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Addressing PH Subtypes: Raising Awareness of Understudied Populations

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Dr. Krasuski:
Thank you for joining us today. I'm Dr. Richard Krasuski from Duke University and our topic today is, "Addressing PH Subtypes, Raising Awareness of Understudied Populations." The learning objectives for this talk are to review the characteristics of PH patient groups that fall outside of the idiopathic category. We'll discuss the screening, diagnosis, and expedient referral of non-idiopathic patients to PH specialty centers from community generalists and specialty healthcare providers. We'll focus on understudied PH groups that require special diagnostic attention by all healthcare providers. And finally, we'll review treatment and management approaches to these understudied PH patients.

Setting the Stage, What Are the Understudied PH Populations? So where have prior studies of PAH been focused? The current classification scheme for pulmonary hypertension is comprised of five major groups. Historically, Group 1 PH, or PAH, has been the most often studied class of adult pulmonary hypertension. PH therapy trials have mainly enrolled white females in their 40s and 50s and have consistently excluded non-WHO Group 1 forms of PH. Initial clinical trials performed in newly diagnosed PAH and CTEPH patients were single-agent, placebo controlled, of short duration, and focused on changes in measures of exercise capacity and comprise of relatively small numbers of patients. Over the past decade, clinical trial designs for PH have evolved into much larger placebo controlled on background therapy and upfront combination therapy trials.

So here is the current clinical classification system of pulmonary hypertension. As you can see, there are five major groupings. Today, we're going to focus predominantly on connective tissue disease, congenital heart disease. And then, as you can see, these fall into Group 1, but they also cross over into Group 3 for connective tissue disease with restrictive lung disease. And finally, the congenital patients also fall into Group 5 under complex congenital heart disease and segmental pulmonary hypertension.

Connective Tissue Diseases: Identifying Patients with Pulmonary Hypertension. Patients with systemic sclerosis can have different reasons for their pulmonary hypertension. As you can see, there's tremendous crossover here. They can have Group 1, or PAH. They can be patients with significant interstitial lung disease, and those folks fall predominantly into Group 3. They can also develop Group 2 disease because it's well known that myocardial problems also can occur. So there's a tremendous overlap that eventually leads to right heart failure.

Here is an example of the different types of pulmonary hypertension in systemic sclerosis. On the left, you can see a patient with interstitial lung disease. In this case, it's much more diffuse than limited. Their very abnormal lung architecture is present. There's reduced vital capacity, and these patients are chronically hypoxic. There's also normal to moderate PA pressure elevation. So these are patients who predominantly have an ILD component with some pulmonary hypertension. On the right, on the other hand, is somebody

with pulmonary arterial disease, in this case, limited considerably is greater than the diffuse type of disease. There is normal or minimally abnormal lung architecture. There's mild basilar fibrosis often. There's very low DLco, and a normal vital capacity. And there's evidence of right ventricular dysfunction. The heart typically becomes significantly greater in size and there's elevated PA pressures. In this case, you have rather significant pulmonary hypertension.

Connective Tissue Disease-Associated Pulmonary Arterial Hypertension, Perspectives for Rheumatologists and Pulmonologists: Working Together to Build Clinical Suspicion. So let's briefly discuss the epidemiology of systemic sclerosis and pulmonary arterial hypertension. Connective tissue diseases are commonly associated with PAH. Systemic sclerosis is the most frequent connective tissue disease that's complicated by PAH. About eight to 12% of all of these patients develop PAH and this accounts for 75% of CTD-PAH cases. It's the leading cause of death in systemic sclerosis, and it's associated with a worse prognosis than patients with idiopathic disease. PAH can be detected in 1 to 5% of patients with SLE, and 3 to 4% of patients with mixed connected tissue disease. Data on the prevalence of PAH in connective tissue diseases other than systemic sclerosis are less reliable owing to the lack of screening, and it's not surprising since screening is only recommended at this time for systemic sclerosis, and also the lack of right heart catheterizations in these patients. So how do we build a clinical suspicion of pulmonary arterial hypertension? First of all, we have general symptoms. These are non-specific things, such as dyspnea, weakness, chest pain, lightheadedness or syncope, or cough, which is, in fact, a little less frequent. Signs and symptoms in advanced disease may include progressive right heart failure, edema, ascites, and abdominal distinction, hemoptysis, Ortner's syndrome, which is hoarseness related to unilateral vocal cord paralysis, this is, in fact, very rare but occasionally can be seen, and arrhythmias. On physical examination, we look for an augmented second heart sound, a large P2 component. A right ventricular lift may be present. Jugular venous distension is often present, hepatojugular reflux, which, remember, you push on the liver, you wait about two or three seconds, if it remains elevated, that's elevated hepatojugular reflux and jugular venous distension. Ascites, hepatomegaly and/or splenomegaly, edema, tricuspid regurgitation or pulmonary regurgitant murmurs, and finally, a right-sided S3 gallop. Successful Identification and Management of Pulmonary Arterial Hypertension Requires Collaboration. There are many specialists that are involved in patients with connective tissue disease care. These can include rheumatologists and community specialists. They can include internal medicine or primary care, cardiologists, community, and PH specialty care, and also pulmonologists, community, and PH specialty care. And finally, at the center of all of this hub is the pulmonary hypertension center. And this communication back and forth is vitally important to make this all work.

