Pulmonary Hypertension Due to Left Heart Disease

Guest editor Teresa De Marco, MD, along with Brian Shapiro, MD, Mayo Clinic, Jacksonville, FL, convened a panel of experts to discuss the challenges in diagnosis and treatment and the emerging science regarding pulmonary hypertension due to left heart disease. Contributing to the engaging discussion were James Fang, MD, University of Utah School of Medicine; Barry Borlaug, MD, Mayo Clinic, Rochester, MN; and Srinivas Murali, MD, Allegheny Health Network, Pittsburgh, PA.

Dr De Marco: Thank you for joining Dr Shapiro and me for a roundtable discussion to explore salient topics in pulmonary hypertension (PH) due to left heart disease. As experienced thought leaders, your perspective on the major issues and challenges we face in dealing with this entity will be valuable to our readers. In recent years, there have been multiple review publications on the topic. Recently, the Fifth World Symposium Task Force on PH and Left Heart Disease published a proposal for the hemodynamic definition, classification, and nomenclature for PH and left heart disease. I would like to start the discussion with you, Dr Fang, as you were the primary author for a summary statement on the topic published in the Journal of Heart and Lung Transplantation. What are your thoughts on the diastolic pulmonary gradient, the trans-pulmonary gradient, and pulmonary vascular resistance (PVR) in the definition for PH in left heart disease? Which hemodynamic parameter or parameters would you advocate utilizing in the hemodynamic definition and why?

Dr Fang: Thank you, Dr De Marco; that’s a great question. We traditionally have used things like transpulmonary gradient and PVR, despite all their limitations, because of the nature of the methods in clinical practice of collecting those data. The issue of the diastolic gradient is an interesting one. The evidence to date has been somewhat controversial. There are studies that suggest that the diastolic gradient is a reflection of pulmonary vascular disease. And other studies have not been able to find that that correlates adequately with outcomes. In terms of the best measurement to make, I still think that our traditional ways of doing it are what we have the largest evidence base for. This idea of mixed PH is an important issue to sort out, because we really don’t understand why people get mixed PH. That being said, I think work by Barry Borlaug and others, looking at compliance of the vascular bed, may in fact be a much stronger and better determinant of right ventricular (RV) vascular coupling as we look into the future. And I do think that these measurements can be made clinically and then integrated into the routine evaluation of patients with secondary PH.

Dr De Marco: Would you like to provide your perspective, Barry?

Dr Borlaug: Yes, I agree with everything Jim is saying. After the initial sort of embrace of the diastolic pressure gradient (DPG) as the way to go, there have been a number of studies in heart failure patients really questioning how useful it is. And we’ve looked at this. We published a paper a couple of years ago looking at different ways to define pulmonary vascular disease and left heart failure. And at that time, DPG wasn’t really out there, so we didn’t even include it, but it really didn’t predict outcome. Whereas, as Jim mentioned, things like pulmonary artery (PA) compliance were the most robust. Which makes sense, because PA compliance starts to fall off, even when the PVR abnormalities are pretty minor, because of the hyperbolic relationship between resistance and compliance. So I think that compliance is probably going to be a better way to do it. And whether that is from problems with the DPG itself or whether that’s just more logistical issues with getting a good DPG in terms of where you’re assessing diastolic pressure and wedge pressure in the respiratory cycle, whip or ringing artifact on the catheters, these are important sort of devil-in-the-detail issues that probably contribute to why it’s not a real good predictor. So, I’m not enthusiastic about using DPG to define pulmonary vascular disease in patients with heart failure.

Dr De Marco: Agreed. More and more data are coming forth that, in fact, the diastolic pulmonary gradient is not related to outcome. Although it makes pathophysiologic sense, since the diastolic pulmonary pressure and, hence, the diastolic pulmonary gradient is independent of stroke volume, reflecting abnormalities of the pulmonary vasculature itself not driven by cardiac output. However, it is ventricular function and cardiac output that is tied to prognosis; therefore, the pulmonary artery systolic pressure and the transpulmonary gradient, which are dependent on stroke volume, may be more predictive of outcomes as is the PVR, which takes into account the cardiac output reflective of ventricular function in the calculation.

So, Dr Murali, why is the presence of PH in the setting of left heart disease important in clinical practice?

