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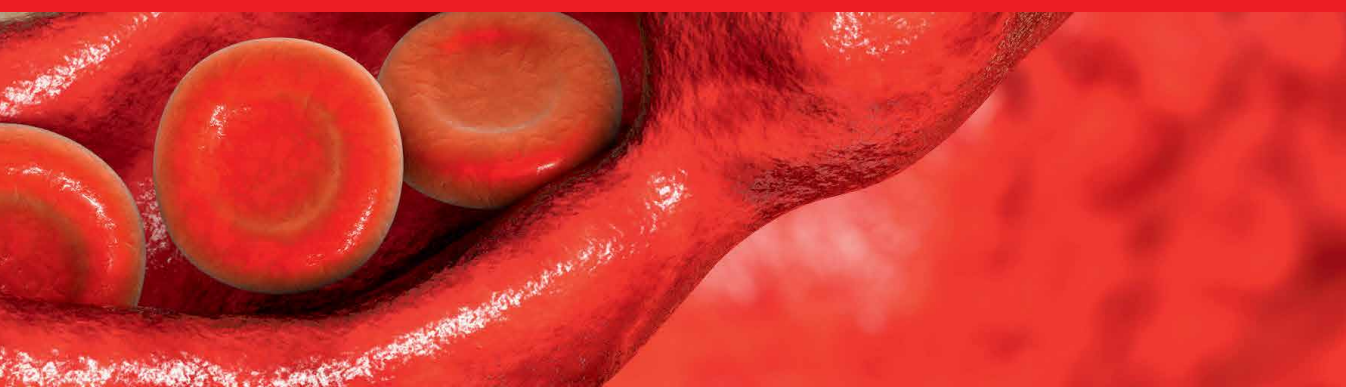
Edited by Salim R. Surani, Muhammad Khyzar Hayat Syed and Munish Sharma



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Meet the editors

Dr. Salim Surani is an adjunct clinical professor at Texas A&M University, USA. He is also a voluntary professor at the University of Houston, Texas, USA, and a research collaborator at the Mayo Clinic, Minnesota, USA. He has served as the program director for the Pulmonary Fellowship Program at the Bay Area Medical Center, Corpus Christi, Texas, USA. He completed his fellowship in pulmonary medicine at Baylor College of Medicine, Houston, Texas, USA. Dr. Surani obtained a master's degree in public health and epidemiology from Yale University, Connecticut, USA, and a master's in health management from the University of Texas, Dallas, USA. Dr. Surani has served as a board trustee for The CHEST Foundation and on numerous national and international committees. He is currently in a leadership position at several national and international societies/boards. He is editor-in-chief, an editorial board member, and a reviewer for several peer-reviewed journals. Dr. Surani has authored more than 400 journal articles and 50 book chapters. He has established himself as a master clinician who has trained many practicing primary care, internal medicine, and emergency physicians and pulmonary critical care fellows in the Coastal Bend region in the United States. Dr. Surani is highly regarded among his peers and is very well respected as a mentor, clinician, and humanitarian.

Dr. Munish Sharma serves as faculty at Baylor Scott & White Health, Temple, Texas, USA. He completed a fellowship in pulmonary hypertension and advanced heart failure from Hackensack University Medical Center, New Jersey, USA. He completed a pulmonary medicine fellowship from HCA Corpus Christi Medical Center, Texas, USA, before graduating from the critical fellowship program at Baylor College of Medicine, Houston, Texas, USA. Dr. Sharma has published more than fifty journal papers. He is one of the pulmonary hypertension specialists at Baylor Scott & White Health's pulmonary hypertension program. He serves as an editorial board member for Health Science Reports. He is a member of the pleural disease section of the American College of Chest Physicians (ACCP). He is engaged in teaching medical students, residents, and pulmonary critical care fellows in his current capacity. Dr. Sharma is very well respected by his peers in the academic community and is highly respected by his mentees and patients.

Dr. Muhammad K. Hayat Syed is a distinguished physician-scientist and clinical faculty at Baylor St. Luke's Medical Center, Houston, Texas. He completed his training in pulmonary/critical care medicine at the University of Minnesota and internal medicine at Columbia University, New York. Dr. Hayat Syed's professional journey is marked by his dedication to the field of pulmonary fibrosis and lung transplant, a focus that has led him to his current role as the co-director of the Interstitial Lung Disease (ILD) Clinical Trials Unit at Baylor College of Medicine. Here, he spearheads drug trials aimed at improving the treatment of pulmonary fibrosis patients. Dr. Hayat Syed is a valued

researcher focused on Idiopathic pulmonary fibrosis and lung transplant patients. He is an investigator for the Registry of Critical Illness (ROCI) at Baylor College of Medicine identifying predictive markers for acute respiratory distress syndrome (ARDS). He has published work on the use of fluids in shock, respiratory compliance in mechanically ventilated patients, and the power of ventilation in patients with ARDS. Dr. Hayat Syed is leading innovation using artificial intelligence to detect the decompensation of hospitalized patients sooner and initiate the timely activation of rapid response teams. As a recognized leader in his field, Dr. Hayat Syed serves as the chair of the Critical Care Section at the American College of Chest Physicians. He is also an active member of the Society of Critical Care Medicine and the American Thoracic Society, contributing to the advancement of his field and the betterment of patient care. This biography offers a glimpse into the life and work of a physician-scientist deeply committed to his profession and the patients he serves.

Contents

Preface

Pulmonary hypertension (PH) is a severe disorder primarily characterized by elevated pulmonary artery (PA) pressure, which affects the right side of the heart, sometimes leading to failure. Despite advancement and education in the field, there is a significant delay from the onset of symptoms to the time of diagnosis, leading to increased morbidity and mortality [1].

According to the World Health Organization (WHO), PH can be organized into five different categories. It can occur in individuals of all ages, genders, and races, making epidemiology difficult to determine. Idiopathic pulmonary arterial hypertension (IPAH) and heritable pulmonary arterial hypertension (HPAH) are both uncommon entities and fall under the WHO categorization 1 PH. Their prevalence is estimated at 5 to 15 cases per million adults [2, 3]. European registries have reported the prevalence of PAH to be around 5 to 52 per million adults [4, 5]. Though PH is prevalent in both genders, females seem to be affected more than males with prevalence rates ranging from 1.7 to 4.8:1.0 [6]. Recent data indicate that PAH-related hospitalizations might be decreasing along with overall deaths. Per a national registry, PAH-related hospitalization decreased to 38/100,000 hospitalizations from 79/100,000 hospitalizations from 2007 to 2011, while population-based deaths reduced to 1.7/million from 4.6/million [7]. Unfortunately, in-hospital mortality during the same period was unchanged. With better diagnostic tools and the advent of PAH-specific therapies, more patients are diagnosed promptly, and treatment modalities are instituted earlier compared to past decades. The reduction in hospitalization and overall death is probably the reflection of advancements in the field of PH.

Initial clinical features of PH are most commonly fatigue and exertional dyspnea. As the PH progresses, patients present with symptoms such as presyncope or syncope, leg edema, weight gain, ascites, and exertional chest pain. Clinical suspicion and timely diagnosis may be delayed since these symptoms can manifest with other or coexisting medical conditions. Initial manifesting symptoms are often attributed to age, deconditioning, or a comorbid medical condition.

Diagnosis of PH starts with a detailed history and clinical examination. An echocardiogram is a useful initial noninvasive diagnostic modality. It helps estimate right ventricular systolic pressure in the presence of a tricuspid regurgitation jet. An echocardiogram also helps in estimating right ventricular systolic function and size, identifying intracardiac shunts and valvular lesions, estimating chamber size, left ventricular function, and presence of pericardial effusion, amongst other findings. All these findings give important clues for further diagnosis. An echocardiogram is also a valuable tool for the follow-up of PH patients [8, 9]. Electrocardiogram, pro-brain natriuretic peptide, and chest radiography are other ancillary tests helpful during initial diagnosis and follow-up of PH patients. Right heart catheterization is the gold standard test in the diagnosis of PH. It is generally performed before initiating PH-targeted therapy. It is also utilized to assess response to PH-specific therapy [10].

PH medical treatment primarily targets WHO group 1 (PAH) patients. With the approval of inhaled treprostinil for patients with PH due to interstitial lung disease and riociguat in chronic thromboembolic pulmonary hypertension, the scope of medical therapy has slightly extended beyond WHO group 1 PH. Agents used for treatment of PAH include phosphodiesterase inhibitors (sildenafil, tadalafil), endothelin receptor antagonists (ambrisentan, bosentan, macitentan), prostacyclin agonists (selexipag, epoprostenol, treprostinil, iloprost), soluble guanyl cyclase receptor stimulator (riociguat), and rarely calcium channel blockers (diltiazem, nifedipine) [11]. Lung transplantation and atrial septostomy are surgical modalities generally used in refractory patients with PAH [12].

This book provides a comprehensive overview of PH. It presents the history of PH and discusses its classification and clinical features, including the role of right heart catheterization in diagnosing and managing patients with PH. In addition, the book reviews the five types of medical management of PH. It also discusses surgical treatment and the role of transplants. In addition, the book explores the role of left heart disease in PH and the role of heart–lung transplant for congenital heart disease with Eisenmenger syndrome and IPAH.

Overall, this book provides a comprehensive understanding of the diagnosis and management of PH. It is a helpful guide for clinicians and healthcare providers who encounter PH in their practice, aiding them in identifying and managing patients and guiding them on when to refer patients to a specialized center.

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References

[1] Humbert M, Kovacs G, Hoeper MM, et al. ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Respiratory Journal. 6 Jan 2023;**61**(1):2200879. DOI: 10.1183/13993003.00879-2022. PMID: 36028254

[2] McGoon MD, Benza RL, Escribano-Subias P, et al. Pulmonary arterial hypertension: Epidemiology and registries. Journal of the American College of Cardiology. 2013;**62**(25 Suppl):D51

[3] Ling Y, Johnson MK, Kiely DG, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: Results from the pulmonary hypertension registry of the United Kingdom and Ireland. American Journal of Respiratory and Critical Care Medicine. 2012;**186**(8):790. Epub 2012 Jul 12

[4] Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: Baseline characteristics from the REVEAL Registry. Chest. 2010;**137**(2):376

[5] Peacock AJ, Murphy NF, McMurray JJ, et al. An epidemiological study of pulmonary arterial hypertension. European Respiratory Journal. 2007;**30**(1):104

[6] Frost AE, Badesch DB, Barst RJ, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: How REVEAL differs from historic and non-US Contemporary Registries. Chest. 2011;**139**(1):128

[7] Stein PD, Matta F, Hughes PG. Scope of problem of pulmonary arterial hypertension. The American Journal of Medicine. 2015;**128**(8):844

[8] Jone PN, Ivy DD. Echocardiography in pediatric pulmonary hypertension. Frontiers in Pediatrics. 2014;**2**:124. Epub 2014 Nov 12

[9] Truong U, Meinel K, Haddad F, et al. Update on noninvasive imaging of right ventricle dysfunction in pulmonary hypertension. Cardiovascular Diagnosis and Therapy. 2020;**10**(5):1604

[10] Abman SH, Hansmann G, Archer SL et al. Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation. Nov 2015;**132**(21):2037-2099. Epub 2015 Nov 3

[11] Montani D, Gunther S, Dorfmuller P, et al. Pulmonary arterial hypertension. Orphanet Journal of Rare Diseases. 2013;**8**:97

[12] Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. The Journal of Heart and Lung Transplantation. 2015;**34**(1):1

Chapter 1

Pulmonary Hypertension: Revisiting the Historical Facts

Shan Samir Lakhani, Shaleen Sunesara, Sharanya Ezhilarasan Santhi, Munish Sharma and Salim R. Surani

Abstract

Pulmonary hypertension is a progressive and potentially fatal medical condition. Around 1% of global population is estimated to be affected by it. With significant advancement in diagnostic and therapeutic modalities in pulmonary hypertension, there has been a surge in interest in medical fraternity. We aim to revisit some of the major historical events pertinent to the evolution of the field of pulmonary hypertension. We try to understand how our predecessors in medicine laid foundation based on which the field of pulmonary hypertension is growing.

Keywords: pulmonary hypertension, BMPR gene, pulmonary hypertension history, CTEPH, lung transplant, heart-lung transplant

1. Introduction

Pulmonary hypertension (PH) is an uncommon, progressive, and potentially life-threatening medical condition that is basically characterized by elevated blood pressure in the pulmonary arteries [1, 2]. The pulmonary arteries are blood vessels that carry oxygen-poor blood from the right side of the heart to the lungs to get oxygenated. Around 1% of the global population is estimated to be affected by pulmonary hypertension [3]. It is more frequently observed in women between the ages of 30 and 60, and Hispanic women and African American women are disproportionately impacted [1, 2]. However, PH can affect people of all ages, and incidence increases with age. There has been advancement in diagnostic and therapeutic modalities in PH in the past decade or so. There seems to be a simultaneous increase in interest and awareness about PH in the medical fraternity as well. PH is an evolving field in medicine. In this chapter, we will be revisiting the historical perspectives and reviewing the major events that have unfolded in the course of understanding this unique disease entity.

2. Early observations and recognition in PH

The earliest known description of PH dates to 1891. A German Physician, Ernst Von Romberg, was presented with a 24-year-old patient suffering from shortness of

breath, tiredness, and cyanosis. Unfortunately, he was unable to treat the young man, who subsequently passed away. During his autopsy, Dr. Romberg noted thickened and damaged pulmonary arteries; to define this previously unidentified condition, he coined the term "Pulmonary Hypertension." Since no tool to measure the pressure in the pulmonary vascular system had been invented yet, the only reliable evidence indicative of elevated pulmonary artery pressure was the presence of cardiac and vascular remodeling during autopsy [4, 5].

Further development in PH followed a decade later. In August 1901, an Argentinian Professor, Dr. Abel Ayerza, expanded the definition of pulmonary hypertension. Dr. Ayerza's patient was a 38-year-old male with polycythemia presenting with a chronic productive cough, dyspnea, cyanosis, and daytime somnolence. His examination revealed crackles and acute wheezing bilaterally in addition to jugular venous distention, hepatomegaly, ascites, and lower limb edema. Laboratory tests depicted an elevated systolic blood pressure of 150 mmHg with a heart rate of 112 bpm [6]. Twenty-four days following admission, this patient also expired. His autopsy revealed right ventricular hypertrophy and right atrial dilation. The pulmonary arteries had thickened media and intimal layers with the presence of microthrombi in the lumen. Dr. Ayerza termed this unique set of symptoms as "Cardiaco Negros (black cardiac)" [7].

Four years later, Dr. Pedro Escudero reported new findings that further deepened the understanding of this condition. He recorded the presence of black cardiac disease in patients with bronchial syphilis [8]. His paper indicated that the disease was a result of syphilis damaging the pulmonary vessels rather than due to pulmonary disease. His work was rapidly followed up on by Dr. F.C Arigilla in 1913, a pupil of Ayerza's. He carried out a case series on 11 patients [9]. His research grouped all those patients with the common symptoms of cyanosis, dyspnea, and polycythemia. "Ayerza's disease" was a term that had begun to be used to describe patients with pulmonary vascular sclerosis presenting with these symptoms [7]. However, Dr. Arigilla's work was novel in noting that these common symptoms were not specific and, in fact, presented various etiologies. Prior to this finding, the absence of any signs of pulmonary disease in patients with such symptoms was puzzling to physicians.

In 1919, the confusion and misconceptions around "Ayerza's" disease seemed to have further been resolved when Dr. Aldred Warthin first discussed the case in the United States at the 34th Meeting of the American Society of Medicine [10]. He presented a patient with the standard clinical presentation of cyanosis, dyspnea, and fatigue, with autopsy results yielding evidence of syphilitic disease. This aligned with Dr. Escudero's and Dr. Arigilla's reports of syphilitic patients as well. Hence, at the time, the consensus was made that this presentation of "Ayerzas Disease" was an outcome of syphilis [6].

The aforementioned theory was challenged in 1935 by Dr. Oscar Brenner. He had studied 100 patients, all with the same symptoms of cyanosis, dyspnea, and fatigue. However, he found that not many of the patients had the same severity of symptoms that were described by Dr. Argilla. Moreover, Dr. Brenner found evidence of pulmonary vascular sclerosis (as described by Dr. Romberg) in patients with no evidence of syphilis [11]. Dr. Brenner himself could not explain the cause of the vascular remodeling in some of his patients. Hence, he concluded that there were a variety of causes of pulmonary hypertension, some of which could not be explained at the time. His work also suggested that the symptoms of Ayerza's disease were not, in fact, a disease but rather an outcome of the pulmonary remodeling, which he hypothesized was due to pulmonary arterial hypertension. This theory was pivotal in shaping how we describe this condition today [7].

Dr. Brenner's publication was widely recognized among the medical community. Pulmonary hypertension became the official term to describe this condition. Multiple reports in the 1940s, including those published in Guy's Hospital and Kings College London, described patients whose presentations matched Dr. Brenner's proposed definition of pulmonary hypertension [12]. Trials carried out at Kings College London reported an enlarged right ventricle and a dilated pulmonary artery in their autopsy reports, which aligned with their X-ray and electrocardiogram (ECG) findings as well [12]. Another interesting finding worth noting was the "Hilar Dance" phenomenon, which refers to the pulsating motion of the pulmonary artery, possibly due to the increased blood flow and pressure in these vessels. This was the first time imaging techniques had been used on patients with PH and would go on to inspire the basis of future imaging techniques [7].

3. Historical perspectives of chronic thromboembolic pulmonary hypertension (CTEPH)

Chronic Thromboembolic Pulmonary Hypertension (CTPH) is an infrequently encountered outcome of pulmonary embolism that was first discussed in the 1950s [13]. The pathogenesis involves multiple pulmonary embolisms lodging in the pulmonary vasculature. Over time, the occlusion of circulation leads to the development of cor pulmonale and eventually right-sided heart failure. However, what makes this condition unique and often hard to identify is the silent asymptomatic period, which occurs after the thrombus lodges in the vasculature. Simultaneously, cardiac remodeling silently occurs in the background.

Following its identification, initial surgical management was tested in the early 1960s, however, with little success. Due to the rarity of this disorder and the lack of existing knowledge about it, surgical outcomes were poor. It was not until 1969 when Ken Moser at the University of California in San Diego developed a new procedure known as the thromboendarterectomy, that the outcomes of this radically improved [14]. After initially carrying out the procedure on a single patient in 1970, Dr. Moser published his breakthrough findings in 1983, when he had successfully managed to improve outcomes in 13 out of the 15 patients through the thromboendarterectomy procedure [14]. By 2002, due to a wide variety of factors, the mortality rate of CTPH had been reduced to 4.4%, with major improvements in patient performance. The development of new diagnostic and imaging tests has led to earlier diagnosis and initiation of treatment for patients with CTPH [14]. Moreover, improvements in surgical techniques and increased experience among doctors have improved patient outcomes. This procedure created by Dr. Ken Moser has saved numerous lives and proved to be an undeniable success in the field of pulmonary surgery [15].

4. Evolution of right heart catheterization in pulmonary hypertension

Cardiac catheterization was first attempted in Germany in 1929 by Dr. Wener Frossman. In his quest to introduce a safe method of studying cardiac and pulmonary hemodynamics, he inserted a urinary catheter into his own heart [16]. While this experiment was somewhat successful, it was deemed dangerous by the medical community, and Forssman was exiled due to his unsafe practice in medicine. However, his work would not go unnoticed. This quickly caught the attention of André Cournand

and Dickinson Richards in the United States of America. They realized how mixed venous blood samples from the catheter would allow the cardiac output to be calculated using the Ficks Equation—a calculation that had previously only been explored theoretically since there was no way to access these blood samples [17].

In 1945, the duo carried out cardiac catheterization more than 250 times, each time with no significant complications to the patients. They also managed to use the catheters to collect the mixed venous samples and calculate the cardiac output using the Ficks Principle. Their work led them, along with Dr. Frossman, to win the Nobel Prize. Right heart catheterization (RHC) paved the way for further research into PH [16, 17].

5. World Health Organization (WHO) Geneva meeting 1973: an important milestone

In November of 1965, Aminorex Fumarate was released into markets in parts of Europe and advertised as an ordinary over-the-counter appetite suppressant helping in weight loss. Its mode of action was increasing the levels of 5-hydroxytryptamine (serotonin) in the bloodstream and releasing norepinephrine from neurons [18]. However, the drug came with an unexpected and fatal side effect in a small portion of the population, leading to a more than a twenty-fold increase in global Primary PH occurrence [19]. This inevitably led to its removal from markets in October 1968.

There were many questions raised regarding the mechanism of how Aminorex caused PPH. However, the most popular theory suggests that the elevated serotonin levels caused the proliferation of the pulmonary arterial smooth muscle, causing precapillary PH. Interestingly, studies conducted by Kay et al. found that when given to animals, Aminorex did not lead to PH development [20]. This raised another question regarding what led to animals, as well as the majority of Aminorex users, not developing any disease. Was there a chance of genetic predisposition in the populations that developed PH? Due to the disease's rarity, there was also limited information available regarding the different etiologies and their causative mechanisms. This led to the WHO calling its first meeting focused solely on pulmonary hypertension.

There were two primary objectives the WHO aimed to address in the meeting in Geneva. The first objective was to create consensus among experts about the true definition of primary pulmonary hypertension. Up until then, the nomenclature regarding PH was rather convoluted, with the same names being given to multiple etiologies of PH. Indeed, at that time, there were two distinct diseases being referred to as primary hypertension: one used by clinicians to define PH due to an unidentifiable cause, and the second one was used by morphologists for a group of histopathological changes in the pulmonary vasculature, which were closely related to pulmonary arterial hypertension [21]. It was decided to rename these morphological changes to plexogenic pulmonary arteriopathy. Additionally, they concluded that hypoxia, drugs (such as Aminorex), connective tissue disorders, and chronic thromboembolism were all causes of PPH [21].

The second objective of this meeting was to establish an international registry of PH patients. Since the disease was so rare, it would be beneficial to record any updates regarding the disease's etiology, patient outcomes, and treatments that could potentially lead to the establishment of a standardized protocol of care for patients with PH [21]. Notably, the criteria for diagnosis of PH were also defined at this meeting. Since histopathological and clinical signs may differ, the gold standard of diagnosis of PH was defined as a pulmonary arterial pressure of $\geq$25 mmHg as measured by cardiac catheterization [21].

Despite the WHO's suggestions, an international registry for PH patients was never established [22]. Instead, the National Institutes of Health's (NIH) Heart Lung and Blood Institute launched its own registry, which managed to collect data for 6 years between 1981 and 1987. There were multiple wings established by the NIH, which aimed to collect a wide variety of patient data and help spread knowledge about the clinical presentation and pathophysiology of PH [22].

On the 25th anniversary of their initial meeting in 1998, the WHO met in Evian, France, to discuss developments in PH research. A new classification system known as the "Evian classification" was created to categorize cases of PH into five groups: (1) Pulmonary arterial hypertension (PAH), (2) pulmonary venous hypertension (PVH), (3) PH due to lung disease, (4) chronic thromboembolic PH, and (5) miscellaneous causes [23].

6. Heart lung transplant in pulmonary hypertension

In 1981, a team of three doctors at Stanford University performed the first heart-lung transplant to treat a patient with PAH [24]. Up until then, the survival rates of PH had been marginal, with the average survival duration being 2.8 years. Hence, the work of Dr. Norman Shumway, John Wallwork, and Bruce Reitz was revolutionary in our understanding of the treatment of PAH. In the following years, multiple different surgical procedures were developed based on the first successful heart-lung transplant. The survival post-lung transplant is improving.

7. BMPR gene mutation

Initial evidence of a genetic link to primary pulmonary hypertension was presented in 1997 by Nichols WC et al. When running a genome-wide search for genes in patients with PH, he discovered that families with a high prevalence of PH had changes on the Q arm of chromosome 2 [25]. Then, in 1998, Deng et al. correctly identified that the bone morphogenic protein receptor 2 (BMPR 2) gene had a group of mutations that were strongly associated with PH [26]. Interestingly, the association of the genes with PH also showed sexual dimorphism, with penetrance in females being three times higher (42%) than males (14%) [26, 27]. This was the first time a genetic link had been established for PH and allowed for a way to identify high-risk families.

For the purposes of genetic testing and alterations, animal testing has been employed, particularly in rodents such as rats and mice. Mice are the animal of choice due to the relative ease with which their genetic sequences can be manipulated [28]. Animal testing has allowed us to identify which sets of mutations lead to a worse outcome of PH, as well as the relationship between BMPR mutations and changes in the Tissue Growth Factor Beta (TGF-B) genes [28]. However, the role of TGF-B is incredibly complex and is a gene that requires further research.

8. Conclusion

Revisiting the unfolding of major events in the field of pulmonary hypertension and medicine, in general, helps us understand the contribution of our predecessors

in medicine. It awakens a sense of appreciation for their effort and encourages us to utilize that information to form a foundation on which further research and development can be done.

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References

[1] Pulmonary Hypertension Association (PHA). Available from: https://phassociation.org/patients/aboutph. [Accessed: November 20, 2023]

[2] NIH. National Heart, Lung and Blood Institute. Pulmonary Hypertension. Available from: https://www.nhlbi.nih.gov/health/pulmonary-hypertension [Accessed: November 20, 2023]

[3] Mandras SA, Mehta HS, Vaidya A. Pulmonary hypertension: A brief guide for clinicians. Mayo Clinic Proceedings. 2020;**95**(9):1978-1988. DOI: 10.1016/j.mayocp.2020.04.039

[4] Romberg E. Ueber Sklerose der Lungen arterie. Deutsches Archiv für klinische Medizin. 1891;**48**:197-206

[5] Van Wolferen SA, Grünberg K, Vonk NA. Diagnosis and management of pulmonary hypertension over the past 100 years. Respiratory Medicine. 2007;**101**(3):389-398

[6] Hewes JL, Lee JY, Fagan KA, Bauer NN. The changing face of pulmonary hypertension diagnosis: A historical perspective on the influence of diagnostics and biomarkers. Pulmonary Circulation. 2020;**10**(1):1-26

[7] Mazzei J, Mazzei M. A tribute: Abel Ayerza and pulmonary hypertension. European Respiratory Review. 2011;**20**(122):220-221. DOI: 10.1183/09059180.00006811

[8] Escudero P. The Black Cardiacs and the Ayerza's Disease. Rev Crit; 1911

[9] Arrillaga FC. Esclerosis Secundaria de la Arteria Pulmonar y Su Cuadro clínico (Cardiacos Negros) [Secondary Sclerosis of the Pulmonary Arteryand its Clinical Findings (Black Cardiac)] [Thesis]. Argentina: University of Buenos Aires; 1912

[10] Sheleg V, Orlovskaia L, Rakova L. A case of Ayerza's disease. Vrach Delo. 1990;**10**:33-34

[11] Brenner O. Pathology of the vessels of the pulmonary circulation: Part I. Archives of Internal Medicine (Chicago, Ill.). 1935;**56**(2):211-237. DOI: 10.1001/archinte.1935.03920020003001

[12] East T. Pulmonary hypertension. British Heart Journal. 1940;**2**(3):189-200. DOI: 10.1136/hrt.2.3.189

[13] Carroll D. Chronic obstruction of major pulmonary arteries. The American Journal of Medicine. 1950;**9**:175-185

[14] Moser KM, Braunwald NS. Successful surgical intervention in severe chronic thromboembolic pulmonary hypertension. Chest. 1973;**64**(1):29-35

[15] Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: Experience and lessons learned in 1,500 cases. The Annals of Thoracic Surgery. 2003;**76**(5):1457-1464

[16] West JB. The beginnings of cardiac catheterization and the resulting impact on pulmonary medicine. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2017;**313**(4):L651-L658. DOI: 10.1152/ajplung.00133.2017

[17] Cournand A, Riley RL, Breed ES, et al. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. The Journal of Clinical Investigation. 1945;**24**(1):106-116. DOI: 10.1172/JCI101570

[18] Rothman RB, Ayestas MA, Dersch CM, et al. Aminorex, fenfluramine, and chlorphentermine are serotonin transporter substrates. Implications for primary pulmonary hypertension. Circulation. 1999;**100**(8): 869-875. DOI: 10.1161/01.cir.100.8.869

[19] Gurtner HP. Aminorex and pulmonary hypertension. A review. Cor et Vasa. 1985;**27**(2-3):160-171

[20] Kay JM, Smith P, Heath D. Aminorex and the pulmonary circulation. Thorax. 1971;**26**(3):262-270. DOI: 10.1136/thx.26.3.262

[21] Hatano S, Strasser T. Primary Pulmonary Hypertension Report on a WHO Meeling. World Health Organization; 1973

[22] Fishman AP. Primary pulmonary arterial hypertension: A look back. Journal of the American College of Cardiology. 2004;**43**(12):S2-S4

[23] Lykouras D, Sampsonas F, Kaparianos A, Efremidis G, Karkoulias K, Tsoukalas G, et al. Pulmonary arterial hypertension: Need to treat. Inflammation & Allergy Drug Targets. 2008;**7**(4):260-269

[24] George MP, Champion HC, Pilewski JM. Lung transplantation for pulmonary hypertension. Pulmonary Circulation [Internet]. 2011;1(2):182. Available from: /pmc/articles/PMC3198646/ [Accessed: September 25, 2023]

[25] Nichols W, Koller D, Slovis B, et al. Localization of the gene for familial primary pulmonary hypertension to chromosome 2q31-32. Nature Genetics. 1997;**15**:277-280. DOI: 10.1038/ng0397-277

[26] Deng Z, Morse JH, Slager SL, et al. Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. American Journal of Human Genetics. 2000;**67**(3):737-744. DOI: 10.1086/303059

[27] Hautefort A, Mendes-Ferreira P, Sabourin J, et al. Bmpr2 mutant rats develop pulmonary and cardiac characteristics of pulmonary arterial hypertension. Circulation. 2019;**139**(7):932-948. DOI: 10.1161/CIRCULATIONAHA.118.033744

[28] Frump AL, Datta A, Ghose S, et al. Genotype-phenotype effects of Bmpr2 mutations on disease severity in mouse models of pulmonary hypertension. Pulmonary Circulation. 2016;**6**(4):597-607. DOI: 10.1086/688930

Chapter 2

Classification and Clinical Features of Pulmonary Hypertension in Adults

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Abstract

This chapter explores the clinical manifestations and initial diagnostic findings associated with pulmonary hypertension (PHTN) at different stages. The definition of PHTN, as proposed in the 6th World Symposium, considers a mean pulmonary arterial pressure at rest (mPAP) of greater than 20 mmHg (previously 25 mmHg) and a pulmonary vascular resistance equal to or exceeding 3 WU. PHTN is clinically classified into five groups: Group 1 includes idiopathic, hereditary, and other forms; Group 2 comprises PHTN due to left heart disease; Group 3 consists of PHTN associated with pulmonary diseases or hypoxia; Group 4 pertains to PHTN caused by pulmonary artery obstruction; and Group 5 encompasses cases with unclear or multifactorial etiologies. The classification of PHTN into these groups holds significant clinical value as it contributes to determining survival rates and treatment responses. The chapter elaborates on the clinical features observed throughout various stages of PHTN and highlights the abnormalities detected during initial diagnostic assessments. The in-depth details will also be outlined in subsequent chapters of the book.

Keywords: pulmonary hypertension, PAH, World Symposium of PH, classification, type 2 PH, type 3 PH, toxins and PH, drugs and PH

1. Introduction

"Pulmonary hypertension" (PH) is characterized by increased mean pulmonary artery pressure (mPAP) of more than 20 mmHg at rest, calculated by the right-sided cardiac catheterization (RHC) [1]. PH refers to a diverse range of conditions marked by an increase in pulmonary vascular resistance that eventually results in right ventricular failure and early death [2]. Given the high burden of the disease, especially in the older population aged 65 years and above [3], the effectiveness of PH treatment is early diagnosis. However, early-stage PH is frequently disregarded because the presenting symptoms are either non-specific or manifest later in the course [2].

This chapter describes in detail the clinical characteristics seen at various phases of pulmonary hypertension, the newly accepted criteria, and the classifications of

treatment groups. It further highlights the abnormalities appreciated during the first diagnostic evaluations and the appropriate treatment measures.

2. The newly proposed pulmonary hypertension criteria

The suggestion to reevaluate the hemodynamic definition of PH has been one of the most important recommendations at The Sixth World Symposium on Pulmonary Hypertension (WSPH) in 2018 [4]. In the sixth WSPH, the diagnostic criterion for mean pulmonary artery pressure (mPAP) was decreased from 25 mmHg or above to greater than 20 mmHg, measured via the right-sided cardiac catheterization in the supine position. The previous definition of pulmonary hypertension was a conclusion of an expert consensus by the World Health Organization based on clinical trials. However, over time, the accumulating data made the thresholds unreliable. Given the ethical concerns of an invasive procedure without an underlying pathology, it was impossible to measure the normative values of mPAP via RHC in individuals. One of the most important factors that led to a change in the criteria was a meta-analysis led by Kovacs et al. [5]. This study of 1187 participants from 13 countries concluded that the supine *mPAP* at rest was 14.0 ± 3.3 mmHg in healthy individuals, and it was unaffected by sex and ethnicity. The upper normal limit of mPAP was 20.6 mmHg in the supine position. Therefore, the mPAP value >20 mmHg was pathological after considering a 2 standard deviation increase to the mean value.

The reliability of the new criteria was under question, as it risked overdiagnosis of patients. Additionally, it raised questions regarding treatment pathways for individuals with previously defined "borderline mPAP values" between 20 and 24 mmHg [6]. In an extensive review of the available literature, a meta-analysis of 16, 482 patients concluded that patients with mild pulmonary hypertension with mPAP 19–24 mmHg had an increase in the risk of all-cause mortality (RR 1.52; 95% CI, 1.32–1.74; $P < 0.001$; $I^2 = 47\%$) [7]. A retrospective analysis of 547 patients supported a similar conclusion. In such patients, an elevated mPAP between 21 and 24 mmHg was an independent predictor of poor survival probability [8].

Regardless of the statistical evidence to support a revised mPAP threshold, experts agree that a simple increase in mPAP alone is not sufficient or reliable to [6] derive a diagnosis of pulmonary hypertension. The physiological basis of this is the probability that it might also be due to a rise in cardiac output (CO) and pulmonary artery wedge pressure (PAWP). In order to hemodynamically characterize PH, as shown in **Table 1**, the sixth WSPH introduced pulmonary vascular resistance (PVR) as well as PAWP [9]. According to the 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension, this introduction allows pre-capillary pulmonary

Definitions	mPAP	PAWP	PVR
Pre-capillary PH	>20 mmHg	≤15 mmHg	≥3 WU
Isolated post-capillary PH (IpcPH)	>20 mmHg	>15 mmHg	<3 WU
Combined pre- and post-capillary PH (CpcPH)	>20 mmHg	>15 mmHg	PVR ≥ 3 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min		

Table 1.
Hemodynamic definitions of pulmonary hypertension.

hypertension to be differentiated from elevated PAP. This is because it is important to differentiate pulmonary vascular disease (PVD) from left heart disease (LHD), elevated pulmonary blood flow, and increased intrathoracic pressure [10].

A retrospective analysis aimed to define the relationship between PVR and survival in patients with mPAP > 20 mmHg. The study established that in patients with an mPAP threshold of greater than 20 mmHg, a linear relation between PVR and mortality for values < 6 WU was appreciated [11].

Inconsistencies were also noted in the PVR cut-off threshold, which was set at 3 WU in the sixth WSPH. Consequently, a recent study evaluated that PVR values ≥3 WU prevented an early Pulmonary arterial hypertension (PAH) diagnosis as a cut-off value ≥2 WU was already associated with pulmonary vascular disease [12]. The complete criterion for diagnosing pulmonary hypertension is mPAP greater than 20 mmHg, PAWP of 15 mmHg or less, and PVR greater than or equal to 3 WU [10]. Patients with pulmonary hypertension are categorized into three major groups: pre-capillary, post-capillary, and combined pre- and post-capillary PH. The pre-capillary PH is a primary elevation in the pulmonary arterial system. For example, conditions belonging to Groups 1, 3, 4, and 5, such as PAH, can lead to a mPAP >20 mmHg and PVR ≥2 WU. On the contrary, Groups 2 and 5 can result in either isolated post-capillary PH or combined pre- and post-capillary PH [13].

By revising the definition, a sizable subgroup of patients who were previously thought to be normal are now classified under PH. This revision emphasizes the importance of early diagnosis in the PH criteria [14]. Where there was skepticism around the increased number of patients from the revised criteria, it also hints at a possibility of a patient population being protected by being in the buffer zone two standard deviations above the normal. The REVEAL registry highlighted that a 2-year delay in the PH diagnosis and symptom onset had increased the burden of diseases [15]. This is compelling clinical justification to accept the newly defined pulmonary hypertension criterion for treatment and diagnosis.

3. Classification of pulmonary hypertension

Multiple clinical diseases are divided into groups by the WHO classification (**Table 2**) based on shared characteristics in the clinical presentation, pathological findings, hemodynamic characteristics, and therapeutic strategy [9, 10]. Therefore, the underlying causes of abnormal mPAP, PVR, and PCWP are divided into five main categories:

3.1 Group 1: pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is largely idiopathic, hereditary with a BMPR2 mutation carrier [16], or drug/toxin-induced, affecting females and the younger population. Besides these, some of the less common causes of PAH include veno-occlusive diseases, persistent pH of newborns, or underlying conditions such as connective tissue disorders, HIV, and portal hypertension. The algorithm to diagnose PAH is the absence of any alternative PH pathology and threshold values of mPAP >20, PWAP ≤ 15 mmHg, or PVR ≥ 3 WU, fulfilling the criteria for pre-capillary PH [17]. Group 1 is divided into two broad categories based on treatment and prognosis. The first subgroup includes patients with positive vasoreactivity testing. These are patients with a decrease of more than 10 mmHg but less than 40 mmHg in the Mpap [18]. This

1. Pulmonary arterial hypertension (PAH).	• Idiopathic. • Hereditary. • Drug and toxin-induced. • pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis-like features in PAH. • Persistent pulmonary hypertension of a newborn. • Associated with the following diseases: ○ Connective tissue disease. ○ Portal hypertension. ○ Congenital heart disease. ○ Schistosomiasis. ○ HIV infection.
2. Pulmonary hypertension due to left heart disease.	• PH due to heart failure with preserved ejection fraction. • PH due to heart failure with reduced ejection fraction. • Valvular heart disease. • Postcapillary PH due to Congenital/acquired cardiovascular conditions.
3. Pulmonary hypertension due to lung disease and/or hypoxia.	• Obstructive lung diseases. • Restrictive lung diseases. • Pulmonary diseases with mixed restrictive/obstructive patterns. • Hypoxia without lung disease. • Developmental lung disorders. • Alveolar hypoventilation syndrome.
4. Pulmonary hypertension due to pulmonary artery obstruction.	• Chronic thromboembolic PH. • Other pulmonary artery obstructions. • Sarcomas. • Other malignant tumors (renal, uterine, germ cell tumor of the testis, other tumors). • Non-malignant tumors (uterine leiomyoma). • Arteritis without connective tissue disease. • Congenital pulmonary artery stenosis. • Hydatidosis.
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms.	• Hematological disorders: ○ chronic hemolytic anemia. ○ myeloproliferative disorders. • Systemic disorders like neurofibromatosis and sarcoidosis. • Metabolic disorders like Gaucher disease, glycogen storage disease, • Fibrosing mediastinitis, • Chronic renal failure (with/without dialysis), • Pulmonary tumorous thrombotic microangiopathy and HIV.

Table 2.
Clinical classification of pulmonary hypertension [10].

Definitive associations	Possible associations
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	l-Tryptophan
Benfluorex	St. John's wort
Mitomycin C (PVOD)	Amphetamines
Toxic rapeseed oil	IFN-α and -β
	Alkylating agents
	Bosutinib
	Direct-acting antiviral agents against hepatitis C virus
	Leflunomide

Table 3.
Drugs and toxins resulting in potential pulmonary hypertension [21].

group of individuals has a better treatment response to calcium channel blockers and, thus, a good prognosis [19]. The second subgroup includes patients with pulmonary capillary hemangiomatosis and pulmonary veno-occlusive disease (PVOD). Treatment of this subgroup risks the development of pulmonary edema and, therefore, poor survival chances [20]. The 2022 ESC/ERS guidelines for diagnosing and treating pulmonary hypertension have established an updated list of drugs and toxins that possibly establish or aggravate the underlying PAH (**Table 3**) [10].

3.2 Group 2: pulmonary hypertension due to left-sided heart disease (LHD) (PH-LHD)

As elaborated in **Table 2**, Group 2 includes a patient population with PH caused by a left-sided heart pathology. These can be due to heart failure with reduced or preserved LVEF, valvular heart diseases, or any pathology that results in post-capillary PH [20].

