of the drivers behind pulmonary hypertension. .I believe it is likely that one feeds into another, so it's hard to pinpoint and say, well, 30% is due to hypoxia and 30% is due to vascular destruction. I think it's a kind of positive feedback loop where everything contributes, to some extent.

Dr Hill: I agree with those comments. I think back to my days in medical school, when the lecture on cor pulmonale had a diagram with hypoxia occupying the central role in causing most of these forms of pulmonary hypertension. Today, now that we know so much more about them, my view is that hypoxia often plays a relatively minor role in the causation. As Steve mentioned, cytokines can play a role, and in COPD, work by Barbera's group in Spain shows increased expression of IL6 and infiltration of certain T-cell types around pulmonary vessels well before these patients become hypoxic, and these are associated with endothelial dysfunction and histologic evidence of a pulmonary vasculopathy.[1] Also, when we think back to the NOTT (Nocturnal Oxygen Therapy Trial) trial, people thought that adding oxygen would reverse the pulmonary hypertension, and yet, it had a relatively minor effect. It slowed the progression a little bit, but it certainly didn't bring about reversal most of the time. This suggests to me that when we're talking about parenchymal lung disease, these other cofactors that Steve was mentioning are often more important than hypoxia alone. On the other hand, I think it depends on what condition you're talking about. Clearly, there are some chronic hypoventilation syndromes where hypoxia plays a central role. I'm thinking of severe chest wall deformities or neuromuscular diseases. It's clear that when you ventilate these people and adequately oxygenate them, you can completely reverse their pul monary hypertension.

Dr Minai: It seems that we all agree that PH in these patients is a multi-factorial process that goes beyond hypoxia, and that co-morbidities seem to play a very important role, be that diastolic dysfunction or obesity or other concomitant diseases that we sometimes don't look for in these patients, like pulmonary embolism, and those should certainly be looked at. One of the questions that we are always asked, and that I always have a difficult time answering, is what is pulmonary hypertension disproportionate to the degree of lung disease? Do you think it exists, how do you define it, and how often does it occur?

Dr Hill: Well, that's one of those proverbial $64,000 questions, and obviously no one really knows the answer. My own view is that disproportionate pulmonary hypertension clearly exists. I see this

in IPF, COPD, and to a certain extent in OSA patients if there are other co-morbidities. I think it's a separate entity from the mild pulmonary hypertension that we've been talking about as more prevalent in association with these diseases and I think the treatment probably needs to be different. Unfortunately, I don't know exactly how you define it, so I'll let Steve expand on that. (LAUGHTER)

Dr Nathan: It's a very difficult concept. We all talk about disproportionate pulmonary hypertension in the context of these diseases, and it's the kind of thing that you think you know it when you see it, but it's very difficult to define what it actually is. And I think it's something that might be different in individual patients and in different diseases. It is also very pertinent in the context of clinical trial designs. Should we try and carve out those patients who we believe have disproportionate pulmonary hypertension and only study them? I think that has been the error in some of the studies to date; namely that we have treated patients as a whole without trying to hone in on that one clinical phenotype that might be more likely to respond to therapy. And it might actually be that you can only diagnose disproportionate pulmonary hypertension in retro- spect. What I mean by that is, if you put a patient on a trial of therapy and they get better, maybe only then can you say, well, that patient probably had disproportionate pulmonary hypertension. If you take a disease like COPD – and this goes back to the question that you raised, Omar, about what is the threshold for pulmonary hypertension, allow we need to define variable thresholds anchored to a variable of the parenchymal lung disease severity. So, for example in COPD, we might use "Steve's Rule of 75" as an example of how maybe we should be thinking about this. So, if in the context of COPD you have an FEV1 of 50%, then maybe the mean PA pressure to define pulmonary hypertension should be greater than 25 mm Hg. If you have an FEV1 greater of 40%, maybe the mean PA pressure should be greater than 35 mm Hg, and all the way down, so that if you have an FEV1 of 25%, then maybe your mean PA pressure should be greater than 50 mm Hg to call it disproportionate. So I don't say that that's going to hold true, but I think conceptually we need to perhaps look at levels of pulmonary hypertension in the context of the severity of the lung disease.

"One thing that we should discuss right off the bat is how we define pulmonary hypertension..."
–Dr Minai

Dr Minai: So an important point is that the severity of the underlying lung disease will, in part, determine whether or not we call the pulmonary hypertension disproportionate to it. But do other factors that we sometimes don't measure have relevance in how we define that? For instance, going back to the scleroderma literature, might the decline in diffusion capacity help us in patients with lung disease? Would that be something that we factor into the equation when we say pulmonary hypertension is "disproportionate," or should we just look at the FVC in interstitial lung diseases and FEV1 in COPD patients?

