On June 20, 2018, Guest Editor Anna Ryan Hemnes, MD, gathered a group of pulmonary hypertension specialists by telephone to talk about the role of metabolic disease in PH. Among the participants in the animated discussion was Roham Zamanian, MD, Director of the Adult Pulmonary Hypertension Program at Stanford University Medical Center. He directs the Vera Moulton Wall Center clinical database and biobank and focuses his research on clinical characterization and impact of novel risk factors such as methamphetamine use, and biomarkers such as insulin resistance in pulmonary arterial hypertension. Readers will recall his participation in the previous issue’s roundtable on drug-induced PH. Joining Dr Zamanian were Ioana Preston, MD, Pulmonary Function Lab Director; Director, Pulmonary Hypertension Center; and Associate Professor, Tufts University School of Medicine; and Advances in Pulmonary Hypertension editor-in-chief Harrison W. Farber, MD.

**Dr Hemnes:** My first question is asking Roham if he could give us some insight and historical context about how he, in particular, and his group got interested in metabolic disease and pulmonary hypertension. It was really a key observation that sparked a lot of research since then.

**Dr Zamanian:** Thank you, Anna. I think it’s interesting. There was an intersection of many groups’ interest at the time that I think sparked that conversation about, if you will, the role of insulin resistance and metabolic syndrome in pulmonary hypertension. I had just graduated from Marlene Rabinovitch’s lab and was working clinically when a fellow by the name of Georg Hansmann, working with Marlene, looked at the animal model of an ApoE-deficient mouse that, when it was fed a high-fat diet, became quite insulin resistant—developed potential signs of overt diabetes. But those animals were profoundly impacted by hypoxia and actually developed pulmonary hypertension. Next, Georg took the animal and addressed the question of whether a therapy for that insulin resistance could affect not only the metabolic disturbances that the high-fat diets would cause in the mouse, but also would it affect the pulmonary vascular disease; and it certainly did. So about the same time, I think several of us got interested in that signal. We looked at fasting triglyceride and HDL profiles as a surrogate of insulin resistance in about 90 PAH females. We want to take away the role of estrogen and testosterone that might play in the propensity to become insulin resistant and compared it to an NHANES cohort, a National Health and Nutrition Examination Survey’s cohort of patients that did not have overt cardiovascular disease. And in that group, we could demonstrate that in PAH about 45% of our women had markers of insulin resistance, whereas in the general population, insulin resistance prevalence rates are about 21%. When we looked at the outcomes of those patients who were insulin resistant, they appeared to have a worse event-free survival. I believe at the same time, you and others published the data on overt diabetes and the evaluation of diabetes and its role in pulmonary hypertension as a prognostic signal. I think that has now been verified in multiple aspects. So, I think that’s where at least the impact of insulin resistance and the finding of insulin resistance in this population started. There are many questions that I think still need to be answered: whether insulin resistance is associated with obesity that is seen in these patients at a higher rate; whether the insulin resistance phenotype is associated with reduced exercise capacity; and if it isn’t really the disease that’s related to insulin resistance and the cause and effect, but rather that these patients are sedentary and their systemic illness is manifested in insulin resistance. If I understand everyone’s perspective correctly, I don’t think anyone believes that this is solely because of obesity or solely because of a lower exercise tolerance. In fact, I think there is an equivalent clinical data set; and, hopefully soon, some of the data that you have and we have that could show that there is a relationship between this disease from a metabolic syndrome perspective that is not associated with just simple obesity and lack of exercise will appear. And then obviously, that opens the path for potential therapeutic implications.

**Dr Hemnes:** Thanks. Go ahead, Hap.

**Dr Farber:** Can I ask Roham a question, or actually, both of you? So just playing the cynic for a minute—which of course I would never do (laughter)—and if I were new to this field and I walked into this and I heard this, there are 2 things that would strike me: one, there are a whole lot of diabetics running around out there who have insulin resistance and very few of them develop pulmonary hypertension unless it’s associated with left heart disease. Two, granted these people have huge precapillary components and look like they have PAH. Now that we know that there are people who have a mixed picture, why aren’t these people who also have some degree of left heart disease and maybe they really aren’t idiopathics?