3.3 Group 3: pulmonary hypertension caused by chronic lung disease (CLD) (PH-CLD) and/or hypoxia

In this group of patients with PH due to lung diseases, chronic obstructive pulmonary diseases (COPD) are the most important cause [22]. Pulmonary hypertension results from a complex nature of decreased functional status and worsening hypoxemia [23]. Studies have identified that in individuals suffering from severe emphysema, the mPAP has an inverse relation with arterial PO2 and a direct association with PCWP. Consequently, there is a close relationship between mPAP, PVR, and the degree of alveolar hypoxia [24, 25]. Therefore, this category falls under the pre-capillary hemodynamic threshold ranges by the new definition.

3.4 Group 4: pH caused by pulmonary artery obstruction

In this subset of patients with PH, pathology arises from obstructed pulmonary arteries such as chronic thromboembolic PH (CTEPH), tumors, and pulmonary artery stenosis. CTEPH potentially results from chronic obstruction with thrombi and as a small vessel disease [25].

3.5 Group 5: miscellaneous mechanisms

Patients with a multifactorial pathophysiological response were often diagnosed with hematologic or systemic disorders, such as sickle cell anemia, sarcoidosis, glycogen storage disease, and Gaucher's [21]. Therefore, it would be likely to find pre- and post-capillary PH mechanisms. The classification groups of PH are originally the same as proposed in the sixth WSPH and the 2015 ESC/ERS Guidelines for diagnosing and treating pulmonary hypertension [26]. Exceptions include updated recommendations that reposition vasoreactive patients with idiopathic pulmonary arterial hypertension (IPAH) [10].

4. Clinical characteristics

4.1 History and physical examination

Pulmonary hypertension (PH) comprises a heterogeneous group of disorders that result from various pathophysiological mechanisms but are all characterized by an elevated mean pulmonary arterial pressure (mPAP) of ≥20 mmHg at rest [9]. The early clinical symptoms of PH are typically nonspecific or easily attributable to comorbid conditions, including congestive heart failure, coronary artery disease, pulmonary embolism, and chronic obstructive pulmonary disease. Hence, diagnosis can be challenging and requires a stepwise evaluation [27]. A detailed history, physical examination, and a high suspicion index are essential to diagnosing PH [28]. The suspicion index should be particularly high in patients presenting with conditions associated with PH, including sickle cell anemia, systemic sclerosis, and HIV. There is a well-documented lag between symptom onset and clinical diagnosis, as evidenced in a study by Humbart et al., who reported that there is an average delay of 27 months from symptom onset to final diagnosis [29]. This delay may be attributed to a lack of screening guidelines for PH in asymptomatic individuals, including in high-risk groups, which contributes to a significant delay in diagnosis [18]. The hallmark initial manifestation of PH includes dyspnea on exertion, while multiple nonspecific symptoms may also be present. Dyspnea could be accompanied by exhaustion, chest tightness, or presyncope initially while exercising and then later at rest [26]. Clinical manifestations in accordance with the progression of PH have been given in **Table 4**. These include fatigue, generalized weakness, early exhaustion, tachycardia, hemoptysis, and syncope/presyncope or light-headedness [26]. Patients may also present with signs of advanced PH leading to right ventricular failure and systemic volume overload state such as weight gain, peripheral edema (e.g., ankle edema), ascites, and abdominal, jugular venous distention, hepatomegaly, hepatojugular reflex, and low-volume arterial pulses [26]. Pulmonary artery (PA) enlargement due to progressive PH may lead to physical manifestations comprising angina, i.e., chest pain on exertion, hoarseness of voice, cough, wheezing, lower respiratory tract infections, and atelectasis [30]. These symptoms manifest due to the compression of various anatomical structures by the enlarged PA, including the left main coronary artery (LMCA), left recurrent laryngeal nerve leading to Ortner Syndrome, and bronchi [13, 30]. Patients may also present with clinical signs owning to underlying comorbidities such as arthralgias, skin rash, cough, history of thrombosis, and daytime sleepiness [13]. Hence, not only a physical examination but also a patient's family, sexual, and travel histories are equally essential when

WHO functional class	Clinical characteristics
Class I	No symptoms; Can perform ordinary physical activity.
Class II	Comfortable at rest; Routine activities cause symptoms of dyspnea, fatigue, angina, or pre-syncopal features.
Class III	Comfortable at rest; Less than ordinary activity causes symptoms.
Class IV	Cannot perform any activity without symptoms. Dyspnea and/or fatigue at rest.

Table 4.
Clinical presentation of pulmonary hypertension.

evaluating them for suspected PH. Multiple findings may be present on physical exam in patients with associated chronic lung diseases, including telangiectasias, Raynaud's phenomenon, digital clubbing, ulceration, symptoms associated with gastroesophageal reflux, crackles/wheezing on lung auscultation, joint edema as well as erythema [13].

4.2 Clinical findings on auscultation

Auscultatory examination suggestive of PH includes accentuated P2, i.e., second heart sound associated with the pulmonic component due to loud closure of the pulmonic valve at the base of the heart as the initial physical finding [31, 32]. As the disease progresses, right ventricular dysfunction occurs. This results in jugular venous distention due to elevated jugular venous pressure, which is seen with a prominent "a" wave with an eventual prominent "v" wave, suggesting tricuspid regurgitation [31]. Tricuspid (pan systolic murmur along the left sternal border that increases in intensity upon inspiration) and pulmonary regurgitation (diastolic murmur also known as the Graham Steell murmur along the left sternal border indicating pulmonary valve insufficiency), right-sided S3 and S4 gallop may be heard, while right parasternal heave may also be present on palpation [33]. Increased PA pressures and eventual RV heart failure may cause these. These may be associated with ascites, abdominal distention, hepatosplenomegaly, and dependent peripheral edema. As right heart failure progresses, pallor, delayed capillary refill, peripheral cyanoses, and dizziness may be evident, indicating decreased cardiac output [13].

4.3 Clinical findings on electrocardiogram

Electrocardiography (EKG) is one of the initial tests obtained from patients to confirm the presence of PH and identify the underlying etiology. The cardiac rhythm in patients with PH is usually sinus. However, electrical abnormalities exist due to RV and RA enlargement. Although a normal EKG report does not exclude the diagnosis of PH, an abnormal finding points toward severe disease, particularly QRS and QTc prolongation [34–38]. Other EKG changes are nonspecific and comprise signs of right-sided cardiac strain and chamber enlargement, including P-pulmonale, right ventricular strain, right-axis deviation, right bundle branch block (RBBB), right ventricular (RV) hypertrophy, and QTc prolongation. As the disease progresses, supraventricular tachycardia, including atrial fibrillation and atrial flutter, may manifest, while ventricular arrhythmia is rare [36]. The EKG findings suggestive of poor prognosis include the increased amplitude of P wave in lead II, $P \geq .25$ mV in

lead II, qR in V1, and the presence of World Health Organization (WHO) criteria for RV hypertrophy [35, 37]. This criterion includes a small S wave in lead V1 (R > 7 mm, S < 2 mm, and R/S ratio > 1), a tall R wave, a tall S wave with a small R wave in lead V_5 or V_6 (R/S ratio < 1), and right axis deviation (QRS axis > 90°) [33]. Electric abnormalities suggestive of right-sided cardiac strain comprise ST-segment depressions and T-wave inversions in the anterior leads, i.e., V1 through V4. Electrocardiographic features indicative of RA enlargement include a P-wave greater than 2.5 mm in leads II, III, and aVF [33].

4.4 Clinical findings on chest radiography

Pulmonary hypertension (PH) is frequently associated with bilateral enlargement of hilar structures representing the central, right, and left main PA. Chest radiography is abnormal in 90% of the patients with PH at the time of diagnosis [39], and clinical features usually show right-ventricular enlargement, a prominent central PA (PA enlargement), peripheral hypervascularity, water-shaped cardiac silhouette, and pruning of peripheral vessels [40–42]. In severe cases of PH, cardiac silhouette on chest radiograph indicates an enlarged RV causing cardiomegaly on the posteroanterior view and increased retrosternal filling on the lateral view [43]. In addition, clinical signs of left-sided heart disease are appreciated. These include pleural effusions, enlargement of the left heart, Kerley B lines, and signs of pulmonary diseases, such as flattened diaphragm (COPD), hyperlucency (COPD), volume loss, and reticular opacifications (fibrotic lung disease) may also be present [40–42].

4.5 Clinical findings on pulmonary function testing and arterial blood gas analysis

Patients with PAH demonstrate reduced diffusion lung capacity for carbon monoxide (DLCO), and low DLCO of <45% is associated with poor prognosis [44, 45]. Patients also present with slightly low partial pressure of oxygen (PaO2), which results in alveolar hyperventilation. This leads to low-to-low normal partial pressure of carbon dioxide (PaCO2) [46].

4.6 Clinical findings on chest computed tomography and abdominal ultrasound

A chest CT helps to identify additional information, which raises suspicion for PH. These clinical features include enlarged diameter of PA, ascending aorta/main PA diameter ratio of >0.9, and enlargement of right heart chambers (RA or RV). The PA diameter of ≥30 mm, with a right ventricular outflow tract thickness of ≥6 mm, and > 140 degrees of septal deviation or right ventricle/left ventricle ratio ≥ 1, is suggestive of PH [47]. Abdominal ultrasound may detect secondary liver and kidney damage as PH progresses, leading to liver abnormalities and/or portal hypertension [48].

4.7 Clinical findings on echocardiography

A transthoracic echocardiogram is considered to be the most important non-invasive diagnostic procedure to estimate the probability of PH, while right heart catheterization (RHC) is required for the confirmation of diagnosis as well as to guide therapy [26, 49–51]. The echocardiogram aids in grading the probability of PH into

Peak tricuspid regurgitant velocity (m/s)	Presence of other PH signs on echocardiography	Echocardiographic probability of PH
< 2.8 or not measurable	No	Low
<2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	Intermediate
2.9–3.4	Yes	High
>3.4	Not required	High

Table 5.
Echocardiographic probability of PH [13].

Ventricles	RV/LV basal diameter/ area ratio > 1.0	Flattening of the interventricular septum (left ventricular eccentric index > 1.1 in systole and/or diastole)	Tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio < 0.55 mm/mmHg
Pulmonary artery	Right ventricular outflow tract acceleration time < 105 ms and/or mid-systolic notching	Early diastolic pulmonary regurgitation velocity > 2.2 m/s	PA > Aortic root diameter PA diameter > 25 mm
Inferior vena cava and right atrium	Inferior vena cava diameter > 21 mm with decreased inspiratory collapse (<50% with a sniff or < 20% with quiet respiration)	RA area (end-systole) > 18 cm^2	

Table 6.
Echocardiographic signs suggestive of PH [13].

three categories, namely low, intermediate, and high probabilities, as laid down by the European Society of Cardiology guidelines shown in **Table 5**. The echocardiographic signs indicative of PH is given in **Table 6.**

4.8 Clinical findings on cardiopulmonary exercise testing (CPET)

Clinical findings on cardiopulmonary exercise testing (CPET) is an important tool to identify the underlying cause of PH when clinical symptoms are induced by exercise. Pulmonary arterial hypertension (PAH) results in low oxygen pulse (VO2/HR), low peak oxygen uptake (VO2), elevated ventilatory equivalent for carbon dioxide (VE/VECO2), and a reduced end-tidal partial pressure of carbon dioxide (PETCO2) [52, 53].

5. Diagnostic evaluation

Despite advanced technological developments to evaluate PH, a considerable delay has been reported between symptom onset and clinical diagnosis. In accordance with the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL registry), 21% of the patients experienced a 2-year delay in receiving the final

diagnosis of PH [54]. This persistent time lag in reaching final diagnosis across the past decades led to the 6th World Symposium of Pulmonary Hypertension (WSPH) task force to update the recommended diagnostic algorithm with the aim of facilitating a more efficient evaluative process [32]. For instance, patients who present with multiple confounding medical comorbidities are complex and challenging to treat, hence prompting the recommendation that they should be referred early to specialized PH centers known as Pulmonary Hypertension Care Centers accredited by the Pulmonary Hypertension Association to guide their long-term management [22, 54–57]. Patients presenting with dyspnea in the absence of signs of specific heart or lung disease or those who present with clinical signs/symptoms indicative of PH should be carefully evaluated with a detailed medical and family history, thorough physical examination, monitoring of body vitals including blood pressure, pulse rate, oxygen saturation, and serum tests comprising brain natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP) with a resting electrocardiogram. This first stage points toward a potential cardiopulmonary cause. The second stage includes a detailed cardiac assessment using echocardiography and the lungs (if the medical history is indicative) using pulmonary function tests, chest imaging modalities comprising X-ray and computed tomography, as well as cardiopulmonary exercise testing in certain cases.

6. Conclusion

Pulmonary hypertension is a multifactorial disease-carrying a high risk of morbidity and mortality. It requires a specialized PH expert center to carry out consistent, detailed evaluation and management. The disease involves progressive loss and obstruction of the pulmonary vasculature, resulting in elevated mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR), which can eventually lead to RV dysfunction and right ventricular heart failure. Careful assessment of medical history, physical examination, echocardiograms, and hemodynamic parameters are essential to identify and classify the different forms of PH.

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References

[1] Mandras SA, Mehta HS, Vaidya A. Pulmonary hypertension: A brief guide for clinicians. Mayo Clinic Proceedings. 2020;**95**:1978-1988. DOI: 10.1016/j.mayocp.2020.04.039

[2] Kondo T, Okumura N, Adachi S, Murohara T. <editors' choice> Pulmonary hypertension: Diagnosis, management, and treatment. Nagoya Journal of Medical Science. 2019;**81**: 19-30. DOI: 10.18999/nagjms.81.1.19

[3] Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, et al. A global view of pulmonary hypertension. The Lancet Respiratory Medicine. 2016;**4**:306-322. DOI: 10.1016/S2213-2600(15)00543-3

[4] Hoeper MM, Humbert M. The new haemodynamic definition of pulmonary hypertension: Evidence prevails, finally! European Respiratory Journal. 2019;**53**:1900038. DOI: 10.1183/13993003.00038-2019

[5] Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: A systematic review. European Respiratory Journal. 2009;**34**:888-894. DOI: 10.1183/09031936.00145608

[6] Gibbs J, Simon R, Torbicki A. Proposed new pulmonary hypertension definition: Is 4 mm(Hg) worth re-writing medical textbooks? European Respiratory Journal. 2019;**53**:1900197. DOI: 10.1183/13993003.00197-2019

[7] Kolte D, Lakshmanan S, Jankowich MD, Brittain EL, Maron BA, Choudhary G. Mild pulmonary hypertension is associated with increased mortality: A systematic review and meta-analysis. Journal of the American Heart Association. 18 Sep 2018;**7**(18):e009729. DOI: 10.1161/JAHA.118.009729

[8] Douschan P, Kovacs G, Avian A, Foris V, Gruber F, Olschewski A, et al. Mild elevation of pulmonary arterial pressure as a predictor of mortality. American Journal of Respiratory and Critical Care Medicine. 2018;**197**:509-516. DOI: 10.1164/rccm.201706-1215OC

[9] Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. European Respiratory Journal. 2019;**53**:1801913. DOI: 10.1183/13993003.01913-2018

[10] Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal. 2022;**43**:3618-3731. DOI: 10.1093/eurheartj/ehac237

[11] Puigrenier S, Giovannelli J, Lamblin N, De Groote P, Fertin M, Bervar J-F, et al. Mild pulmonary hemodynamic alterations in patients with systemic sclerosis: Relevance of the new 2022 ESC/ERS definition of pulmonary hypertension and impact on mortality. Respiratory Research. 2022;**23**:284. DOI: 10.1186/s12931-022-02205-4

[12] Xanthouli P, Jordan S, Milde N, Marra A, Blank N, Egenlauf B, et al. Haemodynamic phenotypes and survival in patients with systemic sclerosis: The impact of the new definition of pulmonary arterial hypertension. Annals of the Rheumatic Diseases.

2020;**79**:370-378. DOI: 10.1136/annrheumdis-2019-216476

[13] Oldroyd HS, Manek G, Sankar A, Bhardwaj A. Pulmonary hypertension. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023

[14] Maron BA, Humbert M. Finding pulmonary arterial hypertension—Switching to offense to mitigate disease burden. JAMA Cardiology. 2022;7:369. DOI: 10.1001/jamacardio.2022.0011

[15] McGoon MD, Miller DP. REVEAL: A contemporary US pulmonary arterial hypertension registry. European Respiratory Review. 2012;**21**:8-18. DOI: 10.1183/09059180.00008211

[16] Montani D, Girerd B, Jaïs X, Laveneziana P, Lau EMT, Bouchachi A, et al. Screening for pulmonary arterial hypertension in adults carrying a *BMPR2* mutation. European Respiratory Journal. 2021;**58**:2004229. DOI: 10.1183/13993003.04229-2020

[17] Maron BA, Abman SH, Elliott CG, Frantz RP, Hopper RK, Horn EM, et al. Pulmonary arterial hypertension: Diagnosis, treatment, and novel advances. American Journal of Respiratory and Critical Care Medicine. 2021;**203**:1472-1487. DOI: 10.1164/rccm.202012-4317SO

[18] Dunlap B, Weyer G. Pulmonary hypertension: Diagnosis and treatment. American Family Physician. 2016;**94**:463-469

[19] Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;**111**:3105-3111. DOI: 10.1161/CIRCULATIONAHA.104.488486

[20] Beshay S, Guha A, Sahay S. Evaluation, diagnosis, and classification of pulmonary hypertension. Methodist DeBakey Cardiovascular Journal. 2021;**17**:86. DOI: 10.14797/OCDF4453

[21] Simonneau G, Hoeper MM. The revised definition of pulmonary hypertension: Exploring the impact on patient management. European Heart Journal Supplements. 2019;**21**:K4-K8. DOI: 10.1093/eurheartj/suz211

[22] Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, et al. Pulmonary hypertension in chronic lung disease and hypoxia. European Respiratory Journal. 2019;**53**:1801914. DOI: 10.1183/13993003.01914-2018

[23] Cuttica MJ. Pulmonary hypertension associated with lung diseases and hypoxemia. Heart Failure Reviews. 2016;**21**:299-308. DOI: 10.1007/s10741-016-9551-x

[24] Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE. Hemodynamic characterization of patients with severe emphysema. American Journal of Respiratory and Critical Care Medicine. 2002;**166**:314-322. DOI: 10.1164/rccm.2107027

[25] Simonneau G, Torbicki A, Dorfmüller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. European Respiratory Review. 2017;**26**:160112. DOI: 10.1183/16000617.0112-2016

[26] Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed

by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). The European Respiratory Journal. 2015;**46**:903-975. DOI: 10.1183/13993003.01032-2015

[27] Stringham R, Shah NR. Pulmonary arterial hypertension: An update on diagnosis and treatment. American Family Physician. 2010;**82**:370-377

[28] Nauser TD, Stites SW. Diagnosis and treatment of pulmonary hypertension. American Family Physician. 2001;**63**:1789-1798

[29] Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: Results from a national registry. American Journal of Respiratory and Critical Care Medicine. 2006;**173**:1023-1030. DOI: 10.1164/rccm.200510-1668OC

[30] Abdelnabi M, Eshak N, Attia I, Abdelkader M, Saleh Y, Almaghraby A. Ortner's syndrome due to large bilharzial pulmonary artery aneurysm. Echocardiography. 2020;**37**:1109-1110. DOI: 10.1111/echo.14757

[31] Sahay S. Evaluation and classification of pulmonary arterial hypertension. Journal of Thoracic Disease. 2019;**11**:S1789-S1799. DOI: 10.21037/jtd.2019.08.54

[32] Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, et al. Diagnosis of pulmonary hypertension. European Respiratory Journal. 2019; **53**:1801904. DOI: 10.1183/13993003.01904-2018

[33] McGoon MD, FusteT V, Freeman WK, Edwards WD, Scott JP. Pulmonary hypertension. In: Giuliani ER, Gersr BJ, McGoon MD, Hayes DL, Schaff HV, editors. Mayo Clinic Practice of Cardiology. 3rd ed. St. Louis: Mosby; 1996. pp. 1815-1836

[34] Sun P-Y, Jiang X, Gomberg-Maitland M, Zhao Q-H, He J, Yuan P, et al. Prolonged QRS duration: A new predictor of adverse outcome in idiopathic pulmonary arterial hypertension. Chest. 2012;**141**:374-380. DOI: 10.1378/chest.10-3331

[35] Wanamaker B, Cascino T, McLaughlin V, Oral H, Latchamsetty R, Siontis KC. Atrial arrhythmias in pulmonary hypertension: Pathogenesis, prognosis and management. Arrhythmia & Electrophysiology Review. 2018;**7**:43-48. DOI: 10.15420/aer.2018.3.2

[36] Bossone E, Paciocco G, Iarussi D, Agretto A, Iacono A, Gillespie BW, et al. The prognostic role of the ECG in primary pulmonary hypertension. Chest. 2002;**121**:513-518. DOI: 10.1378/chest.121.2.513

[37] Henkens IR, Gan CT-J, van Wolferen SA, Hew M, Boonstra A, Twisk JWR, et al. ECG monitoring of treatment response in pulmonary arterial hypertension patients. Chest. 2008;**134**:1250-1257. DOI: 10.1378/chest.08-0461

[38] Rich JD, Thenappan T, Freed B, Patel AR, Thisted RA, Childers R, et al. QTc prolongation is associated with impaired right ventricular function and predicts mortality in pulmonary hypertension. International Journal of Cardiology. 2013;**167**:669-676. DOI: 10.1016/j.ijcard.2012.03.071

[39] Galiè N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension: The task force on diagnosis and treatment of pulmonary arterial

hypertension of the European Society of Cardiology. European Heart Journal. 2004;**25**:2243-2278. DOI: 10.1016/j.ehj.2004.09.014

[40] Ascha M, Renapurkar R, Tonelli A. A review of imaging modalities in pulmonary hypertension. Annals of Thoracic Medicine. 2017;**12**:61-73. DOI: 10.4103/1817-1737.203742

[41] Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. Journal of the American College of Cardiology. 2013;**62**:D42-D50. DOI: 10.1016/j.jacc.2013.10.032

[42] Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. Annals of Internal Medicine. 1987;**107**:216-223. DOI: 10.7326/0003-4819-107-2-216

[43] Krowka MJ. Pulmonary hypertension: Diagnostics and therapeutics. Mayo Clinic Proceedings. 2000;**75**:625-630. DOI: 10.4065/75.6.625

[44] Trip P, Nossent EJ, de Man FS, van den Berk IAH, Boonstra A, Groepenhoff H, et al. Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: Patient characteristics and treatment responses. European Respiratory Journal. 2013;**42**:1575-1585. DOI: 10.1183/09031936.00184412

[45] Sun X-G, Hansen JE, Oudiz RJ, Wasserman K. Pulmonary function in primary pulmonary hypertension. Journal of the American College of Cardiology. 2003;**41**:1028-1035. DOI: 10.1016/S0735-1097(02)02964-9

[46] Mélot C, Naeije R. Pulmonary vascular diseases. Comprehensive Physiology. 2011;**1**:593-619. DOI: 10.1002/cphy.c090014

[47] Swift AJ, Dwivedi K, Johns C, Garg P, Chin M, Currie BJ, et al. Diagnostic accuracy of CT pulmonary angiography in suspected pulmonary hypertension. European Radiology. 2020;**30**:4918-4929. DOI: 10.1007/s00330-020-06846-1

[48] Rosenkranz S, Howard LS, Gomberg-Maitland M, Hoeper MM. Systemic consequences of pulmonary hypertension and right-sided heart failure. Circulation. 2020;**141**:678-693. DOI: 10.1161/CIRCULATIONAHA.116.022362

[49] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. 2015;**28**:1-39.e14. DOI: 10.1016/j.echo.2014.10.003

[50] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography. Journal of the American Society of Echocardiography. 2010;**23**:685-713. DOI: 10.1016/j.echo.2010.05.010

[51] Foale R, Nihoyannopoulos P, McKenna W, Kleinebenne A, Nadazdin A, Rowland E, et al. Echocardiographic measurement of the normal adult right ventricle. Heart. 1986;**56**:33-44. DOI: 10.1136/hrt.56.1.33

[52] Sun X-G, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation.

2001;**104**:429-435. DOI: 10.1161/hc2901.093198

[53] Dumitrescu D, Nagel C, Kovacs G, Bollmann T, Halank M, Winkler J, et al. Cardiopulmonary exercise testing for detecting pulmonary arterial hypertension in systemic sclerosis. Heart. 2017;**103**:774-782. DOI: 10.1136/heartjnl-2016-309981

[54] Brown LM, Chen H, Halpern S, Taichman D, McGoon MD, Farber HW, et al. Delay in recognition of pulmonary arterial hypertension. Chest. 2011;**140**:19-26. DOI: 10.1378/chest.10-1166

[55] Vachiéry J-L, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, et al. Pulmonary hypertension due to left heart disease. European Respiratory Journal. 2019;**53**:1801897. DOI: 10.1183/13993003.01897-2018

[56] Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. European Respiratory Journal. 2019;**53**:1801915. DOI: 10.1183/13993003.01915-2018

[57] Sahay S, Melendres-Groves L, Pawar L, Cajigas HR. Pulmonary hypertension care center network: Improving care and outcomes in pulmonary hypertension. Chest. 2017;**151**:749-754. DOI: 10.1016/j.chest.2016.10.043

Chapter 3

Right Heart Catheterization: The Role of Hemodynamic Assessment in the Diagnosis and Management of Pulmonary Arterial Hypertension

Aaron C. Miller

Abstract

Right heart cardiac catheterization remains the gold standard for the diagnosis of pulmonary arterial hypertension and is an essential component to classify and characterize the type of pulmonary hypertension. Performing a diagnostic right heart catheterization for the assessment of pulmonary hypertension requires a detailed understanding of waveform physiology, cardiac output assessment, right ventricular afterload evaluation, vasoreactivity testing, and accurate left atrial pressure measurement. Furthermore, right heart catheterization can be used to unmask left heart disease by utilizing fluid challenge testing and exercise right heart catheterization. Additionally, the determination of pulmonary artery compliance, in conjunction with pulmonary vascular resistance, can help provide a more comprehensive assessment of pulmonary artery load and right ventricular afterload. Lastly, hemodynamic information obtained by right heart catheterization can be used as a risk assessment tool to guide management and predict mortality.

Keywords: right heart catheterization, pulmonary hemodynamics, pulmonary artery pressure, pulmonary vascular resistance, hemodynamic risk assessment

1. Introduction

Pulmonary hypertension generally refers to an abnormal elevation of the pulmonary artery pressure, and it represents a complex and multifactorial disease process with significant morbidity and mortality implications for patients. Right heart catheterization remains the gold standard for the appropriate classification and diagnosis of pulmonary hypertension. Accurately diagnosing and classifying pulmonary hypertension requires careful analysis and accurate interpretation of the hemodynamic waveforms obtained during right heart catheterization. Accurate interpretation of hemodynamic data is a powerful skillset that provides important risk assessment information and serves as the basis of treatment decisions that can have a meaningful impact on patient morbidity, mortality, and quality of life.

The World Symposium on Pulmonary Hypertension last convened in 2019 and defined pulmonary hypertension as a mean pulmonary artery pressure (mPAP) >20 mmHg [1]. Hemodynamically, pulmonary hypertension is further classified into pre-capillary, post-capillary, and combined pre- and post-capillary pulmonary hypertension. Pre-capillary pulmonary hypertension is defined as a mPAP >20 mmHg, a pulmonary vascular resistance (PVR) >2 wood units, and a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg [2]. Post-capillary pulmonary hypertension is generally associated with left heart disease and is defined by a mPAP >20 mmHg, PVR ≤ 2 woods units, PCWP >15 mmHg. Lastly, combined pre- and post-capillary hypertension is characterized by a mPAP >20 mmHg, PVR > 2 woods units, and a PCWP >15 mmHg. **Table 1** provides a summary of the different hemodynamic classifications of pulmonary hypertension.

Once the hemodynamic classification is determined, then pulmonary hypertension can be further classified into one of five groups, as outlined in **Table 2**. To appropriately classify pulmonary hypertension, additional testingis needed to assess for left heart disease, chronic pulmonary disease or sleep-related breathing disorders, chronic thromboembolic disease or other pulmonary artery obstruction, and other disorders such as hematologic disorders, systemic disorders, chronic kidney disease/end-stage renal disease, and fibrosing mediastinitis. Basic testing that is essential for the appropriate classification of pulmonary hypertension includes the following: laboratory testing to assess for HIV, chronic kidney disease, connective tissue disease, and hematologic/systemic/metabolic disorders; complete pulmonary function testing, arterial blood gas analysis, chest X-ray, CT chest imaging, ventilation-perfusion scan, transthoracic echocardiogram, and polysomnography. This initial barrage of testing helps clarify the clinical context with which to interpret the hemodynamic results. Interestingly, only the Group 2 and Group 5 patients have a post-capillary component to their pulmonary hypertension. Groups 1, 3, 4, and 5 can all have a pre-capillary hemodynamic pattern depending on the results of the previously mentioned test results. Therefore, an appropriate classification of pulmonary hypertension requires both the cardiac catheterization results and a thorough clinical evaluation. For many patients, there could be a combination of pulmonary hypertension groups contributing to the development of pulmonary hypertension. For these more complicated, multifactorial cases, identification and optimization of all underlying disorders must be performed as part of a patient's treatment plan.

Finally, hemodynamic data from a right heart catheterization can be utilized to assess the function and afterload of the right ventricle. Right ventricular failure represents the leading cause of death in pulmonary hypertension patients [3, 4]. Therefore, accurately

Classification	Hemodynamic criteria
Pre-capillary PH	mPAP>20 mmHg, PAWP≤15 mmHg, PVR > 2 WU
Post-capillary PH	mPAP>20 mmHg, PAWP>15 mmHg, PVR < 2 WU
Combined pre–/post-capillary PH	mPAP>20 mmHg, PAWP>15 mmHg, PVR > 2 WU

This table summarizes the hemodynamic classification of pulmonary hypertension. The mPAP, PAWP, PVR are obtained during the right heart cardiac catheterization.
Abbreviations: PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; WU, wood units.
Source: Eur Heart J. 2022 Oct 11;43(38):3618-3731.

Table 1.
Hemodynamic classification of pulmonary hypertension.

Group 1: Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 PAH associated with drugs/toxins
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal Hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn
Group 2: Pulmonary hypertension (PH) associated with left heart disease
2.1 Heart failure:
2.1.1 heart failure with preserved ejection fraction
2.1.2 heart failure with reduced ejection fraction
2.2 Valvular heart disease
2.3 Congenital/acquired cardiovascular conditions
Group 3: PH associated with lung diseases and/or hypoxia
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with mixed restrictive/obstructive pattern
3.4 Hypoventilation syndromes
3.5 Hypoxia without lung disease (e.g. high altitude)
3.6 Developmental lung disorders
Group 4: PH associated with pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
Group 5: PH with unclear and/or multifactorial mechanisms
5.1 Hematological disorders
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Chronic renal failure with or without hemodialysis
5.5 Pulmonary tumor thrombotic microangiopathy
5.6 Fibrosing mediastinitis
Source: Eur Heart J. 2022 Oct 11;43(38):3618-3731.

Table 2.
Clinical classification of pulmonary hypertension.

assessing right ventricular function using hemodynamics is an essential component of treatment planning for pulmonary arterial hypertension. Cardiac output measurements are obtained during right heart catheterization to assess right ventricular function

and to help calculate pulmonary vascular resistance and pulmonary artery compliance (PAC). PVR and PAC provide important information regarding right ventricular afterload and can provide crucial information to optimize right ventricular function.

2. Right heart cardiac catheterization: Essential components and evidenced-based measurements for pulmonary hypertension assessment

2.1 Basic setup and supplies

Right heart catheterization remains the gold standard for the diagnosis and classification of pulmonary hypertension. Therefore, completing the right heart catheterization requires expertise in terms of setup and pressure acquisition. The basic essential components of performing a right heart catheterization are a catheter; a transducer; a fluid-filled tubing to connect the catheter to the transducer; a physiologic recorder to display, analyze, print, and store the hemodynamic waveforms [5].

The most common catheter used to measure right heart and pulmonary pressures is the Swan-Ganz catheter. At a minimum, the Swan-Ganz catheter has a distal port for pressure measurements, a proximal port that is located 30 cm from the tip used for manual thermodilution cardiac output measurements, a balloon tip for flotation to the pulmonary artery, and a thermistor at the distal tip which allows for the measurement of temperature changes duringthe thermodilution cardiac output assessment. The Swan-Ganz catheter is generally 110 cm in length and comes in different sizes, usually ranging from 5 to 8 Fr. Also, the Swan-Ganz catheter comes in different types. Usually, the Swan-Ganz catheters that are placed in critically ill patients for hemodynamic assessment include a thermal filament that allows for continuous thermodilution cardiac output monitoring. The Swan-Ganz catheters used in the cardiac catheterization lab do not have the thermistor coil since thermodilution cardiac output measurements in the cardiac catheterization lab can be done manually by infusing chilled saline through the proximal port (**Figure 1**).

The transducer and tubing are also important components of accurate hemodynamic assessment. The tubing should be stiff pressure tubing to avoid waveform damping. The transducers are generally table-mounted and fluid-filled. The pressure

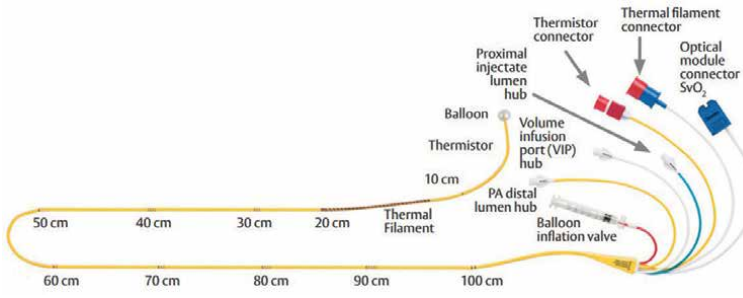

Figure 1.
This image identifies the major components of a Swan-Ganz catheter (Model 782F75M). This type of catheter has a thermal filament that is generally used in a critical care setting for continuous cardiac output monitoring. (Source: Edwards Lifesciences, Irvine, CA, USA).

Figure 2.
This is an image of a transducer. The small black object in the transducer unit is the membrane that deforms creating the electrical signal that generates waveforms. (Source: N Engl J Med. 2017 Apr 6;376(14):e26.)

wave is transmitted through the fluid-filled catheter, through the stiff pressure tubing, and finally to a membrane in the transducer. The pressure transmitted from the catheter deforms the membrane resulting in a change in electrical resistance. This electrical signal is transmitted to the analyzing computer and converted to a graphic representation of the pressure wave (**Figure 2**).

The Swan-Ganz catheter, tubing, and transducer circuit must be set up appropriately to ensure accurate right heart and pulmonary pressure assessment. Important principles to help optimize setup and data integrity include the following: 1) avoid air, blood, kinks, and soft tubing as these can result in overdamping the signal, 2) use the shortest tubing length possible and avoid the use of numerous stop cocks as this can result in underdamping the waveform. Over- or under-damping results in inaccurate pressure measurements which can compromise the integrity of the waveforms resulting in misdiagnosis or incorrect classification of a patient's pulmonary hypertension. If the hemodynamic waveforms do not appear normal or the pressures do not make sense physiologically, then a square wave test can be used during the right heart catheterization to determine if the waveforms are over- or under-damped.

Lastly, to ensure the waveform pressures are accurate during set-up, the catheter or transducer should be zeroed and aligned with the mid-thoracic level [6]. At the mid-thoracic level, the catheter is level with the left atrium. Making the transducer level with the left atrium will allow for the most accurate measurement of the pulmonary artery wedge pressure (PAWP). The PAWP is one of the most important determinants when classifying the type of pulmonary hypertension; therefore, obtaining an accurate PAWP is essential for making the appropriate pulmonary hypertension diagnosis and determining the appropriate treatment for the patient.

2.2 Evidence-based measurements recommended to be obtained during right heart catheterization

Ideally, right heart cardiac catheterizations should be performed at an expert pulmonary hypertension center. When the right heart catheterization is performed at

an expert center, the frequency of serious events is only 1.1%, and procedure-related mortality is only .055% [7]. In addition to these favorable complication rates, an expert center can review the hemodynamic waveforms and interpret them in the context of the patient's clinical presentation and diagnostic testing.

During the right heart catheterization, there are hemodynamic parameters that are directly measured and others that are calculated. The measured values are as follows: right atrial pressure, systolic pulmonary artery pressure, diastolic pulmonary artery pressure, mean pulmonary artery pressure, pulmonary artery wedge pressure, cardiac output, mixed venous oxygen saturation measured from the pulmonary artery, arterial oxygen saturation, and systemic blood pressure. The calculated values determined by right heart catheterization results are as follows: pulmonary vascular resistance, pulmonary vascular resistance index, total pulmonary resistance, cardiac index, stroke volume, stroke volume index, and pulmonary artery compliance. Pulmonary vascular resistance is especially important in the classification of pulmonary hypertension; therefore, it must be calculated in all patients undergoing right heart cardiac catheterization [2].

When measuring cardiac output during the right heart catheterization, there are 2 most common methods utilized: 1) indirect Fick, 2) thermodilution cardiac output. The indirect Fick is calculated based on the following formula:

$$CO = \frac{\left[\mathrm{O_2\ consumption}\left(\frac{mL}{\min}\right)\right]}{\mathrm{Arterial\ O_2\ content - Venous\ O_2\ content}}. \quad (1)$$

Oxygen content of the blood can be calculated by the following formula:

$$Ca\mathrm{O_2} = \left(1.34 \times hgb \times Sa\mathrm{O_2}\right) + \left(Pa\mathrm{O_2} \times .003\right)$$

The same formula can be used to calculate the O_2 content of venous blood, but the SvO_2 would be used instead of the SaO_2 for venous blood. Therefore, in the cardiac catheterization lab, the hemoglobin, SaO_2, SvO_2 can be easily obtained to determine the arteriovenous oxygen difference (A-VO_2). For indirect Fick, the oxygen consumption must be calculated. The Dehmer Formula is the simplest and only requires the patient's body surface area. Other formulas, such as the LaFarge and Bergstra formulas, can also be used. Direct Fick is considered the gold standard for measuring cardiac output, but this method is not clinically practical since oxygen consumption must be simultaneously measured during the right heart catheterization [2].

Thermodilution cardiac output is the second most common method used for measuring cardiac output, and it is the preferred method for determining cardiac output in pulmonary hypertension patients [8]. Thermodilution cardiac output is determined by injecting 10 mL of chilled normal saline through the proximal port located 30 cm from the catheter tip. The chilled saline causes the blood to transiently cool, creating a decrease in blood temperature that is detected by the thermistor at the distal tip of the Swan-Ganz catheter. The blood eventually warms back to normal with time. This temperature change creates a skewed bell-curve graphic. The area under the bell curve is inversely proportionate to the cardiac output based on the modified Stewart-Hamilton conservation of heat equation. This equation is as follows:

$$CO(Td) = \frac{\left[(Tb - Ti)\, x\, Vi\, x\, K\right]}{\left(\int \Delta Tb\, x\, dt\right)} \quad (2)$$

In the numerator of the modified Stewart-Hamilton equation, Tb = blood temperature, Ti = injectate temperature, Vi = injectate volume, and K = correction constant. The denominator of the equation represents the area under the thermodilution curve. Therefore, a large area under the curve will result in low cardiac output. Alternatively, a smaller area under the curve will correspond to normal or high cardiac output. **Figure 3** illustrates this important concept about the relationship between the area under the thermodilution curve and the cardiac output.

The thermodilution and indirect Fick cardiac output measurements were compared in a large clinical trial [8]. The results of this trial demonstrated a poor correlation between indirect Fick and thermodilution. Interestingly, thermodilution cardiac output results correlated significantly to patient mortality, whereas the indirect Fick measurements did not have a mortality correlation. Therefore, thermodilution cardiac output has become preferred since it correlates with patient mortality, whereas indirect Fick does not. The cardiac output range in this study varied from 1.7–7.8 L/m, making thermodilution a reliable measure of cardiac output within the studied range. When comparing direct Fick to thermodilution across the cardiac output range, thermodilution correlated closely to direct Fick in both the low and normal cardiac output groups. Hence, thermodilution can be reliable even in low cardiac output states [9].

