Pulmonary Hypertension: Clinical Workup & Diagnosis

- Explain the complexity of pulmonary hypertension and the importance of a rigorous diagnostic workup.
- Describe the basic diagnostic algorithm to accurately classify the type of pulmonary hypertension encountered in a specific patient.

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Dr. Hassoun, thank you for joining us today.

DR. HASSOUN: Thank you, Bob. It's a pleasure to be here.
MR. BUSKER: In your newsletter issue, you presented the most recent information on classifying patients with pulmonary hypertension, a basic algorithm for diagnostic workup, and the types of therapies currently available. Our focus today is to see how some of this information can impact clinical decision-making. So please start with a patient scenario.

DR. HASSOUN: This is a 63-year-old gentleman who presented for evaluation of pulmonary hypertension. He was essentially in good health until about 2000, when he started experiencing severe exertional dyspnea. At the time, he was overweight, so a sleep study was obtained and it revealed mild sleep apnea with mild desaturation. His apnea-hypopnea index was about 10 per hour so he was started on BiPAP. Since 2000, the patient has intentionally lost about 100 pounds and started exercising on a treadmill for about 30 minutes four days a week.

His medical history is unremarkable otherwise, aside from systemic hypertension. In particular, he has no history of coronary artery disease, asthma, or COPD. He smoked about 15-20 pack years but has not smoked since 1988. Of note, he lived for about 30 years at an altitude of 8,200 feet in Colorado but moved to Maryland three years ago.

As mentioned, he was able to exercise several times a week. He denies significant exertional dyspnea; however, he is short of breath walking up a hill. He denies any chest pain, cough, hemoptysis, pedal edema, orthopnea, or PND, and has no history of syncope.

On physical examination, his vital signs were fairly unremarkable. His oxygen saturation was a little low at 94% on room air. The chest was clear. Cardiac examination revealed a loud 2nd pulmonic sound and a 2/6 systolic murmur best heard in the left lower sternal border. Abdomen was benign. Extremities were free of pedal edema, clubbing, or cyanosis.

MR. BUSKER: Summarize this patient for us please.

DR. HASSOUN: We are dealing with a 63-year-old gentleman with a history of sleep apnea and obesity, with some functional limitation when walking uphill. Also of note is that his oxygen saturation on room air was only 94%.

MR. BUSKER: In evaluating this patient for pulmonary hypertension, what are your thoughts after this first visit?

DR. HASSOUN: Several thoughts went through my mind. First, does pulmonary hypertension explain his symptoms, and if yes, what group could this be? He clearly has symptoms, such as dyspnea climbing up a hill, and signs, such as a loud P2 and a systolic murmur of tricuspid regurgitation, that suggest pulmonary hypertension. For instance, the history of systemic hypertension would be significant for group 2 disease, as this can cause diastolic dysfunction and secondary pulmonary hypertension.

The history of sleep apnea, on the other hand, is also of concern for group 3 pulmonary hypertension; however, he was quite diligent and lost about 100 pounds.

A repeat polysomnogram is in order. Nothing in his history suggests connective tissue disease, HIV, other associated diseases. He lived at high altitude but has been living in the Baltimore area for over three years; therefore, high altitude pulmonary hypertension related to chronic hypoxia would be very unlikely.

MR. BUSKER: What would be the next step in your diagnostic workup?

DR HASSOUN: Our algorithm for diagnosis of pulmonary hypertension is pretty straightforward. We start with baseline laboratory data, chest imaging, a ventilation-perfusion scan — the latter to rule out thromboembolic disease. We typically obtain a 6-minute walk test in-clinic to evaluate the patient’s functional status. Among the laboratory data, we get a serum NT-probrain natriuretic peptide or proBNP. A screening echocardiogram is the necessary screening test for any evaluation of pulmonary hypertension. And then a repeat sleep study to ascertain that his sleep apnea syndrome is indeed under good control.

MR. BUSKER: And the results of these initial tests?

DR. HASSOUN: The chest film and chest CT scan revealed very large pulmonary arteries bilaterally; the parenchyma, however, was clear, there was no lesion or mass. An echocardiogram revealed elevated right ventricular systolic pressure of about 55 mmHg. There was a moderately dilated right ventricle and dilation of the right pulmonary artery, suggesting the presence of pulmonary hypertension. A ventilation/perfusion scan was completely unremarkable, with a normal lung perfusion. A repeat polysomnogram revealed an apnea-hypopnea index less than 5 per hour, which is completely normal.

Because of the findings of his echocardiogram, the very large pulmonary arteries on chest CT scan, and no obvious disease to explain these findings, a right heart catheterization would have to be obtained to rule out pulmonary hypertension.