**Dr Zamanian:** Anna, why don’t you go ahead and start, and I can take an aspect of it, as well.

**Dr Hemnes:** I think the issue is that it’s very hard epidemiologically to link pulmonary arterial hypertension to really any exposure. And we know that pretty well from the prior anorexigen story that it took really deep detective
and epidemiologic work to be able to make that link. I think it's possible that patients who have insulin resistance are more likely to get PAH or other forms of pulmonary hypertension. I think we just don’t know. As a country, we’re sort of awash in patients who have obesity and insulin resistance and it’s really hard to tease out an increased prevalence of a very rare disease within that context. I do think that it’s possible that there may be sort of subclinical left heart disease that’s complicating PAH in diabetic patients, but I think the jury is sort of still out on that. I guess what I’m saying is that I don’t think that it’s clear that diabetes does not predispose to PAH or other forms of pulmonary hypertension. I think we just don’t know. Did you have any thoughts, Roham, on this?

Dr Zamanian: I agree with you. If it was simply that this was a finding solely because of all the mechanisms of all the overt diabetes—meaning that diabetes was a “risk factor” for development of pulmonary hypertension—there are small signals that this may not really be the case, so I agree with Anna. So, for example, while the insulin-resistant patients in the NHANES cohorts that we find, their insulin resistance is linked; where the presence of insulin resistance is linked with systemic hypertension and obesity, that was not the case that we saw in our small PAH cohort. Now, as you know, I think it’s really difficult to talk about this because I think a large-number prospective study hasn’t been conducted. But I think hopefully soon there will be data to address this issue of diastolic dysfunction. We have some data and I hope others will, as well, to show that I don’t think it’s solely because of diabetes and pulmonary hypertension being linked to postcapillary disease, and that’s where the phenomenon is being picked up. But I can’t disagree with what Anna was saying.

Dr Preston: So I think there are 2 separate questions. Is the pure idiopathic or familial PAH associated with a metabolic derangement? And if it is, what does this derangement play in worsening outcome? And second, how does the metabolic syndrome of Group 2 PAH affect the pulmonary vasculature and the right ventricle? So going back to the first question, is the pure PAH of younger-age women, who are not necessarily obese or have insulin resistance, have a metabolic derangement at the molecular level? And I think in a paracrine manner, it is. You, Anna, showed that in the RV of these patients, there is lipid deposition. So I think there is an altered metabolic pathway that involves different lipid molecules, as well as glucose metabolism. Now, let me speculate. If it happens that that patient with PAH, who has a genetic predisposition and develops PAH, to also have a prediabetic state, that maybe plays a role in aggravating the molecular pathways that are normally in the pulmonary vasculature in the RV. And also LV, which turns out suffers, too, in patients with PAH.

Dr Farber: Well, it’s sort of interesting, because if you look at the literature on diastolic heart disease—and there actually are quite a few studies that suggest that metabolic derangements of the left ventricle, be they hypertension, diabetes, obesity, whatever—can actually affect the right ventricle itself.

Dr Preston: You know, it could be.

Dr Farber: So, I mean, it could be that in part, Ioana, what you were talking about is that there is this derangement that may have started in the left ventricular, but it does at some point have an effect on the right ventricle and we don’t really know about the pulmonary circulation itself.

Dr Preston: Correct. And then it’s also PAH in Group 2 are inflammatory states. So it’s the inflammation, inflammatory milieu, which also affects the molecular function, the cellular function in the lung and the heart.

Dr Zamanian: Could I ask a fundamental question maybe of our host, Anna (laughter)? When we talk about a metabolic derangement, that is such a broad term. There are so many components, like Ioana just mentioned, I wonder if you begin to, in your mind, think it’s not only the insulin resistance that we’re talking about, like we’re talking about mitochondrial dysfunction and all the whole slew of pathways beyond that. So I don’t know, how do you compartmentalize this concept of metabolic derangement in PAH, because it is a systemic disease in a sense, right?

Dr Hemnes: I think that’s really a challenge that I thought about probably about, I don’t know, 11 years ago. I set out to study metabolic syndrome and how it could potentially cause or be associated with pulmonary arterial hypertension. But metabolic syndrome is really too broad. As you know, it encompasses waist-hip ratios, and lipid abnormalities, and insulin resistance, and other features. And it’s hard to study so many things at once. So we really tailored it down to insulin resistance and sort of lasered in on animal models of insulin resistance or hyperglycemia promoting pulmonary vascular disease. Then I was reminded, maybe 2 or 3 years ago, that among the other things that—among regulating glucose homeostasis, insulin also tightly regulates lipids. And so as you know from your original paper, one of the most sensitive markers of insulin resistance is elevation in triglycerides and suppression in HDL. And that’s basically because insulin regulates that also. So then I got thrown back into studying the lipids and am now looking at sort of how insulin resistance in PAH may be more closely characterized by lipid abnormalities than by glucose homeostatic metrics, like glucose and insulin and impaired glucose tolerance, for instance. So I do think you have to compartmentalize them in order to study them, but the features of the metabolic syndrome are all highly prevalent in PAH, as well as other forms of pulmonary hypertension. So as you said, I try to compartmentalize it, but the problem is that they’re all linked together, so it’s really hard to dissect each feature out.