Dr Nathan: That's a difficult question to answer, because PFTs are inexact in all these diseases, and they don't tell the whole story. But I think I would perhaps rely on the diffusion capacity a little more, because there appears to be a closer link between the diffusion capacity and pulmonary hypertension, so the 2 kinds sort of go hand-in-hand. In the scleroderma literature, at least, the ratio between the FVC and the DLCO has been used as a predictor of underlying pulmonary hypertension, but I'm not sure we can define disproportionate pulmonary hypertension on that basis.

Dr Minai: Nick, do some patients with lung disease truly have very elevated pressures and therefore have disproportionate pulmonary hypertension, or is it that these patients happen to have pulmonary arterial or pre-capillary pulmonary hypertension and also are unlucky enough to have underlying lung disease?

Dr Hill: Well, I would see this as a series of Venn diagrams, in a way, because as Steve pointed out, as the parenchymal disease and the physiologic dysfunction become worse, you might expect the pulmonary hypertension to become greater, and this is where we get at the issue of defining disproportionate PH. So if you have someone who has COPD, let's say with an FEV1 of greater than 50%, and they have severe pulmonary hypertension, then maybe they have an overlap syndrome. I wouldn't expect COPD of that level of severity to give someone severe pulmonary hypertension and I would look very carefully for other co-factors that might be contributing to it. But if I can't find them and the patient has, say, a mean PA pressure of over 50 mm Hg, I think they are unlucky enough to have both COPD and PAH. But as the parenchymal disease becomes more and more severe, then I am willing to accept higher mean PA pressures as related to the lung disease. In COPD, where a fair amount of epidemiologic work has been done by Weitzenblum and his group, we do know that it's quite unusual, even in severe COPD, to see mean PA pressures greater than 35 mm Hg, certainly less than 10% of cases.[2] These patients with severe PH seem to differ from the others in that they have less airway obstruction and more severe hypoxemia than those more mildly affected, raising the question that they really are a distinct subpopulation.

Dr Nathan: I think you've raised an important point conceptually in terms of how we approach those patients and, if someone has disproportionate pulmonary hypertension, take the example that Nick gave of FEV1 greater than 50%, mean PA pressure greater than 50 mm Hg, do you call them WHO Group I pulmonary arterial hypertension who happen to have a co-morbidity of COPD, in which case you can justify maybe treating them with the conventional therapies you have available for Group I, or is it that the COPD was the primary event and, for whatever reason, genetic or otherwise, the patient developed this so-called disproportionate pulmonary hypertension? And it might be semantics, and it probably is, but I think if you're looking for justification to treat under those circumstances, and I think most of us would agree with Nick, then you might think of it conceptually as Group I with co-morbid COPD, although that might not strictly be the case.

Dr Minai: Lets transition from disproportionate pulmonary hypertension to this idea of severe pulmonary hypertension in patients with WHO Group III. When severe PH has been defined, it has been defined as mean PA pressure greater than 40 mm Hg at rest. Is that a reasonable definition of severe pulmonary hypertension or should we add in things like vascular resistance and measures of right ventricular function, like cardiac index or cardiac output? Would that be a better way of defining severe pulmonary hypertension, or is mean PA pressure alone a reasonable way of doing this?

Dr Hill: Well, I think any number you pick – and I think Steve and I were getting at this point a few moments ago – is arbitrary. I do think that you get into a very small proportion of the patients with pulmonary hypertension when you pick a cutoff like 40 mm Hg; as I said, the epidemiologic studies in COPD patients suggest that that constitutes probably less than 5% of the patients. I think it's pretty clear that a PA pressure that high imparts a worse functional capacity and prognosis. What are the therapeutic implications of picking a number like that? We don't really know. Does it make sense to treat those patients differently, say, than those with mean PA pressures under 40 mm Hg? Perhaps. So I think as an arbitrary cutoff, 40 mm Hg makes sense for practical purposes, because we need to have some conceptual framework from which to work. But I also think we have to admit to ourselves that it's arbitrary and we don't know a lot about the implications of selecting that number.

"We all talk about disproportionate pulmonary hypertension in the context of these diseases,...but it's very difficult to define what it actually is."–*Dr Nathan*

Dr Minai: Steve, do you think that patients with interstitial lung diseases have more severe pulmonary hypertension than patients with COPD? Both diseases produce hypoxia and cause parenchymal destruction. Is the PH more "severe" in patients with ILD than in those with COPD?

Dr Nathan: I think if you look at a histogram distribution of PA pressures in patients with advanced COPD versus IPF, it actually looks very similar. Most of the patients with COPD have milder pulmonary hypertension clustered around 25 to 30 or 35 mm Hg, which looks very similar to patients with IPF. If you want to discuss an entity that is a little different from these conditions, that would be sarcoidosis. The distribution of PA pressures in my experience is a little different in these patients, where there is a propensity for a higher prevalence, certainly in stage IV disease, of more severe pulmonary hypertension. So it's not uncommon to see sarcoidosis patients with mean PA pressures 40-50 mm Hg, whereas in IPF and COPD, even though you can see that, it's still a relatively rare occurrence.

