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Sleuthing Unexplained Dyspnea: Diagnostic Tools

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Dr. Preston:
Hello, my name is Ioana Preston and I'm an associate professor of medicine at Tufts University School of Medicine in Boston. And I direct the Pulmonary Hypertension Center at Tufts Medical Center. Thank you for joining us today. Our topic for today is "Sleuthing Unexplained Dyspnea: Diagnostic Tools."

So, there are many causes of dyspnea, many possibilities, so always this symptom needs to be taken seriously. Now, if we visit the causes of dyspnea, let's look, acute dyspnea could be associated with almost any medical condition it seems, especially in conditions that affect the heart or the lungs, but not always. We know about asthma, lung infections, allergic reactions, collapsed lung and so on, as well as heart failure, pulmonary edema, and pulmonary hypertension, of course, we shouldn't forget systemic disorders such as anemia or hypo and hyperthyroidism. But if you look at this table, the last conditions that cause dyspnea that are highlighted in blue can be associated with various forms of pulmonary hypertension. So pulmonary hypertension is in fact a common cause of unexplained dyspnea.

So, let's see, can we measure how bad it is? Breathlessness is a predominant symptom among patients with cardiopulmonary disease and has been shown to have a strong correlation with anxiety and depression with health-related quality of life and causes activity limitations and associated with increased mortality. There is a score that semi-quantifies dyspnea, it's called Dyspnea-12 or D-12. It's a short instrument that assesses the breathlessness and its severity, and it taps its physical and emotional components. The D-12 has acceptable reliability and validity for using patients with PAH and it correlates with WHO functional class as it is shown in the graph below. So, on the right-hand side of the slide, the 12 questions of the D-12 questionnaire are highlighted.

One of the key points that I would like you to take is always suspect it could be pulmonary hypertension, but never assume it is pulmonary hypertension. So, this has to be investigated thoroughly. So, you can have pulmonary artery systolic pressure by doppler on the echo estimated at 51 millimeters of mercury or PA systolic pressure and other components can be measured by the right heart catheterization, and let's assume it was found to be 68 millimeters of mercury. So, if we have a systolic pressure measured invasively or estimated non-invasively, what's the type of pulmonary hypertension? So now we have to think and go into the differential diagnosis. Is it a heart condition such as left heart failure, valvular disease? And those conditions are associated with high left-sided feeling pressures or wedge pressure. Or is it a pulmonary condition such as advanced COPD, sleep apnea, pulmonary embolism? Or it is a precapillary pulmonary vascular disease or PAH group 1. So, the point is if you have only the systolic pressures estimated by echo, first of all, they may not be accurate, and second, you cannot find what type of pulmonary hypertension you are dealing with. So, PH has a very broad differential diagnosis, never assume it's always PAH if you find an abnormal echo.

For example, when the patient has an underlying disease or you expect them to be at risk for PAH, you must test for it. So, patients with various connective tissue disorders, specially systemic sclerosis, but also lupus and other connective tissue disorders such as mixed connective tissue disease or a combination of those, they are at risk for PAH. In addition, patients with advanced lung disease, such as pulmonary fibrosis or sleep apnea, or a combination of those are at risk for pulmonary hypertension that is not group 1 but is group 3. In addition, patients who have had pulmonary embolism in the past, and not only those with a prior PE, those who are at risk for chronic thromboembolic disease, they have pulmonary hypertension group 4. And other are the disorders such as schistosoma or sarcoidosis are known to be associated with pulmonary hypertension, and these are part of group five pulmonary hypertension.

So if unexplained dyspnea is not fully explored, what are the implications, especially if it is pulmonary hypertension? So let's think about common pitfalls in PAH patient care. It is easy to dismiss dyspnea as something else, and many of my patients were referred to me after being told that they're anxious and depressed and that's why they feel short of breath, especially the young ones. So there is lack of screening of at risk populations. We have to recognize these at risk patients who have underlying conditions such as scleroderma or mixed connective tissue disease, or those who have a familial history of PAH.

