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"//connect.facebook.net/en_US/all.js#xfbml=1"; fjs.parentNode.insertBefore(js, fjs);
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Vol 10, No 1 (Spring 2011)

## PH and Left Heart Disease: Defining the Clinical Dilemma

A panel of experts convened by telephone on April 20, 2011 to discuss their experiences and recommendations regarding diagnosis and management of patients with Group 2 PH. The conversation was facilitated by **Myung Park, MD**, Associate Professor of Medicine and Director, Pulmonary Vascular Disease Program, Division of Cardiology at University of Maryland School of Medicine and guest editor of this issue. The participants were **Rene Alvarez, MD**, Associate Professor of Medicine and Director, Advanced Heart Failure/Pulmonary Hypertension Outreach Program, University of Pittsburgh School of Medicine; **Teresa De Marco, MD**, Professor of Medicine, Director, Heart Failure and Pulmonary Hypertension Program and Director, Heart Transplantation, University of California San Francisco Medical Center; **Marc Semigran, MD**, Medical Director of the Heart Failure

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and Cardiac Transplant Program at the Massachusetts General Hospital Center and Associate Professor of Medicine at Harvard Medical School; and **Ivan Robbins, MD**, Assistant Professor of Medicine and Director, Lung Transplant Program, Vanderbilt University Medical Center.

**Dr Park:**

I would like to welcome everybody to our Roundtable for the Spring 2011 issue of *Advances in Pulmonary Hypertension*. Thank you all very much for joining me today. I would like to take this opportunity to discuss a clinical situation that I think I can safely say really takes a lot of our time as practitioners: Group 2 Pulmonary Hypertension. We have made amazing advances in Group 1 PAH, now with 10 FDA-approved treatments that have been shown to improve symptoms as well as survival. Unfortunately, we have not been able to make significant breakthroughs in pulmonary hypertension that deals with left-sided heart disease. However, this is a common entity that we are seeing more and more in our clinical practice, specifically pulmonary hypertension with preserved left ventricular function. The increase in its prevalence is quite phenomenal, and I believe this trend is going to continue as our population ages and as the epidemic of obesity makes its mark. So, I would like to start by asking each of you what impact does this group of patients, those presenting with dyspnea and diastolic dysfunction, have in your clinical practice. Teresa, starting with you, how much of this do you see?

**Dr De Marco:**

Yes, as a matter of fact, because we are a heart transplant- advanced heart failure center, as well as a pulmonary hypertension center, we see a lot of patients just referred for unexplained dyspnea. And in that group, I would say that there's about 60%, in my experience, who have pulmonary hypertension with associated heart failure due to heart failure with preserved ejection fraction. This entity does impact our practice because obviously we're going to have to approach it a little bit differently from the usual PAH patient both from diagnostic and management perspectives. The demographics are also different.

**Dr Park:**

I agree and the difference in approach is a critical point and we will come back to that. Rene, how much does this impact your clinical practice?

**Dr Alvarez:**

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Well, just like Dr De Marco mentioned, I practice at a big transplant center also, but I also practice and spend a lot of my time in the community at some of the outreach sites at our institution where the demographics are different, but it's a significant portion of what we get referred in the community. In fact, the majority—I would say over 50-60% of the patients that we get referred for PH—are patients who have mostly diastolic abnormalities, at least as assessed by history, physical, and echo. So it's a huge percentage of the patients that we get referred for PH.

**Dr Park:**

Thanks, Rene. Marc, how about you?

**Dr Semigran:**

I direct the heart failure program at MGH and have a slightly different perspective, but I would say that about a third to 40% of the heart failure patients that we're seeing are heart failure patients with preserved ejection fraction, the majority of whom have elevated pulmonary pressures both at rest and with exertion. And they're often some of the most difficult patients to manage.

**Dr Park:**

Your collective responses definitely reaffirm how prevalent diastolic dysfunction is in our patient population. In my practice also it comprises over half of my referrals for dyspnea and abnormal echocardiogram. And all of you have touched on the diagnostic dilemma that is associated with this disease process in that, at first glance, PAH and PH associated with preserved LV function can look almost identical. It's only when you dig under the surface that you can unmask some of the elements that differentiate the 2 entities.

