Integrating Current Strategies for Continuing Assessment of Pulmonary Arterial Hypertension


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In this discussion four experts shared insights on what might be considered the "gestalt" of diagnosing and monitoring pulmonary arterial hypertension. They ranged over a broad spectrum of issues that included thromboembolic pulmonary hypertension, exercise testing, hemodynamics, imaging studies, and response to therapy. The discussion was moderated by Vallerie V. McLaughlin, MD, Associate Professor of Medicine, Director, Pulmonary Hypertension Program, University of Michigan Health System, Ann Arbor, Michigan. The participants included Richard N. Channick, Associate Professor of Medicine, Pulmonary and Critical Care Division, University of California, San Diego Medical Center, San Diego, California; Ivan M. Robbins, MD, Director, Pulmonary Hypertension Center, Vanderbilt University, Nashville, Tennessee; and Victor F. Tapson, MD, Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina.

Dr McLaughlin: We welcome everyone and thanks for joining us. Today's Roundtable is going to elaborate on the issues regarding diagnosis that were raised in the three articles in this issue of the *Journal* and also focus on the continuing assessment of patients with pulmonary hypertension. One important aspect of the diagnostic algorithm includes the evaluation for thromboembolic disease. The guidelines clearly state that the ventilation perfusion scan is the test of choice for this. However, we commonly see patients with some amount of interstitial lung disease, for example, in the setting of scleroderma, in whom the V/Q scan can be problematic. Rich, how do you evaluate thromboembolic disease in patients in whom the ventilation perfusion scan might be problematic because of underlying lung disease?

Dr Channick: We still are big fans of V/Q scans here at UCSD. Our experience has been that we don't see small, matched defects in patients who have operable thromboembolic pulmonary hypertension but typically we're talking about large, segmental or greater or multiple defects. Even in the setting of underlying lung disease the V/Q scans in those cases can be very useful. CT angiography does have a role in some of these patients to confirm the diagnosis and also to look for other abnormalities in the mediastinum. We're concerned about patients who have false-negative CT angiograms in the setting of chronic thromboemboli, and we have some clear examples of that, so we would never eliminate a patient from surgery based on a negative CT angiogram.

Dr McLaughlin: But say you have a patient with scleroderma with mild pulmonary fibrosis and quite severe pulmonary hypertension that you really think is PAH associated with scleroderma. The lung scan is interpreted as intermediate probability. What do you do at that point?

Dr Channick: There are many kinds of "intermediate probability" scans. That's such a broad term. Any matched defects are going to be intermediate probability, but if you're experienced in looking at V/Q scans, you will get a lot more information by looking at the scan and so if we see several large perfusion defects even if there may be a small ventilation abnormality in an area with fibrosis, that appearance will certainly be suspicious enough for us to probably proceed with pulmonary angiography. Because, again, even if you do a CT angiogram and it looks "unremarkable," you should give the patient the benefit of the doubt and proceed with a definitive study before deciding he or she is not going to be a candidate for surgery.

Dr McLaughlin: Vic, how do you handle those patients?

Dr Tapson: I completely agree with Rich. There are a couple of key things that people who do not practice at PH centers may not realize. You really cannot rule out chronic thromboembolic pulmonary hypertension with a spiral CT scan. You may see clues. Mosaic perfusion is a great clue; it is not

diagnostic. The key about V/Q scans is that in certain patients sometimes even a so-called high probability V/Q scan can throw you off. Certain centers will realize that if a patient has interstitial lung disease and sarcoidosis and has a high probability scan, sometimes that's not thromboembolic disease. That's where a PA angiogram can be very helpful. We have had at least 5 or 6 cases like that. CT and V/Q can complement each other, but I always hate to say someone does not have chronic thromboembolic pulmonary hypertension on a CT scan.

Dr McLaughlin: Ivan, anything to add?

Dr Robbins: It's hard to argue with these two experts. All I would say is that we have been using a 64-slice CT scanner recently. The interventional radiology people here are even advocating a CT angiogram over a pulmonary angiogram in some patients. The images are phenomenal. Now I know there are not studies comparing it with an angiogram. What they like about it is that you get a view of the thickness of the vessel wall, whereas with a pulmonary angiogram you just get the inside of a vessel. You get some very nice pictures of the irregularities of the vessel wall with CT angiography.

Dr Tapson: That's a good point. I agree with Ivan. CT has come a long way. With 64-slice scanners it's hard to know exactly what its sensitivity is, but clearly it's a fast, easier study, there's less concern about breath hold, and patients can get a better quality study.