Dr Hill: Yes, I think sarcoidosis does stand out. We certainly see sarcoidosis patients who have relatively mild pulmonary dysfunction and yet have severe PA pressure elevation. I don't want to spend too much time on nosology but, of course, PH related to sarcoidosis is now classified as Group V for reasons that have never made any sense to me. It often shares features with Group III and sometimes with Group I.

Dr Nathan: Yes, even though PH related to sarcoidosis is included in Group V, when I think about it intuitively I think of it as being part of Group III, and I think it was put in Group V because several factors such as sarcoid granulomas and mediastinal lymphadenopathy could be contributing to the PH.

Dr Minai: We haven't talked much about the epidemiology and pathophysiology of PH in patients with sleep apnea. Nick, in your opinion, are co-morbidities such as obesity and thromboembolic disease more important in these patients or is the distribution of the Venn diagram very similar to what we see in other WHO Group III diseases?

Dr Hill: I think obstructive sleep apnea, by itself, in the absence of co-morbidities, generally does not give you a lot of pulmonary hypertension. Of course, many of our patients with OSA have multiple co-morbidities; commonly they are obese and have the metabolic syndrome. They are referred to us because their echoes show increased RV systolic pressure estimates, and when we cath them, many of them turn out to have LV diastolic dysfunction. Usually, we don't see severe pulmonary hypertension in them—not as high as in Group I—but sometimes, the pressure elevations are pretty impressive; but I ascribe that more to the co-morbidities than to the OSA itself. We also see patients with COPD and OSA, sometimes referred to as the "overlap syndrome," and they can have pretty significant pulmonary hypertension too. When this occurs, we worry about chronic thromboembolic disease, because they certainly are at risk for that. We also see OSA patients who have severe hypoventilation, maybe obesity hypoventilation, and as I pointed out before in relation to patients with neuromuscular disease, some of these patients respond very well to noninvasive ventilation and restoration of adequate oxygenation. I have seen complete reversal of pulmonary hypertension in that setting. So OSA is a mixed bag; most of the time it's relatively mild. By itself, I don't think it causes much pulmonary hypertension; in the presence of co-morbidities, it can cause a lot of pulmonary hypertension.

Dr Minai: Now, let's turn our attention to diagnostic strategies. We all use echo in trying to screen for pulmonary hypertension, but we also know that echo is not very accurate. What, in your estimation, is the role for echo in patients who have lung disease or sleep apnea where the echo windows may not be great due to lung disease or morbid obesity?

Dr Nathan: I think echo is a good screening tool, but as you alluded to, it's not a diagnostic tool in the context of pulmonary hypertension. That holds true for pulmonary arterial hypertension and certainly holds true for patients with any form of parenchymal lung disease, because of the inaccuracies that you mention. I think it's one of the things that we can use as a clue to the presence of underlying pulmonary hypertension. However even if the echo is normal or there's no mention of a tricuspid regurgitation stream or RV dysfunction, if you clinically suspect pulmonary hypertension, I don't think the echo's enough to exclude it. If patients have significant exercise desaturation, maybe disproportionate to what you might expect from their lung disease, if they have a very low DLCO and you clinically suspect they might have pulmonary hypertension, even if the echo doesn't have any suggestion of pulmonary hypertension, my recommendation would be to go on to the next step, which would be right heart catheterization.

Dr Hill: I agree entirely with that. We all are familiar with the studies of Kotloff's group at Penn in the patients with parenchymal lung disease being evaluated for lung transplantation showing disappointingly poor correlations between what is measured by right heart cath and the estimates from cardiac echo.[3] The echo can both over-estimate and under-estimate the cath pressures. Sensitivity and specificity are poor, and I think the point that Steve made about pursuing a right heart cath if your suspicion is high, despite a normal estimated pressure on echo, makes a lot of

sense. Nonetheless, I do think the echo still plays an important role in screening.

Dr Minai: Most patients with lung diseases or sleep apnea probably don't have significant pulmonary hypertension. Are there non-invasive strategies that we can use, other than or in combination with echo, to try to define who we should take for right heart catheterization? In other words, is there a role for techniques such as exercise testing, BNP levels, or CT scanning in non-invasive evaluation?

Dr Nathan: I agree with all of that, but I think the BNP can be quite helpful in guiding you in terms of suspicion for pulmonary hypertension. PFTs, not the FVC, but the DLCO, especially once you get below 35 or 30% of predicted, should make one suspicious of pulmonary hypertension. I think the 6-minute walk test, both desaturation and distance, can also provide an important clue to the existence of underlying pulmonary hypertension. So most times, it's putting the package together, looking at all those parameters and deciding what your clinical index or suspicion is and what the appropriate timing is to go ahead and do a right heart cath. I think that the underlying prevalence of pulmonary hypertension in IPF, for example, is very much dependent on when you do the right heart cath. If you do it very early on, it makes intuitive sense, you're not going to see much PH; but if you wait for patients to have had the disease longer, you're probably going to see a higher prevalence. So I think it's very much an unanswered question: specifically, when do you take that next step and go on to do a right heart cath? I think this is very important as it pertains to many issues around pulmonary hypertension in these diseases; for example, in terms of looking for co-morbid disease, therapy or no therapy, and enrollment in clinical trials. I think there is a reluctance among physicians to subject these patients to right heart cath, as opposed to the patients in WHO Group I who we do right heart caths in all the time. I think this is a paradigm that maybe we need to try to modify, because I think in a lot of cases it is important to go that next step.