Dr Zamanian: Is PVDOMICS planning to study that inflammatory link with insulin resistance? Or the triglyceride abnormality?

Dr Hemnes: Yeah, there’s not a specific ancillary proposal right now to do that.
So if somebody's interested in that, there is a mechanism through the NIH to look at those features. And I think that would be a really compelling one to look at. Particularly in non-Group 1 pulmonary hypertension, where we really don’t have a lot of data.

Dr Farber: So actually, as you were talking, Anna, this struck me. Maybe part of the problem of trying to figure all this out is the fact that the nomenclature and the separation of what we have into specific groups is completely wrong. That this idea that maybe most, if not a lot or all forms of pulmonary hypertension are somehow related to metabolic abnormalities that involve glucose, lipids, et cetera. And yet, we’ve taken this and tried to separate them out into people who really have Group 2 disease versus those who have Group 1. In fact, they all have some component of the same disease and maybe we’ve made this harder by the way we’ve tried to separate them.

Dr Hemnes: Yeah. I think that’s an interesting point. And as you were talking, I was sort of thinking nobody’s really ever looked at like chronic thromboembolic pulmonary hypertension, because if the problem is cardiovascular limitation driving sedentary lifestyles, driving insulin resistance, then those folks, at least a high percentage of the time, are rapidly corrected. And if insulin resistance is not driving their disease, you know, that’s sort of a natural experiment where you could see the role of insulin resistance in pulmonary vascular disease.

Dr Preston: Yes. You know, Anna, I was thinking, that would be a great idea. But how about focusing on young and kids with chronic thromboembolic disease who undergo surgical correction as endarterectomy, because those with CTEPH tend to be older and have a lot of comorbidities that make the insulin resistance, should it be there, not go away, just because of the other comorbid illnesses. But in a pure younger population, maybe pediatric population of CTEPH, may be a good cohort to start with.

Dr Hemnes: Yeah, that’s a great idea.

Dr Farber: Along those lines, it’s probably a much messier cohort, but if you look at people who’ve undergone bariatric surgery, they reverse over time—actually a relatively short period of time—most of their metabolic abnormalities, glucose intolerance, lipid abnormalities, et cetera. And in those people who do have pulmonary hypertension, it tends to go away. Now, whether that’s because you fixed their diastolic heart disease or their sleep apnea or something else, I don’t know. But the fact remains that the hemodynamics do improve.

Dr Hemnes: Yeah.

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person had insulin resistance, potentially have an effect on them?

**Dr Hemnes:** Maybe.

**Dr Zamanian:** Maybe.

**Dr Farber:** So, you might have expected ASK1, or more currently bardoxolone to improve people’s insulin resistance profile. I don’t know if anybody’s ever looked to see if it actually did any of that.

**Dr Preston:** Yes, Roham, and I agree. But maybe the inflammatory pathways that these 2 investigational drugs affect may not be the primary triggers or the guilty party in the abnormalities in PAH. I wouldn’t, if these don’t pan out and ASK1 did not, I wouldn’t put aside the inflammatory pathway and not try to attack it, you know, to….

**Dr Zamanian:** I agree. I mean, I think this is a conversation that needs, as well as the time has come, for us to ask some of these fundamental pathways to be evaluated in both NIH- or government-sponsored research and industry-sponsored research. I mean, if we had the data from ASK1 to look at it, we could ask the question of whether there was insulin resistance or a metabolic derangement, however you want to define that. And did the drug actually have a pharmacodynamic effect on that pathway? But I wanted to ask: so Anna, you’re setting up the metformin study. I suspect that you’ll have some of these questions that you want to ask in that study?

