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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

A Stimulating Cause of PAH: Methamphetamine-Induced PAH

Dr. Rajagopal:
Hi, my name is Sudarshan Rajagopal. I'm an Associate Professor of Medicine at Duke University School of Medicine. And today I'm going to tell you about a stimulating cause of pulmonary arterial hypertension, methamphetamine-induced PAH.

So, I'll tell you about at this patient. He's a 59-year-old gentleman, and he presented in 2015. His past medical history was notable for hypertension type two diabetes, hyperlipidemia, and obesity. And he developed progressive shortness of breath and chest tightness, yet a history of a provoked PE and worked as a truck driver. So this shortness of breath progressed to the point where he was short of breath with any degree of exercise or even simple exertion. He had not passed out but had multiple presyncopal episodes as well as palpitations. So he was seen by his local physician and was sought to be functional class four and was noted to require oxygen, and was given a diagnosis of COPD, although he had never smoked. There was a concern raised for shunting at that time, but he preferred not to be in continuous oxygen either. So he is referred to as community hospital.

There, he was admitted and he had a right heart catheterization that demonstrated severe pulmonary hypertension. He had a right arterial pressure of 10, a PA pressure of 112 over 56 with a mean PA pressure of 77. They could not obtain an accurate wedge pressure. And his cardiac estimate, cardiac index by thick was 1.4, but we did not have the full report available. At this time, he was referred to our center. So he saw us as an outpatient, and he had an echocardiogram that demonstrated a normal ejection fraction with mild LVH, but he had flattening of the interatrial septum and a moderately enlarged right ventricle with a mild decrease in function. He had right ventricular hypertrophy and his IVC was normal in size with normal respiratory collapse. His PFT were notable for a TLC of 95% predicted. His FEV1 was 74% predicted, and his FEV1 over FVC was 61% consistent with some COPD, and his DLCO was normal at 107% predicted.

He had an echocardiogram again at our institution. And this is just showing you the bubble study. And I think what you can appreciate here is there's very early shunting. You can see that this agitated saline solution is injected and within three beats, you see it on the left side of the heart. So, there's clearly an intracardiac shunt that's present, that's likely contributing to his hypoxemia.

You'll see a VQ scan or his very low probability for PE. He had a CT chest without contrast that really didn't have any significant findings other than some severe coronary artery calcifications. And again, he was admitted from our clinic and had a repeat right heart catheterization with similar numbers as his outside study. His right atrial pressure was 12. His mean P, sorry. His PA pressure was 110 over 49 with a mean PA pressure of 74 and a wedge of 14. His cardiac output by fick was 3.8. His cardiac index was 1.7, and his PVR was an 19.2 wood units. With his shunting noted on his echocardiogram, he had a shunt run, and this did not show any significant shunt. And he also had stable oxygenation during his catheterization. So it was felt that he had some degree of orthodeoxia.

So we have this patient who clearly has severe PAH by hemodynamics with a markedly elevated PVR and a depressed cardiac index. What would be an appropriate initial course of treatment for this patient? In this patient whose functional class four, we chose to start therapy with a parental prostacyclin as part of initial triple combination therapy. So he is admitted to the hospital, he was started on IV treprostinil, tadalafil and ambrisentan. His treprostinil was up-titrated to 30 nanograms per kilogram, per minute during his hospital stay. Now, during this time, there were concerns about his level of social support. He lived alone while he had some family nearby, he was a bit of a loner. There were concerns about alcohol use and his general, his ability to manage a parental prostacyclin. But after a lot of

discussion, he had some family members who could help, and who felt that he was a suitable candidate. Notably, his exertional hypoxemia had resolved by hospital discharge, while initially he required 15 litres with ambulation in the halls. By the time he was on the that dose of treprostinil, he no longer required oxygen which made us think that this was likely a patent foramen ovale that had popped open in the setting of his very high right-sided pressures. And with treatment of his right-sided pressures, this had improved. He was discharged from the hospital at 30 nanograms per kilogram, per minute. And his treprostinil was further up-titrated to 120 as an outpatient.