Dr Hill: Well, I guess the thing I would emphasize, and I think Steve made this point, is that no single test by itself has much specificity or sensitivity in detecting pulmonary hypertension in patients with underlying lung diseases. But when you put them all together, they can be more valuable. Also, you are looking for disproportionalities to raise your clinical suspicion. For example, we know in interstitial lung disease associated with connective tissue disease that a disproportionately low DLCO increases the suspicion for pulmonary hypertension. A BNP that is elevated in a patient with interstitial lung disease, whose echo shows relatively normal LV function, for example, would raise my suspicion for PH. The 6-minute walk distance is problematic because a lot of patients are deconditioned or have non-cardiopulmonary limitations, so I don't find it that useful diagnostically; I do find it useful in monitoring patients to assess their response to therapy. But I do think that putting results of these tests together – PFTs, BNP, and others, can help to formulate a clinical suspicion. And I think the level of clinical suspicion that one might use to decide on getting a right heart catheterization should be relatively low, as Steve suggests.

Dr Minai: In that context then, given the limitations of echo, at what sort of right ventricular systolic pressure numbers would you send your patients for right heart catheterization both in the presence of and in the absence of RV dysfunction?

Dr Nathan: That's a tough question to answer. The higher the RVSP, the greater the likelihood is that the patient has pulmonary hypertension. But as you look at different cut-points for the RVSP, say you go 30, 40, 50, 60 mm Hg, you lose sensitivity and you gain specificity for PH. So if a patient has an RVSP of greater than 70 mm Hg, you can be pretty sure, perhaps 90% sure, that they're going to have pulmonary hypertension. But, you're going to potentially miss a lot of patients with pulmonary hypertension if you're just waiting for an RVSP that high. I think an important mistake that some clinicians make out there is they see an RVSP of 70 or 80 mm Hg and they say, ah-ha, this has to be pulmonary hypertension and there's no point in going on and doing the right heart cath. Well, Nick mentioned earlier that you can have falsely elevated RVSPs in a lot of cases, and I think that's one reason to go on and obtain a right heart cath. But, one thing I got a sense of by looking at the UNOS database of all the COPD patients listed with right heart caths, is that the higher the RVSP, the greater the likelihood that the wedge is going to be high as well; the point being that right heart cath is very important, if for nothing else but to rule out potential diastolic dysfunction, which you might treat much differently. If you're looking for a case or justification to do right heart cath in these patients, if you take a patient with IPF for example, about 15-20% of them will have elevated wedge pressures. Well, in the context of a disease that we don't have any treatments for, finding 15% or 20% of patients where you might be able to treat a co-morbidity that could impact their outcomes, I believe is very important.

Dr Hill: I think it's important to emphasize that the RV systolic pressure estimate, by itself, has problems with sensitivity and specificity, but when combined with other findings on the echo, can be more useful. I pay attention to RV size and function, and so even when the RV systolic pressure estimate isn't that high but there's marked RV enlargement and systolic dysfunction, I'm much more apt to bring that patient to cath. One other factor I consider is the severity of pulmonary dysfunction. This especially applies to COPD patients and it partly is my bias, based on no data. But if I have a patient whose FEV1 is 30% or less (GOLD Class IV) and they have a slight or even moderate elevation of their RV systolic pressure on echo, I'm not interested in cathing that patient, because even if I successfully treat their pulmonary hypertension, I don't know that I've helped them functionally or prognostically because I've done nothing for their severe airway obstruction. I'd be interested in Steve's view on that.

Dr Nathan: I think that raises an important point, and that is: OK, so we're recommending right heart cath, but what do you do with those data? Why is it important to get the right heart cath? I mean, you're probably not going to treat and a patient's not going to benefit if they have a very low FEV1 in the context of mild to perhaps even moderate pulmonary hypertension. You're going to be kidding yourself. They're going to still continue to have a ventilatory limitation to exercise. So it raises another conceptual question: Do we, or should we do, right heart cath purely for prognostic reasons? I don't know if there's a right or wrong answer to that. I think you do get important prognostic information from the right heart cath and there are probably other tests that are similarly invasive that we do for prognostic purposes only. It might also be a

decision that varies on a case-by-case basis. I think we always have to talk to the patient when we do any kind of invasive tests. It is incumbent on us to inform them of what we hope to accomplish with the information. In some patients I might not even talk to them about a right heart cath even if I am suspicious of PH but do not feel that I am not going to alter their management with right heart cath data. So I think we have to tailor how we manage these patients, depending on the overall global clinical circumstances.

