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Review Article

Pulmonary Hypertension in Connective Tissue Diseases

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Abstract

Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure >20 mmHg at rest, confirmed by right heart catheterization (RHC). The European Society of Cardiology and the European Respiratory Society (ESC/ERS) published a new guideline in 2022 with recommendations for the classification, diagnosis, and treatment of PH. Pulmonary arterial hypertension (PAH) is a subgroup of PH and is most commonly seen together with connective tissue diseases after the idiopathic form. PAH may develop in connective tissue patients, most commonly in cases of systemic scleroderma. The presence of PAH significantly affects the quality of life and survival in connective tissue patients, especially in scleroderma. In PAH cases, early diagnosis and treatment before organ damage develops is the golden rule in treatment. Diagnosis should first be triggered by complaints such as unexplained dyspnea and syncope that develop in the presence of an underlying connective tissue disease such as scleroderma, which increases the risk of PAH and is made by RHC in the light of data obtained from examinations such as electrocardiogram, echocardiography, pulmonary function tests, and diffusing capacity for carbon monoxide. When planning treatment, pharmacological treatments are used in addition to non-pharmacological measures. Drug selection should be made by taking into account the patient's other characteristics. Combination oral therapy with an endothelin receptor antagonist and a phosphodiesterase 5 inhibitor is often the first-line treatment in scleroderma-PAH. During follow-ups, treatment may be changed according to the patient's clinical and laboratory data and risk analysis. For patients with functional class IV (the most severely ill patients), additional triple combination therapy consisting of a prostaglandin analog may be considered. Treatment is determined and followed according to the ERS/ESC 2022 guideline and other guidelines mostly developed in light of this guideline. Lung transplantation should not be ignored in cases resistant to these treatments. Despite current developments, the prognosis in PH cases is still poor and patients should be followed and treated in experienced centers specialized for PH.

Keywords: Connective tissue diseases; endothelin receptor antagonists; phosphodiesterase 5 inhibitors; prostacyclin analogs; pulmonary arterial hypertension; pulmonary hypertension; scleroderma.

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Bağ Dokusu Hastalıklarında Pulmoner Hipertansiyon

Özet

Pulmoner hipertansiyon (PH), sağ kalp kateterizasyonu ile doğrulanan, istirahatte 20 mmHg'den daha yüksek ortalama pulmoner arter basıncı olarak tanımlanır. Avrupa Kardiyoloji Derneği ve Avrupa Solunum Derneği (ESC/ERS) 2022 yılında pulmoner hipertansiyon sınıflandırma, tanı ve tedavisine dair önerilerin yer aldığı yeni bir kılavuz yayınlamıştır. Pulmoner arteryel hipertansiyon (PAH) pulmoner hipertansiyonun bir alt grubu olup

idyopatik formundan sonra en sık bağ dokusu hastalıkları ile birlikte görülmektedir. Bağ dokusu hastalarında en sık olarak sistemik skleroderma olgularında PAH gelişebilmektedir. PAH varlığı bağ dokusu hastalarında, özellikle de sklerodermada yaşam kalitesi ve sürviyi belirgin olarak etkilemektedir. PAH olgularında organ hasarları gelişmeden erken tanı ve tedavi tedavideki altın kuraldır. Tanı öncelikle altta yatan ve PAH riskini arttıran skleroderma gibi bir bağ dokusu hastalığının varlığında gelişen açıklanamayan dispne, senkop gibi yakınmalar uyarıcı olmalıdır ve bu hastalarda yapılacak EKG, Ekokardiyografi, SFT, DLCO gibi tetkiklerden elde edilecek veriler ışığında uygulanacak sağ kalp kateterizasyonu ile yapılır. Tedavi planlarken nonfarmakolojik önlemlere ilaveten farmakolojik tedavilere başvurulur. İlaç seçiminde hastanın diğer özellikleri de göz önüne alınarak ilaç seçimi yapılmalıdır. Bir endotelin reseptör antagonisti ve bir fosfodiesteraz 5 inhibitörü ile kombinasyon oral tedavi, skleroderma-PAH'da sıklıkla birinci basamak tedavidir. Takiplerde hastanın klinik ve laboratuvar verileri ile yapılacak risk analizine göre tedavi değiştirilebilir. Fonksiyonel sınıf IV olan hastalar (en ağır hastalar) için ek olarak prostaglandin analoğundan oluşan üçlü kombinasyon tedavisi için düşünülebilir. ERS/ESC 2022 kılavuzu ve çoğunlukla bu kılavuz ışığında geliştirilen başka kılavuzlara göre tedavi belirlenir ve takip edilir. Bu tedavilere dirençli olgularda akciğer nakli göz ardı edilmemelidir. Mevcut gelişmelere rağmen PH olgularında prognozu hala kötü olup hastalar PH için özelleşmiş deneyimli merkezlerde takip ve tedavi edilmelidir.