Thermodilution cardiac output has been thought to be inaccurate in patients with severe tricuspid regurgitation. In theory, severe tricuspid regurgitation would cause

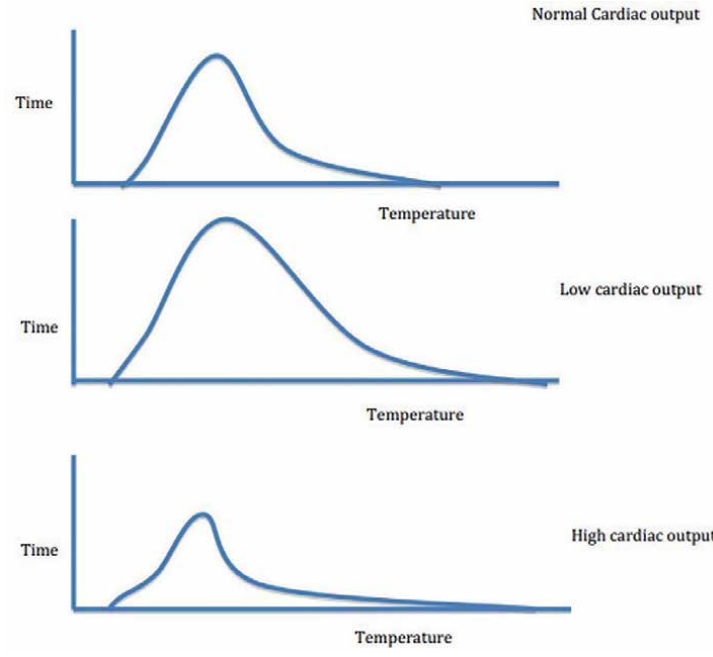

Figure 3.
These three different graphs represent different thermodilution curves corresponding to a normal, low, and high cardiac index. These curves illustrate the concept that the area under the thermodilution curve are inversely proportionate to cardiac output. (Source: Top Companion Anim Med. 2016 Sep;31(3):100-108.)

the chilled 10 mL normal saline injectate to recirculate, which would potentially cause a falsely low cardiac output. In reality, this recirculation theory does not seem to be true. When the thermodilution cardiac output method was compared to direct Fick across a spectrum of mild/moderate and severe tricuspid regurgitation patient groups, there was no significant variability in cardiac output measurements, even in the severe tricuspid regurgitation group. Therefore, thermodilution cardiac output can still be used in both low cardiac output states and in patients with severe tricuspid regurgitation.

In some cases, patients with pulmonary hypertension have intra-cardiac shunts. In patients with an intra-cardiac shunt, thermodilution cardiac output is unreliable and should be avoided. In these cases, direct Fick cardiac output assessment is preferred [2].

3. Right heart catheterization: fundamentals of waveform interpretation

The main goal of a hemodynamic study is to accurately reproduce and analyze changes in pressure in a heart chamber or in the pulmonary circulation during the cardiac cycle. The pressure transducer used in the cardiac catheterization procedure contains a diaphragm that generates an electrical current when it is triggered by fluid waves that are transmitted from the heart through the Swan-Ganz catheter tip. This electrical current from the transducer is used to generate pressure waves over time. These generated waves can then be utilized to diagnose and characterize the type of pulmonary hypertension present in a patient.

The waveforms obtained during a right heart catheterization procedure should be carefully analyzed to ensure proper fidelity. Also, the waveforms should be carefully aligned with an electrocardiogram (EKG) to appropriately identify the filling and emptying phases of the cardiac cycle. Furthermore, careful attention to identifying end-expiration is important since this is the respiratory cycle phase where the pulmonary pressures are least impacted by pressure shifts associated with the chest wall and diaphragm. All pressures, especially the PAWP, should be measured at end-expiration without breath holding [2].

3.1 Atrial waveforms

The right atrium and left atrium have similar appearing waveforms; however, the normal pressure in the atria is slightly different. The right atrium is characterized by a relatively low pressure of 2–6 mmHg, while the left atrial pressure is normally 4–12 mmHg.

Generally, an atrial waveform has an "a" wave and a "v" wave as well as an "x" and "y" descent. The "a" wave corresponds to the pressure increase associated with atrial contraction. This first atrial wave usually follows the P wave on EKG by approximately 80 msec. The "x" descent follows the "a" wave and represents the pressure decay associated with atrial relaxation and the downward movement of the atrioventricular (AV) junction that occurs due to ventricular contraction. The "v" wave follows the "x" descent and corresponds to passive venous filling during atrial diastole. This occurs in conjunction with ventricular systole when the tricuspid valve is closed. The "v" wave can be identified as occurring at the end of the T wave of the EKG. The "y' descent occurs following the "v" wave and represents rapid emptying of the right atrium when the tricuspid valve opens. In a normal clinical setting, the "a" wave is generally taller than the "v" wave. **Figure 4** demonstrates how to identify the "a" and "v" waves relative to an EKG on an actual patient.

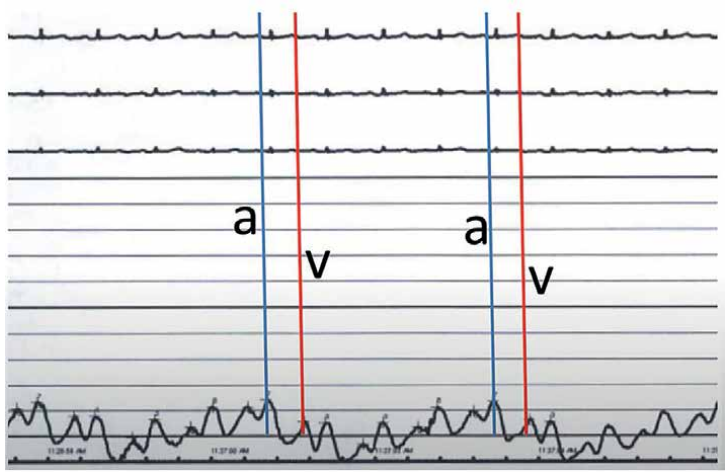

Figure 4.
This figure represents a right atrial waveform with the "a" and 'V' waves labeled relative to the EKG. Image created by Aaron Miller.

Conceptually, the right and left atrial waveforms have "a" and "v" waves and an x and y descent. However, the left atrial waveform does have some important differences compared to the right atrial waveform. First, the fine details of the left atrial waveform are not present due to damping associated with the longer distance the pressure signal is traveling from the left side of the heart to the catheter tip in the pulmonary artery. Second, the "v" wave is generally slightly taller than the "a" wave, related to the slightly higher-pressure gradients on the left side of the heart compared to the right heart. Lastly, there is a much larger delay in the left atrial waves and descents relative to the EKG tracing compared to the right atrium. Again, this reflects the increased distance the signal travels from the left atrium to the catheter tip in the pulmonary artery. The left atrial "a" wave occurs 240 msec after the P wave on EKG. The "v" wave occurs shortly after the T wave on the EKG.

Measuring the left atrial pressure from the pulmonary arteries requires temporary, complete occlusion of the pulmonary artery with the balloon on the tip of the Swan-Ganz catheter. Obtaining a high-quality pulmonary capillary wedge pressure is arguably the most difficult wave to obtain during a right heart catheterization, and it is the most important component to distinguish pre- and post-capillary pulmonary hypertension. Identifying a high-quality PCWP requires a few key components. First, there should be a clearly identifiable "a" and "v" wave. Recognizing a clear "a" and "v" wave can help the provider ensure the balloon is not under-wedged. In the case of an under-wedged waveform, the wave tends to resemble a damped pulmonary artery waveform and loses the "a" and "v" waves. Second, there should be obvious respiratory variation. In the case of an over-wedged waveform, the PCWP waveform tends to flatten and lose clear variability with respiratory effort. Third, when the balloon is deflated in a wedge position, the waveform should quickly return to a pulmonary artery waveform. Fourth, blood gas can be collected from the distal tip of the Swan-Ganz catheter when the catheter tip balloon is inflated. This blood gas sample should have a $SpO_2 > 90\%$ [10]. Lastly, fluoroscopy can be used to confirm the correct position of the Swan-Ganz catheter tip. The ideal location for the catheter tip on fluoroscopy is below the level of the left atrium in West lung zone 3. **Figure 5** visually summarizes the key components of the PAWP waveform.

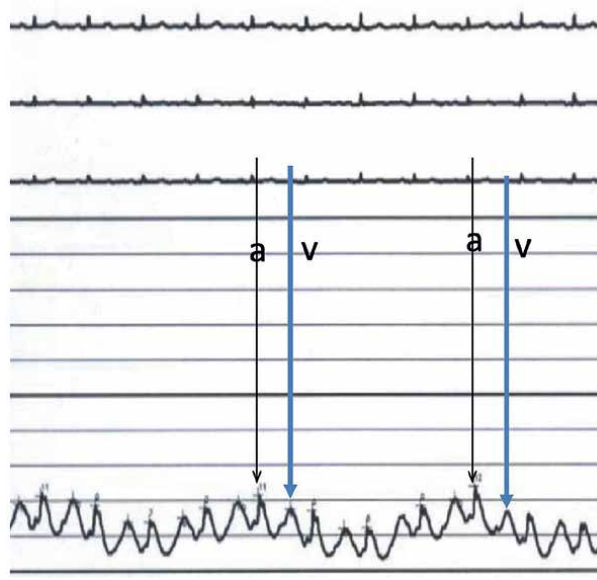

Figure 5.
This image demonstrates a PAWP waveform. Relative to the EKG, the "a" and 'V' waveforms have been identified. Image created by Aaron Miller.

3.2 Right ventricular waveform

Normally, the right ventricle systolic pressure is 20–30 mmHg, and the diastolic pressure is 0–8 mmHg. In the absence of significant tricuspid valve disease, the diastolic right ventricular pressure should be similar to the right atrial pressure. The pressure tracing increases during right ventricular systole. The pressure waveform will then decrease with pressure decay after the systole completes, and the downsloping side of the waveform corresponds to a rapid filling phase. A slow-filling phase precedes the systolic phase of the next cardiac cycle. **Figure 6** summarizes the key components of the RV waveform.

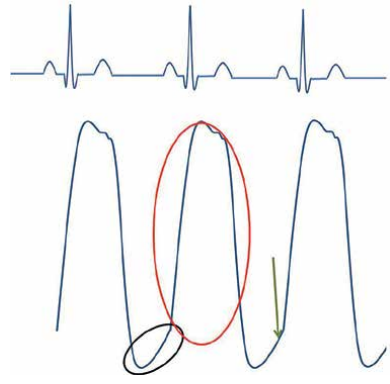

Figure 6.
This schematic represents an RV waveform. The red circle corresponds to an increase in pressure associated with systole followed by a rapid decrease in pressure as the RV empties into the PA. The black circle corresponds to the diastolic or filling phase of the RV. Sometimes, there is an "a" wave located at the green arrow that represents atrial kick. Image created by Aaron Miller.

Measured values	Normal range
Right atrial pressure, mean (RAP)	2–6 mmHg
Right ventricular systolic pressure	15–30 mmHg
Right ventricular diastolic pressure	0–6 mmHg
Pulmonary artery pressure, systolic (sPAP)	15–30 mmHg
Pulmonary artery pressure, diastolic (dPAP)	4–12 mmHg
Pulmonary artery pressure, mean (mPAP)	8–20 mmHg
Pulmonary artery wedge pressure (PAWP)	≤15 mmHg
Cardiac output (CO)	4–8 L/m
Mixed venous oxygen saturation (SvO_2)[a]	65–80%
Arterial Oxygen saturation (SaO_2)	95–100%
Calculated Values	
Pulmonary vascular resistance (PVR)[b]	.3–2.0 WU
Total pulmonary resistance (TPR)[c]	<3 WU
Cardiac Index (CI)	2.5–4.0 L/m/m^2
Stroke Volume (SV)	60–100 mL
Pulmonary artery compliance (PAC)[d]	>2.3 mL/mmHg

WU, Wood units
[a]*SvO_2 is derived from a blood sample collected from the pulmonary artery*
[b]*PVR = (mPAP-PAWP)/CO*
[c]*TPR = mPAP/CO*
[d]*PAC = SV/(sPAP-dPAP)*
Source: Eur Heart J. 2022 Oct 11;43(38):3618-3731.

Table 3.
Normal hemodynamic values obtained during right heart catheterization.

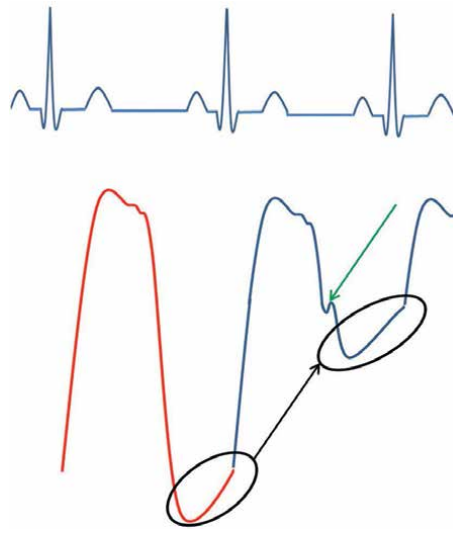

Figure 7.
This schematic represents the transition from RV to PA during a right heart catheterization and highlights two important difference between the RV and PA waveforms. The red waveform represents the RV pressure. The black circles demonstrate the diastolic step-up that occurs when the catheter tip enters the PA. Also, the green arrow points to the dicrotic notch that is also a characteristic feature of the PA. Image created by Aaron Miller.

3.3 Pulmonary artery waveform

The pulmonary artery pressure waveform has a normal systolic pressure of 20–30 mmHg and a diastolic pressure of 4–12 mmHg. **Table 3** summarizes all of the normal hemodynamic values commonly measured during right heart catheterization. In the setting of a normal pulmonic valve, the systolic pulmonary artery pressure should be similar to the systolic right ventricular pressure. Likewise, the diastolic pulmonary artery pressure is generally slightly higher than the PAWP. Also, one helpful concept that helps differentiate the right ventricular waveform from the pulmonary artery waveform is a diastolic step-up in pressure between the right ventricular diastolic pressure and the pulmonary artery diastolic pressure. This pressure change represents the increased resistance due to the high pulmonary artery surface area. These concepts can help confirm that the recorded hemodynamic pressures during a right heart cardiac catheterization make sense physiologically. Excessive pressure gradients should prompt a close assessment of the waveform quality, and it should prompt a close evaluation of cardiac structure on imaging to explain the gradients. Excessive pressure gradients could represent significant valvular disease.

Another important component of the pulmonary artery waveform that distinguishes it from the right ventricular waveform is the dicrotic notch found on the curve's down-sloping side. The dicrotic notch represents the pulmonic valve's closure, marking the beginning of diastole. **Figure 7** provides a schematic that visually highlights the major differences between the RV and PA waveforms.

4. Right heart catheterization: role and interpretation of vasoreactivity testing, fluid challenge testing, and exercise testing

Vasoreactivity testing plays an important role in evaluating and managing patients with pulmonary arterial hypertension. The main purpose of this test is to determine which patients would benefit from treatment with high dose calcium channel blockers as opposed to traditional pulmonary vasodilators. Based on the most recent guideline recommendations, vasoreactivity testing should be completed in patients with idiopathic pulmonary arterial hypertension, hereditary pulmonary arterial hypertension, and drug/toxin-induced pulmonary arterial hypertension [2]. This vasodilator challenge test can be completed with inhaled iloprost or inhaled nitric oxide. Intravenous epoprostenol can be used but requires incremental dose increases and serial measurements, which can significantly prolong the procedure, making this approach less practical [11]. Intravenous adenosine had been previously listed as an acceptable medication for use during vasoreactivity testing; however, due to frequent side effects, adenosine is no longer recommended.

A positive vasoreactivity test response can be defined by the following criteria: decrease in mPAP by $\geq$10 mmHg to reach an absolute value in the mPAP to $\leq$40 mmHg with an unchanged or improved cardiac output. This positive response is not common in patients with PAH. In a study that included 557 patients with Idiopathic PAH, approximately 13% of patients had a positive vasodilator response [11]. In patients with PAH due to causes other than Idiopathic PAH, such as anorexigen use, HIV, connective tissue disease, congenital heart disease, and pulmonary veno-occlusive disease, a sustained positive vasodilator response was rare, with the exception of patients with anorexigen-associated PAH. In patients with anorexigen PAH, there was close to a 10% success rate of sustained response to calcium channel

blockers [12]. Patients with the appropriate pulmonary arterial hypertension diagnosis and a positive vasodilator challenge test can be treated with high dose calcium channel blocker therapy. Commonly used calcium channel blockers and acceptable doses are as follows: nifedipine 20 mg 2–3 times daily, amlodipine 15–30 mg daily, diltiazem 120–360 mg twice daily, felodipine 15–30 mg daily. The general approach is to start a low calcium channel blocker dose and gradually increase it as tolerated [11].

There are clinical scenarios where calcium channel blocker therapy may not be an ideal treatment option. Patients with a depressed cardiac output on right heart catheterization, systemic hypotension, known hypersensitivity to calcium channel blockers, history of postural hypotension, hemodynamic instability, bradycardia, or heart block may not tolerate calcium channel blocker therapy. Also, patients who do not undergo vasoreactivity testing or patients with a negative vasoreactivity test should not be started on calcium channel blocker therapy [11–15].

Lastly, vasoreactivity testing can provide important prognostic information depending on the calcium channel blocker response duration. After initiating calcium channel blocker therapy, patients must be followed closely at intervals of 3–6 months to ensure adequate clinical response. Repeat right heart catheterization is recommended in that follow-up interval to determine if the patient has a persistent vasodilator response and to determine if the patient achieved an ideal hemodynamic improvement defined by mPAP<30 mmHg and PVR < 4 WU. Calcium channel blocker therapy can be increased if there is persistent vasoreactivity or if the patient has not reached ideal hemodynamic improvement. The 5-yr survival in patients who were long-term responders to CCB was >90% [11]. Therefore, vasoreactivity testing can also be used as a tool for predicting mortality.

One important purpose of performing a right heart catheterization in diagnosing PAH is to exclude left heart disease and confidently confirm the presence of pulmonary vascular disease. More recent epidemiologic data from the USA and Europe indicate that PAH is now frequently diagnosed in older patients >65 years old [16]. This older patient population can be much more challenging to confirm PAH due to co-morbid conditions such as essential hypertension, diabetes, atrial fibrillation, and BMI > 30 kg/m^2 since these comorbid conditions are also risk factors for heart failure with preserved ejection fraction (HFpEF), coronary artery disease and other left heart issues [17, 18]. Distinguishing pulmonary vascular disease from left heart disease can be challenging, and the pulmonary capillary wedge pressure can be normal in patients with left heart disease who are euvolemic due to optimized diuretic dosing. Fluid challenge testing and exercise testing during the right heart catheterization can help unmask left heart disease and more confidently confirm the presence of pulmonary vascular disease.

The fluid challenge test can be helpful in revealing left ventricular diastolic dysfunction in patients with normal pulmonary capillary wedge pressure and clinical risk factors for left heart disease. Generally, the fluid challenge test is performed by giving approximately 500 mL (7–10 mL/kg) normal saline bolus over 5–10 minutes. If the pulmonary capillary wedge pressure increases to ≥18 mmHg after the fluid challenge, then this would confirm left heart disease [18]. Unfortunately, additional data is needed to better validate this fluid challenge assessment. Also, there is insufficient data assessing the hemodynamic response to a fluid challenge in patients with PAH [19].

The gold standard assessment for cardiopulmonary hemodynamics during exercise and to define exercise PH is the exercise right heart cardiac catheterization [20]. For the purposes of pulmonary hypertension assessment, the main purpose of an exercise right heart catheterization is to assess patients with unexplained dyspnea

Classification	Hemodynamic criteria
Exercise changes in PAH	mPAP/CO slope > 3 mmHg/L/min
	PAWP/CO slope < 2 mmHg/L/min
Exercise changes in left heart disease	mPAP/CO slope <3 mmHg/L/min
	PAWP/CO slope >2 mmHg/L/min
	PAWP increase to >25 mmHg

This table summarizes the hemodynamic classification for exercise-induced pulmonary hypertension. The mPAP, PAWP, CO are measured during the right heart cardiac cathterization at consistent intervals during exercise.
Abbreviations: PAH, pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; CO, cardiac output
Source: Eur Heart J. 2022 Oct 11;43(38):3618-3731.

Table 4.
Hemodynamic classification of exercise-induced pulmonary hypertension.

and normal resting hemodynamics. This test allows early detection of pulmonary vascular disease or left heart disease. Furthermore, exercise hemodynamics can reveal important prognostic and functional information in patients at risk for developing PAH such as systemic sclerosis patients [21]. Exercise right heart cardiac catheterization has been shown to have a safety profile and a complication rate similar to resting right heart catheterization [20].

The exercise right heart catheterization should follow an incremental exercise protocol such as a ramp or step protocol. Repeat hemodynamic measurements should be gathered at predefined time intervals to maximize the clinical utility of the test. The most important hemodynamic variables to be collected during the exercise right heart catheterization include the following: right atrial pressure (RAP), pulmonary artery pressure, pulmonary artery wedge pressure (PAWP), cardiac output, cardiac index, heart rate, and systemic blood pressure. In patients with pulmonary vascular disease, there is a steep rise in mean pulmonary artery pressure relative to the change in cardiac output. The mPAP/CO slope will be >3 mmHg/L/min in patients with early pulmonary vascular disease. Additionally, the PAWP should not increase significantly relative to the patient's cardiac output making the PAWP/CO slope < 2 mmHg/L/min. Conversely, patients with left heart disease would be expected to have an mPAP/CO slope < 3 mmHg, L/min and a PAWP/CO slope > 2 mmHg/L/min [2]. Additionally, to confirm a diagnosis of HFpEF, the PAWP should increase to >25 mmHg during supine exercise [22] (**Table 4**).

5. Right heart catheterization: evaluating right ventricular afterload using pulmonary vascular resistance and pulmonary artery compliance

Normally, the right ventricle (RV) is thin-walled and crescent-shaped, and it is designed to accommodate the entire systemic venous return to the heart while maintaining the same effective stroke volume as the left ventricle. The RV relies on the highly distensible, low resistance pulmonary arteries to accomplish this purpose. In pulmonary arterial hypertension (PAH), the pulmonary arteries become remodeled, causing them to lose their normal distensibility and low impedance, essential in maintaining normal RV function. The changes to the pulmonary circulation from pulmonary vascular disease in PAH result in increased RV afterload and eventual RV failure and death. Measuring RV afterload is an important component of PAH diagnosis and

management. In clinical practice, RV afterload can be best understood and measured using the three-element Windkessel model [23], which defines RV afterload in three components: pulmonary vascular resistance (PVR), pulmonary arterial compliance (PAC), and pulmonary arterial impedance (PAI). These three components represent both static and dynamic components of RV afterload.

PVR is the most used parameter of the three components of RV afterload since it is an essential component in the definition of pulmonary arterial hypertension. Interestingly, PVR is estimated to represent approximately 75% of total RV afterload which partly explains why it's a necessary component to the definition of PAH [24]. PVR represents a static component of RV afterload and is determined by the principles of Poiseuille's law, which establishes an inverse relationship to the fourth power between the radius of the blood vessel and resistance. Due to the static nature of PVR, it does not account for the pulsatile component of pulmonary circulation or the effect of blood volume [25]. Therefore, assessing RV afterload requires an assessment of both static and dynamic parameters to more accurately determine which patients truly have pulmonary vascular disease.

Pulmonary artery compliance (PAC) is a second important component of RV afterload measurement, and it accounts for approximately one-fourth of the total RV afterload [23]. The PAC is generally distributed throughout the pulmonary circulation and includes both distal and proximal pulmonary vessels. The main, proximal left and right pulmonary arteries together contribute approximately one-fifth of the total PAC. The distal pulmonary arteries contribute the major portion of both resistance and compliance in the pulmonary circulation. Normally, the pulmonary circulation has a high compliance that is designed to handle large blood volume changes with exercise while maintaining a relatively normal pressure. In pulmonary arterial hypertension, pulmonary artery compliance decreases [26, 27], and it correlates with pulmonary hypertension severity [27]. Additionally, a decrease in pulmonary artery compliance has been associated with pulmonary vascular remodeling in the proximal pulmonary arteries [28–30]. Interestingly, evidence suggests that decreased PAC occurs early in the disease process of PAH and can be present in patients with normal resting pulmonary pressure. In these patients with low PAC and normal resting PA pressures, an exercise right heart catheterization would be needed to unmask exercise-induced pulmonary hypertension [25]. The PAC decreases due to disruption of the internal elastic lamina, which generally occurs prior to pulmonary artery smooth muscle cell hypertrophy and endothelial cell proliferation [31].

Calculating PAC in vivo is challenging, and there are many proposed formulas for measuring arterial stiffness [32]. In clinical practice, PAC is most commonly estimated by the following formula: PAC = stroke volume/pulmonary artery pulse pressure. Pulmonary artery pulse pressure is the difference between systolic and diastolic pulmonary artery pressures. PAC is an important parameter for estimating RV afterload, and it has been shown to be an independent predictor of mortality in patients with PAH, scleroderma-related PAH, and congestive heart failure [26, 33, 34].

Decreasing PAC significantly impacts RV function by increasing pulsatile workload [35]. This increased workload forces the RV to generate increased pressure to eject blood [36]. These changes ultimately lead to increased RV wall stress and increased O_2 consumption. Structurally, in response to this increased workload, the RV becomes hypertrophied and dilated, which progresses to reduced cardiac output, ultimately leading to RV failure and death [37, 38]. A decrease in PAC has been independently associated with RV dysfunction, dilation, and hypertrophy [39].

Compared to PVR, the contribution of PAC to RV stroke work index is 1.2–18-fold higher, highlighting the significant contribution of PAC on RV function [39].

The final component of measuring RV afterload is pulmonary artery impedance (PAI). Fundamentally, PAI evaluates the ratio of the pulmonary arterial pressure waveform to the blood flow waveform throughout the cardiac cycle [32]. In essence, PAI represents the opposition of proximal pulmonary arteries to pulsatile blood flow. Therefore, the impedance is another dynamic measurement of RV afterload, and it accounts for the effect of blood mass on RV afterload. Additionally, it factors in the stiffness of the proximal pulmonary arteries. The contribution of PAI on total RV afterload is small and is not routinely used [23]. In clinical practice, the role and relevance of PAI have not been clearly established. More studies are needed to better determine the clinical application of PAI.

6. Right heart catheterization: using hemodynamic results as a risk assessment tool to guide management and predict mortality

Pulmonary hypertension management follows an organized, goal-directed approach to ensure patients are responding favorably to treatment. Risk assessment tools such as REVEAL 2.0 [40], REVEAL Lite 2.0, [41] COMPERA 2 [42], FRENCH Risk Score [43], and the 2015 ESC/ERS Guidelines Risk Tool [44] can be used to assess response to treatment and mortality risk on an ongoing basis. Guidelines in pulmonary arterial hypertension management recommend the regular use of a risk assessment tool when managing and evaluating pulmonary arterial hypertension patients. These risk assessment tools are superior to physician gestalt alone and can provide inciteful and objective information about how well patients are responding to treatment [45]. When patients have not reached a low-risk status based on the risk assessment tools, then the treatment approach should be escalated if appropriate until low-risk status is achieved.

Within the REVEAL 2.0 and the 2015 ESC/ERS Guidelines risk assessment tools, there are hemodynamic variables that have a meaningful and significant impact on mortality as isolated numbers. Also, the change in some of these hemodynamic variables in response to treatment has an impact on patient mortality. In the 2015 ESC/ERS Guideline Risk Assessment tool, there are a few hemodynamic variables with important prognostic significance which are as follows: right atrial pressure (RAP), cardiac index (CI), and SvO_2. Conceptually, these variables are markers of RV dysfunction severity which is generally the most common cause of death in patients with pulmonary arterial hypertension. Therefore, preserving RV function is the cornerstone of treatment in patients with pulmonary arterial hypertension. Multiple clinical studies have been performed over the years to confirm that CI>/= 2.5 L/m/m^2 is an independent predictor of mortality in patients with PAH [46, 47]. Additionally, patients were more likely to have a worse outcome if the CI did not improve by >/= .5 L/m/m^2 or if the CI did not improve by>2.5 L/m/m^2. This supports the importance of utilizing hemodynamic data as a marker of mortality but also as a marker of treatment response. Mean RAP >10 mmHg and a SvO_2 < 65% at baseline were also associated with higher mortality rates [46]. If the SvO_2 increased to >65% on follow-up after treatment for 1 year, patients have a more favorable outcome from a mortality perspective.

Another commonly used risk assessment tool that includes hemodynamic parameters to measure risk and estimate mortality is the REVEAL 2.0 score. In the latest

edition of the risk score, the PVR and mean RAP are included in the risk assessment tool. For this score, if the PVR is <5 Wood units, then the patient gets a reduced score which would favor an improved mortality estimation. If the mean RAP is >20 mmHg, then the patient would receive a higher total score which would be associated with worse outcomes. In the original study that established the REVEAL score, a multivariate analysis was completed that established PVR and mean RAP as independent predictors of mortality. In the original study, the PVR cutoff was 32 Wood units [48]. The more recent study that led to the revised REVEAL 2.0 score demonstrated that the reduced PVR cutoff of 5 Wood units improved the calculator's predictive power as a risk assessment tool. Therefore, targeting a PVR goal of <5 Wood units is in-line with a goal-directed treatment approach.

The role of mPAP as a measurement of estimated mortality has been unreliable in many previous studies; therefore, mPAP is not included in any of the risk assessment scores. Previous studies have shown that the baseline mPAP and change in mPAP after treatment did not show a significant correlation to increased risk of death [46, 47]. The one exception to this trend was patients who were considered positive vaso-responders when challenged with vasoreactivity testing during cardiac catheterization. Long-term responders to calcium channel blockers successfully maintained a mean PAP of <40 mmHg and had a percent change in mPAP of >31% [11]. The patients who were long-term responders to calcium channel blockers had a significantly improved mortality risk compared to those patients who were unable to maintain a positive response to pulmonary vasodilators.

More recently, a study cohort evaluating a population of patients managed in Japan demonstrated that mean PAP did have a significant correlation with mortality. In this study, patients who achieved a minimum mPAP <42 mmHg had lower mortality rates compared to the nonsurvivor patient group. Interestingly, the few patients who reached a minimum mPAP <42 mmHg in the nonsurvivor group were highly likely to die from causes unrelated to PAH. Also, mPAP data was plotted on a ROC curve for this study. The area under the curve for mPAP was the largest compared to other variables tested, such as BNP, cardiac output, and 6-minute walk distance. These results supported the conclusion that a mPAP cutoff of approximately <40 mmHg could be a useful target for improving survival in PAH patients. Perhaps, based on the results of this study, mPAP will become a more generally accepted marker of treatment response and mortality in patients with PAH.

7. Conclusions

Pulmonary hypertension is a disorder associated with an abnormal elevation of the pulmonary artery pressure, and it represents a complex and multifactorial disease process with significant morbidity and mortality implications for patients. Right heart catheterization remains an essential tool for the appropriate diagnosis and classification of pulmonary hypertension. Performing right heart cardiac catheterization well requires a thorough and methodical approach to ensure all the appropriate supplies are acquired and to ensure the catheterization setup is performed correctly. While obtaining hemodynamic data, careful attention to the waveforms is needed to ensure good data integrity. End-expiratory pressures should be identified and used when interpreting the waveform results. In addition to obtaining waveform data, cardiac output monitoring is performed, preferably using the thermodilution technique. The thermodilution cardiac output can be used in combination with the

mPAP and PAWP waveforms to calculate the PVR, which should always be performed when evaluating a patient for pulmonary hypertension. In the appropriate setting, vasoreactivity testing should be performed to identify patients who would be good candidates for calcium channel blocker therapy. The hemodynamic results can also be used to assess right ventricular afterload and to assess the risk of mortality based on risk assessment scoring systems such as REVEAL 2.0 and the 2015 ESC/ERS risk assessment. Overall, the hemodynamics of pulmonary hypertension can be a powerful diagnostic and management tool when performed correctly and comprehensively.

Conflict of interest

I have conflicts of interest with Janssen Pharmaceuticals and Merck & Co Pharmaceutical company.

Notes/thanks/other declarations

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References

[1] Simonneau G, Montani D, Celemajer D, et al. Hemodynamic definitions and updated clinical classification of pulmonary hypertension. The European Respiratory Journal. 2019;**53**(1):1801913

[2] Humbert M, Kovacs G, Hoeper M, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal. 2022;**43**(38):3618-3731

[3] Schrier R, Bansal S. Pulmonary hypertension, right ventricular failure, and kidney: Different from left ventricular failure? Clinical Journal of the American Society of Nephrology. 2008;**3**(5):1232-1237

[4] Campo A, Mathai SC, Le Pavec J, et al. Outcomes of hospitalisation for right heart failure in pulmonary arterial hypertension. The European Respiratory Journal. 2011;**38**(2):359-367

[5] Ragosta M. Textbook of Clinical Hemodynamics. 2nd ed. Philadelphia: Elsevier; 2018

[6] Kovacs G, Avian A, Olschewski A, Olschewski H. Zero reference level for right heart catheterization. The European Respiratory Journal. 2013;**42**(6):1586-1594

[7] Hoeper M, Lee S, Voswinckel R, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. Journal of the American College of Cardiology. 2006;**48**(12):2546-2552

[8] Opotowsky A, Hess E, Maron B, et al. Thermodilution vs estimated Fick cardiac output measurement in clinical practice: An analysis of mortality from the veterans affairs clinical assessment, reporting, and tracking (VA CART) program and Vanderbilt University. JAMA Cardiology. 2017;**2**(10):1090-1099

[9] Hoeper M, Maier R, Tongers J, et al. Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. American Journal of Respiratory and Critical Care Medicine. 1999;**160**(2):535-541

[10] Viray M, Bonno E, Gabrielle N, et al. Role of pulmonary artery wedge pressure saturation during right heart catheterization: A prospective study. Circulation. Heart Failure. 2020;**13**(11):e007981

[11] Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;**111**(23):3105-3111

[12] Montani D, Savale L, Natali D, et al. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. European Heart Journal. 2010;**31**(15):1898-1907

[13] Opitz C, Wensel R, Bettmann M, et al. Assessment of the vasodilator response in primary pulmonary hypertension. Comparing prostacyclin and iloprost administered by either infusion or inhalation. European Heart Journal. 2003;**24**(4):356-365

[14] Jing ZC, Jiang X, Han ZY, et al. Iloprost for pulmonary vasodilator testing in idiopathic pulmonary arterial hypertension. The European Respiratory Journal. 2009;**33**(6):1354-1360

[15] Baumgartner H, Backer J, Babu-Narayan S, et al. 2020 ESC guidelines

for the management of adult congenital heart disease. European Heart Journal. 2021;**42**(6):563-645

[16] Lau E, Giannoulatou E, Celermajer D, Humbert M. Epidemiology and treatment of pulmonary arterial hypertension. Nature Reviews. Cardiology. 2017;**14**(10):603-614

[17] Kittleson M, Panjrath G, Amancherla K, et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: A report of the American College of Cardiology Solution set Oversight Committee. Journal of the American College of Cardiology. 2023;**81**(18):1835-1878

[18] Vachiery JL, Tedford R, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. The European Respiratory Journal. 2019;**53**(1):1801897

[19] D'Alto M, Romeo E, Argiento P, et al. Clinical relevance of fluid challenge in patients evaluated for pulmonary hypertension. Chest. 2017;**151**(1):119-126

[20] Kovacs G, Herve P, Barbera JA, et al. An official European Respiratory Society statement: Pulmonary haemodynamics during exercise. The European Respiratory Journal. 2017;**50**(5):1700578

[21] Zeder K, Avian A, Bachmaier G, et al. Exercise pulmonary resistances predict long-term survival in systemic sclerosis. Chest. 2021;**159**(2):781-790

[22] Pieske B, Tschope C, Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: The HFA-PEFF diagnostic algorithm: A consensus recommendation from the heart failure association (HFA) of the European Society of Cardiology (ESC). European Heart Journal. 2019;**40**(40):3297-3317

[23] Saouti N, Westerhof N, Postmus P, Vonk-Noordegraaf A. The arterial load in pulmonary hypertension. European Respiratory Review. 2010;**19**(117):197-203

[24] Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013;**62**(16):e147-e239

[25] Thenappan T, Prins K, Pritzker M, et al. The critical role of pulmonary arterial compliance in pulmonary hypertension. Annals of the American Thoracic Society. 2016;**13**(2):276-284

[26] Mahapatra S, Nishimura R, Sorajja P, et al. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. Journal of the American College of Cardiology. 2006;**47**(4):799-803

[27] Sanz J, Kariisa M, Dellegrottaglie S, et al. Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. JACC: Cardiovascular Imaging. 2009;**2**(3):286-295

[28] Dodson R, Morgan M, Galambos C, et al. Chronic intrauterine pulmonary hypertension increases main pulmonary artery stiffness and adventitial remodeling in fetal sheep. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2014;**307**(11):L822-L828

[29] Ooi CY, Wang Z, Tabima D, et al. The role of collagen in extralobar pulmonary artery stiffening in response to hypoxia-induced pulmonary hypertension. American Journal of Physiology. Heart and Circulatory Physiology. 2010;**299**(6):H1823-H1831

[30] Kobs R, Muvarak N, Eickhoff J, et al. Linked mechanical and biological aspects of remodeling in mouse pulmonary arteries with hypoxia-induced hypertension. American Journal of Physiology. Heart and Circulatory Physiology. 2005;**288**(3):H1209-H1217

[31] Wallace W, Nouraie M, Chan S, Risbano M. Treatment of exercise pulmonary hypertension improves pulmonary vascular distensibility. Pulmonary Circulation. 2018;**8**(3):2045894018787381

[32] Ghio S, Schirinzi S, Pica S. Pulmonary arterial compliance: How and why should we measure it? Global Cardiology Science Practise. 2015;**2015**(4):58

[33] Tji-Joong Gan C, Lankhaar J-W, Westerhof N, et al. Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. Chest. 2007;**132**(6):1906-1912

[34] Campo A, Mathai S, Le Pavec J, et al. Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. American Journal of Respiratory and Critical Care Medicine. 2010;**182**(2):252-260

[35] Wang Z, Chesler N. Pulmonary vascular wall stiffness: An important contributor to the increased right ventricular afterload with pulmonary hypertension. Pulmonary Circulation. 2011;**1**(2):212-223

[36] Castelain V, Herve P, Lecarpentier Y, et al. Pulmonary artery pulse pressure and wave reflection in chronic pulmonary thromboembolism and primary pulmonary hypertension. Journal of the American College of Cardiology. 2001;**37**(4):1085-1092

[37] Rich S. Right ventricular adaptation and maladaptation in chronic pulmonary arterial hypertension. Cardiology Clinics. 2012;**30**(2):257-269

[38] Van de Veerdonk MC, Kind T, Tim Marcus J, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. Journal of the American College of Cardiology. 2011;**58**(24):2511-2519

[39] Stevens G, Garcia-Alvarez A, Sahni S, et al. RV dysfunction in pulmonary hypertension is independently related to pulmonary artery stiffness. JACC: Cardiovascular Imaging. 2012;**5**(4):378-387

[40] Benza R, Gomberg-Maitland M, Greg Elliott C, et al. Predicting survival in patients with pulmonary arterial hypertension: The REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. Chest. 2019;**156**(2):323-337

[41] Benza R, Kanwar M, Raina A, et al. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. Chest. 2021;**159**(1):337-346

[42] Hoeper M, Pausch C, Olsson K, et al. COMPERA 2.0: A refined four-stratum risk assessment model for pulmonary arterial hypertension. The European Respiratory Journal. 2022;**60**(1):2102311

[43] Humbert M, Farber H, Ghofrani H-A, et al. Risk assessment in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. The European Respiratory Journal. 2019;**53**(6):1802004

[44] Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the

diagnosis and treatment of pulmonary hypertension. The European Respiratory Journal. 2015;**46**:903-975

[45] Sahay S, Tonelli A, Selej M, et al. Risk assessment in patients with functional class II pulmonary arterial hypertension: Comparison of physician gestalt with ESC/ERS and the REVEAL 2.0 risk score. PLoS One. 2020;**15**(11):e0241504

[46] Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. Journal of the American College of Cardiology. 2002;**40**(4):780-788

[47] Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. The European Respiratory Journal. 2012;**39**(3):589-596

[48] Benza R, Miller D, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation. 2010;**122**(2):164-172

Chapter 4

Left Heart Disease in Pulmonary Hypertension

Ellie Anderson, Mustapha Abubakar, Osman Imam Abbas Ahmed, Jonard Carpio, Rajwinder Nijjar and Ajay Suri

Abstract

Pulmonary hypertension (PH) due to left heart disease (LHD) is the most common type of pulmonary hypertension. Pulmonary hypertension due to LHD has two subgroups: isolated post-capillary PH due to left sided filling pressures, and then in long-standing cases, the pre-capillary component is added due to pulmonary vascular disease developing, which is termed post- and pre-capillary PH. These groups have differing clinical implications. We describe the hemodynamic, from left and right heart cardiac catheterization, pathophysiology, and the role of pulmonary vasodilators and studies of this up to date. We will also discuss the left heart diseases that cause PH, such as congestive heart failure and valvular heart disease. We will also discuss future areas for research in this area of PH.

