Sickle Cell Disease and Pulmonary Hypertension: Addressing the Mixed Pathology and Special Considerations in Diagnosis and Treatment


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This discussion was moderated by Evelyn M. Horn, MD, Associate Professor of Clinical Medicine and Director, Pulmonary Vascular Disease, Center for Advanced Cardiac Care, Columbia University Medical Center, New York, New York. Panel members included Harrison W. Farber, MD, Director, Pulmonary Hypertension Center, Boston Medical Center, Boston University School of Medicine; Mark Gladwin, MD, Chief, Vascular Medicine Branch, National Heart, Lung, and Blood Institute, Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, MD; Myung H. Park, MD, Director, Pulmonary Vascular Disease Program, University of Maryland School of Medicine.

Dr Horn: We would like to start with just a general introduction to hemolytic anemia, and then go directly to sickle cell disease.

Dr Gladwin: A number of hereditary and acquired hemolytic diseases are associated with chronic intravascular hemolysis. As the survival of these patients is improving, they are developing many end-organ complications, including pulmonary hypertension (PH) and pulmonary vascular disease. This has been best characterized in thalassemia intermedia, thalassemia major, and sickle cell disease, where as many as 10% to 30% of patients are developing PH.

Dr Horn: At this stage we should probably define the PH that these patients have, because the hemodynamics are somewhat different from conventional PAH hemodynamics.

Dr Farber: Actually, even before that, I would add another factor that may contribute to PH in hemolytic disorders. A lot of these patients either have had a splenectomy or have functional splenectomy, and splenectomy is one of the risk factors associated with an increased risk of developing PH. I think it is important to point out, when we talk about PH in this group of patients, how it is defined. Because if you look at the thalassemia literature, for example, you can find studies where 90% of the people have PH, but it is all echocardiographically defined.

Dr Horn: That is precisely why I would like to define it now, not only because some studies define PH by echo criteria, but also because we have to include issues related to high cardiac output and wedge pressures.

Dr Gladwin: Worldwide, there are numerous echocardiographic screening studies in patients with hemolytic anemias, and all have followed a similar approach. Generally, sickle cell and thalassemia patients are thin and have relatively normal lung parenchyma, so they have an excellent echo window. At this point, we have screened close to 300 patients in the Washington DC-Baltimore area. Using the tricuspid regurgitation {TR} jet velocity to noninvasively estimate the pulmonary artery systolic pressure (PASP), we've found that 30% of the patient population has a jet velocity higher than 2.5 m/s, which gives you a PASP of 30 to 35 mmHg. Ten percent, or to be precise, 9.2%, has a TR jet velocity higher than 3 m/s, which is more of a traditional definition of PH. In a series at Chapel Hill researchers found that 20% had a TR jet over 3 m/s, but they chose patients who had respiratory symptoms. Almost all of the studies are finding a similar prevalence of 30% of TR jet over 2.5 m/s and 10% of TR jet over 3 m/s.

Dr Horn: Okay, but one issue that we have to be very keenly aware is that a TR jet doesn't differentiate in terms of left-sided hemodynamics. So PH can include patients who have high output heart failure, heart failure with preserved ejection fraction or diastolic dysfunction with an elevated wedge and/or left ventricular end-diastolic pressure, and they may all coexist in patients with sickle cell disease.

Dr Park: In fact, in sickle cell patients who undergo right heart catheterization, the wedge pressure is slightly elevated, higher than what we would usually define in the typical PAH patient. And the majority of patients have an increased left atrial size.

Dr Horn: One notable thing has been exactly that, while there is a significant transpulmonary gradient and pulmonary vascular disease perhaps out of proportion to the degree of left atrial enlarge-

ment and elevated wedge pressure, the hemodynamics clearly are somewhat different from what we usually conceive of as strict PAH.

