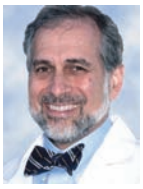
Pulmonary Arterial Hypertension Associated With Scleroderma


Harrison Farber, MD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This discussion was moderated by Harrison (Hap) Farber, MD, Professor, Department of Medicine, Boston University School of Medicine, and Director, Pulmonary Hypertension Center, Boston Medical Center, Boston, Massachusetts. Panel members included Richard M. Silver, MD, Professor of Medicine and Pediatrics and Director of the Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, South Carolina; Virginia D. Steen, MD, Proffessor of Medicine, Georgetown University, Washington, DC; and Charles Strange, MD, Professor of Pulmonary Medicine, Division of Pulmonary and Critical Care Medicine, Medical University of South Carolina, Charleston, South Carolina.

Dr Farber: What do you think is the real incidence of PAH [pulmonary arterial hypertension] in people with scleroderma?

Dr Steen: The incidence is very hard to determine because there are so many different kinds of pulmonary hypertension in scleroderma. We have patients that have fairly typical pulmonary arterial hypertension, similar to idiopathic pulmonary hypertension. These are the classic limited scleroderma patients that are typically anticentromere positive. Probably 10% of patients with limited scleroderma will have pulmonary arterial hypertension. There is also a group of patients that have secondary pulmonary hypertension as a consequence of severe interstitial lung disease, which are mostly the topoisomerase-positive patients. Another group of scleroderma patients have a combination of both fibrosis and pulmonary arterial problems, and another group has diastolic dysfunction resulting in pulmonary venous hypertension. Adding these groups together, probably 30% of patients with scleroderma will eventually get some form of pulmonary hypertension.

Dr Strange: The only thing to add to that is that pulmonary hypertension may occur in many of the other connective tissue diseases, not just scleroderma.

Dr Silver: I think the data are even softer when you look at lupus and myositis patients. In patients with lupus or mixed connective tissue disease, you have another variable and that is the patients who have antiphospholipid antibodies resulting in a hypercoagulable state and subsequent chronic thromboembolic disease, adding yet another form of pulmonary hypertension to the list. In terms of the actual incidence or prevalence of pulmonary hypertension in lupus or MCTD, I think it is anybody's guess. It is probably far less than what we see in scleroderma. Wouldn't you agree Ginny?

Dr Steen: Yes, and there is even another form of pulmonary hypertension seen in the connective tissue diseases and that is an inflammatory pulmonary vasculitis.

Dr Silver: Right, definitely a true vasculitis of the pulmonary circulation. It think that is very rare and would actually be in the lupus/MCTD [mixed connective tissue disease] group and those patients often will improve with immunosuppressive therapy. That's probably the one group where we can say that immunosuppressive therapy is generally indicated.

Dr Steen: Agreed.

Dr Strange: One of the other difficulties in determining incidence and prevalence, stems from referral bias, ie, whether these patients are seen in a pulmonary hypertension clinic, interstitial lung disease clinic, [by a] general pulmonologist, or general rheumatology practice, which would result in a different denominator.

Dr Farber: Do you think the effect of these different forms of pulmonary hypertension is equal among the groups? Is the effect on life expectancy similar?

Dr Steen: I don't think that the people with diastolic dysfunction have quite the horrible outcome as the PAH patients. My experience with patients that have pulmonary hypertension secondary to pulmonary fibrosis is also not as bad as the PAH group. This is in contrast to what has been reported by the Hopkins group, who report a worse mortality than the pulmonary arterial hypertension patients.

Dr Strange: My experience has not been different from what is reported by the Hopkins group. The

interstitial lung disease-related pulmonary hypertension patients have a much worse outcome now that we have effective therapies for isolated PAH.

Dr Silver: That has not been my experience.

Dr Steen: Not mine either.

Dr Silver: We see the worst outcome in those patients who have isolated pulmonary arterial hypertension. Most of them have limited disease, many of which are centromere positive. I think if you add in diastolic dysfunction, those patients do even worse.

