Controversies and Consensus: Identifying the Key Issues in Exercise Testing


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This discussion was moderated by Ronald J. Oudiz, MD, Associate Professor of Medicine, UCLA School of Medicine and Director, Liu Center for Pulmonary Hypertension, Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California. Participants included: Hunter C. Champion, MD, PhD, Assistant Professor, Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland; Robert Naeije, MD, PhD, Professor and Chairman of the Department of Physiology and Pathophysiology at Erasme University Hospital, Brussels, Belgium; Virginia D. Steen, MD, Professor of Medicine and Director of the Rheumatology Fellowship Program, Georgetown University School of Medicine, Washington, DC; and David Systrom, MD, Director, Cardiopulmonary Exercise Lab, Department of Medicine, Pulmonary Critical Care, Massachusetts General Hospital, Boston, Massachusetts.

Dr Oudiz: I would like to thank you all for participating in this roundtable. Our roundtable is designed to provide practical and expert discussion with insight into the issues surrounding exercise and pulmonary hypertension, specifically with respect to diagnostic modalities. As you all know, this issue of *Advances in Pulmonary Hypertension* focuses on diagnostic modalities in pulmonary hypertension, and covers the topics of hemodynamics, echocardiography, ambulatory monitoring, and cardiac MR [magnetic resonance] imaging in pulmonary hypertension, but without specific focus on exercise. Thus, the purpose of this roundtable discussion is to give our readers an opportunity to understand from experts in the field what the issues are surrounding exercise.

The first question I would like to ask is, why is the evaluation of pulmonary hypertensive patients during exercise important? Perhaps Robert can discuss some points here, such as the importance of exercise measurements in general, and then specifically the utility of unmasking pulmonary vascular disease with exercise as a diagnostic tool.

Dr Naeije: Thank you. I am not sure I am the expert on this panel, but I would surmise that is what we try to do ourselves. It is mainly useful in screening studies, even though there is no robust evidence showing that a diagnosis of pulmonary hypertension can be made on the basis of an exercise test. Assessing the dynamics is really relevant and we really do not know yet what exactly the prognosis is for these patients and what exactly the indications for treatment are. We have used it mainly in patients with scleroderma to identify those with what we thought could be an abnormal response. We can discuss this as well. We have also used this for screening family members of pulmonary hypertensive patients and we have used it a little bit at higher altitudes to try to understand why some people are really intolerant to exercise. But again, I think it is a diagnostic modality so you make measurements of the pulmonary circulation and you measure the amount of exercise. I have to say that I have no available evidence to prove that this is really the way to go forward, to improve the diagnosis of what would be an early phase or difficult to understand form of pulmonary hypertension.

Dr Steen: We recently did a survey on exercise studies on the PHA [Pulmonary Hypertension Association] Web site and I just thought maybe this might be a good time to share a little bit of that information. As was just said, the most common causes of why people wanted to do exercise studies were scleroderma, unexplained dyspnea, and diastolic, or as Hunter Champion calls it, nonsystolic heart failure. Interestingly, most people who were doing it were doing it using the upper extremities, yet they all felt that lower extremity ergonomic-type of activities should be the gold standard. However, most people did not have the equipment to be able to do it that way. Thoughts of what the cut-off for the pulmonary artery pressure is on exercise, were quite variable, but most used the previous guidelines of greater than 30 mmHg.

This is an important issue as far as identifying early disease. The question I have is whether the Dana Point meeting definition of early disease, a mPAP [mean pulmonary arterial pressure] of 20-25 mmHg on cath is better than an exercise PAP of greater than 30 mmHg. I think exercise induced pulmonary hypertension is very important and we shouldn't exclude it until we have more studies showing the outcome of these pa-

tients. The report of the recent British study by Condiffe et al [*Am J Respir Crit Care Med*. 2009;179:151-157] summarizes their experience with pulmonary hypertension in scleroderma patients. They included 42 patients with exercise induced pulmonary hypertension. Within 3 years, 19% went on to develop resting pulmonary hypertension and 12% died. So it is clear that at least in some patients it is a predictor of future resting pulmonary hypertension.