Keywords: left heart disease, isolated post capillary PH, postcapillary and precapillary PH, left heart catheterization, hemodynamic, valvular heart disease, congestive cardiac failure, pulmonary vasodilators

1. Introduction

Right heart catheterization has been covered extensively in this book. Left heart catheterization is considered the gold-standard test for coronary artery disease diagnosis but can also provide further diagnostic and therapeutic uses.

Left heart catheterization is performed via percutaneous access of the femoral or, in preference to this, via the radial artery due to reduced complications from bleeding [1]. Through various arterial branches, access is gained to the aorta and left ventricle, where pressures can be transduced. Similarly, to intubation of the coronary arteries in which catheters can measure pressures and take images of each artery, the anatomy of the aorta and left ventricle can be delineated by aortogram and ventriculogram, respectively.

Therefore, left heart catheterization can be used to evaluate and treat coronary artery disease as well as assess valvular disease, defects, and cardiomyopathies. Aortic stenosis is typically assessed by echocardiography, but cardiac catheterization can add important information through pressure transducing. Mitral stenosis can also be assessed with gradients across the valve in stenosis assessed by left ventricular pressure readings and the pulmonary artery wedge pressure (PAWP) being taken as a

surrogate for left atrial (LA) pressure, although direct LA measurements can also be taken via trans-septal puncture from the right atrium via venous access. Both aortic and mitral regurgitation can also be measured.

Right heart catheterization will produce pressure waveforms. An important measurement achieved from right heart catheterization is PAWP, also known as the pulmonary capillary wedge pressure (PCWP). This is measured by "wedging" the pulmonary arterial catheter tip into a small pulmonary artery. By measuring pressures at end-expiration at end-diastole (the p wave on the ECG), the blood flow between the pulmonary artery and left atrium is static, and therefore, the pressure represents the left ventricular end-diastolic pressure (LVEDP). Pressures are normally 6–12 mmHg, which is generally 1–5 mmHg less than pulmonary artery diastolic pressure. Pressures of more than 18 mmHg are suggestive of left heart failure.

Left heart catheterization is not performed in all patients where pulmonary artery hypertension is being assessed but should be performed where invasive right-sided heart pressures are being measured to assess for the left heart diseases mentioned [2].

2. Pulmonary hypertension secondary to left heart disease

Left heart disease is the most common cause of PH where mean pulmonary artery systolic pressure is >20 mmHg and pulmonary capillary wedge pressure > 15 mmHg during right heart catheterization [3].

Pulmonary hypertension can be defined as pre- or post-capillary according to the PCWP.

PH is defined as precapillary when PCWP measurement is <15 mmHg, as the left-sided pressure measurement is considered normal. If the pulmonary capillary wedge pressure measurement is >15 mmHg, it is defined as postcapillary pulmonary hypertension.

Pulmonary hypertension can be classified as isolated postcapillary pulmonary hypertension and combined post-and precapillary pulmonary hypertension.

Pulmonary vascular resistance, transpulmonary pressure gradient, and diastolic pressure gradient is obtained through right heart catheterization and can help to define the subtype of pulmonary hypertension caused by left heart disease.

Pulmonary vascular resistance is calculated by subtracting pulmonary capillary wedge pressure from mean pulmonary artery pressure and then dividing this by the cardiac output. A measurement of <3 wood units suggest that the left atrial pressure is raised and that the pulmonary vasculature remains normal. This is called isolated postcapillary pulmonary hypertension, as only the left atrial pressure is abnormal.

A measurement of >3 wood units indicates that there is raised left atrial pressure alongside pulmonary vascular disease. The diastolic pressure gradient is pulmonary capillary wedge pressure subtracted by diastolic pulmonary artery pressure. A low diastolic pressure gradient of <7 mmHg suggests isolated postcapillary pulmonary hypertension. Where gradients are >7 mmHg, this would suggest post-and precapillary involvement.

3. Pathophysiology of left heart disease causing pulmonary hypertension

Heart failure (both with preserved and reduced ejection fraction) and valvular heart disease can lead to an increase in left atrial pressure and volume. This can lead to

reduced left atrial compliance [4]. This reduction in compliance increases the hydrostatic pressure of the pulmonary veins.

As the left atrial volume and pressure increase, the left atrium cannot act as a barrier between elevated left ventricular pressure and pulmonary vascular resistance. This passive pressure transmission to the pulmonary vascular tree results in isolated postcapillary pulmonary hypertension [5], which will gradually lead to structural abnormalities in the pulmonary vasculature. This includes intimal fibrosis and medial hypertrophy, which results in reduced vasodilator response, pulmonary vasoconstriction, and elevated pulmonary vascular resistance [3]. This is how postcapillary pulmonary hypertension can lead to combined pre- and post-capillary pulmonary hypertension. The increased hydrostatic pressure of the pulmonary veins will over time cause increased pressure of the pulmonary arteries.

Elevated pulmonary capillary wedge pressures result in a reduction in pulmonary vascular compliance for a given pulmonary resistance due to alterations of right ventricular pulsatile load. As the pulmonary circulation becomes less compliant, there is accompanying endothelial dysfunction that leads to a reduction in nitric oxide production and an increase in endothelin levels [3].

Nitric oxide is an important pulmonary vasodilator because as the levels reduce, the pulmonary vascular resistance increases. Endothelin is a vasoconstrictor and proliferative cytokine, so increased levels further increase the pulmonary vascular resistance. This increase in pulmonary vascular resistance will cause an increase in right ventricular afterload and result in right ventricular dysfunction/heart failure.

4. Clinical classifications

There are 5 broad pulmonary hypertension clinical categories that focus on the underlying cause of abnormal pulmonary artery pressure. The table below illustrates these, with the prevalence showing left heart disease (group two) is the most prevalent subtype (**Figure 1**) [6].

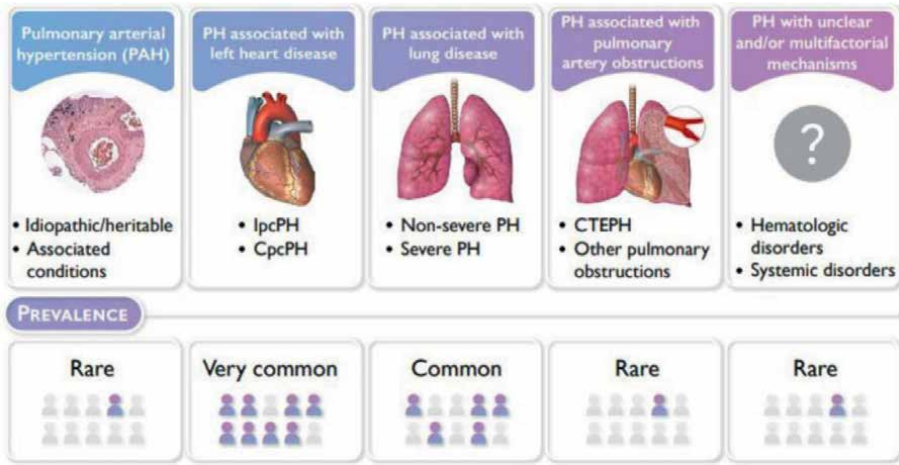

Figure 1.
Clinical classifications of pulmonary hypertension [6].

The most common left heart disease causing pulmonary hypertension is left ventricular dysfunction, where systolic contraction is impaired [7].

It is important to note that while there are vasodilator therapies available to treat pulmonary arterial hypertension with robust evidence to support their use, there are no specific treatments for managing pulmonary hypertension due to left heart disease apart from optimization of the underlying etiology [8]. The treatments for individual left heart diseases are broad and varied. Ensuring accurate diagnosis and confirmation of the cause of pulmonary hypertension is therefore important so the correct treatment can be offered.

5. Treatment

Multiple pharmacological therapies for pulmonary artery hypertension include prostanoids, endothelin-1 receptor antagonists, phosphodiesterase-5 inhibitors, and soluble guanylate cyclase stimulators. Trials using these therapies in pulmonary hypertension with left heart disease have not yet shown enough evidence to promote their use, and at the 6th World Symposium on Pulmonary Hypertension, these therapies were strongly recommended against use for this group [9].

Treatments for left heart disease are dependent on the specific disease itself. Left ventricular systolic dysfunction or heart failure, which is the most common cause of PH, has pharmacological and surgical treatment. Coronary artery disease is treated medically or by percutaneous coronary intervention or coronary artery bypass grafting. Pharmacological treatment of heart failure follows a strong evidence base of prognostic medications such as ace-inhibitors, angiotensin-2 receptor blockers, aldosterone antagonists, cardioselective beta-blockers, aldosterone receptor antagonists, angiotensin receptor neprilysin inhibitors, sodium-glucose cotransporter 2 inhibitors and digoxin which is a cardiac aminoglycoside. Although diuretics are not prognostic in left ventricular systolic dysfunction, they form the cornerstone of symptomatic benefit. Surgical or rather procedural treatment of left ventricular systolic dysfunction is by the placement of biventricular pacemakers, also known as cardiac resynchronization therapy. Here, pacing leads are placed in the right ventricle and a branch of the coronary sinus to improve cardiac function and contractility, where patients fulfill various guidelines, the main one being the electrocardiogram criterion of the left bundle-branch block.

Aortic and mitral regurgitation are initially treated with ace-inhibitors or angiotensin-2 receptor blockers, but ultimately, the treatment is percutaneous or surgical. Aortic and mitral stenosis are both only treated by percutaneous or surgical replacement of the valves. Similarly, shunts such as atrial septal defects and ventricular defects can be treated percutaneously or surgically. Cardiomyopathies encompass a huge spectrum of diseases, each with specific and varied treatments, as do the rarer causes of left heart disease that cause PH.

6. Trials

Previous clinical trials have often grouped both post-capillary with combined pre-and postcapillary pulmonary hypertension, which may have contributed to the results not showing significant benefits. Many clinical trials are now focusing on

these subtypes separately, as the previous trials of drugs described above could have conflicting results due to differing results on each subtype.

In the CHAMPION study, an implantable sensor called CardioMEMS™ was used and provided for the funding [10]. The study enrolled patients with symptomatic heart failure irrespective of left ventricular ejection fraction in 64 centers across the USA. The sensor allowed a home measurement of pulmonary arterial pressure as a surrogate of pulmonary capillary wedge pressure. Diuretics were used significantly more in the intervention group due to these readings, and there was a lower composite outcome of death and all-cause hospital admissions over a 31-month follow-up for the intervention group. The addition of pulmonary artery pressure information to signs and symptoms allowed for much-improved heart failure management.

The REDUCE LAP-HF II trial was a prospective randomized controlled trial with an intervention group treated with an interatrial shunt device. [10] 626 patients with heart failure with preserved ejection fraction with isolated post-capillary pulmonary hypertension were treated with the device or placebo for up to 24 months. The study showed no significant effects of the device on the primary composite outcomes, which included cardiovascular deaths. The trial was analysed further to discriminate patients with latent pulmonary vascular disease by using the measurement of peak exercise pulmonary vascular resistance. The patients with no evidence of latent pulmonary vascular disease showed clinical benefit from the device. This is also a possible area for research in future trials.

7. Future areas of research

Two therapies that are being studied currently for pulmonary hypertension with left heart disease are sodium-glucose cotransporter 2 inhibitors such as empagliflozin, and angiotensin receptor neprilysin inhibitors such as sacubitril/valsartan. Some studies have shown significant improvements in pulmonary artery pressures; however, these studies have been small and, therefore, need repeating on a much larger scale.

8. Conclusion

Pulmonary hypertension due to left heart disease is an important but complex disease process. Identifying the cause of pulmonary hypertension through use of right and left heart catheterization is vital to ensure appropriate treatment can be started. Current guidelines for treatment are limited due to multiple studies showing poor evidence for use of traditional pulmonary hypertension treatments in this subgroup. Treating the left heart disease is currently the best treatment option, however through ongoing research additional treatments will hopefully be discovered.

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References

[1] Ahmed I, Hajouli S. Left heart cardiac catheterization. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564323/

[2] Oudiz RJ, Langleben D. Cardiac catheterization in pulmonary arterial hypertension: An updated guide to proper use. Advances in Pulmonary Hypertension. 2005;**4**(3):15-25. DOI: 10.21693/1933-088X-4.3.15

[3] Al-Omary MS, Sugito S, Boyle AJ, Sverdlov AL, Collins NJ. Pulmonary hypertension due to left heart disease. Diagnosis, pathophysiology and therapy. Hypertension. 2020;**75**:1397-1408. DOI: 10.1161/HYPERTENSIONAHA.119.14330

[4] Rossi A, Gheorghiade M, Triposkiadis F, Solomon SD, Pieske B, Butler J. Left atrium in heart failure with preserved ejection fraction. Circulation. Heart Failure. 2014;**7**:1042-1049. DOI: 10.1161/CIRCHEARTFAILURE.114.001276

[5] Guazzi M, Naeije R. Pulmonary hypertension in heart failure: Pathophysiology, pathobiology, and emerging clinical perspectives. Journal of the American College of Cardiology. 2017;**69**:1718-1734. DOI: 10.1016/j.jacc.2017.01.051

[6] Maron BA. Revised definition of pulmonary hypertension and approach to management: A clinical primer. Journal of the American Heart Association. 2023;**12**:e029024. DOI: 10.1161/JAHA.122.029024

[7] Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation. 2012;**126**:975-990. DOI: 10.1161/CIRCULATIONAHA.111.085761

[8] Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European Heart Journal. 2016;**37**:67-119. DOI: 10.1093/eurheartj/ehv317

[9] Lteif C, Ataya A, Duarte JD. Therapeutic challenges and emerging treatment targets for pulmonary hypertension in left heart disease. Journal of the American Heart Association. 2021;**10**(11):e020633. DOI: 10.1161/JAHA.120.020633. Epub 2021 May 25

[10] Ltaief Z, Yerly P, Liaudet L. Pulmonary hypertension in left heart diseases: Pathophysiology, hemodynamic assessment and therapeutic management. International Journal of Molecular Sciences. 2023;**24**(12):9971. DOI: 10.3390/ijms24129971

Chapter 5

Classification, Diagnosis, and Medical Treatment of Pulmonary Hypertension

Andrew Tenpas, Ladan Panahi, George Udeani, Chioma Ogbodo, Joy Alonzo, Anne-Cecile Mingle, Pooja Patel, Frank North, Merlyn Joseph, Sara Rogers and Chinonso Paul

Abstract

Pulmonary hypertension is a condition characterized by elevated blood pressure in pulmonary arteries due to increased muscle mass of vessel walls, leading to arterial constriction and reduced blood oxygenation. Commonly classified into five major groups, pulmonary hypertension is often viewed as quite rare when, in fact, it is far more common than traditionally advertised. It is also an extremely debilitating disease with far-reaching economic, societal, personal, and psychosocial impacts, especially in underserved populations. Though 10 FDA-approved medications—targeting four different biological pathways—have come to market over the last 20 years, more recent research has focused on complex signaling pathways regulating hypoxic and metabolic signaling, proliferation, apoptosis, senescence, and inflammation. In this chapter, we provide an overview of pulmonary hypertension's prevalence and widespread impact, its underlying pathophysiology and clinical presentations, currently recognized treatment strategies, recommended regimens in special populations, and emerging therapeutic options and fields of research.

Keywords: pulmonary, hypertension, phosphodiesterase, endothelin, prostanoid, PH

1. Introduction

Pulmonary hypertension (PH) is a pathological condition characterized by elevated blood pressure in the pulmonary arteries (i.e., mean pulmonary arterial pressure or mPAP >20 mmHg at rest) due to increased muscle mass of the vessel walls, leading to arterial constriction and reduced blood oxygenation [1, 2]. Definitions for PH are based on hemodynamic assessment by right heart catheterization (RHC). While hemodynamics is key in defining PH, the final diagnosis and classification must consider the entire clinical scenario, incorporating findings from all diagnostic evaluations [2].

This multifactorial disease is influenced by a variety of etiological factors, with left heart disease and chronic lung disease being the most common [1, 3]. It exhibits

a higher prevalence among women, non-Hispanic Black populations, and the elderly [1]. Clinically, PH initially presents with nonspecific symptoms like dyspnea and fatigue, which can delay diagnosis, later progressing to more severe manifestations like syncope and chest pain [1]. While there is no cure for PH, treatment often focuses on symptom management and includes pharmacotherapy, diuretics, and oxygen therapy. Preventive strategies tend to emphasize lifestyle modifications and management of underlying conditions like systemic hypertension and coronary artery disease [1].

PH is often classified into five major groups based on similar pathophysiological mechanisms, clinical presentation, hemodynamic characteristics, and therapeutic management (**Table 1**) [2, 3]. Besides variations in hemodynamics, groups include a wide spectrum of underlying conditions, each with its own prevalence and distinctive treatment strategies [2, 3].

1.1 Prevalence of disease: United States and abroad

Unfortunately, the medical establishment has historically focused on rarer forms of PH—like PAH and chronic thromboembolic pulmonary hypertension—leading to the belief that PH, as a whole, is extremely rare [4]. However, as stated by Rich and colleagues, "*Pulmonary hypertension should stop being treated as a rare disease of high-income countries and should be acknowledged as an important global disease, with a high prevalence that is largely neglected…The reality is that pulmonary hypertension has a spectrum from mild to severe and is associated with common disorders…Estimates suggest that pulmonary hypertension might be the fourth most prevalent cardiovascular disease in the world*" [5]. With a prevalence of about 1% globally—and increasing up to 10% in patients greater than 65 years of age—as many as 20–70 million individuals could be afflicted with PH [4, 5]. Domestically, a population-based study from the United States found that 20% of older patients (i.e., 72–96 years old) showed echocardiographic evidence of PH, while a Canadian cohort study demonstrated a 28% increase in disease prevalence between 1993 and 2012 from 100 to 127 cases per 100,000 individuals [5, 6].

Approximately 80% of afflicted patients live in developing countries, where PH is frequently associated with congenital heart disease and infectious disorders like schistosomiasis, HIV, and rheumatic heart disease [4]. It is estimated that nearly 200 million individuals may be infected by *Schistosoma* species, nearly 85% of which live in Brazil and sub-Saharan Africa. Left-sided heart failure—particularly heart failure with preserved ejection fraction (HFpEF)—may be a leading cause of PH, affecting about 5–10% of individuals 65 years or older, or nearly 30 million patients worldwide [4]. Moreover, another 25 million individuals 40 years or older might be affected by PH due to COPD [4]. Chronic high-altitude exposure—impacting over 140 million people worldwide—is a known, yet sparsely researched, cause of PH. There is believed to be a strong association between a higher prevalence of PH and occupation at altitudes exceeding 4000 meters [4, 7]. **Table 2** depicts crude estimates of the total number of patients worldwide afflicted with PH due to its frequent underlying disorders. It is self-evident that PH is far more common than traditionally advertised.

1.2 Economic, societal, and personal impact of pulmonary hypertension

PH is a complex and often debilitating cardiovascular disorder characterized by high blood pressure in the pulmonary arteries, which can lead to right heart failure and a reduced quality of life. While PH affects individuals from various backgrounds, it

Group 1	Group 2	Group 3	Group 4	Group 5
PAH	PH caused by LHD	PH caused by lung diseases and/or hypoxia	PH caused by pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
1.1 Idiopathic PAH 1.2 Heritable PAH 1.3 Drug- and toxin-induced PAH 1.4 PAH associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.5 PAH long-term responders to calcium channel blockers 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement 1.7 Persistent PH of the newborn syndrome	2.1 PH caused by heart failure with preserved LVEF 2.2 PH caused by heart failure with reduced LVEF 2.3 Valvular heart disease 2.4 Congenital/acquired cardiovascular conditions leading to postcapillary PH	3.1 Obstructive lung disease 3.2 Restrictive lung disease 3.3 Other lung disease with mixed restrictive/obstructive pattern 3.4 Hypoxia without lung disease 3.5 Developmental lung disorders	4.1 Chronic thromboembolic PH 4.2 Other pulmonary artery obstructions	5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders 5.2 Systemic and metabolic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, Gaucher disease, glycogen storage disease, neurofibromatosis 5.3 Others: fibrosing mediastinitis, chronic renal failure (with or without dialysis) 5.4 Complex congenital heart disease

Abbreviations: LVEF = left ventricular ejection fraction; PAH = pulmonary arterial hypertension; PCH = pulmonary capillary hemangiomatosis; PVOD = pulmonary veno-occlusive disease; LHD = left heart disease.

Table 1.
Clinical classification of pulmonary hypertension [2, 3].

	Heart failure	Moderate-to-severe COPD	HIV	Schistosomiasis	Rheumatic heart disease	Sickle cell disease
Worldwide estimates	61 million	250 million	30 million	200 million	15 million	20 million
Estimated PH-associated cases	30 million	25 million	150,000	Unclear	3.75 million	2 million

Table 2.
Estimated PH-associated cases due to underlying disorders.

disproportionately impacts underserved minority populations, exacerbating existing health disparities. This overview will discuss PH's economic, societal, personal, and psychosocial impacts, with a special focus on its effects on underserved minorities.

PH imposes a substantial economic burden on individuals and healthcare systems. Ogbomo and colleagues detected significant direct and indirect healthcare costs associated with PH among commercially insured patients in the United States [8]. Their study found that the average annual healthcare cost per patient was approximately $105,943, including direct costs such as hospitalizations, specialized treatments, and medications. This financial burden can be particularly challenging for underserved minority populations, as they often face barriers to accessing healthcare services and insurance coverage [8].

The economic impact extends to Medicare and other healthcare programs. A 2017 United States Government Accountability Office (GAO) report discussed Medicare Part D and how it oversees prescription drug plan sponsors' fraud and abuse programs. This work is relevant because it sheds light on how government healthcare programs address pharmaceutical costs associated with conditions like PH, which can have implications for underserved populations [9].

The societal impact of PH is profound since it can limit an individual's ability to work and engage in daily activities. Patients often require frequent hospitalizations and specialized treatments, which can disrupt daily routines and reduce their capacity to participate in social events and contribute to society. A study by Badlam and company provided insights into the demographics of patients with PH in the United States, helping us understand populations affected by the disease [10]. Underserved minority communities may face additional challenges, such as limited access to healthcare facilities specializing in PH diagnosis and treatment, which can further exacerbate these disruptions [11].

Moreover, a study by Namuyonga and colleagues examined the impact of PH in underserved populations, specifically South African children. This case series highlighted the unique challenges and disparities in pediatric care, emphasizing the broader societal impact of the disease, especially in resource-limited settings [12].

Undoubtedly, PH takes a toll on mental health and well-being. Anxiety and depression are common comorbidities, and the afflicted may experience feelings of isolation and hopelessness. Underserved minority patients may face unique psychosocial challenges related to cultural stigma, mistrust of the healthcare system, and limited access to mental health resources, exacerbating their mental health burdens [11].

Underserved minority populations—including African Americans, Hispanics, and Native Americans—often face disparities in healthcare access and outcomes related to PH. African American and Hispanic patients with PH tend to have worse outcomes

and higher mortality rates compared to their white counterparts, as reported in a 2021 study published in the European Respiratory Journal [13]. Such disparities can be attributed to socioeconomic factors, systemic racism, and cultural differences, often resulting in delayed diagnosis and inadequate care.

Addressing these disparities requires a comprehensive approach. Healthcare policies should focus on eliminating barriers to access, improving early diagnosis through community outreach and education programs, and providing culturally competent care. Research efforts should also prioritize understanding the determinants of PH in underserved minority populations to develop more personalized treatment approaches [11].

Ultimately, PH is a debilitating disease with far-reaching economic, societal, personal, and psychosocial impacts. Underserved minority populations bear a disproportionate burden of this disease, highlighting the need for targeted efforts to address healthcare disparities and improve outcomes for these individuals. By implementing comprehensive strategies that address both medical and social determinants of health, we can work toward reducing the disparities in PH management and enhancing the quality of life of all affected individuals.

2. Pathophysiology of pulmonary hypertension

The mechanisms behind PH include increased pulmonary vascular resistance, pulmonary venous pressure, and/or pulmonary venous flow due to congenital heart disease [14]. The progressive narrowing of blood vessels is caused by a combination of endothelial dysfunction and increased contractility of small pulmonary arteries, proliferation, and remodeling of endothelial and smooth muscle cells, and *in situ* thrombosis [15]. There is also increased activity of vasoconstrictors like thromboxane A2 and endothelin 1, along with reduced activity of vasodilators like prostacyclin and nitric oxide [14, 15].

Group 1 PAH is primarily caused by a loss and remodeling of the pulmonary vascular bed [16]. Thrombotic coagulopathy due to platelet dysfunction, increased activity of plasminogen activator inhibitor type 1 and fibrinopeptide A, and decreased tissue plasminogen activator activity may also contribute to an increase in pulmonary vascular resistance [14]. Group 4 PAH is generally caused by a pulmonary embolism or obstruction to pulmonary arteries, which thereby increases pulmonary vascular resistance [17].

Several mutations associated with idiopathic or hereditary PAH have been identified, including BMPR2, SMAD1, SMAD9, KCNK3, and CAV1 [18]. Most cases of hereditary and idiopathic PAH may be due to such mutations [14]. Of these, the most common include mutations in the BMPR2 gene, leading to disruptions in TGF-β/BMP endothelial cells and increased pulmonary vascular resistance [14, 15].

Increased pulmonary venous pressure, commonly seen in Group 2 PAH, is typically caused by disorders affecting the left side of the heart [16]. Persistently elevated pulmonary venous pressure can damage the alveolar-capillary wall and eventually lead to irreversible thickening of alveolar-capillary membrane walls and decreased lung function capacity [14]. Group 3 PAH is caused by chronic lung disease that elevates mean pulmonary arterial pressure and results in the loss of lung vasculature, vascular distensibility, and reduced vessel recruitment [16]. Lastly, increased pulmonary venous blood flow due to congenital heart disease may cause PH [14].

3. Clinical presentation of pulmonary hypertension

Signs and symptoms of PH differ depending on the stage of the disease. Initial signs and symptoms are general in nature and may include dyspnea, fatigue, and weakness. These early signs and symptoms are nonspecific in nature, making it difficult to diagnose PH in its early stages [19]. As the disease progresses, additional signs and symptoms may appear, including exertional chest pain, exertion intolerance, dyspnea at rest, worsening fatigue, bloating, distention of the abdomen (ascites), anorexia, lower extremity edema, and syncope [19].

When evaluating patients for PH, some objective signs include audible S_2 at the apex of the heart, mid-systolic ejection murmur, palpable left parasternal lift, right ventricular S_4 gallop, and a prominent "a" wave. These observed signs—along with the symptoms described above—are associated with right ventricular dysfunction, eventually leading to PH's complication of right-sided heart failure [19].

However, as PH advances, signs and symptoms become more pronounced. More pronounced symptoms include further worsening of chest pain, dyspnea, and fatigue, as well as worsening signs like mid-systolic ejection murmur progressing to diastolic murmur of pulmonary regurgitation. Clinicians may also see a pansystolic murmur of tricuspid regurgitation, audible S_2 no longer at just the apex of the heart, an audible right ventricular S_3 gallop, distension of jugular veins, hepatojugular reflux, hypotension, and worsening of lower extremity edema accompanied by cool extremities suggestive of decreased cardiac output and increased vasoconstriction in the periphery [19].

Since signs and symptoms of PH are nonspecific, diagnosis is obtained via the exclusion of differential diagnoses. The first step involves determining the underlying cause of those signs and symptoms. Since fatigue and dyspnea are among the first, examination of physical indicators of PH like audible murmurs and distention—along with a good patient history—must be conducted [20]. This should be followed by imaging tests such as a chest X-ray or an echocardiogram to evaluate the presence of disease markers. If markers are present and support suspicions of PH, confirmation should be completed through right heart catheterization (RHC) [20].

RHC is ultimately used to confirm the presence of conditions like PAH [21]. It is an outpatient surgical procedure that measures pulmonary artery pressure in the lungs [21]. The measurements obtained are mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PAWP), and pulmonary vascular resistance (PVR) [22]. Depending on the value of these measurements (e.g., mPAP > 20 mmHg, PAWP $\leq$ 15 mmHg, PVR > 2 WU), the presence of conditions like PAH may be confirmed [22]. In addition, performing an RHC provides insight into the severity of the disease, allows the assessment of congenital heart defects (including the exclusion of left-side heart disease), assesses patient response to vasodilator challenge, and helps guide clinical decision-making of pharmacotherapy [21, 23, 24].

RHC is not performed on all patients for a wide range of reasons. Reasons may include lack of knowledge or training to perform the procedure, overall cost, perception of elevated risk (due to its invasive nature), or presence of inadequately controlled pre-existing conditions [24, 25]. Since it is not performed on all patients, it is important to note that without an RHC, clinicians cannot—and typically should not—prescribe PH-specific therapies [21].

4. Medical treatment of pulmonary hypertension

The World Health Organization (WHO) has classified PH into five groups based on different underlying causes and pathophysiological mechanisms. The 2022 ESC/ERS guidelines recommend targeting treatment approaches based on the specific group. Below is an overview of the treatment strategies for each of the five groups:

4.1 Group 1: pulmonary arterial hypertension (PAH)

4.1.1 General measures

The comprehensive management of pulmonary arterial hypertension (PAH) involves a spectrum of general measures aimed at enhancing both the quality of life and overall well-being of affected individuals.

- *Exercise training*: With PAH patients on stable medical treatment, exercise training has positively influenced both exercise capacity and overall quality of life [26].

- *Anticoagulation*: PAH has been associated with a procoagulant state, but the use of anticoagulation therapy is tempered by elevated bleeding risk. Due to the absence of studies demonstrating clear clinical benefits, routine anticoagulation therapy is currently not recommended. Instead, decisions regarding the initiation of anticoagulation should be approached on an individualized basis, considering a careful assessment of the specific risks and potential benefits for each patient [24].

- *Diuretics*: In those experiencing right-sided heart failure with fluid retention, the use of loop diuretics, thiazides, and mineralocorticoid receptor antagonists can be considered either as standalone therapy or in combination, depending on the patient's clinical condition and renal function [24].

- *Oxygen*: Due to the lack of robust data regarding oxygen therapy in PAH, current recommendations are based on data from COPD patients. If the PaO_2 is <8 kPa (60 mmHg; alternatively, SaO_2 < 92%) on at least two occasions, oxygen can be administered to achieve a PaO2 > 8 kPa [24].

- *Iron*: In PAH patients, iron deficiency can lead to impaired myocardial function and increased mortality risk. Therefore, routine monitoring of iron status and iron replacement is recommended. In patients with severe iron deficiency anemia (hemoglobin < 7–8 g/dL), IV iron supplementation is recommended [24].

- *Vaccines*: At a minimum, patients with PAH should receive vaccinations for influenza, Streptococcus pneumonia, and SARS-CoV-2 [24].

4.1.2 Treatment of vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension

Calcium channel blockers (CCB): For patients exhibiting positive responses to acute vasoreactivity testing, CCB therapy can be titrated to high doses. However, it is

important to note that only 10% of individuals with idiopathic, hereditary, or drug- or toxin-induced PAH typically show positive results in vasoreactive tests. Additionally, a positive vasoreactive test does not reliably predict long-term response. Therefore, for such patients, the consideration of continuing CCB therapy is warranted in WHO-FC I or II with marked hemodynamic improvement. In cases where patients persist in World Health Organization Functional Class (WHO-FC) III or IV—or fail to show significant hemodynamic improvement despite high-dose CCB therapy—the introduction of additional PAH-specific therapies is recommended [24].

4.1.3 Recommendations for the treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension who present without cardiopulmonary comorbidities

For patients presenting at low-to-intermediate risk of death, initial combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase 5 inhibitor (PDE-5 inhibitor) is recommended (Class I recommendation). These patients can be considered for the addition of selexipag during follow-up to reduce the risk of clinical worsening. Alternatively, if receiving ERA/PDE-5 inhibitor therapy, the PDE-5 can be switched to riociguat if treatment-escalation is required [24].

Patients with a high risk of death should receive initial combination therapy with PDE-5 inhibitor, ERS, and IV/SC prostacyclin analogs (Class IIa Recommendation). If the addition of an intravenous (IV) or subcutaneous (SC) prostacyclin analog is not feasible, selexipag can be added, or the PDE-5 inhibitor can be switched to riociguat [24].

4.1.4 Recommendations for the treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension who present with cardiopulmonary comorbidities

There is a lack of conclusive evidence regarding the optimal treatment for elderly patients with PAH and cardiopulmonary comorbidities. As a result, the current recommendation suggests initiating monotherapy with a PDE-5 inhibitor with an ERA. Nevertheless, individualized consideration for additional therapy is advisable, particularly for those at intermediate or high risk of mortality while on monotherapy [24].

4.1.5 Interventional therapies

Balloon atrial septostomy and the Potts shunt are surgical procedures that decompress the right heart and increase systemic blood flow. However, these procedures are rarely performed due to the substantial risk of procedure-related mortality. Pulmonary artery denervation (PADN) applies radiofrequency to the pulmonary arterial baroreceptors to decrease sympathetic activation in PAH. While PADN showed positive benefits for a 6-minute walk distance in a small study, this therapy is considered experimental [24].

4.1.6 Lung and heart-lung transplantation

If patients remain refractory to optimized medical therapy, lung transplant is an important treatment option, and referral to a transplant center should be considered

early. Most patients receive bilateral lung transplants, while heart-lung transplants can be considered in patients with non-correctable cardiac conditions [24].

4.2 Group 2: pulmonary hypertension due to left heart disease (LHD)

For individuals with PH due to left heart disease (PH-LHD), the primary focus of therapy should revolve around optimizing the management of the underlying cardiac condition. In cases where fluid retention is a concern in PH-LHD, diuretics serve as a cornerstone of treatment. Notably, drugs approved for PAH are generally not advisable for PH-LHD, since available data suggests inefficacy and heightened risk of adverse effects, including fluid retention [24].

While no specific recommendation is provided for the use of PDE-5 inhibitors in the context of heart failure with preserved ejection fraction (HFpEF) and combined post and precapillary pulmonary hypertension (CpcPH), it is worth noting that PDE-5 inhibitors may be safely considered for administration in this population [24].

4.3 Group 3: pulmonary hypertension due to lung diseases and/or hypoxia

For an individual's lung disease and PH, it is recommended to optimize the treatment of the underlying lung disease. Overall, the use of PAH medications is not recommended in patients with lung disease and nonsevere PH. In severe PH, referral to a PH center is recommended for individualized treatment decisions and consideration for lung transplantation. PH centers may consider PDE-5 inhibitors in severe PH associated with ILD [24].

4.4 Group 4: chronic thromboembolic pulmonary hypertension (CTEPH)

In patients with confirmed CTEPH, lifelong anticoagulation is recommended due to the risk of recurrent pulmonary thromboembolism. If the condition is operable, pulmonary endarterectomy (PEA) is the treatment of choice. If symptoms are persistent or recurrent, medical therapy followed by possible balloon pulmonary angioplasty (BPA) is recommended. PEA will treat proximal PA fibrotic obstructions, BPA will treat distal PA fibrotic obstructions, and medical therapy will treat microvasculopathy [24].

Riociguat and SC treprostinil are indicated in patients with inoperable CTEPH or persistent/recurrent PH after PEA. Other medical therapies are primarily used off-label in symptomatic patients with inoperable CTEPH. For example, PDE-5 inhibitors and ERAs are common treatments in CTEPH with severe hemodynamic compromise despite the lack of data from recent trials. General measures recommended in PAH are recommended in CTEPH, including exercise training, which has been shown to be safe and effective in cases of operable and inoperable CTEPH [24].

4.5 Group 5: pulmonary hypertension with unclear and/or multifactorial mechanisms

For patients in Group 5, the therapeutic approach is directed toward identifying and managing underlying conditions contributing to PH [4]. In cases such as sickle-cell disease (SCD), the limited available data suggests a cautious stance regarding the use of PAH drugs in SCD-associated PH. Optimal management for these patients necessitates the expertise of multidisciplinary teams capable of tailoring treatment

strategies to address underlying conditions effectively. On the other hand, preliminary data supports the use of PAH drugs in specific populations—such as potential improvement in a 6-minute walk distance in sarcoidosis with PH—these findings warrant validation through larger-scale studies to conclusively establish their therapeutic benefits (**Table 3**) [24, 27].

Non-drug treatments are part of a comprehensive approach to managing PH, which focuses on reducing symptoms, preventing complications, and improving patient quality of life. PH sufferers may want to avoid certain medications or drug classes. For example, cardiovascular drugs used in systemic hypertension or left-sided heart failure—such as angiotensin-converting enzyme inhibitors (ACEs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 inhibitors (SGLT-2is), beta-blockers, and ivabradine—may cause potentially dangerous drops in blood pressure and heart rate in PH patients. Thus, their use is generally not recommended unless necessary for comorbid conditions [24].

While guidelines do not explicitly mention limiting sodium intake, this is a common recommendation in managing heart failure and conditions like PAH since it helps to reduce fluid retention and pressure on the heart. Immunization against SARS-CoV-2, influenza, and *Streptococcus pneumoniae* is recommended for patients with PH. This is also important for preventing infections that may exacerbate PH [24].

Group 1: Pulmonary arterial hypertension (PAH)	*Vasodilator therapy*: Medications such as prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors are commonly used. The number of agents will depend on whether patients are at low-intermediate- or high risk of death. *Supportive therapies:* Diuretics, anticoagulants, and oxygen therapy may be used to manage symptoms and improve exercise tolerance. Iron therapy should be administered in patients with iron deficiency. *Vaccines*: influenza, *Streptococcus pneumoniae*, SARS-CoV-2 If acute vasoreactivity test is positive, titrate calcium channel blockers to high doses; however, many patients will not have sustained long-term response.
Group 2: Pulmonary hypertension due to left heart disease	*Treatment of underlying cause*: Management focuses on addressing the underlying heart condition and optimization of fluid status. Diuretics may be prescribed to manage fluid overload.
Group 3: Pulmonary hypertension due to lung diseases and/or hypoxia	*Treatment of underlying lung disease*: Managing conditions such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease is essential. Refer to a PH center for individualized decision-making. Oxygen therapy may be needed. *Pulmonary rehabilitation*: Exercise and pulmonary rehabilitation therapy may be beneficial.
Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)	*Anticoagulation*: Long-term anticoagulation therapy is often prescribed to prevent further clot formation. *Pulmonary endarterectomy* (PEA): Surgical removal of chronic blood clots from the pulmonary arteries is the preferred treatment when feasible. *Balloon pulmonary angioplasty* (BPA): In cases where PEA is not possible, BPA may be considered as an alternative. Medical therapy is indicated in patients within operable CTEPH or persistent/recurrent PH after PEA.
Group 5: Pulmonary hypertension with unclear or multifactorial mechanisms	*Treatment of underlying causes*: Identify and manage any underlying conditions contributing to pulmonary hypertension.

Table 3.
Treatment strategies for pulmonary hypertension by group.

Long-term oxygen therapy is recommended for those with an arterial blood oxygen pressure below 8 kPa (60 mmHg). Evaluation for obstructive sleep apnea and nocturnal oxygen therapy should be considered in the case of sleep-related desaturation [24].

Surgical interventions are typically reserved for advanced or complex cases of PH where other medical treatments have failed to provide adequate symptom relief or slow disease progression. The choice of intervention depends on the specific type of PH, the patient's overall health, and the availability of surgical expertise and resources.

a. *Lung transplantation* is for patients with certain types of PH refractory to optimized medical therapy. Early referral to a lung transplantation center is advised for those eligible for transplantation, especially in cases of treatment failure, progressive disease, recent hospitalization for worsening disease, need for IV or SC prostacyclin therapy, and presence of high-risk variants such as pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH), systemic sclerosis, large and progressive pulmonary artery aneurysms, or secondary liver or kidney dysfunction due to PH [24].

b. *Heart-lung transplantation* is considered for rarer cases unresponsive to medical treatment, with limited availability due to organ availability and lesion complexity. Unfortunately, this treatment option is associated with high mortality during the first year after surgery [24].

PEA for CTEPH is recommended when the risk of pulmonary embolism recurrence is intermediate or high. Surgical PEA is the treatment of choice for those with accessible pulmonary artery lesions. Operability decisions are based on team experience, accessibility of lesions, the correlation between PH severity and degree of artery obstructions, and comorbidities [24]. Balloon atrial septostomy and Potts shunts are considered interventional therapies in the management of PH, especially in advanced cases where other treatments might not be sufficient or applicable [24].