Dr Gladwin: Absolutely, but we have to recognize two things about this. One is that if you have a high TR jet velocity and sickle cell disease, your prospective risk of death is enormous. The NIH-PH screening study says that the risk of death is tenfold greater if your TR jet is over 2.5 m/s. In an analysis of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH} trial using B-type natriuretic peptide (BNP) as a surrogate biomarker for pulmonary pressure, the death risk associated with that was fivefold. So having PH or having a high TR jet is a biomarker for death. Now, what does the high TR jet mean? It could mean (1) pulmonary vascular disease, so increased transpulmonary pressure associated with pathologic vascular remodeling, or (2) diastolic dysfunction, or (3) a high output state. We can discuss later more data on the percentages of causes, or a more mathematical definition of how much these factors contribute to TR jet pressure, but all three of those factors figure into the TR jet and all three appear to contribute to risk of death.

One issue that we have to be very keenly aware is that a TR jet doesn't differentiate in terms of left-sided hemodynamics. So, PH can include patients who have high output heart failure, heart failure with preserved EF or diastolic dysfunction with an elevated wedge and/or LVEDP, and they may all coexist in sickle cell disease patients. – *Dr Horn*

Dr Farber: Right, but let's look at this for a minute outside of sickle cell disease. If there is an elevated transpulmonary gradient in a patient with elevated wedge pressure, depending on what the left ventricular systolic function is, there is either systolic or diastolic left ventricular dysfunction, both of which people with sickle cell disease, as they live longer, clearly can have and do have. And when you add the high output state to a left ventricle that may or may not be normal, you get long-term elevation of the wedge pressure, which eventually leads to pulmonary vascular remodeling and to some increase in transpulmonary gradient.

Dr Horn: Right. And this finding is more and more appreciated in a multitude of diseases, including left heart failure. Whatever the cause, presence of PH and right ventricular dysfunction brings with it a higher mortality.

Dr Gladwin: So what are you suggesting about the etiology of PH in sickle cell disease?

Dr Farber: I think it is multifactorial. There are people who have PH from left ventricular dysfunction, either systolic or diastolic. There are people with sickle cell disease who have true intrinsic pulmonary vascular disease without left ventricular disease. There may also be a small subgroup who have PH solely on a high-output base.

Dr Horn: Yes, I think we all agree with that, but how should we approach the diagnosis and how can we best tease out these components in terms of treatment modalities?

Dr Gladwin: Let me share with you some data we have just published in *JACC.* We very carefully looked at diastolic dysfunction in our sickle cell cohort, using tissue Doppler and conventional echocardiographic assessments. First of all, it was surprising to find moderate-to-severe diastolic dysfunction was quite rare, whereas mild diastolic dysfunction was common.

Dr Park: How was that defined?

Dr Gladwin: We defined it based on deceleration time, E/Em, DT, and E-to-A ratio, and as you know the E/A value can be high or low with diastolic dysfunction. Mild diastolic dysfunction was defined by an E/A ratio of less than 1.0 and/or a deceleration time of more than 240 ms. Moderate diastolic dysfunction was defined by an E/A of 1.0 or greater and an E/Em ratio of greater than 10, while severe diastolic dysfunction was defined by an E/A ratio higher than the 95th percentile for age or deceleration time less than 140 ms and E/Em greater than 10. Using these definitions, approximately 18% of the patients had diastolic dysfunction while 30% had a high TR jet, but when you looked for an interaction, they were not one and the same. In fact only a fraction, about one third, of patients with a high TR jet (11% of the entire population) also had echo measurements consistent with diastolic dysfunction. If you look at correlative analyses, then diastolic dysfunction or high left atrial size will correlate with a high TR jet, but R-squared values are quite low (0.12). Only about 12 % of the variability in TR jet can be accounted for by diastolic dysfunction. The second fascinating thing was when we looked at mortality. Both measures of diastolic dysfunction, in particular low E-to-A ratio, and a high TR jet were associated with high prospective mortality. When adjusted for each other, the risk ratio of death drops only a little bit, but when you add them together, they are more than additive. If there was both a low E-to-A and a high TR jet, there was a 12-fold increased risk ratio of death. So, the echocardiographic data suggest that both conditions were common, but they are largely independent of each other and are associated with additive or synergistic mortality. And then when we looked at 32 catheterized patients, we saw the same thing. If we catheterize the patients with a TR jet over 3 m/s, which is about 9% of the population, most of them have a mean PAP over 25 mmHg. Half of them will have a normal wedge pressure, less than 15 mmHg, and the other half will have a wedge pressure greater than 15 mmHg but will still have a high transpulmonary pressure gradient. There is clearly a population that has pure PAH and then there is a group that has mixed diastolic dysfunction and pulmonary vascular disease.