Dr Murali: Pulmonary hypertension, when it coexists with left heart disease, irrespective of the particular kind of left heart disease—whether it is a muscle disease or if it’s a valve disease—is associated with a significantly higher morbidity and mortality. As we continue to find novel ways to improve morbidity and mortality in left heart disease, we have to tackle the man-
Dr De Marco: Thank you. So Brian, would you like to take it from here?

Dr Shapiro: You got it. So this one’s to Dr Borlaug. And the question is, how does one differentiate those patients with Group 1 pulmonary arterial hypertension (PAH) from those patients with PH with left heart disease secondary to heart failure with preserved ejection fraction (HFpEF), based clinically, based on symptoms and signs, as well as echocardiography.

Dr Borlaug: The only way to really do it definitely obviously is with a catheter, because it’s a hemodynamic definition, based on the presence or absence of high left heart filling pressures. But you can probably get a very good sense clinically, as you suggest, Brian. The things you would look for would be typical risk factors that would be associated with Group 2 HFpEF-related PH, which would be older people, so probably above 65, at least 60, with common comorbidities that we see in HFpEF, like systemic hypertension, which is in the vast majority, along with other things like diabetes or metabolic syndrome, obesity, female sex, though of course many women also have Group 1 PH, so the discrimination there probably isn’t as good. In terms of ventricular function in echocardiography, typical things that we’d see in patients with HFpEF-related PH would be left atrial enlargement, concentric ventricular remodeling or hypertrophy, though that’s not necessary, of course—and echo Doppler estimates indicative of high left heart filling pressures, though again those are very imperfect measures. In studies that have looked at this, they don’t seem to discriminate real well. But those are the things that I would look for ahead of time. And in people where you really can’t tell, obviously you need to do a hemodynamic assessment.

Dr Shapiro: Yes.

Dr De Marco: I have a question for you, Barry. What’s the value of assessing “notching” of the Doppler signal in the right ventricular outflow tract? What about other novel parameters? Is there a role for that or are they too difficult to ascertain on a regular echo?

Dr Borlaug: That’s a great, great point, Teresa. You know, Paul Forfia’s group has published a number of papers on this. I think in the right hands, in groups that have a lot of expertise, it seems to be a pretty good indicator. People with a lot of pulmonary vascular disease get this big reflected wave, which decelerates flow or causes this notch. In our hands, we don’t tend to see it quite as often, but I can tell you sort of anecdotally. I haven’t looked at it really systematically in our reports, but I think the people that we do tend to see it in more are the people with really more advanced Group 1 PH or maybe chronic thromboembolic PH. We don’t tend to see it as often in patients with left heart disease-related PH. Whether that’s just that they don’t have such profound pulmonary vascular disease or not, I don’t know. I think if you see it, that’s very useful. I think if you don’t see it, the question then is: is it an issue with the quality of the echo or the severity of the pulmonary vascular disease, or something else?

Dr De Marco: And do you differentiate between a midsystolic notch versus a late systolic notch? Have you found that useful in clinical practice?

Dr Borlaug: I have not. In my practice, which is mostly heart failure patients, not non-heart failure-related PH, I have not found it to be a real helpful thing to look for.

Dr Shapiro: So Barry, if there are one or two things that you would look for on the echo that would help convince you more it was HFpEF, what would you say would be your most reliable findings?

Dr Borlaug: I think the presence of left atrial enlargement would be very helpful. I think that if there is profound diastolic dysfunction, that would be helpful. So if the ratio of transmitial flow to tissue Doppler early diastolic velocity, or the so-called E/E prime ratio, is really high—greater than 15 or 20—that would be helpful. If there is really profound abnormal mitral filling pattern, you know, a restrictive or at least Group 2 type pattern there, I think those would also be helpful. The old thinking used to be that you almost had to have concentric hypertrophy or at least concentric remodeling, which we would define by an increase in wall thickness relative to end diastolic dimension. We see a lot of people these days with HFpEF that have normal geometry. So I’m not sure that is as useful as we used to think it was. I think the indicators of either high left heart filling pressures at the time of the study, namely the Doppler and tissue Doppler parameters, and then the markers of more chronic, sustained elevation of left heart pressures, like left atrial enlargement, would probably be the most useful.