So, with that being said, one area we are coming to learn more are the similarities that exist between risk factors associated with metabolic syndrome and diastolic dysfunction and how these risk factors could potentially be implicated in the pathogenesis leading to pulmonary vascular disease. So could you comment on if and how you take those factors into your evaluation process and what would lead you to proceed to perform right heart catheterization? How often does it happen that you say, "You know what? This patient has primarily diastolic dysfunction based on clinical and echo features and I'm going to treat it as such?"

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**Dr Alvarez:**

I think that there are many features of these patients, both from history and physical exam and even on echo, that can help us sort of risk-stratify these patients and give us a clue in terms of who may have diastolic dysfunction; for example, the obese person with diabetes and hypertension, which are risk factors for diastolic dysfunction. So the history and the physical exam, I think, are very, very important. The echocardiographic features, for example, mitral regurgitation and left atrial enlargement or left ventricular hypertrophy, all are clues that these patients may have diastolic abnormalities. I think at certain centers, they're very good at—at least—what we know currently in terms of assessing diastolic dysfunction by echo. They are very good at giving us a sense of whether someone has elevated filling pressures or diastolic abnormalities and even grading the diastolic dysfunction. So right heart catheterization, especially when you provoke these patients in the cath lab, can be very helpful in understanding their physiology and at least beginning to address how you are going to intervene.

**Dr Park:**

I think we rely on these similar evaluations as well to help us determine if the problem leading to patient's symptoms are primarily pulmonary venous hypertension or pulmonary arterial hypertension, and what factors may be amenable to therapy. Teresa, is there any one element of either the echo or clinical features that you rely on to give you a sense of whether the patient has PAH or diastolic dysfunction?

**Dr De Marco:**

Well, again, you have to look at all one has to evaluate of the history, the physical exam, and the echocardiographic findings in concert. But then, when I look at the echo, I'm really most interested in the structure and function of the right heart. Right heart failure contributes to morbidity and mortality as well as reduced exercise capacity. Pulmonary venous hypertension is usually associated with enlarged left atrium, mitral or aortic valve abnormalities, and evidence of LV diastolic or LV systolic dysfunction. With pulmonary arterial hypertension, the left-sided chambers and valve structure and function are usually normal. There may be evidence for grade 1 LV diastolic dysfunction due to diastolic ventricular interdependence. I'm interested in seeing what the right heart is doing and if there's any right heart enlargement. If on echocardiography the PA pressures are only mildly to moderately elevated in the appropriate setting where PH with left heart failure and preserved ejection fraction is likely, then I think it is important to understand if we are dealing with pure post-capillary PH, or a combination of both pre- and post-capillary. PH is operative where both chronically elevated

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left-sided filling pressures are causing an up-regulation of neural hormones, cytokines, endothelin, and other mediators. They then feed back on the pulmonary arterial tree and will cause vasoconstriction of the pulmonary arterial bed, with or without remodeling, leading to pulmonary hypertension out of proportion to left-sided filling pressure because they're distinctly different hemodynamic profiles. So for me, the most useful approach is to assess the patient symptoms, the appropriate demographics, evaluate the echo, and if PH due to the common variety of left heart failure with preserved ejection fraction is likely, then treat the patient accordingly and then do a trial of treatment for diastolic heart failure, which, as everybody knows, is very, very difficult. But then, if the patient continues to be symptomatic despite standard therapy, which involves treating an underlying condition such as hypertension and with diuretics, I think it's appropriate to proceed with a right-heart catheterization if the diagnosis is in question. I would cath and try to assess what we're actually dealing with.

### **Dr Park:**

Marc, I think you were going to make a comment here?