The Community Physician and the PH Center: Disease Identification and Treatment Must Be a Collaborative Approach. For community generalists and specialists, they are involved in the initial assessment. They're identifying at-risk patient populations. They are focusing with the primary provider for care. They're identifying early disease. They're screening at-risk patients, such as patients with systemic sclerosis, and they're providing routine medical care after diagnosis. But they're also collaborating and communicating with the PH specialty center where the confirmation of diagnosis occurs when there is uncertainty. There, they have PH specialty physicians. They have advanced diagnostics available. They're experienced in advanced therapies, including prostacyclins and IP receptor agonists. They're involved in trials of PH therapy. They can provide extra services, such as lung transplantation assessment. Presence of support groups are also at these centers. Nursing expertise and support teams are available. And finally, there's advanced patient education programs. So this collaboration and communication back and forth is critically important for success in this.

Screening the CTD Patient for Development of Pulmonary Arterial Hypertension: Why Must We Do This? Active screening identifies patients earlier and earlier detection equals better survival. So this is data from the French registry, and this was a program looking at systemic PH detection versus routine clinical practice. As you can see in this particular study, they identified patients earlier, provided therapy for those patients earlier, and there was a significant improvement in survival that was seen. So again, identifying the disease at its earlier stages and getting that therapy on board can potentially make a huge difference in patient survival. Screening of High-Risk Patient Populations for Pulmonary Arterial Hypertension. Annual screening is recommended in asymptomatic patients with systemic sclerosis spectrum diseases and should include a two-step approach. In this case, you look for the presence of telangiectasia. You measure the anti-centriole antibodies. You look at the pulmonary function tests and DLco measurements. You look at the electrocardiogram and cardiac biomarkers, such as NT-proBNP and uric acid. And this is the initial stage. After this, echocardiography can be performed, and then there is consideration of right heart catheterization in patients with abnormal findings. Screening should be part of a scientific protocol or registry whenever possible. Patients with systemic sclerosis and other connective tissue diseases with clinical signs and symptoms of PH should be evaluated by right heart catheterization. Scleroderma, or systemic sclerosis, and scleroderma spectrum diseases, again, annual screening is recommended and screening for scleroderma spectrum with uncorrected DLco less than 80% of predicted. Screening tools should include the DETECT algorithm, the 2015 ESC/ERS recommendations for echo or forced vital capacity over DLco calculation with a ratio of greater than 1.6, assuming none-to-mild interstitial lung disease, and greater than twofold of the upper limits of normal elevation in the NT-proBNP. If any of these tests are positive, these patients should be referred for right heart catheterization. When the uncorrected DLco is greater than 80% of predicted, echo screening may be used.

So the bottom line is, if your patient has systemic sclerosis, screen them annually for development of PH. Again, how often this should be done? Yearly in a patient with systemic sclerosis or mixed connective tissue disease with scleroderma features. These patients should be screened with tests, including echos, PFTs, NT-proBNP, and then the use of the DETECT protocol if the DLco is less than 80%. If these tests are abnormal, the patient should get a right heart catheterization. Other testing includes echocardiography, especially if there's new symptoms, NT-proBNP, pulmonary functions with DLco, and again, DIRECT algorithm. And finally, remember that if the patient presents with other connected tissue diseases, it's not currently recommended to screen these patients due to the low prevalence of pulmonary hypertension.

How Do We Determine If a Systemic Sclerosis Patient Needs to Be Sent to a PH Specialty Center? Here is the rationale for the two steps of the DETECT algorithm. Again, in step one, this is non echocardiographic data. These are six variables that can be easily obtained by a rheumatologist to then determine the need for echocardiography. In step two, again, if a echo is indicated, we look at two specific variables and then a cardiologist determines whether the next step, a heart catheterization, is necessary. So by using the two steps to determine referral for right heart catheterization, DETECT optimizes resource usage and reduces the burden on particular medical departments.