Dr Shapiro: I know a lot of programs are also starting to do these exercise echo hemodynamics, where you get exercise pulmonary pressures and exercise E/E prime, suggestive of increased filling pressures. Would you trust those or do you rely on those, or how do you find those fit in your clinical practice?

Dr Borlaug: I don’t trust them a great deal. I mean, the Pearson R value for E/E prime versus directly measured wedge pressure usually runs in the range of 0.4 to 0.5. So there’s a lot of scatter. We’ve looked at this. We have unpublished data from a very large population of patients that had simultaneous assessments. And they’re definitely correlated with one another, but not really strong. In particular, the change in E to E prime is not a very robust indicator of the change in wedge pressure. So what we typically see, for example, in HFpEF or heart failure with reduced ejection fraction (HFrEF) patients is the wedge pressures going from maybe 17 to 35. And the E/E prime is maybe going from 14 to 15 or something like that. So there’s not this nice linear relationship between the two. And I don’t have a lot of confidence in that personally. There’s a number of studies now. I think one in Circulation Heart Failure recently sup-
ports the problems with E/E prime exercise as an indicator. The PA systolic pressure, if you can get a good Doppler envelope, I think is good. An old study from years back indicated that when they did it with agitative saline, that does appear to help and gets you a little bit better signal, but it makes it a little bit more of a pain to do. In our study, again this is unpublished, we were able to get a PA systolic pressure estimate during exercise about 50% of the time. So not great, but we got one about 50% of the time. And in that case, we saw a very good correlation with invasively measured PA pressures. The correlation weakens with exercise because your PA pressure estimate obviously is based on the tricuspid regurgitation (TR) velocity, which is telling you the gradient between the RV and the right atrium (RA). We often make this assumption that the RA pressure is just 5 or 10 in everybody. But in reality, in heart failure patients with exercise, we see RA pressures that vary from 0 to 50 or 60 mm Hg. So during the exercise, we can substantially underestimate the true PA systolic pressure, even if you're able to get a good envelope. Now, if the velocity is high, at least you know that it's probably very significant. You just have to keep in mind that you might be underestimating it. And if you don't have a good signal, you're still kind of left wondering.

**Dr Borlaug:** One more point I would make on that. And I don't mean to come out anti-echo. It's certainly a very useful test. But as a person whose practice is largely doing invasive exercise tests, a lot of the referrals I get are people that already had a noninvasive and sort of echo exercise test that ended up being kind of abnormal or equivocal. And then you just sort of wonder, how often they should have just been referred directly to the cath lab in the first place to save a little bit of money. Of course, it's a referral population, so that might be a little biased.

**Dr Shapiro:** I tend to agree with you on the exercise echoes. Interpreting the E or the TR envelope can be so difficult, particularly with the scatter that you get on the TR signal and so forth, that can make it very difficult to get an accurate measurement.

**Dr Murali:** I agree with both your comments on that. You know, I think when you ask the question, what is the best way to recognize early PH related to left heart disease in a community setting, I think an exercise echo would not be the test of choice.

**Dr De Marco:** So with that regard, how would you differentiate PAH from PH with left heart disease in the setting of HFpEF based on invasive hemodynamics? Do you have a set invasive protocol, Srinivas, that you can recommend to us?

**Dr Murali:** Well, again, I think unfortunately, this is one of the gaps in our knowledge at this point in time. Clearly, there is a dire need to have a standardized protocol in making this assessment, and different institutions and different investigators have adopted protocols that they find and that they feel is most appropriate. In our institution, we do have an exercise hemodynamic laboratory, where we are able to do supine bicycle exercise, with the catheters placed in the neck. And we typically follow a ramp protocol, increasing workload by 10 every minute. We certainly measure PA pressures and around the time the patient gets to peak exercise, we would quickly measure the wedge pressures, as well, and do a mixed venous oxygen saturation and do thermodilution cardiac outputs at that setting. We are not equipped in our laboratory to measure oxygen consumption simultaneously, which some laboratories are able to do. It's a VO2 assessment, as well, which I think is extremely useful.