Another pitfall that is very common is relying on only systolic PA pressure estimates of measurements from the echocardiogram imaging, instead of obtaining the evidence for structural signs of RV dysfunction in combination with the right heart catheterization. So, a common pitfall is to focus on the systemic pressures but not to look at the RV function on echo. The most common and the most dangerous I should say pitfall is not confirming the diagnosis with the right heart catheterization because certain medications are indicated in certain types of PH and are not indicated in other types. So, we really need to sort out what the group of pulmonary hypertension we're dealing with.

And the last one that comes to my mind is lack of risk assessment leading to delay in correct therapy and escalation. And we know that for the past 20 years, the average time from an onset of symptom to diagnosis of PAH is over two years. So, we have to reduce that and be proactive in working it out. And why is that? Two years is a long time. Because PAH is a progressive structural disease. And if you look at this very famous diagram, the top graph shows pathology of an early pulmonary vessel in early PAH phase, and then in the middle as more symptomatic, more severe remodeling. And in the last phase, actually, there are lungs patients who underwent lung transplant and shows very severe pulmonary vasculopathy. And these changes are accompanied by hemodynamic effects, where in the phasing of an increased vascular resistance in the pulmonary vasculature, the PA pressure increases to overcome this resistance. And in the beginning cardiac output, the force with which the right ventricle pushes blood through the lungs is maintained by the RV being hypertrophied, but in time it decompensates and cardiac output drops, but also the pulmonary artery pressure drops because the RV cannot mount that much of a pressure and patients develop right heart failure and this is their most common cause of death.

So, what factors influence time to definitive PAH diagnosis? Some of the factors that we should take into consideration are time between patient reported onset of symptoms and the definitive PAH diagnosis. If this is consistently delayed then we have to work on that. The DELAY study out of Australia retrospectively examined factors contributing to diagnostic delays and the time for definitive PAH diagnosis. So, in 32 patients and the majority were females, they were reporting exertional dyspnea, the mean time from symptom onset to diagnosis was 47 months on an average. Patients reported to over five general practitioner visits and an average of three specialists were reviewed before being seen at the PH Center. So, there was a lot of back and forth for these patients. So that's where we have to get better. Factors significantly associated with delay diagnosis, advanced age, number of GP visits, the heart rate, and the systolic blood pressure, which is very interesting. And this diagram shows the length of the journey of our patients from onset of symptoms to the final diagnosis.

So how can we make it easier for our general practitioners and community physicians and healthcare providers to be aware and develop that index of suspicion for PAH? We will talk about the roles of the community physician and the PH Center in reaching the correct diagnosis and promoting referral in a timely manner. So, let's build a clinical suspicion for PAH. The symptoms are very non-specific. They're short of breath, usually with exertion. They have weakness. Sometimes they have chest pain and lightheadedness but only when the disease is very advanced. And less frequent, they have a cough. In more advanced disease, one may also observe signs of right heart side failure, the swelling of the legs, ascites, abdominal distension. Few patients have hemoptysis, and very rare, they have the hoarseness or Ortner's syndrome as well as arrhythmias. The physical findings are also not very overt. You have to look for them. In the early stages, there's only a loud second sound of the heart. So a P2 component that's slightly louder, and that's it. Sometimes in more advanced, you have a right ventricular lift, jugular venous distension, hepatojugular reflux, ascites, hepatomegaly, sometimes splenomegaly, definitely edema in more advanced condition and murmurs of tricuspid regurgitation. In some patients, you can hear an S3 gallop that's right-sided. So if they don't have overt signs of right heart failure, the physical exam is very subtle so you have to think about pulmonary hypertension. when you put the stethoscope.

In the current era, what clinical data are needed for assessment of a patient with suspected PAH? So, let's look at the battery of tests