Anahtar sözcükler: Bağ dokusu hastalıkları; endotelin reseptör antagonistleri; fosfodiesteraz 5 inhibitörleri; prostasiklin analogları; pulmoner arteryel hipertansiyon; pulmoner hipertansiyon; skleroderma.

Introduction

Pulmonary hypertension (PH) is defined as a resting mean pulmonary artery pressure (mPAP) >20 mmHg, confirmed by right heart catheterization (RHC).[1] Previously, PH was defined as mPAP >25 mmHg measured by RHC and pulmonary capillary wedge pressure ≤15 mmHg without any evidence of significant pulmonary parenchymal disease. However, at the Sixth World Symposium on PH in 2018, PH was defined as mPAP >20 mmHg. These figures are supported by studies evaluating the upper limit of normal PAP in healthy subjects and data from studies investigating the prognostic significance of increased PAP. These data come from a 2009 study by Kovacs et al.[2] who analyzed all available data from RHC studies in healthy subjects to determine normal values of mPAP at rest and during exercise. Here, data from 47 research including 1187 normal participants were examined. At rest, mPAP was calculated to be 14.0±3.3 mmHg, which was independent of gender and ethnicity and was little affected by age and posture. Adding two standard deviations shows that the mPAP is >20 mmHg and over the upper limit of normal (i.e., above the 97.5th percentile), given that the mPAP is 14.0±3.3 mmHg. Therefore, the definition of mPAP >20 mmHg for the definition of PH is no longer arbitrary but based on a scientific approach.[3]

PH Classification

The previous classification's general structure was maintained at the Sixth World Symposium on PH, but a few modifications were made. These changes and recommendations for follow-up and treatment can be found in the relevant literature.[1]

PH can be classified according to its hemodynamic characteristics and possible underlying etiology (clinical classification). Hemodynamically, it can be classified as pre-capillary, post-capillary, combined pre- and post-capillary, and exercise PH.

Post-capillary PH is hemodynamically defined as mPAP >20 mmHg and PAWP >15 mmHg. Pulmonary vascular resistance is used to distinguish patients with post-capillary PH with a significant pre-capillary component PVR >2 WU-combined post- and pre-capillary PH (CpcPH) from those without PVR≤2 WU-isolated post-capillary PH.

Exercise PH is defined by an mPAP/cardiac output (CO) slope of >3 mmHg/L/min between rest and exercise. mPAP/CO slope is highly age dependent, with an upper limit of normal between 1.6 and 3.3 mmHg/L/min in the supine position. mPAP/CO slope >3 mmHg/L/min is not physiologic in subjects younger than 60 years of age and is rarely found in healthy subjects older than 60 years. A pathologic increase in pulmonary pressure during exercise is associated with poor prognosis in patients with exercise dyspnea and several cardiovascular conditions. Although an increased mPAP/CO slope defines an abnormal hemodynamic response to exercise, it does not allow differentiation between pre- and post-capillary causes. The simplest way to differentiate between pre- and post-capillary causes of exercise-induced PH is to utilize a PAWP/CO slope with a threshold >2 mmHg/L/min.

