Pulmonary Hypertension Roundtable: Clinical Experiences With Drug- and Toxin-Related PH

Sonja Bartolome, MD, pulmonary hypertension specialist and Director of Liver Transplant Critical Care at University of Texas Southwestern Medical Center, Dallas, facilitated a comprehensive discussion among 4 additional clinical experts regarding their experiences with the broad-ranging issues related to treating patients with drug- and toxin- related pulmonary hypertension. Joining the call on May 3, 2018, were Vinicio de Jesus Perez, MD, Assistant Professor of Medicine and staff physician and Roham Zamanian, MD, Associate Professor of Medicine and Medical Director, from the Pulmonary Hypertension Clinic at Stanford University School of Medicine; Kelly Chin, MD, Director of the Pulmonary Hypertension Center at University of Texas Southwestern Medical Center; and Konstadina Darsaklis, MD, Assistant Professor at the University of Connecticut, and cardiologist at Hartford Hospital where she started the pulmonary hypertension clinic.

Dr Bartolome: Joining us today are Drs Zamanian, Darsaklis, Chin, and de Jesus Perez. Vinicio, why don't you begin? Tell us about yourself.

Dr de Jesus Perez: Hi, my name is Vinicio de Jesus Perez. I am an assistant professor of medicine and a staff physician at the Pulmonary Hypertension Clinic at Stanford. My current interest is in investigating genetic and environmental determinants of pulmonary hypertension.

Dr Bartolome: Dina, how about you tell us a little about yourself?

Dr Darsaklis: I'm Dina Darsaklis. I am a cardiologist at Hartford Hospital and also cross-appointed as assistant professor at University of Connecticut, as of today. I specialize in advanced heart failure, transplant, mechanical circulatory devices, and also have started our pulmonary hypertension clinic here at Hartford Hospital.

Dr Bartolome: So, Kelly, even though I'm pretty familiar with your surroundings, would you introduce yourself to the rest of the group?

Dr Chin: Hi, this is Kelly Chin. I'm an associate professor of medicine and director of the pulmonary hypertension program at UT Southwestern. And I trained in San Diego, which is where my interest in methamphetamine-associated PAH started.

Dr Bartolome: Great. And finally, Roham, what are you up to these days?

Dr Zamanian: I'm up to no good. Good morning, everyone. My name is Roham Zamanian. I'm an associate professor of medicine at Stanford University School of Medicine and I'm the medical director of the pulmonary hypertension program. My interests are in facilitating clinical translational research, where my focus right now is taking drugs from bench to bedside, early clinical development and testing, and an approach to precision medicine and phenotyping in PAH.

Dr Bartolome: As you all know, this issue of *Advances* is about drug- and toxin-related pulmonary hypertension. This is certainly something we all see in our clinics. And these patients present with not only their medical problems, but may have social, legal, and practical problems as well that become a barrier to therapy. Managing all of this in a medical clinic can be challenging, so I wanted to start by talking about illicit stimulants, such as amphetamine, methamphetamine, and cocaine, and their relationship to pulmonary hypertension. Although we hear a lot in the news about the opioid epidemic, methamphetamine use is also increasing in the US population with the highest rates at least initially in Southern, Western, and Midwestern states. But Dina, you live out East. Are you seeing these patients in your clinic?

Dr Darsaklis: Yes, that's a great question. So, there has been a rise in methamphetamine use in the Northeast. I think there was actually an article just published in the *New York Times* about it (Editor's note: "Meth, the Forgotten Killer, Is Back. And It's Everywhere" was published February 18, 2018). And we have seen this in maybe the last 3 months. We still have a relatively small clinic, but we've seen an influx of patients with PAH and drug exposures recently. A lot of these patients come in with recent or even current methamphetamine use, often reporting that they have tried to stop within maybe the last 6 months or so. So, I am seeing some consequences of it in the clinic. In the CCU, we're also seeing patients with methamphetamine abuse that come in basically in shock, sometimes from pulmonary hypertension but also confounded with left heart failure as well.

Dr Bartolome: Vinicio, methamphetamine can be taken several different ways. So, just to familiarize our audience with the substance, since you all have studied it extensively out there on the West Coast, can you talk a little bit about how it's used recreationally, different routes, and the complications associated with them? I think Dina already touched on some cardiac complications.

