Pulmonary hypertension related to interstitial lung disease

Introduction

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).

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).

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.

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.

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

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.

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.

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

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.

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 name Tyvaso), 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.

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 and tadalafil, 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, ambrisentan, bosentan) and another medication called riociguat (brand name 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.

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.

REFERENCES

1. Nikkho SM, Richter MJ, Shen E, Abman SH, Antoniou K, Chung J, Fernandes P, Hassoun P, Lazarus HM, Olschewski H, Piccari L, Psotka M, Saggar R, Shlobin OA, Stockbridge N, Vitulo P, Vizza CD, Wort SJ, Nathan SD. Clinical significance of pulmonary hypertension in interstitial lung disease: A consensus statement from the Pulmonary Vascular Research Institute's innovative drug development initiative-Group 3 pulmonary hypertension. Pulm Circ 2022; 12: e12127.

2. Klinger JR. Group III Pulmonary Hypertension: Pulmonary Hypertension Associated with Lung Disease: Epidemiology, Pathophysiology, and Treatments. Cardiol Clin 2016; 34: 413-433.

3. Hassan NF, Pellikka PA, Krowka MJ, Chaowalit N, Decker PA, Ryu JH. Pulmonary hypertension in patientsd with idiopathic pulmonary fibrosis. Chest 2005; 128: 7.

4. Leard LE, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, Campos SV, Christon LM, Cypel M, Dellgren G, Hartwig MG, Kapnadak SG, Kolaitis NA, Kotloff RM, Patterson CM, Shlobin OA, Smith PJ, Solé A, Solomon M, Weill D, Wijsenbeek MS, Willemse BWM, Arcasoy SM, Ramos KJ. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2021; 40: 1349-1379.

5. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, Costabel U, Richeldi L, de Andrade J, Khalil N, Morrison LD, Lederer DJ, Shao L, Li X, Pedersen PS, Montgomery AB, Chien JW, O'Riordan TG. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med 2013; 158: 641-649.

6. King TE, Jr., Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, Behr J. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011; 184: 92-99.

7. Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. Eur Respir J 2013; 42: 1622-1632.

8. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010; 363: 620-628.

9. Han MK, Bach DS, Hagan PG, Yow E, Flaherty KR, Toews GB, Anstrom KJ, Martinez FJ. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. Chest 2013; 143: 1699-1708.

10. Kolb M, Raghu G, Wells AU, Behr J, Richeldi L, Schinzel B, Quaresma M, Stowasser S, Martinez FJ. Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis. N Engl J Med 2018; 379: 1722-1731.

11. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest 2007; 131: 897-899.

12. Zimmermann GS, von Wulffen W, Huppmann P, Meis T, Ihle F, Geiseler J, Leuchte HH, Tufman A, Behr J, Neurohr C. Haemodynamic changes in pulmonary hypertension in patients with interstitial lung disease treated with PDE-5 inhibitors. Respirology 2014; 19: 700-706.

13. Saggar R, Khanna D, Vaidya A, Derhovanessian A, Maranian P, Duffy E, Belperio JA, Weigt SS, Dua S, Shapiro SS, Goldin JG, Abtin F, Lynch JP, 3rd, Ross DJ, Forfia PR, Saggar R. Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis. Thorax 2014; 69: 123-129.

14. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, Foley C, Yanez-Lopez M, Babalis D, Marino P, Maher TM, Renzoni EA, Spencer L, Elliot CA, Birring SS, O'Reilly K, Gatzoulis MA, Wells AU, Wort SJ. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2014; 190: 208-217.

15. Nathan SD, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez FJ, Corte TJ, Keogh AM, Leuchte H, Mogulkoc N, Ulrich S, Wuyts WA, Yao Z, Boateng F, Wells AU. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. Lancet Respir Med 2019; 7: 780-790.

16. Raghu G, Nathan SD, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Wells AU, Shao L, Zhou H, Henig N, Szwarcberg J, Gillies H, Montgomery AB, O'Riordan TG. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. Eur Respir J 2015; 46: 1370-1377.

17. Behr J, Kolb M, Song JW, Luppi F, Schinzel B, Stowasser S, Quaresma M, Martinez FJ. Nintedanib and Sildenafil in Patients with Idiopathic Pulmonary Fibrosis and Right Heart Dysfunction. A Prespecified Subgroup Analysis of a Double-Blind Randomized Clinical Trial (INSTAGE). Am J Respir Crit Care Med 2019; 200: 1505-1512.

18. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, Allen R, Feldman J, Argula R, Smith P, Rollins K, Deng C, Peterson L, Bell H, Tapson V, Nathan SD. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. N Engl J Med 2021; 384: 325-334.

19. King CS, Flaherty KR, Glassberg MK, Lancaster L, Raghu G, Swigris JJ, Argula RG, Dudenhofer RA,

Ettinger NA, Feldman J, Johri S, Fernandes P, Parsley E, Shah PS, Nathan SD. A Phase-2 Exploratory Randomized Controlled Trial of INOpulse in Patients with Fibrotic Interstitial Lung Disease Requiring Oxygen. Ann Am Thorac Soc 2022; 19: 594-602.

20. Bellerophon Therapeutics Announces Completion of Enrollment in Phase 3 REBUILD Study for INOpulse in Fibrotic Interstitial Lung Disease. Bellerophon Therapeutics, Inc (gcs-web.com). January 23, 2023].

21. A Study to Evaluate the Safety and Tolerability of Treprostinil Palmitil Inhalation Powder in Participants With Pulmonary Hypertension Associated With Interstitial Lung Disease - Full Text View - ClinicalTrials.gov.

