

Introduction

1. What is pulmonary hypertension?

Pulmonary hypertension (PH) is a condition in which high blood pressure develops in the pulmonary arteries (blood vessels in the lungs). To understand pulmonary hypertension, it is important to understand the way blood travels around the body or through the “circulation”. There are two sides to the blood circulation, and two sides to the heart. The left sided circulation is where the left heart pumps blood from the heart through the arteries to supply the body with oxygen. When blood comes back to the heart from the body, it travels through the veins to the right side of the heart and the right-sided circulation. The job of the right side of the heart is to pump blood to the lungs where it absorbs oxygen and eliminates carbon dioxide, after which it travels back to the left side of the heart. Typically, the pressure in the right-sided circulation (pulmonary circulation) is low, much lower than the blood pressures generated by the left side of the heart (i.e. the type of blood pressure we can measure in your arm). PH is a condition in which there is increased pressure and resistance in the pulmonary circulation. It has many causes including genetic mutations, illicit drug use, and associated conditions including connective tissue disease, congenital heart disease and chronic lung conditions such as pulmonary fibrosis (PF).

2. How is pulmonary hypertension related to pulmonary fibrosis?

One of the associated diseases that can cause pulmonary hypertension is pulmonary fibrosis, which causes chronic damage in the tissues of the lungs. PF, which is a form of interstitial lung disease (ILD), can have many causes and they can all be associated with PH. When the PF is more severe, there is a greater chance of developing PH. The ways in which ILD or PF can lead to the development of PH are not completely understood. It is thought that damage to the tissue and structure of the lung can cause some increase in pressure in the pulmonary vessels. Low oxygen levels caused by ILD can lead to the constriction of blood vessels in the lungs, which could contribute to PH. Finally, there are molecules that are active in the lungs in PF that can cause blood vessel changes associated with PH. PH related to ILD is one of the types of PH in “group 3” of the World Health Organization PH classification system, which includes PH related to other types of respiratory problems, such as chronic obstructive pulmonary disease (COPD).

3. What are symptoms of pulmonary hypertension related to interstitial lung disease?

Patients with pulmonary hypertension related to interstitial lung disease (PH-ILD) have symptoms that are very similar to symptoms of ILD without PH, including shortness of breath, lightheadedness, fatigue, and chest discomfort. Leg swelling can develop, because PH can cause strain on the heart, leading to a back up of fluid into the leg veins. PH related to ILD can also cause hypoxemia, or low oxygen levels, sometimes lower than ILD alone.

4. How common is pulmonary hypertension related to interstitial lung disease?

It has been shown that one in twenty patients (about 5%), who are seeing a doctor for the first time for pulmonary fibrosis, may also have pulmonary hypertension. In patients with idiopathic pulmonary fibrosis (IPF), some studies have shown that approximately 15%-50% of patients may have associated PH. These numbers are similar in patients with PF from autoimmune disease, hypersensitivity pneumonitis and other types of PF. When patients with IPF are at the point they are being evaluated for transplant, it is more common, with 30-45% of patients also having PH. Patients who have both emphysema and PF are at a particularly higher risk, with some studies showing PH affecting up to 65% of these patients.

5. How is pulmonary hypertension related to interstitial lung disease diagnosed?

The blood pressure in the pulmonary circulation is measured directly by a procedure called a right heart catheterization, where a catheter is placed into the right side of the heart and the blood vessels of the lungs. The condition pulmonary hypertension is defined by having a mean pulmonary artery pressure >20 mmHg, and a pulmonary vascular resistance being higher than 3 Wood units; these are measurements taken during the right heart catheterization procedure. By comparison, a normal left sided circulation blood pressure is 120/80 mmHg or lower as measured in the arms.

Right heart catheterization is essential for making the diagnosis of PH-ILD, and also in distinguishing between some of the different causes of pulmonary hypertension. Right heart catheterization is generally safe and well tolerated even among patients with advanced ILD including those who require supplemental O₂. A right heart catheterization is different from a left sided heart catheterization, which is used to look for blockages in the blood vessels that feed the heart and can be used to open those blockages when found. A left sided heart catheterization uses contrast, which is not used in right heart catheterization and has higher risk of bleeding due to higher pressures in the left sided circulation. A patient may have a right heart catheterization and a left heart catheterization at the same time, if both are necessary.

Screening and diagnosis

1. Which patients with interstitial lung disease should be screened for pulmonary hypertension ILD?

Symptoms of interstitial lung disease are often similar to symptoms associated with pulmonary hypertension, and symptoms and physical exam findings alone are not enough to determine

whether PH has developed. Worsening breathing symptoms, physical exam findings, oxygen levels, or changes in breathing tests and/or walking tests should prompt consideration of and evaluation for PH-ILD. Understanding that patients who develop PH-ILD have more symptom burden and worse outcomes, it is important to screen ILD patients for PH early after ILD diagnosis and repeat screening at time intervals based on patients' clinical course and symptoms.

2. What tests can indicate the presence of pulmonary hypertension in interstitial lung disease?

Screening tests are done when there is concern or suspicion for pulmonary hypertension and more information is needed to thoroughly evaluate that possibility. These screening tests are generally easily accessible and noninvasive. Many of the routine tests patients with interstitial lung disease complete for monitoring can also be used as screening tests for PH.

Pulmonary function tests (PFT) are breathing tests that help to monitor disease stability or progression in ILD. Six-minute walk testing (6MWT) monitors a patient's oxygen saturations, heart rate response to activity, and distance walked. Results can be compared to patient's previous testing results, and unexplained changes in the measurements can raise the probability of PH.