Responders to calcium CCB therapy demonstrate a reduction in PAP and PVR, with an increase in cardiac output during the test. Long-term treatment may include high doses of CCBs like nifedipine, diltiazem, or amlodipine. Regular follow-up and monitoring are recommended to ensure continued responsiveness and management of potential side effects from high-dose therapy. Conversely, some "non-responders" may not show significant improvement during a vasoreactivity test; CCB therapy is generally not effective and may even be harmful in such patients. Treatment typically involves alternative PAH-specific therapies, such as ERAs, PDE-5 inhibitors, or prostacyclin analogs. Management is focused on the underlying pathophysiological mechanisms. Only a small percentage of patients with PH are actual "responders" to CCBs. Therefore, careful assessment and close monitoring are essential to determine the appropriate therapy for each individual [24].

5. Pharmacologic treatment of pulmonary hypertension

5.1 Endothelin receptor antagonists (ERAs)

Bosentan: Endothelins (ETs) are made of 21 amino acid peptides and three different isoforms: ET-1, ET-2, and ET-3. The most common isoform, ET-1, is seen in airway epithelial lining, lung parenchymal cells, pulmonary tumors, pulmonary vessels,

kidneys, small intestine, and cardiac myocytes [28]. Once endothelins are produced and secreted, they bind to endothelin G protein-coupled receptors, known as endothelin A and endothelin B (ETA, ETB). More specifically, bosentan is a nonselective ET-1 receptor antagonist.

Pulmonary vasculature and airway smooth muscles are populated with ETA receptors, though ETB receptors are mainly found in the endothelium [29]. The binding of endothelin to ETA receptors causes vasoconstriction while binding to ETB receptors causes bronchoconstriction. Because of the functions and locations of endothelin, they are associated with many respiratory diseases, including asthma, pulmonary hypertension, COPD, connective tissue disorders, bronchiolitis obliterans, and lung transplant rejections. Bosentan antagonizes receptors in lung tissue, causing smooth muscle relaxation along the pulmonary vasculature and decreasing pulmonary pressure and resistance [28]. Adverse effects of bosentan include nasopharyngitis, headache, chest pain, syncope, flushing, hypotension, sinusitis, arthralgia, abnormal liver enzymes, peripheral edema, palpitation, and decreased hemoglobin. Bosentan's target dose is 125 mg by mouth twice daily—with monthly liver function testing—since dose-dependent increases in liver transaminases (though reversible) may occur in approximately 10% of patients.

Macitentan: As a dual ERA, it demonstrates superior receptor-binding properties, with improved tissue penetration and a longer duration of action, which allows for daily dosing. The recommended dose for oral macitentan is 10 mg by mouth once daily.

This drug has a favorable side effect profile with little evidence of increased risk of hepatotoxicity or peripheral edema, though concentrations may be reduced by significant anemia [30]. Notable side effects include reduced sperm counts during spermatogenesis, leading to oligospermia and infertility. It is, therefore, contraindicated in pregnancy due to the risk of fetal harm. Though it may elevate hepatic enzymes, little evidence exists for hepatotoxicity. It may also cause anemia, peripheral edema, nasopharyngitis, and hypersensitivity reactions.

Ambrisentan: It works as a selective ERA for treating idiopathic, heritable, and connective tissue disease-associated PAH [31]. Ambrisentan enhances exercise capacity and hemodynamics by inhibiting endothelin, reducing lung pressures, and reducing right heart stress. Side effects include peripheral edema, elevated liver enzymes, and respiratory-related side effects (i.e., nasal congestion, sinusitis, and cough). Recommended oral dosages are 5 and 10 mg by mouth once daily.

5.2 Phosphodiesterase-5 inhibitors (PDE-5)

This class works by inhibiting the phosphodiesterase type 5 enzyme, which is abundant in pulmonary vasculature. This inhibition leads to increased levels of cyclic guanosine monophosphate (cGMP), causing relaxation of pulmonary arterial smooth muscle cells and vasodilation [24].

Sildenafil: It is an orally active, potent, and selective inhibitor of PDE-5, which is often found in high concentrations in pulmonary arteries and the corpora cavernosum [32]. It has been shown to improve exercise capacity, symptoms, and hemodynamics. The recommended dose is 20 mg by mouth three times daily. Adverse effects include headache, flushing, and dizziness. Priapism has also been reported in post-marketing surveillance [33].

Tadalafil: It is a once-daily PDE-5 inhibitor shown to have positive outcomes on exercise capacity, symptoms, hemodynamics, and time to clinical worsening in PAH

patients [24]. Recommended doses are up to 40 mg once daily. Side effects are usually mild to moderate and are mainly related to vasodilation, including headache, flushing, heart palpitations, syncope, and epistaxis [34].

General: PDE-5 inhibitors should not be combined with soluble guanylate cyclase stimulators or nitrates, as this may lead to systemic hypotension. Interactions between PDE-5 inhibitors and protease inhibitors have been reported, resulting in major increases in PDE-5 drug concentrations. Caution is advised when combining these drugs; lower dosages and close monitoring of potential side effects like hypotension are recommended [24]. Regular follow-ups to monitor hemodynamics, exercise capacity, and clinical symptoms are crucial. Patients should be educated about potential side effects and when to seek medical attention.

5.3 Soluble guanylate cyclase stimulators

Riociguat: It is a soluble guanylate cyclase (sGC) stimulator with a dual mode of action. It acts in collaboration with endogenous nitric oxide and directly stimulates sGC, independent of nitric oxide availability. This action ultimately increases cyclic guanosine monophosphate (cGMP) production, causing vasorelaxation, antiproliferative, and anti-fibrotic effects. Side effects include hypotension, bleeding, vomiting, diarrhea, and GERD [35].

5.4 Prostacyclin pathway or prostanoids

Prostanoids include *epoprostenol* (IV), *treprostinil* (IV, SC, inhaled), *iloprost* (inhaled), and *selexipag* (oral) [36]. This class binds to prostacyclin receptors, thereby increasing cyclic adenosine monophosphate (cAMP) and leading to vasodilation, antiproliferative and antithrombotic effects. Common side effects include flushing, jaw pain, headache, diarrhea, nausea, rash, and muscle aches (particularly in legs and feet). Side effects can be dependent on the dosage and can be eliminated with dose reductions [37].

5.5 Calcium channel blockers (CCBs)

CCBs inhibit the flow of extracellular calcium through ion-specific channels that spread through the cell wall. When its inward flow is prevented, vascular smooth muscle cells relax, leading to vasodilation and a decrease in blood pressure. In heart muscles, contractility is decreased, and the sinus pacemaker and atrioventricular conduction velocities are slowed [38, 39].

Nifedipine: It blocks the entry of calcium ions by inhibiting voltage-dependent L-type channels in smooth muscles of vessels and myocardial cells. During the depolarization phase in smooth muscle cells, there is usually an influx of calcium ions through voltage-gated channels. Since intracellular calcium is reduced by nifedipine, there is decrease PVR and dilatation of coronary arteries, leading to a reduction in systemic blood pressure and increased myocardial oxygen delivery. Thus, nifedipine has both hypotensive and antianginal properties. Its immediate-release formulations are available in 10–20 mg capsules, while extended-release formulations are available in 30, 60, and 90 mg tablets [39].

The recommended dose for PH is 20 mg by mouth daily [40]. Key side effects include peripheral edema, dizziness, headache, and flushing. Hypersensitivity reactions like pruritus, urticaria, and bronchospasms tend to be rare. Discontinuation

after long-term use can lead to hypertension or angina. Nifedipine is absolutely contraindicated in hypersensitivity and ST-elevated myocardial infarction, while relative contraindications include severe aortic stenosis, unstable angina, hypotension, heart failure, and moderate-to-severe hepatic impairment. Patients should be monitored for peripheral edema, dizziness, and flushing; regular blood pressure checks are recommended [39].

Amlodipine: It is a long-acting, lipophilic, third-generation dihydropyridine (DHP) CCB that prevents the influx of calcium ions into smooth muscles of vessels and myocardial cells, leading to decreased PVR. Due to its long half-life, it is typically dosed once daily, which is favorable for patient compliance. The recommended starting dose is 5 mg by mouth once daily, with a maximum dose of 10 mg. The 2.5 mg dose is usually reserved for elderly patients and those with hepatic failure.

Side effects may include peripheral edema, dizziness, fatigue, headache, palpitations, and nausea. Amlodipine is contraindicated in cases of breastfeeding, cardiogenic shock, and unstable angina. Its vasodilatory effect can lead to reduced cardiac output in aortic stenosis [41]. Moreover, it should be used cautiously in those with hepatic diseases and titrated in small doses. Using amlodipine together with dihydrocodeine may increase plasma concentrations of dihydrocodeine, increasing the likelihood of opioid adverse reactions like hypotension, respiratory depression, sedation, coma, or death.

Diltiazem: It is used in treating stable and unstable angina and systemic hypertension (mild-to-moderate) but has also proven effective at terminating supraventricular tachycardia and controlling ventricular feedback in atrial fibrillation/flutter. Diltiazem has complex cardioprotective effects, which have been beneficial after intracoronary administration to patients undergoing coronary angiography and bypass procedures [42]. The dosages of 120–360 mg by mouth once daily are used for systemic hypertension and angina pectoris, while those in the 480–720 mg per day range are used for pulmonary hypertension [43]. Side effects include edema, nausea, headache, dizziness, asthenia, and rash [42]. It is contraindicated in acute myocardial infarction, pulmonary congestion, sick sinus syndrome, and severe ventricular arrhythmia. Coadministration with acalabrutinib may cause infection, bleeding, and atrial arrhythmias. Monitoring parameters include blood pressure, EKG, heart rate, liver function tests, and serum creatinine.

General: Current PAH guidelines suggest that the effectiveness of this class is limited to a small percentage of patients with significant acute responses to CCBs (i.e., "responders"). According to recent guidelines, specific advanced agents are recommended for treating patients with PAH [44].

5.6 Combination therapies

Combination therapies involve drugs with different mechanisms of action to achieve a more effective management of PH. Unfortunately, a significant number of patients with PH require two- or three-drug regimens due to the complexity and severity of the disease. This approach may be based on various factors, including:

a. *Disease progression and severity*: PH is a progressive disease, and many patients may not respond adequately to monotherapy. As the disease advances, it often becomes necessary to add additional medications to achieve better control of symptoms and to slow disease progression [24]. Recent guidelines suggest starting dual-combination therapy if the patient can tolerate it.

b. *Targeting multiple pathways*: PH may involve the endothelin, nitric oxide, and prostacyclin pathways. Using drugs that target different pathways can provide a more comprehensive treatment approach. For instance, an ERA can be combined with a PDE-5 inhibitor and/or a prostacyclin analog to cover multiple aspects of the disease process [24].

c. *Clinical evidence*: Recent research has demonstrated the benefits of combination therapy in PH. For instance, the TRITON study, which investigated treatment-naïve patients with PAH, demonstrated the superior efficacy of initial dual-combination therapy with macitentan and tadalafil or triple-combination therapy with macitentan, tadalafil, and selexipag. Though combination therapies have been associated with a significant reduction in the risk of clinical worsening in PAH patients, their impact on all-cause mortality is less clear [24].

d. *Individualized treatment plans*: The decision to use two- or three-drug regimens is based on individual patient factors, including response to initial therapy, side effect profiles, and presence of comorbid conditions. This personalized approach helps to optimize treatment effectiveness and manage risks associated with advanced PH.

e. *Initial combination therapy*: In the TRITON study mentioned above, treatment-naïve PAH patients were assigned to initial dual-combination therapy with macitentan and tadalafil or initial triple-combination therapy with macitentan, tadalafil, and selexipag. For those presenting at low or intermediate risk, initial combination therapy with an ERA and PDE-5 inhibitor is recommended. Initial combination therapy with ambrisentan and tadalafil, as well as macitentan and tadalafil, is recommended. However, initial combination therapy with macitentan, tadalafil, and selexipag is not recommended [24].

f. *Sequential drug combination therapy*: For those with idiopathic, heritable, or drug-associated PAH, the addition of macitentan to PDE-5 inhibitors or oral/inhaled prostacyclin analogs is recommended to reduce the risk of morbidity/mortality events. In patients receiving ERA/PDE-5 inhibitor combination therapy, the addition of selexipag was shown to reduce the risk of clinical worsening events compared to placebo [24]. Combination therapy has been associated with significant risk reduction for clinical worsening; however, its impact on all-cause mortality remains unclear. A substantial proportion of patients may still experience clinical worsening or death despite combination therapy [24].

6. Special populations

6.1 Treating pulmonary hypertension in pregnancy

In cases of PH, including idiopathic PAH responsive to CCB therapy, there have been instances of successful pregnancy outcomes [24]. However, pregnancy in women with PH is still fraught with unpredictable risks and can potentially worsen disease progression [24]. At any point during or after pregnancy, women are vulnerable to health deterioration [24]. It is essential for healthcare providers to thoroughly discuss the potential risks associated with pregnancy with patients, enabling women and their families to make well-informed decisions [24].

For women with PH who conceive or are diagnosed with PAH during pregnancy, treatment in specialized centers with expertise in managing PH in pregnant patients is recommended. Ongoing pregnancy may necessitate adjustments in disease treatment protocols [24]. Drugs such as ERAs, riociguat, and selexipag are typically discontinued due to their potential or unknown risks to fetal development [24, 45]. Conversely, treatments like CCBs, PDE-5 inhibitors, and prostacyclin analogs administered via inhalation, IV, or SC routes are generally deemed safe during pregnancy [24, 45].

To manage right heart failure decompensation symptoms, diuretics such as torsemide or furosemide may be utilized [24, 45]. However, the use of spironolactone is not recommended during the first trimester due to its antiandrogenic properties [24, 45]. When administering diuretics, it is crucial to regularly monitor renal function and serum electrolytes to prevent complications like volume depletion, which could further reduce cardiac output and systemic blood pressure [45].

During pregnancy, women are often hypercoagulable, elevating the risk of thrombosis. Heparins are the first-line anticoagulants recommended—particularly low molecular weight heparin (LMWH)—due to their reduced fetal impact and osteoporosis risk. They are recommended for those with cardiopulmonary dysfunction and PH to mitigate thrombosis risks [45]. However, the effectiveness of LMWH in preventing valve thrombosis is limited. Warfarin, though used in specific dosages during the second and third trimesters, poses teratogenic risks and its use remains controversial during pregnancy [45]. Novel oral anticoagulants like dabigatran and rivaroxaban lack robust evidence for safety and efficacy in pregnant women and are associated with higher risks of miscarriage and birth defects; as a result, their use is generally not recommended [45].

6.2 Treating portopulmonary hypertension and pulmonary arterial hypertension associated with congenital heart disease

Management of portopulmonary hypertension (PoPH) and PAH associated with congenital heart disease (PAH-CHD) requires a multidisciplinary management approach [46]. Larger clinical trials have either underrepresented or excluded patients with these conditions, leading to treatment strategies often based on the experience of clinical experts or findings from retrospective studies [47].

Supportive therapy, such as the administration of diuretics and oxygen, along with supervised exercise rehabilitation, plays an important role in the management of both PoPH and PAH-CHD [46]. The use of beta-blockers, anticoagulants, and CCBs is not recommended in this patient population [46, 48].

Medications that target three different pathways—nitric oxide, endothelins, and prostanoids—have shown increasing evidence of efficacy in those with PAH-CHD [49]. PDE-5 inhibitors like sildenafil and tadalafil are cheaper options and work by increasing intracellular cGMP levels [48]. These agents have been shown to improve hemodynamics and exercise capacity [47]. Agents exerting their action through the endothelin pathway include bosentan, macitentan, and ambrisentan; they have achieved favorable results in patients with PAH-CHD. Endothelin-1 has been shown to be a potent mediator of vascular constriction [47].

Bosentan, a dual-receptor endothelin antagonist, is increasingly used in symptomatic patients with PAH-CHD. There is ongoing debate about whether ambrisentan or macitentan is preferred. Ambrisentan is relatively ETA selective with fewer drug-drug interactions. On the other hand, macitentan has slow dissociation kinetics, high receptor occupancy half-life, and provides noncompetitive antagonism at the

endothelin receptor [48]. Single-center clinical trials of bosentan and ambrisentan—but not macitentan—have proven effective in improving hemodynamics in this PAH subpopulation [47]. Targeting the prostanoid pathway involves prostaglandin analogs like epoprostenol and iloprost. Oral or inhaled therapies are preferred in CHD patients as opposed to IV therapies since use of central lines may lead to sepsis or paradoxical emboli in those with unrepaired defects. Lastly, surgical options such as ductal stenting, Potts shunts, atrial septostomy, and lung transplantation remain as non-pharmacologic treatment options for patients [47–49].

6.3 Treating pulmonary hypertension in patients with connective tissues disease

PAH is a severe complication of connective tissue disorders, and connective tissue disease-PAH (CTD-PAH) is the second recognized cause of PAH after the idiopathic type [50]. As previously discussed, PH is classified into five groups. Those with PH hypertension in association with connective tissue disorders can be found in Groups 1, 2, 3, and 4 [51].

PH has a severe impact on daily living. Since it is life-threatening, sufferers should receive psychological, social, and emotional support, which specialized nurses can provide [52]. Physical activity within limits is also advised. Patients with CTEPH require anticoagulants, diuretics, and digoxin for heart failure, and long-term oxygen may be necessary. Vaccinations against influenza and pneumococcal pneumonia and iron supplementation may also be indicated.

PAH treatment in those with connective tissue disorders is a complex strategy based on preliminary evaluation of severity and prognostic risk, as well as subsequent response to treatment. Patients with PH should be referred to expert centers and treated by multidisciplinary teams of rheumatologists, cardiologists, chest physicians, and specialized nurses [36].

7. Current clinical investigations and future therapeutic options

Over the last 20 years, 10 FDA-approved medications—targeting four different pathways—have come to market, but, as many experts lament, the medical establishment is still far away from developing a cure for PH [53]. Encouragingly, there is no shortage of novel drug targets or medications on the horizon [54].

The first medication to show recent promise is sotatercept, a first-in-class fusion protein containing a domain of human activin receptor type IIA paired with the Fc domain of human IgG1. Blocking proliferative pathways in pulmonary vessels incites death in excess cells, helping to reopen those vessels. In the STELLAR (Study of Sotatercept for the Treatment of Pulmonary Arterial Hypertension) trial, the drug dramatically improved the 6-minute walking distance in the treatment group compared to those given placebo. It also produced an 84% reduction in the risk of death or clinical worsening.

Two tyrosine kinase inhibitors, imatinib, and sorafenib have received significant attention as adjunct therapy in patients resistant to more traditional drug combinations targeting the nitric oxide, endothelin, and prostacyclin pathways. The IMPRES (Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study) trial demonstrated significant improvement in 6-minute walking distance and PVR in patients receiving two or traditional PAH therapies [55]. Meanwhile, sorafenib has been connected to improvements in functional class and mPAP and is being further investigated for refractory PAH [55].

Other novel drugs or delivery systems include inhaled vardenafil, which can be used as needed for PAH symptom exacerbations. Rodatristat ethyl, which inhibits tryptophan hydroxylase and blocks the synthesis of serotonin from tryptophan, is also under investigation. It is believed that excessive serotonin could contribute to vasoconstriction and vascular remodeling seen in PAH [55]. As the first dedicated hemodynamic study comparing two drugs versus one alone, the A DUE trial (Macitentan/Tadalafil Fixed-Dose Combination in Pulmonary Arterial Hypertension) showed that use of a combination pill containing fixed doses of macitentan and tadalafil led to a two-fold greater reduction in PVR compared to either drug alone. The distinct advantage of a single, once-daily combination pill lies in its potential to dramatically increase patient adherence [53].

As stated by George and colleagues, "*New therapies have emerged that move us beyond vasodilation, vasoconstriction, and endothelial dysfunction, toward more complex signaling pathways that regulate hypoxic and metabolic signaling, proliferation, apoptosis, senescence, and inflammation*" [56]. The first such signaling pathway involves growth suppressor TSC2, which is lacking in small pulmonary arteries of PAH sufferers. Biologically, SC2 controls cell growth; if present in larger quantities, it could block the stiffening and remodeling of pulmonary arteries seen in the disease [56]. Since TSC2 is regulated by the protein SIRT1, researchers have tested the effect of the SIRT1 activator molecule SRT2104, which caused improved lung function and reduced PH in rodent models. SRT2014 is now undergoing further clinical study [57].

Other novel signaling pathways tied to PH pathogenesis—and serving as the basis for future clinical investigations—include the following: (a) inhibition of propyl hydroxylase domain-containing protein 2 (PHD2); (b) inhibition of mammalian target of rapamycin complex (MTORC); (c) inhibition of *hypoxia-inducible factor-1* (HIF-1α); (d) activation of Forkhead box protein O1 (FOXO1); (e) activation of AMP-activated protein kinase (AMPK); (f) inhibition of pyruvate dehydrogenase kinase (PDK); (g) inhibition of carnitine palmitoyltransferase (CPT1A); (h) inhibition of phosphatidylinositol-glycan biosynthesis class F protein (PIGF); and (i) improvement of insulin sensitivity or activation of ketogenesis using drugs like metformin, pioglitazone, or SGLT-2 inhibitors [56].

Finally, recent research has targeted the following pathophysiological mechanisms: (a) fatty acid oxidation using ranolazine and trimetazidine; (b) glycolysis using dichloroacetate; (c) modulation of Nrf2 and NF-κB pathways using bardoxolone methyl; (d) metabolic syndrome and AMPK signaling using metformin; (e) modulation of cytokine pathways using anakinra and tocilizumab; (f) inflammation using ubenimex; (g) modulation of estrogen pathways using anastrozole and fulvestrant; and (h) improvement in oxygenation using acetazolamide [54].

Though there has been incredible progress over the last two or three decades in the treatment of PH, researchers hope that the therapies outlined above will help to move the field toward truly effective and targeted therapies capable of reversing the underlying pathology in disease sufferers, dramatically increasing quality of life and overall mortality rates [54–56].

8. Conclusion

Recent research suggests that PH is more commonplace and widespread than traditionally advertised, particularly in developing countries. It also has far-reaching economic, societal, personal, and psychosocial impacts, particularly in underserved

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minority populations. Though current therapies tend to focus on the use of ERAs, PDE-5 inhibitors, CCBs, prostanoids, and soluble guanylate cyclase stimulators, recent clinical investigations have focused on underlying signaling pathways and pathophysiological mechanisms, with the promise of significantly improved outcomes and, perhaps, a cure 1 day. The diagnosis and treatment of PH have undergone substantial changes in recent decades, and it will continue to evolve even more significantly in the coming years.

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References

[1] Centers for Disease Control and Prevention (CDC). Pulmonary hypertension. 2019. Available from: https://www.cdc.gov/heartdisease/pulmonary_hypertension.htm. [Accessed: November 30, 2023]

[2] Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal. 11 Oct 2022;**43**(38):3618-3731. DOI: 10.1093/eurheartj/ehac237

[3] Anderson JJ, Lau EM. Pulmonary hypertension definition, classification, and epidemiology in Asia. JACC Asia. 2022;**2**(5):538-546. DOI:10.1016/j.jacasi.2022.04.008. PMID: 36624795; PMCID: PMC9823284

[4] Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. The Lancet Respiratory Medicine. 2016;**4**(4):306-322. DOI: 10.1016/S2213-2600(15)00543-3

[5] Rich S, Haworth SG, Hassoun PM, Yacoub MH. Pulmonary hypertension: The unaddressed global health burden. The Lancet Respiratory Medicine. 2018;**6**(8):577-579. DOI: 10.1016/S2213-2600(18)30268-6

[6] Wijeratne DT, Lajkosz K, Brogly SB, et al. Increasing incidence and prevalence of World Health Organization groups 1 to 4 pulmonary hypertension: A population-based cohort study in Ontario, Canada. Circulation. Cardiovascular Quality and Outcomes. 2018;**11**(2):e003973. DOI: 10.1161/CIRCOUTCOMES.117.003973

[7] Dubroff J, Melendres L, Lin Y, Beene DR, Ketai L. High geographic prevalence of pulmonary artery hypertension: Associations with ethnicity, drug use, and altitude. Pulmonary Circulation. 2020;**10**(1):2045894019894534. DOI: 10.1177/2045894019894534

[8] Obgomo A, Tsang Y, Mallampati R, Panjabi S. The direct and indirect health care costs associated with pulmonary arterial hypertension among commercially insured patients in the United States. Journal of Managed Care & Specialty Pharmacy. 2022;**28**(6):608-616. DOI: 10.18553/jmcp.2022.28.6.608

[9] Centers for Medicare and Medicaid Services (CMS). CMS strategy to combat Medicare part D prescription drug fraud and abuse. 2014. Available from: https://www.cms.gov/newsroom/fact-sheets/cms-strategy-combat-medicare-part-d-prescription-drug-fraud-and-abuse [Accessed: January 12, 2024]

[10] Badlam JB, Badesch DB, Austin ED, et al. United States Pulmonary Hypertension Scientific Registry: Baseline characteristics. Chest. 2021;**159**(1):311-327. DOI: 10.1016/j.chest.2020.07.088

[11] Burgoyne DS. Reducing economic burden and improving quality of life in pulmonary arterial hypertension. The American Journal of Managed Care. 2021;**27**(3 Suppl):S53-S58. DOI: 10.37765/ajmc.2021.88611

[12] Namuyonga J, Mocumbi AN. Pulmonary hypertension in children across Africa: The silent threat. International Journal Of Pediatrics. 2021;**2021**:9998070. DOI: 10.1155/2021/9998070

[13] Boon GJA, van den Hout WB, Barco S, et al. A model for estimating

the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension. ERJ Open Research. 2021;**7**(3):00719-2020. DOI: 10.1183/23120541.00719-2020

[14] Gladwin MT, Levine AR. Pulmonary Hypertension. Merck Manual Professional Version. Revised/Reviewed September 2022. Available from: https://www.merckmanuals.com/professional/pulmonary-disorders/pulmonary-hypertension/pulmonary-hypertension. [Accessed: December 12, 2023]

[15] Lai YC, Potoka KC, Champion HC, Mora AL, Gladwin MT. Pulmonary arterial hypertension: The clinical syndrome. Circulation Research. 2014;**115**(1):115-130. DOI: 10.1161/CIRCRESAHA.115.301146

[16] Mandras SA, Mehta HS, Vaidya A. Pulmonary hypertension: A brief guide for clinicians. Mayo Clinic Proceedings. 2020;**95**(9):1978-1988. DOI: 10.1016/j.mayocp.2020.04.039

[17] Bosseau S, Sobrano Fais R, Gu S, Frump A, Lahm T. Pathophysiology and new advances in pulmonary hypertension. BMJ Medicine. 2023;**2**(1):e000137. DOI: 10.1136/bmjmed-2022-000137

[18] Oldroyd SH, Manek G, Sankari A, et al. Pulmonary hypertension. NCBI Bookshelf. StatPearls [Internet]. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482463. [Accessed: December 12, 2023]

[19] Moote R, Attridge RL, Levine DJ. Pulmonary Arterial Hypertension. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, editors. Pharmacotherapy: A Pathophysiologic Approach, 10e. McGraw-Hill Education; 2017. Available from: https://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146058555 [Accessed: January 12, 2024]

[20] McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. Journal of the American College of Cardiology. 2009;**53**(17):1573-1619. DOI: 10.1016/j.jacc.2009.01.004

[21] Zamanian R. Right Heart Catheterization for Pulmonary Hypertension (PH). 2016. Available from: https://med.stanford.edu/wallcenter/patient-resources/articles-external-and-videos/rhc-for-ph.html#:~:text=Introduction%3A,is%20causing%20the%20pulmonary%20hypertension. [Accessed: January 12, 2024]

[22] Pulmonary Hypertension RN. Right Heart Catheterization. 2022. Available from: https://pulmonaryhypertensionrn.com/right-heart-catheterization-rhc. [Accessed: January 12, 2024]

[23] PAH Initiative. Diagnosing PAH. 2023. Available from: https://www.pahinitiative.com/hcp/pah-overview/diagnosing-pah-criteria. [Accessed: January 12, 2024]

[24] Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal. 2022;**43**(38):3618-3731. DOI: 10.1093/eurheartj/ehac237

[25] Rosenkranz S, Preston IR. Right heart catheterization: Best practice and pitfalls

in pulmonary hypertension. European Respiratory Review. 2015;**24**(138):642-652. DOI: 10.1183/16000617.0062-2015

[26] Grunig E, MacKenzie A, Peacock A, et al. Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: Results from a large European multicentre randomized controlled trial. European Heart Journal. 2021;**42**(23):2284-2295. DOI: 10.1093/eurheartj/ehaa696

[27] Shlobin OA, Kouranos V, Barnett SD, et al. Physiological predictors of survival in patients with sarcoidosis-associated pulmonary hypertension: Results from an international registry. The European Respiratory Journal. 2020;**55**(5):1901747. DOI: 10.1183/13993003.01747-2019

[28] Boss C, Bolli MH, Gatfield J. From bosentan (Tracleer®) to macitentan (Opsumit®): The medicinal chemistry perspective. Bioorganic & Medicinal Chemistry Letters. 2016;**26**(15):3381-3394. DOI: 10.1016/j.bmcl.2016.06.014

[29] Valerio CJ, Coghlan JG. Bosentan in the treatment of pulmonary arterial hypertension with the focus on the mildly symptomatic patient. Vascular Health and Risk Management. 2009;**5**:607-619. DOI: 10.2147/vhrm.s4713

[30] Canadian Agency for Drugs and Technologies in Health (CADTH). CRD Clinical Review Report for Opsumit. 2015. Available from: https://www.cadth.ca/sites/default/files/cdr/clinical/SR0364_Opsumit_CL_Report_e.pdf. [Accessed: January 12, 2024]

[31] Rivera-Lebron BN, Risbano MG. Ambrisentan: A review of its use in pulmonary arterial hypertension. Therapeutic Advances in Respiratory Disease. 2017;**11**(6):233-244. DOI: 10.1177/1753465817696040

[32] Rabe KF, Tenor H, Dent G, et al. Identification of PDE isozymes in human pulmonary artery and effect of selective PDE inhibitors. The American Journal of Physiology. 1994;**266**(5 Pt 1):L536-43. DOI: 10.1152/ajplung.1994.266.5.L536

[33] Barnett CF, Machado RF. Sildenafil in the treatment of pulmonary hypertension. Vascular Health and Risk Management. 2006;**2**(4):411-422. DOI: 10.2147/vhrm.2006.2.4.411

[34] Vanni Frajese G, Pozzi F, Frajese G. Tadalafil in the treatment of erectile dysfunction; an overview of the clinical evidence. Clinical Interventions in Aging. 2006;**1**(4):439-449. DOI: 10.2147/ciia.2006.1.4.439

[35] Kenny M, Clarke MM, Pogue KT. Overview of riociguat and its role in the treatment of pulmonary hypertension. Journal of Pharmacy Practice. 2022;**35**(3):437-444. DOI: 10.1177/0897190020961291

[36] Vonk MC, Vandecasteele E, van Dijk AP. Pulmonary hypertension in connective tissue diseases, new evidence and challenges. European Journal of Clinical Investigation. 2021;**51**(4):e13453. DOI: 10.1111/eci.13453

[37] Badesch DB, McLauglin VV, Delcroix M, et al. Prostanoid therapy for pulmonary arterial hypertension. Journal of the American College of Cardiology. 2004;**43**(12 Suppl S):56S-61S. DOI: 10.1016/j.jacc.2004.02.036

[38] Elliott WJ, Ram CVS. Calcium channel blockers. Journal of Clinical Hypertension (Greenwich, Conn.). 2011;**13**(9):687-689. DOI: 10.1111/j.1751-7176.2011.00513.x

[39] Khan KM, Patel JB, Schaefer TJ. Nifedipine. NCBI Bookshelf. StatPearls [Internet]. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537052. [Accessed: January 12, 2024]

[40] Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. The New England Journal of Medicine. 1992;**327**(2):76-81. DOI: 10.1056/NEJM199207093270203

[41] Fares H, DiNicolantonio JJ, O'Keefe JH, Lavie CJ. Amlodipine in hypertension: A first-line agent with efficacy for improving blood pressure and patient outcomes. Open Heart. 2016;**3**(2):e000473. DOI: 10.1136/openhrt-2016-000473

[42] Buckley MM, Grant SM, Goa KL, McTavish D, Sorkin EM. Diltiazem: A reappraisal of its pharmacological properties and therapeutic use. Drugs. 1990;**39**(5):757-806. DOI: 10.2165/00003495-199039050-00009

[43] Kiely DG, Elliot CA, Sabroe I, Condliffe R. Pulmonary hypertension: Diagnosis and management. BMJ. 2013;**346**:f2028. DOI: 10.1136/bmj.f2028

[44] Medarov BI, Judson MA. The role of calcium channel blockers for the treatment of pulmonary arterial hypertension: How much do we actually know and how could they be positioned today? Respiratory Medicine. 2015;**109**(5):557-564. DOI: 10.1016/j.rmed.2015.01.004

[45] Zhang X, Huangfu Z. Management of pregnant patients with pulmonary arterial hypertension. Frontiers in Cardiovascular Medicine. 2022;**9**:1029057. DOI: 10.3389/fcvm.2022.1029057

[46] Savale L, Manes A. Pulmonary arterial hypertension populations of special interest: Portopulmonary hypertension and pulmonary arterial hypertension associated with congenital heart disease. European Heart Journal Supplements: Journal of the European Society of Cardiology. 2019;**21**(Suppl. K):K37-K45. DOI: 10.1093/eurheartj/suz221

[47] Jone P-N, Ivy DD, Hauck A, et al. Pulmonary hypertension in congenital heart disease: A Scientific Statement From the American Heart Association. Circulation. Heart Failure. 2023;**16**(7):e00080. DOI: 10.1161/HHF.0000000000000080

[48] Pascall E, Tulloh RM. Pulmonary hypertension in congenital heart disease. Future Cardiology. 2018;**14**(4):343-353. DOI: 10.2217/fca-2017-0065

[49] Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European Heart Journal. 2016;**37**(1):67-119. DOI: 10.1093/eurheartj/ehv317

[50] Zanatta E, Polito P, Famoso G, et al. Pulmonary arterial hypertension in connective tissue disorders: Pathophysiology and treatment. Experimental Biology and Medicine (Maywood, N.J.). 2019;**244**(2):120-131. DOI: 10.1177/1535370218824101

[51] Condliffe R, Howard LS. Connective tissue disease-associated pulmonary arterial hypertension. F1000Prime

Reports. 2015;7:06. DOI: 10.12703/P7-06 eCollection 2015

[52] Guillevin L, Armstrong I, Aldrighetti R, et al. Understanding the impact of pulmonary arterial hypertension on patients' and carers' lives. European Respiratory Review. 2013;**22**(130):535-542. DOI: 10.1183/09059180.00005713

[53] Kuehn BM. Experimental drug, combination pill show promise for treating pulmonary hypertension. Circulation. 2023;**148**(10):852-854. DOI: 10.1161/CIRCULATIONAHA.123.065252

[54] Sitbon O, Gomberg-Maitland M, Granton J, et al. Clinical trial design and new therapies for pulmonary arterial hypertension. The European Respiratory Journal. 2019;**53**(1):1801908. DOI: 10.1183/13993003.01908-2018

[55] Swisher JW, Weaver E. The evolving management and treatment options for patients with pulmonary hypertension: Current evidence and challenges. Vascular Health and Risk Management. 2023;**19**:103-126. DOI: 10.2147/VHRM.S321025

[56] George MP, Gladwin MT, Graham BB. Exploring new therapeutic pathways in pulmonary hypertension: Metabolism, proliferation, and personalized medicine. American Journal of Respiratory Cell and Molecular Biology. 2020;**63**(3):279-292. DOI: 10.1165/rcmb.2020-0099TR

[57] Connolly L. UC Davis Health News. Study Finds New Treatment for Pulmonary Hypertension Holds Promise. 2023. Available from: https://health.ucdavis.edu/news/headlines/study-finds-new-treatment-for-pulmonary-hypertension-holds-promise/2023/08. [Accessed: January 27, 2024]

Chapter 6

Surgical Treatment in Pulmonary Hypertension

Alina Ligia Cornea, Claudiu E. Nistor, Diana Parau and Alexandru Mihai Cornea

Abstract

Pulmonary hypertension (PH) is a medical condition with complex physiopathology due to several diseases involving heart, lung, connective tissue, or multifactorial. This chapter analyzes the main surgical procedures used in PH, starting with lung transplantation, pulmonary endarterectomy for chronic thromboembolism, mechanical circulatory support, and right-to-left shunts as palliative procedures. The indications for surgery, donor organ procurement, and preservation techniques are also reviewed.

Keywords: pulmonary hypertension, lung transplantation, pulmonary artery endarterectomy, mechanical circulatory support, right-to-left shunts

1. Introduction

Pulmonary hypertension (PH) is a manifestation of high pulmonary artery pressure, which targets pulmonary artery vasculature by stimulating pathological transformations ending with increasing pulmonary vascular resistance and right heart failure. Pulmonary hypertension definition means a mean pulmonary artery pressure equal to or higher than 20 mm Hg at rest [1].

The clinical classification of PH incorporates five distinctive categories, group 1, pulmonary arterial hypertension (PAH). Group 2, PH associated with left heart disease (LHDPH). Group 3, PH associated with lung disease (LDPH). Group 4, PH related to thromboembolic obstruction of pulmonary arteries (CTEPH), and group 5 with unclear or multifactorial mechanism.

Pulmonary hypertension is very common in group 2, common in group 3, and rare in groups 1, 4, and 5 [1]. The main therapeutic, surgical procedure for PH is lung transplantation, mainly for group 1 and for group 3 in selected cases, and pulmonary artery endarterectomy is dedicated to group 4, including CTEPH [1]. Other surgical procedures as temporary mechanical circulatory support or shunt palliations can also be used as bridge to transplantation.

2. Lung transplantation

Is the procedure used to end-stage damage of pulmonary vasculature in group 1 (PAH) and for group 3 (LDPH), when there is recommendation to refer the patients for lung transplant evaluation and listing [1].

2.1 Indication for lung transplantation (LT)

Pulmonary arterial hypertension treatment for idiopathic, heritable, drug associated, and connective tissue disorders on risk 4 strata and intermediate and high risk recommends prostacyclin analog and evaluate for lung transplantation, class IIa [1].

For group 3 (LDPH) for pulmonary hypertension associated with hypoxia, it is recommended to send the qualified patients to lung transplant evaluation (class Ic) [1].

A 2014 consensus document for the selection of lung transplant candidates [2] mentioned end-stage lung disease general criteria:

1. High (>50%) risk of death from lung disease within two years if LT is not performed.

2. High (>80%) likelihood of surviving at least 90 days after lung transplantation.

3. High (80%) likelihood of 5-year posttransplant survival from a general medical perspective if adequate graft function exists.

Pulmonary hypertension secondary to congenital heart disease is common and responsive to curative surgery, but on severe PAH, lung transplantation can be used when medical therapy is futile. Contraindications for lung transplantation [3] are a recent history of malignancy (less< than 5 years), sepsis, severe organ dysfunction such as liver failure, heart failure, kidney failure, bleeding, severe obesity, severe chest wall deformity, no social support, psychiatric disease, drugs, alcohol intake, nonadherence to medical therapy, and no social support. For severe cases of PAH is preferable to bilateral lung transplantation [4]; for interstitial lung disease, single lung transplantation (SLT) or double lung transplantation (DLT) could be both options. In COPD, it depends on age if they are older SLT if they are younger BLT [4]. Patients with septic or infected lungs should have a DLT [4].

2.2 Donor lung selection, evaluation, procurement, and transportation

2.2.1 Donor lung selection and evaluation

Donor selection considers history, cause of death, clinical data, bronchoscopy findings, arterial blood gases evaluation, and other clinical tests such as chest X-Ray, CT thorax linked with intraoperative lung examination (organ inspection, color, absence of nodules, compliance, atelectatic areas, recruitable or not, pneumonia signs, trauma). Extended donor criteria are important for increasing the number of transplants and reducing the declining rate of organs. We try to accept older donors with secretions on bronchoscopy, recruitable atelectasis, or even with limited pneumonia (**Table 1**) [4].

Standard donor lung selection criteria	Extended lung selection criteria
Age < 55	Age > 55
Smoking history < 20 pack-years	Smoking history
P/F ratio > 300 on FIO_2 100% and PEEP 5	P/F ratio < 300
No chest trauma	Unilateral lung infiltrate in double lung transplantation
No aspiration	Chest X-Ray abnormalities
No prior cardiothoracic surgery	EVLP
No infection	DCD
No purulent secretions on bronchoscopy	
Clear chest X-ray	

Table 1.
Donor allocation criteria [4].

