The Role of Exercise in Clinical Practice and Clinical Trials

On May 20, 2019, Guest Editor Ronald Oudiz, MD, Director of the Pulmonary Hypertension Program at Harbor-UCLA Medical Center in Los Angeles, California, led a discussion with Aaron Waxman, MD, PhD, Director of the Center for Pulmonary Heart Disease at Brigham and Women's Hospital and Harvard Medical School in Boston, Massachusetts, and Robert Naeije, MD, Professor Emeritus at the Free University of Brussels, Belgium.

Dr Oudiz: Today, we're going to talk about many concepts in exercise as they relate to pulmonary hypertension, specifically, diagnosis, prognosis, and treatment. Let me start off by saying thank you to Robert and Aaron for joining us in this discussion today.

The first topic I'd like to touch on is, how can exercise help us in our diagnosis of pulmonary hypertension in terms of helping us understand the nature of the limitation of the patient with pulmonary hypertension, helping us understand or categorize pulmonary hypertension? Then we will go from there. I'll start with Aaron. How would you approach the answer to that rather broad and generic question?

Dr Waxman: I think from a very broad worldview, I look at exercise as an additional screening tool, specifically when we talk about exercise with the addition of gas exchange and some sort of protocolized approach. There are some physiologic parameters that we can see with exercise testing that might tell us there's a physiologic defect, but it's not going to give us a diagnosis per se.

Dr Oudiz: Robert, how is exercise important in the broad scope of pulmonary hypertension? Why is it important?

Dr Naeije: If we are still discussing the diagnosis or use of [cardiopulmonary exercise tests (CPETs)] for diagnosis, I would say that I agree with Aaron that exercise testing is for functional diagnosis, not for clinical diagnosis. When a patient is referred to the [pulmonary hypertension (PH)] center, we perform a CPET as part of the initial workup to assess whether or not the exercising profile fits with the diagnosis of pulmonary hypertension.

Dr Oudiz: Would you all agree that an evaluation of a PH patient that includes resting echocardiography, as well as resting hemodynamics, is a rather incomplete evaluation of this patient, without the knowledge of what happens to the patient when they exercise?

Dr Waxman: I would certainly agree with that. I would also echo what Robert had said earlier. We do exercise as part of our complete pulmonary hypertension evaluation from the approach of unexplained dyspnea. It informs us of the contributors to shortness of breath and exercise limitation. It also provides us a physiologic baseline to compare back to when we start treatment. To me, that's the real power of the exercise test at the time of diagnosis, to track the impact of treatment.

Dr Naeije: I fully agree. We always did and still do an initial CPET whenever a patient gets into a workup process for the diagnosis of hypertension. It's really essential because it's not only about functional profile; it's the understanding of the contribution of the disease to exercise limitation in the follow up, for early detection of the duration, and understanding of the effects of therapeutic interventions.

In Brussels, we really use CPET in the initial diagnostic process, but then also in follow up and on a regular basis for better understanding of the patient's symptoms and the effects of drugs.

Dr Oudiz: Robert, you talked a little bit about categorization of PH I think. Would you agree that, in patients whom we see who have maybe a little bit of interstitial lung disease, maybe a scleroderma patient, and maybe they're older and you suspect that they have diastolic dysfunction, that sometimes we aren't absolutely sure, even after we've done the complete workup according to the classic diagnostic algorithm, if the predominant physiology indeed is a pulmonary vascular limit to exercise? And therefore, the exercise test, particularly with gas exchange, may be helpful in helping to confirm or refute the diagnosis of one kind of pulmonary hypertension.

Dr Naeije: I certainly agree. In the process, as you allude it to, the trick is to assess the contribution of chronic lung disease, essentially. Of course, you also have the lung function test to help you in that, and I think blood gases are really important. In the end, in using the results in our staff meeting discussions, I think we've focused very much on the ventilatory responses.

A patient who is hypercapnic or who becomes hypercapnic during exercise does not have pulmonary arterial hypertension, or has it with symptoms overwhelmed by the ventilator limitation of lung disease. The interpretation of CPET requires also lung function tests, and thus lung mechanics and blood gases to assess gas exchange. That's how it mainly goes because patients with PH or heart failure, when they're symptomatic enough to go to the hospital, they're hyperventilating, and they have an increased ventilation for this level of CO_2 output, and they tend to be hypocapnic. A patient who is not hypercapnic and not hyperventilating is probably not PH, in our experience.