Dr McLaughlin: Do you think MRI will ever replace the CT scan or pulmonary angiography in the diagnosis of chronic thromboembolic pulmonary hypertension?

Dr Channick: Certainly the images can be impressive and there is the potential in the future to replace conventional angiography. I would not use it as a screening test but some of the images on MR angiography approach conventional pulmonary angiography. I don't think it's quite there yet, but if I see an MR angiogram that shows clear-cut findings of chronic thromboembolic disease and let's say you already have hemodynamics from a cath, then we'll proceed with surgery based on that study.

Dr McLaughlin: Let's move on to echo. There are some pitfalls to echo, including overestimation and underestimation of PA pressures. And there's much more to echo than the PA pressures. Any pearls you want to share as you interpret echo results?

Dr Robbins: I agree that I do not look at it for the pressure at all. To me, it's a good test to look at the RV function, RV size, and RV hypertrophy, and to exclude valvular disease. Patients and even other physicians ask what the pressure is. They'll quote you the pressure but it is so dependent on the TR jet, so I just like to look at the RV function. Having said that, I'm sure everyone has had the experience of a complete disconnect between what the echo shows the RV function to

be and how your patients are doing. I think it's a good screening tool. I don't know what the perfect screening tool is. It's becoming more apparent that resting hemodynamics don't tell us the whole story either.

Dr Tapson: Ivan makes a good point about echo and that is number one, estimated RV systolic pressure is not always terribly accurate. When patients ask us what their pressures are we try to get away from that. As they get worse, their pressures may actually go down some. As they get better, they may go up a little bit. Even if it was accurate, you need to be careful interpreting that. RV function is the key issue with echo.

Dr McLaughlin: Those are some of the issues I wanted to bring out. For example, if a patient is at risk, such as a scleroderma patient who has a normal estimated PA pressure, but when you look at the echo the right ventricle is big and the septum is flattened, that leads me to believe the patient has pulmonary hypertension no matter what the echo estimate is. That patient should still have a further evaluation, including the heart cath. And the other way around, too. Sometimes the echos can overestimate pressures. They can misinterpret the tricuspid closure sound as the TR jet. If someone has a pressure estimated to be 70 and the right ventricle is nice and small with normal function and the septum moves normally, I question that pulmonary artery pressure. So, as Ivan said, we're looking at more than just the PA pressure on echo, we're looking at the size and function of the right ventricle too. But Ivan, you made another point that is really interesting. We measure the hemodynamics at rest and, most commonly, patients complain of symptoms with exercise. Many practices are starting to incorporate exercise echo or exercise cath in their protocols. What are your thoughts on exercise hemodynamics and how do you make treatment decisions based on them?

Dr Channick: I have quite a bit of experience in that, but the answer to your questions is I don't really know, even though we do exercise hemodynamics on virtually every patient who has normal or near normal pulmonary artery pressures and find abnormal increases in pressure not uncommonly—at least half the time we do these tests. All these patients are symptomatic. What we don't really know is clinical significance. A fair number of these patients don't in fact have pulmonary arterial hypertension but have left ventricular diastolic dysfunction. Even in the patients we diagnose as having PAH just with exercise, we don't have a really good sense of whether it is important to treat those patients or, if we do treat, what medication to use. We have followed many of these patients now for several years with yearly exercise tests and, for the most part, the disease remains stable. In other words, we continue to see the abnormal exercise response. Patients still have some symptoms. They have not gotten better or worse. We haven't done a systematic look at treatment effect on this phenomenon, but many of these patients are not getting any active treatment and remain basically the same for now up to 7 years for some of these patients we have followed.

Dr Robbins: That's one of the biggest problems with doing that. We don't do that at all because there is no good standard as to what is a normal hemodynamic response to exercise.

Dr McLaughlin: There are a couple of things. The first is the point Rich made about diastolic dysfunction. That is something you are not going to be able to tell on an echocardiogram because if you do an exercise echo and your PA pressures go up, there's really no good way to tell if it's because your left heart pressures went up too. Rich, were you referring to exercise echo or exercise cath that you had the most experience with?

I think we are raising the treatment standards, we're raising the bar. We are much less likely to accept the same now as we were a year or two ago because we have other options and we understand the prognostic value of certain treatment goals. My plea would be for us to try to figure this out in a controlled fashion.

