Pulmonary Hypertension Roundtable

• Recapping Highlights from the 2006 PHA Scientific Sessions
• Reviewing New Perspectives on Inflammation, Genetics, and Imaging
• Redefining Exercise-Induced PH
• Future Considerations in Translational Research


Karen A. Fagan, MD


David B. Badesch, MD


C. Gregory Elliott, MD


Robert P. Frantz, MD

This discussion was moderated by Karen A. Fagan, MD, Associate Professor of Medicine, University of Colorado Health Sciences Center, Denver, Colorado. Panel members included David B. Badesch, MD, Professor of Medicine, Divisions of Pulmonary Sciences & Critical Care Medicine, and Cardiology Clinical Director, Pulmonary Hypertension Center, University of Colorado Health Sciences Center, Denver, Colorado; C. Gregory Elliott, MD, Professor of Medicine, University of Utah School of Medicine, Pulmonary Division, LDS Hospital, Salt Lake City, Utah; and Robert P. Frantz, MD, Assistant Professor of Medicine, Mayo Clinic College of Medicine, Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minnesota.

Dr Fagan: I would first like to acknowledge your efforts, Greg, in organizing the meeting with your committee. I know that we all agree that the meeting was a great success. The Scientific Sessions of PHA this year focused on three major themes: the importance of inflammation, the importance of genetics, and new evolving imaging modalities in the diagnosis and monitoring of patients with pulmonary arterial hypertension (PAH). Greg, perhaps you can provide your thoughts on why you and the committee chose these topics for the Scientific Sessions.

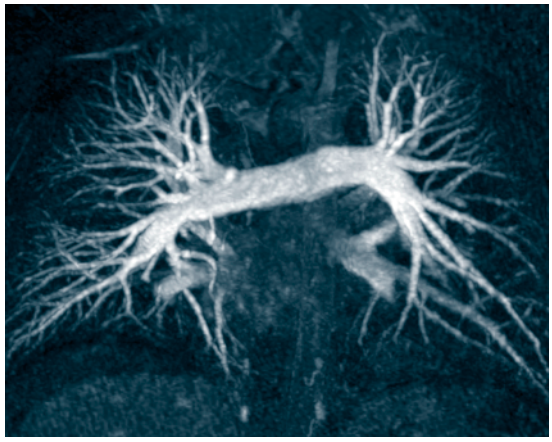
Dr Elliott: The three subjects are very important and potentially linked. For example, one thinks about the inherited basis of pulmonary arterial hypertension as providing susceptibility. We know that not everyone with mutations will ultimately develop disease and so we must consider that there are other stimuli that lead to disease in genetically susceptible individuals. Inflammatory conditions or mediators may be an additional stimulus in a susceptible host, especially given the relationship of PAH with inflammatory diseases. The lectures on imaging may provide us with tools for earlier detection, which is very important for a disease that often remains silent for so long, and is only discovered at the later stages. Obviously, being able to recognize the disease earlier will allow us either to prevent it from ever occurring or at least to modify the course before irreversible pathologic changes occur. The themes, I think, for me were always interconnected and had a lot of potential for the audience.

Dr Badesch: The first major talk, Paul Ridker's talk on inflammation and systemic vascular disease was outstanding. He emphasized how well developed the theme of inflammation is in systemic vascular disease and he focused quite a lot on CRP (C-reactive protein) as a marker of systemic vascular inflammation, looking at it in a variety of systemic vascular disease processes. I thought that was a wonderful introduction to inflammation in vascular disease, and it helps us to realize what we need to be looking at in pulmonary vascular disease. That was followed by a great talk by Norbert Voelkel on inflammation in pulmonary arterial hypertension.

Dr Fagan: One of the things that was important about Dr Ridker's talk was that he really demonstrated how high quality translational research using patients with systemic vascular diseases has opened up an entire new paradigm of thinking in that disease. He has shown us the potential we have to look at similar themes in our patients and to open up entire new avenues ultimately, hopefully, leading to therapies in our patients. And I thought that bringing someone in who has done such terrific work in the systemic circulation really was a tremendous addition to the discussion of the pulmonary circulation. Norbert's talk showed us some of the mounting evidence of inflammation in PAH and the possibility that autoimmunity plays a role. Clearly, more work will need to be done but perhaps, like in the systemic circulation, this may represent a new or additional paradigm for the pathogenesis of PAH.