Here is the DETECT protocol. In the first step, again, clinical information is looked at. If in fact the score that's calculated is elevated here, an echo is then recommended. Then, this echo is looked at specifically for these characteristics, including right atrial area, TR velocity. And then if this then highly scores again, the patient should proceed to a heart catheterization. A smartphone app has been developed for this to make this easier for the physicians in the community to identify the patients that need to proceed through this scoring system. Collaborative Assessment of the PH Patient: This is Data to Collect and Where Testing Should Occur. There are a number of different variables that have been shown to predict outcome in patients with pulmonary arterial hypertension. In yellow here, you can see the variety of different clinical characteristics that can predict survival and other outcomes in patients with pulmonary arterial hypertension. Some of this testing should occur in the community level or the PH center. And you can see these are the characteristics that are reasonable to consider early on in the diagnostic process. And then when the patient reaches the specialty center, certain things, such as echocardiography if it hasn't already been performed, a V/Q scan often is best performed in these centers, and finally hemodynamic evaluation. The Revised Diagnostic Algorithm Must Be Seen in 2 Parts: Step 1: Triage and Diagnosis of Common Conditions are done in the community. So again, you have patients with a history that's suggestive, they have some symptoms and/or laboratory tests that are suggestive of pulmonary hypertension. They undergo an echocardiogram. If that echocardiogram is a low-risk echocardiogram, consider other causes. There are many different causes of dyspnea, chest pain, of the symptoms that these patients can present with. If they have high or intermediate risk of pulmonary hypertension, for some of these patients, a fast track referral should occur. In others of these patients, proceeding with the additional workup, including a V/Q scan to screen for CTEPH, considering a V/Q scan to screen for CTEPH. If left heart disease is a high probability, again, this should be looked at. Some patients may have intrinsic lung disease as well. If there's no clinically significant left heart disease or lung disease, ideally, these are patients that then need to be sent to a PH expert center. With echo, there's a variety of different criteria here, but if you're just looking at the TR velocity, if the TR velocity is 2.9 or higher, this is someone you should be very concerned has pulmonary hypertension, and even possibly pulmonary arterial hypertension. But it's important to recognize that PH often has many different ideologies, particularly left heart disease.

Now, in the revised diagnostic algorithm, step two is the role of the PH expert center. Ideally, these are patients that probably need to have their V/Q scan performed at the specialty center, but at the least, that V/Q scan should be reviewed at the specialty center. If there's any mismatched perfusion defects, the patients should be carefully evaluated for the presence of possible chronic thromboembolic pulmonary hypertension. Some of these patients will in fact not have pulmonary hypertension. Some of these may have a CTEPH that is known as CTED, in which case, it becomes a little more challenging to know whether interventions are indicated or not. In some cases, basically, CTEPH is confirmed. And in that case, classifying how to approach these patients and making sure that surgery is considered is very important. But review by a multidisciplinary PH team is particularly important in the patient with CTEPH and assessing that patient and ensuring they get rapid medical therapy and potentially surgery and/or balloon pulmonary angioplasty.

The Echocardiogram Is of Central Importance to Connective Tissue Disease Pulmonary Arterial Hypertension, and for that, All Types of PH, Diagnosis and Referral. The Importance of Structural Changes of the Right Ventricle in Pulmonary Arterial Hypertension. Right ventricular function is the single most important prognostic determinant of survival in various forms of pulmonary hypertension. PH has been shown to result in right ventricular remodeling at different stages, organ level hemodynamics to tissue stiffening, fiber reorientation, and altered myocyte contractility and mitochondrial energetics. The right ventricle initially responds to increased pressures in pulmonary arterial hypertension by undergoing concentric hypertrophy. This helps to reduce right ventricular wall stress and results in increased organ level contractility. Increased wall thickness results in maintained cardiac output and ejection fraction during the early stages of right ventricular remodeling. With further progression of pulmonary hypertension, however, right ventricular hypertrophy reaches a

plateau while the PA pressures continue to rise. This is how this looks. Remember that pulmonary arterial hypertension is a process that is based on increased pulmonary vascular resistance. The right ventricle adapts in its early stages, but eventually this becomes maladaptive. The ventricle dilates. Often, the right ventricular ejection fraction goes down. RV-PA coupling become inefficient, and the patient becomes progressively sicker. Ideally, we should be picking up patients in this asymptomatic or adaptive phases, but unfortunately, many patients are still picked up in the maladaptive phase.

Let's discuss the importance of echo in uncovering PH related changes in heart structure. The most common opportunity to spot a new PH patient is either in the review of the echocardiographic images or in the echo report. Emphasis on the echocardiogram should be on structural changes associated with the heart and not just on the pressures. Remember that the pressures that are obtained are useful, but they're estimates only, and ideally, pressures should be assessed with right heart catheterization. Some of the key structural features of the heart in pulmonary arterial hypertension include the right ventricular size. If you're looking at the right ventricle to left ventricle basal diameter ratio, if it's greater than one, it should make you suspicious the patient has pulmonary hypertension. If the right atrial size is increased, if the right atrial area end-diastole is greater than 18 centimeter squared, that's very suspicious. If the intraventricular septum is flattened, particularly during systole, that should make you very concerned that that patient has pulmonary hypertension. If it's flattened during diastole, it should make you think of volume loading issues. Inferior vena cava diameter fluctuates with the respiratory cycle. If you have a dilated IVC that's greater than 21 millimeters and it does not collapse at least 50% with inspiration, that should make you very suspicious for an increased right atrial pressure. And finally, the diameter of the pulmonary artery, which can be pretty easily assessed with echo, if it's greater than 25 millimeters, it should make you concern that PH is present.

