Management of PAH in Adults with Congenital Heart Disease: Impact and Dilemmas

Guest editor Richard Krasuski, MD, convened a group of experts by telephone on January 17, 2013, to discuss current trends in diagnosis and treatment of pulmonary hypertension among patients with congenital heart disease. Joining the call were Professor Maurice Beghetti, Head of Pediatric Subspecialties, Division Head of Pediatric Cardiology Unit, Children's University Hospital, Geneva, Switzerland; Curt Daniels, MD, Director, Adolescent and Adult Congenital Heart Disease Program Nationwide Children's Hospital, The Ohio State University, Columbus, Ohio; Wayne J. Franklin, MD, Texas Children's Hospital, Houston; and Michael J. Landzberg, MD, Associate Director, Adult Pulmonary Hypertension Program and Director, Boston Adult Congenital Heart Program, Boston Children's Hospital.

Dr Krasuski: We are here today to discuss the impact and dilemmas in the management of pulmonary arterial hypertension (PAH) in adults with congenital heart disease (ACHD). There are now up to a million ACHD patients, and we believe that up to 40% of these patients are at risk for PAH; 10% of ACHD patients will actually develop PAH. So we're talking about 100,000 such patients existing in the United States alone, and possibly up to 40,000 that have developed Eisenmenger syndrome. So it's a large and growing group and an exciting and challenging field to practice in. It's very impressive in terms of what's happened in the last decade or 2, regarding the development of multifaceted management strategies for these people. I am going to begin by asking the following question of this prestigious panel: "how can we best identify those patients with congenital heart disease who have pulmonary hypertension and who might be candidates for some of the therapeutic interventions that we now have available?"

Dr Daniels: We know a group of patients from the large congenital heart disease population, who are higher-risk patients. Those are patients who have shunt lesions and some of our more complex lesions. So these are the patients we must be aware of as having the potential to either have pulmonary hypertension or develop pulmonary hypertension. Then we also have to be aware, as an educational point to ourselves and our community, but also other cardiologists and even possibly pulmonologists who see patients, to rule out pulmonary hypertension or evaluate for pulmonary hypertension because patients may be completely repaired and still develop pulmonary hypertension. We know a percentage of patients, even if they have shunts closed, even at what we consider an earlier age, still may develop pulmonary hypertension down the road as an adult. There are risk factors that lead to those with shunt lesions and complex congenital heart disease that makes them more vulnerable to develop pulmonary hypertension, such as timing of when a septal defect was closed, surgical shunts that may have been placed, length of time with a shunt before they had a complete repair. So we have to be aware that the congenital heart disease population as a whole is at risk, but there are certain patients, certain populations within the congenital heart disease population, that are at higher risk for developing pulmonary hypertension, and be aware and be able to evaluate those patients, looking specifically for signs, symptoms of pulmonary hypertension.

Dr Landzberg: What Curt identified were findings that many of us, as congenital heart disease docs, would recognize, but I wonder if we can extend that a little bit. For the general practitioner or for the internist who is out there, if one is fortunate enough to have the preoperative history on these folks, we could say that, almost everybody's at risk but, in particular, folks who may have had preprocedural large-volume shunting. Maybe if you had ventricular dysfunction going into the shunt repair. If you had a lot of volume coming back to your left side of your heart, as well, that's a sign that someone may be at increased risk for the development of pulmonary hypertension after closure. I think many of us will see arrhythmia as a preoperative arrhythmia or postoperative arrhythmia as a sign that the patient may be having increased risk for developing pulmonary hypertension. Persistent RV dysfunction, functional decline, just in general, if someone's not doing well with congenital heart disease afterwards, that puts the thought into my head, could this person have pulmonary hypertension, and just age alone. So I think that anyone that's not doing well, anyone that's getting older, anyone that has heart muscle dysfunction, I'm thinking has the potential for pulmonary hypertension.

Dr Beghetti: I think you both raise a very important point. So we may ask adult physicians to see these patients and refer to "adult congenital heart disease." I think one important point that you both raised is that we need to know what happened at an early age, especially in the ones that had surgery, and then come back to the adult clinic with PH later in life. And I think the

transition and the connection between the pediatric cardiology and the adult cardiology with regard to these patients is very important, to be sure that we have the data on what happened and how the decision was done to do the surgery, to close the shunt, and exactly what Mike just raised now: if there were specific problems that can be identified and indeed, the risk factors for this population, and then identify the risk factors that will allow you to identify the patients that are at high risk to develop postoperative pulmonary hypertension. Because I think in our database now, what we see is that the Eisenmenger population is an old population. We should see fewer of these patients. But the growing population is patients with PH after repair. And so we need to identify these patients and the risk factors for these patients.