### **Dr Semigran:**

Myung, could I just add 2 things to these very important comments? The first is that I definitely agree that left-atrial enlargement is an important marker of left-ventricular filling pressure elevation and that when it is present it really makes me concerned that left-ventricular dysfunction is going on. If the echocardiographic LVEF is normal, then I am particularly concerned that diastolic dysfunction is present.

The second is that we'd often like to use the plasma B-type natriuretic peptide (BNP) as a marker of left-ventricular strain and dysfunction, but in patients with the metabolic syndrome it can often be depressed relative to the degree of left-ventricular strain, so it may not be elevated if these patients have heart failure. Therefore, you can't use it as a means of ruling out heart failure with preserved ejection fraction, for example.

### **Dr Park:**

Hearing all of your remarks really zeroes in why this problem remains such a diagnostic dilemma. Unfortunately, there is not one single measure or test that you can rely on for a consolidated diagnosis, such as you can obtain with systolic heart disease or myocardial infarction. However, I am glad that you mentioned the relative significance of left-atrial

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enlargement. This was just brought up at a recent national meeting, where it was suggested that the presence and degree of left-atrial enlargement can be viewed similarly as how one uses hemoglobin A1C for evaluation of diabetes. That is, it can be used as an indirect marker to signify presence, duration, and severity of increased left-sided filling pressure. So I think that with any enlargement of left atrium, you have to be very suspicious that there's left-heart disease present.

**Dr Semigran:**

Agreed.

**Dr De Marco:**

Agreed. The other problem that confounds what we're looking at is that these patients tend to be older, have hypertension and diabetes, tend to be obese, and most of them are women. In addition, a fair number of these patients also have sleep apnea, which contributes not only to pulmonary arterial hypertension but also to elevation in left-sided filling, aside from just the left-heart disease. So it becomes difficult to determine what the primary cause of the PH is as teasing it out is actually quite difficult without going a bit further and actually measuring cardiopulmonary hemodynamics. In certain situations, exercise hemodynamics may also be required.

*At this point, Dr Robbins joined the call.*

**Dr Park:**

Ivan, thank you for joining us. We have Rene Alvarez from Pittsburgh, Teresa De Marco from San Francisco; and Marc Semigran from Boston.

**Dr Robbins:**

Oh, a very esteemed group.



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**Dr Alvarez:**

Welcome. Thank you.

**Dr Park:**

You are joining us at a perfect time because we were just finishing up our discussion about the presence and importance of risk factors associated with metabolic syndrome and I know you have studied this in your pulmonary hypertension population. We were just covering how important accounting for these factors is during evaluation and diagnostic workup. Can you add a comment to that based on your own research and observation?

**Dr Robbins:**

Sure. We've done some research on the association of the metabolic syndrome and PH. What we found in our study was that if you have 2 or more of the 4 clinical features of the metabolic syndrome, that significantly increases your risk of left-ventricular diastolic dysfunction—and it goes up with each factor that you have. I will also say is that it's not foolproof, because we see—and I'm sure all of you see this—patients who are obese, diabetic, and hypertensive. And you do a careful cath; you even measure left ventricular diastolic pressure—and we even give them fluid challenge sometimes—and they still have a normal wedge pressure. So the odds ratio for a post-capillary cause of PH is very high with multiple features of the metabolic syndrome, but I don't think there's any one test that can identify people without hemodynamic evaluation.

**Dr Park:**

So would you say they are useful discriminators?

**Dr Robbins:**

Well, it's a good discriminator, I think, but you can't absolutely diagnose patients based on their risk factors. You've talked about this, but obviously when I see a big left atrium on echo

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or MRI, that, to me, is a big tip-off for left-sided cardiac causes of PH.

**Dr Park:**

Yes, we were discussing that the finding of enlarged left atrium is a significant indicator of presence of left-sided heart disease. So now, I would like to discuss how we use information from right heart catheterization in this patient population. Beyond the accepted definitions of assessing filling pressures and pulmonary pressures, which is what we use in PAH, in patients with both PH and left-sided heart disease, the term “out of proportion” is often used. So specifically, what is meant by patients who present with pulmonary hypertension “out of proportion” to their underlying left-heart disease? Can I ask each of you to comment as to what parameters you use when you're doing right heart cath to say whether a patient's hemodynamics are out of proportion to their left-heart disease? Rene, could I ask you to start us off?