that patients suspected for PAH need to undergo. On the left-hand side, pulmonary function tests, biochemical markers, and clinical assessment, as well as the non-invasive exercise tests, such as 6-minute walk distance, and the echocardiographic evaluation. All these can and should be done at the community level. The primary care practitioner or the primary rheumatologist, or the primary pulmonologist or cardiologist who suspects pulmonary hypertension, all these non-invasive tests should be done initially. Now, the more complex tests that require more expertise, these are the V/Q scan and the hemodynamic evaluations, the right heart catheterization with or without exercise, these can be completed at the PH Center. So, where the initial testing, including all non-invasive tests can be performed very well close to the patient's home at their physicians. The finish of the workup and confirmation of the PAH diagnosis should be done at the PH Specialty Center. That's how a strong collaboration between the community healthcare providers and PH Center can be developed to help these patients be diagnosed early and properly.
So, what information should we get from PFTs? Always obtain full PFTs in the PAH workup, not only spirometry, we need lung volumes and DLco because in certain diseases, DLco is associated with the presence of pulmonary hypertension and I'm talking about patients with scleroderma. The presence of markedly abnormal PFTs with severe obstruction and/or restriction then prompts us to think about pulmonary hypertension associated with lung disorders with hypoxemia, and this is a group 3 type of pulmonary hypertension which has a different treatment.

So, the only serologic biomarker for pulmonary hypertension is BNP or it's promolecule NT-proBNP, and they're very well established in the PAH world. They are sign that the right ventricle is overworked and overstretched, and it has been associated with prognosis, and it's part of the parameters that we assess the risk scores. So, it's a very simple test. A lot of hospitals use it as a point of care. And we strongly recommend in the workup of patients with pulmonary hypertension. The guidelines that show the importance of NT-proBNP or BNP are showed below and highlight the importance and its role in assessing the prognosis of these patients.

Let's talk about echocardiography. It's not definitive for PAH, but essential to determine the need for referral to PH Center. It's the best screening tool. From an echocardiogram, one of the most important factors that we can derive is the right ventricular function and size. And that gives us a lot of information about the possibility of the presence of pulmonary hypertension but also the severity. Because the right ventricle response to increased resistance in time by becoming thicker or hypertrophied, and in the end, the thickness is lost because the RV starts dilating. So a dilated RV is a sign of severe disease. It's also very important to look in perspective of the left-sided chambers and understand whether the patient has significant left-sided disease, whether it's systolic/diastolic dysfunction, left atrium enlargement or valvular disease which could explain the abnormalities seen on the right ventricle.

Using echo to uncover PH related changes in heart structure. You absolutely need good images of the right heart. The most common opportunity to spot a new PAH patient is either in the echo review or in the echo report. Emphasis of echocardiogram should not be on pressures. Pressures are just estimates and can widely vary from the actual pressures, but on structural changes associated with the right heart. And that can give you very important information on the possibility of presence of PAH and also severity. So, if you look at a multitude of parameters that the echocardiogram can give you, there are several that are very important, the right ventricular size, the right atrial size, the interventricular septal function, the IVC diameter fluctuations with respiratory cycle, and then the diameter of the pulmonary artery. Now the last two are a little bit more difficult to obtain, but the interventricular septum function for example, is easy to spot. And to see this, if there's a D shape of the septum bowing towards the left ventricle which is an abnormality or not. Also, the right ventricular size and function is very crucial to obtain.

Now, there are key considerations. The three parameters put together can increase your suspicion for pulmonary hypertension. And these three parameters are peak tricuspid regurgitation velocity, the presence of other echo signs suggestive of PAH that I mentioned, and it gives you the probability of PH. So, if the tricuspid velocity is 2.8 or less and there are no other signs, your suspicion will probably be low. If the tricuspid regurgitation velocity is in between 2.9 and 3.4 but there are no other signs, the risk is intermediate, probability is intermediate. If it's a normal velocity, but there are other signs, again, it's intermediate. And if the TR velocity is over 3.4, regardless of other signs on the echo, your suspicion should be high.

So, the echo signs suggesting PH can be used to assess the probability of PH in addition to TR velocity measurement. So, let's look at the ventricles. The right ventricle/left ventricle basal diameter ratio over one, flattening of the interventricular septum, those are two signs that should increase your suspicion. Let's look at the pulmonary artery. The right ventricular out outflow Doppler acceleration time and/or mid-systolic notching, or the early diastolic pulmonary regurgitation velocity over 2.2, as well as pulmonary artery diameter over 25 millimeters, should increase suspicion. And looking at inferior vena cava and right atrium, the IVC diameter over 21 millimeters with decreased inspiratory collapse, or right atrial area at end-systole of more than 18 centimeter square. So those are other parameters that should be taken into consideration when you assess this clinical, the echo suspicion for PH.