Dr Krasuski: I completely agree. Between a randomized trial and several prospective registries, we've accumulated quite a bit of data about Eisenmenger patients. But as time goes on, hopefully we can identify and intervene in these patients early enough to prevent them from developing Eisenmenger physiology. We have developed trials focused on Eisenmenger syndrome, including the published BREATHE-5 study and newly enrolling MAESTRO trial. These are randomized, placebo-controlled trials examining the role of pharmacologic therapy. But for patients with earlier forms of PAH, how can we apply these data to them? Should we be more aggressive at earlier stages of the disease? And how can we apply what's been learned in other etiologies of pulmonary hypertension to our ACHD patients?

Dr Beghetti: Eisenmenger patients and the ones who present with PH after complete repair may be a bit different. For the Eisenmenger patients, as you said, the MAESTRO will include patients with, I would say, functional class II, which would be considered as mildly symptomatic, and we'll see what happens with this population. I think the other group appears really quite affected with the preliminary result we have. And with the group that presents with PH after repair, it seems, even if we do not have still all the data, that we need to be a bit more aggressive with this population, compared to Eisenmenger patients. Even if we think we still need to have more data on Eisenmenger patients to see also the benefit from early aggressive therapy.

Dr Daniels: I agree. I think that finding a patient with complete repair of a shunt, for instance, who has developed pulmonary hypertension, has the pathophysiology of advancing pulmonary hypertension. And so far, there is no evidence to the contrary, to believe that this particular patient population is not going to follow a pathway with a closed, repaired shunt, almost similar to an idiopathic PH patient. Of course, we don't know this and we know the Eisenmenger population has a very different course in terms of their prognosis. But the patient with a closed, repaired shunt, and found later to have pulmonary vascular disease, we have to believe this is an advancing disease process. We certainly see that as we follow patients now, we're collecting more information. Therefore, we have to believe that early therapy is quite important and not waiting until they are more symptomatic, which we all know means that the right ventricle is becoming more dysfunctional from a systolic and diastolic and a compliance standpoint. So early treatment certainly seems to be the best course of action for these patients.

Dr Franklin: I think that the Eisenmenger data for us, specifically in Houston, have been very helpful the past few years. Because in the past, where I think we would just start them on maybe one medicine and that was all. Often these are Down syndrome patients. I think now we've been more aggressive to try to get them on advanced therapies, whether it's 2 drugs or 3 drugs. Usually it's 2; often they do not tolerate 3 drugs. But I also agree with Curt closely that the ones that we think are repaired, we're still following every year. And I think maybe we should think about starting them earlier on therapy. So I think there has been the real emphasis on early detection now, as well.

Dr Krasuski: Let me shift gears a little bit and ask the group to briefly discuss what type of workup they do in the newly diagnosed ACHD-PH patient. So you have a patient who has a congenital heart lesion and develops pulmonary hypertension, though not yet Eisenmenger syndrome. What types of studies should we perform to look for other sources of pulmonary hypertension? Should we be doing a full pulmonary workup for these patients, such as VQ scanning and pulmonary function testing? Bloodwork assessing for collagen vascular disease? Sleep-disordered breathing workup? What is your standard practice in these patients? Particularly in this era of cost containment, do you run the whole gamut and follow the same algorithm as for any newly diagnosed PH patient? Or do you focus on what you think the most likely etiology is?

Dr Landzberg: Before we address this, let me shift back a little bit. There were a couple of things that folks mentioned that gave me a bit of a twitch, only because it underscored that we're missing some data or there are some additional data out there that may be

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helpful in the Down syndrome population. And folks like Michelle Dalto and others have underscored that it may be as high as 25-plus percent of the congenital heart disease population with pulmonary hypertension that has Down syndrome. And we have scant data in this country with regard to the triggers in that population that make us particularly concerned. Our data on therapies are limited to cohort studies, so that there is a whole batch of workup that needs to be done in this population. I know that we all worry about how little data we have in just congenital heart disease after a repair. The REVEAL dataset makes me worry. It's clearly in a patient population that came to advanced heart—pulmonary hypertension clinics rather than adult congenital heart disease clinics, but it was suggested a terrible prognosis in that small patient group. But there are 2 ongoing registries in this country that are going to hopefully define that for us. And as part of those registries, we are mandating exactly what you mentioned, Rich, that we go through the full evaluation. Our patients with congenital heart disease have many other triggers for pulmonary hypertension. So I'm a big fan of a full and complete evaluation, despite the fact that somebody had a shunt to begin with and despite the fact that somebody has congenital heart disease—there are way too many times that we find other contributors that have their own independent therapies.

