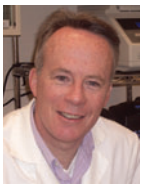
Pulmonary Hypertension Roundtable

Controversies and Consensus in PH With Left Heart Disease: Dosing Issues, Transplant Considerations, Wedge Pressure Targets, Postop Drug Selection, and More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This discussion was moderated by James P. Maloney, MD, Associate Professor, Division of Pulmonary Science and Critical Care Medicine, University of Colorado, Denver, Colorado. The participants included Robert P. Frantz, MD, Assistant Professor of Medicine, Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota; Michael A. Mathier, MD, Assistant Professor of Medicine, Director, Pulmonary Hypertension Program, and Associate Director, Cardiovascular Fellowship Program, University of Pittsburgh, Pittsburgh, Pennsylvania; and James B. Young, MD, Professor and Chairman, Division of Medicine, and George and Linda Kaufman Chair, Cleveland Clinic Foundation, Cleveland, Ohio.

Dr Maloney: How big a problem is pulmonary hypertension associated with left heart disease, particularly pulmonary hypertension out of proportion to left heart failure?

Dr Young: I can speak as a heart failure clinician and also as someone interested in sorting out those patients with heart failure and pulmonary hypertension who might benefit from heart transplantation. It's a huge problem for us and not one that's been very carefully studied. We see several scenarios in our advanced heart failure patients. One, patients with terribly disturbed left ventricular systolic function and very high pulmonary artery pressures noted in conjunction with a high wedge pressure that responds to dropping the wedge pressure with different tools that cause the pulmonary hypertension to improve, but leaves the patient still walking around with pulmonary artery systolic pressures in the 50 to 60 mmHg range. This is still disturbing. Then you see the patient with ejection fractions in the 35% to 40% or maybe 50% (low normal) range, with severely hypertrophied ventricles and so-called "diastolic dysfunction" and pulmonary hypertension that is surprisingly out of proportion to where one would think those pressures should be. Finally, you can see a third type of patient who clearly has two distinct physiologic problems and will have pulmonary hypertension with clear-cut gradient across the lungs that is significant and a pulmonary artery diastolic pressure to wedge pressure gradient that points toward two different processes. Now, how does one sort out those three scenarios without catheterization and simply with noninvasive studies? What we do with brain natriuretic peptide measurements, and even more important, how do we treat them with the medicines we have available, is a contentious subject.

Dr Maloney: That sounds like that's particularly a problem with patients who are being evaluated for heart transplants in that now they have these chronically elevated wedge pressures and you know that once you get them a new heart that pulmonary vascular remodeling is not going to go away. How do you approach those patients pretransplant, and then also posttransplant when you are left with a well-functioning left ventricle but you have someone who's had pulmonary vascular remodeling from years of heart failure? How do you evaluate those patients beforehand for such problems, and how do you approach them after the transplant?

Dr Mathier: During pretransplant evaluation we largely screen out patients who are eventually going to end up in that category, so if we see, as Jim pointed out, a high transpulmonary gradient during the transplant evaluation process, we actively look to see if we can bring that gradient down into a normal or perhaps just mildly elevated range. If we're successful at doing that, we generally feel comfortable going on with an orthotopic heart transplant, and in my experience, in general, those patients don't tend to go on to have very high pulmonary pressures following transplant. Occasionally, one will sneak through so that you are left with significant pulmonary hypertension even with normal or near normal left-sided filling pressures and normal cardiac function. If that's the case, then that person in my mind falls into that nebulous category of pulmonary hypertension

out of proportion to left heart disease and I would consider specific pulmonary hypertension therapy in that setting. Fortunately, this is not a terribly common patient in our experience.