Dr Badesch: I visited Boston about a year an a half ago and had the opportunity to see Paul Ridker's operation and how he has put together this incred-

ible infrastructure to conduct population biology studies. He can store many thousands of samples. They are not only catalogued, but correlated with the relevant clinical information. He can pull from that bank of samples to look at biomarkers in systemic vascular disease and he has published many studies from those samples, and it is something from which we can learn. We have done a number of clinical trials, and we probably have not done such a great job of storing clinical samples on our patients for future analysis. His work shows the value of that kind of bank of biologic samples that are correlated with clinical information.



Images from PHA Scientific Sessions: Pulmonary contrast-enhanced magnetic resonance angiography depicts normal pulmonary artery.

Dr Fagan: You have made an excellent point. Another area where access to stored samples and clinical data might be useful is in assessing the response to specific therapies. As an example, are there inflammatory markers (ie, CRP?) that change with treatment? Do these changes correlate with clinical outcome measurements? Like you, I came away with the idea that we should be storing these materials. This would allow investigators to test a hypothesis in a large sample of patients. It is going to be very helpful at some point to also link specific biomarkers to the disease and begin to use these to predict who is at risk. It would be great to have a "screening" test for PAH. So, I think the opportunities with stored samples and identifying biomarkers exist in at least two areas: one is identifying progression of disease and response to therapy, and another in predicting who is at risk.

Dr Frantz: I certainly agree with all of those comments. It was also wonderful to hear Dr Valentin Fuster talking about the imaging aspects in terms of MRI, looking at the right ventricle, and potentially getting to a point where we may be able to get an image of the pulmonary vasculature as well. I think all of us feel that we are on the cusp of a new era targeting inflammation and proliferation, going beyond simple vasodilators, and looking at this not only as an issue of prognostic inflammatory markers, but also better understanding the pathophysiology and the effect of treatment on the vasculature. So much work to date in the treatment of pulmonary hypertension has focused on improving the six-min-ute walk and short-term hemodynamic results. We are heading in the direction of understanding the pathophysiology, the genetics, the proteomics, and targeting vascular inflammation and then having to define endpoints to be able to decide if we are impacting on that. And so, it really is exciting to see the developments in these areas.

Dr Fagan: We are very good at measuring functional endpoints, but I think that one of the themes, that I certainly took away, was that there are other things that we probably can and should measure to evaluate patients with PAH or as screening tests for persons at risk for disease. Along those lines was Ekkehard Grünig's presentation about the usefulness of exercise or stress echocardiography in looking at first-degree relatives of patients with PAH and whether or not that may impact how we think about the families of some of our patients.

Dr Frantz: I agree. The exercise echo in that population is interesting, but our own experience with exercise echo is that it is sometimes hard to interpret. There is such a range of pressure response in patients who may be at lower risk that I don't always know what to do with the information. Certainly, as we identify more patients who carry genetic receptor abnormalities with the risk of PAH, may-be early intervention will be something that we can do. It is really astonishing though when we think about the penetrance of this disease as only being in the range of 20% in families who carry the BMPR2 mutation. It is surprising, really. It just raises the question, why more of them don't develop it. The key may be looking for modifier genes that may seem important.

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Dr Elliott: I agree. Maybe I could follow up on your point and ask you, as a cardiologist, if you had an exercise echocardiogram that suggested the presence of pulmonary arterial hypertension, would your confidence level still be low enough that you would want to perform right heart catheterization to confirm or refute the presence of pulmonary hypertension?

Dr Frantz: Absolutely. I view a positive stress echo in terms of rising PA pressures by echo estimates as a risk factor for exercise-related pulmonary hypertension and have felt fairly strongly about taking the patient to the catheterization laboratory. There we do supine bike exercise with the Swan-Ganz catheter in place, to confirm whether those pulmonary artery pressures are, in fact, rising to the extent that they may appear to on exercise echo. We know that the respiratory excursion with exercise is substantial and the intrathoracic pressure swings are huge, and trying to image the tricuspid regurgitant signal during exercise echo is difficult. I have certainly had the experience of having patients referred for the testing of exercise-related pulmonary hypertension based on stress echo, only to put a catheter in and

really find that the pressures weren't rising nearly as much as was suspected on the stress echo.