Dr Waxman: I would add to that. One thing we've already learned from the [Pulmonary Vascular Disease Phenomics (PVDOMICS)] Network is that there is almost no such thing as a single entity

of PH, that very often in the real world, there's overlap of multiple [World Symposium on Pulmonary Hypertension (WSPH)] groups in each patient. To be able to differentiate some of those contributors to dyspnea when you're starting to treat a patient, it can help guide you and inform the patient why certain medication may require adjustment, may not fully resolve the patient's dyspnea, or other therapies may be indicated.

Dr Oudiz: You're both referring specifically to gas exchange measurements. Can you talk a little bit about how exercise has been used in PH clinical trials in the last 20 years?

Dr Waxman: I think there's good and bad that's happened in clinical trials. Obviously, the 6-minute walk test has been the hallmark exercise test. I think, as we've moved into the phase of most patients entering clinical trials on multiple background therapies, the 6-minute walk test becomes less and less helpful. Unfortunately, with CPET, we had previous clinical trial protocol designs where there were no specified exercise protocols and no central reading core; every study site was doing it their own way. The readout was done differently in each center.

I think, if we could redesign trials to include CPET utilizing a clear exercise protocol that was performed the same way at every site, and all the data [were] analyzed at a single central core, we would probably get more out of those trials. I think it would be much more informative, especially with multiple background therapies.

Dr Naeije: Yes, surely true. In fact, there were 2 trials in which peak $\dot{V}O_2$ was the primary endpoint: the drugs tested were sitaxsentan and beraprost. Both failed on the primary endpoint, while there was a significant improvement (with sitaxsentan) or trend to improvement (with beraprost) in the 6-minute walk distance, suggesting efficacy.

As Aaron alluded to, there's really a problem of quality control of CPET in many centers, even some reputation and tradition, because access testing is not as easy as it seems, even when it's automated in new digital devices, more recent devices. Moreover, with tested monotherapies, the effect size on peak $\dot{V}O_2$ or any other CPET variable is usually very small. The 6-minute walk test is easier to standardize and more sensitive to therapeutic interventions in severe PH. This is why many [pulmonary arterial hypertension (PAH)] drugs were made available after positive trials with 6-minute walk as the primary endpoint.

If your peak $\dot{V}O_2$ changes from say, 11 to 12.5 or to 13, I think, on average, you would have 1.5 to 2 mL/kg/min. You have an error on the measurements that's about the same range. Of course, you cannot expect trials to become positive. I think that, currently, many centers are learning to do it better, and we have more efficacious multidrug therapies with more impressive changes in hemodynamics and 6-minute walk. It is now very likely that, should we do it again, peak $\dot{V}O_2$ is a primary endpoint with a triple initial combination therapy, such a trial would be positive.

Dr Oudiz: Robert, it's been my impression that, in the [European Union (EU)], there are PH experts that not only believe in, but actually use gas exchange measurements, more so than in the United States. Aaron, maybe you see that, or maybe you disagree?

Dr Naeije: No, I'm not sure about that. I think it's a general phenomenon. Further, on the subject of trials, it is intriguing that, in considering CPET as primary endpoint rather than the 6-minute walk, it was only about peak $\dot{V}O_2$, while several studies have shown that, like in advanced left-sided heart failure, the ventilatory equipment for CO_2 ($\dot{V}E/\dot{V}CO_2$) is more sensitive to clinical state and a more potent predictor of outcome. Maybe in single drug trials in PAH, $\dot{V}E/\dot{V}CO_2$ would have been more sensitive to the tested intervention. This would be something to revisit in databases. Again, CPET is not only peak $\dot{V}O_2$, there are lots of other measurements. Maybe also we should have considered a combination or composite CPET measurement score if we had more seriously discussed the use of CPET as primary endpoint in these studies.