Dr Beghetti: I definitely agree with that, because you can have a congenital heart defect and also have other triggers or other risk factors. And that's extremely, extremely important to know. On top of this, it's extremely important also to re-cath the patients, for the reasons that Mike raised before, to be sure that there is not a combination of pre- and postcapillary pulmonary hypertension, and also to see if there are any clots in the lung. Because they had surgery, sometimes they have catheters in place for a long time after surgery. So I think definitely we need to look at everything before starting these therapies, because otherwise you will blame the therapy for not working, but maybe that's because the indication was not exactly the one you thought. And the complete workup should help make the diagnosis correctly.

Dr Daniels: I would completely agree. And I think to bring it back to a specific patient population that we all see is the atrial septal defect (ASD) patient. A patient with an ASD that's been closed or even remains open and has pulmonary hypertension, this is a population we all see. We're not sure many times is the ASD truly causing the pulmonary vascular disease or an innocent bystander, or possible a contributor. And so I think this highlights, at least for me in the evaluation and workup, we do need to perform a complete workup, even on our congenital heart disease patients, not knowing if this is cause and effect or an innocent bystander. We don't want to miss a diagnosis, as Maurice says, go down the wrong pathway in terms of our therapies when we should have been looking in a different direction.

Dr Krasuski: Those are all excellent points. Now, Maurice, you alluded to the importance of heart catheterization and potentially repeat heart catheterization while on therapy to assess therapeutic response. What about performing hemodynamic challenges in the cath lab? How often do you do vasodilator challenges, fluid challenges, and other such studies to assess the physiologic response? Do you reserve such procedures to the first catheterization or is it worth reassessing?

Dr Beghetti: I tend to do complete caths all the time, including vasoreactivity testing. It's not because I think that I will find the patients becoming reactive, because this is extremely, extremely uncommon. But based on some data coming from Belgium, from the group of (s/l Vander Butz), and also from (s/l Mikhaila Douto) in Italy, this could be a good way to identify some risk factors for this population. When you still have some reactivity, it seems based on these 2 studies that the patient may have a better outcome. They also may have a better response to some of the therapies, because there is some vasodilatory reserve. So that may be the reason to assess vasodilatory reserve. I think the fluid challenge, especially if the patient is older or if there is some history of ventricular dysfunction, can unmask diastolic dysfunction, and I think that's very important to know in our population. I think maybe we mismanage these kinds of things in some of our patients. In terms of follow-up caths, I think it's important to do follow-up caths in the population where there is closed shunt in PH. That will be exactly the same follow-up that you do in idiopathic PH. In Eisenmenger syndrome, and I'm sure that Mike will have strong ideas on that, the problem is to reproduce the data properly and really be sure that you can compare data from cath to cath. And sometimes it's not easy because these caths with open shunts are sometimes a bit difficult, as you all know. So I think you need also to adapt a little bit to the population that you follow.

Dr Landzberg: All of us in this group perform catheterizations. And have different opinions about how often to cath, but I think we all probably share the opinion that cath plays a vital role. The number of times that we find something unexpected at a cath in somebody who has congenital heart disease and pul-

monary hypertension is far too often. And I would say that, as we've underscored before in terms of the many triggers to pulmonary hypertension development, our patients are prone to pericardial construction and have reasons to have pulmonary venous stenosis, restrictive myocardial disease, other unexplained or unexpected pulmonary arterial stenoses. And so I underscore that during the very first catheterization, it's critical to do a full, complete angiographic, hemodynamic, multiple maneuver catheterization. I have been amazed at the more than rare patient that is responsive to pulmonary vasodilator acute therapy, and I know that we all believe slightly differently in terms of whether or not somebody can respond to a calcium antagonist in our population or should respond. In the same breath, I agree that it's vitally important to know whether or not somebody is responsive. It tells you something about their prognosis as well. My toughest point is what about serial catheterizations? And this applies to the patient with idiopathic disease, as well as to our own patients. There is so much hour-to-hour variation of the hemodynamics of our patients, in a normal host, or a patient with pulmonary hypertension that small differences, even small to moderate differences, don't necessarily tell us a lot, but there are still key prognosticators that we get from hemodynamics. I often repeat caths, but I have no idea how often it should be. Certainly, when there is a functional decline, that's a marker for us to go back and reassess hemodynamics.