In our studies in scleroderma, a positive exercise test strongly correlated with other risk factors for pulmonary vascular disease, including a low DLco and a high FVC/DLco ratio [ratio of forced vital capacity to diffusing capacity of the lung for carbon monoxide]. As part of our longitudinal study we are looking to see whether the positive exercise test is a better risk factor for developing resting pulmonary hypertension than the resting PAP, the DLCO or the PFT [pulmonary function test] ratio. So, hopefully with time we will have some of that information. But, I think the biggest problem is whether we can develop a standardized way of doing the exercise studies as well as doing the measurements which apparently is one of the biggest difficulties.

"We exercise based on heart rate and the goal is to try to get someone to 85% of their age-predicted maximal heart rate and then see where their hemodynamics are at the time of that heart rate."
–Dr Champion

Dr Champion: I completely agree with Robert and Virginia. I think that a resting right heart catheterization has some limitations because, for the most part, the majority of our patients are not terribly symptomatic at rest. In fact, I think that the exercise catheterization can be very useful as long as we make sure that it is done in a standardized manner and correlated so that we know what the outcomes are.

I also think that more dynamic testing, whether it is in the form of exercise or fluid challenge, can be very helpful in terms of trying to figure out what is actually causing the patient's symptoms. For us, the way we generally do the exercise portion is much like we would for a standardized exercise protocol when looking for coronary disease. We exercise based on heart rate and the goal is to try to get someone to 85% of their age-predicted maximal heart rate and then see where their hemodynamics are at the time of that heart rate. Certainly, if the patient's exercise PCWP [pulmonary capillary wedge pressure] is 5 mmHg versus 25 mmHg, this gives you a better idea in terms of what to do with that patient.

Things get a little bit tricky if you have someone who meets criteria for PAH [pulmonary arterial hypertension] by resting hemodynamics —mPAP rest > 25 mmHg and PCWP < 15 mmHg— you then exercise that patient and you find that at the time of the symptom threshold the wedge pressure is 22 mmHg. Where does that patient get placed in terms of therapeutic options? We will need to standardize our approach to such case-scenarios over the next few years to get a better idea of what we are actually dealing with.

Dr Systrom: Our invasive CPET [cardiopulmonary exercise testing] lab is designed to sort out reasons for unexplained dyspnea and fatigue. Using maximum incremental leg cycling exercise with right heart and radial artery catheters in place and measurements of ventilation and breath-by-breath pulmonary gas exchange, we recently published our 4-year experience in *Circulation* [Tolle et al. *Circulation*. 2008;118:2183-2189]. Interestingly, exercise induced PAH was responsible for roughly half of the cases of unexplaing dyspnea. We defined exercise-induced PAH as the patient with normal mPAP at rest and *both* (the National Institutes of Health definition) mPAP > 30 mmHg *and* an abnormal maximal PVR [pulmonary vascular resistance] at maximum exercise. We compared the exercise-induced PAH hemodynamic phenotype to the normal and to resting PAH (mPAP rest > 25 mmHg and PCWP < 15 mmHg). We found 2 distinct patterns of change in mPAP with exercise, plotted against VO_2 that suggested a pathohysiologic progression from the normal through exercise-induced PAH and finally to resting PAH, all suggesting that exercise-induced PAH is an early phase of the disease.

Of note, our 78 patients had a resting mPAP of only 18.6 mmHg +/- 3.2 (SD) suggesting the "borderline" mPAP at rest between 21-24 mmHg proposed at Dana Point may not be sufficiently sensitive to capture early disease.

Dr Oudiz: How do you incorporate PVR into your assessment? In other words, we all know that, due to obesity and/or advancing age and possibly other factors, some patients have elevated pulmonary pressure without necessarily signifying pulmonary vascular disease. For example, some people have high cardiac outputs along with their high PA pressures and their PVR may not be significantly elevated.

Dr Systrom: I agree totally, Ron, there are patients with pulmonary venous hypertension, high cardiac output states and even endurance athletes who have maximum exercise mPAP above 30 mmHg, but with a normal PVR fall. Thus, we believe the maximum exercise PVR is essential to differentiate PAH with some combination of pulmonary vasoconstriction and remodeling, from other forms of PH. Based on limited published data, we use a cutoff PVR max of < 120 dynes.sec.cm-5 as normal.