Using echocardiography to get a handle on heart structure and function in PH. Echocardiogram, the TRjet gives only an estimate of PA pressures, and it's reliable when the images of the echocardiogram are well performed. The quality of the TRjet and the expertise of

echocardiography reader matters. Take a look at a good TRjet that can be measured versus a moderate TRjet that doesn't have a nice peak and a poor TRjet where you actually cannot even estimate the PA pressure, and that's why we call it an estimation of PA pressure because it can vary depending on the window and on the skills of the echocardiographer.
But the echo is not all about pressures. Again, the pressure is of the least accurate parameter that the echo can give you. The function and the size of the chambers I think it's the most important, and this nice example shows the four-chamber view where the atria are upside down, they're down, and then the ventricles are up and it can show a normal versus abnormal picture. Now, there are differences between precapillary versus post-capillary echocardiogram. In post-capillary echocardiogram, you can see abnormalities in the left ventricle and even if you don't see the left ventricle, most commonly the left atrium size is abnormal. So, if you have a very enlarged left atrium but also abnormalities on the right, that suggests that probably the PAH is due to left heart disease or group 2.

The other parameters that may be used on the parasternal short axis view is the eccentricity index. And it's the change in diameter between the long axis and the short axis as you can see the diagram, it's the ratio. So that tells you that the interventricular septum is displaced towards the right. And then in the 4 chamber view like we showed before, the RV/LV ratio over one or the right atria over 18 centimeters square suggests the presence of pulmonary hypertension.

The Tissue Doppler assessments are also important because they give you an idea of the right ventricular function. They are very simple and reproducible and it can pick up regional wall abnormalities or global wall function or motion. The fractional area of change is one relatively newer parameter that measures how much it changes between systole and diastole in the right ventricle and indicates as it says the right ventricular function. There is a high inter-observer variability unfortunately, but it may be a good test to follow up within same patient and if you have an echocardiography lab that's dedicated for PH research, or they have experience in PH.

Imaging modalities, newer tools for PAH diagnosis at the PH Center. Let's talk about a patient who underwent the initial screening at the family physician or their primary care healthcare provider with a high index of suspicion for pulmonary hypertension. There are several new diagnostic modalities that may be available at a PH Center that we can review. So, we all use V/Q scan to rule out or suspect pulmonary hypertension secondary to chronic thromboembolism, but there is a V/Q single photon emission or SPECT that shows a pulmonary perfusion that measures pulmonary perfusion. There's also dual-energy CT or DECT for pulmonary perfusion. Another way to assess lung perfusion is with a three-dimensional dynamic contrast-enhanced magnetic resonance. So, we know that the typical MRI doesn't pick up lung abnormalities very well, but this modality that is focused on measuring the lung perfusion has been developed and maybe very useful in the future. Now for ventilation, there is functional magnetic resonance image and it can compliment the ventilation part of a V/Q scan information. Now cardiac MRI is crucial because it can assess the right ventricular function and size more accurately probably than the echocardiogram. It can pick up subclinical dysfunction of the right ventricle. It can do parametric mapping. It can measure right ventricular strain, which is one of the novel parameters that have been developed for pulmonary hypertension. And it can do pulmonary artery for dimensional flow imaging. The cardiac MRI is very important also because it can pick congenital heart defects that can cause pulmonary hypertension, and on occasion, we diagnose congenital heart disease even in adults. There is intravascular ultrasound and optical coherence tomography for PAH. There are also wearable technologies that can measure not necessarily within the diagnosis of PAH but can assess the severity of impairment caused by PAH. And very recently, there's artificial intelligence tools that are being tested to be used in the diagnosis in early diagnosis of PA.