Defining stress-induced or exercise-induced PH

Dr Badesch: I was just going to ask all three of you how you would define stress-induced pulmonary hypertension or exercise-induced pulmonary hypertension. It would be interesting to know if our definitions are similar or not, and is it the same for all patients? Is the definition the same say, for an obese, deconditioned patient who demonstrates a rise in pulmonary arterial pressure with exercise, as it is for someone else? What do you call pulmonary hypertension with exercise? Is there a threshold?

Dr Elliott: David, let me clarify. Are you asking all three based on echocardiography?

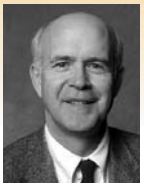
Dr Badesch: Either echo or hemodynamics.

Dr Frantz: I feel we have to also look at the systemic pressure and the cardiac output response, in the sense that if you have a performance athlete who can generate incredibly high cardiac output, and may push the systemic pressure to 200 systolic, the PA pressure may go up to 60 to 70 mmHg systolic in some of these patients who would otherwise be considered normal, and so the pulmonary vascular resistance at those higher flows may be normal. Many of the patients we see can't exercise that vigorously, but their systemic blood pressure response is extremely variable. They may generate in the cath lab a pulmonary artery systolic pressure of 60 mm of mercury with a systemic pressure of 180, and a cardiac output of 12 liters per minute, and I don't think that is an abnormal response. I personally think it is a relatively murky area in the sense that to look at what happens in the normal population you have to go back to some very old literature, where the PA pressure variability during exercise is quite remarkable.

Dr Badesch: I think that the definition probably varies depending upon the patient population you're looking at. My guess is that none of us have a good definition for exercise-induced pulmonary hypertension. Greg, my best guess from the literature is that if the estimated PA systolic pressure is greater than 45 mmHg with exercise, it is considered by some to represent pulmonary hypertension, but I don't personally consider that to necessarily be true.

Dr Elliott: David, we looked at this a number of years ago, particularly when we had so many of these echocardiograms performed in people who had taken anorexigens and it seemed to us that the definition of an estimated PA systolic pressure above 45 mm of mercury identified a population in whom you might find pulmonary hypertension. However, unless the PA systolic estimate was above 60 mm of mercury, I am not confident that I'll find pulmonary hypertension at right heart catheterization. So, I think it is hard to draw a threshold and certainly there are false positives and false negatives, depending upon the population whom you are testing and the pretest probability. Obviously, we can encounter lots of false positives when we are dealing with a population that should be healthy as opposed to a population that has other evidence that they may have pulmonary arterial hypertension. So, as I think you've said, and emphasized, this is a difficult area, the echo estimates of pulmonary pressure, whether at rest or with exercise.

Dr Fagan: Given that concern, the notion of focusing on patients who may be at risk, to limit the false positive rate, might be the more reasoned approach. I think Ekkehard Grünig is doing this in Germany. He is focusing on family members, on those who may have an additional risk factor.



PHA has done a terrific job of lobbying Congress and certainly the Pulmonary Hypertension Clinicians and Researchers Organization has been good at keeping us aware of funding opportunities as well. If we can understand the biology of pulmonary hypertension, it has so much applicability to the pathobiology of other disorders. Pulmonary hypertension may be a relatively rare disease but the role of inflammation and proliferation applies to many other diseases. *– Dr Elliott*

Screening patients with scleroderma

Dr Badesch: Another population that I have heard suggested for screening with exercise echocardiography, and I think there is an investigator looking at this, is the scleroderma population. The thought is that it might be possible to identify patients with a propensity toward the development of pulmonary hypertension earlier. You are right, Karen, selecting that proper patient population and then doing a formal screening study probably makes sense.

Dr Elliott: David, knowing that you are a very good pulmonologist, I might ask you, would you use an exercise echo to screen those patients, assuming that there weren't any musculoskeletal limitations to exercise, or what do you think about the DLCO as a screening test?