Dr de Jesus Perez: Well, methamphetamine can be taken any way you want it. And I think that's one of the allures and why the drug is so popular. It can

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be snorted. It can be ingested. It can be injected. It can be popped under the skin. It can be given rectally. It can also just be smeared inside the oral mucosa. The drug is easily absorbed and quickly reaches the bloodstream. Once inside, the first organ that gets to deal with it is the lung, which has a faster uptake of methamphetamine compared to the brain. But, I think ultimately it's unclear to us as to whether one route is worse than others. Roham and I are just wrapping up a study where we have been looking at the impact of methamphetamine in exacerbations of chronic lung disorders, so like asthma, pneumonia, respiratory failure, COPD. And, there's certainly an impact. These patients seem to have greater exacerbations for some of these diseases compared to others. So, I think there's something critical about the methamphetamine that certainly affects patients with chronic lung diseases, or in the case of pulmonary hypertension, can cause these diseases.

Dr Bartolome: You all found that the lungs may be particularly sensitive to methamphetamine toxicity. Kelly, while the stimulants are considered to be associated with PH, do you have any insight into the mechanism where stimulants might be associated with pulmonary arteriopathy?

Dr Chin: I think that's a really interesting question. It's one that many basic scientists began asking from the time of the earliest aminorex and later fenfluramine diet pill studies. Margaret MacLean recently wrote an updated review on the "serotonin hypothesis" in pulmonary hypertension, covering this in some detail. One of the interesting things is that there are multiple different potentially negative interactions. From the pulmonary vascular standpoint, acute vasoconstriction can be seen, mediated by increased signaling at serotonin and/or norepinephrine receptors. However, this is generally fairly modest and is not seen in all studies. Longer-term animal studies suggest that pulmonary vascular remodeling may also occur, likely mediated by neurotransmitter transporters and receptors together. Direct myocardial effects might also contribute to the overall severity. Notably, there are considerable differences in receptor and transporter affinity across the spectrum of stimulants in use today. In particular, methylphenidate lacks significant serotonin transporter and receptor activity, while methamphetamine has activity at both the norepinephrine and serotonin transporters and receptors. So, this difference could also potentially impact the presence and strength of any associations with PAH.

Dr Bartolome: Roham, you and Vinicio wrote an extensive prospective review about your experience with methamphetamine-related PH, including pathologic, anatomical, and follow-up data. What interested you first in that area of clinical research? And can you discuss what you've found about the outcomes of these patients?

Dr Zamanian: Yeah, absolutely. You know, I think the broad question is that I became very interested in clinical research when I joined the fellowship here at Stanford. And right about that time, in 2003, our institute had been formed and the database was put into place. And those are the early days, as Kelly had mentioned, where there was a lot of interest in the high rates of methamphetamine use we were seeing. So, the study was born as a prospective phenotyping, comparing methamphetamine-associated PAH to idiopathic disease. I think really clean phenotyping and documenting the outcomes is what we were really, really interested in. We found that methamphetamine patients who were exposed to at least 3 months of either daily or at minimum 3 times a week exposure with methamphetamine use anytime during their lifetime were at substantially higher risk of morbidity and mortality compared to a similarly phenotyped idiopathic PAH cohort who were demonstrated to have negative tox screen and followed without any overt evidence of acute abuse. What was interesting was that we found that the patients with a history of methamphetamine abuse appeared to have similar hemodynamics, but their RV function on echocardiography appeared to be substantially worse. These were descriptive findings, but the RV size and function was much larger and worse in terms of function than the idiopathic patients. But in our logistic regression analysis, we did not—we could not—demonstrate that these baseline differences were a substantial moderator of the outcomes. In fact, the only thing that we found that was remotely related to the difference between the 2 groups was red cell distribution width; but that accounted only for 14% of the effect estimate that we could demonstrate in terms of worse outcomes. What we did see significantly was our own practice pattern. I think that we are more reluctant as a group to treat these patients with IV prostacyclin or subcutaneous. And when we do, we start them later. While these methamphetamine patients had more inhaled and oral prostacyclin use, the idiopathics were exposed much quicker and much larger in percent of the population to parenteral prostacyclin analogs. So, I think it identifies a population at risk for many reasons. Obviously, I think everyone is aware that compliance or adherence with medical therapy may be an issue, and also that relapse in terms of getting involved with abuse of methamphetamine over and over again is particularly a risky issue for these patients. But in our statistical models, those were not contributory in terms of the outcomes. But a lot of this work needs to be, I think, also validated. It's a single-center experience. But I think it does identify a population at risk. And maybe I can editorialize it a little bit, as well, is that first and foremost, I think the work that Kelly has done in the past and this paper of ours hopefully bring a lot of attention to this epidemic. There is a surprising elevated risk of methamphetamine use in the suburbs, especially in the Southwest. It's not an East/West Coast-only phenomenon. There are, as has been mentioned, pockets of substantial abuse and increasing methamphetamine abuse on the East Coast. The Atlanta area is notoriously documented to have very high rates, even similar to, I think, the Southwest and the West Coast. And the second thing, which I think that we already touched on a little bit, is there's a tremendous discrepancy in terms of route of administration across different