**Dr Alvarez:**

Sure. That's a difficult question and I think I've been incredibly impressed by many of the patients that we take who have been aggressively diuresed, like Dr De Marco mentioned, I've been impressed that when you take many of these patients to the cath lab, their wedges are 14, 15, 16; yet their mean PA pressures and their TPGs are elevated. And then when you provoke them and you stress them or you volume load them, you can bring out a significant abnormality in diastolic function. So I'm not sure that as a clinician I have a certain number where I say, “Hmm, this is not diastolic dysfunction.” I've seen several patients in our PH clinic who have had fairly normal hemodynamics at rest and then when you exert them, they have very abnormal responses to exercise. Members of our group has been very interested in defining exercise pulmonary hypertension and exploring various interventions and their effects on exercise tolerance and survival. The question is what do you do with those patients and how do you treat them long-term. Many of these patients remodel their pulmonary vasculature and have abnormalities of their pulmonary vasculature and abnormal responses to exercise. So I guess that long answer is: I don't know if there's a cut-off that really would differentiate these patients.

**Dr Park:**

So in your practice, if your clinical suspicion of diastolic dysfunction is high and yet the hemodynamics seem fairly within the “definition of PAH,” you proceed to employ provocative maneuvers, whether it be fluid challenge or exercise?

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**Dr Alvarez:**

We've been doing that. It's been our practice at Pitt.

**Dr Park:**

Which one do you use more—the fluid challenge or exercise?

**Dr Alvarez:**

Exercise. We have an exercise bike in the cath lab that we use.

**Dr Park:**

OK. Teresa, how do you approach this problem?

**Dr De Marco:**

You asked what sort of cutoff one would use. Obviously, first of all, we don't have a standard nomenclature or cut-off value that define PAH due to left-heart disease. And that's something that I think, as a PH community of physicians, we should develop. But the reason pulmonary hypertension in patients with left-sided heart disease is important is that it does reduce exercise capacity, increase morbidity and mortality in this patient population, predominantly as a result of its effect on the right heart. There have been studies that show that when the pulmonary vascular resistance is over 2.5 to 3.0 Wood units, survival is greatly impacted. In my opinion, if the transpulmonary gradient is greater than 12 to 15 and the PVR is greater than 2.5 to 3 Wood units, that raises the specter of pulmonary hypertension out of proportion to left-sided filling pressures, or what I prefer to call mixed pulmonary hypertension, because this entity shares hemodynamic features of both pulmonary venous as well as pulmonary arterial hypertension. Provoking a challenge with vasodilators or other agents is worthwhile to determine reversibility and whether or not we're dealing with predominantly vasoconstrictive

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pulmonary arterial hypertension or an element of vascular remodeling, or both. Now, in the event that the transpulmonary gradient and the PVR are elevated in the setting of a mildly elevated pulmonary arterial wedge pressure, an enlarged left atrium then I advocate the same maneuvers that Rene so eloquently described, I also go on to perform supine exercise cath on these patients with unexplained dyspnea and a marginal hemodynamic profile. Again, the major problem is how we should treat them as the evidence base is lacking.

**Dr Park:**

I do agree with you on that, I think the time has come where we, as a community of physicians who encounter this clinical dilemma on a regular basis, come up with a consensus or hemodynamic definition that we agree reflects this pathologic situation. But that's a discussion for another time. Ivan, Marc, what are your thoughts?

**Dr Semigran:**

I agree with both Rene and Teresa. I think that there is value in, as you said, having a degree of elevation of PA pressure or transpulmonary gradient that will set off an alarm in physicians. Perhaps a transpulmonary gradient, as Teresa was saying, greater than 12 to 15 mm Hg should be a reminder to physicians to look for other possible causes of pulmonary hypertension in heart failure patients. Examples of this would be chronic thromboembolic disease, or sleep apnea, which was mentioned earlier as well. These disorders do lead to different therapies that we would not immediately deploy for our heart failure patients. In addition, as Rene was pointing out, a large number of heart failure patients, both with preserved or even reduced ejection fractions, have an abnormal pulmonary vasodilator response during exertion. I do believe that this is a target for therapy that must be explored.