So echo is not all about the pressures. Structural changes are essential. Here on the left, you can see a patient with precapillary pulmonary hypertension. This patient has a dilated right ventricle and their function is down. Remember the right ventricle contracts like a piston. You typically get up and down motion. In this particular patient, the TAPSE, the tissue annular plain systolic excursion, appears to be reduced. There's also a pericardial effusion, and there's a small left atrium with a septum that's been shifted from the RA over. So the interatrial septum pushes over into the LA. So this is somebody who has classic precapillary pulmonary hypertension. Contrast this with the echo on the right. This is a patient with left heart disease and postcapillary pulmonary hypertension. This patient normally has pretty normal left ventricular function. They have left ventricular hypertrophy, often related to things such as hypertension, and they have normal sized right-side chambers and they have left atrial enlargement that can be pretty dramatic. Now I tend to use, I call them Krasuski calipers. I put my fingers on the right ventricle for diameter and I compare it to the diameter of the right ventricle. If that right ventricle is the same size or larger than the LV, that I'm very concerned that a process involving the RV, like pulmonary hypertension, is present.

Roles of the Pulmonologist and Cardiologist at the PH Center: Confirming the Diagnosis. The hemodynamic evaluation of suspected pulmonary hypertension is very important and it's still the only validated method to confirm and grade pulmonary hypertension and should be best performed at a PA center. Even patients with a mean PA pressure less than 20 millimeters of mercury or a mean PA pressure between 21 and 24 at rest can still develop pulmonary hypertension during exercise, something that we refer to as exercise-induced pulmonary hypertension. Screening and referral of connective tissue disease, especially systemic sclerosis patients, to a PH center may allow the use of cardiopulmonary exercise testing that can uncover latent pulmonary arterial hypertension. Use of exercise hemodynamic measurements in symptomatic patients with profusion defects and normal resting mean PA pressure can reveal the presence of abnormal cardiodynamic responses to effort, especially patients with chronic clots like in chronic thromboembolic pulmonary hypertension. For all these reasons, hemodynamic evaluation of suspected PH is best performed at a PH center.

Recommendations for Right Heart Catheterization for Systemic Sclerosis and Scleroderma Spectrum Disorders. So when you're assessing a patient to determine whether they should have a heart catheterization or not, they are really three things that you're thinking about: are they symptomatic? And then when they've had an echocardiogram and pulmonary function tests, how to incorporate these here. So if the patient is symptomatic and has a TR velocity between 2.5 to 2.8 meters per second, that's sufficient for heart catheterization. On the other hand, if they're asymptomatic, you're looking at a greater threshold here, 2.8 meters per second or greater. Now, if they have RA or RV enlargement, there again, you don't even have to have that pressure elevation. That is somebody, ideally, even if they're asymptomatic, should have a heart catheterization. With pulmonary function testing, if they're symptomatic and they have a FVC to DLco ratio greater than 1.6 and/or a DLco less than 60% predicted, they should undergo catheterization. If they're not symptomatic, then you ideally want to measure NT-proBNP as well. And if that's twofold of the upper limits of normal, then proceed to catheterization. And again, a composite measure here, you want to meet the DETECT algorithm in patients with a DLco less than 60% predicted and a disease duration less than three years. Even without symptoms, that is somebody that should undergo a catheterization. Here again, we're trying to maximize our sensitivity, and also our specificity for patients that have pulmonary arterial disease.

Essentials of PAH Diagnosis: Right Heart Catheterization. So this is part three of the diagnostic algorithm, again, is a heart catheterization. This allows us to confirm the diagnosis. We want to calculate the pulmonary vascular resistance. We want to be able to

guide therapy for pulmonary arterial hypertension, exclude other causes of pulmonary hypertension. I personally believe that every patient undergoing their initial catheterization for pulmonary hypertension should have a careful shun run to exclude the possibility of intracardiac or extracardiac shunts. Now, the thing you should look at very carefully here is the pulmonary capillary wedge pressure. It is, in fact, probably the most important measure and the most challenging measure in some of these patients with pulmonary hypertension to obtain. So you want to make sure that that is very carefully collected. If in fact you don't have a pressure that you trust, you should go into the left ventricle and measure a left ventricular and diastolic pressure. And then you're going to look at measures that look at the degree of ripe ventricular dysfunction, things such as the right atrial pressure and the cardiac output calculation. Now, hemodynamic values in terms of assessing the severity of risk for the patient during heart catheterization really are three things we're looking at here by the ESC and ERS guidelines: the right atrial pressure, the cardiac index, and the mixed venous saturation. And you can see, if the right atrial pressure is low, the index is high, and the mixed venous saturation is good, that's somebody who is going to fall into the lower function classes, or the normal function classes. As the function classes get worse, the RA pressure tends to increase, the cardiac index starts to drop, and the mixed venous saturation start to drop as well.