Dr Frantz: For patients with left heart failure who are undergoing heart transplant evaluation and are found to have pulmonary hypertension that raises concern about risk of donor right ventricular failure, we administer nitroprusside in the catheterization laboratory in an effort to document reversibility of the pulmonary hypertension. The goal here is to mimic the posttransplant state, ie, what would the pulmonary artery pressures be if left-sided hemodynamics were normal? If the pulmonary capillary wedge pressure normalizes but pulmonary artery pressures stay high, eg, with a transpulmonary gradient of 14 or greater, then transplant will be risky or impossible. Sometimes ability to administer nitroprusside is limited by systemic hypotension, and it may not be possible to bring down the pulmonary capillary wedge pressure because of advanced cardiac failure. If the pulmonary capillary wedge pressure cannot be corrected because of advanced congestive heart failure, and the pulmonary artery pressures stay high, then other maneuvers such as short-term administration of inotropes to increase cardiac output may be helpful in demonstrating reversibility. Occasionally we add inhaled nitric oxide to intravenous nipride in an effort to maximize pulmonary vasodilation while still trying to lower pulmonary capillary wedge pressure. In addition, sometimes administration of inotropes such as milrinone continuously for several weeks as an outpatient (if the patient has a defibrillator to protect against risk of sudden death) has been successful in our experience in lowering pulmonary artery pressures into a transplantable range. This may reflect a more sustained unloading of the pulmonary vasculature. Occasionally this phenomenon occurs following left ventricular assist device placement as well, thereby making the patient a more suitable heart transplant candidate.

For patients with preserved systolic function but documented diastolic heart failure, it is critically important first to achieve excellent blood pressure and heart rate control. This includes documentation of good blood pressure control during exercise, since high systemic and left ventricular pressures during exercise often drive the symptomatology. Many patients with longstanding systemic hypertension, especially the elderly, develop substantial diastolic heart failure that may be improved just with really good conventional antihypertensive therapy.

Dr Maloney: What are the lessons you feel we can draw from trials such as the epoprostenol in chronic heart failure trial, which was called FIRST, the Flolan International Randomized Survival Trial? As new drugs come on board for pulmonary arterial hypertension, the pharmaceutical companies look to expand indications to more common disease, such as congestive heart failure. It seems that just about every time that's been done, the drugs that work for pulmonary hypertension don't work for congestive heart failure, such as endothelin receptor antagonists. Still, some people were tempted to use these drugs in patients who had a component of pulmonary hypertension related to left heart disease. What's your experience in interpreting these studies and your advice to clinicians?

Dr Young: I'm old enough that I participated in some of those "ancient" trials. The FIRST was pretty disappointing, with observations indicating that Flolan, though effective in some individual patients with high pulmonary artery pressures, produced problems more often than not. You could turn some patients awfully blue pretty quickly as you precipitated intrapulmonic shunting if you weren't terribly careful. Indeed, it remains a bit of a mystery why some vasodilators have been associated with less than robust and beneficial outcomes, including the endothelin antagonists. If you think about it, in congestive heart failure, endothelin antagonists should have worked great, and in some of the initial dose findings studies, data raised great hope based on pulmonary pressure lowering as well as improvement in flow through the lungs. In the end, it just didn't quite pan out. That suggests maybe it's the wrong dose we're using. Maybe there are other subtle issues related to right heart and left heart function that we haven't quite cleared up, but interestingly enough, I'm not ready to completely throw out those drugs in the patient with terrible pulmonary hypertension. I just think we need to do some smarter studies to, perhaps, figure out the nuances of dosing these drugs.

Dr Mathier: If I might add, the studies we have available were performed in patients with heart failure, but not specifically with pulmonary hypertension complicating it.

Dr Maloney: Very good point.

Dr Mathier: And secondly, with the endothelin antagonist trials, the REACH-1 (Research on Endothelin Antagonism in Chronic Heart failure) is the only one for which we have detailed data. The doses were clearly inappropriate compared to those we use for pulmonary arterial hypertension today. So I think Jim may be exactly right that there are dosing issues that were just not well worked out at the time those studies were performed.

Dr Frantz: I agree that we may have missed an opportunity with endothelin antagonists in left heart failure by virtue of having the dosing wrong, but we have to acknowledge that is conjecture. In addition, we are wiser now about the issues of fluid retention sometimes accompanying use of endothelin antagonists, and might have dealt with that better with diuretic adjustment. I draw an analogy to the lessons of beta-blocker use in congestive heart failure, where we need to be very cautious initially in order to reap the longer term benefits as the heart remodels.