Dr Daniels: I completely agree. The first cath is critical. And this is where the data are so important that it's accurate and done with detail and in an organized fashion. You know, for the audience that will be reviewing this roundtable discussion, many may not be congenital heart disease experts in performing cardiac catheterizations on patients with shunts. And I would emphasize the point of collaborating with congenital heart disease experts with cardiac catheterization data, because collecting data in a correct fashion will make the difference between which pathway you will go with that particular patient, whether it's pulmonary hypertension-specific therapy, whether it's deciding to close the shunt, whether it's deciding therapy should be headed toward heart failure, diastolic dysfunction. And so it's critically important that the correct information is obtained, under the right conditions. The oxygen saturation data: is the patient on supplemental oxygen? That the vasodilator trial is done correctly. Because this is the one shot in the catheterization lab to obtain correct information. So I would emphasize, even if you are in a center that performs cardiac catheterization for pulmonary hypertension, but maybe not specifically for congenital heart disease, collaboration with congenital heart disease experts is critical to obtain the correct data.

Dr Krasuski: It's great to hear such a strong consensus on the importance of hemodynamically defining the disorder and properly collecting the data. This really sets you on the proper path toward appropriate therapy. My next question is: "how do you follow ACHD-PH patients in terms of assessing their disease progression and response to treatment?" The 6-minute walk has gotten kind of a black eye recently as a surrogate for outcomes in pulmonary hypertension. Do you guys regularly measure the 6-minute walk in your CHD-PH patients? Do you utilize metabolic stress testing? Do you measure biomarkers? Do you regularly perform echocardiograms? We've already discussed catheterization and the importance of potentially repeating it at some point, though we may differ perhaps in what we believe the appropriate interval should be. When you see your patients back in clinic, what are those essential tools that you use to assess how the patient is doing and how successful therapy has been?

Dr Franklin: It's interesting, Rich. The 6-minute walk, as you mentioned, has been controversial lately. But I still use it. I still use it for enrolling patients and starting therapy and monitoring patient responses. The test is easy to do. It's a good, sustainable test, if you will. But I also use echo; I use saturations. Some of our patients that are pretty debilitated are not able to do even a submaximal stress test. So that's where I think the 6-minute walk continues to be very useful. It would be interesting to see what the group consensus is about repeat catheterization. I usually will save that until there's either some unusual response, or the patient is not responding, or I'm going to start a second drug, or it's been a year and the patient may be a surgical candidate, or something like that. But I tend to use more of the noninvasive measures, rather than cathing them more than once or twice.

Dr Beghetti: Yeah, that's what I said before. I think we should clearly differentiate Eisenmenger and non-Eisenmenger patients. I think repeating caths in Eisenmenger, again it's very difficult to see a major difference. And there is always some risk to redo the cath in this population; you never know what can happen. So I think I would do exactly what you say. If the patient is not responding as you expected or you plan maybe to add another drug, that is one of the good reasons to repeat the cath. But if an Eisenmenger patient is doing well, I would not do repeated routine cath. This may be different in a closed shunt. Some

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centers are following exactly the same approach if a patient is doing perfectly well with all the noninvasive assessment, they would keep the cath only for patients that have inadequate response to treatment. And I would do exactly as you said, a 6-minute walk test, saturation at rest and at end of exercise, BNP, echo and a function class assessment. I still think the functional class one can gain from discussing with the patient is sometimes just as helpful. It's simple but still very helpful in these patients. I think the CPET for the Eisenmenger patient is a bit of a tricky test, even if it becomes a little more used in the other populations. I think in the very blue patient, it's very difficult to have reliable data.

Dr Daniels: I would pose to the group that one of the aspects that we are most concerned with is right ventricular performance. And certainly, newer data seem to suggest that maybe we should be looking at the right ventricle in a different way. Certainly, we all look at our patients with echocardiograms on some regular basis. I find the echocardiogram for PH probably to be the least helpful in following patients, just because most patients with advanced disease, and certainly with Eisenmenger patients, we really do not gain much information beyond what everybody's mentioned: how they are feeling clinically, their oxygen saturation data, exercise data. But certainly evaluating the right ventricular systolic function is an important parameter that we probably should be following more closely. And whether or not that allows us to change our therapy, add therapy, consider other therapies may be important for the future. In our Eisenmenger patients, we do have a difficult time in the cath lab, I agree. And a difficult time really with obtaining accurate and consistent data. I'd be interested to see what others think.

Dr Beghetti: MRI should be one of the options.

Dr Krasuski: With regard to MRI and some of the other novel, newer techniques for disease assessment, such as strain imaging on echo, is there anything that you all see that will change how we practice in this patient population? Maybe there are some biomarkers that are easy to follow? How do you utilize measurement of natriuretic peptides?