Dr Oudiz: You know, the regulatory agencies are one of the determinants of what an endpoint will be in a PH clinical trial, particularly in a trial that is used for registration of a new drug. I'm somewhat familiar with [Food and Drug Administration (FDA)] guidance that $\dot{V}E/\dot{V}CO_2$ today doesn't seem to be an acceptable endpoint; however, peak $\dot{V}O_2$ would be. I agree with you that $\dot{V}E/\dot{V}CO_2$ may be the better measurement, and certainly, the more relevant measurement clinically. Aaron, do you think that's true?

Dr Waxman: I think I would agree 100%. That would open the door also not just at maximal testing, but also submaximal testing, which might be an easier approach to a clinical trial. We do that now as part of our clinical practice. Using a simple 5-minute submaximal step exercise test, we track several simple objective readouts, such as the $\dot{V}E/\dot{V}CO_2$ slope, as well as measurements of end tidal CO_2, all as indirect measures of blood flow. I think that has real potential, both in daily management of these patients and their responses to treatment, as well as a potential outcome measure in a clinical trial.

Dr Oudiz: Great. Well, let's do a little bit of a shift and talk about exercise hemodynamics because the theme of this journal issue is exercise, not only gas exchange, but also what exercise can do to either unmask or characterize the nature of one's pulmonary hypertension. Is it done fairly regularly, and if so, is there a standard protocol, and where would we find that protocol?

Dr Waxman: Invasive CPET is done regularly in a small number of centers. Our center at the Brigham and Women's Hospital does a lot. I think we do close to 400 a year. We have refined and standardized our protocol over many years, but that's not to say that other centers don't do it differently. One big difference between centers is whether it's done in the supine, upright, or semirecumbent position. We have always focused on doing upright because that's how patients live and function day to day. We felt that was most reflective of true normal, or

what the patient experiences when they are dyspneic on a regular basis.

Dr Oudiz: Is there a role for those centers that may not have expertise in gas exchange to do exercise hemodynamics alone without the gas exchange?

Dr Naeije: Combining exercise hemodynamics and CPET is ideal but really challenging, but exercise hemodynamics and CPET can be done separately. Exercise hemodynamics can be noninvasive. What matters most is stressing the cardiovascular system if one is aiming at the detection of latent disease or complex differential diagnosis.

Dr Waxman: I think, if you do it without gas exchange so that you don't have a $\dot{V}O_2$ measurement, then you need to be at least aware of how to determine a cardiac output properly. Technically, if you're going to do it right, you need to change the exercise protocol so that you can do an accurate thermal dilution, but thermal dilution is really hard to do in that setting. You can't use an assumed fit or an estimated $\dot{V}O_2$ in that setting. That's the one major drawback.

Dr Naeije: In my center, we prefer to do CPETs and exercise hemodynamics separately. Of course, combining CPET and exercise hemodynamics, as done in some centers, is still worthwhile, too, for research purposes. The approach has allowed for a lot of progress in the understanding of exercise-induced PH, differential diagnosis of unexplained dyspnea, and effects of rehabilitation programs.

We know the limit of normal of exercise hemodynamics even better than those of various CPET measurements. All these measurements have to be integrated in the context, of course. The ideal is to do it all together, like in Aaron's center, but practically, in many centers, we all have to dissociate these examinations, and sometimes we satisfy for a while with a noninvasive approach.

Dr Oudiz: Great. Aaron, you said you were doing 400 per year. How is it done?

Dr Waxman: Our approach is, first, in the [catheter] lab, to place a right heart catheter through the internal jugular vein using local anesthesia. We generally use a Paceport Swan so that we can record pressures, obtain wave forms simultaneously from the right atrium, right ventricle, and pulmonary artery. We wedge the catheter every minute during the test to get a pulmonary arterial wedge pressure. We also place a radial arterial line so that we can draw an arterial sample as well as the venous sample every minute.

We are measuring gas exchange continuously, and the patient will perform a full symptom limited incremental load standard cardiopulmonary exercise test. We first get measurements at rest, then the patient will start with 2 minutes of unloaded cycling, and then they go into a ramp protocol. That workload ramp is based on what the patient tells us prior to the test, same as we would do with a standard noninvasive CPET. We have the patient exercise to peak exercise, that point of exhaustion, we take away the workload, and then we'll do 2 minutes of recovery phase.