Donation after cardiac death (DCD), usually in Maastricht category III, [4] has been successfully used in the last years with the purpose of donor pool extension. DCD donation exposes the organs to higher ischemic risk but can be used for lung retrieval. *Ex vivo* lung perfusion (EVLP) is a method of lungs preservation outside the body, focusing on lung repair, and evaluation (by gas analysis, and other blood criteria and repeat bronchoscopy) if they are qualified to be implanted.

2.2.2 Donor lung procurement (harvesting)

2.2.2.1 Lung procurement in DBD

The ideal lung donor may be less than 55 years old, a nonsmoker, and without infections. Additionally, the lungs may have the same size, size matching being very important in ruling out the organ [5]. Oversizing is accepted, but under-sizing is forbidden. The height, weight, and predicted total lung capacity are considered for sizing. A single lung transplantation assessment requires selective gases from each pulmonary vein [5]. Bronchoscopy is done prior to surgery; the tracheobronchial tree is analyzed, and samples for microbiology are taken. Cautious bronchial inspection and lavage are performed to improve the quality of the lungs. The surgical technique starts with opening the chest through median sternotomy, entering pleural cavities, and lung examination. The organs are inspected carefully and palpated to identify eventual masses, nodules, and recruitment maneuvers are performed on the atelectatic areas. If suspicious nodules are identified, a biopsy and the tissue will be sent to pathology [5]. The donor receives heparin, and when all teams are ready, the pulmonary trunk is cannulated, and the prostaglandin is given; the IVC is divided, the left atrial appendage is open for heart venting, and 3–4 liters of lung preservation solution Perfadex is administered antegrade in main pulmonary artery. The heart is explanted maintaining a good cuff around both right and left pulmonary veins to be used in both heart and lung transplantation. If the heart is not harvested for transplantation, an extensive atrial cuff is taken in favor of the lung, which is taken as a double lung block [5]. After the left atrial incision, IVC and SVC are cut, and aorta and pulmonary trunk are divided, and the heart is removed. Lung harvest begins with pulmonary ligament division, parallel with the esophagus on both sides, detaching the adjacent

tissues on the left side until we reach the aorta, which is transversally cut at the site of the distal arch and on the right until the azygos vein, which is divided as well. The trachea is then freed from surrounding tissues and divided between two stapled lines, with the lungs semi-inflated at FIO_2 70% under a Valsalva maneuver. The lungs are examined on the back table, and 1 liter of Perfadex is administered retrogradely throughout the pulmonary vein's ostia sequentially. The last step is lung separation, by section with a stapler of the left bronchus and packing in three bags. Each lung's first bag contains a preservation solution, and the other two with ice, and the lungs are ready for cold preservation and transportation.

2.2.2.2 Lung procurement in DCD donors

Withdrawal of life support is made in ICU when all the circulatory support and inotropic medication are stopped. Systemic heparin is necessary to prevent thrombosis of the donor organs, and warm ischemic time is starting. This agonal status usually cannot be longer than 60 minutes for lungs, and it varies between 30 and 180 minutes with *ex vivo* lung perfusion in experienced centers [4]. Once the death is confirmed by asystole, there is a no-touch period between 2 and 10 minutes (usually 5 minutes) to exclude the spontaneous return of circulation [4]. Then the surgical team proceeds to harvest the organs, and a skin incision is made. The patient is reintubated at 15 minutes from cardiac arrest, the aorta is clamped in the thorax, the arch vessels are clamped to prevent brain reperfusion, the pulmonary trunk or right ventricular outflow tract is cannulated, and preservation solution delivery is started [4]. The bronchoscopy can be performed at this moment, and the lungs are recruited. The PEEP is maintained at 5 and FIO_2 50% and tidal volume 6–8 cc/kg. The heart is excised as usual, and for the lungs, the pulmonary ligament is incised, and dissection is prolonged at the margin of the esophagus until the aorta on the left and azygos on the right. Then a stapler is applied to the carina, and with lungs inflated at 60%, the trachea is stapled and divided. The lungs are removed from the chest, and retrograde pneumoplegia 250 ml on each pulmonary vein is given.

2.2.3 Donor lung preservation and transportation

The lungs are separated by dividing the mediastinal tissue, the atrial cuff and pulmonary artery cuff split into two equal pieces, and the left main bronchus is divided between two stapler lines applied on the proximal half of the left main bronchus far from the carina. They are placed in three sterile transport bags, first with Perfadex solution, tied securely, and in additional two plastic bags with cold saline. The bags are placed in separate containers with ice for transportation [5]. Donor lung preservation is commonly used in cold storage, and low temperature minimizes cellular damage and oxygen consumption by reducing cellular metabolism [5]. Another procurement strategy for DCD donors is by *in situ* thoracoabdominal normothermic regional perfusion (TA-NRP) for cardiothoracic organs recovery [6], and this method uses extracorporeal membrane oxygenation as a delivery pump (see **Figure 1**). Cannulation uses ascending aorta and right atrium (on central ECMO) or femoral vessels for peripheral approach. Extracorporeal circulation starts, and reperfusion time could extend to 90 minutes. Afterward, the assessment, retrieval, and preservation are identical as in DBD donors [6].

Another lung preservation and repair technique is the *ex vivo* lung perfusion technique, developed by the Toronto group when lungs are ventilated and perfused

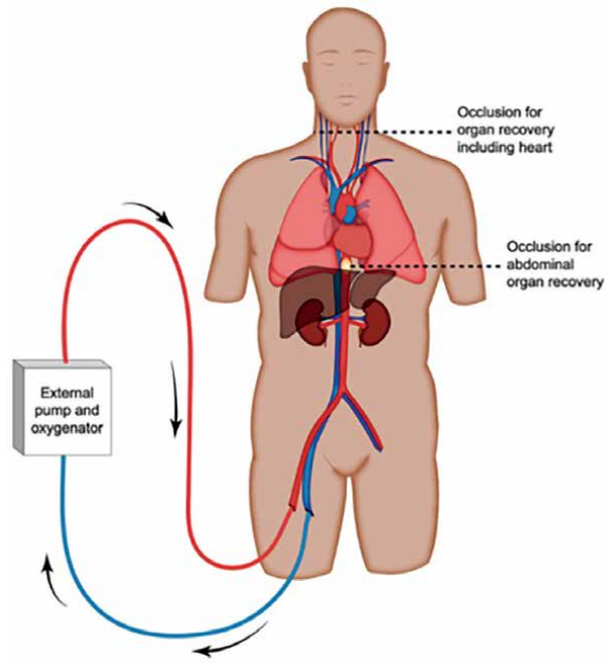

Figure 1.
Veno-arterial extracorporeal membrane oxigenation. From Ref. [7] Open Access: This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source =, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third-party material in this article are included in the article's Creative Commons license unless indicated otherwise in a credit line to the material.

outside the body to recondition and extend the preservation time [5]. There are three EVLP protocols, Toronto, Lund, and organ care system (OCS) Transmedics [8].

Toronto EVLP technique is a lung support system for lung ventilation, a modified ECMO circuit that offers perfusion. The perfusate is Steen solution, a solution based on dextran and albumin. The method uses lung perfusion and ventilation, during a rewarming process, at 30 degrees and 37 degrees, gradually increasing the perfusion flow. Lung assessment is performed hourly for a minimum of 3 hours, and pulmonary veins gases are analyzed. If the lung's gases are improving and PO_2 is more than 350 mm Hg, and the pulmonary artery pressures are stable or improving and stable or improving airway pressures and compliance after 4–6 hours of EVLP, the lungs can be used for LT [8].

2.3 Implantation technique

2.3.1 Bilateral sequential lung transplantation (DLT)

The chest entry (see **Figure 2**) approach is a clamshell incision (bilateral thoracotomy with transverse sternotomy with ligation of mammary arteries [10]. Separate bilateral thoracotomy or sternotomy are other options. Clamshell incision offers the best lung and heart exposure when cardiopulmonary bypass or central ECMO is necessary.

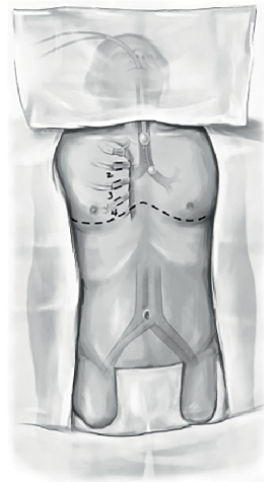

Figure 2.
The clamshell incision for double lung transplantation. From Ref. [9] Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third-party material in this article are included in the article's Creative Commons license unless indicated otherwise in a credit line to the material. Suppose the material is not included in the article's Creative Commons license, and your intended use is not permitted by statutory regulation or exceeds the permitted use. In that case, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

Intubation requires a left-sided double-lumen tube for unilateral ventilation because lung transplant is done sequentially. Usually, the most affected lung is transplanted first. The pneumonectomy and preparation of the hilum vasculature by stapling the pulmonary artery and pulmonary veins are followed by bronchus division and the lung removal from the chest. The donor's lung is transported with cold storage and is prepared for implantation by careful dissection on the back table. Microbiological samples are taken from the bronchus after trimming the excess tissue and resizing [10]. After positioning in the chest, implantation began with the bronchus running suture on the membranous part and interrupted stitches on the cartilaginous part.

The pulmonary artery is sutured next with running 5/0 Prolene and the left atrial cuff with 4–0 Prolene running everting suture (see **Figure 3**). Deairing is the next step, followed by clamp removal from the pulmonary artery and veins. Ventilation is started on a protective mode and is recommended 10 minutes of controlled reperfusion time with partial compression on the pulmonary artery [10] to avoid volume overload of the lung. Then the second lung is explanted in the same fashion, and implantation follows the same rules. Bilateral pleural drainage is inserted, and the incision is closed in anatomical layers.

2.3.2 Extracorporeal support

Patients with severe pulmonary hypertension with high pulmonary artery pressures or patients who are desaturating or becoming unstable during transplant are not tolerating manipulations and pulmonary artery clamping. Veno-arterial ECMO

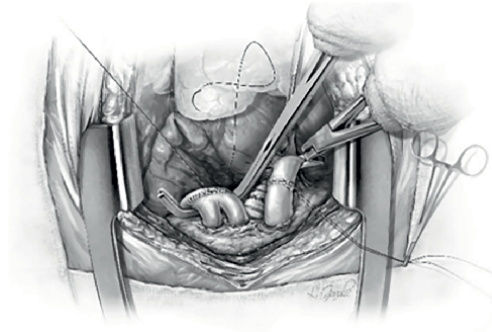

Figure 3.
The bronchial, pulmonary artery, and left atrial cuff anastomosis. From Ref. [9] Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third-party material in this article are included in the article's Creative Commons license unless indicated otherwise in a credit line to the material. Suppose the material is not included in the article's Creative Commons license, and your intended use is not permitted by statutory regulation or exceeds the permitted use. In that case, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

can be inserted by peripheral or central cannulation and used intraoperatively during lung implantation and can be prolonged early after surgery in severe primary graft dysfunction. Cardiopulmonary bypass is another technique for extracorporeal support, which tend to be less used today because of full heparinization and increased risk of bleeding [10].

2.3.3 Size-reducing lung transplantation

Lung transplantation size-mismatch as oversizing is frequent, and until 20% is not a major problem. There are some size-reducing techniques as a nonanatomical wedge resection. When the over-sizing is more, a lobar reduction may be performed, usually the right middle lobe or a lobar resection, which can be performed on the back table after the dissection of interlobar vessels in the fissure [10].

2.3.4 Single lung transplantation

Single lung transplantation is not usually indicated in PT secondary pulmonary fibrosis and chronic obstructive pulmonary disease only in selected cases and is the operation of choice for frail patients with other comorbidities, offering the advantage of having an increased number of transplants in the benefit of very sick patients. Preoperative evaluation of the heart function is important to identify PH. Quantitively V/Q scan is important to determine which lung is less perfused and is a candidate for a single lung transplant. The left side has more space for lung hyperinflation than the right, as the liver is an obstacle on the right side. The position of the patient for a single lung transplant is on full lateral decubitus for posterolateral thoracotomy or for anterolateral for an antero-axillary approach. Single lung ventilation with a left-sided double-lumen endotracheal tube is used for SLT. Pneumonectomy is done in a usual manner by dissecting the hilum elements. The technique for pneumonectomy and implantation is similar to that presented for DLT.

2.3.5 Lobar lung transplantation from living donors (LDLLT)

In the condition of pediatric patients severely ill, with the scarcity of donors for this age group, living lung donation of one lobe (from two living donors) was practiced in Japan when a DBD donation was not legally approved. Nakajima and Date [11] showed that survival after 5 and 10 years in very specialized centers is 79% and 64.6%. Standard LDLLT involves three surgical teams because there are two living donors for harvesting one lobe (usually inferior) and one on the back table. In this way, the ischemic time and duration of surgery are maximally shortened. LDLLT is indicated in critical patients who cannot survive until a DBD donor is available, as in pediatrics or in adults where graft mismatch is possible when the donor's lower lobes are too small for the recipient's requirements. The surgical procedure involves two lobar grafts (lower lobes), and implantation is done on ECMO as routine. CPB is used only if there is a cardiac anomaly that may be corrected at the same time [11]. If the transplant is done in children and there is important oversizing single lobar transplant can be performed [11]. Functional size matching uses a formula developed by Nakajima and Date [11], and if the graft FVC is >45% or 50% for pulmonary hypertension, it can be used for lobar transplantation. Anatomical size matching uses 3D computed tomography volumetry; the upper limit of graft volume accepted to the recipient's chest is 200% [11]. If the lower lobes are too small, the upper lobes of the recipient can be preserved (native upper lung-sparing procedure) to increase the lung parenchyma, or in children can be used adult lower lobes, which are oversized for the same reason.

Two right lower lobes from two living donors implanted, one to the right, and the other one inverted as a left lung, can be used to increase the lung volume when the lobes are two small, but the implantation technique is more demanding (see **Figure 4**).

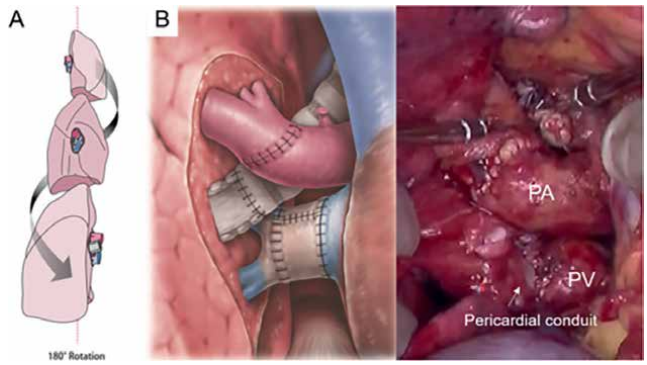

Figure 4.
Right single lung transplantation using an inverted left donor lung. From Ref. [12] Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article unless otherwise stated.

3. Heart and lung en bloc transplantation (HLT)

3.1 Indication of heart and lung en bloc transplantation

Primary pulmonary hypertension with right ventricular failure and congenital heart disease with severe cardiomyopathy (Eisenmenger syndrome) is the most frequent indications for HLT. Also, patients with end-stage lung disease and complex cardiac disease with multiple surgeries are qualified for the same procedure [4].

3.2 Heart and lung en bloc procurement and transportation

The donor is approached by a longitudinal incision over the chest and abdomen. Both thoracic and abdominal teams expose the target organs. Both heart and lungs will be dissected, and the aorta and pulmonary trunk will be cannulated after systemic heparinization. Prostaglandin is given in the pulmonary trunk before retrieval. After SVC ligation and transection of IVC, 500 mcg of PGE-1 are administered in the pulmonary artery, the aorta is vented, and both cardioplegia and pulmoplegia are delivered. Next, the aorta, pulmonary artery, IVC, and SVC are transected. The lung ventilation is continued until the trachea is clamped. Trachea is divided between stapler lines, SVC and IVC are transected, and the heart and lungs are removed from the thorax [10]. Transportation of en bloc heart and lung can be on cold storage, in Perfadex solution, or by using the Paragonix transportation system. This has the advantage of maintaining a constant temperature preventing the freezing of the organs as in the cold ice storage technique.

3.3 Heart and lung en bloc transplantation-implantation technique

The heart and lungs bloc are removed from the transport container, and the trachea is transected one ring above the carina**.** Median sternotomy or clamshell are currently used for chest openings. The most important is to preserve the important nerves as phrenic, vagal, and laryngeal recurrent. Systemic heparinization and cardiopulmonary bypass with two cava veins are necessary, and the heart is clamped and arrested with cardioplegia. The heart is explanted by transecting the two cava veins, aorta, and pulmonary trunk, and only the left atrium remains attached by the posterior wall. Then the left atrium is divided between the pulmonary veins and mobilized together with the pulmonary artery and bronchus after the transaction of these structures in the same way. The lungs are sequentially removed from the thorax. The heart and lungs bloc implant begins with tracheal anastomosis, followed by IVC and SVC anastomosis, and lastly, the ascending aortic anastomosis to the donor aorta. The aorta and pulmonary are desired, and the aortic clamp is removed [10].

4. Pulmonary artery endarterectomy (PEA)

4.1 Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as a thrombus in pulmonary arteries and branches due to acute embolism with fibrotic changing

1. Mean PAP > 30 mm Hg
2. PVR > 300 dyneseccm-5
3. NYHA class >/= III
4. The embolus is in the proximal part of the pulmonary artery (central type).

Table 2.
Indication for PEA [14].

or chronic persistent embolism. CTEPH is precapillary pulmonary hypertension with mean pulmonary artery pressure > 20 mm Hg at rest, a pulmonary vascular resistance (PVR) > 3 Wood units, and a wedge pressure < 15 mm Hg [13]. CTEPH is from group 4 of the functional classification of PH. Usually, acute embolism resolves by clot lysis and restoring normal hemodynamics. In the situation that part of the clots is still persistent at 3 months after the embolic episode will determine a flow restriction and increase in PVR secondary to an increase in pulmonary artery pressures and right heart failure [14]. Inflammation, infection, coagulation abnormalities, abnormal platelet function, or cancer are some of the predisposing causes of CTEPH. The surgical procedure for CTEPH is pulmonary artery endarterectomy (PEA).

4.2 Surgical technique in PEA

The goal of PEA is to remove all the obstructive lesions from pulmonary arteries and their branches to facilitate remodeling and decrease PVR with a secondary reduction of the workload of the right ventricle. The approach in PEA is median sternotomy and uses cardiopulmonary bypass with two cava veins drainage, with 20-degree Celsius cooling and a period of deep hypothermic circulatory arrest (DHCA). Indications for pulmonary endarterectomy are presented in **Table 2** [14].

DHCA offers a bloodless field mandatory for pulmonary artery endarterectomy, and it will be on short periods of 10 minutes time for brain protection [15]. Both pulmonary arteries are open, and the embolic material is removed until the very distal segmental and subsegmental branches. The key to the endarterectomy is the correct plane between the intima and media of pulmonary arteries [16].

For these techniques, special instruments for endarterectomy are used to help with emboli removal as special dual action forceps or suction and dissection devices [16]. After completing the endarterectomy, the pulmonary arteries are sutured, CPB restored, and the patient is rewarmed to normothermia and weaned from bypass.

5. Balloon pulmonary angioplasty (BPA)

Is addressed to CTEPH patients considered "inoperable" by risk and benefit evaluation for PEA, or the lesions are too distal (see **Table 2**) by the European Society of Cardiology/European Respiratory Society guidelines (class IIb recommendation, level C), [17]. The vascular access is percutaneous through the femoral or internal jugular vein, and a long catheter is placed in the pulmonary trunk and branches. The main important stenosis is treated first, and the right lower lobe is usually targeted after because it contains more blood flow [17]. After the catheter is positioned into the lesion, the balloon is inflated and expanded to 5–8 atmosphere. Repeat dilatations may be performed with bigger balloons to attain a good result [17]. The distal vascular

1. Difficulty in performing PEA or residual PH after PEA
2. Insufficient response to medical treatment: NYHA class more than III or PAP pressure more than 30 mm Hg.
3. The patient wishes to use BPA after being fully informed of their medical condition and the BPA risks and benefits.
4. Exclusion criteria as multiorgan failure or renal dysfunction.

Table 3.
Indications for BPA [14].

bed anatomy is important in the success of the procedure. The main complications are reperfusion pulmonary edema, vascular injury, and vessel rupture. Indications for BPA are presented in **Table 3**.

Usually, three to ten sessions are recommended, depending on how many lesions each session focuses on the segmental artery of one lobe. BPA can be used in patients who have surgical indications, but the risk for open surgery is too high, or BPA can be combined with PEA in some circumstances [17].

6. Mechanical assist devices as a bridge for lung transplantation

6.1 Extracorporeal membrane oxygenation (ECMO)

Extracorporeal membrane oxygenation is a device used as support for the heart and lungs when they are fully compromised, or medical therapy is not helpful until a donor for lung transplantation is available (bridging therapy). The procedure has many complications (bleeding, infections, and multiorgan dysfunction) because of long-term mechanical support [18]. The most common ECMO configuration is veno-arterial (can be venovenous as well) and can be implanted centrally (using for cannulation right atrium and ascending aorta) or most often peripherally using femoral vein and artery.

Special circumstances require different techniques as awake implantation on local anesthesia, which is useful and can be done safely [18]. Peripheral artery cannulation is performed through a prosthetic graft, which is anastomosed to the femoral artery and for the femoral vein in preferred direct venous cannulation. There are other approaches using the internal jugular vein and carotid artery for patients estimated to be on a long time on ECMO. This type of cannulation allows walking and keeps the patient active. There are three methods of ECMO implantation surgical, percutaneous, or combined [19].

Surgical implantation uses an inflow or drainage cannula inserted in the right ventricle or right atrium and a return or outflow cannula in the femoral artery. The percutaneous method uses the classical Seldinger method to cannulate the right internal jugular vein or inferior vena cava and femoral artery. Mixed implantation surgery is used to surgically insert the femoral artery cannula inside a prosthesis (femoral artery), and the Seldinger method is used for internal jugular vein cannulation.

6.2 Right ventricular assist devices (RVAD)

Right ventricular assist devices are used in severe PH when the right ventricle fails, and other devices such as Veno-arterial ECMO show no benefit. Mechanical

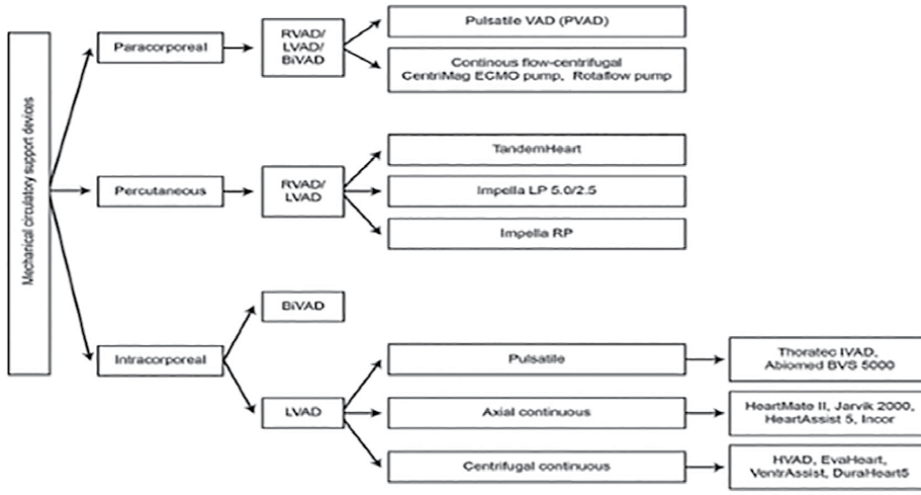

Figure 5.
Classification of mechanical circulatory support devices. BIVAD, biventricular assist device, LVAD, left ventricular assist device, RVAD, right ventricular assist device. From Ref. [20] Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article unless otherwise stated.

assistance of the right ventricle improves contractility and can be used as a bridge or destination therapy [19]. RVAD decreases RV loading, improves septal motion and contractility of the right ventricle, and helps the left ventricle improve stroke volume and aortic pressure. RVAD can use both the right atrium and right ventricle as inflow blood sources, and outflow cannula ends in the pulmonary trunk, usually throughout a prosthesis [19]. The main categories of mechanical circulatory support and main approaches are presented in **Figure 5**.

Impella RP heart pump is a device that uses a peripheral vein approach, and a pump is inserted in the right ventricle, a pulmonary artery trunk that can give 4.5 liters of flow. Aria CV PH system is a new device that uses a balloon that inflates and deflates in the pulmonary trunk synchronized with the cardiac cycle (inflates in diastole and deflates in systole), reducing the RV workload and increasing the output [17]. The balloon is introduced in the pulmonary trunk and positioned by a stent and uses a gas that assures inflation and deflation. There is no external power supply; the approach is through a subclavian vein [19].

7. Right-to-left shunting

Are palliative methods used in children with severe pulmonary hypertension unresponsive to medical therapy? To decrease the proper ventricle pressures, right-to-left shunts are helpful by increasing the left ventricle preload and increasing the systemic blood flow [19]. Atrial septostomy (AS) is a percutaneous method that makes or enlarges an atrial septal defect using balloon dilatation to generate a right-to-left shunt when the pressures in the pulmonary artery are supra-systemic as can

be performed surgically or transcatheter with a balloon used to increase the septal orifice. Stacey [19] reported mean duration of survival was 63.1 months [19]. Severe desaturation (<90%) or low cardiac output with mean right atrial pressures of more than 20 mm Hg are considered contraindications of the procedure [19].

Another method is a surgical systemic-to-pulmonary shunt, as Potts shunt (anastomosis between descending aorta and left pulmonary artery) or modified Potts when a prosthesis with unidirectional valve is used for the same purpose. The Potts shunt is recommended for severe idiopathic PAH in children and seems to have better oxygen saturation for the brain and heart [19]. The condition for Potts shunt is to have supra systemic pulmonary artery pressures and good right heart valves. To avoid flow reversal in the shunt, a unidirectional valve can be created as a modified Potts shunt, but still, the long-term results on larger groups are necessary [19].

8. Conclusions

Double lung transplantation is the main surgical therapeutic option for severe pulmonary arterial hypertension. Some circumstances as congenital heart disease, in which severe PAH in children may need atrial septostomy or Potts shunt to create Eisenmenger circulation, can extend life until donor organs are available. Lobar lung transplantation is an alternative for pediatric patients, but technically more demanding and might be performed in centers with experience. Extracorporeal support with ECMO or right ventricular assistance can provide survival until the transplant, but many complications can occur. There are many techniques for lung reservation, the cold storage and transportation are still most used. The normothermic perfusion for lung recovery in DCD patients has gained more interest and ex vivo lung perfusion has spread now in many centers because increases preservation time and assures good assessment, assistance, and repair for the lung.

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References

[1] Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. European Respiratory Journal. 2022:2200879. DOI: 10.1183/13993003.00879-2022. In press

[2] Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014—An update from the pulmonary transplantation Council of the International Society for Heart and Lung Transplantation. The Journal of Heart and Lung Transplantation. 2015;**34**(1):1-15. DOI: 10.1016/j.healun.2014.06.014

[3] LoCicero III J, Feins RH, Colson YL, Gaetano R, editors. Shields' General Thoracic Surgery. 8th ed. USA: Wolters Kluwer; 2019. p. 1115-1143. Available from: https://lccn.loc.gov/2017051947

[4] Lemaitre PH, Tikkanen JM, Mariscal A, Singer LG, Keshavjee S. Lung transplantation. In: Darling GE, Baumgartner WA, Jacobs JP, editors. Pearson's General Thoracic Surgery. USA: STS Cardiothoracic Surgery E-Book. STS 2021. Ebook.sts.org. Available from: https://ebook.sts.org/sts/index/Pearsons-General-Thoracic/Thoracic; [Accessed: May 2023]

[5] Krishnan P, Sahar-AL-Sadat S. Procurement of lungs from brain-dead donors. Indian Journal of Thoracic and Cardiovascular Surgery. 2021;**37**(Suppl. 3):S416-S424. DOI: 10.1007/s12055-021-01140-1

[6] Zhou AL, Ruck JM, Casillian AJ, et al. Early United States experience with lung donation after circulatory death using thoracoabdominal normothermic regional perfusion. Journal of Heart and Lung Transplantation. 2023;**42**:693-696. DOI: 10.1016/j.healun.2023.03.001

[7] Schiff T, Koziatek C, Pomerantz E, et al. Extracorporeal cardiopulmonary resuscitation dissemination and integration with organ preservation in the USA: Ethical and logistical considerations. Critical Care. 2023;**27**:144. DOI: 10.1186/s13054-023-04432-7

[8] Watanabe T, Cypel M, Keeshavjee S. Ex vivo lung perfusion. Journal of Thoracic Disease. China; 2021;**13**(11):6602-6617. DOI: 10.2103/jtd-2021-23

[9] Murala JS, Hanif HM, Pelz M, et al. Lung transplantation: How we do it. Indian Journal of Thoracic and Cardiovascular Surgery. 2021;**37**(Suppl. 3):S454-S475. DOI: 10.1007/s12055-021-01218-w

[10] Mathiesen DJ, Morse CR, Fisher JE, editors. Master Techniques in Surgery. Thoracic Surgery Transplantation, Tracheal Resections, Mediastinal Tumors, Extended Thoracic Resections. Wolters Kluwer; 2015. 1-31 p. ISBN 978-1-4511-9072-4

[11] Nakajima D, Date H. Living-donor lobar lung transplantation. Journal of Thoracic Disease. 2021;**13**(11):6594-6601. DOI: 10.21037/jtd-2021-07

[12] Yamamoto H, Miyoshi K, Otani S, et al. Right single lung transplantation using an inverted left donor lung: Interposition of pericardial conduit for pulmonary venous anastomosis-a case report. BMC Pulmonary Medicine. 2020;**20**:46. DOI: 10.1186/s12890-020-1075-4

[13] Al Abri Q, Lu AJ, Ramchandani MK. Chronic thromboembolic pulmonary

hypertension: A comprehensive review and multidisciplinary approach to surgical treatment. Methodist DeBakey Cardiovascular Journal. 2021;**17**(2):e17-e28. DOI: 10.14797/IQTU6714

[14] Otani N, Watanabe R, Tomoe T, Toyoda S, Yasu T, Nakamoto T. Pathophysiology and treatment of chronic thromboembolicpulmonaryhypertension. International Journal of Molecular Sciences. 2023;**24**:3979. DOI: 10.3390/ijms24043979

[15] Nistor CE, Tsui S, Kirali K, Ciuche A, Aresu G, Kocher GJ, editors. UK: Springer; 2020. 1013-1026 p. DOI: 10.1007/978-3-030-40679-0

[16] Guth S, Mayer E, Prufer D, Wiedenroth CB. Pulmonary endarterectomy: Technique and pitfalls. Annals of Cardiothoracic Surgery. 2022;**11**(2):180-188p. DOI: 10.21037/acs-2021-pte-185

[17] Lang I, Meyer BC, Ogo T, et al. Balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension. European Respiratory Review. 2017;**26**:160119. DOI: 10.1183/000617.0119-2016

[18] Bartolome S, Hoeper MM, Klepetko W. Advanced pulmonary arterial hypertension: Mechanical support and lung transplantation. European Respiratory Review. 2017;**26**:170089. DOI: 10.1183/16000617.0089-2017

[19] Stacel T, Latos M, Urlik M, Necki M, Antonczyk R, Hrapkowicz T, et al. Interventional and surgical treatment for pulmonary arterial hypertension. Journal of Clinical Medicine. 2021;**10**(3326):1-1p. DOI: 10.3390/jcm10153326

[20] Sen A, Larson JS, Kashani KB, et al. Mechanical circulatory assist devices: A primer for critical care and emergency physicians. Critical Care. 2016;**20**:153. DOI: 10.1186/s13054-016-1328-z

Chapter 7

Lung Transplantation for Pulmonary Artery Hypertension

Thirugnanasambandan Sunder, Paul Ramesh Thangaraj, Madhan Kumar Kuppusamy, Kalimuthu Balasubramanian Sriraman, Chinnasamy Selvi and Srinivasan Yaswanth Kumar

Abstract

This manuscript discusses the role of lung transplantation in patients with pulmonary hypertension. The indications and timing for referral to a transplant unit and timing for wait-listing for lung transplantation are discussed. The type of transplantation—isolated (single or double) lung transplantation and situations when combined heart and double lung transplantation is indicated—will be elaborated. Escalation of medical therapy with the need and timing for bridging therapies such as extracorporeal membrane oxygenation until an appropriate organ becomes available will be discussed. Challenges in the postoperative period, specific to lung transplantation for pulmonary artery hypertension, will be reviewed. The outcomes following lung transplantation will also be considered in greater detail.

Keywords: lung transplantation, heart–lung transplantation, pulmonary hypertension, primary graft dysfunction, bridge to transplantation, mechanical circulatory support, ECMO

1. Introduction

Lung transplantation (LT) is a recognized therapy for appropriate patients with end-stage lung disease (ESLD) due to idiopathic pulmonary artery hypertension (IPAH) who remain symptomatic and continue to clinically worsen despite maximal medical therapy. It offers both symptomatic and survival benefits in such patients [1].

This review begins with a historical note on pulmonary hypertension (PH) and LT in general and for PH. The current global burden of the disease is discussed, along with the number of LTs done annually worldwide, to highlight the current supply-demand imbalance. The indications, with timing for referral and listing for transplantation and contraindications, are reviewed. Surgical considerations, along with possible complications and outcomes, are elaborated. The global and Indian scenarios are discussed, along with a mention of the possibilities for the future and the road ahead.

While data for all aspects of (PH) and LT are available for the developed countries, data are sparse and of rather modest quality from developing countries like India—

whose economy is on the rise. We shall also discuss the global scenario and that of India with a brief mention of data from our unit.

2. Historical considerations

2.1 Historical aspects of PH

Despite being initially classed an "orphan disease," numerous randomized controlled trials (RCT) for targeted therapy in PAH have been performed [2], and a lot of research done on this disease shows that from a global perspective, PH has indeed attained epidemic proportions.

Since the late 1800s, varied reports about PH have been available in the literature. A review article in 2019 highlighted the pivotal position of the development of right heart catheterization (RHC) and discussed the history of diagnosis of PH in 2 different eras—the pre-RHC and post-RHC eras [3].

2.1.1 Pre-RHC Era

Ernst von Romberg, a German physician, was the first to describe post mortem findings of sclerosed pulmonary blood vessels (pulmonary vascular sclerosis) in 1891. The 24 year-old patient had no obvious cardiac or lung disease, but suffered from severe dyspnea, chronic dizziness and cyanosis shortly before death.

In 1901, Abel Ayerza, an Argentina physician, described a similar clinical condition referring to it as "cadiaco negros" or black cardiac disease, and it became to be known as "Ayerza's disease."

Over the next few years, Escudera and Warthin in 1919 felt that this was due to syphilis. Oscar Brenner refuted the syphilitic etiology in 1935 [3] after a study of 100 cases. The term PH was suggested with reluctance by Terence East after a report on 3 cases in 1940 [4]. Although De Navasquez et al. suggested the term "pulmonary arteriosclerosis" briefly in their article, after an autopsy report of 3 cases in 1940, in their concluding remarks, they recommended using the term "idiopathic right ventricular hypertrophy" for this condition [5]. The diagnosis, then, was mostly made postmortem, and the absence of any technique to measure the pulmonary artery (PA) pressure antemortem stood in the way of confidently making a diagnosis of PH.

2.1.2 RHC

The first ever cardiac catheterization by Werner Forsmann (in himself), a German medical resident in 1929, opened the gates to the subsequent development of a cardiac catheterization lab [6]. The contributions of Cournand and Richards in 1944 led to accurate hemodynamic studies by RHC [7].

2.1.3 Post-RHC era

Following the advent of objective hemodynamic studies, the term "primary" pulmonary hypertension was then used in 1951 by Dresdale et al. [8].

2.2 Historical aspects of LT

Hardy et al. described the first LT in humans in 1963 [9]. Cooley did the first combined heart-lung transplantation (HLT) in a patient who survived only 14 h.

The first successful HLT for pulmonary vascular disease was performed in 1981 and reported by Reitz et al. [10], and the first successful isolated LT was reported in 1983 by the Toronto Lung Transplant Group [11]. The same group reported the first successful bilateral LT in 1986 [12].

The Indian scenario, as regards LT, has been one of gradual progress [13]. Of note, due to conditions peculiar to the Indian subcontinent, HLT is more often performed when compared to the developed countries [14].

2.3 Historical aspects of therapy for PH

It is, indeed, noteworthy that the first ever definitive treatment for PH was HLT—which was successfully performed in 1981. It was only 14 years later, in 1995, that the first drug—epoprostenol—was approved by the Food and Drugs Administration, United States (FDA) as targeted therapy for PH. Subsequently, over the years, numerous drugs have been found to be beneficial and approved for use by the FDA.

3. Number of LT performed worldwide and current global burden of PH: a supply–demand imbalance

While exact figures for the prevalence of this disease are unknown, global estimates suggest a prevalence ranging from 20 million to 70 million people [15, 16]. The prevalence is more in developing than in developed countries [17]. It is estimated that 80% of patients with PH live in developing countries, and the likelihood of developing PH is twice that in developing countries as compared to in developed countries [18].

As per the International Society for Heart and Lung Transplantation (ISHLT) Registry data, 67,493 LTs were performed worldwide from Jan 1992 to June 2018. Of these, 62,446 (92.5%) were performed in developed countries (North America and Europe). The remaining 7.5% of the cases were performed in the rest of the world—including developing countries. It has been estimated by the ISHLT that the figures reported may represent 80% of the transplant activity globally [19].

Another data set looking at transplants done worldwide between Jan 1995 and June 2018 reported only 1863 (2.9%) LTs done for PAH out of a total number of 63,530 LTs done worldwide during that period [20].

Based on data from Global Observatory on Donation and Transplantation (GODT), for the year 2021, a total of 6470 LTs were done worldwide [21]. Of these 6470 LTs, the contributions from each of the World Health Organization (WHO) regions [22] are as under: Region of Americas (AMR) 3096, European Region (EUR) 1964, Western Pacific Region (WPR) 1233, South East Asian Region (SEAR) 134, Eastern Mediterranean Region (EMR) 43, and African Region (AFR) 0. The number of LT from the SEAR, EMR, and AFR is only 177 (2.7%) LT in the year 2021.

The above data demonstrates the big divide between developed and developing nations. While the prevalence of PH is very high, the number of LT is disproportionately low, demonstrating an acute supply–demand condition.

In India, the data from Indian Transplant Registry (INTRAN) shows that a total of 473 LTs have been done until Feb 2023 [23]. A recent review article [24] has

summarized the evolution of LT in India with available data stratified by the number and types of operations in various states from inception until the time of publication.

We have previously reported a 3-year survival in LT performed for ESLD due to all lung disease categories (including IPAH) of 76.2% [25].

In our unit in Chennai, India, 18 patients with ESLD due to IPAH have been wait-listed for transplantation.

Of these 18 patients, 14 patients underwent HLT. Given the late presentation, which is a common problem in India, all the patients had significant right ventricular (RV) dysfunction. Our unit's policy has been to consider HLT for patients with severe RV dysfunction. Three patients died on the waiting list due to disease progression, and one patient currently awaits transplantation.

Among the 14 patients who were transplanted, there were 3 early deaths—1 due to bleeding and 2 patients succumbed to sepsis. There were 5 patients (36%) who developed primary graft dysfunction (PGD), out of which 4 patients required veno-venous (VV) extracorporeal membrane oxygenation (ECMO) for Grade 3 PGD. Three out of the 4 patients (75%) with post-op ECMO recovered fully, while 1 patient developed septic shock and died. The 1-year survival after HLT for IPAH in our unit is 79%.

4. Registries and risk stratification models in PH

4.1 PH registries

Numerous registries exist for PH [26], which help in the understanding of the disease and help in the development of risk stratification of models, which include the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL); Swedish Pulmonary Arterial Hypertension Registry (SPAHR); Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA); and French Pulmonary Hypertension Network Registry (FPHR). Others include registries in developing countries [27] and the Spanish Registry survival of PH [28].

4.2 Risk scoring systems

Notable risk stratification scores for PH include REVEAL Score 2.0; FPHR, SPHAR, and COMPERA risk assessment strategies; and the 2015 ERS/ESC PH risk table, which have been analyzed and reported.