**Dr Park:**

Yes, very good point. Ivan?

**Dr Robbins:**

Yes, I agree. Let me ask the group this question: is there a wedge pressure above which you

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would not treat someone?

**Dr Alvarez:**

That's a great question.

**Dr Park:**

Ivan, when you say treat someone, you mean using PAH-specific vasodilators?

**Dr Robbins:**

Yes, using PAH-specific medication. I mean, let's say you have someone whose PA pressure is 100/40, but their wedge pressure's 25.

**Dr Park:**

Yes, so I guess the question is which hemodynamic measurements are most indicative of an “out of proportion” pulmonary arteriopathy state? Is it the pulmonary pressures or the derived calculations—namely the transpulmonary gradient and the pulmonary vascular resistance?

**Dr Robbins:**

Right, well, I don't know. I sort of have in my mind that above the low 20s, I'm not going to treat these people with PAH medications, regardless of their PH, because I have concerns that I may increase their filling pressure to the left side and they may go into pulmonary edema. They may not be able to handle the increased blood flow if they vasodilate the pre-capillary vasculature.

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**Dr Park:**

Some have proposed the 20/20 parameter as a rough guideline for out of proportion—so wedge pressure below 20 and transpulmonary gradient above 20. Some advocate incorporating PVR greater than 5 Wood units as part of the criteria. So again, there are many different range and numbers that clinicians use but for me, it would be for PCWP above 18 to 20.

**Dr Robbins:**

I like the 20/20 rule. I had not heard that one, but that's reasonable.

**Dr Semigran:**

I would agree that once the LV filling pressure is above 18 to 20 mmHg, you really have to start considering that this secondary pulmonary hypertension differs from the usual PAH, and that you have to be cautious about what agents you use to treat this patient. When we look among our pulmonary vasodilators, some of the agents are systemic vasodilators as well. Their use in the patient with heart failure and secondary pulmonary hypertension might avoid the problem that I believe Ivan was mentioning a moment ago about increasing LV filling to the point the patient might develop pulmonary edema.

**Dr Robbins:**

Well, to follow up on that, what we do sometimes—and particularly in patients who are hypertensive—is give them a nitroprusside infusion in the cath lab. And we have found people—not if their wedge is 8, but if it's 15 or if it's a little higher—where the pressures nearly normalize when you get their wedge down. We routinely give a fluid challenge in patients with normal wedge pressure, so we sort of prime the system to bring out latent LV diastolic dysfunction in addition to trying to afterload reduce hypertensive patients.

**Dr Park:**

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So do you do both, Ivan?

**Dr Robbins:**

Well, if their wedge is up, we don't give them fluid, but if we have someone around 14 or 15 and we really suspect it's diastolic dysfunction and in the cath lab their blood pressure's 180/110, then we will give them nitroprusside, and we've seen significant improvement in pulmonary pressures. The one comment I'd like to make about the fluid challenge is that we do this in lieu of exercise because I find—and maybe you all have a better way of doing this—many of these patients are deconditioned and obese. You start exercising them even at low levels and they get huge changes in the pleural pressure, and it becomes very hard for me to determine where their wedge pressure is.

**Dr Park:**

That is undoubtedly one of the most challenging aspects in performing and interpreting these data that all of us face. And even more so when you consider how pivotal it is to obtain the accurate wedge pressure in order to arrive at the correct diagnosis. It is definitely challenging.

**Dr Robbins:**

Right. Now, granted, fluid does not recapitulate exercise, but it does stress the system somewhat and it avoids the large pleural pressure swings.