Dr Steen: That's been my experience too, which is supported by our data. Patients who have a mild secondary hypoxic-driven type of pulmonary hypertension are not the ones with the worst outcome. I wonder if the Hopkins group is describing a group of patients with vasculopathy on top of hypoxic-driven pulmonary hypertension. This is a group of patients that aren't likely to be antitopoisomerases or anticentromeres. They have a combination of both fibrosis and primary vasculopathy and have bad disease.

Nucleolars are found in only maybe 15% of scleroderma patients, yet there is a high prevalence of bad lung disease in this cohort.
–Dr Steen

Dr Silver: Do you have a particular autoantibody profile?

Dr Steen: Those are the nucleolar antibodies.

Dr Strange: In my experience as the one pulmonologists here, the people that do the worst seemingly are the people who have bad interstitial lung disease and have pulmonary artery pressures out of proportion to what would be expected by the interstitial lung disease alone, suggesting concomitant PAH. No matter what you do for these patients, it doesn't seem to work.

Dr Steen: But that's different than secondary hypoxic-driven pulmonary hypertension.

Dr Strange: I agree.

Dr Silver: Ginny, how big or small is that group?

Dr Steen: You know, I'm seeing a lot of nucleolar antibodies in African-Americans, but also in some Caucasian patients. Up to 30% of the patients with nucleolar antibodies can have severe pulmonary hypertension; it's a very high percentage. Even though the nucleolar antibodies are a small group of the patients compared to the autoantibodies such as centromere, the topos, and the RNA polymerase III, which are each found in 20% to 25% of scleroderma patients. The nucleolars are found in only maybe 15% of scleroderma patients, yet there is a high prevalence of bad lung disease in this cohort.

Dr Strange: I have actually been impressed by the fact that different scleroderma centers seem to be reporting different kinds of patients. Are we seeing the same patients and looking at them differently, or are we truly, in fact, seeing different patients depending on maybe where we are, what our referral patterns are, whatever?

Dr Silver: There are some disparities in terms of race, so in some areas we will see more African-Americans. I would imagine that Hopkins sees more African-Americans than Pittsburgh, but I don't know about Georgetown. Ginny?

Dr Steen: We [Georgetown] have 23%, Hopkins has 23%, Pittsburgh has 8%, you have nearly 30%. I don't know what Boston has. There are clearly different patient populations, but also I think that people are looking at it differently. I know at Hopkins they haven't paid as much attention to the autoantibody profile when characterizing their patients with pulmonary hypertension. So, I think there may be 2 different groups of patients with pulmonary fibrosis and pulmonary hypertension.

Dr Strange: Ginny, I guess I will just challenge you. How much fibrosis does it take to give you a combination patient as opposed to an isolated, knowing that a lot of people have a little bit of reticular change on their baseline CT scan?

Dr Steen: I think you can have a reasonable amount. I like to think that the patient has to have been hypoxic at some time before they develop secondary pulmonary hypertension.

Dr Silver: So the question to the pulmonologist is how much restrictive disease by PFTs [pulmonary function tests] or disease by CT [computed tomography] does one have to have before you have exercise-induced hypoxemia?

Dr Strange: The answer is, nobody knows. It seems to be variable from patient to patient.

Dr Steen: But there are patients that have very mild FVCs [forced vital capacity] of 65%, never have been hypoxemic, and yet develop PA [pulmonary artery] pressures that are clearly vasculopathic with high PA pressures without hypoxemia.

Dr Silver: Is this secondary to scleroderma, or would you see the same in patients with IPF [idiopathic pulmonary fibrosis], Charlie?

Dr Strange: You don't. Usually in IPF, FVCs are clearly below 60% or 50% before you start seeing pulmonary hypertension. By the time you get to lung transplant referral, 50% of all IPF patients have pulmonary hypertension.

Dr Steen: But what degree of pulmonary hypertension is it, Charlie? Is it the really severe kind or is it sort of a moderate degree?