Dr Landzberg: Let's focus on MR and anatomy. Our world of congenital heart disease underscores that the progressive decline or the ability of the patient to succeed with pulmonary vascular disease is in part related to the pulmonary vascular bed and in part related to the supporting structures that mount the flow to the pulmonary vascular bed. And so that the standard right ventricle in idiopathic pulmonary arterial hypertension or acquired PAH is very different for our patients who often don't have a normal ventricle, don't have a normal atrioventricular valve, or don't have a normal conduit system in terms of passage of preload to the subpulmonary ventricle. So I think that understanding how that ventricle is doing, not just from a hemodynamic standpoint but from an imaging standpoint, is particularly valuable in the management, but also in the primary classification of what's going on. So MR for us, and Curt, I'm glad you underscored it, is an increasingly valuable aspect of not just the management but also in terms of the very classification of our patients.

Dr Krasuski: Would someone want to comment on the routine measurement of natriuretic peptides?

Dr Beghetti: I measure them, but I'm a bit careful. I think the data that has just been published by the (s/l Brompton) group is very interesting. But I think that sometimes you have to be very careful not to over rely on the BNP values. We still have to learn about how this works. In patients that have Eisenmenger, some renal dysfunction, that are using diuretics. Sometimes doing a BNP during the day, in the morning or in the evening, you may have surprise that the level is a bit different, if it's before or after Lasix dose, depending of the renal function in your patient. And so I think we need to learn a little bit more. But the data coming out from some studies are quite interesting. And definitely in the MAESTRO trial, we would like to measure that in a standardized way, to see if in a standardized way in a large cohort of patients, this can be used to address if the treatment is or is not working.

Dr Landzberg: Is it reasonable to say, Maurice, that most of us will collect natriuretic peptide will use it as part of the assessment, but none of us will take it in isolation? And I think that the recent data would underscore that it's an important part of the mix, but not to be taken in isolation.

Dr Beghetti: Definitely. That's exactly what I meant.

Dr Daniels: And I would agree, it's a part of the follow-up and evaluation of our patients, a perfect way to say it but not the sole decision maker about adding additional therapy or changing therapy, but it's added to our process of evaluation.

Dr Krasuski: In our program we collect a lot of data at each clinical visit. We look at functional status, natriuretic peptides, echoes, and 6-minute walks. One of the things that I like to examine is the general trend

in each of these. I've found that taking patients to the catheterization laboratory is most helpful for clarification of the disease state when there are conflicting data. If all the data are heading in the wrong direction, I'm fairly confident that our chosen clinical strategy is probably not right. When there are, for instance, improvements in the 6-minute walk and functional state but the natriuretic peptides are increasing, then I'll start thinking about some of the things that Maurice mentioned: maybe it's the measuring technique or the time of day when the measurement was made. But if I have more conflicting data, like evidence that the right heart is failing despite no worsening of the patient reported function state, then this is the time where catheterization may be most helpful—to know which direction the hemodynamics (pressures and pulmonary/systemic blood flows) are going. So why don't we now move into how we approach these patients therapeutically? Let's start by reviewing lifestyle modification. I think one of the areas that has always been controversial, and where we're learning more that some of the recommendations we made in the past weren't correct, is exercise. What do you tell your patients, particularly the ones that have pulmonary hypertension and congenital heart disease, about exercise? Do you encourage them to participate in programs? What kinds of restrictions do you place?

Dr Daniels: Well, we will at our center encourage patients with new diagnosis of pulmonary hypertension, whether it's congenital heart disease or not, to initially be involved in a rehab program. It's difficult in the United States to have patients approved through insurance companies for cardiac rehab, so many of our patients will go through pulmonary rehab. With a pulmonary hypertension diagnosis, they can proceed with pulmonary rehabilitation, which I think allows them to begin an exercise program, and allows them to have confidence in what they'll be able to do. And as they hopefully improve on therapy, they'll be able to accelerate their own exercise performance. So I guess as an opener, I would say that we try to incorporate an exercise program into the pulmonary hypertension population, and the congenital heart disease patients fall into this mix.

Dr Beghetti: When you consider again the Eisenmenger and the closed shunt, do you give the same possibility of exercise to both? Or you would advise them differently?

Dr Daniels: Well, I would say we're a little more cautious with Eisenmenger patients, only from the standpoint of some of the isometrics. There's always some component of isometrics with a rehab program.

Dr Daniels: I think we are a little less willing to freely open the door to the isometric program that's part of rehab with the Eisenmenger population. That is probably the only difference and caveat. But otherwise, the aerobic performance, the aerobic activity, we prescribe in a similar fashion.