Dr Minai: That is a nice discussion of the nuances of the diagnostic strategy in these patients. We all have slight differences in whom we would send for right heart catheterization and when; however I think that at least anytime we are contemplating treating a patient for PH in the presence of parenchymal lung disease or sleep apnea, with a PH-specific medication, that we should do a right heart catheterization before initiating any treatment. Would both of you agree with that statement?

Dr Hill: That is our firm practice.

Dr Nathan: Yes, I agree 100%. If you're going to commit a patient to medications, which potentially have side effects and are very expensive, you need to do it on the basis of a right heart cath.

Dr Minai: One other thing I wanted to touch on is screening. Are there any populations within WHO Group III that you feel have a high enough prevalence of pulmonary hypertension that they should be screened for pulmonary hypertension, whether by echo or by other non-invasive means?

Dr Nathan: That's a difficult question, and not to cop out, but I think it should be on a case-by-case basis. I think there are so-many variables that come into play that it's very difficult to make a blanket statement. Probably as a general rule, the younger the patient, the more limited the patient, the more likely it is you're going to screen and look for things that you can potentially impact on. Conceptually, the patient who has symptoms that appear disproportionate to their underlying parenchymal lung disease should probably be screened.

Dr Hill: Right, and I think many of these patients get PFTs before they get echoes, so in IPF patients or scleroderma patients, a low DLCO might lean you toward getting an echo. Some people might send off a BNP before they get an echo and the high BNP might lean them toward getting an echo.

Dr Minai: Let's move on to management of these patients, which is, if anything, an even more controversial issue. Let's start first by addressing the role of oxygen supplementation in these patients. There are some studies, at least in the COPD literature, that have shown that long-term oxygen supplementation may help reduce the speed of worsening of pulmonary hemodynamics. When would you use supplemental oxygen in these patients: in all patients with pulmonary hypertension and parenchymal lung disease, only in those with exertional or nocturnal hypoxia, or only in those that have resting daytime hypoxia?

Dr Hill: Well, you're referring, of course, to the NOTT and MRC trials that were done in patients with hypoxemic COPD. As you well know, these were patients who had resting daytime PaO2's of 55 mm Hg or less on room air and survival was improved in those studies, of course. So I think it's reasonable to treat patients with daytime hypoxemia even though we don't have data on patients with PH, per se. But we don't have data to answer the other questions: what do we do with patients who have just nocturnal hypoxemia or patients who have exertional hypoxemia, either in the COPD or PH populations, so we must rely mainly on opinion and belief. My own approach in those patients is to assess their resting daytime oxygenation and, if they meet Medicare standards, I think it's a no-brainer—I prescribe oxygen therapy for them. If they—and this is often the case with PH—have normal oxygenation at rest and yet desaturate very quickly and severely with exercise and have nocturnal desaturation in addition, my practice is to provide oxygen supplementation for exertion and sleep. What you do with the patient who has lone exercise-induced hypoxemia, I don't know. I don't usually use oxygen in that setting, although sometimes these patients can exercise farther with oxygen supplementation. I run a pulmonary rehabilitation program and we generally supply oxygen supplementation when we're training them, but the problem I have is that many if not most of them absolutely refuse to use oxygen therapy outside of the program. (LAUGHTER) And I don't know for sure whether oxygen supplementation works for these patients, either to improve their functional capacity, quality of life, or prgnosis. When they say, "Doctor, I don't want oxygen," I usually back off.

Dr Nathan: I agree with Nick's approach. I think oxygen supplementation is very important for the reasons as stated, but you have to temper this with the data, which are limited aside from those studies that Nick mentioned. Once you commit a patient to oxygen with one of these diseases, it becomes a lifelong commitment. Even though it can improve their functional ability, it does impact quality of life to the extent that they have to lug oxygen around with them all the time. But with that said, I think one thing that we do rely on clinically, which actually might not be a very accurate gauge of what they're doing on a day-to-day basis, is the 6-minute walk test. I think there's a growing appreciation, certainly in the ILD literature, that the 6-minute walk might underrepresent what the patient does on a day-to-day basis, and if you walk them up stairs for example, they're going to desaturate more. There's also data to suggest that what they do with their nocturnal oxygenation is very different from what they do in their day-to-day activity. So that's very much an unanswered question: how far do we chase their oxygen levels and how exactly should we approach this? Is this going to affect their functional status or survival? Should all of these patients get nocturnal, overnight oximetry? Will it affect the subsequent incidence of pulmonary hypertension if we treat their hypoxia more aggressively? We don't know.

Dr Minai: I would now like to bring up 3 things that I feel require emphasis when we are managing these patients. We already mentioned one of these, namely the importance of looking for the comorbidities and managing them. Secondly, the role of rehabilitation in improving functional capacity in these patients; as Nick mentioned, these patients may be very deconditioned when they come to us initially. Thirdly, treating the underlying lung disease itself and maximizing that therapy before treating the pulmonary hypertension. What is your practice in this regard?