**Dr De Marco:**

This whole entity of hypertension with elevated SVR and elevated PVR is very interesting. I think that what's most useful to me is determining the PVR to SVR ratio. And if indeed the ratio is at or over 0.5, I'm pretty sure that I am dealing with pulmonary disease above and beyond a diffuse vasoconstrictive state that is affecting both the systemic as well as the pulmonary vessels' vasculature. And in that setting, we may be dealing with a different entity from just diffuse hypertensive disease.

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**Dr Park:**

I like your comment about thinking about this as mixed pulmonary hypertension, because it's not one or the other; it's definitely mixed. What we are attempting to delineate is trying to determine which problem is the major contributor in creating the pathophysiology and therefore leading to the symptoms.

**Dr De Marco:**

And the PVR to SVR ratio really does help me to try to understand that.

**Dr Park:**

Absolutely. Great point. So in the remainder of our discussion, I'd like to shift our focus to therapy. As already mentioned, there are no approved treatments for PH in the setting of left-sided heart disease, as commonly as we see it. There are several different agents that have been studied—not successfully—and some that are being evaluated. So the PDE-5 inhibitors appear to be the agent of choice for initial treatment mostly because it seems to be relatively well-tolerated in these patients with some secondary features. So Marc, I'd like to turn to you first for comment on this. In your opinion, how promising is the role of PDE-5 inhibitors for this mixed pulmonary hypertensive group? Are we using this out of desperation because we have nothing else to offer, or is there evidence that it is effective in patients with diastolic dysfunction and PH?

**Dr Semigran:**

Well, I think that this therapy is quite promising for patients with left-ventricular dysfunction and secondary pulmonary hypertension. I think that several laboratories, including our own, have shown in patients with heart failure and a reduced ejection fraction that the PDE-5 inhibitors do improve exercise capacity and that they improve ventilatory efficiency. Marco Guazzi recently published that this beneficial effect of PDE-5 inhibition on exercise capacity persists for at least 12 months and is accompanied by beneficial left-ventricular remodeling. I think that that's certainly very encouraging. I must say that Marco's work focused on all heart failure reduced ejection fraction patients. It was our experience initially that it was just those who had some degree of resting pulmonary hypertension that received the benefit in the improved exercise capacity, but given that we think that the majority of heart failure reduced



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ejection fraction patients have secondary pulmonary hypertension, it's not surprising that Marco was able to show a benefit in his study of all comers.

I think the heart failure preserved ejection fraction patient population is a difficult group to study, in part because they have so many co-morbidities, as others have mentioned earlier. We do have the RELAX trial ongoing—hopefully we'll get some results from that early next year—which is looking at a group of patients with heart failure preserved ejection fraction and randomizing them to a PDE-5 inhibitor vs placebo, with the primary endpoint being exercise capacity. We'll look at LV remodeling in that group as well. I think that the possibility of the reversal of adverse LV remodeling, particularly in heart failure preserved ejection fraction, is particularly intriguing, based on the work of David Kass's laboratory, where in murine models of thoracic aortic constriction there was a beneficial effect on LV hypertrophy and function when the mice were given a PDE-5 inhibitor in their chow.

### **Dr Park:**

So, from your collective experience with this compound on the effect that it produces both on the myocardium and pulmonary vasculature, can you give us one or two properties of this drug that make it the best candidate so far for treatment of Group 2 PH patients?

### **Dr Semigran:**

Well, I think that we know that the enzyme PDE-5 is fairly heavily expressed in pulmonary vascular smooth muscle cells, so it does make it, I think, a target for pulmonary vasodilator therapy. And, as I think Teresa was mentioning earlier, looking at the ratio of PVR over SVR, PDE-5 inhibitors are able to vasodilate the pulmonary circulation at least equally, if not to a greater extent, than the systemic circulation, so is beneficial to these patients. This is unique when compared to other vasodilators, such as ACE inhibitors, that we use to treat heart failure patients

### **Dr De Marco:**

On the other hand, as was also mentioned earlier, the concern, particularly in patients with heart failure with reduced ejection fraction, of increasing LV filling without a compensatory decrease in afterload is a valid one. However, since PDE-5 inhibitors do reduce cardiac filling pressures systemic vasodilation as well, I think that that makes this class of drugs potentially uniquely beneficial.