Dr Badesch: An isolated fall in diffusing capacity may be another means of early identification of pulmonary vascular disease in patients with scleroderma. So, both exercise echocardiography and the DLCO may be good tools.

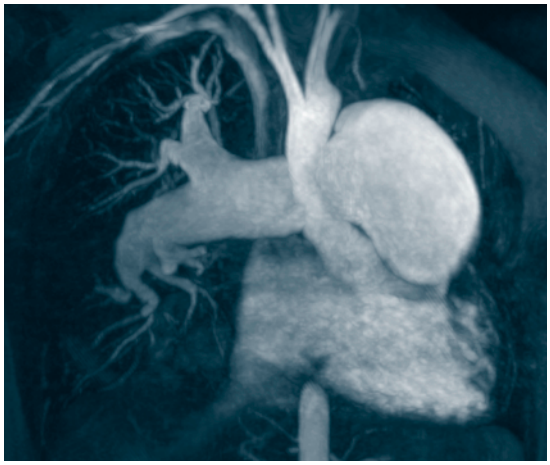
Dr Frantz: And then of course, we would need to see if identifying them early and intervening really has an impact. All of us are trying to get at this issue. We know, especially in patients with scleroderma, that once they develop severe gas exchange problems with very low diffusing capacity for carbon monoxide and severe pulmonary hypertension, they often don't respond well to our therapies. We are getting better at identifying the patients early, because the rheumatologists refer them, and then we may be left with a situation of mild pulmonary hypertension at rest, or exercise-related pulmonary hypertension, or maybe their DLCO is 50% of predicted. We know that they are developing some gas exchange trouble and then I suppose we really need to do

some randomized studies to see if intervening early could have an impact. I would view them as being more of a concern if they have a combination of a low DLCO, plus a tendency to exertional hypoxemia, and a pulmonary arterial pressure with exercise that seems disproportionate for their situation.

Dr Elliott: In our experience the falling DLCO often is caused by another process such as alveolitis and not always pulmonary arterial hypertension.

Dr Frantz: Karen, do you have a particular pressure elevation in the cath lab that you take as being diagnostic of exercise-induced pulmonary hypertension?

Dr Fagan: No, not really. And, again, I don't think that we have enough experience to really know. We could use the classic hemodynamic definition of a mean pulmonary pressure greater than 30 with exercise. Should we be looking at the pressure elevation or should we be looking at the resistance calculations? Perhaps in exercise it is not so much the pressure elevation, but whether or not there is a significant change in the resistance, and the best way to measure resistance, is to go into the cath lab and have a patient exercise. I think that that recruitment and distensibility of vessels with exercise, or lack of these responses in pulmonary vascular disease may be very important. Measuring resistance is one way to evaluate this.



Images from PHA Scientific Sessions: Pulmonary contrast-enhanced magnetic resonance angiography reveals severe pulmonary hypertension.

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Lean times ahead for research funding

Dr Fagan: I want to change topics slightly but it is certainly related to the overall mission of the Scientific Sessions. There is concern regarding a decrease in funding of clinical as well as basic science research over the next few years. How do you think this will impact research in pulmonary circulation? I think including this in the discussion of the Scientific Sessions provides a good opportunity to see what kind of impact we think this will have in the near future.

Dr Badesch: Unfortunately, I think it is going to negatively impact investigator-initiated studies. This would include basic research studies as well as translational studies. In the clinical arena we have previously been fairly heavily dependent upon support from the pharmaceutical industry in investigating new forms of therapy. As we may want to soon look at more novel therapies, perhaps initially in smaller pilot studies, I think that obtaining adequate funding may be challenging. The next family of studies, if you will, ought to be of agents that have antiproliferative and antiinflammatory activity. My guess is that it might be somewhat challenging to convince the pharmaceutical industry that those kinds of studies are worthy of a large investment, without pilot data. Funding for smaller scale pilot clinical studies will need to come from sources like the NIH. I do believe that such funding is going to be very challenging to obtain. There are a number of novel agents out there that we might want to look at, and it would certainly be advantageous to have support from the NIH and other funding agencies.