Dr Strange: There are varying kinds. We will occasionally see people with IPF with pulmonary pressures of 70 to 80 or 100 systolic. Although this is not the norm.

Dr Farber: So the norm is usually less than 60, don't you agree?

Dr Strange: But every once in a while you get these PAH-like looking ones. One of the last ones I actually saw had scleroderma, but nobody had diagnosed it.

Dr Farber: When we observe these out-of-proportion PA pressures in an IPF patient, it makes us look for connective tissue disease.

Dr Steen: Right.

Dr Strange: Definitely.

Dr Farber: So given all of these issues, do you think we should be adhering to the ACR [American College of Rheumatology] recommendations about PFTs and echocardiograms every year in scleroderma patients? Is this sufficient? Do we need some other type of screening test?

One of the lessons we have learned from attempts at COPD [chronic obstructive pulmonary disease] screening is how difficult it is to push spirometry into areas where it isn't part of the culture.–*Dr Strange*

Dr Steen: I really think that the screening test to look for the potential of pulmonary hypertension is the pulmonary function tests, specifically the DLCO [carbon monoxide diffusing capacity] and the FVC/DLCO ratio. Patients with pulmonary fibrosis with concomitant pulmonary hypertension have a lower DLCO than someone who has pulmonary fibrosis alone. Although pulmonary function tests are not diagnostic, they are a good screening test in conjunction with the echocardiogram, although a right heart catheterization is still required for confirmation.

Dr Silver: I agree, and I think more people need to be aware of Ginny's paper where she and her colleagues went back and looked at a group of limited patients, with or without pulmonary arterial hypertension. There was evidence of a falling DLCO 5, 10, and 15 years before the clinical diagnosis of pulmonary arterial hypertension. By itself, the diffusion capacity is not diagnostic and can be highly variable, but it is a very sensitive test. If there is a consistent fall in the DLCO, particularly if the FVC is normal, that should be a red flag to the rheumatologist or the pulmonologist that these patients have pulmonary vascular disease.

Dr Steen: That is even true in the patients that have some fibrosis.

Dr Strange: One of the lessons we have learned from attempts at COPD [chronic obstructive pulmonary disease] screening is how difficult it is to push spirometry into areas where it isn't part of the culture. I guess in those places where spirometry and diffusion are not available, the other test that I always thought was helpful was the 6-minute walk test. The problem in a connective tissue disease patient though are Raynaud [disease] and its impact on detecting desaturation. Most of our interstitial lung disease and pulmonary hypertension patients will desaturate, even at mild degrees of disease. It is really the presence of desaturation rather than the walk distance, which is often limited by arthralgias and connective tissue disease symptoms, that I use as a screen.

Dr Silver: As Charlie indicated, there is a technical issue in the scleroderma or connective tissue disease patient that usually is not considered in your average pulmonary patient, and that is just the fact that the oximeter on the earlobe or the fingertip doesn't work well and is not reliable in these patients who have Raynaud phenomenon.

Dr Strange: That's why we use the forehead probe which does take a level of sophistication that many office-based practices don't have.

Dr Farber: This actually brings up a very important issue. How good do we believe the 6-minute walk test is in people with connective tissue disease? Or, is there any kind of screening test that might be better?

Dr Steen: The biggest problem with the 6-minute walk [test] in scleroderma, besides the technical issues, is that it doesn't differentiate between pulmonary fibrosis, pulmonary hypertension, or functional difficulties. There are numerous studies, including many abstracts that will be presented this year at ACR, that highlight the limitations of the 6-minute walk test. Our initial studies were primarily looking at pulmonary hypertension or high-risk pulmonary hypertension, and we were able to show, in that group of patients, that the 6-minute walk correlated with symptoms based on the health assessment questionnaire, scleroderma visual analog scale, as well as the dyspnea index of the University of California at San Diego. In this patient population, the 6-minute walk test correlated quite well, including serially. However, it is less clear whether this test is as effective in scleroderma patients with pulmonary fibrosis versus pulmonary hypertension. I think the 6-minute walk test will be difficult to use as a diagnostic tool, but it is not clear whether it might be useful to determine the effectiveness of treatment within an individual.