Dr Landzberg: The pulmonary rehab that you mention, Curt, is so attuned to what our patients can and should be doing in terms of their mixed diseases that are going on, in terms of both pulmonary parenchyma, Bellows, and peripheral musculature. Those programs are often well designed to what our patients need. It really is remarkable at how the referring clinician population frequently is so concerned about our patients going to physical therapy and rehab and yet the patients so desperately welcome it. And there are accruing data, not just for the idiopathic pulmonary arterial hypertension population but also for the congenital heart disease population, which you underscored, Curt. It's now a routine part of all of our practices to have patients with congenital heart disease, associated pulmonary hypertension, go for rehab. It's one of the first, if not the first things that we do.

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Dr Daniels: Maurice, what do you do?

Dr Beghetti: So, it's a bit difficult to send them to cardiac rehab. And so the pulmonary hypertension center is run in the adult field by pulmonologists and we're working together. So it seems that the possibility from this side is a little bit better. The only concern that sometimes they have, and as we are not directly involved, is the saturation of the patients. And did you need to teach a little bit the people taking care of them to not be too scared about the saturation? Because if you send them to the pulmonary rehab, where they're used to stress a little bit if the sats go below 90, just imagine when they have patients satting in the low 70s- so that's more the physician, the nurses, and the technicians that you need to teach sometimes about the disease.

Dr Daniels: Yes. Good point. Education for the rehab program for these particular patients is key.

Dr Krasuski: With regard to oxygen saturations, what are your individual practices in terms of prescribing oxygen? Do you recommend it for all patients going through rehabilitation? Focusing on the Eisenmenger patient, I think we all recognize that the data here are very, very limited and that perhaps we've been overzealous with oxygen. Certainly, we have all experienced one of our Eisenmenger patients getting

admitted to the hospital overnight; and when we walk in room on the following morning, the patient is on 100% oxygen by non-rebreather mask. We obviously have work to do in terms of educating our nursing staff and other physicians that take part in the care of our patients. What do you recommend in terms of oxygen prescriptions and the use of supplemental oxygen at night and during exercise?

Dr Beghetti: I would like to answer before Michael, because I know that he has strong ideas about that. I would say that I don't know. But what I'm sure is that the workup of the lungs of these patients should be done, because that may help you to decide if the patient needs or does not need oxygen. Because if he or she has some restrictive disease, restrictive lung disease, or some gas exchange problem, I think that's very important to know. Because in this population, there may be a good chance that oxygen may help. And then there's maybe a population that oxygen may not help. And that's why we still have a lot of controversy about the use of oxygen in this population. But I'm sure that Michael will comment on that.

Dr Landzberg: All of us respect the work that was done by Julio Sandoval in Mexico City, who has taught us much about pulmonary arterial hypertension. The study that most people refer back to is a very small study that relates to nocturnal oxygen use in chronically cyanotic patients with general heart disease. It's a difficult study to extrapolate from. And without being controversial, I would suggest exactly as Maurice said. The key here is to assess the underlying pulmonary parenchymal and Bellows disease that so many of our patients have. I don't restrict oxygen away from our patients, but I put it into the mix if they have combined disease.

Dr Daniels: And I think also since our population is different, many of them would have had open-heart surgery. They would have had surgical procedures, a sternotomy. We know now from our congenital heart disease data that many of our patients have restrictive lung disease. And so they do have limitations of their lung capacities, which in many cases will lead to areas of lung that do not participate in oxygen exchange in a normal fashion or the capacity at which we consider to be normal. So a workup of lung disease is important. And I think all of us have found patients, that surprisingly, do feel better on oxygen can exercise longer and do perform better. And at the end of the day, it is all about patients' feeling better and improving their quality of life. And so it's important, I think, to assess whether or not patients that are desaturated need oxygen, whether they respond to oxygen. Do they feel better with oxygen? Does it improve their quality of life? And I guess to be quite frank, we many times will allow patients to make that decision. You know, if you feel better on oxygen and you're able to exercise and your quality of life improves, then that's fine. If you really don't feel better and the chore of having oxygen, carrying oxygen actually worsens your quality of life and we really do not see a response, then obviously we wouldn't prescribe oxygen.

Dr Beghetti: Yes, we need to remember that sometimes they've had several surgeries. And so they may have chest deformity, not only lungs, chest deformity. And it is well known that cyanotic patients sometimes have scoliosis. So if you had the chest deformity because of the surgery, the scoliosis, and maybe some lung disease, clearly you will find some patients that after the complete lung workup, they will require oxygen.