Dr Oudiz: I think that begs the question then, what percentage of those 50% of patients that have left-sided dysfunction are being misdiagnosed because they are not undergoing the proper procedures to obtain an accurate diagnosis?

Dr Systrom: I think it is sizeable. Efforts have been made to estimate the pulmonary capillary wedge pressure with cardiac ECHO, but have not been well-validated during exercise.

Dr Oudiz: Robert, do you have your own set of cut-off values for exercise hemodynamics?

Dr Naeije: Actually we do, but it has been mainly inspired by Jack Reeve's work. Because what we like to do together, we always plot all the components of the pulmonary vascular resistance equations during the exercise. So, actually, Jack calculated the slopes of mean pulmonary artery pressure and pulmonary capillary wedge pressure versus mean cardiac output. He found that in young, normal people the slope of mean pulmonary artery pressure as cardiac output is 1 to 1, so you have a 1 mmHg increase for every liter of cardiac output. If you go for older people in their 60s and 70s and so on, the slope increases to about an average of 2.5. But there is quite a bit of variability there. So, this is to say that you can't defend a limit of normal just based on pressure resistance. You have to look at the whole curve. Actually I am not even sure we have a clear idea of the exact limits of normal. The same goes for the wedge pressure.

For example, in the reconstructions of the normal curves by Jack Reeves, he always found in young and old people that about half of the slope of mean pulmonary artery pressure and functional flow was caused by the increase in the wedge pressure. This is to say that the wedge is also going to increase and it can increase markedly if you push the cardiac output far enough. Therefore, of course, obvious very quick increases in the wedge pressure are diagnostic of diastolic dysfunction, but I am not sure that we have a clear idea about the limits of normal and it may be that in centers such as David Systrom's we could revisit the normal patients or the normal subjects and redefine the limits of normal so that we know exactly how far the mean pulmonary artery pressure and the wedge pressure can go before we qualify it as an abnormal response.

Dr Oudiz: Clearly the purpose of defining all this up front is so that we make the correct diagnosis.

Dr Naeije: Sorry, I wanted to complete an idea. I think you will have diastolic dysfunction in everybody starting at about 40 to 50 years of age. We found that when we looked at the ECHO and diastolic function of the left ventricle looking for controls for scleroderma patients, we had clear signs of diastolic dysfunction in aging, already in the 40s. So, I think that if you stress the system enough, either by increased flow or exercise, or an increase in volume-giving fluid, you will get an increase in the wedge pressure. In older people you will get it more spectacularly without this being clearly a pathologic response in the sense that we don't know exactly the limits of normal.

"We all have a feeling that diastolic dysfunction occurs more often in scleroderma and it does. But, when you take adequately matched controls, it has to be most often in older people—in the classical PAH patients. You will see that there is also diastolic dysfunction, so it makes the wedge more sensitive to fluid challenge or exercise challenge, but I wouldn't know exactly the limits of normal unless somebody else has an idea, but I would not go as far as that." *–Dr Naeije*

Dr Steen: But what should the pulmonary pressure response be at that point? That is a problem in a "normal" patient with diastolic dysfunction. Should their PA pressures be significantly elevated as they are so often in scleroderma patients when they have diastolic dysfunction? I have not been able to determine these features in nonscleroderma diastolic dysfunction patients.

Dr Naeije: I think diastolic dysfunction is something extremely difficult to diagnose. I don't think that it is an increased wedge pressure. I don't think it is an increased change in E [early ventricular filling] to A [atrial kick] ratio that comes from atrial measurement. I think if you really want a definition of diastolic dysfunction, you need the whole pressure volume curve. That is, of course, except for Hunter, perhaps extremely difficult to obtain. So we don't exactly know. We all have a feeling that diastolic dysfunction occurs more often in scleroderma and it does. But, when you take adequately matched controls, it has to be most often in older people—in the classical PAH patients. You will see that there is also diastolic dysfunction, so it makes the wedge more sensitive to fluid challenge or exercise challenge, but I wouldn't know exactly the limits of normal unless somebody else has an idea, but I would not go as far as that.