So he was doing well until three years later when he walked next door to his niece's house, and he felt dizzy with palpitations. Didn't have syncope, but the patient's niece called the EMS because his heart rate was in the one sixties and his systolic blood pressure was in the sixties. At the outside hospital, his heart rate was noted to be markedly elevated with the low blood pressure. He was given adenosine which lowered his heart rate but demonstrated was still sinus tachycardia. He was given IV fluids and transferred to our hospital. During this transfer, he again had three episodes of SVT for which he was given 12 milligrams of adenosine, three times and 150 milligram amiodarone push. Upon arrival at our hospital, his heart rate was in the one forties with a low blood pressure. He completed the amiodarone bolus and then converted to normal sinus rhythm with a heart rate in the nineties. He was alert and oriented and denied any symptoms at that time. He reported that he wasn't taking all of his medications regularly. He did use the treprostinil which he was getting through his IV pump as his niece helped him with it, but he did miss other doses of his pills. He did mention that he smoked marijuana a few days prior to admission, but denied IV drug use or other illicit substance use. But during that admission, he had a urine toxicology screen sent, and it was noted to be positive for amphetamine. And on further discussion after this positive test, he did endorse that he'd been using amphetamine for around five years.

So what do we know about methamphetamine associated pulmonary arterial hypertension? A lot more than we did a few years ago. Although there is significant geographic variation in the presentation of this disease, this is data from colitis and coworkers, looking at the PHA registry and the numbers of patients who have methamphetamine associated PAH in idiopathic PAH. What you can see is that 83% of methamphetamine associated PAH cases are in the Western United States with much lower numbers in the rest of the US. Indeed, in the Western US, methamphetamine associated PAH is nearly as common as idiopathic PAH. Of course, I practice in North Carolina, and we don't see a ton of methamphetamine associated PAH. If you see, there are only nine cases in the PAH registry compared to 156 cases of IPAH. But I think this is something we all have to be aware about as methamphetamine use spreads across the US.

What do we know about the pathology of methamphetamine associated PAH? Well, work from the Stanford group, this is from Roham Zamanian and Vinicio de Jesus Perez shows that the pathology is very similar to IPAH. So this is looking at pathology from, of pulmonary arterials from control lung, an idiopathic PAH lung, and a methamphetamine associated PAH lung. And what you can see in the control lung is the arterials are nice and open. And in the idiopathic PAH, you see a classic plexiform lesion with obstruction of these pulmonary arterials, and you see a very similar lesion in methamphetamine associated PAH. So, it's causing a very similar pulmonary vascular disease to idiopathic PAH.

And indeed the outcomes are similarly poor to idiopathic PAH. Again, this is data from the Stanford group, and you can see that the outcomes over 10 years are actually significantly worse than idiopathic PAH. Although some of this is also, while some of it might be related to the biology, some of it may also be related to the fact that patients who use methamphetamine are going to be at risk for poor outcomes in general.

So what should we do with our patient now? Should we, now that we know that he's been using illicit drugs, should we transition him from IV treprostinil to another option like oral treprostinil? Or should we just not make any changes to his therapies?

We chose to continue him on his therapies. In fact, the fact that he was getting his prostacyclin through a parental route, ensure that he was getting some medication, while we wouldn't be sure of that if we switched him to oral drugs. And so we continued that as, also, we were not concerned about IV drug use, but we did discuss with his patient and his niece about the importance of a adherence to his medications and abstinence from drug use. As stopping methamphetamine use has also been associated with improvement in pulmonary vascular disease. At follow-up, he continued on triple therapy with IV treprostinil a PDE5 inhibitor and ERA. He's now normalized as RV size and function, and his reveal 2.0 risk score confirms a low-risk status. Now, it's difficult for us to say how much of his improvement is due to his PAH drug therapy versus abstinence from methamphetamine, but we are continuing him on these therapies as he's doing very well. Thank you.