Dr Maloney: The FIRST results were interesting in that the dose of epoprostenol was quite low compared to what is used for pulmonary arterial hypertension, yet those congestive heart failure patients hemodynamically improved. But they had increased mortality. I guess it gets to the bigger

issue in that very commonly patients are referred to a pulmonary hypertension center because an echocardiogram shows a pulmonary systolic pressure of 50 mmHg and a left ventricle with diastolic dysfunction. We do a heart catheterization and find out they have a wedge pressure of 30 mmHg. Yet their main pulmonary arterial and pulmonary diastolic pressures may seem elevated out of proportion to that. At what point, even if you pushed treatment to such patients for their diastolic dysfunction, do you become nervous on the level of wedge pressure? Where do you like to see that wedge before using drugs that we typically would reserve for pulmonary arterial hypertension? Is there a wedge pressure cutoff that either of you have that you just simply won't treat someone with a pulmonary hypertension drug?

Dr Mathier: I don't think there is any hard and fast number in my mind. If a patient presents, and we see this quite a bit, especially with so-called diastolic heart failure, where they may have a wedge pressure of 30 mmHg, then obviously we try to optimize their heart failure care and drive their wedge pressure down to what we think is the optimal level for that patient. I like to see a wedge pressure under 20 mmHg with a persistently elevated transpulmonary gradient before I would consider a specific pulmonary arterial hypertension therapy in a patient who appears to have heart failure with complicating pulmonary hypertension.

Dr Young: Yes, I would agree with that number too. That's exactly the target I would endorse. I usually tell the fellows who are watching the patients in the unit, 16 to 20 mmHg. The magic number of 20 or 16 mmHg isn't necessary, but somewhere in that range, I agree completely. The problem is if that wedge drops too low, and you start giving these agents, and that left ventricle underfills, you can get into a lot of systemic problems with hypotension and renal dysfunction.

Dr Frantz: I agree that the probability of causing more harm than good is very real when using selective pulmonary vasodilators in patients with a wedge of 18 mmHg or above. For patients with preserved systolic function but documented diastolic heart failure, it is critically important first to achieve excellent blood pressure and heart rate control. This includes documentation of good blood pressure control during exercise, since high systemic and left ventricular pressures during exercise often drive the symptomatology. Many patients with longstanding systemic hypertension, especially the elderly, develop substantial diastolic heart failure that may be improved just with really good conventional antihypertensive therapy.

Dr Maloney: What percentage of your patients in that range of wedge pressures you gave us would you estimate you actually have on additional therapies, such as sildenafil, endothelial receptor antagonists, and prostenoids?

Dr Young: Well, it's not very many, and the reason it's not is because there still is some concern about a) which patient might benefit from this off-label use of these drugs, and b) how to dose the drugs and maybe even how to choose the drugs that are available. There is some reluctance to turn to these agents, which I think actually could be very helpful based on data from small clinical trials. Usually what happens is they'll get admitted to the hospital and pounded with phosphodiesterase inhibitors like milrinone or maybe a trial of nitric oxide inhalation will be attempted. It's rather paradoxical, because if you think about it, there aren't any more data with phosphodiesterase inhibitors than with these other newer concepts. If you look at the number of patients who would be eligible for these tactics, I would say as many as 1 in 10 of the real serious patients who get evaluated for heart transplant are. I'd be curious to hear other estimates.

Dr Mathier: I agree that 10% is a reasonable number. Another reason for the reluctance to use these agents off-label is that patients must meet every one of a set of criteria: They must have a degree of pulmonary hypertension that is judged to be "out of proportion" to their left heart dysfunction; they must be able to attain a low enough wedge pressure to give an adequate safety margin with which to work before we begin a specific pulmonary arterial hypertension therapy; they must be persistently symptomatic despite having a reasonable wedge pressure so as to warrant a trial of a specific pulmonary arterial hypertension therapy; and lastly, they must have some evidence of a clinical response for me to want to continue to use that agent. It's a relatively small percentage, I think, that meets all of those criteria.

Dr Frantz: I agree it is a small number of patients. Most of these patients with left ventricular systolic failure and pulmonary hypertension benefit most from optimization of conventional heart failure therapies.

Dr Maloney: In those patients who get a heart transplant, a small subset develops symptomatic pulmonary arterial hypertension afterward. It's challenging to choose what would be the drugs to treat those patients. Sildenafil might be chosen, but could interfere with antifungal drugs; we like to avoid epoprostenol because of line infection risk; endothelial receptor blockers might seem a good choice as long as fluid retention isn't an issue. Is there any particular go-to drug you might tend to use in that postoperative setting?