REVEAL 2.0 scoring system [29] has 14 variables and categorizes patients into 3 groups: low risk (REVEAL Score </= 6), intermediate risk (REVEAL Score 7 & 8), and high risk (REVEAL Score >/= 9). The 2015 ERS/ESC PH guidelines [30] have also categorized patients based on predicted 1-year mortality into 3 groups: low risk (<5%), intermediate risk (5–10%), and high risk (> 10%).

4.3 Need for serial risk stratification

Risk stratification using objective scoring systems is a very important aspect of treatment for IPAH because treatment recommendations and algorithms are recommended based on risk stratification. At the same time, the first risk assessments allow the physician to decide on appropriate targeted therapy. Serial assessments by objective scoring help in assessing response to therapy and prognosis. Any

deterioration is picked up early, and either therapy is escalated, or referral to an LT center is done—before it is too late [31].

4.4 Other assessments for risk stratification

Since both the above models have some limitations, in addition to the above scores, further clinical assessments like 6MWT (6-minute walk test) and investigations echocardiogram, cardiac MRI (magnetic resonance imaging), and serial biomarkers like NT-pro-BNP should be considered for serial risk assessment.

5. Clinical trials in PH

PH has been the subject of numerous clinical trials, which have changed the landscape of this dreadful disease over the decades, thereby improving the outlook of numerous patients. A review article has elegantly discussed the evolving landscape of clinical trials in PH [32]. There has been a sea change in IPAH from the rather dismal "the kingdom of near dead" [33] to "multiple clinical trial meta-analysis" [34]. As many as 41 RCTs in PH have been described until recently [35].

6. Indications, contraindications, and candidacy assessment for LT

6.1 Indications and candidate selection for LT

The general indications (apart from specific indications) for LT in end stage lung disease who are very symptomatic despite maximal optimal medical therapy include the following:

- 50% chance of dying in the next 2 years without a transplant
- 80% chance of surviving 90 days posttransplant
- 80% chance of surviving the next 5 years from a medical perspective, provided the graft function is adequate.

For LT, disease-specific indications have also been described [36].

The available risk stratification models allow serial risk assessments and pick up patients who are deteriorating early on, thereby permitting earlier and timely referral for LT.

The indications and selection of candidates for LT were well-documented in 2015 [37] and the updated 2022 ERS/ESC PH guidelines [38] as well as the ISHLT 2014 consensus document [39] and updated ISHLT 2021 consensus document [40].

LT appears to be the only definitive therapy in patients who deteriorate despite full medical therapy. It is not a therapeutic option that can be provided at short notice. LT requires assessment for candidacy and wait-listing, which can be time-consuming. Moreover, the waiting times are unpredictable, and if HLT is needed, waiting times could be longer.

Given the nature of IPAH and its propensity for sudden deterioration despite therapy and the uncertainties involved in LT, it is suggested that patients are referred

to a transplant center at an earlier stage prior to major clinical deterioration—so that valuable time is not lost.

6.1.1 Types of timing

In view of the uncertain disease progression in PH and uncertainties in LT, guidelines and consensus documents emphasize the importance of "timing," which is of 2 types.

6.1.1.1 Timing for referral to a transplant center

Referral for transplantation is ideally done well in advance before the patient deteriorates and becomes urgently in need of transplantation.

Patients on targeted therapy for IPAH should be risk stratified, and this has to be serially done. The goal of therapy is to maintain a "low risk" status by either REVEAL or ERS 2015 risk assessment tools. In case of failure of therapy to prevent progression to "high risk" status after 3–6 months, the guidelines recommend referral to a transplant center. Consideration of referral to a transplant center does not necessarily mean that the patient will be wait-listed immediately. It is just to get assessments for candidacy and discuss future options.

The ISHLT 2021 consensus document [40] suggests the following *"timing for referral when*

- ESC/ERS intermediate or high risk or REVEAL risk score 8 despite appropriate PAH therapy.
- Significant RV dysfunction despite appropriate PAH therapy
- Need for IV or SC prostacyclin therapy.
- Progressive disease despite appropriate therapy or recent hospitalization for worsening PAH
- Known or suspected high-risk variants such as PVOD/PCH, scleroderma, and large and progressive pulmonary artery aneurysms
- Signs of secondary liver or kidney dysfunction due to PAH
- Potentially life-threatening complications such as recurrent hemoptysis."

6.1.1.2 Timing for listing in a transplant center

Timing for listing as opposed to "referral" is when the patient has deteriorated further, and decisions for LT have been made.

The ISHLT 2021 consensus document [40] suggests the following *"timing for listing when*

- ESC/ERS high risk or REVEAL risk score > 10 on appropriate PAH therapy, including IV or SC prostacyclin analogue

- Progressive hypoxemia, especially in patients with PVOD or PCH Progressive, but not end-stage, liver or kidney dysfunction due to PAH

- Life-threatening hemoptysis"

The 2022 ERS/ESC PH Guidelines [38] offer similar recommendations regarding timing for referral and listing for LT.

- "It is recommended that potentially eligible candidates are referred for LTx evaluation when they have an inadequate response to oral combination therapy, indicated by an intermediate–high or high risk or by a REVEAL risk score > 7

- It is recommended to list patients for LTx who present with a high risk of death or with a REVEAL risk score ⩾10 despite receiving optimized medical therapy, including s.c. or i.v. prostacyclin analogues."

The level of evidence for both the above recommendations is C [38].

6.1.2 Contraindications for LT:

Due to advances in all disciplines—surgical, pharmacological, immunology, basic sciences, care in the intensive care unit (ICU), and mechanical circulatory support—patients are now being considered for LT, whose clinical profiles a few decades ago might be considered prohibitively risky. The current contraindications for LT are listed in a recent consensus document by INSHLT [40].

6.1.3 Pretransplant workup, candidacy assessment, and decision-making process

This requires a comprehensive work of all systems of the body and has already been described previously [13, 40, 41].

Following the workup, we follow a 3-question decision-making process [13]:

1. Have we confirmed the disease is end stage, and no non-transplant options are available?

2. Are the other body systems adequately functioning to cope with a transplant operation?

3. Have we ruled out major absolute contraindications?

If the answers to all three questions are in the affirmative, a decision to proceed with wait-listing is considered after fully informed consent by the patient and family.

The risk assessment process takes the following into account.

Risk versus benefit of the proposed transplant.

Risks with transplant versus risks without transplant.

If the above risk profile is acceptable and patients provide fully informed consent, the patient is wait-listed for the appropriate transplant operation.

7. Pretransplant management of wait-listed patients

7.1 Care of stable patients at home

Maintenance of the status quo by taking care, whenever possible, to prevent deterioration until an organ is available would be the central aim. The cornerstone would be adherence to maximal and optimal medical therapy, ensuring compliance with salt and fluid restrictions and nutritional [42] and physical rehabilitation. Ensuring adequate intake of vitamins and trace elements while adhering to prescribed salt and fluid restriction is mandatory.

Physical therapy has plenty of beneficial effects [43–47] and is best performed under the guidance of the physiotherapist. Graded exercise regimens are to be undertaken to avoid heart rates of over 110/minute during exercise. Point-of-care testing could be done at home, such as pulse oximetry and blood pressure recordings. 6MWD can be easily measured at home. Any deviation from the accepted range of values can be brought to the attention of the transplant team for immediate action.

Avoidance of infection and oxygen supplementation, as advised, should be followed religiously.

7.2 Care of patients with clinical deterioration in ICU

7.2.1 Evaluation and monitoring

In addition to basic monitoring like continuous ECG, pulse oximetry, and respiratory rate on a cardiac monitor, these patients will also require invasive hemodynamic monitoring such as conitnuous arterail pressure and central venous pressure (CVP) monitoring. Insertion of Swan Ganz catheter may be needed in sick patients for monitoring pulmonary artery pressures (PAP), pulmonary capillary wedge pressures (PCWP), cardiac index (CI), pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR). In these sick patients accurate fluid balance records must be maintained. Insertion of urinary catheter helps by monitoring hourly urine output. Almost always, these patients are volume overloaded, and boluses of volume infusion during hypotension must be avoided [48, 49].

7.2.2 Optimizing RV function

Optimizing RV function is the most important after treatment of the precipitating cause of exacerbation. Echocardiographic assessment of the RV indices, including RA, RV chamber size, and septal position, guides therapy and monitoring response. CVP measurements are monitored, and negative fluid balance with a view to reducing RA pressure is done. Bolus doses and infusion of intravenous diuretics often help. If adequate diuresis is not achievable, ultrafiltration needs to be considered.

Atrial arrhythmias are to be controlled by the correction of electrolyte imbalance and antiarrhythmic drugs, and if not controlled by the above, DC cardioversion is considered.

IV ionodilators such as milrinone and dobutamine help in optimising RV function, but frequently require concomitant vasopressors such as noradrenaline and vasopressin. Of the 2 vasopressors, vasopressin is preferable due to its pulmonary vasodilatory effects [50, 51].

Intravenous or inhaled pulmonary vasodilators are to be used when available. IV prostacyclin or inhaled prostaglandin, or IV sildenafil—given that the oral absorption of orally available pulmonary vasodilators may be suboptimal—is to be considered and used appropriately.

7.2.3 Mechanical ventilation

When other methods of oxygen delivery fail, and MV is mandatory, the deleterious effects on RV function need to be borne in mind, being ready to commence suitable inotropes and being ready for further escalation with mechanical circulatory support (MCS), if required.

7.2.4 Escalation to bridging therapies

Bridging therapies are only considered in

- Patients where recovery from the current deterioration is likely—Bridge to recovery (BTR)
- Suitable patients awaiting LT or are LT candidates—Bridge to Transplant (BTT)

7.2.4.1 Bridging by percutaneous intervention

7.2.4.1.1 Balloon atrial septostomy (BAS):

Done percutaneously, this helps to off-load the RA into the left side, but at the expense of oxygen saturation [52], and improves cardiac output by augmenting preload of the LV. Resting oxygen saturations below 90%, RA pressure greater than 20 mmHg, and LVEDP greater than 18 mmHg are contraindications [53].

7.2.4.1.2 Potts Shunt

This procedure can be done both percutaneously and surgically. Given that the right-to-left shunt is distal to the LSCA, the heart, brain, and upper limbs receive oxygenated blood, and this helps in preserving myocardial function while decompressing the right heart at the same time.

7.2.5 Bridging by MCS

7.2.5.1 ECMO

The most commonly used MCS for RVF [48, 54] due to PH is ECMO, which can be safely instituted at the bedside. ECMO is used most often as a BTT and occasionally as a BTR.

Most often, it is a peripherally inserted veno-arterial (VA) ECMO with distal arterial perfusion to avoid ischemic complications of the lower limb. On rare occasions, central-paced ECMO may be needed. ECMO helps off-load the right ventricle and helps oxygenation.

In peripheral VA ECMO, if gas exchange in the lungs is poor, there is a risk of differential oxygenation (Harlequin syndrome), with the heart and blood getting

deoxygenated blood from native circulation and the lower limb getting oxygenated blood from the retrograde blood from the ECMO machine [55]. This will affect cardiac function and may need conversion to a veno-arterial-venous (VAV) configuration with an additional cannula to the superior vena cava (SVC) or RA from the arterial end of the ECMO machine to improve upper body oxygenation.

7.2.5.2 PA-LA shunt

This shunt requires surgical insertion of 2 cannulae in the PA and LA and connected to a pumpless oxygenator. The high pressure in the RV generates the flow. The main advantage is that of the oxygenated blood reaching the left side and, importantly, increasing the input to the LV, thereby preparing it for an eventual luxuriant flow from the transplanted lungs [56].

7.2.5.3 RVAD

While isolated RAVD as a support in PH has been reported [57], in comparison to ECMO, there are heightened risks of pulmonary edema and bleeding, as a result of which, it has not found widespread usage.

7.2.5.4 Outcomes after MCS for RVF in PH

The outcomes are very acceptable, given that these patients would not have survived without MCS support. A report in 2019 [48] elegantly summarizes the data from 11 studies on the outcomes after MCS in PH. Out of a group of 81 patients, 77 patients had MCS as a BTT. Of these, 72 patients out of 77 (94%) had LT. Among the 72 patients who had LT, 56 patients (78%) were discharged home.

8. Surgical considerations of LT for IPAH

8.1 The choice of type of LT

Currently, whenever feasible and in appropriate patients, DLT is the operation of choice for patients with ESLD due to IPAH and is the most commonly performed operation worldwide for this indication [20].

8.1.1 Single lung transplantation (SLT)

In view of the scarcity of organs, SLT is an alternative to HLT, which was initially done for patients with IPAH [58, 59]. It is now given up in most centers largely due to better outcomes with DLT in terms of survival, degree of recovery of right heart function, and symptomatic relief [60].

8.1.2 DLT

It is the most commonly performed type of LT for IPAH. This is borne out of the fact that 95% of all LTs for IPAH were DLTs [20]. DLT has even been recommended to be the preferred operation of choice over HLT, irrespective of the degree of right ventricular dysfunction, provided the left ventricular function is normal [61].

Furthermore, in patients with surgically correctable cardiac lesions such as septal defects, valve diseases, and coronary artery diseases, with normal left ventricular function, concomitant corrective cardiac surgery with DLT is the preferred option [62]. In patients with pulmonary artery (PA) aneurysms due to IPAH, PA plasty with DLT [63] has been reported.

8.1.3 Combined heart-lung transplantation

HLT has traditionally been the transplant operation of choice, being the first ever definitive therapy, in 1981, for ESLD due to IPAH [61, 64, 65]. By 1986, 28 cases of HLT were reported; however, at that point in time, caution was expressed in recommending it as a routine clinical intervention in view of the lack of long-term data [66]. As of now, HLT is usually considered for a subset of patients with IPAH, while the remaining great majority are offered DLT.

In IPAH patients with intrinsic LV dysfunction and objective evidence of fibrosis and scarring of RV on Cardiac MRI, HLT can be considered [62]. Anatomical aspects such as severe cardiac enlargement, which may encroach on the pleural space [62], or the presence of giant aneurysms of the PA [67] may also lead to the consideration of HLT.

HLT is being considered in some centers, given the challenges of immediate post-operative balancing of LV and RV function after DLT patients [68]. The immediate postoperative ICU management of hemodynamics is much easier in HLT, provided there is no bleeding. Furthermore, the incidence of PGD is less compared to the patients who underwent DLT [69].

8.1.4 DLT vs. HLT in patients with IPAH

The debate continues as to the most appropriate transplant surgery for IPAH.

Given the scarcity of donor organs, DLT appears to have logical appeal, and the growing literature supports its use [69, 70]. However, in a subset of IPAH patients, outcomes after DLT may fall short, and its use may result in the loss of precious organs—again, in the background of scarce resources.

While there are reports suggesting that patients with severe RV dysfunction do better with HLT [64], some authors argue that RV dysfunction, no matter how severe, should not be a contraindication for DLT [48]. Objective evidence of RV recovery after DLT for IPAH has been confirmed by CMRI [71], further supporting the choice of DLT. Despite the reduced incidence of PGD following HLT, DLT is preferred by some centers [69], given that the overall survival and freedom from chronic lung allograft dysfunction (CLAD) are similar.

Some authors [70] have defined a subset of patients for whom HLT is more appropriate. There is an increased 3-month mortality following DLT for IPAH—mostly due to severe RVF or PGD. Furthermore, there are some patients whose RV does not recover. These authors believe identifying such a subset for HLT will be beneficial. They suggest that patients below 65 years with a high risk of RV failure, PGD, and low likelihood of RV recovery should be offered HLT.

Following their institutional policy of considering HLT for patients with severe RV dysfunction, in a center in France, the reported long-term outcomes between DLT and HLT for IPAH in 291 patients showed no significant difference [68], lending credence to the view that identifying subsets of patient for HLT results in overall better outcomes.

8.1.5 Giant PA aneurysms complicating IPAH

Giant PA aneurysms rarely occur in patients with severe IPAH. While HLT can be considered [67], given the higher risk of bleeding, the scarce resource, and the increased waiting time for HLT, consideration of DLT with surgical repair of PA aneurysm is appropriate and has been reported [72–74]. Two case series [75, 76] of patients with giant PA aneurysm who have been successfully managed with DLT without recourse to HLT suggest that the option of DLT with surgical repair of PA aneurysm must be considered whenever possible.

8.2 Incisions and access to the chest cavity

8.2.1 For DLT

We routinely use clamshell incision (bilateral anterior thoracotomy with transverse sternotomy) for access [25, 77] though many centers prefer median sternotomy [78]. The clamshell incision offers excellent exposure but can be painful and affect chest wall mechanics. Sternotomy, on the other hand, is less painful, but the exposure is not as good as in a clamshell incision, especially for the pulmonary vein (PV) anastomosis on the left side [79]. While some authors report better outcomes and results with sternotomy [80, 81], there are reports showing no statistically significant differences between either approach [82]. Some centers recommend bilateral anterior thoracotomy without sternal split [83, 84]. A minimally invasive video-assisted approach has also been described for DLT [85].

8.2.2 For HLT

The most common access for HLT is *via* median sternotomy, though at times, clamshell may be used in case of multiple previous surgeries or anatomical situations wherein sternotomy may be a challenge.

8.3 The technique of LT

The operative techniques of LT have been well described [77, 25, 86, 87]. Only those aspects of operative technique with more than one way of performing and that significantly impact outcomes are elaborated here in greater detail.

8.3.1 Avoidance ("Off-pump") or use of circulatory support ("On pump") during LT

Large volume centers have routinely performed the LT "Off-pump" in about 70% of their patients [88] without the use of circulatory support, resorting to their use only in cases of intraoperative hypoxemia, hypercarbia, hypotension, or cardiac instability [89]. The newly implanted lung oxygenates the body when the second lung implantation is in progress. This requires special protective ventilatory strategies to "protect" the newly implanted lung during bilateral sequential LT.

The proponents [90] for the use of cardiopulmonary bypass (CPB) argue that not all lung injury is due to the deleterious effects of CPB and that there is 35% alveolar damage in LT performed off-pump. Furthermore, a lot of lung injury results from increased hydrostatic pressure when the clamps are released. Also, when significant hypoxia develops because of severe mismatch due to perfusion in the native lung, the

native PA must be clamped urgently to improve oxygenation. This results in the entire cardiac output being diverted to the newly grafted lung. Although gradual unclamping of PA can be done, controlled reperfusion to mitigate the effects of free radical injury during reperfusion as possible with CPB is seldom possible. The planned use of CPB is always preferable to "crashing" onto CPB with uncontrolled situations leading to suboptimal outcomes.

Those arguing for the avoidance of CPB [91] often cite the deleterious effects of CPB, such as complement activation, cytokine release, exposure of blood to the air-fluid interface in the reservoir, and the ensuing intense pro-inflammatory states that occur with CPB. Furthermore, they point out the need for systemic anticoagulation and increased incidence of bleeding—requiring transfusion of blood products that could cause lung injury.

8.3.2 CPB vs ECMO

The type of circulatory support could be either conventional CPB or ECMO, which has become more prevalent in the last 2 decades. With the premise that avoiding blood products is beneficial to LT patients, the advantages of intraoperative ECMO over intraoperative CPB include lesser anticoagulation with reduced likelihood of bleeding and requirements of blood products. Studies comparing intraoperative use of ECMO and CPB have been reviewed recently [92].

While some authors report worse outcomes with the use of ECMO during LT [93], most of the studies recommend ECMO over CPB for circulatory support during LT when needed [94–96]. A meta-analysis in 2017, looking at 6 studies comparing the use of ECMO and CPB during LT [97], reported that ECMO was beneficial in terms of shorter periods of ventilation and ICU stay and reduced incidence of PGD with reduced mortality rates at 3 months and 1 year in the ECMO group.

8.3.3 "Planned" extension of intraoperative ECMO onto postoperative period

Patients with long-standing and severe IPAH have an increased PVR, which limits the return to the left ventricle leading to an underfilled LV. These patients, after DLT, are unable to tolerate the copious return to the LV through the new lungs, which have a low PVR.

To mitigate this unfavorable effect on the "unprepared" LV, it was hypothesized that a period of the planned extension of VA-ECMO onto the postoperative period would be beneficial and would gradually help the LV adapt, remodel, and handle the extra inflow. This technique resulted in survival benefits at 3 months and 1 year [98]. Other reports further confirmed this finding along with excellent cardiac function [96, 99, 100]. A reduction in the incidence of PGD was also reported following this technique [101]. A review of these studies on the prolongation of intraoperative ECMO has been reported [92].

9. Postoperative aspects and complications after LT for PH

Only postoperative aspects and complications specific to LT for PH are discussed here.

9.1 PGD

PGD is the condition most often happens within 72 h after LT and is associated with hypoxemia and opacities on chest X-ray (CXR). Based on severity, PGD can be graded from grade 0 to grade 3 [102–104]. Grade 3 PGD is often treated with ECMO, and the sooner ECMO is instituted, the better are the outcomes.

PGD occurs more often when LT is done for PH and is an important cause for heightened early mortality seen after LT for these patients [102].

9.2 Maintenance of tenuous balance between LV and RV function

The real challenge of balancing the RV and LV function after DLT for PH is one of the reasons HLT is preferred in a few units.

In severe IPAH, because of the very high PVR, a relatively reduced amount of blood gets past the pulmonary circulation onto the left atrium and LV. Thus, the native LV is chronically underfilled, resulting in a small cavity, "stiff LV" with diastolic dysfunction. After a DLT, the new lung with low resistance allows a luxuriant flow across it to the left side. This sudden "flooding" of an unprepared LV results in pulmonary edema.

Hence, the fluid balance must be judiciously managed, aiming for negative balance by reducing IV fluids and forcing diuresis. This method of treating the "flooded" LV is poorly tolerated by the dilated RV, which needs more filling. The scenario is exacerbated when there is concentric hypertrophy of RV in response to severe PH—creating a "right-sided-HOCM-like-picture" resulting in a type of dynamic RVOTO. Again, this scenario, quite paradoxically, needs volume infusion "to open" up the RV and avoidance of inotropes that can worsen RVOTO (very similar to how inotropes aggravate LVOTO in HOCM by systolic thickening of the hypertrophied ventricle).

Thus, diametrically opposing therapies must be cautiously balanced in the immediate postoperative period. For this reason, some authors electively "plan" to prolong the VA ECMO onto the postoperative period—to "prime" the LV, and excellent reports have been reported with this technique.

10. Outcomes

The outcome following LT depends on the preoperative clinical characteristics and the lung disease for which LT was performed. This is because, unlike other solid organ transplantation, the outcomes following LT depend on the disease for which LT was performed [105].

Among other classes of lung diseases requiring LT, in IPAH, the risk of developing PGD and early mortality after LT is higher than with other diseases [41].

Despite this early hump, more encouragingly, among the LT patients for IPAH who survive 3 months, the survival improves, with even further survival benefits conditional on surviving 1 year [20].

Table 1 summarises the data in a report from the ISHLT in 2019 [20] and depicts the median survival for LT all classes of lung disease. It can be seen from **Table 1** that if the patients survive more than 1 year after LT, the IPAH patients enjoy an excellent median survival of 12 years, which is second only to patients with cystic fibrosis.

Disease category	Overall	3 month conditional survival	1 year conditional survival
CF	9.9	11.2	12.4
IPAH	7	10.6	12
AIATD	7.1	8.4	9.3
COPD	6	6.7	7.4
ILD – not IPF	6.7	7.6	8.5
IPF	5.2	6.3	7.3

Table 1.
Median survival in years after LT – all classes of disease.

11. Road ahead

11.1 Global perspective

Clearly, the outcome following LT has improved due to technological advances in all fields, leading to a better understanding of immunology, translating into better care postoperatively—in terms of diagnosis and treatment of rejection. While donor-derived cell-free deoxyribonucleic acid (dd-cfDNA) has been available [106, 107], methods using donor-derived cell-free ribonucleic acid (dd-cfRNA) as a liquid biopsy to give us early warning signs prior to the development of clinical rejection is very promising. Developments and advancements in the equipment for MCS further improve outcomes. The use of drones helps increase the donor pool. *Ex vivo* lung perfusion (EVLP) has been known to increase the donor pool. Various methods in order to "repair" donor lungs prior to transplantation have been reported [108], along with superior immunosuppression, surgical techniques, and better donor organ preservation. Donor preservation systems, while being available for decades, have improved further in recent times with regard to maintaining uniform cold temperatures with good clinical outcomes [109]. Most recently, the introduction of the Lung Composite Allocation System (CAS) in early 2023 has been expected to reduce waitlist mortality, improve posttransplant outcomes, and improve overall measures of equity [110]. A well-written editorial has been published recently, which discusses the future directions for LT makes interesting reading [111].

11.2 Indian perspective

While considerable strides have already been made in the field of heart and LT [25], it is worth keeping in mind that cutting-edge healthcare delivery across the spectrum can be labor- and resource-intensive with attendant high financial costs. Furthermore, in India, penetration by health insurance companies is very small, and most people may have to self-fund their healthcare expenses.

To minimize costs and to make this therapy available to all, several research teams involving the collaboration of clinicians and, basic science experts, mechanical engineers are in the process of developing indigenous models for drones, circulatory support needed for the care of these patients at a fraction of the current costs and thereby benefit more patients—who currently cannot afford the same.

12. Conclusion

The outlook of patients with IPAH is promising. Once an orphan disease with a bleak prognosis, the landscape of IPAH has undergone a paradigm shift. Among those patients undergoing LT, the current survival rate is excellent, with good quality of life.

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References

[1] Kolaitis NA. Lung transplantation for pulmonary arterial hypertension. Chest. 5 May 2023;**S0012-3692**(23)00649-9. DOI: 10.1016/j.chest.2023.04.047

[2] Barst RJ. Pulmonary hypertension: Past, present and future. Annals of Thoracic Medicine. 2008;**3**(1):1-4. DOI: 10.4103/1817-1737.37832

[3] Hewes JL, Lee JY, Fagan KA, Bauer NN. The changing face of pulmonary hypertension diagnosis: A historical perspective on the influence of diagnostics and biomarkers. Pulmonary Circulation. 2020;**10**(1):2045. DOI: 10.1177/2045894019892801

[4] East T. Pulmonary hypertension. Heart. 1940;**2**(3):189-200. DOI: 10.1136/hrt.2.3.189

[5] De Navasquez S, Forbes JR, Holling HE. Right ventricular hypertrophy of unknown origin: So-called pulmonary hypertension. British Heart Journal. 1940;**2**(3):177-188

[6] Nossaman BD, Scruggs BA, Nossaman VE, Murthy SN, Kadowitz PJ. History of right heart catheterization: 100 years of experimentation and methodology development. Cardiology in Review. 2010;**18**(2):94-101. DOI: 10.1097/CRD.0b013e3181ceff67

[7] Cournand A et al. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. The Journal of Clinical Investigation. 1945;**24**(1):106-116. DOI: 10.1172/JCI101570

[8] Dresdale DT, Schultz M, Michtom RJ. Primary pulmonary hypertension: I. clinical and hemodynamic study. The American Journal of Medicine. 1951;**11**(6):686-705. DOI: 10.1016/0002-9343(51)90020-4

[9] Hardy JD, Webb WR, Dalton ML Jr, Walker GR Jr. Lung Homotransplantation in man: Report of the initial case. JAMA. 1963;**186**(12):1065-1074. DOI: 10.1001/jama.1963.63710120001010

[10] Reitz BA et al. Heart-lung transplantation: Successful therapy for patients with pulmonary vascular disease. The New England Journal of Medicine. 1982;**306**(10):557-564. DOI: 10.1056/NEJM198203113061001

[11] Toronto Lung Transplant Group. Unilateral lung transplantation for pulmonary fibrosis. The New England Journal of Medicine. 1986;**314**(18):1140-1145. DOI: 10.1056/NEJM198605013141802

[12] Dabak G, Şenbaklavacı Ö. History of lung transplantation. Turkey Thoracic Journal. 2016;**17**(2):71-75. DOI: 10.5578/ttj.17.2.014

[13] Sunder T, Paul Ramesh T, Madhan Kumar K, Suresh M, Singh SP, Seth S. Lung transplant: The Indian experience and suggested guidelines – Part 1 selection of the donor and recipient. Journal of Cardiovascular Science. 2018;**4**:88-95. DOI: 10.4103/jpcs.jpcs_46_18

[14] Sunder T, Paul Ramesh T, Madhan Kumar K. Heart & Heart Lung Transplantation : Indian Scenario. In: Guha S, editor. Cardiology Update 2015. Vol. 2016. New Delhi: Jaypee Brothers. pp. 1460-1464

[15] Rich S, Haworth SG, Hassoun PM, Yacoub MH. Pulmonary hypertension: The unaddressed global health burden.

The Lancet Respiratory Medicine. 2018; **6**(8):577-579. DOI: 10.1016/S2213-2600(18)30268-6

[16] Emmons-Bell S et al. Prevalence, incidence, and survival of pulmonary arterial hypertension: A systematic review for the global burden of disease 2020 study. Pulmonary Circulation. 2022;**12**(1):e12020. DOI: 10.1002/pul2.12020

[17] Butrous G. Pulmonary hypertension: From an orphan disease to a global epidemic. Global Cardiology Science Practice. 2020;**1**:e202005. DOI: 10.21542/gcsp.2020.5

[18] Hasan B et al. Challenges and special aspects of pulmonary hypertension in middle- to low-income regions. Journal of the American College of Cardiology. 2020;**75**(19):2463-2477. DOI: 10.1016/j.jacc.2020.03.047

[19] Hayes D et al. The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: Twenty-second pediatric lung and heart-lung transplantation report—2019; focus theme: Donor and recipient size match. The Journal of Heart and Lung Transplantation. 2019;**38**(10):1015-1027. DOI: 10.1016/j.healun.2019.08.003

[20] Chambers DC et al. The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart–lung transplantation report—2019; focus theme: Donor and recipient size match. The Journal of Heart and Lung Transplantation. 2019;**38**(10):1042-1055. DOI: 10.1016/j.healun.2019.08.001

[21] 2021-data-global-report-1 by Global Observation on Donation and Transplantation.pdf

[22] List of WHO regions. Wikipedia. 2022 [Online]. Available from: https://en.wikipedia.org/w/index.php?title=List_of_WHO_regions&oldid=1106609195 [Accessed: July 12, 2023]

[23] Annual Report of the Heart and Lung Transplant Registry (INTRAN) of the Indian Society for Heart and Lung Transplantation 2023. Available from: https://www.j-pcs.org/article.asp?issn=2395-5414;year=2023;volume=9;issue=1;spage=37;epage=40;aulast=;aid=JPractCardiovascSci_2023_9_1_37_375807 [Accessed: July 10, 2023]

[24] Sunder T. The evolution of lung transplantation in India and the current scenario. Indian Journal of Thoracic Cardiovascular Surgery. 2022;**38**(Suppl 2):211-228. DOI: 10.1007/s12055-021-01248-4

[25] Sunder et al. Lung transplantation: The Indian experience and suggested guidelines part II A: The technique of lung transplantation. Journal of Practical Cardiovascular Science. 2020;**6**(3):278. DOI: 10.4103/JPCS.JPCS_108_20

[26] McGoon MD et al. Pulmonary arterial hypertension: Epidemiology and registries. Journal of the American College of Cardiology. 2013;**62**(25):D51-D59. DOI: 10.1016/j.jacc.2013.10.023

[27] Idrees M et al. Pulmonary hypertension in the developing world: Local registries, challenges, and ways to move forward. Global Cardiology Science Practise. 2020;**1**:e202014. DOI: 10.21542/gcsp.2020.14

[28] Escribano-Subias P et al. Survival in pulmonary hypertension in Spain: Insights from the Spanish registry. The European Respiratory Journal. 2012; **40**(3):596-603. DOI: 10.1183/09031936.00101211

[29] Benza RL et al. Predicting survival in patients with pulmonary arterial hypertension: The reveal risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. Chest. 2019;**156**(2):323-337. DOI: 10.1016/j.chest.2019.02.004

[30] Galiè N et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). The European Respiratory Journal. 2015;**46**(4):903-975. DOI: 10.1183/13993003.01032-2015

[31] Benza RL et al. Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: A registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL) analysis. The Journal of Heart and Lung Transplantation. 2015;**34**(3):356-361. DOI: 10.1016/j.healun.2014.09.016

[32] Weatherald J et al. The evolving landscape of pulmonary arterial hypertension clinical trials. The Lancet. 2022;**400**(10366):1884-1898. DOI: 10.1016/S0140-6736(22)01601-4

[33] Robin ED. The kingdom of the near-dead: The shortened unnatural life history of primary pulmonary hypertension. Chest. 1987;**92**(2): 330-334. DOI: 10.1378/chest.92.2.330

[34] Galiè N, Palazzini M, Manes A. Pulmonary arterial hypertension: From the kingdom of the near-dead to multiple clinical trial meta-analyses. European Heart Journal. 2010;**31**(17):2080-2086. DOI: 10.1093/eurheartj/ehq152

[35] Galiè N et al. Risk stratification and medical therapy of pulmonary arterial hypertension. The European Respiratory Journal. 2019;**53**(1):1801889. DOI: 10.1183/13993003.01889-2018

[36] Nathan SD. "Lung transplantation: Disease-specific considerations for referral.," Chest. 2005;**127**(3): 1006–1016. DOI: 10.1378/chest.127.3.1006

[37] Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European Heart Journal. 2015;**37**:67

[38] Humbert M et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. The European Respiratory Journal. 2023; **61**(1):2200879. DOI: 10.1183/ 13993003.00879-2022

[39] Weill D et al. A consensus document for the selection of lung transplant candidates: 2014 – An update from the pulmonary transplantation Council of the International Society for Heart and Lung Transplantation. The Journal of Heart and Lung Transplantation. 2015; **34**(1):1-15. DOI: 10.1016/j. healun.2014.06.014

[40] Leard LE et al. Consensus document for the selection of lung transplant candidates: An update from the

International Society for Heart and Lung Transplantation. The Journal of Heart and Lung Transplantation. 2021;**40**(11): 1349-1379. DOI: 10.1016/j.healun.2021.07.005

[41] George MP, Champion HC, Pilewski JM. Lung transplantation for pulmonary hypertension. Pulmonary Circulation. 2011;**1**(2):182-191. DOI: 10.4103/2045-8932.83455

[42] Callejo M, Barberá JA, Duarte J, Perez-Vizcaino F. Impact of nutrition on pulmonary arterial hypertension. Nutrients. 2020;**12**(1):169. DOI: 10.3390/nu12010169

[43] Hume E, Ward L, Wilkinson M, Manifield J, Clark S, Vogiatzis I. Exercise training for lung transplant candidates and recipients: A systematic review. European Respiratory Review. 2020;**29** (158):200053. DOI: 10.1183/16000617.0053-2020

[44] Benjamin N, Marra AM, Eichstaedt C, Grünig E. Exercise training and rehabilitation in pulmonary hypertension. Heart Failure Clinics. 2018;**14**(3):425-430. DOI: 10.1016/j.hfc.2018.03.008

[45] Babu AS, Morris NR. Patients support exercise training and rehabilitation—What more should we be doing to ensure cardiopulmonary rehabilitation is more readily available for those with pulmonary hypertension? Pulm. Circ. 2020;**10**(4):2045. DOI: 10.1177/2045894020975312

[46] Zeng X, Chen H, Ruan H, Ye X, Li J, Hong C. Effectiveness and safety of exercise training and rehabilitation in pulmonary hypertension: A systematic review and meta-analysis. Journal of Thoracic Disease. 2020;**12**(5):2691-2705. DOI: 10.21037/jtd.2020.03.69

[47] Abidi Y et al. Lung transplant rehabilitation-a review. Life Basel Switzerland. 2023;**13**(2):506. DOI: 10.3390/life13020506

[48] Hoeper MM et al. Intensive care, right ventricular support and lung transplantation in patients with pulmonary hypertension. The European Respiratory Journal. 2019;**53**:1801906. DOI: 10.1183/13993003.01906-2018

[49] Tilea I, Varga A, Georgescu A-M, Grigorescu B-L. Critical care management of decompensated right heart failure in pulmonary arterial hypertension patients – An ongoing approach. Journal of Critical Care Medicine. 2021;**7**(3):170-183. DOI: 10.2478/jccm-2021-0020

[50] Mizota T, Fujiwara K, Hamada M, Matsukawa S, Segawa H. Effect of arginine vasopressin on systemic and pulmonary arterial pressure in a patient with pulmonary hypertension secondary to pulmonary emphysema: A case report. JA Clinical Report. 2017;**3**(1):1. DOI: 10.1186/s40981-016-0072-3

[51] Augoustides JGT, Savino JS. Vasopressin: The perioperative gift that keeps on giving. Anesthesiology. 2014; **121**(5):914-915. DOI: 10.1097/ALN.0000000000000431

[52] Chiu JS et al. Balloon atrial septostomy in pulmonary arterial hypertension: Effect on survival and associated outcomes. The Journal of Heart and Lung Transplantation. 2015; **34**(3):376-380. DOI: 10.1016/j.healun.2015.01.004

[53] Al Maluli H, DeStephan CM, Alvarez RJ, Sandoval J. Atrial septostomy: A contemporary review. Clinical Cardiology. 2015;**38**(6):395-400. DOI: 10.1002/clc.22398

[54] Grant C, Richards JB, Frakes M, Cohen J, Wilcox SR. ECMO and right ventricular failure: Review of the literature. Journal of Intensive Care Medicine. 2021;**36**(3):352-360. DOI: 10.1177/0885066619900503

[55] Sekela M, Noon G, Holland V, Lawrence E. Differential perfusion: Potential complication of femoral–Femoral bypass during lung transplantation. The Journal of Heart and Lung Transplantation. 1991;**10**: 322-324

[56] Strueber M et al. Bridge to thoracic organ transplantation in patients with pulmonary arterial hypertension using a pumpless lung assist device. American Journal of Transplantational Official Journal of American Society. 2009;**9**(4): 853-857. DOI: 10.1111/j.1600-6143.2009.02549.x

[57] Rosenzweig EB, Chicotka S, Bacchetta M. Right ventricular assist device use in ventricular failure due to pulmonary arterial hypertension: Lessons learned. The Journal of Heart and Lung Transplantation. 2016;**35**(10): 1272-1274. DOI: 10.1016/j.healun.2016.07.010

[58] Pasque MK, Trulock EP, Kaiser LR, Cooper JD. Single-lung transplantation for pulmonary hypertension: Three-month hemodynamic follow-up. Circulation. 1991;**84**(6):2275-2279. DOI: 10.1161/01.CIR.84.6.2275

[59] Pasque MK, Kaiser LR, Dresler CM, Trulock E, Triantafillou AN, Cooper JD. Single lung transplantation for pulmonary hypertension: Technical aspects and immediate hemodynamic results. The Journal of Thoracic and Cardiovascular Surgery. 1992;**103**(3):475-482. DOI: 10.1016/S0022-5223(19)34988-8

[60] Bando K et al. Indications for and results of single, bilateral, and heart-lung transplantation for pulmonary hypertension. The Journal of Thoracic and Cardiovascular Surgery. 1994; **108**(6):1056-1065

[61] Toyoda Y, Toyoda Y. Heart-lung transplantation: Adult indications and outcomes. Journal of Thoracic Disease. 2014;**6**(8):1138-1142. DOI: 10.3978/j.issn.2072-1439.2014.06.01

[62] George P, Davis RD, Klepetko W. Lung transplantation in pulmonary hypertension. In: Pulmonary Hypertension and Right Heart Failure. Vol. 9. Birmingham, Alabama: UAB Printing, University of Alabama at Birmingham; 2015. pp. 308-321

[63] Shayan H, Sareyyupoglu B, Shigemura N, Thacker J, Bermudez C, Toyoda Y. Lung transplant, double valve repair, and pulmonary artery aneurysm resection. The Annals of Thoracic Surgery. 2012;**93**(1):e3-e5. DOI: 10.1016/j.athoracsur.2011.07.067

[64] Le Pavec J, Hascoët S, Fadel E. Heart-lung transplantation: Current indications, prognosis and specific considerations. Journal of Thoracic Disease. 2018;**10**(10):5946-5952. DOI: 10.21037/jtd.2018.09.115

[65] Reitz BA. The first successful combined heart-lung transplantation. The Journal of Thoracic and Cardiovascular Surgery. 2011;**141**(4): 867-869. DOI: 10.1016/J.JTCVS.2010.12.014

[66] Burke CM et al. Twenty-eight cases of human heart-lung transplantation. Lancet London (England). 1986; **1**(8480):517-519. DOI: 10.1016/s0140-6736(86)90881-0

[67] Eadington T, Santhanakrishnan K, Venkateswaran R. Heart-lung transplantation for idiopathic pulmonary

arterial hypertension and giant pulmonary artery aneurysm – Case report. Journal of Cardiothoracic Surgery. 2020;**15**(1):169. DOI: 10.1186/s13019-020-01221-z