So, this table, I know it is quite busy, but it highlights the relative strengths and weaknesses of imaging modalities in the context of pulmonary hypertension. And if we look at chest radiography and V/Q scan, which are the more commonly used tools and are available everywhere, then we can look at the characteristics of SPECT V/Q, single-energy CT angiography, dual-energy CT angiography, as well as MRI. And lastly, we haven't talked about, but pulmonary angiography, which is an invasive test, but it is essential if you suspect or you found chronic thromboembolism. So, it's a very important tool and that should be done at the PH Center for sure, because you require an invasive radiologist or cardiologist with a trained eye.
V/Q scans and computer tomographic approaches to PAH diagnosis, finding chronic thromboembolic pulmonary hypertension, or CTEPH. The first key point that I would like to address is that always, always, always rule out CTEPH because it's very hard to diagnose and it has a slightly different treatment approach. So, it's very important to always rule out CTEPH, and V/Q scan is currently the only screening tool to screen for the presence of chronic clots. This is an example of a proximal chronic clot from a patient who underwent thromboendarterectomy or pulmonary endarterectomy, which is a surgical, very complex surgical procedure that has a chance to cure the disease, so that's why it's very important to rule out CTEPH. If you can look at the lung perfusion scan, it has a sensitivity of over 95% and the specificity of over 95% because it can pick up not only proximal clots, but more importantly, more distal clots.

V/Q scintigraphy and SPECT, they're a little more detailed tests. The SPECT is not quite available everywhere but it does give you a better picture of the defects. So, SPECT scan is an imaging test that shows how blood flows to tissues and organs, and it may be used to help diagnose several conditions such as seizure disorder, stroke, but also pulmonary hypertension. The top images show a planar ventilation and perfusion image, and it shows multiple segmental and sub-segmental defects. You can see the sharp demarcation

between perfused and non-perfused areas. And this is a picture of a CTEPH patient so this type of abnormalities are very suggestive of CTEPH. Now the lower images are SPECT perfusion images, which provide a more detailed analysis of perfusion defects in a coronal plane. So you can see the sharpness of the defect much better with the SPECT.

Now let's talk a little bit about CTA. Advanced CTA of the lung has sensitivity and specificity regarding CTEPH related to changes of 92 to 100% and 95 to 97% respectively at the main, lobar, and segmental pulmonary artery levels, but that's it. Because a conventional CTA does not provide functional information concerning pulmonary perfusion so it does not tell you anything about how the blood flows, or if it flows into that area that you may or may not see a clot. And its sensitivity is 64 to 70% for depiction of sub-segmental chronic thromboembolism compared to selective pulmonary angiography. So, the sensitivity of a CTA drops dramatically as the clots are smaller and in the more peripheral pulmonary artery branches. Now it can show direct vascular signs of CTEPH such as complete obstruction, partial obstruction, bands, or webs, but you have to have a trained eye to pick them up and look at the very thin cuts in order to pick up webs and bands. It also can show you the size of the right ventricle, right? And that would be an indirect sign that there may be chronic clots. It also can show in large main pulmonary arteries and also a mosaic lung pattern, those are all signs of pulmonary hypertension.

So again, a CT scan is the diagnosis of choice for acute P, V/Q is for chronic P. These are two examples of acute Ps in the operating room, a fresh clot that is dark, that is dark red and very fryable. And then the CT scan that shows the main pulmonary arteries obstructed almost in its entirely, especially look at the left lower lobe is completely blocked with an acute clot, and very poor perfusion throughout both lungs. So, this is a massive, massive pulmonary embolism and we don't know clinically the importance of it, but looking at the fresh clot in the picture, one might suspects that this was a fatal event.

The angiography confirms CTEPH. Again, it has to be done by a more experienced radiologist because the amount of contrast may be changed if they suspect high pressures and also to look carefully and in different angles and different planes where is an obstruction, whether it's acute or complete or partial. And that will map out whether, and how a surgeon can address this type of disease surgically. There are pouches there's absent branches and no perfusion in their bands, but these are subtle signs and you have to look for them.
Another modern imaging, dual-energy computed tomography angiography, or DECT. It enables a combined functional and morphological analysis of the lung. So, this is a very interesting, and hopefully a very useful imaging modality in the near future. Now, attenuation properties of iodine occur at two different photon energies, and this dual energy, and that's why it's called dual energy technique can generate pulmonary blood volume maps correlated to pulmonary perfusion. In comparison to a conventional CT, no additional intravenous iodine contrast is needed. The functional image processing is simply added. It's a software upgrade if you would. DECT is not associated with increased radiation levels so not more IV dye, not more radiation, but it's more expensive, and because there is another software added. Study examining correlation between DECT and single photon emission computer tomography or SPECT in 51 patients found that DECT with iodine maps has a sensitivity of 96%, a specificity of 76% for CTEPH. So, it's very good tool that warrants further investigation whether it can be used in clinical practice.