The other important benefit of invasive CPET, especially when you have patients who have respiratory issues and might hyperventilate during the test, is that we have a number of different ways of being able to measure the peak exercise points, beyond just the [respiratory exchange ratio (RER)] and heart rate. We can look at the venous pO_2 (<29 mm Hg), and track the $M\dot{V}O_2$ (<27%) and cardiac output (>80% of max predicted) as well as measuring arterial lactates and a host of other dynamic Fick principle data.

Patients tolerate it really well. We have patients who even volunteer for a second time as part of studies. Importantly, the first test is always a clinically indicated test to evaluate unexplained dyspnea as well as characterize pulmonary vascular disease.

Dr Oudiz: It's quite impressive in what you do, and you make it sound maybe not simple, but not impossible, yet I think, for many of us, as Robert had pointed out, there are certain barriers in the sophistication of one's lab, let alone an understanding of the physiology and how to marry the 2 technologies. Congratulations are in order.

Do you think there is potential for either you or others to teach the rest of us, or at least teach those qualified to learn, and going forward, will there be more centers worldwide that are doing this?

Dr Waxman: Absolutely. In fact, I can tell you that there are centers that will come and visit with us, spend a day or two just seeing how we do it, and they're starting to develop their own programs. That's what's happening at the University of Pittsburgh. Cornell is setting up a program. Obviously, the University of Arizona and the Mayo Clinic in Rochester, Minnesota, have been doing it for a while.

In fact, as part of our program to evaluate the cause of unexplained dyspnea, we are having to set up 2 satellite centers in our area because we're booked out so far. These centers will be in community hospitals. It can be done. I think the biggest hurdle is just the concept itself; most people think of a Swan only in critically ill patients. The approach is very safe, and it can be done in a fairly routine manner.

Dr Oudiz: That's great, Aaron. Let's touch a little bit on exercise as it relates to risk assessment. Robert, I know you have a strong opinion on this.

Dr Naeije: CPET variables have a tendency to disappear in recently adjusted European [European Respiratory Society/European Society of Cardiology (ERS/ESC)] guidelines for risk assessment scoring systems for PAH patients. The US-derived [Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL)] score, which is the most rigorously validated risk assessment score in PAH, never included CPET variables. The problem with currently available risk assessment scores in PAH is that they were fed with data available in most PH centers. Only a minority of PH centers rely on CPET. The same can be said, unfortunately, about imaging, by echocardiography or magnetic resonance imaging. So the absence of CPET or imaging variables in risk assessment scores does not argue for the futility of these measurements.

We have to understand this because, with all the current risk assessment scores, we can predict very poor outcome, and we can predict excellent outcome. The majority of patients will stay in some sort of a gray zone. I think that wasn't enough encouragement currently to revisit CPET, but also echo imaging, which is available, and collect in a multicenter way a maximum of this data and see if we can improve the prognostication in PH based on scores.

Dr Oudiz: Yes, Robert, I agree that the guidelines fall short of exploiting the great virtues of CPET in prognosis, and this is based on a lack of data. I suppose the main question is, how are we going to get data? How can we get more systematic, unbiased, maybe multicenter data going forward?

Dr Naeije: More multicenter collaborations and more centers devoting time and energy and resources to CPET are crucially needed. We need to convince all these people to work together and to build up new databases, largescale and main centric to improve our capability to assess risk. That's very important in adjusting therapies.

I was alluding, initially, to the apparent great success of initial triple combination of drugs targeting different pathways in PH when patients initially get their diagnosis and really encouraging data coming. It's very, very expensive and difficult to do. It would be better if we had improved tools to assess risk and use the full capability of all the CPET variables to adjust and probably be able to prescribe in a more rational way double combinations or maybe single drug therapies that will be equally efficient.

Dr Oudiz: Sure. Aaron, are you aware of any efforts, either on your own or multicenter, US or worldwide efforts to acquire this data for risk assessment?