**Dr De Marco:** What do you do, Barry?

**Dr Borlaug:** So we do both supine and upright exercise. We tend to do more supine because it's just easier, it's more feasible. It's a little trickier to get catheters in, have everything zeroed at the phlebostatic access and then get them back up again, especially in older people, and get them onto the upright bike. But we can certainly do both. So what we'll do is get access in the radial artery and in the jugular. We'll put a 9-French sheath in the neck, so we can measure the right atrial pressure throughout the case. And I think that's very important, as well. Then we put a balloon wedge catheter to get samples and high fidelity pressure data at rest and during exercise. We do expired gas analysis during the test and, you know, there is a bit more expense there. There is a bit more training. There is calibration needed on a daily basis. But we find it to be extremely useful, because I think most people would agree that direct Fick outputs to measure cardiac output at rest and exercise would be considered the gold standard. If you look at how much the oxygen consumption goes up during exercise, you can accurately say whether the cardiac output reserve was appropriate or not. That's because it's well known in humans that for every 1 mL increase in oxygen consumption, there should be a 6 mL increase in cardiac output, if the heart is doing its job, to meet the body's metabolic needs. So in these PAH patients, we can see if they have high filling pressures obviously, but this really gives us a good sense for the adequacy of their cardiac output reserve, which is very often abnormal in patients with PH and left heart disease. Having the right heart pressures, their RA pressure and the wedge pressure or the PA pressure together is useful, because sometimes you see these people where the 2 go up in tandem and they almost equalize. And while not well-studied, that suggests that those people are having more pericardial restraint and they might have a somewhat different kind of disease compared to somebody whose wedge pressure goes up to 35 but their RA pressure stays at 10. So again, that's not well-studied, but we think that that's probably useful to understand that.

**Dr Shapiro:** What do you do for volume loading and things of that nature in the cath lab or how often does one have to perform that?

**Dr Borlaug:** We do volume loading. We published a paper earlier in 2015 where we compared volume loading and exercise in the same patients. They did...
exercise first; everything came back to recovery. And then they got a very aggressive volume load, 10 cc/kg, wide open, over 5 minutes. So it’s about 150 cc a minute, prewarmed so we don’t drop their core temperature. And we see that filling pressures go up. But the increase in heart failure patients with saline is not nearly what we see with exercise. And, in fact, it’s not statistically different from what we see in normal people, in whom also it’s not uncommon to have an increase in wedge pressure above 15. So the saline loading, it’s better than nothing, but it’s not as sensitive or specific as exercise. Another group from Vanderbilt published a paper where their practice has just been to give 500 cc much slower, I think over 10 minutes, and they do see a number of people that had an elevation in wedge pressure above 15 mL. Again, as I mentioned, we do see this not uncommonly in some of the normal people, maybe 20% of the time. So I think that there are some issues there with the specificity of that finding.

**Dr Shapiro:** I would have to believe that nationally and internationally, you know, the rate of a program having the ability to exercise, do exercise-invasive hemodynamics must be low. There may be a number out there, I don’t know, but I would expect it to be low. But for those programs or those practices out in the community that, you know, want to make this diagnosis invasively, but only have the ability to do baseline-type hemodynamics, is that accurate? Is that a good way to go? Or what could they be doing to enhance that?

**Dr Borlaug:** Well, I think saline is better than nothing. I mean, any sort of provocative maneuver, any sort of stress, is going to help to bring out abnormalities. So I still think there’s value to doing it. I think that if the wedge pressure goes above—probably above 18 with the saline load—that would be pretty good evidence that they probably do have significant left ventricular (LV) diastolic dysfunction. It’s just not quite as good as what we see with exercise.

**Dr Borlaug:** But it’s better than nothing.

**Dr De Marco:** So I have a question for Srinivas. What is the role of vasoreactivity testing in WHO Group 1 versus WHO Group 2 PH? What agents do you use? What are you looking for? What is the purpose of the testing induced in these 2 clinical scenarios?

**Dr Murali:** Yes, that’s true, Teresa. But I think saline loading is something that can be done in the community. I agree. We use 500 cc over 5 minutes. If you can do that, a rise in wedge pressure to greater than 18 will have a fairly small percentage of risk of being a false-positive result. I think that’s a good thing, which can easily be done in a community setting. I agree with the arm exercise, using light weights or saline bags or anything like that almost always results in the elevation of all pressures.