Computed tomography (CT) scans are completed on patients with ILD to assess the lung tissue, but they also show the pulmonary arteries. The main pulmonary artery being larger than normal is evidence of possible PH.

Lab monitoring includes checking the brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP), a protein released by the heart when there is high pressure. If it is found to be elevated, it could indicate heart failure, which can be caused by PH or by other heart problems.

3. Can echocardiogram be used to diagnose pulmonary hypertension related to interstitial lung disease?

Transthoracic echocardiography, also known as an echo, is a noninvasive test that uses ultrasound waves to look at the heart and provide information on its size and function. Pulmonary hypertension is a condition that affects the right side of the heart, and echo is a good tool for estimating the blood pressure on the right side of the heart and in the pulmonary artery. However, it is just an estimate of the blood pressure and not accurate enough to use for diagnosis. Obtaining clear images in patients with interstitial lung disease can be difficult, because the damaged lung tissue can distort the echo image.

Based on results of the screening tests, if suspicion remains for PH, a right heart catheterization is required to confirm the diagnosis.

Treatment

1. Is pulmonary hypertension related to interstitial lung disease treated in the same way as pulmonary hypertension without interstitial lung disease?

Treatment of pulmonary hypertension is complex and differs depending on the type of PH, but often includes supportive care such as oxygen supplementation, pulmonary rehabilitation, and medications that lower blood pressure in the pulmonary arteries. Up until 2022, there were no specific treatments for patients with pulmonary hypertension related to interstitial lung disease (PH-ILD). The treatment plan for PH-ILD may include a type of medication called a pulmonary vasodilator that lowers blood pressure by relaxing the pulmonary blood vessels to help the heart beat more efficiently and pump more blood. Treatment of PH-ILD is best undertaken by an experienced center that can monitor response to therapy and for any complications.

When considering treatment of pulmonary hypertension, one should also consider treatment of the underlying ILD. Antifibrotic agents, pirfenidone (Esbriet) or nintedanib (OFEV) can be used along with treatment for PH related to ILD in patients with IPF or other progressive fibrotic ILD. Immunosuppressive medications for inflammatory types of ILD, such as in autoimmune disease, may also be used with treatment for PH related to ILD.

2. What medications are FDA approved to treat pulmonary hypertension related to interstitial lung disease?

The inhaled form of the medication treprostinil is FDA approved for the treatment of pulmonary hypertension related to interstitial lung disease. It is also approved for another type of PH, pulmonary arterial hypertension (PAH), which causes narrowing of the blood vessels in the lungs. Inhaled treprostinil (brand names Tyvaso, Yutrepia), is inhaled directly into the lungs, where it helps blood vessels relax and open so that the heart can pump blood more easily.

There are two ways to take inhaled treprostinil: a nebulizer inhalation system and a dry powder inhaler (DPI), both of which are taken four times a day. Potential side effects of the medication are low systemic blood pressure, coughing, headaches, shortness of breath, dizziness, nausea, fatigue, diarrhea, and throat irritation.

The treprostinil DPI is sometimes prescribed after a patient has been using the inhalation system and is found to be tolerating the medication and responding well to treatment. Since the consequences of untreated PH-ILD are serious, patients and clinicians have to work hard at making sure the prescribed medication is used correctly. Proper training on how to take treprostinil may come from the clinician's office and the specialty pharmacy providing the medications. Other measures and medications may be recommended to manage treprostinil side effects.

3. Are other pulmonary vasodilators used for pulmonary hypertension related to interstitial lung disease?

Data on a class of medications called phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil (Revatio) and tadalafil (Adcirca), for pulmonary hypertension related to interstitial lung disease has been variable. If treatment with PDE5 inhibitors is being considered specifically for PH-ILD, this is best done at an expert center, because there is potential for adverse effects in certain groups of patients. Future studies should assess the effectiveness of PDE5 inhibitors for this indication. Of note, PDE5 inhibitors are FDA approved for pulmonary arterial hypertension, but not for PH-ILD.

The endothelin receptor antagonist (ERA) class of medications (macitentan (Opsimut), ambrisentan (Letairis), bosentan (Tracleer)) and another medication called riociguat (Adempas) should not be used to treat PH-ILD. They have been shown in clinical trials to be ineffective, and both ambrisentan and riociguat were shown in studies to cause harm in patients with ILD.

4. Are there other treatments for pulmonary hypertension related to interstitial lung disease?

Comorbid conditions may contribute to the development of pulmonary hypertension in patients with interstitial lung disease. Therefore, if there is clinical suspicion, conditions such as sleep disordered breathing and chronic thromboembolic disease should be diagnosed and treated.

Non-pharmacological treatments such as supplemental oxygen and pulmonary rehabilitation should be utilized when appropriate. We recommend supplemental oxygen in patients with PH-ILD who have low oxygen levels with exertion or at rest. Pulmonary rehabilitation has a positive impact on functional capacity and quality of life in PH-ILD patients.

The diagnosis of PH-ILD is an indication for lung transplantation, so referral for transplant evaluation should be discussed early and initiated promptly in appropriate candidates who don't have other serious conditions that exclude them as transplant candidates.

For patients with symptoms of fluid retention, dietary changes such as fluid and salt restriction, as well as diuretic therapy, are recommended.

Palliative care is specialized care that focuses on symptom relief for patients with chronic illness and is in addition to, not a replacement for, disease-focused treatments. Palliative care is recommended for patients with ILD to address symptom burden and quality of life and may be especially helpful for those with PH-ILD who may have more severe symptoms.

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