ethnic groups, cultural groups, and also gender. It's well known that in the West Coast and the Mexican population of patients that women prefer to inhale and ingest, where men prefer to inject. So, it will be really interesting to see whether some of these gender differences in terms of patterns of use and other social/cultural reasons for determining the specific route of administration are at play here, as well.

Dr Darsaklis: You know, I think that's really interesting. I just wanted to ask the group here about typical presentations for patients you are seeing in your practices. Here on the East Coast, I am seeing both a rise in the number of patients with methamphetamine and cocaine use, but I am also finding that patients are presenting sicker when they come in. And part of it, from my understanding, is that the drugs that they're abusing today are more active and more addictive. We've seen many who unfortunately present after suffering a cardiac arrest. But have you seen in your outpatient practice a difference in the type of severity that these patients present with? And when they do, are you more aggressive with their treatments or…?

Dr Chin: I'm not sure that I'm seeing more patients presenting in cardiogenic shock now versus 10 years ago, but I would agree that patients with a history of methamphetamine use do seem to be more likely to present initially as an ICU admission with severe RV failure, compared to other PAH patients. I am not sure how much of that has to do with the drug itself, meaning do these patients have a more rapid onset or worse cardiac function, versus other factors? For some it definitely may also have to do with their social situations. Many of these patients, especially in Texas which was an opt-out state for Obamacare, nearly 20% of the population lacks health insurance. So it can be difficult to go to the doctor until things really get desperate, and then patients end up in the emergency room and ICU.

Dr Zamanian: Yeah, I'll add to that. I totally agree with what Kelly is saying. I think that as you alluded to earlier, it is now—the UN World Drug Report has demonstrated now—that the purity of the methamphetamine certainly in the West Coast that's coming through Mexico is up to above 95, 97%. It never used to be that way in the last wave. And the price has plummeted. So, that is certainly a consideration. And purity is directly correlated with addictiveness. The second part of it is that we are in a second major boom of methamphetamine abuse epidemic. The biggest epidemic in California was in 2006, where these patients were presenting at a rate of about 18 per 10,000 hospital admissions related to methamphetamine abuse. As of last month, we're well above 24, 25 hospital admissions per 10,000. That's really staggering. And then the last point in our paper that we found, when we quantified the duration of abuse, it wasn't that we found patients abusing for a month or 2—our cutoff was 3 months—but it was a patient was abusing for a year or 2. The average for us was, in fact, something around 8 years, plus or minus a year or so. So, there is a chronicity of exposure here. And when you're dealing with marginalized patients, maybe they do seek medical care in a different way than the rest of us.

Dr Bartolome: Everyone's talked a little bit about compliance issues and insurance issues and all of those things, which certainly complicates this group of patients. Kelly, can you talk a little bit about choosing therapy for this group? Do you offer a prostacyclin therapy? Do you think we are a little slower to offer it for this group, much like they thought they were on the West Coast?

Dr Chin: I think there are definitely some added challenges in this patient population, but for many it can be lifesaving as well. I recall one particular patient who had been on IV therapy for years without issue and suddenly she was being admitted for right heart failure. I remember the PH clinic nurse saying, "Oh, you better get a tox screen, as this is what usually happens to her when she has fallen off the wagon and relapsed." And sure enough, she had. But she recovered and then redoubled her efforts to stay clean and was again able to get her PH under better control.

So, from the beginning of my own practice, I've been inclined to offer this when appropriate, using similar criteria to those I use for other patients. I have subsequently had some conversations with other physicians about the use of IV therapy in patients with a stimulant use history, and I've been a little surprised to learn that that some basically didn't offer it *at all,* while others do offer it but are very restrictive. While I understand the concern that patients might fail at the self-administration, or could potentially even use their line to abuse drugs, these patients are generally so sick when we are considering IV therapy that there just don't seem to be good alternatives.