So let's switch gears a little bit and discuss congenital heart disease. Congenital Heart Disease Related Pulmonary Arterial Hypertension: What to Look for and When You Should Refer to the PH Center, a Short Tour of Congenital Heart Disease Associated

Pulmonary Arterial Hypertension. So let's talk a little bit about adult congenital heart disease. Congenital heart disease affects slightly less than 1% of live births in the US, and this excludes bicuspid aortic valve and mitral valve prolapse. Pulmonary hypertension is a common complication of congenital heart disease, somewhere between five and 10% of all patients, particularly if the congenital heart disease is significant and un-repaired. With newer and improved diagnostic techniques and evolving medical catheter-based and surgical interventions, there are now over 1.4 million adults with congenital heart disease living in the United States. And roughly about a decade and a half ago, we reached a point where there were more adults than children. Unfortunately, most physicians get minimal exposure to congenital heart patients during their training. And ideally, all adult congenital heart disease patients should be seen by an ACHD specialist at least once during their lifetime. Complex patients need follow up every 6 to 12 months at an accredited ACHD center. Specific aspects of pulmonary hypertension in congenital heart disease include higher flow and more downstream shunt lesions that are more likely to cause pulmonary arterial hypertension. Like any case of pulmonary hypertension, ACHD-related pulmonary hypertension can be either pulmonary venous or pulmonary arterial and emphasizes why catheterization is so important for the diagnosis. We use the same hemodynamic criteria for diagnosis as other Group 1 disease. Differentiation of etiology dramatically impacts management, and ideally catheterization should be performed by a board certified ACHD physician.

Now, there have been a lot of advances that I've mentioned in congenital heart disease and this has led to a much larger patient population of adults with congenital heart disease. If you were born in the 1960s, you can see your chances of dying within the first year were about 50%. Your chances to survive to adulthood with congenital heart disease was only about 15%. Whereas if you're born in 2010, your chances of surviving to adulthood is now probably close to 90%. So there are 1.4 million adults with congenital heart disease. Many patients are only palliated for their disease. Their lesions can recur and the palliative methods can cause problems. And even the simple lesions, we consider shunt lesions to be some of the simplest lesions, they can result in pulmonary hypertension, arrhythmias and heart failure, even after successful repair. And that's why it's so important for these patients to be closely followed. Epidemiologic studies are limited. There's varied complexity of these patients. And in the United States, at least, there's no centralized database, although there's definitely work being done towards that process and hopefully, we'll have one in the next decade.

So, in patients with congenital heart disease and pulmonary hypertension, we can classify them into four distinct groups of patients. In Group 1, we have Eisenmenger syndrome. These are patients who develop increased pulmonary vascular resistance with un-repaired shunts. When they develop progressive increase in their pulmonary vascular resistance, they get right-to-left shunting cyanosis and its various complications. The second group is persistent systemic-to-pulmonary shunts. These can be either repairable or unrepairable lesions. And the third group are small coincidental defects, in which case it's simply pulmonary arterial hypertension and an incidental defect, such as a small atrial septal defect. And finally in Group 4 are patients who've undergone defect correction, and many years later, potentially, can develop pulmonary hypertension. For patients with shunts, repaired and un-repaired, they need to be screened at an ACHD center for the development of pulmonary arterial hypertension. And then, finally, recommendation-wise, postoperative PH screening should occur in subgroup 4, patients who have undergone defect correction who don't have pulmonary arterial hypertension at the time of their surgical repair. But this workup should include clinical echocardiographic and ECG screening during follow-up visits starting at three to six months after the defect correction, and then ideally yearly follow-up afterwards and long-term cardiovascular clinics.

So let's briefly discuss the manifestations and common physical exam findings in patients with pulmonary arterial hypertension. So here is a patient with a milder form of pulmonary arterial hypertension. This patient will likely have an elevated jugular venous pressure. It's important to look at the JVP and compare it to the carotid pulse. In most of these patients, you will see an A and a B wave. You'll also be

able to push on the liver and assess for a hepatojugular reflux. Occasionally, there can be no decline in the jugular venous pressure with inspiration or a Kussmaul sign, suggesting some element of either constriction or restriction. They can have relatively clear lung fields if they have no concomitant lung disease. On auscultation, you'll hear an increased pulmonary closure sound, oftentimes a narrow splitting of the second heart sound. They will have both pulmonary regurgitation and/or tricuspid regurgitation, and often a right-sided S4, which is heard just below the right clavicle. And by palpation, they can have a prominent P2 and a right ventricular lift. And then depending on the degree of pulmonary hypertension, they may have some degree of cyanosis.