Dr Farber: I think we are talking about the same thing. What we're all saying is that this is not a hemodynamically pure patient population.

Dr Gladwin: Yes.

Dr Farber: This is a very mixed population with elevated pulmonary pressure for various different reasons, and we cannot differentiate them without a right heart catheterization. And if in fact they all have approximately the same risk of death, should they all be treated in the same way, and if not, how do we treat them?

Dr Horn: That is a reasonable next question to ask. How do you approach the treatment of the patient with sickle cell disease and PH?

Dr Park: Well, going back to your original question, are we considering a new threshold to define who has PH for this subset, or are we being more cognizant of the fact that the majority of these patients may have other factors?

Dr Horn: I think we would like to emphasize that, in fact, this is a mixed pathology and perhaps we shouldn't lump them all together.

Dr Farber: You have brought up a very good point. If we look at the general PH population, we do not treat people who have intrinsic PH, true pulmonary vascular disease, the same way we treat people who have PH associated with left ventricular disease.

Dr Horn: Precisely.

Dr Farber: So, if we don't do that outside of sickle cell disease, we shouldn't be doing it in sickle cell disease.

Dr Horn: Precisely. I would take that a step further to say that, particularly as we are doing studies looking at sickle cell disease and PH, we want to be extra careful how we define PH in sickle cell disease. Which patients should perhaps be treated with nitrates? Which patients might be considered for pulmonary vasodilator therapy, and which patients might receive just hematological treatment?

In our catheterized sickle cell patients, the mean PAP is 37 mmHg, whereas in IPAH the pressures are near systemic. The argument that we have made is that the traditional IPAH patient has a single organ problem. They have a normal hemoglobin level, they have no end-organ dysfunction, they have no intercurrent severe insults such as vaso-occlusive crisis, or acute chest syndrome. While sickle patients with hemoglobin of 7 g/dL, required CO of 12 L/min, multiorgan dysfunction, frequent pneumonias and vaso-occlusive crises just can't tolerate the same hemodynamic perturbation. – *Dr Gladwin*

Dr Gladwin: As we've said, this a mixed patient population, but we have to be very careful to recognize that, whatever this amalgam is, this surrogate of PASP defines a patient cohort at a 10-fold increased risk of death. In the general population, there are very few things that attribute such a high risk of death, and we have to really be aggressive with these patients. We all agree that we don't exactly know what to do, which means we have to enroll these patients in clinical trials. For now, our approach is to intensify sickle cell therapy for patients with a TR jet velocity over 2.5 m/s. This means that we consider hydroxyurea, or, if patients are already receiving hydroxyurea, we push the dose; we consider transfusion therapies, we consider iron chelation. These patients may have mild PH, but when they have an intercurrent crisis or acute chest syndrome they have more hemodynamically significant PH. If their TR jet is over 3 m/s, we recommend right heart catheterization to assess whether there is pure PAH physiology, which we find in 50% of our catheterized patients, or whether they fall into the group that has mixed diastolic dysfunction and pulmonary vascular disease. The best recommendation is to enroll them in a clinical trial because we have some current clinical trial options looking at whether this population will respond in the same way PAH patients have responded.

Dr Farber: None of us would disagree with the fact that anybody with some major end-organ problem related to their sickle cell disease should be aggressively treated for their underlying disease. I do agree that, until we know more about who responds to what treatment, most of these patients, if not all of them, should at least have the option of getting into a clinical trial for a couple of reasons. One, we obviously need to get more information about each of these subgroups and who responds to what treatment, and two, since we don't know as yet with certainty what we are treating, we don't want to do a disservice to the patient.