Dr Systrom: There are also symptomatic patients who have elements of both heart failure with preserved ejection fraction and bona fide PAH by maximum invasive cardiopulmonary exercise testing. A confusing hemodynamic subset is a PVR > 120 dynes.s.cm-5 and a pulmonary capillary wedge pressure > 20 mmHg at peak exercise. Is this PAH first with ventricular interdependence causing a rise in wedge pressure, or is this primary LV diastolic dysfunction with a secondary "reactive" pulmonary arterial vasoconstriction, or both? Further study, best in my view combining echocardiogram and invasive cardiopulmonary exercise testing, is needed.

Dr Oudiz: I think one of the major issues surrounding hemodynamics in exercise-induced PH is what the long-term outcome implications are, regardless of how one defines it as abnormal. And then, of course, what the treatment implications are. I wonder if, taking the sildenafil experience for example, we will ever know whether any change in outcome that might be seen is due to a direct alteration of a pulmonary vascular process or something else, such as peripheral muscle blood flow. So, I would like to know if any of you have any ideas on how to handle the difficult situation of exercising patients with documented or suspected pulmonary hypertension.

Exercise-induced PH is a very difficult entity to define, and it is very difficult to create thresholds using a single measurement. What should we recommend to the practicing pulmonary hypertension doctor that may not have the ability or the sophistication that you all do in terms of managing these patients who we are either screening for early disease, or we are evaluating for unexplained dyspnea, or in those in whom we are further trying to characterize their disease. How do we tell the rest of the world how to deal with exercise?

Dr Steen: You had wanted to talk about the exercise ECHO and I will just make some comments about our experience with that. We based our criteria on the Grunig study for familial pulmonary hypertension. He actually used an increase of 15 mmHg, but we were even more conservative and used an increase of 20 mmHg. When we compared this to the exercise catheterization, we found that 80% of those with a positive exercise ECHO had either definite or exercise-induced pulmonary hypertension. This was really quite good and since most of the others had diastolic dysfunction with an increase in both the pulmonary pressures and the wedge pressure with exercise, they still had an exercise component to it. It just wasn't a pulmonary arterial process.

Others have studied patients with an abnormal exercise ECHO when the RSVP [right ventricular systolic pressure] goes above 40 mmHg, but these studies didn't correlate with other risk factors and they weren't confirmed on catheterization. So, I think we have to be very careful in encouraging people to do exercise ECHOs without really having a definition as to what a positive test is. It is hard enough to get some cardiologists to even report RSVP in many patients, let alone figure out how to do it right after exercise. So, as much as it would be nice to encourage it, we really can't until a standardized procedure is developed. I think it is important just to make people recognize that this may be an important feature.

Dr Systrom: Noninvasive cardiopulmonary exercise testing, as Ron and his group have shown, is clearly useful in the detection of resting PAH. In our hands, noninvasive cardiopulmonary exercise testing parameters such as ventilatory inefficiency were insufficiently sensitive to be useful screening tests for exer- cise-induced PAH. I think the future lies with biomarkers and our group is working with the MGH [Massachusetts General Hospital] Cardiology Division and the Broad Institute at MIT [Massachusetts Institute of Technology] and Harvard on such an approach. For the time being, however, I think exercise-induced PAH is best diagnosed by invasive cardiopulmonary exercise testing and that requires evaluation in a specialized center.

Dr Steen: We do it within 1 minute. I couldn't come up with many reasons for a false positive although I knew false negatives certainly would be possible. So that is why we ended up using an increase in the RVSP over baseline of 20 mmHg. So, I guess if we could educate an echocardiographer how to do that, it certainly can be done. It is usually the technicians that are doing it. It is not like it takes real science to physically do it.

Dr Champion: What I am hearing is that the use of exercise echocardiography should at least be limited to be used as an experimental technique or to be used at a center with expertise in knowing not only how to do the procedure, but also how to interpret it, realizing that even that interpretation has differing implications for long-term outcome and treatment.

"I think we have to be very careful in encouraging people to do exercise ECHOs without really having a definition as to what a positive test is. It is hard enough to get some cardiologists to even report right ventricular pressure in many patients, let alone figure out how to do it right after exercise. So, as much as it would be nice to encourage it, we really can't until a standardized procedure is developed."–*Dr Steen*

Dr Steen: I think the best thing would be to try to come up with, as Hunter says, a standardized protocol that could be used by various centers to start to collect data. Once there is a standard approach, then the collection of the data will be able to give us an idea as to what the long-term outcomes are, but this is hard to do.