So here is the progression of pulmonary arterial hypertension related to congenital heart disease to Eisenmenger syndrome. You start with a left-to-right shunt. You get increased pulmonary blood flow and pressure. This leads to pulmonary vascular remodeling, an increase in the pulmonary vascular resistance, and, eventually, when that PA pressure exceeds the pressure in the systemic bed, you can reverse the shunt. And now you're shunting right to left. You get cyanosis and Eisenmenger syndrome related to the cyanotic complications. So in Eisenmenger syndrome, the physical exam becomes more extreme. For those patients, they're almost always going to have an elevated jugular venous pressure. They may have headaches, seizure, stroke related to their increased thrombotic potential, related to their congeal heart disease and polycythemia. They, again, are going to have often clear lung fields, a very increased P2, sometimes a single S2 only as heard, just the P2 is heard, a high-pitched pulmonary regurgitation, TR murmurs again heard. Right-sided S4 is very common. They're going to have, very commonly, a palpable P2 sound and a right ventricular lift. These patients oftentimes are going to be tachycardic as well at baseline. They are going to be cyanosed, but in addition, they'll have clubbing. Their nail bed angle will change and they'll have large, clubbed fingers and sometimes toes. If you see a patient and they have a right hand that is not cyanosed but they have a left hand and both feet or just both feet, that is called differential cyanosis. Very classic for patent ductus arteriosus with development of Eisenmenger syndrome. They'll have hepatomegaly, often a pulsatile liver. They're prone towards gallstones and development of ascites. They also develop kind of this patchiness on their skin we call livedo reticularis. They're at increased risk for bleeding. They have complications such as leg cramps, abdominal cramps related to hyperviscosity, and peripheral edema, and also a predilection to gout. So what are the unique considerations in the congenital heart disease-related pulmonary hypertension patient? First of all, we want to ask the question is there too much or too little pulmonary blood flow? We don't often think about this, but in a congenital patient, there is often an important balance between ensuring adequate blood flow and preventing over circulation. So in the infant, oftentimes, we'll band the pulmonary arteries to reduce the risk for over circulation. And likewise, if they're undercirculated, we'll create a shunt so that patient can make it through their early years and allow their lungs to develop. If there's a defect present, is it correctable? If the defect is correctable, what's the best method in which to correct it? For some patients, a defect can be corrected through a surgical approach only, and in other patients we have transcatheter options. And I will say that defects that we thought were only correctable through surgical means we are now approaching percutaneously in the little over two decades that I've been practicing. We have advanced medical therapies, but have they been adequately tested? And do they work in some of the patients with congenital heart disease?

So let's talk about the basic lesion types in adult congenital heart disease. So there are many different lesions present in pulmonary hypertension and congenital heart disease, but very few have been included in prospective studies. On this slide, you can see there are different defects. And the ones in red here are the ones that predisposed towards pulmonary hypertension. In congenital heart disease, we break down lesions into simple, moderate, and complex lesions. In each of these various lesions, we have specific disorders that are more prone to the development of pulmonary hypertension, but it's important to recognize, the studies that have been done have focused on two main groups, the Eisenmenger group here, and these are in the complex group, and then the simple shunt lesions and slightly more complicated primum defects. But we have a lot of defects here that have not yet been well studied with advanced medical therapies. And I think that's a real gap in our current knowledge.

So shunt lesions are the most common causes of pulmonary hypertension. Patients with repaired and un-repaired defects can develop pulmonary hypertension. Up to 10% of those who do not have defect correction will develop pulmonary hypertension. And as many as 2 to 5% of patients with corrected lesions will develop pulmonary hypertension. These patients will have often subtle symptoms, increasing dyspnea, declining exercise capacity, and you'll see a progressive increase in PVR if you perform invasive assessment. 25 to 50% of congenital heart disease-related pulmonary hypertension patients, if they're not treated, can progress to Eisenmenger syndrome. So again, earlier recognition and treatment appears to be helpful as in other forms of pulmonary hypertension.

So again, breaking down the subgroups. in Group 1, you have Eisenmenger syndrome. These are cyanotic patients. They get secondary erythrocytosis. They get multisystemic disorders. In Group 2, you have the shunt lesions. There are correctable shunt lesions who have pulmonary hypertension. Oftentimes, these are people that are just over circulated. If you correct the lesion and/or treat their pulmonary hypertension medically, they will improve. There are also patients that are non-correctable. These patients have moderate to large defects. They haven't quite reached Eisenmenger syndrome, but they may be heading in that direction. These patients are not cyanotic at rest, but if you ambulate them, sometimes they'll develop cyanosis. So these are a little bit more challenging. When the

Eisenmenger syndrome patient walks through your office door, it's pretty obvious. They're cyanotic, they're clubbed. It doesn't take a rocket scientist to know that they have pulmonary hypertension. But a patient who has milder disease, you may only see them get cyanotic when you actually push them, exercise-wise. In Group 3, you have patients with pulmonary arterial hypertension and small coincidental shunts. These patients, in general, are not going to get better with defect closure. And, often, defect closure is contraindicated. They may be using that defect as a pop-off valve for their right side. So if they get sick or they exercise, they may shunt more, but it's a compensatory mechanism to increase their cardiac output at the expense of dropping their saturation. In Group 4 are the patients after defect correction. This pulmonary arterial hypertension can develop immediately or many years potentially after their correction. And it can occur in the absence of significant postoperative hemodynamic lesions. Now, the first thing you want to do whenever you assess one of these patients is make sure they don't have postoperative hemodynamic lesions, because, again, this may be somebody that's correctable/reversible in that case, but we now know that this is a very aggressive phenotype that needs to be rapidly identified and rapidly treated.