**Dr De Marco:** And Jim, what do you use in the various scenarios? For example, with WHO Group 1 or WHO Group 2?

**Dr Murali:** Our institution uses inhaled nitric oxide. So our protocol goes from 10 parts per million, all the way to 40 parts per million, for both scenarios, for both groups.

**Dr De Marco:** Even for patients with PAH and left heart disease? Have you run into elevations in wedges and pulmonary edema in the WHO Group 2?

**Dr Murali:** We haven’t quite gotten into pulmonary edema, but we have seen elevations in wedge pressure in WHO Group 2 patients. So that’s one of the things to keep in mind when you test them. But it is quite valuable. The other agent—which is not an acute vasoreactivity testing agent—we have used in some patients—especially if their cardiac indices are low, is to start them on milrinone infusion and then bring them back to the cath lab after a few days of milrinone therapy to see if the numbers have improved.

**Dr De Marco:** And Jim, what do you do in these scenarios for WHO Group 2? What’s your protocol?

**Dr Fang:** We do also use inhaled nitric oxide. Probably most commonly, we use Nipride, if the systemic vascular resistance (SVR) is elevated. And we titrate the Nipride to potentially hypotension or just short of that. We do know patients who get very hypotensive from Nipride from the old Stanford experience don’t do well. Secondly, if the SVR is low and
the PVR is high, we will sometimes just try nitrates. And then, like Srinivas, we also are a big fan of using milrinone. We use the protocol of the bolus of milrinone, 50 mcgs per kilo over a minute or two. You see the peak effect somewhere between 5 and 15 minutes. This primarily lowers the PVR by increasing the output, at least from the calculated point of view.

**Dr De Marco:** And for both of you, what do you feel are the important considerations relevant to PAH and left heart disease, in the context of heart transplantation and left ventricular assist device (LVAD) implantation? So you want to start, Srinivas?

**Dr Murali:** I think transplantation criteria are a little bit stricter. We would, in our program, have certainly wanted to see the transpulmonary gradient be less than 12 and the pulmonary vascular distance to be as close to 3 Wood units as possible before they are listed for transplantation. As far as LVAD is concerned, it’s a slightly different approach. I think that we have generally not excluded patients for consideration for LVAD implantation on the basis of transpulmonary gradient and/or PVR. It’s been our experience that in many of those patients with the currently used LVADs in clinical practice, both the HeartMate II axial flow pump, as well as the HVAD centrifugal pump, we have been able to unload the left ventricle with improvements in hemodynamics, as it relates to pulmonary pressures, transpulmonary gradient, and PVR over a variable period of time. So for transplant, we want to see the numbers come down before re-enlisting them. But for LVADs, we would proceed with the LVAD, as long as we feel comfortable with respect to the risk of right heart failure postoperatively and then follow their hemodynamics on LVAD and wait until they improve to the levels I alluded to before listing for transplant.

**Dr De Marco:** I agree. In fact, we’re using VADs at our institution, again provided the RV function is in a reasonable range, as a bridge to transplant. And over time, the PVR markedly improves in virtually all of these patients and then they do become transplant candidates. And oftentimes, we may, in addition, add phosphodiesterase inhibitors to those patients where we haven’t attained a PVR that would allow them to go to transplant. So these are 2 strategies that we’ve employed. What about you, Jim?

**Dr Fang:** Well, I would concur and echo everything that both you and Srinivas have said. From a pathophysiologic standpoint, I think a great example of how they’re really 2 components physiologically to the elevation in PVR and the PH: one, of course, is a dynamic component that we tend to try to affect acutely with vasodilators, diuretics, etc. And, of course, there is the more anatomic part of the equation that obviously requires a, for lack of a better word (laughs), putting down the rage of activation, so you can get the positive remodeling that you want to see in the pulmonary circulation. And I think the VADs help to provide that.

**Dr Shapiro:** Absolutely. I think, Barry, we were going to switch gears a little bit to treatments. In terms of the comorbidities, what are the most important comorbidities that one looks for in a typical patient with HFpEF, PH with left heart disease? And, in our experience, what are the ones that are most successfully treated and make a difference in a positive outcome?