Dr Mathier: In the immediate postoperative setting, we tend to look for a quicker acting agent with direct delivery, so it's not unusual for us to use inhaled nitric oxide immediately post-op. I don't think that's terribly controversial. I believe most centers that do a reasonable volume of transplants are using that sort of approach. The question gets a little trickier when you start to think about medium and longer term therapies, and as you point out, each of these drugs—just as they do in the nontransplant setting—has pros and cons associated with them. I think that if somebody has really significant pulmonary hypertension and I feel that a prostanoid would be of value, then I'm increasingly comfortable using inhaled iloprost in that setting, specifically to avoid catheter-

related complications, as you mentioned. If I think an oral drug will be valuable, I tend to use an endothelin antagonist, but with a careful eye on hepatic function, especially since we like to employ statin therapy simultaneously in the post-transplant patient.

Dr Frantz: It is important to point out that there is a serious pharmacokinetic interaction between bosentan and cyclosporine, and concomitant use is not recommended.

Dr Young: I think that's a great summary and it points to the fact that there are really separate periods where pulmonary hypertension after heart transplantation can get you into trouble. One is the immediate postoperative period, including challenges and troubles weaning off of cardio pulmonary bypass. Generally, if there are any issues in the operating room or early on in the intensive care unit, inhaled nitric oxide is what we turn to. Actually in the operating room, we have a low threshold for putting in a right heart mechanical bypass system. The second group represents a problem where you come out of the operating room with pulmonary hypertension, but it doesn't cause cardiogenic shock or an early disastrous problem, but then at day 10, 12, 14, three weeks, the patient is swollen with terrible tricuspid insufficiency and right heart failure due pulmonary hypertension. In these patients I'll move toward a phosphodiesterase inhibitor earlier, and lots of diuretics to try to dry them out, as much as their kidneys will let us, in hopes that we will see a turnaround. If they don't, you have to turn to some of the other agents that were mentioned. The third type of patient is the one who's out long term, and to me that's the biggest problem because these patients usually have renal insufficiency. Their livers aren't in the greatest shape either. They've had pulmonary hypertension ever since transplant and the right heart is now really failing. This is a miserable patient and a terrible outcome is usually guaranteed.

Dr Maloney: Are there other issues you would like to bring up?

Dr Young: I have two issues I'd like to see addressed and, really, it's a plea for better studies. Perhaps we could do multicenter studies focused on how best to handle these patients in the early postoperative phase when we see a lot of tricuspid insufficiency and pulmonary hypertension that can't really be sorted out; how much is fixed and how much is going to turn around over time. The second issue relates to tricuspid insufficiency itself and to determining how much might be due to the mechanical implantation of the allograft versus right heart failure due to pulmonary hypertension. It's always been challenging to sort through these difficulties related to the way the heart was sutured into place versus a variety of combinations of right heart failure and pulmonary hypertension. I'd be curious to hear what others think about that.

Dr Mathier: I would add one other thing to the mix, and that is what we do to a patient's tricuspid apparatus with repeated endomyocardial biopsies. I'm not sure that any of us have a good way to really reliably assess right ventricular structure and function and their interrelationship with tricuspid valve function. One thing I would like to add to this discussion is a plea, an ongoing plea, from a cardiologist to other cardiologists in the pulmonary hypertension community to recognize the absolute importance of right heart catheterization. Too often, as you pointed out, Jim, we see patients with a suggestion of elevated pulmonary pressure on echo, with perhaps normal left ventricular systolic function, with or without ancillary evidence for a diastolic abnormality, who are just started down a pathway of pulmonary hypertension therapy without a formal hemodynamic study to determine whether there are, in fact, elevated left heart pressures. These patients, in my opinion, absolutely must undergo a hemodynamic study so that we can know exactly which disease it is we're dealing with.

One thing I would like to add to this discussion is a plea, an ongoing plea, from a cardiologist to other cardiologists in the pulmonary hypertension community to recognize the absolute importance of right heart catheterization. Too often we see patients with a suggestion of elevated pulmonary pressure on echo, with perhaps normal left ventricular systolic function, with or without ancillary evidence for a diastolic abnormality, who are just started down a pathway of pulmonary hypertension therapy without a formal hemodynamic study to determine whether there are, in fact, elevated left heart pressures.