Dr Silver: One legitimate value of this test, especially if it is done correctly with the forehead probe, is that if the patient does desaturate during exercise, that patient needs supplemental oxygen, at least during exercise.

Dr Steen: That is particularly important in the interstitial lung disease patients that I think rheumatologists haven't been very perceptive or concerned about. Again, hypoxemia

is a driving factor for pulmonary hypertension in pulmonary fibrosis. That has never really been studied.

Dr Strange: We do have a little bit of information on how the 6-minute walk does not perform very well in the scleroderma interstitial lung disease population. The Build-2 study was a study in which the 6-minute walk test was used as a primary end point in a treatment study for scleroderma interstitial lung disease. It didn't work very well in this cohort.

Dr Steen: But you don't know whether the 6-minute walk didn't work well because the drug didn't work, or because it doesn't work. It certainly hasn't been validated, but with that kind of study it is hard to tell.

Dr Silver: The problem with using the 6-minute walk serially in a given patient is that unlike idiopathic pulmonary arterial hypertension or idiopathic pulmonary fibrosis, patients with scleroderma and other connective tissue disease have a multisystem disease, and so their decline in distance walked in a given period of time may or may not relate to pulmonary vascular or lung function. For example, it may relate to worsening skin disease, joint disease, deconditioning, overlapping myositis, and a host of other nonpulmonary factors.

It has been shown in most of the clinical trials that for the same functional class, scleroderma patients walk a lesser distance than individuals with other forms of PAH.
–Dr Farber

Dr Steen: But it is still not clear, Rick, whether that on a serial basis these other factors will make that much difference.

Dr Silver: Yes, I think you just don't know until studies are done, but we have all had patients whose skin disease waxes and wanes, or joint disease or muscle disease waxes and wanes. You could certainly predict that the 6-minute walk would change, as a result, and this may be reflective of nonpulmonary involvement.

Dr Strange: The other thing we have noticed is a fair number of patients that complain of fatigue during their 6-minute walk. I wonder if this is a correlate of decreased cardiac output related either to diastolic dysfunction or a consequence of small vessel disease in the muscles, which are other variables influencing the utility of the 6-minute walk in the scleroderma population as opposed to patients with pure pulmonary disorders.

Dr Farber: As a final point, it has been shown in most of the clinical trials that for the same functional class, scleroderma patients walk a lesser distance than individuals with other forms of PAH. And, once again, it is an issue of whether it is actually because of the PAH itself, the interstitial fibrosis, or some other form of the systemic disease, such as diastolic dysfunction. I think it is a very difficult group in which to use a 6-minute walk; I echo Rick's point that if they do deteriorate, I often do not know whether it is because of the pulmonary disease, be it fibrosis or vasculopathy, or because the patient had a bad day because of a flare of arthritis.

Dr Strange: What we end up doing there is defaulting into the CT scan, full spirometry with diffusions and lung volumes, echocardiogram, and even right heart catheterization to try and sort it all out.

Dr Silver: Plus enzymes, sedimentation rate, and things of that sort as well.

Dr Farber: So, should we approach scleroderma patients with PAH differently than other patients in the PAH group?

Dr Silver: I think we have to look at them differently because if you look at the results of virtually any study, these patients do not fare as well as those with idiopathic pulmonary arterial hypertension for whatever reason, whether it's lung fibrosis, or cardiac disease, or other factors.

Dr Steen: There really are different populations of patients. Also, the question is how long their disease duration has been and whether they have really had it longer than the IPAH patients, whether they are older and have cardiac issues. Unfortunately, I think if you really look back at the clinical trials and the comparison between an IPAH group which tends to be a pretty pure group, and the scleroderma group which is a very unpure group, it is hard to tell what the differences are due to. If you took a pure isolated pulmonary arterial hypertensive patient at the onset of his or her disease, early on, when you could first diagnose it, it may be the same. But, the problem is that we don't make this diagnosis right away. These people have adapted to their shortness of breath. They have compensated and said, "Oh, it is just related to my disease." We really have to fight with them to get them to even acknowledge that they are short of breath, so that by the time they are diagnosed with pulmonary hypertension they may have had it for a much longer period of time.