MR. BUSKER: How did the results of right heart catheterization inform your diagnosis?

DR. HASSOUN: There was severe elevation in mean pulmonary arterial (PA) pressure, to 70 mmHg, above the cutoff of 25 mmHg considered normal, as this is close to systemic-level pressure. The pulmonary capillary wedge pressure was, however, normal, less than 15 mmHg, so the numbers are consistent with precapillary pulmonary arterial hypertension.

Pulmonary vascular resistance was severely elevated at 12 Wood units; normal is less than 3 Wood units. However, the cardiac index was preserved at 2.44 L/min². Based on these values and the clinical history, this patient does have severe idiopathic pulmonary hypertension, or IPAH, with hemodynamics consistent with this syndrome. His preserved functional status and performance—remember that he exercises daily—can only be explained by the fact that he has a fairly preserved right ventricular function, a near normal cardiac index, in the face of severely increased pulmonary vascular load.

MR. BUSKER: The results of the right heart catheterization allowed you to make an evidence-based diagnosis of severe idiopathic pulmonary hypertension. What therapy did you recommend?

DR. HASSOUN: Although his symptoms were mild, he had functional class II symptoms. He was started at the time in 2003 on monotherapy with sildenafil, a phosphodiesterase inhibitor. This drug belongs to one of the two classes of oral agents available at that time. He was advised to continue using his CPAP nightly, mainly to prevent obstructive sleep apnea complicating the picture and worsening his already severe pulmonary hypertension. He was also advised to exercise regularly. This is recommended routinely for patients with pulmonary hypertension because exercise, as in any form of
MR. BUSKER: What happened to this patient? What was the final result of your diagnosis and care?

DR. HASSOUN: He remained in functional class I or II on various examinations on sildenafil therapy for about 15 years, which is quite remarkable considering his initial severe hemodynamics. He was followed routinely every four to six months and did not require a single hospitalization for complication of pulmonary hypertension, which in my experience reflects his excellent right ventricular function.

However, because of persistent severe elevation on a recent repeat right heart catheterization, addition of an endothelin receptor antagonist agent would now be recommended in light of the results of the recent AMBITION trial with up-front combination therapy with tadalafil and ambrisentan, the trial I mentioned in my newsletter.

He is currently awaiting clearance from his health insurance before instituting ambrisentan therapy. Combination therapy will clearly increase health costs for this patient and for other patients on combination therapy; however, as also mentioned in the newsletter, recent studies suggest that the increased cost is offset by the beneficial effect of these drugs on health, mainly related to decreasing the rate of hospitalization of these patients with pulmonary hypertension.

MR. BUSKER: Thank you for that case and discussion doctor. We’ll return with Dr. Paul Hassoun from Johns Hopkins in just a moment.

MR. BOB BUSKER: This is Bob Busker, managing editor of ePulmonology Review. ePulmonology Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to clinicians treating patients with pulmonary conditions.

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Thank you.

MR. BUSKER: Welcome back to this ePulmonology Review podcast. I'm Bob Busker, managing editor of the program. We've been speaking with Dr. Paul Hassoun from the Johns Hopkins University School of Medicine about how the newer information about the classification and diagnosis of pulmonary hypertension reviewed in his newsletter issue can translate into improved clinical practice. Let's continue in that vein, Dr. Hassoun. Please bring us another patient scenario.

DR. HASSOUN: A 67-year-old woman with Raynaud’s phenomenon since age 20 and newly diagnosed CREST syndrome was referred for evaluation of pulmonary hypertension by her rheumatologist. She had also been evaluated in general pulmonary clinic for possible interstitial lung disease. She had been complaining of breathing difficulty for the past two years, which became significantly worse six months before I examined her. She was eventually started three months ago on supplemental oxygen because of significant hypoxemia.

Her past medical history is remarkable for diabetes, sleep apnea for the past five years for which she has been on CPAP at night at 10 cm of water pressure, although she admits somewhat poor compliance with that therapy. She had a myocardial infarction at age 40, for which she had a stent placed in the right coronary artery.

From a respiratory standpoint, she cannot walk more than 15 to 20 feet without being completely out of breath. She denies any chest pain. However, she has frequent swelling of the legs and has been complaining of increased abdominal girth and a feeling of bloating and discomfort. She denies any lightheadedness or syncope.