Dr Horn: I think everybody would agree with that. We are highlighting that there is a subgroup that has a different form of PAH. So perhaps we should turn next to the issue and discuss the different treatment modalities.

Dr Gladwin: We published a small open-label, phase 2 study of sildenafil in our patient population with sickle cell disease. In this study, with all its limitations, we saw pretty dramatic results, such as a mean 78-meter increase in 6-minute walk test distance and drops in PASP. Subjectively, the patients felt better and improved in NYHA functional class status. We've also looked at acute sildenafil dosing in the cath lab and we've seen sildenafil associated with a drop in pulmonary vascular resistance, an increase in cardiac output, a drop in the mean PAP, and the PVR/SVR ratio. There is a placebo-controlled multicenter trial of sildenafil in sickle cell patients conducted by the Heart, Lung, and Blood Institute that should be launching in a number of months. One interesting thing about sildenafil is that it may also improve both diastolic and systolic left ventricular dysfunction. Work from the Kass group at Johns Hopkins has shown that it improves diastolic dysfunction and left ventricular remodeling in both normal volunteer studies on dobutamine and animal models and there is evidence based on work by Marc Semigran at the MGH that sildenafil therapy in patients with systolic left heart failure improves exercise hemodynamics. So it may be a unique drug that can hit some of the varied hemodynamic problems in sickle cell dis-

ease. It also promotes the actions of nitric oxide, and there is an acute deficiency of nitric oxide in sickle cell disease associated with hemolysis. The current ASSET trial going on in 20 active centers studies the efficacy of bosentan in this population. The nice thing about that trial is that patients are being stratified based on the wedge pressure and pulmonary vascular resistance, so it will attempt to answer the question of whether patients with more classic PAH will respond in one way and whether patients with higher wedge pressures respond or not. As you know, endothelin receptor blockers can increase the wedge pressure, and this may be harmful in the presence of diastolic dysfunction. Does anyone want to add anything to those considerations?

Dr Horn: I think these are all appropriate. The other concern could be the associated anemia. We would hope to see that differentiation.

Dr Gladwin: I want to share an anecdote quickly that just happened to us in our hospital, but is very important to understanding this disease. The question that everybody asks me is how can the attributable mortality rate be so high when the pressures are only modestly elevated? In our catheterized sickle cell patients, the mean PAP is 37 mmHg, whereas in idiopathic PAH the pressures are near systemic. The argument that we have made is that the traditional idiopathic PAH patient has a single organ problem. These patients have a normal hemoglobin level, they have no end-organ dysfunction, they have no intercurrent severe insults such as vaso-occlusive crisis, or acute chest syndrome. While sickle patients with a hemoglobin level of 7 g/dL required CO of 12 L/min, multiorgan dysfunction, frequent pneumonias and vaso-occlusive crises just can't tolerate the same hemodynamic perturbation.

Dr Horn: I think the other comment I would make along those lines is that a normal cardiac output for this patient is 12 L/min. The other patient population that has hemodynamics that don't look as "bad" as those of the conventional PAH patient is some of the portopulmonary hypertension patients with cirrhosis, who also have high cardiac output but do poorly, with lower PAP means than the typical idiopathic PAH hemodynamics.

Dr Farber: And a third group would be the hyperthyroid patients who don't necessarily have severe PH, but who will go into right heart failure relatively easily. Possibly, in people in a high-output state, just a small elevation in pulmonary pressures is much more detrimental than we believe.

Dr Gladwin: This takes me back to the anecdote I want to share with you. We have had, unfortunately, three deaths in the last month among our sickle cell patients with PH. They all had moderate PH at baseline, in steady state. One young patient was 26 and he had a hemoglobin level of 10 g/dL. We had just performed catheterized on him a month earlier and he had a mean PAP of only 25 mmHg, a normal wedge pressure of 15 mmHg, and a cardiac output of 7 to 9 L/min. And nobody would have called that—

Dr Horn: Severe pulmonary hypertension.