This is an example of DECT imaging of the lung where it shows arterial stenosis. The left-hand side are the conventional imaging, but on the right-hand side, it shows the functional aspect of DECT where there are perfusion defects.

Cardiac MRI as a tool for diagnosis in pulmonary hypertension. So cardiac and lung perfusion MRIs. MRI can provide anatomical and functional assessment of both pulmonary circulation in the heart with a major advantage of not using ionized radiation. Diagnostic for congenital abnormalities has a strong potential. With video techniques, it gives robust qualitative and quantitative assessment of the right ventricle but also of all the other chambers. And it can measure the stroke volume, not only of the left, but also of the right ventricle, and flow cardiac index. The curvature of the left ventricular septal wall is a classic sign to depict elevated RV systolic pressures. Now, on the other hand, the phase-contrast MRI can also quantify blood flow and peak velocity, not only in the main pulmonary artery but also in all of the vessels within the chest. So, it can give a better estimation of the regional areas where the flow decreases significantly. The sequences assess differential blood flow to the right and the left lung and seem to reflect PA pressure measurements obtained by invasive right heart catheterization. Now cardiac MRI, although it gives beautiful pictures and also functional aspects of the heart, both right and the left, it's not as of today the main diagnostic tool to confirm pulmonary arterial hypertension. The right heart catheterization is still the diagnostic tool.

So, is there a role for cardiac MRI in pulmonary hypertension? Well, the pros are it's non-invasive. It aids in the diagnosis and prognosis of pulmonary hypertension patients. It gives you a very accurate function of the RV and it can pick up potential congenital abnormalities that again, as we were talking a little earlier, can be diagnosed in the adulthood. Now, the cons are they're difficult for patients who are receiving pump therapy for PH for example. They're difficult for patients who are claustrophobic, and it's not only a five-minute test. For a cardiac MRI, patients can stay in the tunnel for quite a long time, and it can be unnerving.

Magnetic resonance angiograms and perfusion images. So, let's talk about these modalities. In IPAH, you can find with these

techniques, vessel tortuosity, and patchy perfusion. Now, this is different from pulmonary hypertension from chronic lung disease, such as COPD, where you have typical vessels splaying seen in patients with COPD or emphysema and areas of associated reduced perfusion in the upper zones, where most of the time emphysema is more severe or only there. Now, in contrast, in CTEPH, you can see vessels stenosis and occlusions and the associated segmental perfusion defect are distal to those stenosis. So, the pictures that the MR angiograms and perfusion images give you can give you a clue of the type of pulmonary hypertension, whether it's idiopathic or group 1, or group 3, or group 4.

So, MRI investigation of suspected pulmonary hypertension, what can we learn? We can see the size of the blood vessels of the pulmonary arteries. And in the left panel, this is an MR in a normal patient, and then on the right patient with severe PH. And you can notice that the blood flow from the pulmonary trunk into the pulmonary arteries in PH patient is delayed and it's abnormal because it doesn't have a laminar flow, it's turbulent, and that can suggest the presence of pulmonary hypertension.

So there other certain cardiac MRI features that can not only help diagnose or estimate the presence of pulmonary hypertension but also can predict the outcomes. The cardiac MRI can give you right ventricular ejection fraction, and RVEF has been shown to be a good prognostic parameter in patients with PAH. And if you look at this study that the graph highlights the results from the RV ejection fraction is associated with survival in patients who are medically treated for PAH. So, if they're medically treated but the RVF is low, there's still high mortality. And this study showed that it was this mortality association was present regardless whether the pulmonary vascular resistance was high or low. So RVF obtained by cardiac MRI has a very good prognostic qualities.