Morbidity and mortality are higher in patients who have congenital heart disease-related pulmonary hypertension compared to patients without. So this is data from the province of Quebec, almost 40,000 patients with congenital heart disease. A little over 2,000, a diagnosis of PH. So that meant that about 1 in 17 patients had congenital heart disease-related pulmonary arterial hypertension. In those patients, the mortality was twofold higher. Their morbidity, hospitalizations was threefold higher, and when they were hospitalized, their hospital days were threefold higher. So this is a sick group of patients that needs very close medical attention. Imaging in the ACHD-PAH Patient, What the PH-CHD Specialty Center Offers. So imaging of the congenital heart disease patient is quite challenging. You identify what your goal should be. Ideally, you should determine the original and current or post-op anatomic relationships. First step often in these patients is to get the old medical record to know exactly what was done for the patient. If those records are not available, try to get as much from clinical notes and simple studies. But if you don't have that information, imaging can be very important. You want to assess for residual lesions, things such as shunts. We've talked about ASDs, VSDs, PDAs, collateral vessels. You want to look for valvular heart disease, either stenosis or regurgitation. You want to look for vascular obstructions in pulmonary arteries and veins, right and left ventricular outflow tracts. You want to measure differential blood flow to the two lungs. You want to assess for the ventricular size, thickness, and function, not only for the subpulmonic chamber, but also for the systemic chamber. And you want to appraise myocardial injury. We now know that a myocardial scar is a very important predictor of long-term clinical outcome, particularly the risk for arrhythmia and sudden death.

Now, there are different modalities available. Echocardiography really is, I think, our often first step in the toolbox. It's non-invasive, there's no radiation, it's readily available, we don't need to sedate the patient. We can visualize the intracardiac anatomy beautifully, and it provides good temporal resolution. Unfortunately, not every patient is well assessed with this modality. Some patients have lung disease or they're obese and they have poor acoustic windows. Also, a lot of scar tissue can impact the ability to visualize the cardiac structures. There's also poor visualization of the extracardiac anatomy. Structures such as the aorta or the descending portion of the aorta can be often limited in its assessment. Nuclear perfusion imaging can allow us to quantify pulmonary blood flow, but it really does provide very limited information and does subject the patient to radiation. CT scanning is noninvasive and has excellent spatial resolution, but again, there's radiation, there's a need for contrast dye which can increase the risk for the development of renal dysfunction. And then there's limited intracardiac anatomy and there's no hemodynamic data oftentimes for these patients, or the hemodynamic data is not as carefully assessed as it is with CMR. So CMR is noninvasive. There's no radiation. It can assess the intra- and extracardiac anatomy, ventricular function, myocardial viability, human dynamic data, and lung perfusion. It sounds like the perfect modality. The problem is it's expensive, it's not readily available, it's time consuming, you get metallic artifact. And some devices, pacemakers, ICDs, are still contraindicated to place into the scanner. Often, there's abandoned leads, pacemaker leads and ICD leads. Those are still a contraindication. Angiography can be performed. This provides excellent visualization of the extracardiac anatomy. You can also get hemodynamics and it facilitates intervention, but this is the most invasive. There's a need for sedation in many of these patients, radiation, and there's poor visualization of the intracardiac anatomy.

So here's just simple echocardiography. This is a very complex patient with congenital heart disease. You can see some of the limitations here. You get a lot of artifact in some of these images, but you do have the ability to use Doppler and assess pulmonary pressures. You can assess systemic chambers and gradients across valves. So it can be very useful from a hemodynamic standpoint. But again, catheterization in some of these patients is the most accurate pressure measures. Here's an example of a nuclear perfusion scan. This is a very helpful study when we're looking for thromboembolic disease, but it can also allow us to quantify the blood flow to the lung segments. And this can be helpful particularly in patients with segmental pulmonary hypertension and peripheral pulmonary stenosis where we look at variable lung perfusion. CMRI provides the most accurate way, or CT is another way to do this. The pictures are beautiful, but again, it requires, an MRI requires, usually, about an hour for a patient. There's a lot of breath holding. It can be quite the challenge for a patient to do this. And again, availability is an issue. CT is much quicker, but it requires radiation and contrast dye. Here is a pulmonary angiogram for a patient with very distorted peripheral pulmonary circulation here. It can provide very nice data, but

it is invasive. There can be complications related to this, but it does allow us to get position in to perform interventions.

Management of the CHD-PAH patient, what are the General Considerations? So all patients with pulmonary arterial hypertension should receive lifelong tertiary care in congenital heart disease patients. Patients and their families should be made aware of the major risks of pregnancy. The mortality for some of these patients, like those with Eisenmenger syndrome, can be as high as one in three, and there's considerable morbidity for the patient and for the fetus. Effective contraception should be provided to patients with complex congenital heart disease and pulmonary hypertension. You want to encourage regular exercise and maintenance of an active lifestyle. Periodic six-minute walk distance or a CPET are recommended to provide prognostic information and to guide management. Immunization against influenza, COVID-19, and pneumococcus is important. And it's also important to provide psychosocial supports for these patients. Now, this is a complex algorithm, but I want to mention that expert referral should be at the top of this. So, ideally, a patient with congeal heart disease-related pulmonary hypertension or Eisenmenger syndrome should be managed in a specialty center. If they have Eisenmenger syndrome, a structural intervention is contraindicated and you should assess functional status and initiate medical therapy if they have any symptoms. If they have a systemic-to-pulmonary shunt, if their PVR is normal or slightly increased, these defects can be safely repaired. If they have a moderately elevated pulmonary vascular resistance, this ideally needs to be managed in a super specialized center because the decision-making here can be very challenging. If their PBR is severely elevated, generally we say that repair contraindicated. We want to treat them medically and we want to reassess them. Some of these patients may respond to medical therapies and become correctable at a later stage. For patients with small defects, we generally, again, do not recommend intervention. We want to assess their functional class, or we want to treat them if they have any symptoms.