Dr Hill: I'm totally onboard with that. I think the approach is to

consider all potentially reversible co-morbidities and treat them pretty aggressively, although when we talk about the hypoxemia, we both allowed that the data are such that we don't know for sure how hard we push on oxygen supplementation. But I think the first step is to attack co-morbidities, optimize them, and then think about specific PH therapies, if they might be a consideration.

Dr Minai: Steve, did you want to add something, especially about treating underlying lung diseases in patients with lung fibrosis and sarcoidosis?

Dr Nathan: Yeah, as you know with IPF, we don't have any proven effective therapies for the underlying lung disease. If or when we do develop such therapies, this approach might make some sense. Sarcoid's a little different; there are some case reports of patients improving their pulmonary hypertension after being treated with steroids, but those cases are few and far between and probably just represent effective therapy of perivascular or endovascular granulomas. I don't think treating stage IV fibrocystic sarcoid with steroids and/or methotrexate is going to impact their pulmonary hypertension. If you are going to treat, I would consider the PAH therapies in certain of those cases. One thing that you raised, which I think is very important and very valuable with limited downside, is the role of pulmonary rehab. I think it's well-established in COPD, but there's a lot of emerging evidence now that it is useful in most patients with various forms of advanced lung disease, from PAH to patients with ILD. I think one thing that's interesting, and I don't believe it has been looked at, is the difference in outcomes from pulmonary rehab in those patients with parenchymal lung disease, with and without pulmonary hypertension. I think that would be a neat little study for someone to do at some point.

"No single test by itself has much specificity or sensitivity in detecting pulmonary hypertension in patients with underlying lung diseases. But when you put them all together they can be more valuable."–*Dr Hill*

Dr Minai: Nick, there are some studies in the sleep apnea literature showing that CPAP therapy may help in improving pulmonary hemodynamics, both echo-based and right heart cath-based. What is your opinion about that? Do you treat patients with sleep apnea who have pulmonary hypertension with CPAP for a defined time before thinking about PH specific therapy, or do you start treating these patients concomitantly, with CPAP as well as with vasoactive medications?

Dr Hill: Well, this is an interesting question and something I've thought about for a long time. I think that there are 2 opposite poles to this question, where you have on one side the OSA population that has associated pulmonary hypertension, usually mild, and yes, I definitely treat those patients with CPAP up front. I think CPAP therapy is effective for those patients in treating the pulmonary hypertension – not always, but I do wait to see whether they respond to CPAP therapy before I would consider any specific PAH therapy. On the other side of the coin, you have patients who have more severe pulmonary arterial hypertension and have associated OSA. If I think the PAH is the predominant pathology, especially if it is more severe, I don't wait for a CPAP response before I treat their PAH. I generally treat their obstructive sleep apnea, as well, but in that scenario, I don't think CPAP alone does much,for the PH.

Dr Minai: Nick, you mentioned before that some patients with hypercapnea and certain lung diseases may benefit from CPAP therapy. Is that true for advanced COPD with hypercapnia as well, or just for patients with restrictive chest wall deformities?

Dr Hill: I think it's certainly true that CPAP and especially BiPAP are effective for treating PH associated with hypoventilation syndromes when lung parenchyma is relatively normal (kyphoscoliosis, chest walll deformities, or obesity-hypoventilation). In COPD patients who are hypercapnic and have PH, though, I don't know that CPAP or BiPAP is effective in treating the PH. These modalities may improve the hypoventilation a bit but there's really no literature on how they affect the pulmonary hypertension. When I think of my own experience, I can't say that I've seen the pulmonary hypertension respond to CPAP or BiPAP in many of these patients. Therefore, I can't say there's much of a role for noninvasive positive pressure ventilation here.

Dr Minai: Patients with lung disease are sometimes referred to me with echoes showing elevated pressures who have been placed on calcium channel blockers with clinical worsening or at least no benefit. What is your opinion of the role of calcium channel blockers in treating patients with pulmonary hypertension and associated parenchymal lung diseases or sleep apnea?

Dr Hill: Well, they can be very effective in treating their systemic hypertension, if they have it, but I don't think they do anything for the pulmonary hypertension. What do you think, Steve?

Dr Nathan: I agree 100%. I think it's an unfortunate mistake and a carryover from an earlier era that we still sometimes see patients with PAH who have been treated inappropriately with calcium channel blocker therapy. This is much more of an issue nowadays because we have so many other more effective therapies. Only about 6 or 7% of patients with IPAH are true calcium channel blocker responders, but there's absolutely no data in the context of parenchymal lung disease that calcium channel blocker therapy does anything.

Dr Hill: Yes, and I would also add that calcium channel blockers and other systemic antihypertensives can render patients with parenchymal lung disease severely hypoxemic by disrupting hypoxic vasoconstriction and worsening V/Q matching. So they can be dangerous.

Dr Nathan: Agreed.