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**Dr Park:**

Definitely has the properties to be relatively well-tolerated.

**Dr De Marco:**

But Marc, don't you get some pulmonary venous dilation as well, working through the cyclic GMP mechanism in the pulmonary vascular tree? And that, in and of itself, can actually lead to reducing the wedge pressure.

**Dr Semigran:**

Correct, and the LV pressure. And then, of course, the direct myocardial effects. Since PDE-5, I believe, is present in cardiomyocytes and ...

**Dr Alvarez:**

Yes.

**Dr De Marco:**

... inhibiting it a potentially beneficial target.

**Dr Park:**

And also, it enhances lusitropy, does it not?

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**Dr Semigran:**

It's been hard for us to show that clinically, but yes, animal models have suggested it.

**Dr De Marco:**

It also improves inotropic effects, as well.

**Dr Semigran:**

Yes.

**Dr Park:**

And so let me ask, how often do you use PDE-5 inhibitors for patients with diastolic dysfunction and PH after you've gone through the appropriate evaluation and you feel that they do have an element of pulmonary vascular disease that is out of proportion to underlying left heart disease and may benefit from PAH-directed treatment? One, is this a therapy that you use as a first line agent; and two, if so, is it effective? What kind of success rate are you seeing?

**Dr Alvarez:**

I think this is a very promising class of drugs, and Marc outlined the clinical data and rationale for its use. Unfortunately, there are no randomized trials, but there is one on the way. I think where we've seen an incredible benefit that we have not published, but hopefully we'll publish soon, is in some of our patients who have been deemed to have a relative contraindication to transplantation because of secondary pulmonary hypertension who we've had on chronic inotropes and patients who have an LVAD who we placed on PDE-5 inhibitors. Many of them have had significant improvement and many of them have actually improved their exercise tolerance; and on repeat right-heart catheterization, many of them have had improvement in their PA pressures and have been able to be listed for transplantation. So I think in that group of patients that we see, it's been very promising, and I have not been using it very often in

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patients with diastolic dysfunction and PH. But I think this is a very promising group of patients. I think it's incredibly promising and there are niches of patients who will benefit. It's now up to us to identify who will respond to these drugs, since some may do worse if they are chosen incorrectly.

**Dr Park:**

So in patients with LV systolic dysfunction and PH, when do you use the PDE-5 inhibitors? Do you have criteria that you use for these patients? For instance, do you perform vasodilator testing to assess the reactivity or treat them as part of preoperative therapy as they are being considered to receive an LVAD?

**Dr Alvarez:**

Well, our practice has been if patients are being considered for transplantation and they have elevated TPGs and have elevated PVRs, we do vasodilator testing in the cath lab. And if they're reversible, many of them will progress with transplant and have done well. Many of them have gone on to LVAD to unload the left ventricle. But we also see a subgroup of patients deemed to not be transplant candidates with irreversible PH. We also have a cohort of patients where we have put them on a PDE-5 inhibitor. It's too early yet to tell from my clinical experience, but many of them have felt better and many of them will come back for a repeat right-heart cath. I'm hoping that many of them will have favorable remodeling of their pulmonary vasculature and be able to be moved forward toward listing. So this is another promising group of patients with systolic dysfunction where these drugs can be very helpful.

**Dr Park:**

Teresa, can you comment on your practice of treating patients with systolic heart failure and PH?