Once we've established that a patient needs to be treated, we want to assess their function class. We generally become more aggressive for patients with more advanced disease. For Eisenmenger syndrome, the recommendations are still a first-line endothelial receptor antagonist, and then stepped-up therapy should their symptoms progress. For patients with a repaired or un-repaired shunt, we often start with first-line combination medical therapies and then step these up, again, depending on clinical deterioration. If they have worsened right heart failure or decreased functional capacity, adecrease in their six-minute walk distance or a lack of increase in that, an increased anti-proBNP, or worsening RV function, these are all indications to become more aggressive in treatment.

Organ transplantation requires extensive discussion and collaboration between many specialists. Transplant options for advanced complex congenital heart disease and pulmonary hypertension are much more complicated. Some of these patients will require lung transplantation. Some of these patients will require heart-lung transplantation. For some of these patients, we may decide to do a lung transplant and a cardiac defect repair. In general, if we have a patient who can be done with less than 60 minutes of pump time, we'll try to repair the defect and then do a lung transplant. But if the repair is more involved, often we'll just do a heart-lung transplant. Congenital heart disease still accounts for a large population of heart-lung transplantation, over a third of the data. This is back from 2011, and it's only growing since. Support options are becoming available as bridges to transplantation. And I think that's a very exciting area to be in at this point.

The Importance of Referring the PAH-ACHD Patient to an Accredited Specialty Center. So why is accreditation of ACHD programs important? First of all, it ensures a minimum standard of care for a very complicated patient population. We want a fluid process with continuous feedback. It helps identify various specialists and institutions and ensures their participation in care provision. This makes sure that patients that have complex issues are seen by physicians familiar with their problems. It helps identify gaps in programs and opportunities to improve provision of care. It helps empower patients to select, participate in, and influence their own care. There are currently 47 ACHA-ACHD accredited centers in 28 different states in a combination of both adult and pediatric hospitals. I've had the great pleasure, actually, of working on this committee and I can tell you it's a very important process that the ACHA is involved in to ensure that complex patients get appropriate care.

There are a variety of criteria that are used, 20 different categories. You can see pulmonary arterial hypertension is one of those categories. These patients have unique characteristics that need to be looked at and managed, not only with regard to heart issues. You can see all the variety of specialists that are often involved in the care of an ACHD patient. There's a plethora of innovative ways that programs have met patient needs and served the community. The steering committee meets regularly, which again, I've had the opportunity to participate in. It's a very important process that we're involved in. And providers at centers who may not be able to become accredited can still use this criteria to elevate their level of care at their individual institutions. And also, it helps them to identify where to send patients when they need advanced specialty care.

In summary, while Group 1 PH or PAH has been the most studied form of pulmonary hypertension with the greatest number of approved medications, some subgroups within this group and other PH groups have received less attention. It's important for all healthcare providers at both the community and specialty center levels to be able to recognize these sub-classifications of pulmonary hypertension. While the diagnosis of all types of PH follows a similar path, each form of the disease may require added attention to certain diagnostic modalities. So what are the takeaways from this talk? For connective tissue disease patients with unexplained dyspnea, annual

screening is mandated, particularly for systemic sclerosis, to detect the presence of PAH. The DETECT protocol is a useful tool for screening CTD-PAH patients. Knowing when a patient must be referred to a PH specialty center is critical for the timely diagnosis and initiation of treatment for all PH patients. Treatment options within Group 1 subcategory of CTD-PAH may benefit from approved Group 1 PH medications and strategies as outlined in current guidelines. Takeaways from congenital heart disease-related pulmonary hypertension. Congenital heart disease-related pulmonary arterial hypertension may present at various ages based on severity of the lesions at birth and the type and age at the time of repair. Specific diagnosis of the underlying cause of CHD-PAH and consideration of medical, surgical, or transcatheter intervention should occur at an accredited CHD-PAH center of excellence. Timely referral from the community level to the specialty center is extremely important in this group of patients. Other than for corrected shunts and Eisenmenger syndrome, the benefit of Group 1 medications in CHD-PAH remains uncertain. For my final thoughts, PH comes in many forms. It's influenced by the presence of comorbid conditions and does not have effective treatment in all cases. Each patient at risk for PH requires regular and complete risk evaluation. Community providers are the front line of PH detection and must work in concert with PH specialty centers to begin the diagnostic process, and later, cooperate in patient management. It is critical in all cases where PH is suspected that timely referral from the community level to the PH specialty center occurs, accompanied by high-quality preliminary screening and diagnostic data collection. Cooperative management between PH specialty centers and community providers is the best way to optimize patient outcomes.

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