On physical examination, she is on oxygen and has great difficulty moving to the examining table. Blood pressure is 154/79, a bit elevated. Pulse oximetry is 91% on 4 L oxygen. Other vital signs were normal. Jugular venous pressure is elevated to the angle of the jaw. Chest auscultation reveals minimal crackles at the bases bilaterally. Heart examination reveals an increased second pulmonic sound without appreciable rub, gallop, or murmur. Abdomen is distended. It is difficult to appreciate the presence of ascites. Extremities reveal 2+ pedal edema up to the level of the knee. The skin is remarkable for telangiectasias over the face.

In summary, we’re dealing with a 67-year-old woman with a history of longstanding Raynaud’s phenomenon and recently diagnosed CREST syndrome. She is WHO functional class III at this time.

MR. BUSKER: Help us unpack that presentation. What are your thoughts about this patient?

DR. HASSOUN: She most likely has some form of pulmonary hypertension complicating her connective tissue disease, her scleroderma. But her presentation is rather complex. First, I cannot exclude a component of interstitial lung disease, which would put her in group 3 if it were severe. I am also intrigued by her profound hypoxemia and what might be causing it, whether it is interstitial lung disease, congestive heart failure, or something else.

On physical examination, she appears to have a clear element of right ventricular failure with elevated jugular venous pressure and marked pedal edema. With her history of cardiac disease, could she have group 2 disease related to left ventricular dysfunction?

MR. BUSKER: What tests would you order before making your diagnosis?

DR. HASSOUN: I would obtain the routine tests that we always obtain for the diagnosis of PH, including general blood work, a chest CT to assess the degree of her interstitial lung disease. A ventilation-perfusion scan is part of the diagnostic algorithm. In her case I would also obtain imaging of the kidneys and brain to assess for a possible shunt. Pulmonary
reviewing the key points of what we’ve talked about today as they relate to our learning objectives. To begin: explain

MR. BUSKER: And the results of these tests?

DR. HASSOUN: The blood test revealed that the ANA, antinuclear antibody, was positive, greater than 1/640, with an anticientromere pattern. The anti-ScI-70 was negative, anti-Ro was negative. And the serum NT-proBNP was quite elevated at 1,600 picogram/mL. A chest x-ray showed mild increased interstitial markings at both bases. The heart was normal in size. A chest CT scan revealed very mild interstitial lung disease, mainly subpleural, consistent with the usual interstitial bilateral pneumonitis pattern; however, this was considered mild.

She underwent a 6-minute walk test today but could only walk 250 feet, which is 20% of predicted for her. This necessitated 10 liters of oxygen by nasal cannula because of significant desaturation. Her saturation was 86% at peak exercise; however, she recovered to 92% at the end of the walk.

An echocardiogram revealed a normal left ventricle size and function. The ejection fraction was 60% to 65%, which is normal. However, the right ventricle was severely dilated, with decreased RV systolic function as assessed by a TAPSE value of 1.7 cm. The right ventricular systolic pressure was 65 mmHg. The left atrium was normal in size and the right atrium was moderately dilated.

A pulmonary ventilation perfusion scan was read as low probability for pulmonary embolism. There was also presence of a right-to-left shunt. She had mild radiotracer activity in the brain and bilaterally in the kidneys. Pulmonary function tests showed an FEV₁ of 76% of predicted; a forced vital capacity of 84% of predicted; a total lung capacity of 96% of predicted. Most of these values are within normal limits. The DLCO, however, was 8.6, severely reduced at 38% of predicted, indicating a severe pulmonary vascular disorder.

MR. BUSKER: You saw this patient because you were asked by her rheumatologist to evaluate her for pulmonary hypertension. Based on these test results, do you believe she has pulmonary hypertension?

DR. HASSOUN: It is very clear that this lady has scleroderma of the limited form based on her serology with a positive ANA and an anticientromere pattern. Her chest CT scan and PFTs suggest some very mild interstitial lung disease, but not enough to account for any form of pulmonary hypertension. The pulmonary function tests, as I mentioned, were fairly preserved.

Her echocardiogram suggests severe pulmonary hypertension with a dilated right ventricle. The left heart, however, appears normal with a normal left ventricular ejection fraction. So left heart disease is quite unlikely to account for any pulmonary hypertension. The ventilation perfusion scan excludes thromboembolic disease, as the perfusion was normal; however, it does suggest a shunt effect, most likely intracardiac. In this case a bubble study would have been very helpful to assess this possibility. The 6-minute walk test suggests very severe functional impairment and significant need for supplemental oxygen. Remember, she required 10 liters of oxygen for her 6-minute walk test.

Her initial diagnostic workup is now pretty much complete. We scheduled her for a right heart catheterization to determine the degree of her pulmonary hypertension and rule out pulmonary venous hypertension, which is still a possibility considering her history of cardiac disease and previous myocardial infarction.