Dr Franklin: Yes, that's a good point, too. It's something that we struggle with, I think, here in Houston. Because I generally don't necessarily start oxygen. But that said, I have patients who've come to me on oxygen and I don't necessarily stop it, either from their pulmonologist or the prior cardiologist that I've inherited from. But, to Curt's point, I'd say yes, some patients feel better on it. Rich, I think you mentioned the nocturnal oxygen. Some patients use it at night and they just feel more rested in the morning. Who knows if that's placebo effect or not. But, like Curt said, quality of life is important, too. But I tend to not necessarily start oxygen if I'm going to start patients on an exercise regimen, per se.

Dr Krasuski: There is a growing body of literature, Wayne, as you're alluding to, that patients with pulmonary hypertension have sleep-disordered breathing. So it certainly makes sense that the ACHD patients with pulmonary hypertension behave similarly and may therefore benefit from nocturnal oxygen. I wanted to bring up another controversial topic: anticoagulation. How do we handle that in our ACHD-PH patients? It's interesting that this controversy has existed for over 2 decades and I'm not sure we're any smarter about this now. I want to know what this expert panel thinks in terms of how we should utilize anticoagulation and what type of impact we make when we do so.

Dr Daniels: I personally separate the Eisenmenger cyanotic patient from the noncyanotic patient. I guess even though it is controversial, I still follow some pretty general rules until I see data otherwise. And the general rules that I continue to follow is if they're a

patient that is cyanotic, this brings a whole host of other hematologic issues of cyanosis, but if they're a noncyanotic patient, a congenital heart disease patient with pulmonary hypertension, then I typically follow the general rules, which is prescribing anticoagulation, unless a contraindication. The cyanotic patient becomes much more difficult and somewhat more controversial. I do not prescribe anticoagulation for a cyanotic Eisenmenger patient, because of the concern, and certainly we see bleeding diathesis. The cyanotic patient has polycythemia, and typically bleeding disorder that aren't always completely worked out, but certainly we know that this is the case. And in those patients, unless there is a strong reason to prescribe anticoagulation, such as pulmonary emboli or atrial arrhythmias, the bleeding risk outweighs preventive anticoagulation.

Dr Landzberg: I think for the last 20 years, I've taught every fellow that if Curt Daniels says something that you need to totally disregard anything I've ever said and listen to what Curt says.

Dr Daniels: Until now. (laughter)

Dr Landzberg: On the same hand, what's underscored in terms of the population of folks who take care of them, the data that are out there, are quite interesting in this very question, because here are centers that are so aligned with each other. And I actually thought Curt was going to say the exact opposite of what he said, because in the practice here, I will tend to use anticoagulation as the last therapy to add onto the patient with a closed shunt who's not cyanotic, because I think the data are the least there, and I try to get those patients onto every other therapy where I might have some data or some cohort observational studies, at the least. And it's the patients with Eisenmenger syndrome that I'm the most concerned with. I know that there are data in terms of prothrombosis; those data are strong. Granted, exactly what Curt said, the data that say that we make a difference with anticoagulation are unknown, but I worry in particular about them. So with the same data, we can argue both sides frequently. But I'll go back to the very first part of my statement, which was if Curt said something, that's what I would argue.

Dr Beghetti: I think this underscores the problem we have. We absolutely do not know. And that's the problem. For example, as a pediatrician, for my idiopathic PH in pediatrics, usually I don't anticoagulate unless they have a severe RV dysfunction. There is no science behind that, but the problem is that the risk of bleeding in a young patient is pretty high because they're still very active. And so we rely more on experience than on real data for this anticoagulation approach. And I think in both patients, idiopathic PH and Eisenmenger. And I don't see how we will indeed design any study at the current time that would help us to really decide for that, unless some of you have an idea. But I think it will be very difficult now to do the study in this population.

Dr Daniels: It certainly will be very important to, as a registry, to try to gather more data on Eisenmenger patients. Who is on anticoagulation? What is their outcome? What is the risk? I mean, it's an incredibly heterogeneous population, so it will be very difficult to find information, except for observational registry. But, you know, Mike's point is, of course, a good one. The risk with Eisenmenger is thromboembolic, but they also develop hemoptysis. Clinically I have seen a greater incidence of hemoptysis than thromboembolic events. So it's an incredibly tough balance. Any scientific evaluation of that population says we see clotting and we see bleeding. And so it makes it very difficult to know what is the proper approach.

Dr Franklin: Very good points. Maybe registries will be the answer. Because I certainly go both ways, but I probably tend to not anticoagulate. I guess no hard data either way. And I tend to think iatrogenic bleeding, whether it's hemoptysis or what have you, is probably worse. And so I tend to not. But hopefully, we'll get smarter about this as some of these registries come through.

Dr Krasuski: I would add that one group I regularly anticoagulate are the Eisenmenger patients with indwelling lines for intravenous therapies.