Dr Gladwin: Or even moderate, but he developed *Pseudomonas* bacteremia, came to the ICU, and got transfused. He was doing quite well and then on day 4, he suddenly hyperhemolized, which these patients can do. His LDH increased to 2000, his hemoglobin decreased, and suddenly his pulmonary pressures rose and his right ventricle acutely dilated and failed. On catheterization his CI was 1.4 L/min/s, his CVP was 30 mmHg, his mean PAP was 65 mmHg, with a mean systemic pressure of 65 mmHg. His left ventricle was normal on echocardiography, and his wedge pressure was low. It was acute-on-chronic pulmonary vasoconstriction and acute right heart failure. We have two other cases where we observed the same thing. They had moderate PH very well compensated, were in NYHA functional class II, and suddenly, during hospitalization, they had an acute worsening with a precipitous increase in PAP and right ventricular failure. We've suggested that the acute hemolysis, very similar to the stroma-free hemoglobin base in blood substitutes, produces nitric oxide scavenging and vasoconstriction, causes oxygen stress, and activates endothelin, and all these acute events can produce acute-on-chronic vasoconstriction. Since these patients need a cardiac output of 12 L/min to survive, and then suddenly, as Dr Farber suggested, they can't maintain their cardiac output even with modest increases in their PAP, they go into right heart failure.

Dr Horn: But they also behave as if it is an acute pulmonary hypertensive crisis, not dissimilar from the acute massive pulmonary embolism. What you are describing is a superimposition of an acute pathological problem that leads to the right heart failure.

Dr Gladwin: Yes and the patients who are predisposed to this one appear to be the ones who have a baseline elevated PASP on echo.

Dr Farber: Sure, as Dr. Horn pointed out, it is the same thing with any PAH patient who, all of a sudden, had a pulmonary embolism. Obviously, because of the underlying condition, anything that affects the pulmonary vasculature to some degree is going to have a greater impact than it would on somebody whose pulmonary vasculature was at that point normal.

Dr Park: So Dr Gladwin, would you say there should be a new criterion to define what a stable cardiac output is for this population?

Dr Gladwin: That is a good question, but I don't think there is an absolute number. The other similarity, I think, is the pregnant patient. Some may have mild PH and they clinically declare themselves during pregnancy. From a hemodynamic standpoint, I think sickle cell disease is almost a state of perpetual pregnancy. They have high total blood volume, high cardiac output, and anemia, and they become symptomatic at a relatively high cardiac output, which is still lower than their normal. Unfortunately, we don't have good

nomograms for what the cardiac output should be at specific age and hemoglobin levels, but I think that is what you are suggesting, and that would be useful.

Dr Park: Right. And similar to patients with scleroderma, where we have changes in the diffusion lung capacity and pulmonary function parameters that help us identify patients at higher risk of developing PH, in the sickle cell population, the inability to maintain what we consider a high cardiac output may be an important factor for pulmonary vascular deterioration.

Dr Farber: I think part of the problem is what Dr Gladwin alluded to. We have really no idea what's a normal cardiac output for patients with chronically low hemoglobin levels. We don't know, in fact, whether their cardiac output is normal or abnormal for their level of hemoglobin.

Dr Park: Right. And this is critical information for the sickle cell population. We know that as soon as their cardiac output falls below 7 to 8 L/min, their chance of developing frank right heart failure is much higher.

Until we know more about who responds to what, most of these patients, if not all of them, should at least have the option of getting into a clinical trial for a couple of reasons. One, we obviously need to get more information about each of these subgroups and who responds to what. And two, since we really don't know what amalgam we're treating, we don't want to do a disservice to the patient. – *Dr Farber*

Dr Gladwin: I think that's exactly true, Even though we haven't quantified or really studied threshold values, when we catheterize patients with hemoglobin of 7, 8 or 9, and we find a cardiac output of less than 9 to 10 L/min, we know that they are not doing well. I think the pulmonary vascular resistance is helpful here. The normal PVR for a sickle cell patient is about 60 to 70 dyn?s?cm^{-5}. Our patients who have a PVR of 170 dyn?s?cm^{-5} or higher are usually very symptomatic and at very high risk of death. So, they are not tolerating much of a decrease in cardiac output very similar to the portopulmonary situation.