Dr Frantz: I am sure that it will be difficult, although it will improve if the NIH continues to support the PAH SCOR proposals, where at least half the projects had to be clinically based. Focused physiologic studies that look at novel approaches toward inflammation, or combination therapies, and studies incorporating cardiac and pulmonary imaging are important avenues for exploration. I think the NIH has some level of commitment to clinical trials in pulmonary hypertension and not just the basic science work. Some of these projects may take novel collaborative effort between industry and government and there has been precedent for that in other areas such as heart failure, where device companies are partners with the NIH in clinical trials.

Dr Fagan: Yes. It is going to be an interesting few years, and the pendulum will likely swing back toward improved funding again. It is a matter of sustaining our momentum forward during the leaner times, so that we don't stall in acquiring new knowledge. And I think partnerships with the NIH and industry are certainly one way to help maintain that momentum forward but we need continued commitment from the NIH. Do you think there is any additional role to what PHA is already doing in terms of advocating for research funding with our legislators? Are there other things PHA as an organization might be able to do?

Dr Badesch: PHA has demonstrated support for clinical investigation. We're trying to put together a multicenter clinical trial looking at anticoagulant and antiplatelet therapy in PH, and PHA has not only been supportive of that effort, but has actually tried to facilitate cooperative funding between the NIH and a foundation. This is a very positive contribution from PHA.

Dr Elliott: Absolutely. PHA has done a terrific job of lobbying Congress and certainly the Pulmonary Hypertension Clinicians and Researchers Organization has been good at keeping us aware of funding opportunities as well. If we can understand the biology of pulmonary hypertension, it has so much applicability to the pathobiology of other disorders. Pulmonary hypertension may be a relatively rare disease but the role of inflammation and proliferation applies to many other diseases. I think the opportunities, although they may be more competitive than years past, will be focused on funding of novel projects that will affect pulmonary hypertension.

The next PHA Scientific Sessions: an exciting agenda, a broad spectrum of topics

Dr Fagan: Greg, that gets back to one of the original concepts that you and your committee had for the Scientific Sessions, which was to network with investigators from other areas to stimulate new ideas and potential collaborations. I felt that you certainly achieved this goal. Are there any ideas anyone has for the next Scientific Sessions? Any general themes that 2 years from now would be good to focus on?

I wonder if in a couple of years we might be ready to hear about pharmacogenomics. Would our therapies be more effective if we were able to select the appropriate patient population. That's an area of tremendous growth in medicine right now. My guess is that studies being conducted by Ray Benza and others might give us enough information to begin talking about pharmacogenomics and pulmonary hypertension. *– Dr Badesch*

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Dr Elliott: David, pharmacogenomics would be an excellent topic to put on the agenda for the next conference. We have our toe in the door of the pulmonary circulation, but there are so many other areas that have focused on this important topic. For example, in cancer there are many genomic markers being used to predict and identify response to cancer chemotherapies.

Dr Frantz: It may also be relevant to focus on which factors we should be following for prognosis. It's an amazingly complex decision about when to change therapy, when to move to lung transplant, and how to integrate RV function, BNP levels, and functional class. A prognostic model remains an important topic.

Dr Elliott: Remember there were two SCORs in pulmonary vascular disease awarded this cycle so hearing from someone in those programs, in basic and clinical areas, would be another good topic for the conference.

Dr Fagan: The focus of those grants was to promote high-quality translational research. So hearing from these programs and what they have been able to accomplish would be very important. The other thing we can do is to encourage junior investigators to participate. Having the oral abstract presentations, highlighting some of those finest abstracts is a way to encourage junior investigators and fellows to participate in this field to get them excited about the pulmonary circulation. PHA does a great job with the fellowship awards and the clinical investigator awards through the NIH, but to incorporate them into the meeting and get them excited is another way we can use the Scientific Sessions for our future.

Dr Elliott: Karen, that's a great idea. We didn't have a young investigator award, and maybe an award that specifically targets the young investigators would be a very nice addition to the scientific program.

Dr Fagan: Keeping people interested and recruiting new people to the field is going to be very important for us. New people bring new skills and methods that they can apply to research in pulmonary hypertension. It helps to invigorate us all.

Dr Fagan: I want to conclude this very lively discussion again by thanking and congratulating Greg on an outstanding program. Thanks to all of you for participating in this roundtable discussion. I always learn a lot from these interactions. Goodbye.