Dr Oudiz: Hunter, what is your approach in exercising patients? Are you doing measurements in the catheterization lab and correlating them with MR measurements?

Dr Champion: We are trying to, as part of the SCCOR [Specialized Center in Clinical Oriented Research] grant. I think that is kind of our next step for this SCCOR. We are primarily doing our hemodynamics in the catheterization lab, both with traditional PA catheterization, but also with right ventricular pressure volume loop analysis. I think that right now, kind of echoing what everybody has said, we sometimes don't necessarily know exactly what it means.

When we see wedge pressures go up above 20 mmHg that certainly captures our interest and raises concerns about possible nonsystolic heart failure. Based on the number of patients that we have exercised with true PAH in general, all I can say is that we really don't see a significant increase in wedge pressure with exercise in that population, recognizing that even a wedge pressure of 14 mmHg still isn't normal. I think that is an important point that was brought up earlier.

We don't really necessarily know what it means to have a mean PA pressure between 16 and say 24 mmHg, nor do we really necessarily understand what it means if you have a wedge pressure between 7 and 14 mmHg. We have been using invasive hemodynamics to look at this. I think sometimes when we exercise these patients and we do uncover diastolic dysfunction or nonsystolic heart failure, it is a little bit like the diagnosis of cardiac amyloid where you say, hey, the good news is we think we know what's wrong with you. The bad news is that we don't necessarily know how to treat it.

I am going to be very happy at some point when someone finds something that will actually improve patients with diastolic dysfunction. Hopefully with the RELAX [Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure] study we will be able to see that, but certainly it doesn't sound like angiotensin-receptor blockers (ARBs) or some of these other agents are necessarily the right answer.

Dr Oudiz: How far away are we from a trial that would attempt to answer some of the questions with respect to the implications of the findings on exercise, particularly with screening, for example, taking a set of patients who don't have pulmonary hypertension at rest who have abnormal findings, however you want to define them, and then half of which get randomized?

I believe it would be ethical to randomize half of those patients to placebo since we don't know how to treat them. We would then see if we have either prevented the progression of overt resting pulmonary hypertension, or somehow altered the outcome, irrespective of what the changes in hemodynamics may be over time.

Dr Systrom: We had a small group of exercise-induced PAH patients who were followed for a mean of 29 months with repeat invasive cardiopulmonary exercise testing. Interestingly they had a small decline in their VO_2max from about 70% down to about 60%, but we could not document that this was related to truly worsening PA pressures. The mean PAP at maximum exercise was the same 2 years later. PVR was the same, and what did decrease slightly was the maximum Fick cardiac output from about 86% to 80% of predicted. So, it is a very limited sample and I hesitate to make any conclusions about inexorable progression from exercise-induced PAH to a resting pulmonary hypertension. I think we all probably have the bias that what we are catching with exercise is early disease and this deserves some attention and potential treatment.

We have some anecdotes, and I will tell you very briefly about a study being done by Dr Aaron Waxman in Boston. One great anecdote is about a runner from Rhode Island who came to Boston with well documented decrement in her long-distance running splits. Ultimately she ended up with invasive cardiopulmonary exercise testing and her diagnosis was exercise-induced PAH. Aaron began her on ambrisentan and she became asymptomatic and returned to her previous splits. He is currently looking prospectively at ET-1 [endothelin-receptor 1] antagonism in exercise-induced PAH.

Dr Naeije: Can I add some anecdotes here? In fact many years ago Dr Grunig and I started looking for abnormal pulmonary artery pressure response to exercise when we were investigating high-altitude edema. That is exactly what happens if you have too brisk a response to pulmonary artery pressure to exercise or to hypoxia. You are at risk of lung edema when you go to high altitudes. That is how Grunig decided that echocardiographic systolic pressures of more than 40 mmHg is identified as abnormal. That is how European networks started a few years ago in the European community.

The paper now has been accepted into *Circulation*, so we screened family members with and without mutations in true PAH patients and we got something like 200. I don't have the numbers here. What we found, compared to about the same number of controls, was that the abnormal responses were at the extremes of the normal phenotypes. In other words, you can be perfectly normal, but have a brisk pulmonary artery pressure response to exercise. The only thing that happens to you is that you have an increased risk of acute lung edema when you go to high places for skiing or hiking, but otherwise nothing. We also found that because of the mutations these abnormal responses were a little bit more frequent in family members of PAH patients.