[68] Fadel E et al. Long-term outcome of double-lung and heart–lung transplantation for pulmonary hypertension: A comparative retrospective study of 219 patients☆. European Journal of Cardio-Thoracic Surgery. 2010;**38**(3):277-284. DOI: 10.1016/j.ejcts.2010.02.039

[69] Brouckaert J et al. Double-lung versus heart-lung transplantation for precapillary pulmonary arterial hypertension: A 24-year single-center retrospective study. Transplant International. 2019;**32**(7):717-729. DOI: 10.1111/tri.13409

[70] Chang SH, Smith DE, Moazami N, Kon ZN. Transplant operative considerations in pulmonary hypertension with severe right heart failure. Seminars in Thoracic and Cardiovascular Surgery. 2020;**32**(4):1024-1029. DOI: 10.1053/j.semtcvs.2020.08.004

[71] Gorter TM et al. Right ventricular recovery after bilateral lung transplantation for pulmonary arterial hypertension. Interactive Cardiovascular and Thoracic Surgery. 2017;**24**(6):890-897. DOI: 10.1093/ICVTS/IVX025

[72] Is it time for a paradigm shift: Should double-lung transplant be considered the treatment of choice for idiopathic pulmonary arterial hypertension and giant pulmonary aneurysm? – Pelenghi – 2021 – Journal of Cardiac Surgery – Wiley Online Library. Available from: https://onlinelibrary.wiley.com/doi/10.1111/jocs.15655 [Accessed: August 13, 2023]

[73] Kalkan S, Güner A, Bayam E, Tasci AE, Ozkan M. Giant pulmonary artery aneurysm caused by idiopathic pulmonary artery hypertension. The Annals of Thoracic Surgery. 2020;**109**(2):e149. DOI: 10.1016/j.athoracsur.2019.08.049

[74] Wekerle T, Klepetko W, Taghavi S, Birsan T. Lung transplantation for primary pulmonary hypertension and Giant pulmonary artery aneurysm. The Annals of Thoracic Surgery. 1998;**65**(3):825-827. DOI: 10.1016/S0003-4975(97)01413-6

[75] Doi A. Surgical management of giant pulmonary artery aneurysms in patients with severe pulmonary arterial hypertension. Journal of Cardiac Surgery. 2022;**37**(4):1019-1025

[76] Schwarz S et al. Lung transplantation for pulmonary hypertension with giant pulmonary artery aneurysm. The Journal of Thoracic and Cardiovascular Surgery. 2020;**159**(6):2543-2550. DOI: 10.1016/j.jtcvs.2019.09.178

[77] Elgharably H, Javorski MJ, McCurry KR. Bilateral sequential lung transplantation: Technical aspects. Journal of Thoracic Disease. 2021;**13**(11):6564-6575. DOI: 10.21037/jtd-2021-22

[78] Gust L et al. Single-lung and double-lung transplantation: Technique and tips. Journal of Thoracic Disease. 2018;**10**(4):2508-2518. DOI: 10.21037/jtd.2018.03.187

[79] Macchiarini P, Le Roy Ladurie F, Cerrina J, Fadel E, Chapelier A, Dartevelle P. Clamshell or sternotomy for double lung or heart-lung transplantation? European Journal of Cardio-Thoracic Surgery. 1999;**15**(3):333-339. DOI: 10.1016/S1010-7940(99)00009-3

[80] Teman NR, Xiao JT, Tribble CG, Parrino PE. Median sternotomy for lung

transplantation: Techniques and advantages. The Heart Surgery Forum. 2017;**20**(3):E089-E091. DOI: 10.1532/hsf.1809

[81] Mody GN, Coppolino A, Singh SK, Mallidi HR. Sternotomy versus thoracotomy lung transplantation: Key tips and contemporary results. Annals of Cardiothoracic Surgery. 2020;**9**(1):60-64. DOI: 10.21037/acs.2020.01.01

[82] Shudo Y et al. Impact of surgical approach in double lung transplantation: Median sternotomy vs clamshell thoracotomy. Transplantation Proceedings. 2020;**52**(1):321-325. DOI: 10.1016/j.transproceed.2019.10.018

[83] Meyers BF et al. Bilateral sequential lung transplantation without sternal division eliminates posttransplantation sternal complications. The Journal of Thoracic and Cardiovascular Surgery. 1999;**117**(2):358-364. DOI: 10.1016/S0022-5223(99)70434-4

[84] Taghavi S et al. Bilateral lung transplantation via two sequential anterolateral thoracotomies1. European Journal of Cardio-Thoracic Surgery. 1999;**15**(5):658-662. DOI: 10.1016/S1010-7940(99)00078-0

[85] Fischer S et al. Video-assisted minimally invasive approach in clinical bilateral lung transplantation. The Journal of Thoracic and Cardiovascular Surgery. 2001;**122**(6):1196-1198. DOI: 10.1067/mtc.2001.118272

[86] Hayanga JWA, D'Cunha J. The surgical technique of bilateral sequential lung transplantation. Journal of Thoracic Disease. 2014;**6**(8):1063-1069. DOI: 10.3978/j.issn.2072-1439.2014.07.02

[87] Boasquevisque CHR, Yildirim E, Waddel TK, Keshavjee S. Surgical techniques - lung transplant and lung volume reduction. Proceedings of the American Thoracic Society. 2009;**6**(1):66-78. DOI: 10.1513/pats.200808-083GO

[88] Yeung JC, Keshavjee S. Overview of clinical lung transplantation. Cold Spring Harbor Perspectives in Medicine. 2014;**4**(1):a015628. DOI: 10.1101/cshperspect.a015628

[89] Nagendran M, Maruthappua M, Sugand K. Should double lung transplant be performed with or without cardiopulmonary bypass? Interactive Cardiovascular and Thoracic Surgery. 2011;**12**(5):799-804. DOI: 10.1510/icvts.2010.263624

[90] Marczin N, Royston D, Yacoub M. Pro: Lung transplantation should be routinely performed with cardiopulmonary bypass. Journal of Cardiothoracic and Vascular Anesthesia. 2000;**14**(6):739-745. DOI: 10.1053/jcan.2000.18592

[91] McRae K. Con: Lung transplantation should not be routinely performed with cardiopulmonary bypass. Journal of Cardiothoracic and Vascular Anesthesia. 2000;**14**(6):746-750. DOI: 10.1053/jcan.2000.18601

[92] Sunder T. Extracorporeal membrane oxygenation and lung transplantation. Indian Journal of Thoracic Cardiovascular Surgery. 2021;**37**(2):327-337. DOI: 10.1007/s12055-020-01099-5

[93] Bittner HB, Binner C, Lehmann S, Kuntze T, Rastan A, Mohr FW. Replacing cardiopulmonary bypass with extracorporeal membrane oxygenation in lung transplantation operations. European Journal of Cardio-Thoracic Surgery. 2007;**31**(3):462-467. DOI: 10.1016/j.ejcts.2006.11.050

[94] Aigner C et al. Institutional experience with extracorporeal membrane oxygenation in lung transplantation. European Journal of Cardio-Thoracic Surgery. 2007;**31**(3): 468-474. DOI: 10.1016/j.ejcts.2006.11.049

[95] Ius F et al. Lung transplantation on cardiopulmonary support: Venoarterial extracorporeal membrane oxygenation outperformed cardiopulmonary bypass. The Journal of Thoracic and Cardiovascular Surgery. 2012;**144**(6): 1510-1516. DOI: 10.1016/j.jtcvs.2012.07.095

[96] Hoetzenecker K et al. Intraoperative extracorporeal membrane oxygenation and the possibility of postoperative prolongation improve survival in bilateral lung transplantation. The Journal of Thoracic and Cardiovascular Surgery. 2018;**155**(5):2193-2206.e3. DOI: 10.1016/j.jtcvs.2017.10.144

[97] Hoechter DJ et al. Extracorporeal circulation during lung transplantation procedures: A Meta-analysis. Extracorporous Circulation on Lungs Transplantation. 2017;**63**(5):551-561. DOI: 10.1097/MAT.0000000000000549

[98] Tudorache I et al. Lung transplantation for severe pulmonary hypertension – Awake extracorporeal membrane oxygenation for postoperative left ventricular remodelling. Transplantation. 2015; **99**(2):451-458. DOI: 10.1097/TP.0000000000000348

[99] Salman J et al. Mid-term results of bilateral lung transplant with postoperatively extended intraoperative extracorporeal membrane oxygenation for severe pulmonary hypertension. European Journal of Cardio-Thoracic Surgery. 2017;**52**(1):163-170. DOI: 10.1093/ejcts/ezx047

[100] Moser B et al. Lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative and postoperatively prolonged extracorporeal membrane oxygenation provides optimally controlled reperfusion and excellent outcome. European Journal of Cardio-Thoracic Surgery. 2018;**53**(1):178-185. DOI: 10.1093/ejcts/ezx212

[101] Dell'Amore A et al. Extracorporeal life support during and after bilateral sequential lung transplantation in patients with pulmonary artery hypertension. Artificial Organs. 2020; **44**(6):628-637. DOI: 10.1111/aor.13628

[102] Singer JP. Pulmonary hypertension and primary graft dysfunction in lung transplant recipients: We still have a long way to go. Annals of the American Thoracic Society. 2017;**14**(10): 1504-1505. DOI: 10.1513/AnnalsATS.201706-480ED

[103] Porteous MK et al. Clinical risk factors and prognostic model for primary graft dysfunction after lung transplantation in patients with pulmonary hypertension. Annals of the American Thoracic Society. 2017;**14**(10): 1514-1522. DOI: 10.1513/AnnalsATS.201610-810OC

[104] Snell GI et al. Report of the ISHLT working group on primary lung graft dysfunction, part I: Definition and grading—A 2016 consensus group statement of the International Society for Heart and Lung Transplantation. The Journal of Heart and Lung Transplantation. 2017;**36**(10):1097-1103. DOI: 10.1016/j.healun.2017.07.021

[105] Thabut G, Mal H. Outcomes after lung transplantation. Journal of Thoracic

Disease. 2017;**9**(8):2684-2691. DOI: 10.21037/jtd.2017.07.85

[106] Trindade AJ et al. Assessment of dd-cfDNA levels in clinically stable lung allograft recipients beyond the initial 2 y Posttransplant. Transplantation direct. 2022;**8**(12):e1411. DOI: 10.1097/TXD.0000000000001411

[107] Keller M, Agbor-Enoh S. Cell-free DNA in lung transplantation: Research tool or clinical workhorse? Current Opinion in Organ Transplantation. 2022; **27**(3):177-183. DOI: 10.1097/MOT.0000000000000979

[108] Wong A et al. Potential therapeutic targets for lung repair during human ex vivo lung perfusion. The European Respiratory Journal. 2020;**55**(4):1902222. DOI: 10.1183/13993003.02222-2019

[109] Neto D, Guenthart B, Shudo Y, Currie ME. World's first en bloc heart-lung transplantation using the paragonix lungguard donor preservation system. Journal of Cardiothoracic Surgery. 2023; **18**(1):131. DOI: 10.1186/s13019-023-02281-7

[110] Valapour M, Lehr CJ, Wey A, Skeans MA, Miller J, Lease ED. Expected effect of the lung composite allocation score system on US lung transplantation. American Journal of Transplantation. 2022;**22**(12):2971-2980. DOI: 10.1111/ajt.17160

[111] Verzelloni Sef A, Sef D, Trkulja V, Marczin N. Current perspectives and future directions in lung transplantation. Life Basel Switz. 2023;**13**(7):1432. DOI: 10.3390/life13071432

Chapter 8

Double Lung and Heart-Lung Transplantation for Congenital Heart Disease with Eisenmenger Syndrome and Idiopathic Pulmonary Arterial Hypertension

Gustavo L. Knop and Alejandra Castro-Varela

Abstract

Patients with pulmonary hypertension who develop concomitant refractory end-stage lung disease and/or chronic end-stage heart disease should undergo evaluation to determine if they are candidates for double lung (DLTx) or heart-lung transplantation (HLTx). Pulmonary hypertension is the indication for approximately 4.5% of total lung transplants. The most common indication for HLTx is complex congenital heart disease (CHD) with Eisenmenger syndrome. HLTx is also indicated in patients with idiopathic pulmonary arterial hypertension and severe right ventricular (RV) failure. Patients with pulmonary hypertension represent a heterogenous group not only in terms of mechanism leading to the development of pulmonary hypertension but also regarding the presence and degree of right and/or left ventricular dysfunction. The choice between double lung transplant (DLTx) and HLTx is based on the etiology, clinical presentation, and other factors. In this chapter, we will discuss the treatment of patients with CHD with Eisenmenger syndrome and idiopathic pulmonary arterial hypertension, including the surgical option of DLTx and HLTx.

Keywords: bilateral lung transplant, heart-lung transplant, Eisenmenger syndrome, idiopathic pulmonary arterial hypertension, pulmonary hypertension

1. Introduction

Pulmonary hypertension (PH) affects 1% of the world population, up to 10% of individuals older than 65 years, and at least 50% of patients with heart failure (HF) [1]. Right-sided heart catheterization is used to diagnose PH and it is defined as a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg. Precapillary PH is present when pulmonary artery wedge pressure (PAWP) is ≤15 mmHg or pulmonary vascular resistance (PVR) is ≥3 Wood units. Post-capillary PH is present when PAWP is >15 mmHg (**Figure 1**) [1]. As shown in **Table 1**, pulmonary hypertension is classified

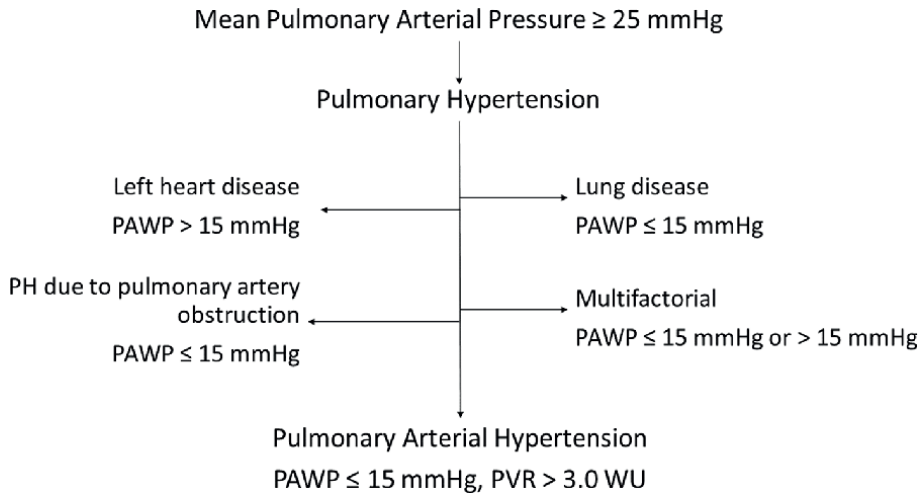

Figure 1.
Diagnostic algorithm for pulmonary arterial hypertension. PAWP: pulmonary arterial wedge pressure, PVR: pulmonary vascular resistance.

Groups	Prevalence
Group 1 – Pulmonary arterial hypertension	Rare
1.1 Idiopathic 1.2 Heritable 1.3 Drug- or toxin-induced 1.4 Associated with certain conditions Including congenital heart diseases	
Group 2 – PH associated with left heart disease	Very common
2.1 Left ventricular systolic dysfunction 2.2 Left ventricular diastolic dysfunction 2.3 Valvular disease 2.4 Outflow tract obstruction and congenital cardiomyopathies	
Group 3 – PH associated with lung disease and/or hypoxia	Common
3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease	
Group 4 – PH associated with pulmonary artery obstruction	Rare
Group 5 – PH with unclear and/or multifactorial mechanisms	Rare
5.1 Hematologic disorders 5.2 Systemic disorders 5.3 Metabolic disorders 5.4 Others	

Table 1.
Classification of pulmonary hypertension (PH).

into five groups: pulmonary arterial hypertension (PAH), secondary to left-heart disease, secondary to lung disease and/or hypoxia, secondary to pulmonary artery obstructions, and multifactorial. PAH is further divided into idiopathic, heritable, drug- and toxin-induced, associated with various conditions including congenital

heart disease (CHD), PAH in long-term responders to calcium channel blockers, with venous and/or capillary involvement, and of the newborn [1]. Regardless of the cause, patients with PAH have deteriorating symptoms, poor long-term prognosis, and increased mortality. This chapter will discuss the use of double lung transplant (DLTx) and heart-lung transplant (HLTx) to treat end-stage idiopathic and congenital heart disease-associated PAH unresponsive to maximal medical treatment.

2. Etiopathogenesis

Idiopathic PAH (IPAH) is a diagnosis of exclusion and accounts for 39–46% of all PAH cases [1]. PAH associated with congenital heart disease can lead to Eisenmenger syndrome (ES), defined as PH at systemic level with a reversed or bidirectional shunt at aortopulmonary, ventricular, or atrial level [2]. Large tertiary CHD cohorts still report ES in 1% to 5.6% of patients [3]. It usually develops in patients with untreated (large atrial or ventricular septal defects) or complex (univentricular hearts) congenital heart defects, as well as surgically created extracardiac left-to-right shunts. The continued development of the field of congenital cardiac surgery has allowed early diagnosis and timely repair of simple defects and thus reduction of ES, particularly in high-income countries. However, ES is still present as a consequence of complex cardiac anatomy, as well as unrepaired defects in low- and middle-income countries. Patients with persistent shunts initially have increased pulmonary blood flow, which eventually leads to pulmonary microvasculature remodeling and pulmonary blood flow obstruction.

3. Histopathology

Patients with PAH undergo loss and obstructive remodeling of the pulmonary vascular bed (**Figure 2**) [1]. The pathological process involves endothelial dysfunction, intimal hyperplasia and fibrosis, smooth muscle proliferation and medial hypertrophy, adventitial proliferation, and *in-situ* thrombosis. Continued arterial blood flow obstruction provokes further remodeling and formation of end-stage characteristic plexiform arteriopathy. Eventually, chronic cases of both diseases cause right ventricle (RV) hypertrophy and right atrium dilatation, which convert these chambers from low-pressure to high-pressure spaces. Eventually, the RV also starts to dilate in order to maintain stroke volume and ensues RV dysfunction.

4. Clinical presentation and diagnosis

Early-stage PH usually presents with nonspecific symptoms such as exertional and at-rest dyspnea, fatigue, chest pressure, or syncope. Late-stage PH is characterized by progressive RV dysfunction that presents with dilated jugular veins, hepatomegaly, ascites, and lower extremity edema. At cardiac auscultation, a pronounced pulmonic component of the second heart sound (P2) and a systolic murmur over the left para-sternal border can be heard if tricuspid regurgitation is present. Eisenmenger syndrome patients also have a variable clinical presentation that depends on the underlying cardiac defect and associated end-organ complications.

Useful imaging tests include electrocardiogram, chest X-ray, and echocardiogram. Electrocardiogram-specific signs include P pulmonale, R wave to S ratio > 1 in the V1

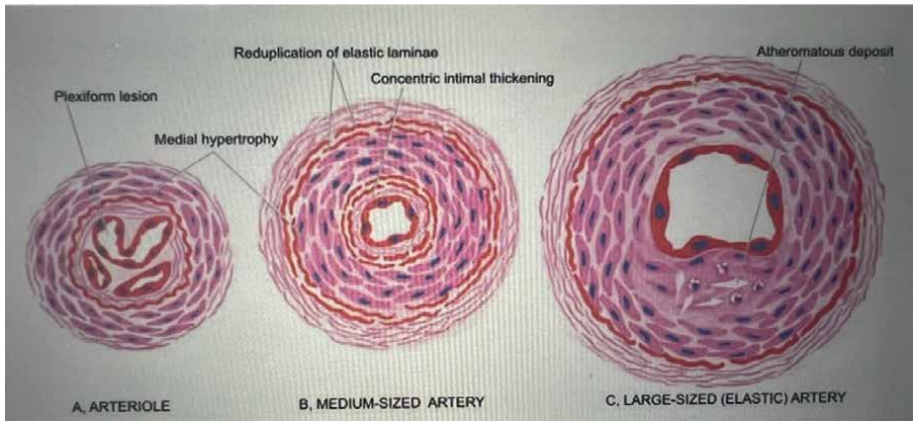

Figure 2.
Histologic changes in PH in different branches of the pulmonary artery.

lead, and right ventricular strain and an S1Q3T3 pattern can sometimes be observed. Chest radiogram can show right atrial enlargement and dilated pulmonary arteries. Echocardiography can help determine the size and function of right-heart chambers, as well as congenital or acquired heart defects.

Right-heart catheterization should be performed in all cases to confirm the diagnosis. Performing vasoreactivity testing during right-heart catheterization is recommended as it allows the identification of patients with a good response to calcium channel blockers.

A ventilation-perfusion scan is obligatory to exclude PH secondary to pulmonary artery obstructions in patients with no left heart or lung disease. Additional tests that can aid in the diagnosis and further characterization of the disease include pulmonary function tests, high-resolution and contrast-enhanced computed tomography, pulmonary angiography, cardiac magnetic resonance imaging, and polysomnography.

5. Prognosis

A baseline systemic evaluation is important for predicting patients' prognosis as it determines initial therapy. Additionally, response to treatment should be evaluated. Useful markers for initial and follow-up assessment include the World Health Organization functional class (I to IV), hemodynamic variables, and echocardiographic parameters. Hemodynamic variables include mPAP, PVR, mean right atrial pressure, cardiac index, mixed venous oxygen saturation, systolic blood pressure, and exercise tolerance [4]. Echocardiographic characteristics that should be assessed include the presence of pericardial effusion or right atrial area in end-systole >18 cm^2. Elevated brain natriuretic peptide may indicate right ventricular overload and increased uric acid levels may indicate tissue hypoxia secondary to venous congestion in patients with PAH [4].

PAH patients are considered low clinical risk when they have a 6-min walk distance greater than 440 m, peak VO2 > 15 mL/min/kg, and a cardiac index >2.5 L/min/m^2 [4]. Of note, pulmonary risk stratification for patients with ES is very limited when compared to IPAH, as they represent very different diseases and the information available for IPAH cannot be extrapolated for ES.

Reported survival rates for PAH are between 68 and 93% at 1 year and 39–77% at 3 years [1]. The long-term prognosis for ES remains unfavorable with survival rates of 74–81% at 5 years and 57% at 10 years. The higher survival rate reported for patients with ES compared to IPAH may be due to ES patients having a slower disease progression and potentially higher plasticity of cardiac myocytes earlier in life, which may lead to a better adaptation of the right ventricle to increased afterload [5–7]. Nonetheless, untreated ES patients continue to have a significantly limited life expectancy, particularly when the underlying heart defects are complex. The current leading causes of death are heart failure, infections, sudden cardiac death, thromboembolism, hemorrhage, and perioperative complications [8]. Studies have associated several risk factors with higher mortality in ES patients. Diller et al. report functional class, presence of heart failure signs, history of clinical arrhythmia, QRS duration and QTc interval, and lower serum albumin and potassium levels as important predictors of mortality [9]. Kempny et al. also found higher mortality associated with age, the presence of a pre-tricuspid shunt, lower oxygen saturation at rest, absence of sinus rhythm or arrhythmias, and presence of pericardial effusion [10]. Moceri et al. created a composite score based on the strongest echocardiographic predictors of outcome which included tricuspid annular plane systolic excursion <15 mm, ratio of right ventricular effective systolic to diastolic duration ≥1.5, right atrium area ≥ 25 cm^2, and ratio of right atrium to left atrial area ≥ 1.5 [11].

6. Treatment

6.1 Medical treatment

Patients with IPAH and positive response to vasoreactivity testing should be treated with calcium-channel blockers. For non-responders, PAH-specific drugs (**Table 2**) that target the endothelin, nitric oxide, or prostacyclin pathways should be considered, as these pathways are associated with abnormal proliferation and contraction of the smooth muscle cells of the pulmonary arteries in patients with PAH [12]. Endothelin receptor antagonists include bosental, ambrisentan, and macitentan. Phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil and tadalafil, and the soluble guanylate cyclase stimulator, riociguat, act on the nitric oxide pathway.

Mechanism of action	Drug name	Administration route
Endothelin-receptor antagonists	Bosentan	Oral
	Ambrisentan	Oral
	Macitentan	Oral
Phosphodiesterase type 5 inhibitors	Sildenafil	Oral
	Tadalafil	Oral
Guanylate cyclase stimulator	Riociguat	Oral
Prostacyclin analogs	Epoprostenol	Intravenous
	Iloprost	Inhaled
	Treprostinil	Subcutaneous or intravenous
	Beraprost	Oral
Prostaglandin I2 receptor agonists	Selexipag	Oral

Table 2.
Approved drug for treatment of pulmonary arterial hypertension.

Prostacyclin analogs include epoprostenol, treprostinil, and iloprost, while selexipag is an oral prostacyclin IP receptor agonist [13]. These medications can be used alone or in combination. Dual combination therapy with a PDE-5 inhibitor and an endothelin-receptor antagonist is the most widely utilized regimen, particularly in patients with low or intermediate risk. The goal of medical treatment is achieving a low clinical risk, which as mentioned previously, is defined as a 6-min walk distance greater than 440 m, peak VO_2 > 15 mL/min/kg, and cardiac index >2.5 L/min/m^2 [4]. When the treatment response is inadequate despite maximal medical therapy, referral for transplant evaluation should be considered.

6.2 Surgical treatment

The 2019 International Heart and Lung Transplantation Registry reports IPAH as an indication of more than 1800 lung transplants and non-IPAH PH to almost 1000 lung transplants from January 1995 to June 2018, representing 4.5% of total lung transplants [14]. Among all lung transplant indications, IPAH has the highest perioperative mortality [15]. Despite being clinically complex patients, the discussion of double lung (DLTx) (**Figures 3** and **4**) or heart-lung transplantation (HLTx) should be initiated early in cases of end-stage cardiopulmonary disease secondary to PH.

A systematic review and meta-analysis evaluated short-term and long-term outcomes of patients with end-stage cardiopulmonary disease of different etiologies after DLTx vs. after HLTx, and found no significant differences between DLTx and HLTx patients in 1-, 3-, 5-, and 10-year survival rates [16].

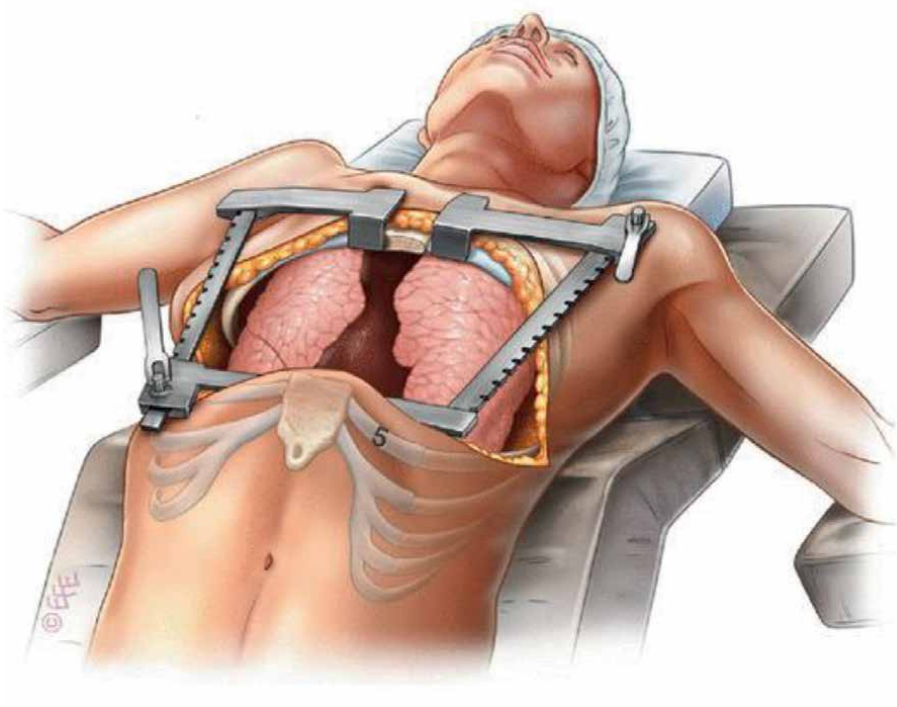

Figure 3.
Surgical incision for double lung and heart-lung transplant.

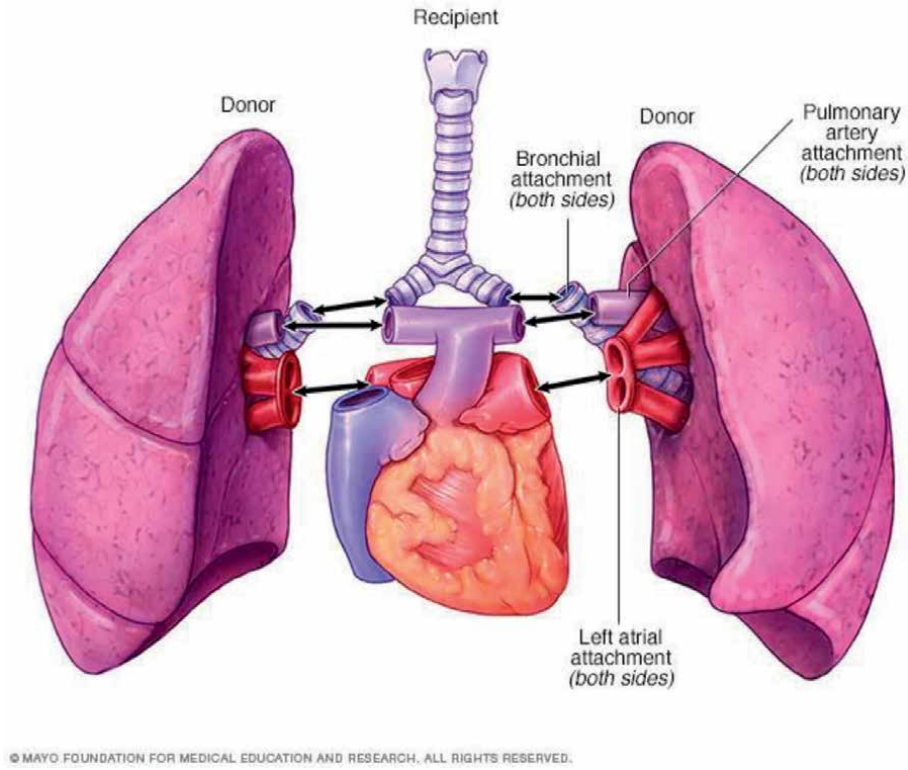

Figure 4.
Anatomy of double lung transplant.

In patients with PAH, DLTx is preferred over single lung transplant [17]. DLTx can be considered in patients with PH and recoverable ventricular function, as a rapid reduction in pulmonary resistance after DLTx frequently results in improved right ventricular function [16]. Hadebank et al. reported a significant decrease in right ventricular systolic pressure and end-diastolic diameter after DLTx [18]. Nevertheless, patients with postoperative LV failure after DLTx are more susceptible to pulmonary venous congestion and early graft failure. Early after DLTx for severe PH, the LV may be unable to handle normalized LV preload [19]. The Hannover group reported successful bridges to recovery in patients with PH with the use of awake venoarterial extracorporeal membrane oxygenation [19]. Complex ES remains the main indication for HLTx in PAH [20].

Most studies report similar short and long-term outcomes of patients with progressive end-stage PH after DLTx and HLTx [16, 21–24]. However, other studies report different post-transplant survival rates [25, 26]. An important outcome predictor of both procedures is the degree of preoperative right ventricular dysfunction. For successful DLTx, authors propose that patients should have a left ventricular ejection fraction between 32 and 55% and right ventricular ejection fraction between 10 and 25% [20, 22, 27, 28]. In most patients with pulmonary arterial hypertension and preserved left ventricular (LV) function, there is no advantage to HLTx compared with isolated DLTx, even in the presence of limited right ventricular dysfunction. However, great disparity continues to exist among centers regarding the lowest acceptable right and LV ejection fraction for DLTx, particularly among patients

with IPAH, and some centers prefer combined HLTx if severe dysfunction exists. Disadvantages of HLTx, however, include exposure of the recipient to risks of both graft coronary artery vasculopathy and chronic lung allograft dysfunction. The availability of new medical therapies for patients with pulmonary arterial hypertension and congenital heart disease with Eisenmenger syndrome has also reduced the need for HLTx. The total number of adult procedures reported has declined from a peak of over 200 per year in the late 1980s and early 1990s to fewer than 60 per year for the last several years, compared with an increasing number of single and DLTx [14].

Hill et al. found that despite a similar adjusted overall survival, critically ill patients hospitalized with IPAH in the ICU had better outcomes after HLTx than after DLTx [25]. Although several studies have reported higher in-hospital mortality after HLTx than after DLTx, the difference was not significant [24]. An important indicator of quality of early graft function is the time on postoperative ventilation [24]. Notably, the waiting list times for HLTx are shorter than for DLTx [29].

Life-threatening complications of DLTx and HLTx include dehiscence after tracheal or bronchial anastomosis and infection. Fadel et al. report that the incidence of complications was similar for patients undergoing DLTx and HLTx for PH [30].

Currently, both DLTx and HLTx are adequate options for end-stage IPAH and ES, but HLTx is needed for patients with complex congenital heart disease or severe ventricular dysfunction [31]. Further studies are necessary to compare the outcomes of both procedures for these two specific indications, including randomized controlled trials if feasible.

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References

[1] Mandras SA, Mehta HS, Vaidya A. Pulmonary hypertension: A brief guide for clinicians. Mayo Clinic Proceedings. 2020;**95**:1978-1988

[2] Wood P. The eisenmenger syndrome: Or pulmonary hypertension week reversed central shunt. The American Journal of Cardiology. 1972;**30**:172-174

[3] Arvanitaki A, Gatzoulis MA, Opotowsky AR, Khairy P, Dimopoulos K, Diller G-P, et al. Eisenmenger syndrome: JACC state-of-the-art review. Journal of the American College of Cardiology. 2022;**79**:1183-1198

[4] Kondo T, Okumura N, Adachi S, Murohara T. Pulmonary hypertension: Diagnosis, management, and treatment. Nagoya Journal of Medical Science. 2019;**81**:19-30

[5] Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. The Journal of Heart and Lung Transplantation. 1996;**15**:100-105

[6] Hopkins WE. The remarkable right ventricle of patients with Eisenmenger syndrome. Coronary Artery Disease. 2005;**16**:19-25

[7] Diller G-P, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. Circulation. 2007;**115**:1039-1050

[8] Hjortshøj CMS, Kempny A, Jensen AS, Sørensen K, Nagy E, Dellborg M, et al. Past and current cause-specific mortality in Eisenmenger syndrome. European Heart Journal. 2017;**38**:2060-2067

[9] Diller G-P, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, Uebing A, et al. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: A combined retrospective and case-control study. European Heart Journal. 2006;**27**:1737-1742

[10] Kempny A, Hjortshøj CS, Gu H, Li W, Opotowsky AR, Landzberg MJ, et al. Predictors of death in contemporary adult patients with Eisenmenger syndrome: A Multicenter study. Circulation. 2017;**135**:1432-1440

[11] Moceri P, Dimopoulos K, Liodakis E, Germanakis I, Kempny A, Diller G-P, et al. Echocardiographic predictors of outcome in eisenmenger syndrome. Circulation. 2012;**126**:1461-1468

[12] Tettey A, Jiang Y, Li X, Li Y. Therapy for pulmonary arterial hypertension: Glance on nitric oxide pathway. Frontiers in Pharmacology. 2021;**12**:767002

[13] Mandras S, Kovacs G, Olschewski H, Broderick M, Nelsen A, Shen E, et al. Combination therapy in pulmonary arterial hypertension-targeting the nitric oxide and prostacyclin pathways. Journal of Cardiovascular Pharmacology and Therapeutics. 2021;**26**:453-462

[14] Chambers DC, Cherikh WS, Harhay MO, Hayes D Jr, Hsich E, Khush KK, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: Donor and recipient size match. The Journal of Heart and Lung Transplantation. 2019;**38**:1042-1055

[15] Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, et al. The registry of the International Society for Heart and Lung Transplantation: Thirty-third adult lung and heart--lung transplant report—2016; focus theme: Primary diagnostic indications for transplant. The Journal of Heart and Lung Transplantation. 2016;**35**:1170-1184

[16] Yan H-J, Zheng X-Y, Huang H, Xu L, Tang H-T, Wang J-J, et al. Double-lung versus heart-lung transplantation for end-stage cardiopulmonary disease: A systematic review and meta-analysis. Surgery Today. 2022:12. Published on line 06 September 2022. DOI: 10.1007/s00595-022-02579-4

[17] George MP, Champion HC, Pilewski JM. Lung transplantation for pulmonary hypertension. Pulmonary Circulation. 2011;**1**:182-191

[18] Habedank D, Ewert R, Hummel M, Dandel M, Habedank F, Knosalla C, et al. The effects of bilateral lung transplantation on ventilatory efficiency, oxygen uptake and the right heart: A two-yr follow-up. Clinical Transplantation. 2011;**25**:E38-E45

[19] Tudorache I, Sommer W, Kühn C, Wiesner O, Hadem J, Fühner T, et al. Lung transplantation for severe pulmonary hypertension—Awake extracorporeal membrane oxygenation for postoperative left ventricular remodelling. Transplantation. 2015;**99**:451

[20] Albinni S, Marx M, Lang IM. Focused update on pulmonary hypertension in children-selected topics of interest for the adult cardiologist. Medicina. 2020;**2020**:56. DOI: 10.3390/medicina56090420

[21] Le Pavec J, Hascoët S, Fadel E. Heart-lung transplantation: Current indications, prognosis and specific considerations. Journal of Thoracic Disease. 2018;**10**:5946-5952

[22] Olland A, Falcoz P-E, Canuet M, Massard G. Should we perform bilateral-lung or heart–lung transplantation for patients with pulmonary hypertension? Interactive Cardiovascular and Thoracic Surgery. 2013;**17**:166-170

[23] de Perrot M, Granton JT, McRae K, Pierre AF, Singer LG, Waddell TK, et al. Outcome of patients with pulmonary arterial hypertension referred for lung transplantation: A 14-year single-center experience. The Journal of Thoracic and Cardiovascular Surgery. 2012;**143**:910-918

[24] Brouckaert J, Verleden SE, Verbelen T, Coosemans W, Decaluwé H, De Leyn P, et al. Double-lung versus heart-lung transplantation for precapillary pulmonary arterial hypertension: A 24-year single-center retrospective study. Transplant International. 2019;**32**:717-729

[25] Hill C, Maxwell B, Boulate D, Haddad F, Ha R, Afshar K, et al. Heart-lung vs. double-lung transplantation for idiopathic pulmonary arterial hypertension. Clinical Transplantation. 2015;**29**:1067-1075

[26] Franke U, Wiebe K, Harringer W, Franke T, Wittwer T, Wahlers T, et al. Ten years experience with lung and heart-lung transplantation in primary and secondary pulmonary hypertension. European Journal of Cardio-Thoracic Surgery. 2000;**18**:447-452

[27] Pielsticker EJ, Martinez FJ, Rubenfire M. Lung and heart-lung transplant practice patterns in pulmonary hypertension centers. The Journal of Heart and Lung Transplantation. 2001;**20**:1297-1304

[28] Bando K, Armitage JM, Paradis IL, Keenan RJ, Hardesty RL, Konishi H, et al. Indications for and results of single, bilateral, and heart-lung transplantation for pulmonary hypertension. The Journal of Thoracic and Cardiovascular Surgery. 1994;**108**:1056-1065

[29] Kearney K, Lau EM, Darley D, Romfh A, Bart N, Kotlyar E, et al. Waitlist and post-transplant outcomes for eisenmenger syndrome: A comparison of transplant strategies. The Journal of Heart and Lung Transplantation. 2021;**40**:841-849

[30] Fadel E, Mercier O, Mussot S, Leroy-Ladurie F, Cerrina J, Chapelier A, et al. Long-term outcome of double-lung and heart--lung transplantation for pulmonary hypertension: a comparative retrospective study of 219 patients. European Journal of Cardio-Thoracic Surgery. 2010;**38**:277-284

[31] McCurry KR. Brief overview of lung, heart, and heart-lung transplantation. Critical Care Clinics. 2019;**35**:1-9

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Pulmonary hypertension (PH) is a diverse group of diseases that elevates pulmonary artery pressure. Globally, PH prevalence is approximately 1%. Pulmonary arterial hypertension incidence is 6 per million patients with a prevalence of 49–55 per million. This book dives into historical facts related to PH, clinical features, treatment, and specialized issues associated with PH. This book is a resource for health professionals such as nurses, medical students, allied health professionals, primary care physicians, pulmonary clinicians, and clinicians caring for patients with pulmonary hypertension.

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