We did recently look back at all of our IV therapy patients, comparing outcomes in those with a stimulant use history versus those without. Interestingly, we found that those with a stimulant use history had a somewhat higher mortality rate over the 5 years of follow-up, but this was not statistically significant (HR 1.7, *P*=NS), and there was no difference in median time from diagnosis to start of the parenteral prostanoid. So, I think our perspective is that if somebody would otherwise have IV therapy indicated, that we at least discuss it with them and go through the pros and cons of that.

Dr de Jesus Perez: Can I add something to that? I think one of the key points in the management of this particular patient population is that you have to screen for anxiety and depression, not only for those who are actively using but for those who are dealing with the sequelae. I mean, these patients come from very complex backgrounds. They've been through a lot. Their families have been affected by this. They lack a lot of social support, which for us is critical in order to ensure that they will have enough backup to sustain use of intravenous or subcutaneous therapies. But most importantly, I think we have to be aware that drugs which require an intravenous catheter for delivery can be hijacked by patients to inject methamphetamine. And this is not necessarily recreational,

but it could also just be part of a suicide attempt. I bring this up because we had a patient in our clinic who was actively using methamphetamine and presented with very severe right heart failure. We put him on triple drug therapy with IV Remodulin and he improved remarkably in the first year. Of course, he stopped methamphetamine. In our clinic, we do random urine checks for methamphetamine as part of a contract that we offer our patients because, as Kelly points out, once the patient starts using the methamphetamine again, compliance drops down and methamphetamine itself may actually have direct effects in the lung pulmonary circulation. The problem here was that the patient did have a tough social situation. He didn't have enough support. And he was having problems finding employment. We did our best to support the patient from our side. But the patient did have significant depression. And at one point, we were called because he was in our emergency room. He presented with decompensated heart failure and subsequently coded. We first assessed whether there was a blockage in his Hickman catheter, which is something that we do for every patient. Indeed, there was a blockage and when we tried to see what was in the line, we started pulling this pasty substance, which turned out to be methamphetamine. Despite our best efforts, the patient unfortunately died—and this was somebody who was doing amazing on the medication! So the question is: did this happen because the patient decided to use or was it a suicide attempt? We don't know; we cannot ask anymore. But I think there's a lot of complexity that comes from managing these patients besides taking care of their pulmonary hypertension. As clinicians, we have to ensure that these patients are supported every step of the way. Once you're on methamphetamine, there is a high chance that you're going to fall back, even after a few years of not being on it.

Dr Bartolome: Do you encounter these social problems in your area of the country and do you offer the same treatment choices to the stimulant-induced PH folks that you do the rest of your patients?

Dr Darsaklis: So, yes, I basically treat them based on the severity of their pulmonary hypertension. We do perform random drug checks to ensure that they have remained drug-free. The one challenge I have been faced with is exactly what you guys are talking about right now: even if they are drug-free, there's definitely an element of depression and anxiety that fits in with this patient population. This may relate to becoming estranged from their family, their behavior, and so forth, but also a feeling that they are a victim in this: why do they suffer from pulmonary hypertension, whereas their friends, for example, who also abused the drug, did not?

The support system is a big issue. I've made sure I've connected them with the Pulmonary Hypertension Association. I've also made sure that they're followed closely with our social worker. Giving these patients the resources to feel that they are not alone is important, because they've made the life change now to stop abusing. I find that once the insight of the disease process and what has happened kind of really sets in for them, it's eye-opening and just to get them through that hump, I try to provide them with as many resources as possible. One question that I've wondered about is that when I refer them to psychiatry, I sometimes get asked whether antidepressants can be used. I was just wondering what the rest of the group does as far as SSRIs and other antidepressants.

Dr Chin: I know there's been concern about SSRIs, based on studies that found increased neonatal pulmonary hypertension in women who took SSRIs during pregnancy. But the adult studies really don't seem to suggest this. Interestingly, there are actually animal data suggesting that SSRIs could even be beneficial. Human data are also really limited on this; we completed a small study not long ago (N=10) and really saw no hemodynamic effect one way or the other. And while this alone doesn't prove that SSRIs are safe, I think that when combined with the animal data and with epidemiology data in PH, we have not held back from recommending them if you have a pretty good reason otherwise. I usually would not tell my psychiatrist to use whichever antidepressant they feel is indicated. Roham and Vinicio, what do you guys do?