"Like the indeterminate or early PAP proposal range of 20 to 25 mm/Hg at rest, we found that the VEVCO 2 [ventilation-carbon dioxide output] measured at the ventilatory anaerobic threshold was not sufficiently sensitive to detect exercise induced PAH."–*Dr Systrom*

In spite of the huge number of controls and family members, we couldn't really make any difference between normal and abnormal. We have seen some of those patients with brisk pressure response to hypoxia or exercise but who otherwise have a normal life who end up with full-blown PAH years later, because now we have several years of follow-up. It is really rare and in isolated cases. If you want to include in a trial all the abnormal responders, unless you really differentiate the elements of normal with the extreme high levels of pressure at exercise, I think you are going to mix perfectly normal people with a few susceptible people and this is going to be very disappointing.

Dr Steen: Unfortunately, none of the companies has really been willing to consider any type of preventive or long-term studies. That has certainly been the problem with any kind of clinical trial. We have been trying to talk with them about some sort of studies in scleroderma as far as a protective, preventive early treatment of scleroderma, but it takes too long, requires too many patients, and costs too much. The observational route is really going to have to be the approach.

Dr Naeije: So then think of normal. I think it will take even more people. It can be done, but the problem is that these drugs are so expensive.

Dr Oudiz: From what I am hearing here today, it is clear that most of you believe the connective tissue disease and familial populations are those that you would target as having pulmonary vascular abnormalities more frequently than in other populations. Are there any other populations that you would consider screening or that you would think might have a higher rate of abnormalities that could turn out to be functionally significant?

Dr Steen: The other group was unexplained dyspnea, on the survey that people thought was important to study.

Dr Systrom: I think that has been our experience. I guess over 4 years, we came up with 78 cases of exercise-induced PAH and twice that number again of unsuspected heart failure with preserved ejection fraction.

Dr Oudiz: Any other comments from the group?

Dr Systrom: I just wanted to comment very briefly on a couple of the logistic challenges of measuring exercise hemodynamics. The major pitfall is pleural pressure swings especially, and the effect on pulmonary capillary wedge pressure in some patients. I think you can really be misled into thinking your patient has an abnormal pulmonary capillary wedge pressure rise when it is clearly related to positive pleural pressure swings at end-expiration. Some will do an electronic mean through the respiratory variations and suggest this is what the right heart is seeing throughout the respiratory cycle.

Dr Naeije: That is the old way! That is how we measured the wedge in COPD [chronic obstructive pulmonary disease] patients 30 to 40 years ago.

Dr Systrom: I agree totally. And I think end-expiration may truly reflect pulmonary vascular caliber in emphysema with auto-PEEP [positive end-expiratory pressure]. In normals and many other diseases though, I suspect much of the end-expiratory increase in mPAP is related to respiratory effort, and perhaps closure of the glottis during expiration.

We try to train the patients before they exercise to keep the glottis open and not take a breath or 2 immediately postexercise during free-wheeling, so they actually have 4 or 5 cardiac cycles devoid of breathing. It has also been our observation that the amount of expiratory pressure swing is usually the same for the mPAP and for the pulmonary capillary wedge pressure during exercise. If this is true, the transpulmonary gradient is a legitimate number and the PVR is therefore useful. So, we put a lot of stock in the PVR at maximum exercise.

Dr Oudiz: Hunter, how do you deal with the pressure swings when you are doing a right ventricular pressure volume load?

Dr Champion: That is a very good question. I think that the main thing, as was pointed out, is the fact that you have to have the patients breathe. I think certainly with exercise there is a tendency for patients to try to hold their breath and you can see huge pressure swings. We should be taking end-expiration pressures for everything. This is actually one of the most important points, not only with exercise, but also with resting right heart catheterization.

Dr Naeije: A last word about the exercise modality because some centers are using double hand grips and so on to increase pulmonary pressure—arm exercises and things like that, but mainly resistive exercise. I think all we have been discussing is dynamic exercise, so perhaps a word of caution should be included. Everything that was said was about dynamic aerobic exercise and not resistive exercise.