Dr Park: And we also have to account for the microvasculature and the right ventricular ischemia that is more prevalent in the sickle cell population than other forms of PH we deal with.

Dr Gladwin: True. These patients have iron overload and there are a number of factors that are independently associated with the risk of PH in a sickle cell patient, such as the hemolytic rate, the iron overload, high alkaline phosphatase, the cholestatic liver dysfunction, and, in men, priapism. It also means that those patients who have PH are likely to have more right ventricular iron overload, they are likely to have more hemolysis, and more microvascular disease. I think that, as they start increasing their PVR, even modestly, their right ventricle is at greater risk. In a way this is a patient population that is already living on the edge of a cliff. The high TR jet suggests that when these patients are exposed to just a slight gust of wind, they're going to fall off that cliff.

Dr Farber: It's also the effect that, in most of these people, this starts to appear as they reach their 30s and up. They have already been through 30 years of vascular injury just from their underlying sickle cell disease. Their "cliff" doesn't have to be quite as high as somebody else's.

Dr Gladwin: I would also like to point out that 50% of the patients we catheterize have PAH. They have a wedge pressure of less than 15 mmHg and a mean PAP of 37 to 40 mmHg, with a PVR of 200 to 600 dyn?s?cm^{-5}. On autopsy they have plexogenic vasculopathy. A solid half of the catheterized patients—I'd say that's half of the TR jets over 3 m/s, which would be about 4% to 5% of the entire sickle cell population and represent 3500 Americans—have classic PAH where you would feel uncomfortable not treating them with an agent like bosentan or sildenafil or prostacyclin. Many of these patients are receiving these agents and they clinically respond to those agents. So even though we are talking about mixed etiology, I want to remind everybody that as high as 5% of the sickle cell population will have classic PAH.

Dr Park: And from your experience, do you see a difference in the outcome of patients, depending on whether they have PAH or mixed etiology?

Dr Gladwin: Our most frequently used drug has been sildenafil. When the sickle cell patients receive sildenafil, their wedge pressures drop, both in the cath lab and with chronic treatment. We've seen a global response with sildenafil for both pure PAH and the mixed types. But we haven't used that much bosentan. Again, we have 5 patients in the ASSET trial and we're blinded. In terms of systemic prostacyclins, since a lot of these patients have lung fibrosis from old chest syndrome, we have seen dropping oxygen saturation, perhaps from worsening the V/Q mismatch.

Dr Farber: I had a few patients referred to me 7 or 8 years ago, when the only choice was epoprostenol. We have a few sickle cell patients who have actually been treated with epoprostenol for more than 5 years and who have done incredibly well, both clinically and hemodynamically. It proves that, in PAH, people respond differently to different drugs and we do not understand why.

Dr Horn: Does anybody have experience with high-dose nitrates in this patient population? We have seen hemodynamic response to high-dose nitroglycerin in the cath lab and we had a few patients doing well with literally megadoses of nitrates as chronic therapy, but there are no studies. One might hypothesize a mechanism not dissimilar to some of the effects of sildenafil. Let me ask a few more questions. Should all patients with sickle cell disease and PH be receiving hydroxyurea?

Dr Farber: I would think that if they can tolerate it, they should be.

Dr Gladwin: I agree, but I would like to clarify that there is no association between the use of hydroxyurea and decreases in the TR jet velocity or BNP levels. We're not seeing that hydroxyurea is sufficient to lower or prevent the PH, probably because the patients have accumulated this vasculopathy, as Dr. Farber said, over a lifetime. But having said that, we know that hydroxyurea dramatically reduces the frequency of chest syndrome and pain crisis, and we know that about half of these patients with PH are dying during an acute chest syndrome episode. If we can prevent that acute-on-chronic hit, we're going to probably improve survival, and for that reason we aggressively treat with hydroxyurea or transfusions.