Dr Farber: Okay. Charlie, what do you think?

Dr Strange: I struggle half the time to figure out who might respond to immunosuppressive therapy. I think we are all aware of the single case here and there that would suggest the presence of an inflammatory vasculitis with pulmonary hypertension that would respond to immunosuppressive therapy. I guess I am interested in what Rick and Ginny have to say about how to find that person.

Dr Silver: I guess I don't really know how to find them and I have always felt that they are most likely to be present in those patients who have an overlap, particularly with lupus, which we know is an inflammatory vasculitis. So, these are patients with RNP [ribonucleoprotein] antibodies and low complements as well as features of lupus on top of their features of scleroderma.

Dr Steen: I have never really been impressed in patients with

pure scleroderma, even in somebody that has significant pulmonary fibrosis, that the treatment of their fibrosis has any effect on the pulmonary hypertension.

Dr Silver: I agree with that.

Dr Strange: I would agree with that too. I haven't seen anybody yet respond to anti-inflammatories. I know they are out there, but I sure haven't found them.

Dr Silver: They don't look like scleroderma, at least at the beginning when they are having pulmonary symptoms. They look more like lupus with puffy hands and arthritis, but they have Raynaud phenomenon, and they tend to have RNP antibodies. They also have dermatitis. If they survive the inflammatory vasculitic portion of the disease, later they will start to look more like a typical scleroderma patient.

Dr Farber: Are there any particular reasons why individuals with connective tissue disease respond to vasodilator therapy less well than individuals with other forms of PAH?

We need our professional society to establish practice guidelines that would include PFTs and echocardiograms and right heart catheterizations in a certain patient who has PFT or echo [cardiogram] findings.
–Dr Silver

Dr Steen: Again I think it's such a multitude of different problems. There are few pure pulmonary vasculopathies. I don't know how many of the patients that have been studied in these comparison groups are pure vasculopathy. They are likely to have some fibrosis, likely to have some diastolic dysfunction. They are older. They have had a longer duration of their disease. It's very hard to compare a typical type of patient that is an IPAH versus a scleroderma.

Dr Silver: I think the difference lies in the fact that the scleroderma patient has a widespread systemic vascular disease. It involves, as Charlie said, the peripheral muscles, cardiac tissue, as well as the lungs and other organs. This is far different than that young female patient with idiopathic pulmonary arterial hypertension whose disease is restricted to the pulmonary circulation. Even if you match scleroderma patients on the basis of cardiac parameters, they do less well than the idiopathic PAH patients. I think that is telling us that there is cardiac disease that we are not able to detect routinely, or that it's just a generalized widespread vasculopathy that makes them less responsive to treatment.

Dr Strange: I have always been impressed looking at the cardiopulmonary exercise test, how early an anaerobic threshold is met. Basically all of the papers on CPET [cardiopulmonary exercise testing] and scleroderma have shown that there is this cardiovascular limitation. The problem in sorting this out though, is how much is intrinsic heart disease and how much is actually coming from the peripheral muscles and small vessel disease. It is my opinion that this really is a small vessel disease at the muscular level that is really driving the lack of response. That's not to say that some of the medicines might not affect that in some way, but you have so much vascular drop-out, making this a different disease.

Dr Farber: Actually, that is an interesting point, which leads to the next question. It is interesting that although scleroderma-associated PAH is included in the PAH group, the pathology doesn't look exactly identical. Furthermore, the incidence of genetic abnormalities, at least the ones that we know of at this point, is markedly less, if even present, in the connective tissue population. So, do you think this may require a sub or reclassification?

Dr Silver: Well, I think it does and actually it may be further complicated if you consider the other connective tissue diseases. So, lupus may be more vasculitic or inflammatory. Myositis may be more inflammatory. Scleroderma is less inflammatory, but as Charlie indicated, is widespread and characterized by endothelial cell dysfunction and drop-out of capillaries that is widespread.