Dr Minai: OK now, let's spend a few minutes talking about the vasoactive or vasomodulatory therapies in pulmonary hypertension. From a big picture standpoint, do you feel that there are differences in terms of response rates or degree of response to these therapies between patients with obstructive lung diseases, those with sleep apnea, and those with interstitial lung diseases? I know that there is no prospective controlled trial evidence one way or the other, so I'm asking you to draw from your personal experience.

Dr Nathan: I think we honestly don't know, and I think right up

front, I'd like to put a plug in for clinical trials. We need to do the clinical trials and I think that should be the first thought for any of these patients before implementing empiric therapy; namely, are they a candidate for any of the currently available clinical trials? And there are a few clinical trials out there. For example, ambrisentan is being trialed in patients with IPF and associated pulmonary hypertension. I think we really need to do what we can as a community to populate these studies, so we can get some definitive answers. It's very attractive and very appealing to treat some of these patients with vasoactive therapy and the higher the pressure, the more attractive and the more appealing it becomes. But there are some cautionary caveats specifically in terms of what Nick alluded to, and that is potentially worsening V/Q matching and rendering them more hypoxic. It's also interesting that one of the conditions that we would regard as a contraindication to vasoactive therapy is pulmonary veno-occlusive disease. Well, if you look at the explants of patients with IPF and patients with sarcoidosis, a lot of them, up to two-thirds of IPF patients, can have veno-occlusive-like lesions. So this is another reason why there is the potential for doing more harm than good in some of these patients. We need to do the appropriate clinical studies to try to define which patients are most likely to respond to therapy and if any patient subgroup is more inclined to do poorly. With that said, I confess that I am guilty of treating some patients with parenchymal lung disease for their pulmonary hypertension; I view each patient as an *n*- of-1 study. If I do implement therapy and I get some good baseline data—specifically a 6-minute walk test—I put them on whichever therapy I choose and then bring them back soon thereafter to make sure I'm not doing more harm than good.

"We need to do the clinical trials... that should be the first thought for any of these patients before implementing empiric therapy..."–*Dr Nathan*

Dr Hill: I agree entirely with those comments. The big problem is we don't have data upon which to base our judgments, so we use theories. For example, in interstitial lung disease, because endothelin has been implicated in pathogenesis, I've heard the view expressed that endothelin-receptor blockers might be particularly effective in IPF. We have the bosentan trials for IPF, but they were not focused on patients with PH, just IPF, so they don't really answer the question. One of the potential downsides of endothelin-receptor antagonists in these patients is that they can promote fluid retention, which can be problematic in these patients One other approach that is supported by a rationale is to use inhaled prostacyclins, like iloprost and now inhaled treprostinil because they can improve oxygenation by enhancing V/Q matching. They are deposited in ventilated areas and can improve blood flow to those areas. In my own anecdotal experience, I've used these drugs in occasional patients with IPF and have seen some improvement in oxygenation associated with their use. So we use these theoretical benefits to justify prescribing these drugs to selected individual patients, but we must be honest in admitting that we really don't know whether we're helping our patients. And if we want to have a confessional here, I also am guilty of treating some patients with PAH-specific agents. In COPD patients, I've leaned more toward PDE5 inhibitors because of their low cost, safety, and side effect profile. Anecdotally, I've seen some COPD patients with "disproportionate" PH manifest favorable symptomatic and functional responses to these agents. But I think when we do this, we have to keep in mind that although we're trying to do our best for individual patients we really don't know what we're doing and we need to do the studies to find out. In a recent cautionary note, Blanco et al examined acute effects of sildenafil in a group of COPD patients with PH and found that although pulmonary hemodynamics were improved, resting oxygenation was worse.[4]

Dr Nathan: Two points to add to that. There is the ongoing study which is being done by the NIH IPF Network looking at sildenafil in patients with IPF. This is the so-called STEP study, which should shed further light on the treatment of PH in the context of IPF. There has been only one prospective, randomized, placebo-controlled study of a vasoactive agent in patients with IPF, and that was the ACTIVE study, using inhaled iloprost. There were 51 patients enrolled in that study, but, unfortunately, it was a negative study. The results were presented at the American College of Chest Physicians' meeting 2 or 3 years ago, but it hasn't made its way into the mainstream literature, which is truly unfortunate. Albeit a negative study, I do think it is important to get that kind of information out there, because there was a suggestion from a prior small pilot study that inhaled iloprost worked for patients with pulmonary fibrosis and associated pulmonary hypertension. However, once subjected to the appropriate randomized prospective study, it didn't pan out. So this provides a cautionary note in terms of the over-interpretation of small pilot studies and making clinical decisions based on these.

Dr Minai: Those are very interesting comments from both of you. Steve mentioned *n*-of-1 trials, and many of us tend to do that in our patients. Since some patients are going to be placed on these medications, I find that we are sometimes reluctant to take patients off the medications when they are not working. So should there be a time limit? Should these *n*-of-1 trials be limited in terms of time; that is, if the patients are not better by 3 months or 6 months or 9 months, should we say that this medication has the potential to create problems for the patient in terms of water retention or other side effects and should be discontinued?