Dr Farber: If you're going to treat someone with hydroxyurea, you want to be aggressive and increase the dosage as far as you can, to as much as the patient can tolerate.

Dr Park: As far as the hemoglobin is concerned, what would be your target?

It is critical information for the sickle cell population that we know that as soon as their CO falls beyond 7-8 L/min, their chance of developing frank right heart failure is much higher. – *Dr Park*

Dr Gladwin: Hydroxyurea increases the fetal hemoglobin level, and if you can get fetal hemoglobin up to over 10%, especially if you can get it over 15%, you'll dramatically reduce the frequency of pain crisis and lower the hemolytic rate. The dose-limiting factor in hydroxyurea therapy is your absolute neutrophil count (ANC). If kidney function is normal, you start at 15 mg/kg, and every 3 months you increase it by 5 mg/kg and follow the ANC, until it drops to 2000 or even 1500/mm^3. You essentially get as much fetal hemoglobin as you can without producing myelosuppression. You also watch your platelet and reticulocyte count, but you need to push toward hematological toxicity.

Dr Farber: This should also be done in concert with a hematologist. We should not be going out and doing this on our own.

Dr Gladwin: PH is not a current clinical criterion for hydroxyurea therapy, so we're sort of changing the paradigm by advocating this. Although we don't know whether hydroxyurea helps, we've got to do something about this high mortality rate, so it seems more than reasonable to intensify proven therapies.

Dr Horn: Should we discuss perfusion scans in these patients?

Dr Gladwin: We have another paper that is in review now in which we describe the perfusion scan characteristics of our cohort of patients who have undergone catheterization. The conventional wisdom was that PH in sickle cell disease is caused by chronic thromboembolic disease. On autopsy one would see thrombosis, but much like PAH, much of this is in situ. A number of patients have thromboembolic disease-associated PH, but this is rare. Probably only 5% of our PH patients have had pulmonary emboli. What we do see is that the perfusion scans get progressively worse as the TR jet rises, just as you see in PAH. Our patients have the mixed diffuse perfusion defects that you see in PAH, not the big mismatches that you see in chronic thromboembolic PH.

Dr Farber: I agree, and even if we don't have enough imaging, perfusion scans are still done to rule out the rare patient who does in fact have chronic thromboembolic PH.

Dr Horn: Another question that comes up with the concept of oxidative stress is whether there is any role for allopurinol. Do we have any data on that?

Dr Gladwin: There are data in the transgenic mouse, but there are no human data with allopurinol. One of the risk factors for PH in the sickle cell population is increasing creatinine and renal insufficiency. That is also an independent risk factor for death in this population, and associated with that is a high uric acid level. Some basic studies suggest that uric acid can induce vasoconstriction and endothelial dysfunction and is associated with PH. For that reason we are treating with allopurinol our patients with renal failure and high uric acid, but we don't have any data.

Dr Farber: I don't think that at this point it is a treatment that everyone should be getting.

Dr Gladwin: We've suggested in our review articles that if you have patients with a high TR jet, you should do careful housekeeping. If patients have a high uric acid level associated with renal failure, it should be treated. If they're not receiving hydroxyurea, you should give them that. If they have renal failure and don't tolerate hydroxyurea, you should consider erythropoietin with hydroxyurea. You look for thromboembolism and consider anticoagulation. If they have nocturnal desaturation, you give them oxygen. You would be amazed how few of these patients have been screened for obvious things that would reduce the risk of PH in any other disease. After you have done that housekeeping work, the patient should undergo catheterization and you should consider therapy if they meet traditional PH criteria, or consider sending them to a center where they can be in a clinical trial.

Dr Farber: Unfortunately the obvious conclusion is that we're lacking a tremendous amount of information in this group of patients with PH. The more data we can collect and the more we can characterize these patients, the more we will be able to treat them in the future. PH