Dr Maloney: That's an absolutely key point. I think we all in the pulmonary hypertension community have tried to convince people that pulmonary arterial hypertension cannot just be diagnosed on an echocardiogram, but dictates hemodynamic evaluation with right heart catheterization and very often, left heart catheterization. Let's say a patient undergoes right heart catheterization and is found have a mean pulmonary artery pressure of 30 mmHg but suspiciously has a wedge pressure that is 18 to 19 mmHg, long-standing systemic hypertension, and a prior suggestion of diastolic dysfunction on the echocardiogram. Many people, myself included, would work with a cardiologist, do an exercise study with this patient in the catheterization lab, and follow the wedge pressure and LVEDP to see if this is a patient who has exertion-related pulmonary hypertension due to diastolic dysfunction. There is a fair spread on how people evaluate that in these cases of mild pulmonary hypertension. What are your experiences and biases?

Dr Mathier: I'm still uncertain about what role measurement of pulmonary pressures during exercise is going to have in the long run. In the situation you described, where there is a relatively modest transpulmonary gradient and elevation of the wedge pressure with evidence of what we would call diastolic dysfunction, I generally would stop there in terms of evaluation and focus my efforts on optimizing the care of the underlying diastolic abnormality, and then follow the patient to see if there is clinical improvement. If, however, there is evidence of a wider transpulmonary gradient, but

the mean pulmonary pressure is still not through the roof, then I might move toward an exercise study to see if there is more of an exaggerated rise than I would expect with exercise.

Dr Young: After having been involved with doing a lot of these studies, I virtually gave up because of the inability to really predict outcomes in patients, but even more, the hassles of trying to do one of these studies. They're extraordinarily bad in reproducibility of information and are just trouble. So I agree completely with that response.

Dr Frantz: In my experience, occasionally exercise hemodynamics in the catheterization laboratory can be helpful in the differential diagnosis of dyspnea. Just today I performed a right heart catheterization for a patient with a history of systemic hypertension that had been variably controlled, but who was still having complaints of exertional dyspnea. Her resting hemodynamics were normal, but her wedge and right atrial pressures rose to around 20 mmHg after 6 minutes of exercise. I think that helped explain her dyspnea.

Dr Maloney: Patients with mitral regurgitation can often be difficult because that can be worse with exercise. There's a subset of patients who have mitral regurgitation who with exercise get pulmonary hypertension from the regurgitation. It's difficult to figure out the best way to evaluate those patients. Some centers have a protocol for exercise such as echocardiography with a recumbent bicycle; some people prefer to do it in the catheterization lab. What do you do?

Dr Young: Again, in the past, I've run into the same problems with getting good reproducible measurements. Getting good pressure tracings you can evaluate is a problem. Personally, I'm not sure what intracardiac pressures mean when obtained lying on your back pedaling a bicycle. If your wedge goes up really high, or your pulmonary artery pressures shoot up, I think it's a bit of problem from a physiologic standpoint, but how do you relate that to someone who is upright walking about? So, rather than doing a lot of exercise, in my experience, if you're trying to flush out the severity of mitral regurgitation, simple things like hand grip, where you're increasing SVR arguably tell you as much as anything. Even more important is careful measurement of the regurgative wave in this situation, and that's a lot different from trying to look at pulmonary artery pressures. I'd be curious to hear what others think.

Dr Mathier: We are primarily doing stress echocardiographic assessment in these patients, with the specific stress employed determined more often by sonographer preference and patient ability than by any programmatic decision. We've done recumbent bicycle, treadmill, and dobutamine protocols. We have, however, shared Jim's observation that trying to do exercise hemodynamic studies is just logistically so difficult that we only rarely do it unless the referring doctor feels that it is the only way to get at the question at hand.

Dr Frantz: We do exercise echo assessments, but also sometimes do supine bike exercise in the catheterization laboratory. I have also had occasional patients with functional mitral regurgitation in the setting of an element of systemic hypertension, where pulmonary artery pressures and wedge pressures come down like a rocket with nipride in the cath lab. In those patients it is a further incentive to aggressively manage their systemic hypertension. Aggressive blood pressure control can be recommended without such hemodynamic assessment, but when patients are referred because of their pulmonary hypertension, the ability to drastically improve it acutely makes the case for the proper medical approach, if mitral surgery is not advisable or appropriate. ■