22. Investigation of H01 in Adults With Pulmonary Hypertension Including Interstitial Lung Disease (The SATURN Study). - Full Text View - ClinicalTrials.gov (Accessed January 23, 2023).

23. Impact of Multiple Doses of BAY63-2521 on Safety, Tolerability, Pharmacokinetics and Pharmacodynamics in Patients With Interstitial Lung Disease (ILD) Associated Pulmonary Hypertension (PH) - Full Text View - ClinicalTrials.gov.

24. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, Richeldi L, Kolb M, Tetzlaff K, Stowasser S, Coeck C, Clerisme-Beaty E, Rosenstock B, Quaresma M, Haeufel T, Goeldner RG, Schlenker-Herceg R, Brown KK. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med 2019; 381: 1718-1727.

25. Petnak T, Lertjitbanjong P, Thongprayoon C, Moua T. Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Chest 2021; 160: 1751-1763.

26. Tahara M, Oda K, Yamasaki K, Kawaguchi T, Sennari K, Noguchi S, Sakamoto N, Kawanami T, Mukae H, Yatera K. Temporal echocardiographic assessment of pulmonary hypertension in idiopathic pulmonary fibrosis patients treated with nintedanib with or without oxygen therapy. BMC Pulm Med 2019; 19: 157.

27. Rigotti NA, Kruse GR, Livingstone-Banks J, Hartmann-Boyce J. Treatment of Tobacco Smoking: A Review. Jama 2022; 327: 566-577.

28. Jacobs SS, Krishnan JA, Lederer DJ, Ghazipura M, Hossain T, Tan AM, Carlin B, Drummond MB, Ekström M, Garvey C, Graney BA, Jackson B, Kallstrom T, Knight SL, Lindell K, Prieto-Centurion V, Renzoni EA, Ryerson CJ, Schneidman A, Swigris J, Upson D, Holland AE. Home Oxygen Therapy for Adults with Chronic Lung Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2020; 202: e121-e141.

29. Visca D, Mori L, Tsipouri V, Fleming S, Firouzi A, Bonini M, Pavitt MJ, Alfieri V, Canu S, Bonifazi M, Boccabella C, De Lauretis A, Stock CJW, Saunders P, Montgomery A, Hogben C, Stockford A, Pittet M, Brown J, Chua F, George PM, Molyneaux PL, Margaritopoulos GA, Kokosi M, Kouranos V, Russell AM, Birring SS, Chetta A, Maher TM, Cullinan P, Hopkinson NS, Banya W, Whitty JA, Adamali H, Spencer LG, Farquhar M, Sestini P, Wells AU, Renzoni EA. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. Lancet Respir Med 2018; 6: 759-770.

30. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S, Weissmann N, Seeger W. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J 2019; 53.

31.. Kimura M, et al. Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. Respiration. 2013;85(6):456-63.

32. Corte TJ, et al. Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic lung disease and suspected pulmonary hypertension. Thorax. 2009 Oct;64(10):883-8.

33. Huppmann P, Sczepanski B, Boensch M, et al. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. Eur Respir J 2013; 42: 444–453

34. ***Screening Strategies for Pulmonary Hypertension in Patients With Interstitial Lung Disease: A Multidisciplinary Delphi Study. Chest. 2022 Jul;162(1):145-155. doi: 10.1016/j.chest.2022.02.012. Epub 2022 Feb 15

35. Lettieri CJ, Nathan SD, Barnett SD, et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006; 129: 746–752

Document Development Group Members

Amy Case, MD, FCCP - Piedmont Healthcare - Co-chair
Steven Nathan, MD - Inova Fairfax - Co-chair

Rodeo Abrencillo , MD - University of Texas Health Science Center at Houston
Bradford Bemiss, MD - Loyola University
Bridget Collins, MD - University of Washington
Sonye Danoff, MD, PhD - Johns Hopkins Medicine
Kevin Flaherty, MD - University of Michigan
Gautam George, MD - Thomas Jefferson
Matthew Hunsucker, MD - Cone Health
Sarah Khan, MD - Johns Hopkins Medicine
Christopher King, MD - Inova Fairfax
Nicholas Kolaitis, MD - University of California San Francisco
Tejaswini Kulkarni , MD - University of Alabama
Joseph Lasky, MD - Tulane University
Ganesh Raghu, MD - University of Washington
Franck Rahaghi, MD, MHS, FCCP - Cleveland Clinic Florida / Pulmonary Fibrosis Foundation
Lori Reed, NP - Piedmont Healthcare
Janell Reichuber, MSN, RN - University of Kansas
Zeenat Safdar, MD - Houston Methodist
Adrian Shifren, MD - Washington University (St. Louis)
Namita Sood, MD, FCCP - University of California Davis
Krishna Thavarajah, MD - Henry Ford Health
Krishnan Warrior, MD - Loyola University
Debabrata Bandyopadhyay, MD - USF Tampa
Julie Porcelli, RN - Columbia
Rick Rudell - Patient Representative
Karen Smoot - Patient Reprentative
Oksana Shlobin, MD - Inova Fairfax
Teresa Demarco, MD - UCSF
Elizabeth Joseloff, PhD - Pulmonary Hypertension Association
Jessica Shore, PhD, RN - Pulmonary Fibrosis Foundation
Ingrid Schwab - Pulmonary Fibrosis Foundation
Aubrey Trecek - Pulmonary Fibrosis Foundation