MR. BUSKER: Would your next step be to go directly to that right heart catheterization?

DR. HASSOUN: Not really. At this time, I am very concerned about her right ventricular failure, fluid overload, and extremely limited functional status, along with the profound hypoxemia. So before proceeding with any further testing, it is urgent to alleviate her symptoms and improve her hemodynamics. For a patient like this, aggressive diuresis with furosemide or some other diuretic is indicated at this time. Once she has reached close to a euvolemic state, right heart catheterization is indicated to assess her pressures, her right ventricular function, and rule out any possibility of left ventricular dysfunction, which is quite possible with her history. She was successfully diuresed and is now ready for right heart catheterization.

MR. BUSKER: So, the catheterization was performed. What were the results?

DR. HASSOUN: The results were consistent with severe precapillary pulmonary hypertension, or PAH, with a mean pulmonary arterial pressure of 60 mmHg, evidence of rather severe right ventricular dysfunction with an elevated right atrial pressure of 12 mmHg, and a profoundly decreased cardiac index of 1.7 L/min/m² with a calculated pulmonary vascular resistance of 14 Wood units. There was no left ventricular dysfunction, as her pulmonary capillary wedge pressure was 10 mmHg, less than the cutoff of 15 mmHg.

Considering her diagnosis of limited scleroderma, the absence of left ventricular dysfunction, limited interstitial lung disease by CAT scan, with normal lung volumes on PFTs, this lady suffers from scleroderma-associated PAH, which is group 1 pulmonary hypertension.

MR. BUSKER: All in all, what was the final result with this patient?

DR. HASSOUN: Shortly after the right heart catheterization, she was enrolled in a clinical trial, the ATPAHSS, with upfront combination therapy with ambrisentan and tadalafil, similar to the AMBITION trial that I mentioned in the newsletter, but this trial was focused on scleroderma-associated pulmonary arterial hypertension.

Within six months of therapy in this open-label trial, she was improved with functional class II symptoms. Her hypoxemia improved to the point that she no longer required supplemental oxygen. Three years later, she remains in functional class II with adequate oxygenation on room air.

MR. BUSKER: Thank you, Dr. Hassoun, for bringing us today’s cases and discussion. Let’s wrap things up now by reviewing the key points of what we’ve talked about today as they relate to our learning objectives. To begin: explain
the complexity of pulmonary hypertension and the importance of a rigorous diagnostic workup.

Both cases presented the clinical elements that might have oriented the clinician toward a different diagnosis. As illustrated in the first case, the patient had lived at high altitude and could have developed high altitude increased pulmonary vascular resistance. He also had the diagnosis of hypertension, which could have given him diastolic dysfunction and would have placed him in group 2 disease. He also had the diagnosis of sleep apnea, like the second patient.

The second patient had a history of coronary artery disease and myocardial infarction, so she could have had some form of left ventricular dysfunction causing pulmonary hypertension. She also had scleroderma that can be complicated by interstitial lung disease and indeed did have some mild interstitial lung disease. If it had been severe, that could have caused pulmonary hypertension and she would have been classified as group 3 pulmonary hypertension.

When patients present, the initial visit is a clue-searching effort where you try to find in the medical history and in the current presentation signals that orient you toward a specific diagnosis or a specific group of pulmonary hypertension.

Also, as shown here, a complete diagnostic workup is essential prior to initiation of any therapy.

MR. BUSKER: And our second learning objective: describe the basic diagnostic algorithm to accurately classify the type of pulmonary hypertension.

DR. HASSOUN: We follow a very specific diagnostic algorithm for any patient who is being evaluated for pulmonary hypertension. The diagnostic algorithm includes obtaining blood tests for routine CBC, a metabolic panel, serum NT-proBNP, TSH, and ANA, and we also obtain a plain chest film and a CAT scan of the chest with contrast, a ventilation perfusion scan, a 6-minute walk test, and extremely important, a screening echocardiogram.

As indicated in these two cases, right heart catheterization is the most important terminal tool in the diagnostic workup. It allows estimation of the degree of pulmonary hypertension, the function of the right ventricle, and exclusion of post capillary forms such as left ventricular dysfunction.

Also, a complete diagnostic workup is essential prior to initiation of any therapy.

MR. BUSKER: Dr. Paul Hassoun, Director of the Pulmonary Hypertension Program at the Johns Hopkins University School of Medicine, thank you for participating in this ePulmonology Review podcast.

DR. HASSOUN: Thank you very much, Bob.

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