Dr Strange: I think we underestimate the benefit that has come from lumping instead of splitting in this whole disease category of PAH and when we start doing subgroups of diseases that are subtly different we lose a lot of the benefits, at least at the FDA level of the drugs that we can use, and boy I sure do like to keep these all in the same subgroup while recognizing the differences at the same time.

Dr Steen: I definitely agree with that. I think that if we start separating them and saying that they are not pulmonary hypertensive, we are going to really get into trouble and not have anything to treat them with. I think we have to go even further and look at the subsets of patients that haven't been looked at in clinical trials for PAH such as the fibrosis patients that have pulmonary hypertension. We also have to look at what these drugs do in patients with concomitant diastolic dysfunction. I don't know where the sitaxsentan trial that looked at diastolic dysfunction is, but the results may be available soon. It may be that our PAH drugs are helpful in some of these other groups, but they haven't been well studied, so we don't know.

Dr Farber: Well, it is interesting that you bring that up, since sitaxsentan, seemingly was at least equally or maybe even a little more beneficial in the subset of connective tissue PAH patients.

Dr Steen: Which is not available?

Dr Farber: Well, unless you are in Europe. So, would we all be interested in seeing trials that address connective tissue patients alone?

Dr Steen: I think that this is really important because including the connective tissue disease patients alone and recognizing the different subsets, even though they are all included in the study, would be really important to see which groups of patients are responsive or not. It would also be nice to study very early patients and even consider doing a preventive study. These are studies that take a long time to do and it has been tough to think about that, but at least if we can do [a study on] pure connective tissue disease patients that have different types of disease, I think that would be very helpful in understanding their responses.

Dr Strange: I think we probably ought to at least touch on the whole controversy around heart catheterization and how important it is in the scleroderma subgroup, not only to pull out the left ventricular dysfunction patients. If people aren't doing well over time, it may be due to the increased cardiac output caused by some of the PAH drugs. This may change diastolic dynamics of the left ventricle. Repeat heart catheterization has never been studied in the connective tissue disease population and probably should as an isolated study group rather than grouping everybody together as PAH.

Dr Farber: I'm with that. In our experience, we have had patients with connective tissue disease who clearly had PAH, were started on vasodilator therapy, deteriorated during therapy, and at recatheterization had evidence of diastolic heart disease. Treatment with vasodilators had obviously unmasked this.

Dr Silver: That's because they have a vasculopathy that decreases capillary capacity in the myocardium, and they can't respond appropriately. Again, it points to the systemic vascular disease that these patients have, which is not present in the idiopathic PAH group.

Dr Steen: How do you tell the difference between somebody who has pulmonary hypertension out of proportion to the degree of diastolic dysfunction? Is it somebody that has mean PA pressures of 60 and a wedge of 17? I mean, that's a group of patients that perhaps still has primarily vasculopathy, even though they have diastolic dysfunction. And then we have the group, the patients that I have been looking at recently, that are the exercise-induced group in which they have resting normal pressures, resting wedge, and you exercise them and they get increased wedges and increased mean pulmonary pressures. So, that is going to be an issue as well.

Dr Strange: I think what all this brings out is the fact that we have evolved to the point where we thought we had very simplistic groups of patients, or at least some of us did who were naive, and these patients are incredibly complicated. Every one of them is probably different. It impresses me that every one of them is hemodynamically different.

Dr Steen: The antibody profile may help. Hunter Champion and I have an abstract for our ACR meeting looking at diastolic dysfunction; 50% of them had a nucleolar antibody.

Dr Farber: There may be ways to categorized these patients based on antibodies or other factors that we have not yet found.

Dr Steen: Antibodies, genetics, pulmonary function tests, I think all of these play a role. I think we used to think very naively 15 years ago when Rick and I first started in this area that pulmonary hypertension was all isolated, all centromere, and it wasn't really until we had these drugs that we started screening for these patients. Prior to available therapy, we didn't want to know that they had pulmonary hypertension.