Dr Beghetti: Definitely, yeah.

Dr Krasuski: This also applies to the same group of patient with pacemakers or defibrillators. These are patients in whom I am worried about the risk for paradoxical embolization. All the points on anticoagulation are well taken. I particularly like the way that Mike was able to explain how you could use the data to argue each side of whether or not to anticoagulate in Eisenmenger and CHD-PAH patients.

Dr Krasuski: We've unfortunately run out of time, though we have covered many of the topics I wanted to discuss. Let me try to partially summarize our discussion for some "take-home" points. We first discussed the at-risk population. That there are certain groups of patients in whom we're worried about the development of pulmonary hypertension. Patients

"I've found that taking patients to the catheterization laboratory is most helpful for clarification of the disease state when there are conflicting data."
Dr Krasuski

with larger shunts (natural or surgically created), older patients, those with ventricular dysfunction early on, and patients who had lesions repaired later in life. These are the patients in whom we don't want to miss the opportunity to screen for PAH. We should be aware of this complication even in the patients that have been previously repaired—this is a very important point for the care providers that don't routinely follow congenital heart patients—having a complete anatomical repair does not always equal a lifetime free of complications. And pulmonary hypertension is a very important complication. We discussed the approach to workup in these patients. The consensus was that a thorough workup is incredibly important, because we have a tendency to lump patients together who may not respond the same way to therapy. The more we know about certain characteristics such as their lung status, the better we'll be able to adapt our therapeutic approach and improve outcomes. The importance of catheterization was emphasized. We each come from the vantage point that all perform heart catheterization. We all agreed that an initial hemodynamic assessment for any of the patients who is going to undergo selective pulmonary therapies is absolutely critical. And that it really sets the patient on the proper path for treatment. We were a little conflicted when discussing if and when we should take the patient back to the cath lab. Our agreement was that recatheterization in the patient with Eisenmenger syndrome who is doing well is unnecessary. For the patient with a corrected shunt, we would be a little bit more likely to reassess hemodynamics, particularly if there are any conflicting data about their clinical status. We talked a little bit about natriuretic peptides. They may be an exciting marker to follow, as is MRI for the assessment of ventricular function. In terms of our therapeutic approach to patients, we all mentioned how important exercise is and that's an important first step in getting patients on the road to feeling better. All of us kind of mentioned the struggle, particularly with insurance companies, that we've each had in getting patients into cardiac rehab. Pulmonary rehabilitation may be an alternative pathway for getting patients properly regimented to start exercising again. The use of oxygen should depend upon whether underlying lung disease is present. There are plenty of patients with congenital heart defects who also have restrictive lung disease and other pulmonary problems, so it's important we properly assess those patients. We don't want to necessarily restrict their oxygen, particularly if it helps them feel better, but supplemental oxygen at this point, particularly in the Eisenmenger patient, remains fairly controversial. Our discussion of anticoagulation illustrated that we haven't gotten very far in research in this area, and we have not come up with any good guidelines for who should be anticoagulated. Because the opinion is so strong among physicians who treat ACHD-PAH, we absolutely need to collect these data in our registries. Perhaps we won't be able to do a randomized trial, but through the newer registries that all of you are part of on this board, we may be able to better answer this question in the future. We only talked a little bit about selective pulmonary vasodilator therapy for these patients. The trend appears toward more aggressive use of combination therapy at an earlier stage in the disease process. I think you guys did a fabulous job, and my job as moderator was pretty easy with such a terrific group of panelists. Are there any other final parting comments or anything that we missed today that we should have covered?

Dr Daniels: I would just say, Rich, it was an outstanding discussion and I think important for the audience, the topics and the synopsis you just provided really goes to the importance of this educational experience and this opportunity for those that are going to be reviewing our roundtable discussion. So thanks, Rich, for putting it together. And I thank my colleagues for their expert opinion.

Dr Beghetti: I have one additional comment. I think the discussion was very interesting for one more reason. You may have noticed, and it's not to minimize the role of the new targeted therapies, because I think these therapies have started again to work on these patients, but we almost did not discuss these new therapies. And we discussed that we still need to understand what happened to our patients and that we need to very well work up our patients before using these therapies. That's a very strong message of this roundtable.

Dr Landzberg: The study of pulmonary hypertension really began with congenital heart disease and its understanding and the pulmonary vasculature. I personally think that our collaboration with our colleagues who study solely pulmonary arterial hypertension is very rich. Future understanding of the coupling between the right (pulmonary) ventricle and the other supporting structures in the arterial vasculature is really going to lay the foundation for better understanding of this disorder.