Dr Zamanian: I totally agree with what you said, Kelly, especially about SSRIs. It's really challenging. Could I just say that I think another aspect of this disease, especially with patients who use methamphetamine chronically, is the neurocognitive change that occurs with these patients. So there's a high degree of frustration because the lack of insight does play into this a bit. And there are numerous cases where along with that is the social support structure of the patient is really the people who enable them to abuse. So, our medical social worker is intimately involved in all of our methamphetamine abuse patients. And it's a big challenge. I think we try to really engage with family members, which we think will be productive. We often have either spouses or boyfriends, girlfriends, or friends who are enablers. And it's very difficult sometimes. Sometimes issues around domestic violence come up when you try to take these patients from those environments. We do refer patients to psychiatry. The issue we have is that access to a good mental health clinic is often difficult. I am disappointed to say that we don't have a typical path that we follow from that perspective. Even from a rehabilitative perspective, it's very difficult. Clearly, it's a big problem and one that's embedded in socioeconomic and other factors. The last thing I can say about this is, as Vinicio alluded and others have said, we try to bring the tough love approach here. We not only do random drug screens, we have a contract with patients. We actually call them up. They don't have to be coming to clinic; we reserve the right to call them at any point in time and ask for a drug screen to be done locally within 24 to 48 hours. That's one approach. And many times when we've had re-abusing patients, we've had to come to the very difficult decision of discharging their care from our clinic to another provider that could provide equal support. And that's a very, very difficult decision. I have to say that that is not uncommon, at least for us here, to see, unfortunately. So very complicated.

I suspect that hopefully as we learn and go forward, there will be a multidisciplinary approach to this. Whether we get psychiatrists, neuropsychiatrists, psychologists, and rehab personnel involved, I think this is something that we need to advocate for our patients, especially those who are very marginalized in society, and also have very limited resources.

Dr de Jesus Perez: One thing that I want to point out also is that not every patient who comes to our clinic who is using methamphetamine is using it recreationally. I just discovered that a couple of months ago when I got a patient who was diagnosed with ADHD and had been using methamphetamine for the last 25 years. This is somebody who had failed other prescription-based stimulants, and methamphetamine just seemed to work. He came to us because he had the PH diagnosis, but they didn't know what to do with him because stopping the methamphetamine meant that his ADHD will not be well controlled. What to do at that point in time? It's fascinating because it's not what you will normally think when you sit down and talk with somebody who uses methamphetamine. The first thing the guy tells me is that "if I don't take it (methamphetamine) … you know, every time I take it, I get fully relaxed." This is totally the opposite of what you expect and proves to be a conundrum, right? Because now, you're dealing with methamphetamine not as a recreational drug but as a treatment for a psychiatric disorder. However, now we know that this is a cause of pulmonary hypertension, so how do you manage this patient population? I think that we're going to start seeing referrals for these patients and we're going to be asked the question: what can we use safely?

Dr Bartolome: I wanted to touch on one other topic before we close out. And that is what happens when we have social barriers to treating our patients? Perhaps more than any other group we've seen down here in our clinic, we occasionally have to navigate treating pulmonary hypertension for these folks while they're incarcerated. Kelly, can you talk a little bit how you navigate that obstacle?

Dr Chin: Not very well, I would say. There seems to be 2 situations we deal with. First off is the local jail, where patients may have a short stay, and the jail is probably not going to be able to supply PAH medications. However, we find that there's a good chance that they will let the family bring in the medications, which will then be given by their nurses, if we can get them to them. And so for that, we do our best, making phone calls and trying to prevent any gap in therapy. Fortunately, so far we've been successful. Also so far this has only been patients on oral therapy. I did have one patient who was in a clinical trial who ended up in prison down in Huntsville. We were particularly worried about him as the study drug had to be stopped per the trial's requirements, and then there was a gap getting him set up for his medications. I was already very worried about him as he was doing poorly and we had been discussing IV therapy, so when this happened I was afraid he would die there. But interestingly he actually did really well, continuing on all his other PAH meds, starting an exercise program, and as he told me later, *finally* truly getting off methamphetamine, such that by the time he was released he looked like a new man.

Dr Bartolome: It's different in every state. Do you all have any different experiences?

Dr Darsaklis: I haven't had much success. I've had 2 patients, both incarcerated, trying to manage their pulmonary hypertension. Again, both patients were on oral combination therapy. The management was extremely difficult. One is still incarcerated. The other one received parole, but then unfortunately kind of disappeared. So, I really haven't had much success. I find managing the pulmonary hypertension when patients are incarcerated is very, very difficult.