Dr Waxman: As part of the PVDOMICS Network, which includes 6 clinical centers, we are doing CPET on the majority of patients. The goal is to do everyone, but some patients aren't able. We'll have a very robust dataset of both invasive and noninvasive CPET in patients, and there is a longitudinal component to the study. Yes, we should have that data. I would expect that we probably already have that data if we were to combine some centers now from a noninvasive CPET standpoint. That approach would be retrospective, but the data from PVDOMICS will be prospective data.

Dr Oudiz: Hopefully, that will be coming soon. Moving onto our final topic of exercise as an intervention for patients with pulmonary hypertension or, if you will, rehabilitative exercise, what is your opinion of exercise from the standpoint of is it safe? Is it effective? Are you using it, Aaron?

Dr Waxman: It is absolutely safe. Because of our experience with maximal exercise testing and invasive testing, we've found it to be very safe. Part of our treatment program in our pulmonary vascular program is exercise. Our exercise physiologists meet with and prescribe a graded exercise program for every patient who goes on treatment. Compliance may not be 100%, but patients definitely do improve just with exercise. The literature is starting to bear that out as well.

Dr Naeije: Back to risk assessment, there is one study which demonstrated added value of CPET. It was done by our colleague Badagliacca and his coworkers at the University of Rome. However, it was on a relatively small cohort of 100 patients with long-term follow-up. It was a step in the right direction, but we need multicentric efforts.

Back to the rehab, I was involved in some of the pioneering studies done by Grunig and his coworkers. Rehabilitation is beneficial in PAH. It may improve exercise capacity, even in patients under optimal multidrug treatments.

The problem I find with rehab programs in PH is that they really work best if done as inpatients in dedicated centers for several weeks. Attending twice or thrice a week a rehab center, on an ambulatory basis, may be too challenging for PAH patients already exhausted by using public transport, climbing stairs, and walking long corridors. Otherwise, exercise training in PAH is safe, except for obviously too ill patients in right heart failure.

Dr Oudiz: That's one of the questions I think that many of us have in terms of the durability of the intervention. If the exercise is maintained to some degree for the patients on their own or in a continued monitored setting, I think the benefits would be clearly sustained. However, at least in the US, it's not feasible to have paid programs support ongoing supervised exercise, and therefore, the prescription is often taken home, and the compliance over the long term has yet to be determined.

Dr Naeije: In recent years, we have seen the development of a lot of monitoring devices, not only invasive PA pressure which remains investigational, but also simple movement monitoring by actimetry, which is by the way already accessible in iPhones. If centers can use these devices to maintain dialogue with the PH patients and monitor the activity and preferably also progress, I think we might improve the situation.

Also, it's a matter of training. When the patients have a good start for a couple of weeks in the dedicated rehab center, and then with a dedicated team staying in contact with the patient so that they continue prescribed exercise daily exercising at home, then the results are very good. There is now a network of such centers in Central Europe; the results are excellent.

Dr Waxman: I would add to this by saying that we're actually working on a wearable device to pair with a prescribed home exercise program so that we can track a patient's activity and be able to assess them on a weekly basis with a very short predefined home exercise test that includes heart rate recovery and a measure of effort during that exercise. I think that will also provide motivation for patients to keep it up.

Dr Oudiz: The advent of better technology and patient-specific targeted therapy is happening even in the home now, Aaron. It sounds wonderful.

Dr Waxman: I think it's really where we're headed. I think it will make the patients much happier.

Dr Naeije: I fully agree it's the way to go, but the loads on the PH team or the rehab team which is staying in the reference center, the workloads on these teams will remain important because it is time consuming and it takes dedication to monitor [these] data on a daily basis or even summaries and to maintain contact with these patients. The cost of rehab programs and home monitoring devices will be an important issue.

We'll see if the insurances can cover that and if it's simply financially feasible to do that because it cannot be developed simply based on the goodwill of interested teams. We need some structure and, of course, evaluation. I agree with Ron that we don't know yet how well it works. It's really likely that it will work just fine, but we need more data, and we need to structure these kind of systems to have it directly funded. Otherwise, it's going to die off, I'm afraid.

Dr Oudiz: Gentlemen, thank you so much. It has been a really a nice treat to have your expertise and discuss an important and timely issue such as exercise in PH. I hope that there are more things to come in the world of exercise PH.