Dr Channick: Exercise cath was what I was referring to. With regard to exercise echos, I would say my overall sense is that they tend to overestimate the actual pressures

Dr McLaughlin: Rich, when you do an exercise cath do you find you can reliably measure the wedge pressure while patients are exercising and while their respiratory rate is so high?

Dr Channick: In some cases you can't. I think it's variable. In some patients you see a lot of artifact and then stop exercise and measure immediate postexercise wedge pressure. And in some of these patients who I believe have diastolic dysfunction you can see an elevated wedge pressure that very quickly returns to normal following cessation of exercise. You can look at end-expiratory wedge pressure even when they're breathing fairly hard.

Dr Robbins: But again I come back to the point that we don't know what the normal response is, necessarily, and I think it's very variable between people. A study was done in Leadville, Colorado, which is at about 3000 meters, where the high school students were studied. The researchers catheterized all of them and found that the champion skier had a mean PA pressure of greater than 100 mm Hg with exercise. So, I don't know what the normal response is. That may be why a lot of patients followed by Rich are fine, because that's just their normal response to activity.

Dr Tapson: I wish there were an easy way to do this because it's a point well taken that resting hemodynamics may not tell the whole story. We have not had good luck with exercise tests—exercise echo or exercise imaging.

Dr McLaughlin: As you all know, exercise hemodynamics will be performed in a subgroup of patients enrolled in the EARLY trial and perhaps we might glean a little bit of information from that. Let's move on to vasoreactivity testing at

the time of the right heart catheterization. The paper from the French group was recently published in *Circulation* that shows this is a very small portion of patients with IPAH who respond to vasodilators at the time of cath and ultimately do well long term with calcium channel blockers. They have also presented data at meetings suggesting that virtually none of the patients with any other type of associated pulmonary arterial hypertension respond in this fashion. Of course at many academic centers we still do vasodilator testing on everyone just because it's part of the evaluation, but in reality it probably does not affect patients with scleroderma or portal hypertension or congenital heart disease all that much. Do you all still do acute vasodilator testing on all of the patients you evaluate for pulmonary arterial hypertension?

Dr Tapson: I would say we still do unless the patient is very sick, for example, class IV patients, those with a low cardiac index. We're not going to use calcium channel blockers in those patients. I will say that we do test some other patients. Although I don't know why, we find a really good responder, about 1 in 3 or 1 in 5 in whom we use calcium channel blockers. We can't get them up to 720 mg of diltiazem a day. We're going to end up treating them with endothelial antagonists anyway or perhaps some other drug, so I think while it's nice to collect the data, it's not nearly as useful as we gather data with new drugs. On the other hand, maybe we will learn something with new drugs, maybe we will find out patients respond to vasodilators and ultimately do better with some new drug we try. But I think it's decreasingly useful.

We always examine the patient and it never ceases to amaze me that in a new patient you might hear findings classic for PH, a booming second heart sound that has not been detected before. It's important for medical students and trainees to understand that there are some very simple classic, dramatic findings in some patients by physical exam in PH.

Dr Robbins: We still tend to do it on everyone except, as Vic says, those who are severely compromised. There's no way they are getting calcium channel blockers. But I think it is useful, and as Vic touched on, it may be helpful, and we don't have enough data on this now, in predicting response to therapy or guiding your medication. The other thing I would point out is that even though we do a vasodilator study in the scleroderma population and have had some patients who have exhibited a fairly profound vasodilatory response with inhaled nitric oxide, these patients do not do well and they feel worse and do worse when you try to treat them with calcium channel blockers.

Dr McLaughlin: As an academic center we tend to use nitric oxide in nearly every patient at the time of the first cath and I think it's very rare that you ever see anyone respond according to the strict definition. Perhaps some day we'll sit down and analyze the prognosis with different medications based on the response to a vasodilator. I'm a little more conservative in the patients who have elevated left heart pressures. We see a lot of left heart disease, so if I see a wedge pressure of 20 mm Hg, I tend not to give a vasodilator in the cath lab for two reasons. First, we're not looking for long-term calcium channel blocker responsiveness in patients with this diagnosis, and second, there is certainly the risk of putting them in pulmonary edema in the cath lab with nitric oxide. Let's move on to how we follow patients. We have good guidelines for diagnosis, although there are little aspects that each of us tweak here and there. But we all follow patients in a different way and this is becoming increasingly important as we have more therapeutic options from different classes to offer patients. In general, consider your average functional class III PAH patients whom you treat with, for example, an oral agent initially. How do you follow those patients, how often do you see them, what tests do you do, and what makes you decide that they are not responding or inadequately responding to a therapy and that it is time to switch or add something?