**Dr Hemnes:** We do. So we just finished a pilot trial of 20 patients with idiopathic or heritable PAH. We gave them metformin for 8 weeks and measured before and after blood. The pilot trial was primarily safety. We also looked at plasma isoprostanates and isoprenes and nitrotyrosine as markers of ROS generation that’s a part of insulin resistance. I can say the preliminary data look like the drug was safe. Based on that, we went on and have planned a multicenter trial that’s a factorial design. So patients will be randomized twice: first to metformin or placebo, and then the second randomization is to exercise intervention or not intervention. The exercise intervention is a mobile health intervention via text, so patients will get texts that say, “Your doctor recommends that you go out and take a walk after dinner,” or something sort of similarly tailored to the individual patient’s preferences. That should begin enrolling probably within the next month. That’s aimed to get at the question of: one, is metformin or an antidiabetic drug effective? And two, might there be an independent and/or additive effect of exercise in patients with PAH? And sort of driven by the really interesting research, primarily from Germany, suggesting that exercise really can increase 6-minute walk distance as much as, or in some cases more, than our drugs that we use to treat PAH. So I hope we’ll have some data, but the preliminary trial really was not powered to answer these sort of bigger, more definitive questions.

**Dr Preston:** Yeah, that’s interesting.

**Dr Farber:** So mechanistically, Anna, why do you think metformin may be beneficial, just by improving insulin resistance? Or have you seen any effects on the pulmonary vasculature in animal models?

**Dr Hemnes:** In our preliminary trials, all the patients in the pilot trial got metformin. And there was an average weight loss of about 2 kilograms. That’s one thing that definitely happened. That was highly statistically significant.

**Dr Preston:** In 8 weeks?

**Dr Hemnes:** Yes.

**Dr Farber:** That is very encouraging, and hopefully it’s sustainable, you know?

**Dr Hemnes:** Yes. It was encouraging in our preliminary trials, as well. So we should have that data out soon. And we’re also looking at that in the multicenter trial, as well. So yeah, that was based on some data. So metformin is a pleiotropic drug. It’s not the ideal drug. And it does many things, including increase fatty acid oxidation in the mitochondria, and that’s how we hypothesized that it would improve right ventricular lipid deposition. But it could
have independent effects on the pulmonary vasculature and insulin sensitivity in endothelial cells, as well.

Dr Hemnes: Let me ask one question that I think is provocative. We have been interested obviously in therapies of insulin resistance. So if insulin resistance may be important in PAH, does correction of insulin resistance improve PAH or survival in pulmonary hypertension, perhaps through right ventricular function? You know, there are ways that you can do it pharmacologically, but certainly bariatric surgery, as we touched on earlier, has also been shown to potentially improve insulin resistance. Have any of you had any experience with patients who’ve had bariatric surgery with PAH or other kinds of pulmonary hypertension?

Dr Farber: Yeah, we’ve had a few. Most of them at least were presumed to have diastolic heart disease before they went for bariatric surgery. But we do have hemodynamics pre- and post-surgery (months later). It’s always interested me that many got better. And it gets back to the same question, did they get better because we improved their lipid profile, we improved their diabetes, we improved whatever? Or is it some other effect? And I don’t know how you’re ever going to separate all those out. But I can think of at least 4 or 5 of these people who have had bariatric surgery, whose hemodynamics got dramatically better 6 or 12 months down the road. But then again, so did everything else. And it may be also, too, that they could actually now walk or exercise a little. So, Anna, I think it’s a fascinating question, how you would parse out which part of it is most important, I don’t know.

Dr Preston: Well, not really, would be just speculation. But, you know, I think to be honest with you, it does pan out that the weight loss, no matter how you achieve it, is a panacea for less disease, left heart disease, right heart disease, pulmonary hypertension.

Dr Zamanian: Yeah, I have to say, we’ve had just a handful of patients that have been of that caliber and have gone through surgery. We haven’t systematically studied them. And I think that what would be interesting, like Hap was saying, is documenting that their insulin resistance profile is, in fact, changed. But then, as has already been mentioned, what is just the physical effect of that weight loss reduction. Regardless, I think that that’s a provocative idea. As you’ve said, the means to achieve that, I wonder if simple surgery versus an exercise regimen have differences in how they affect systemic and vascular health. I would assume that exercise as a means would be much more effective. But again, that needs to be shown.

Dr Preston: So, I have a question for you guys. Looking at the insulin resistance and its potential role in PAH, and focusing on patients with scleroderma PAH who tend to be leaner, thinner, and not have obesity-related metabolic derangements, Roham, have you seen an increase in insulin resistance prevalence in these patients?