Dr Zamanian: Yeah, I agree. I think that we as the medical community recognize that incarcerated patients are vulnerable to less than standard quality of care. I don't think this is a controversial statement. But, you know, we also find ourselves—or at least I have—in this intersection of wrong and right. I was called in to court to testify at a hearing for an inmate that had very severe … eventually we prescribed IV epoprostenol for her to help resolve her acute incarceration status. What came out of that experience for me was that she had committed some very horrendous crimes. And here I was, trying to help provide a treatment which obviously wasn't going to be done in an incarcerated setting; the only way to do that is to try to get her home. I felt really mixed emotions in what I was trying to do: advocate for my patient but also recognizing that this is someone … some of these patients have led highly criminal lives. So it becomes, probably, also an ethical/moral dilemma.

Dr Bartolome: It does. I just want to add, I used to practice in the Midwest. I had an experience of an inmate coming to my clinic and she actually had connective tissue disease, pulmonary hypertension that was undiagnosed, and had been syncopizing in the population of prison. They actually did bring her regularly to my clinic. We started her on a prostacyclin infusion. They kept her in the infirmary and paroled her. So, in some states, it can be done. I think it also depends on local support.

So, I would like to round out the discussion with future directions. So, anybody in the group who would like to talk about some of the unanswered clinical or scientific questions that you'd like to see addressed in the near future for this group of patients?

Dr Zamanian: I think one very low-hanging and immediately actionable item is for us to recognize what it is about methamphetamine, I should say specifically illicit methamphetamine, that appears to have this relationship with PAH. An understanding whether, as was mentioned a couple of minutes ago, oral prescription-based amphetamines pose the same risk for patients. And understanding a bit more about the exposure to methamphetamine as route-specific or gender-specific, or what

are the maybe even genetic or personal reasons, or use habits, that predict that relationship with methamphetamine. I think as we point out in our paper, illicit methamphetamine is not a pharmaceutical-grade drug. So I would probably challenge our bench scientists to also understand whether the purity or impurities within this drug also increase the risk, as well. So, from my perspective, those are the low-hanging fruit that we should be looking at fairly immediately.

Dr. Chin I like that idea of the impurity question. I was reading a paper about cocaine, which has a mechanism of action rather different from both methamphetamine and from the previously implicated diet pills. The majority of cocaine in the United States has various substances added to it, and one of them is levamisole, which is an anthelmintic used in veterinary medicine, but it also has some stimulant properties. What I found really interesting about it is that it gets metabolized to aminorex. This wasn't known until relatively recently, and it was only figured out when some racehorses were testing positive for aminorex, a banned substance given its stimulant properties. So, here we have this diet pill that was banned in the 1960s in Europe due to its causing PAH, and now people are using cocaine and basically being exposed to it. To me this really highlighted how much we don't necessarily know about what patients are actually taking when they are using an illicit drug.

Dr de Jesus Perez: So, the one thing I will add also as part of the priorities is, as Roham said, genetic factors. Not everybody who uses meth gets PH. Roham and I conducted a whole exome screen of 17 of our PH patients and identified a gene called carboxylesterase-1 (CES1), which interacts with the cytochrome P-450 2D6, the enzyme responsible for detoxifying methamphetamine. What we found is that variants that reduced CES1 enzymatic increased the susceptibility of endothelial cells to dying when exposed to methamphetamine. This is really interesting because I think CES1 is part of a common pathway that has been evolutionarily developed to protect cells against environmental toxins. Most recently, we have become interested in looking at the interaction between methamphetamine and HIV because many of these patients are also HIV-positive. At this point in time, we are interested in seeing how these 2 environmental stimuli interact with genetic determinants to unleash the phenotype of PAH. This is going to be really interesting, because there are fundamental mechanisms that are shared across all the different forms of PAH and others that will be unique about this form of the disease that will tell us how gene and environments interact to create pulmonary hypertension in selected patients.

Dr Darsaklis: I agree. I think the future of medicine is personalized medicine. So, anything, genetic sequencing, bioinformatics, all that, will be very important to see exactly, like you said, why does one patient develop PAH and one patient doesn't? The other thing, in addition to HIV, I find a lot of these patients also have concomitant hepatitis C and that also brings kind of another kettle of fish to the equation. Because then you could be dealing with portal hypertension but also the effects of the treatment of the hepatitis C and so forth. So, I think it's a very difficult patient population to treat. It definitely requires a multidisciplinary approach. And I think there is lots of room for future research in it.

Dr Bartolome: Great. I'd like to thank our group for a really active discussion on this topic. I learned a lot today. And we really appreciate your participation.