**Dr De Marco:**

Well, with diastolic dysfunction patients like Rene mentioned, obviously you're going to throw the kitchen sink at them. The target will be to relieve congestive symptoms due to left-sided

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filling pressure with the loop diuretics and spironolactone as well as maneuvers to reduce blood pressure or excessive tachycardia, if present, and reduce hospitalization with the ARBs. We also should not forget to assess for chronotropic incompetence which can be operative in this patient population. We should ensure the ARBs, spironolactone, and make sure that they don't have chronotropic incompetence that it is contributing to their symptoms and, if they do, address it accordingly, because this is a huge feature in this patient population, as well, that we can't forget. So once we've employed all the standard strategies and therapies that we know of and the patient continues to be symptomatic and I feel that is due to residual untreated pulmonary hypertension vascular disease, at that point I'll have no problem with adding a trial of a phosphodiesterase-5 inhibitor. I then follow the patients closely to watch for evidence of improved symptoms and their exercise capacity. In my experience, I have not had a situation where this approach has resulted in pulmonary edema or worsening clinical status of the patient. Capacity goes up if their symptoms improve. And if I've done my job well with standard therapy to begin with before I use these agents, I've never had any situation where they've gone into pulmonary edema or they've gotten worse. That's my experience.

### **Dr Park:**

I agree that it is a very important point to stress: we really need to maximize and optimize standard regimens on these individuals, such as paying meticulous attention to blood pressure, volume control, and appropriate heart rate response to activity. So I think all of those features need to be optimized with standard heart failure therapies first and to give sufficient time for response before other treatments are considered.

### **Dr Park:**

Ivan, can I ask your comment on the approach for these patients?

### **Dr Robbins:**

Well, I can add a little from the pulmonary side. (LAUGHTER) So basically, in my practice, I don't see any of the systolic heart failure people, so we do use PDE-5 inhibitors in patients with preserved ejection fraction and left-heart failure, but it's really based on extrapolation from studies that I've seen with systolic heart failure. The other thing I would point out, which I'm sure we all think about, is that many of these patients are severely deconditioned and obese. I really stress strongly cardiac rehab in these patients, weight loss, and a nutritionist evaluation, because it's awfully hard to tell what is a limiting feature in these patients when they are short of breath. So I try to do these things first in this patient population. Sort of, "If

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we're going to do all of this for you, you need to help yourself, too.”

**Dr Park:**

Yes, absolutely, great point. Marc, any other thoughts you wish to share?

**Dr Semigran:**

Well, I very much agree with Ivan that we've got to have patients make the appropriate lifestyle changes to help themselves get better and give them appropriate counseling as to how to do that. And I'd also have to say that I remain in equipoise about the efficacy of the PDE-5 inhibitors in heart failure patients. Teresa mentioned earlier that they do increase intracellular cyclic AAMP, as was nicely shown by Evangelos Michelakis' lab. If that's an important mechanism by which PDE-5 inhibitors are acting, it may not be beneficial to clinical outcomes. Our experience with agents that increase cyclic AAMP in heart failure in the past has not been very rewarding.

**Dr De Marco:**

Yes, that's true.

**Dr Park:**

We should point out that we need to distinguish between PH associated with reduced ejection fraction versus preserved ejection fraction. They are quite different pathophysiologic processes so we need to be very cautious as to not extrapolate data obtained from one disease to another.

**Dr Semigran:**

Yes. We need some good clinical trials.

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## Dr Park:

Thank you all for your time in sharing your thoughts with us. This has been a terrific discussion, and I think it's evident from our stimulating conversation that we have much work to do in this arena of PH and heart failure. Like we said in the beginning, this is a population that we are going to see more in the future. I do think that it is imperative that we try our best to agree on how to best approach them, define them, and determine what target is most crucial that will make a long-lasting impact—not only improvement in their symptoms, but also survival as well. I remain optimistic that through active participation of our colleagues and our continued efforts to launch these pivotal clinical trials, that we will derive some answers, hopefully in the not-too-distant future.

So with that, again, I thank you for all your time!

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## **Charles Burger, MD**

Immediate Past Editor, Advances in Pulmonary Hypertension, Mayo Clinic Florida-Jacksonville, Fla.

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801 Roeder Road, Ste. 1000, Silver Spring, MD 20910  
301-565-3004 | [PHAOnlineUniv@PHAssociation.org](mailto:PHAOnlineUniv@PHAssociation.org)