Let's talk about when to refer your patients to the PH Center. Know when to refer your patients to the PH Center. So first, if you suspect pulmonary hypertension, the PH Center can offer hemodynamic evaluation because the right heart catheterization is still the only validated method to confirm and grade pulmonary hypertension and it's best performed at the PH Center. The recent studies have shown that even patients with mean PA pressure less than 20 or a mean PA pressure between 21 and 24 at rest may develop pulmonary hypertension sometimes during exercise. And this is what we call exercise induced pulmonary hypertension. So minimal elevations in PA pressures may be a trigger to think that this patient may develop pulmonary hypertension in the future. The use of exercise hemodynamic measurements in symptomatic patients with pulmonary perfusion defects and normal resting mean PA pressure can reveal the presence of abnormal cardiodynamic response to effort, especially in patients with chronic clots. So doing an exercise during the right heart catheterization in patients with chronic PEs, or with prior PEs can uncover the defects that are significant during exercise. And that's what we call exercise-induced pulmonary hypertension. On the other hand, exercise in patients with pulmonary hypertension that looks like a type one PH, and they have a normal wedge, may uncover abnormalities in the left heart and increases in wedge with exercise. So just the presence of diastolic left heart disease that may account for the increased pressures on the right heart side. So, in other words, group 2 pulmonary hypertension. So that's why a center can perform these more complex studies during the right heart catheterization.

And that's why we recommend the right heart cath be done at a PH Center. So, let's see the diagnosis of PAH. We have to confirm it by the right heart cath. We can calculate resistances after we do all the direct measurements. It can give us a guidance to what type of therapy we should implement. It excludes other diagnosis of PH, other etiologies of PH, such as left heart disease. And it measures the right ventricular function by measuring the right atrial pressure and by measuring the cardiac output. On the right-hand side, this table gives you the variables that we are typically measuring during the right heart catheterization. The last point is very important for patients in whom we suspect idiopathic PAH, or drugs and toxins induced PAH or familial PAH. The vasodilator challenge is a crucial step at the end of a right heart cath to identify those folks who may benefit from calcium channel blocker treatment only. So they won't need the more expensive, more advanced therapies. The lower part suggests that hemodynamic values used in the ESC/ERS guidelines, the functional class, and the hemodynamic parameters together can give you a good assessment of how severe the pulmonary hypertension is.

Summing up, know when unexplained dyspnea is something really serious. Where's the air? The importance of explaining the unexplained dyspnea. Patients may develop dyspnea from many, many, many causes that can be part of their lungs, heart, or their systemic disease. But the importance of uncovering the cause of dyspnea cannot be understated. The route diagnosis is multifactorial. You have to do a multitude, a battery of tests to find the cause of the dyspnea. And unlike when we say PAH is a rare disease, if you think about all PH, PH caused by lung disease, PH caused by heart disease and other causes, chronic clots altogether, PH actually is not that uncommon. So, keep it in mind. Now, the key event is developing an index of suspicion for pulmonary hypertension. And if you find on the screening echo abnormalities suggestive of PAH, we recommend immediate referral from the community to the PH Center so the collaborative effort can start early. Certain diagnostic tools form essential components to constructing the suspicion that PAH is at the root cause of dyspnea and those include imaging and assessment of the heart, as well as assessment of the lung function and structure. And lastly, the only biochemical marker that suggests RV dysfunction is BNP or NT-proBNP, and all these together can help you, the practitioner increase the index of suspicion and refer the patient for a confirmatory diagnosis, right heart catheterization, and

prompt initiation of the correct therapy.

Echo, probably the most important tool for the community physician and the PH Center specialist. The echo imaging must gather good structural pictures. So, it's very important to get a good look at the right ventricle, right atrium, but again, they are estimates. Other imaging techniques such as V/Q scintigraphy with angiography and other newer techniques such as SPECT, DECT and cardiac MRI provide complementary information and more detailed information on the structure and/or the function of the heart and the lungs. The confirmation of PH must be accomplished by the right heart catheterization. And the interpretation of data and eventual management of the patient becomes a shared process between the PH Center and the referring physician. So very important to establish a collaboration with a center near you so you can refer these patients in a timely manner. This sums up our talk for today. I thank you for listening and I hope the information was helpful and interesting.

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