Dr Systrom: That is something that I think really needs to be

looked at systematically—the comparison of the two—the cardiopulmonary responses to arm exercise and especially isometric arm exercise are exaggerated when compared to isotonic leg cycling for instance.

One final point related to invasive cardiopulmonary exercise testing is leveling the playing field in terms of filling pressures. At Dana Point, Dr Trevor Williams of Melbourne, Australia suggested it is important that we always require normal saline boluses, in 500 mL aliquots, to make certain that the resting pulmonary capillary wedge pressure in the upright position, appropriately transduced, is 5 mmHg or greater. We don't want to document dehydration or decrease the sensitivity of invasive cardiopulmonary exercise testing for heart failure with preserved ejection fraction because the patient has been fasting since midnight.

Dr Oudiz: This is a good point. I just want to be clear that these volume challenges are given to patients in whom we are trying to unmask subtle pulmonary vascular abnormalities and are not done in patients with right ventricular dysfunction.

I would like to thank you all for your expert discussion and for clearly outlining the issues, not all of which are insurmountable as we go forward trying to understand what the effects of exercise are on pulmonary circulation. ■

International Corner

A Meeting of Minds From Around the World

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Dr Francisco Soto offered me the chance to review the fall 2008 issue of *Advances in Pulmonary Hypertension*. The issue discusses the 2008 Pulmonary Hypertension Association (PHA) International meeting. For those of us who have been actively involved in the pulmonary hypertension (PH) field for many years now, witnessing the growth of the PHA and its international conference is a humbling experience. While one must acknowledge that we still have far to go, it is also clear that we, the PH community, seem to be doing the right thing. The conference continues to grow in international appeal and has become a great venue for the meeting of great PH minds from around the world. In addition to excellent scientific lectures and poster presentations, the 2008 conference provided a great opportunity for networking. In this structure, the conference more closely matches established scientific meetings in related fields.

Many articles in the fall 2008 issue of *Advances in Pulmonary Hypertension* provide additional support for previous positions and statements that address topics presented at the 2008 APH meeting. Drs Bugger and Abel provide a lucid discussion of the metabolic syndrome, an entity that most of us see every day, regardless of geographic location. The potential role of mitochondrial dysfunction that compromises cardiac adenosine triphosphate (ATP) generation and, in turn, leads to cardiac dysfunction, is exciting. If a similar mechanism is found to contribute to right ventricular dysfunction this could have important therapeutic implications in our field.

The article by Dr Stenmark discusses current projects that address pulmonary vascular disease in infants and children. One of them, noninvasive inhaled nitric oxide (NO) for premature newborns, seeks to decrease the rate of early and late pulmonary vascular disease abnormalities in this neonatal population. If successful, this could become an intervention with long-term cost-effective benefits, even for less industrialized countries with high rates of premature births.

Dr Hassoun and his group report on current initiatives to evaluate the mechanical properties and characteristics of right heart chambers and their role as predictors of treatment response and prognosis. Confirming the value of noninvasive tools to assess prognosis is something that PH communities in less-industrialized countries will greatly appreciate.

At the personal level, it was very gratifying to see the number of Hispanics participating in the PH conference. A large number of PH patients currently followed in Latin American PH centers came to the conference and actively participated in the sessions, especially those conducted in Spanish. In addition, I was pleasantly surprised by the large attendance of Hispanic patients with PH who currently live in the United States. Having access to sessions in Spanish allowed many of them to get a better understanding of their disease, especially in cases where language barriers exist.

Finally, I want to thank the PHA for the opportunity to participate in the current issue of *Advances in Pulmonary Hypertension*. This invitation reflects the importance that PHA gives to the PH community around the globe. The rapid growth experienced by the PH field in the last decade has been transmitted to our Latin American PH community. We are confident that the increased interest in PH shown by physicians in Spanish-speaking countries will lead to further development and better access to PH care.

As physicians treating PH in environments with limited medical resources, we are pleased to see that our patients have access not only to life-saving techniques such as atrial septostomy but also to a wider variety of PH interventions. The opportunities, such as those offered by PHA and its international conference, should provide mechanisms to increase the participation of the Latin American community in research projects, both industry sponsored and investigator initiated. This should be a win-win situation for the PH field. ■

(Vea el Rincón Internacional en Español en la página 418)

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