**Dr Borlaug:** Well, I’m afraid I don’t have real good experience versus real positive outcomes. It’s such a challenging disease. I mean, I think that the people with PH and HFpEF in general are just the people with more advanced HFpEF. So there are some people that have high filling pressures and PH that’s just restricted to exercise. These people are profoundly limited. They have very bad, lifestyle-limiting symptoms. I mean, many of them are crying literally in the office. They are miserable. But they’re not getting admitted for pulmonary edema or peripheral edema; they’re not going into the hospital. It’s more lifestyle changes. The people with more advanced disease who have high filling pressures at rest, these are the people that tend to have more PH. And we’ve started to look at what distinguishes these people. It’s probably more prolonged heart failure, more comorbidities, so they tend to have more hypertension, more diabetes and metabolic syndrome, greater age, and worse kidney function, which is probably not surprising. When the kidneys are not able to excrete the solute anymore, that seems to accelerate the progression. You know, in terms of managing the comorbidities, we often look at good blood pressure control, weight loss, treating sleep apnea: of course you’re going to do all this. The evidence that that is going to lead to clinically meaningful improvements in their heart failure is slim and none. We do have some data now on single-center retrospective data from Mayo that we published last year, looking at coronary disease as a comorbidity in HFpEF, regardless of the presence or absence of PAH. And the patients with coronary disease have worse outcomes. And revascularization was associated with better outcomes. We don’t know what that’s doing in terms of the hemodynamics and the filling pressures and the pulmonary artery pressures, but that’s one comorbidity that in these, at least in HFpEF patients with PAH, I have a very low threshold to look for.

**Dr Shapiro:** So provided that all the comorbidities are being addressed and you’ve got a patient who is in your office with severe HFpEF and secondary PAH, what are your favorite go-to both pharmacologic and nonpharmacologic treatments that have been most successful for you?

**Dr Borlaug:** We said for years that there’s “no evidence for diuretics in heart failure.” But, of course, we’ve always known that’s not the case. And now with the evidence from the Champion study of the PA pressure sensor device, we know that when you manage people with heart failure based on their hemodynamics and modify their diuretics, that you can reduce hospitalizations. And that’s been shown even stronger in HFpEF, in another analysis from that.
trial. So yeah, good old loop diuretics I think are the only thing that I’m convinced really works. People talk about nitrates. We will have data on that soon. There was a large, or pretty good-sized, phase 2 trial of isosorbide mononitrate, which has now been completed and will be reported in HFpEF. We know from the RELAX trial that PDE-5 inhibitors were not effective, though there was a small single-center study that showed benefits in a very atypical HFpEF population that had much more advanced PH. Beta-blockers, not good evidence. Same thing with calcium channel blockers. And then other people are using off-label things, like ranolazine and such, but there’s really no good data to support any of those. So, for me, it’s diuretics. I look forward to what the others think.

**Dr De Marco:** Okay. I have one final question for Jim. From your perspective, what are the most important diagnostic and treatment gaps that remain in the knowledge base for PAH due to left heart disease? And what does the future hold?

**Dr Fang:** Well, great question. I think one of the basic knowledge gaps that is still one of the elephants in the room is whether or not it’s a disease marker or a risk factor. It does fall out often in multivariate analyses as an independent predictor, which would suggest that it’s a factor. But one of the unexplored areas is how much of that is really just a surrogate for time. Time in most heart failure studies is poorly controlled for, primarily because the onset of the disease is very difficult to quantify or to have any precision about. If we think about the pathophysiology of PH, clearly the upregulation of growth factors and other factors, like endothelium that lead to pulmonary vascular remodeling, are time-dependent issues. So I think that still remains a very important issue that really outlines a whole field. Because, in fact, if it’s simply a risk marker, then we need to be a little bit more proximal in our targeting of PH. Number 2 is that if we agree that it’s a separate issue unto itself and not simply an unrecognized surrogate of something else, the issue is to find drugs that are selective for the pulmonary bed or methods of delivery that are selective for the pulmonary bed. One of the things that complicate the treatment of pulmonary vascular disease, of course, is trying to find specificity for that organ bed without producing systemic and off-target effects. So that’s sort of very brief, but I think the two most important issues.

**Dr Shapiro:** On behalf of Dr De Marco and myself, I really want to thank Drs Fang, Murali, and Borlaug for this excellent discussion on PH and left heart disease. I am confident that your insights will be a huge asset to those who care for patients with this common disease. And once again, I want to thank you so much for your help.

**Dr De Marco:** Thank you, everyone.