Dr Nathan: I think it's very much case-by-case, and I think it is important when you put a patient on therapy to decide, in your mind, what your goal and what your endpoint's going to be. With that said, in the absence of clinical worsening from these medications, it's sometimes very difficult to stop the medication once you have the patient on it. A lot of times, you're faced with a dilemma when the patient stays the same. You end up thinking, well, gosh, if I didn't have the patient on this medication, maybe they'd be in worse shape than what they are now.

Dr Hill: Yeah, and *n*-of-1 trials are pretty much all you have when you're dealing with a single patient. I guess almost every therapeutic intervention is, in a sense, an *n*-of-1 trial if you're the patient. But they have to be taken with caution, because you know, we don't double-blind these patients and the placebo effect can be quite powerful. So you put someone on a med, they feel better; you take it away, they feel worse. You don't know for sure that's truly an effect of the med. Also, a problem that we encounter in Group I patients all the time and is relevant to these Group III patients is that when we start a therapy and patients maybe stay the same or might deteriorate a little bit, it doesn't

necessarily mean that the medication isn't working, because they might be a lot worse without it. Our experience of taking people off PAH medications in that setting is that they sometimes deteriorate substantially over the next week or two, and so you have to be very careful interpreting their initial clinical response and withdrawing medications, based on that.

Dr Minai: We mentioned volume retention as one of the potential side effects, but there's also the specter of V/Q mismatching and worsening hypoxia with parenteral agents. Are there any instances where you would consider using parenteral agents in these patients, whether IV or subcutaneous, when they have PH in association with parenchymal lung diseases?

Dr Nathan: We do have patients on parenteral therapies, and we base that decision on the severity of the underlying pulmonary hypertension. For those patients who clearly have more severe pulmonary hypertension, and I'm talking about mean PA pressures 50 or more in the context of a cardiac index that's maybe borderline-low to low, we would regard them as very similar to a WHO Group I patient and look to go straight to a parenteral therapy.

Dr Minai: Lastly in terms of treatment, I would like to cover lung transplantation, just a couple of sentences about when should we refer these patients for lung transplant. My own practice is that if someone has moderate or severe parenchymal lung disease and they have pulmonary hypertension, that to me is an indication that long-term it's in their best interest to start lung transplant evaluation. At what point do you think about referring patients for lung transplantation?

Dr Nathan: If you look at the guidelines for IPF in particular, we make it very easy. We recommend that patients who are appropriate candidates for lung transplantation, vis-à-vis age less than 65-70, no significant co-morbid conditions, etc., should be referred to a transplant center at the time of diagnosis. And the reason for this is that even if patients are asymptomatic, the course of patients with IPF is very difficult to predict. Unfortunately, we see it all too often that patients can have an acute or sudden deterioration and go from being asymptomatic to having Class IV symptoms in a month or less with an acute exacerbation. So it behooves us to make sure that every patient who's an appropriate candidate gets worked up for lung transplantation, in the event they have a course like that. One of the advantages of having a workup for lung transplantation is that everyone gets a right heart cath, so we are able to make an assessment of whether or not they have any pulmonary hypertension. So it's pretty easy in the context of IPF in terms of when to refer for a transplant evaluation. I think for sarcoid and COPD, it's a little different with a little bit more thought required. I think as a general rule, once patients develop Class III and certainly Class IV symptoms, they should be sent for a transplant evaluation. And if they do undergo an evaluation, they should also get a right heart cath.

Dr Hill: Steve, of course, runs a transplant center. I don't have a transplant center where I practice, so I will give the non-transplant center perspective on that. But I agree with everything that Steve has said about making referrals in regard to IPF. Also, with COPD I pay more attention to the severity of the airway obstruction and other factors. But when I think of the proportion of my IPF and COPD patients who actually go for transplant referrals, it's relatively small because they're usually too old or have some other co-morbidity that precludes their referral, so it actually applies to a relatively small percentage of these patients. And the PH is really not a major factor in making the decision to refer to a transplant center most of the time. Also, I can't ever recall sending a patient with mainly OSA for a transplant evaluation; it would have to be one of those patients who has PAH and happens to have OSA in addition.

Dr Minai: To summarize, it seems that there are still several challenges in terms of diagnosis, and clearly several challenges in terms of treating these patients. The most important thing before starting treatment is to make an accurate diagnosis by performing right heart catheterization in all patients in whom we are contemplating initiating PH specific therapy. Second, we should always think about the role of oxygen supplementation and rehabilitation, rule out co-morbidities, and try to optimize the treatment of the underlying condition. The role of vasoactive agents is unclear and patients with disproportionate pulmonary hypertension are more likely to benefit from such therapy. We should try to enroll patients in clinical trials to better define who would benefit from such therapy. Lastly, patients with more advanced lung disease with pulmonary hypertension should be sent for lung transplant evaluation. I want to thank both of you for taking the time to participate in this roundtable, and I'm hoping that our readers will get some nice insights from our discussion.

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