Dr Zamanian: Yes, actually, so that is the study that I was mentioning earlier, in which we took treatment-naïve patients and randomized them to mono- or dual therapy. Hopefully, the study will be published fairly soon. We followed them for 24 weeks. The primary endpoint was change in RVEF, just a PAH cohort study. What we did, an exploratory endpoint was insulin resistance. So when we looked at the—so I should back up. Half of the patients, a small study, 24, 25 patients, the majority of these patients were connective tissue disease, scleroderma, PAH patients, by just the luck of draw, I guess. When we look at this group as a cohort, they are all insulin resistant, with a very low BMI. And this is the group that I was mentioning, that after 24 weeks of either monotherapy with tadalafil or dual therapy with tadalafil plus Tyvaso, there was really no change in the area under the curve of insulin or glucose measured during an oral glucose tolerance test. So yeah, again, I feel that one cannot discount the effect of obesity here in this cohort of patients. But there are patients who are thin and who are still insulin resistant. And, you know, I think one of the things that we can do is look at the relationship of BMI to severity of insulin resistance. It’s kind of tricky, as Anna already mentioned. There are different surrogates of insulin resistance and the one that works very well is this triglyceride/HDL ratio. But that’s not routinely used as a continuous variable; it’s really more categorical based on certain thresholds. But one can test that hypothesis. I assume several centers will have data like this and it will be interesting to see if there is that relationship.

Dr Farber: While you were talking about that, I just remembered that in one of the REVEAL papers that looked at comorbidities, the BMI at entry was not that high. But once again, we noted an obesity paradox; the people who had the higher BMIs actually had a better outcome. It is mentioned in the discussion, but we never actually followed up on it. [Editor’s note: Poms AM, Turner M, Farber HW, Meltzer LA, McGoon MD. Comorbid conditions and outcomes in patients with pulmonary arterial hypertension: A REVEAL analysis. Chest 2013;144:169-176.]

Dr Preston: Yeah, and that has panned out in other cardiovascular disorders.

Dr Farber: Yeah, congestive heart failure, all kinds of crazy diseases.

Dr Hemnes: Yeah, those are crazy. I think it’s panned out in a lot of diseases, like ARDS also.

Dr Farber: Yeah. So although being obese might get you sick, once you’re sick, it’s somehow protective.

Dr Zamanian: Is that driven by extremes? But—?

Dr Preston: Oh, no, I don’t think….

Dr Zamanian: … could it be that being very …?

Dr Preston: … morbid obesity fits into this, for example.

Dr Zamanian: No, no, I’m….  

Dr Preston: So, I’m not sure.
Dr Zamanian: … the other way. I meant the other way. That being too thin or cachectic is a marker of poor outcomes because of severe malnutrition, gastrointestinal, whatever it is. Are some data being skewed by extremes from a malnutrition perspective?

Dr Farber: I’d have to go back and look. But, if you look at REVEAL, the average BMI was like 27. So there really were no….

Dr Preston: Now, that’s another point to take into account. Patients who are thinner in all our cohorts tend to be the scleroderma patients. Scleroderma patients tend to have poorer outcomes, compared to idiopathics. So I don’t know if it’s an independent predictor, the fact that patients who have a little bit of extra weight do better. So that may be confounding factors.

Dr Farber: No, but also, if you look at the scleroderma people, even though they may or may not be overweight or can be thin, they have a whole bunch of other metabolic abnormalities because their GI absorption is so bad.

Dr Preston: That could be.

Dr Hemnes: Right. Yeah, we have shied away from studying the scleroderma patients. I’m excited to hear that you have data on them, Roham. I’m curious….

Dr Zamanian: Well, Anna, you’ll see the paper, you are a coauthor, and so is Ioana. (laughter) I think you guys were the DSMBs—.

Dr Hemnes: Oh, yeah, I remember that.

Dr Zamanian: … if I remember correctly. It’s been a long time in coming. You will see the data.

Dr Hemnes: I’m excited, too.

Dr Preston: Happy to help in any way.

Dr Hemnes: Yes.

Dr Preston: Very exciting and a lot of work we need to do, guys.

Dr Hemnes: Yes. I think that wraps up all the comments or things that I wanted to bring up. Is there anything anybody else wanted to discuss?

Dr Farber: I would just like to say that for a completely off-the-cuff discussion, this was really an amazingly informative and very cool discussion.

Dr Preston: Well, thanks to Anna; she led very well. Good job.

Dr Zamanian: Yes, that’s right.

Dr Farber: No, it really was. It was just fascinating listening to all this.

Dr Hemnes: I enjoyed it, too. Thank you, everybody.