Dr Farber: I think one very important point to which we have all alluded, and which Charlie emphasized, is the importance of right heart catheterization given the complexity of these patients and the hemodynamic changes over time. Not only is right heart catheterization imperative for diagnosis, but also to characterize patients if they deteriorate.

Dr Silver: I think that most rheumatologists have gotten the message on the importance of right heart catheterization for initial diagnosis, although we still see patients who are put on drugs without right heart catheterization. I think we do need to emphasize the point that right heart catheterization should be considered to either evaluate the effect of the treatment or to reassess the patient who is not responding in the way that we anticipate they should.

Dr Steen: I think that rheumatologists need to understand a little bit more about the presence of diastolic dysfunction and concomitant cardiac involvement in the connective tissue disease patient.

Dr Strange: Conversely, the pulmonologist and cardiologist needs to understand the nuances of the connective tissue disease patient.

Dr Farber: What lies in the future?

Dr Steen: The first thing we have to do is to get the connective tissue disease patient evaluated and diagnosed sooner rather than later. These patients are not good at telling you that they are short of breath, so you can't use that as a parameter. They will inevitably say, "Oh, I'm fine, I'm not short of breath, don't worry." You have to rely on their echo[cardiogram] and particularly their pulmonary function tests. Diagnose them early and get them treated early. I don't know whether that is going to make any difference. It certainly makes sense that it should make a difference, but until we consistently do this in all our patients with scleroderma, we are not going to know.

Dr Strange: Ginny, I do think we need that trial that randomizes WHO [World Health Organization] functional class I patients to early treatment in order to answer your questions.

Dr Steen: I don't think we are ever going to get a company to do that.

Dr Silver: Ginny, I go back to your article, which I quote many times, where you looked at the differences between the group of patients that developed pulmonary hypertension and the group that did not, and found that the group that developed pulmonary hypertension was less likely to have received a calcium channel blocker. Am I correct?

Dr Steen: That is definitely correct.

Dr Silver: That would suggest that early treatment, although in this case it was treatment of Raynaud phenomenon, might make a difference. I would think that this would be ammunition one might use to get such a study.

Dr Steen: It's ammunition, but that's all it is. All we can say is that at least one company has chosen to do a study looking at a catheterization at one point and 3 years later another catheterization as a "time to event."

Dr Farber: Do you think the majority of patients with connective tissue disease are getting screened on a yearly basis or getting screened when they become symptomatic?

Dr Steen: No. As much as my area knows about my interests and experience, I still get patients who are referred maybe for something else and have not had PFTs in 6 years. I don't understand this. Providers are still relying on symptoms.

Dr Farber: How about South Carolina?

Dr Silver: Well we know from the UNCOVER study that if you go into a community's rheumatology practices, 20% to 25% of the patients who have an echo[cardiogram] because of evidence of pulmonary hypertension have never even had an echo[cardiogram] offered before that study. So, it's not on the radar screen of many rheumatologists in the community.

Dr Farber: It would seem relatively easy to educate physicians to do; however, it obviously has been difficult.

Dr Steen: I think that there has been an emphasis on the echo[cardiogram] and not enough emphasis on the pulmonary function tests. The echoe[cardiogram]s are so variable in that middle range. I used to think that everybody with scleroderma had a PA pressure of 30 or 35, and didn't realize that normal people really were lower than that. So, that range of 30 to 45 is sort of a very hazy group. You don't know what their PA pressure is until you do the catheterization.

Dr Silver: I think we need our professional society to establish practice guidelines that would include PFTs and echocardiograms and right heart catheterizations in a certain patient who has PFT or echo[cardiogram] findings. That's probably the only thing that is going to drive this because, otherwise, we know that what we have done so far has not really gotten the attention of the community of rheumatologists.

Dr Strange: Should we redefine the diseases while we are doing it Rick?

Dr Silver: Well, I would say let's take one thing at a time. ■