Dr Tapson: As a general rule we follow most of our PH patients every 3 months. We have less severely ill patients whom we see less often. Like many big PH centers we have patients from far away, from Florida, from Maryland, so we try to take that into account. But 3 months is the general rule. At every 3 months we do a 6-minute walk test, an echo at 6 months, and we don't have any specific time when we repeat a right-heart catheterization. We always do a right-heart catheterization at the onset and we don't necessarily repeat it at a year or two, but we do it as clinical status and therapy dictate. We do other tests now, brain natriuretic peptide (BNP) levels every 3 months in all of our patients. I wouldn't use that alone, although in some patients we have found that BNP level correlates very well with worsening of the echo and worsening of clinical status and the walk test. It may be that in certain patients that might reduce the need for more invasive testing or more expensive testing. We don't do a formal Borg test or dyspnea evaluation. We always report the functional class of each patient. To be old fashioned, one of the most important things we do is talk to the patient. Usually in talking to the patient we know after 5 minutes whether they are better or worse. Your clinical studies usually confirm that. We always examine the patient and it never ceases to amaze me that in a new patient you might hear findings classic for PH, a booming second heart sound that has not been detected before. It's important for medical students and trainees to understand that there are some very simple classic, dramatic findings in some patients by physical exam in PH.

Dr McLaughlin: Ivan?

Dr Robbins: In general with oral therapy we see patients back, during the first year, every 3 months. As they get better we stretch it out a little if they're stable, anywhere from 4 to 6 months. Some patients will wait at home while they're getting worse and not let you know, even with fairly frequent follow-up. But most patients will, hopefully, tell you. We in general do a repeat cath at about one year after starting a new therapy. If there's deterioration and we're thinking of

another therapy, we usually do another right-heart cath. Obviously, if they are in severe right-heart failure, we would not delay getting patients epoprostenol or other therapy waiting for a repeat cath. We are following BNP levels now. We probably don't have the database that Vic has, but we've seen some patients who were in severe heart failure, and their BNP levels were not terribly high. They weren't normal but they weren't as high as those of some other patients. We've found that it's pretty variable. That may reflect how we do the test here. I'm not sure.

Dr Channick: The way I look at it very simply is that you want to determine whether a patient is better, worse, or the same. Given the fact that we have multiple other therapeutic options, it is important to make that determination. If a patient is clearly improved, and I agree that there is not any single predictor of what we mean by improvement—function, walk distance, hemodynamics—I think you have to look at all of those things in composite without any clear guidance for specific levels of the parameters. If a patient is clearly improved at 3 to 4 months, I would not change therapy. If a patient is worse, and you could also debate what we mean by worse—worsening function or walk test at 3 to 4 months or even increasing BNP—we like to do a cath to confirm worsening, and then obviously we would add another therapy. A sizable number of patients fall into the third group: they are about the same. In other words, they're functionally about the same, their walk distance is about the same. Those are the patients we will really learn from because now that we have other therapies, either experimental or approved, that we can add on, we are gaining experience in this combined approach.

Dr McLaughlin: I think we are all saying the same thing in a slightly different way. Those stable patients, not the critically ill patients whom we give parenteral therapy immediately, but those stable patients in whom we might start oral therapy, we tend to see them every 3 to 4 months. The patients will tell you how they are doing, whether we call it functional class or whether we talk to the patient for 5 minutes. We will have a pretty good idea of how the patient is doing. The other testing helps add to our database when we make decisions on those patients and we, too, do the 6-minute walk test regularly at visits every 3 to 4 months and get a BNP. You put all those together when you try to make decisions for the patient. We tend to do a right-heart cath after patients have been receiving a therapy for about a year and that time may shrink now that we're thinking about other additive therapies. I think we are raising the treatment standards, we're raising the bar. We are much less likely to accept the same now as we were a year or two ago because we have other options and we understand the prognostic value of certain treatment goals. My plea would be for us to try to figure this out in a controlled fashion. Many of us are starting to add other therapies because we are trying to do the best thing for our patients, and I wonder if we're ever going to know unless we do a controlled trial. I think the next wave of clinical trials in pulmonary hypertension is going to be the combination trials, and I am hopeful that these patients Rich described will be entered into combination trials so we can answer this question in an evidence-based fashion.