There are also patients with high mPAP (>20 mmHg) but low PVR (≤2 WU) and low PAWP (≤15 mmHg). These patients are often characterized by high pulmonary blood flow and although they have PH, they do not meet the criteria for pre- or post-capillary PH. This hemodynamic state can be described by the term "unclassified PH." Patients with unclassified PH may present with congenital heart disease (CHD), liver disease, airway disease, lung disease, or hyperthyroidism, which may explain the mPAP increase. Clinical follow-up of these patients is usually recommended. In the case of increased pulmonary blood flow, the etiology should be investigated.[1]

Clinical Classification

The ECR/ERS 2022 clinical classification has broadly maintained the 2015 classification (Table 1). As PH groups according to the clinical classification represent different clinical conditions, there may be additional clinically relevant hemodynamic thresholds (e.g., for PVR) for individual PH groups besides the general thresholds of the hemodynamic definition of PH discussed in the relevant sections.

Pulmonary arterial hypertension (PAH) is a subgroup of PH and is a much rarer disease than PH.[4] Patients with PAH are hemodynamically characterized by the presence of pre-capillary PH in the absence of other causes of pre-capillary PH, such as chronic thromboembolic pulmonary hypertension and

Table 1. Clinical classification of pulmonary hypertension (according to literature no: 1)

Group	Basic hemodynamic properties
Group 1 Pulmonary arterial hypertension (PAH)	Precapillary PH: mPAP >20 mmHg
1.1. Idiopathic (IPAH)	PCWP ≤15 mmHg
1.1.1. Non-responders in the vasoreactivity test	PVR ≥3 Woods Unit
1.1.2. Acute responders in the vasoreactivity test	
1.2. Hereditary (HPAH)[a]	
1.3. Associated with drugs and toxins[a]	
1.4. Related to:	
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 PH associated with left heart disease	Post-capillary PH; mPAP >20 mm Hg
2.1. Heart failure:	PAWP >15 mm Hg; PVR <3 WU
2.1.1. with preserved ejection fraction	Or combined precapillary and post-capillary PH
2.1.2. with reduced or mildly reduced ejection fraction[b]	mPAP >20 mm Hg
2.2. Valvular heart disease	PAWP >15 mm Hg
2.3. Congenital/acquired cardiovascular conditions leading to post-capillary PH	PVR ≥3 WU
Group 3 PH associated with lung diseases and/or hypoxia	Precapillary PH: mPAP >20 mmHg
3.1. Obstructive lung disease or emphysema	PCWP ≤5 mm Hg
3.2. Restrictive lung disease	PVR ≥3 WU
3.3. Lung disease with mixed restrictive/obstructive pattern	
3.4. Hypoventilation syndromes	
3.5. Hypoxia not caused by lung disease (e.g., high altitude)	
3.6. Developmental lung disorders	
Group 4 PH associated with pulmonary artery occlusions	Precapillary PH: mPAP >20 mmHg
4.1. Chronic thromboembolic PH	PCWP ≤15 mmHg
4.2. Other pulmonary artery occlusions[c]	PVR ≥3 WU
Group 5 PH with unclear mechanisms and/or multifactorial	Predominantly precapillary PH, but post-capillary
5.1. Hematologic disorders[d]	and combined pre- and post-capillary Contains in PH
5.2. Systemic disorders[e]	
5.3. Metabolic disorders[f]	
5.4. Chronic renal failure with or without hemodialysis	
5.5. Pulmonary tumor thrombotic microangiopathy	
5.6. Fibrosing mediastinitis	

[a]: Patients with inherited PAH or PAH associated with drugs and toxins may be acute responders; [b]: Left ventricular ejection fraction for HF with reduced ejection fraction: ≤40%; for HF with mildly reduced ejection fraction: 41–49%; [c]: Other causes of pulmonary artery occlusions include sarcomas (high or intermediate grade or angiosarcoma), other malignant tumors (e.g. renal carcinoma, uterine carcinoma, germ cell tumors of the testis), non-malignant tumors (e.g. arteritis without connective tissue disease, congenital pulmonary arterial stenoses, and hydatidosis; [d]: Including hereditary and acquired chronic hemolytic anemia and chronic myeloproliferative disorders; [e]: Including sarcoidosis, pulmonary Langerhans cell histiocytosis, and neurofibromatosis type 1; [f]: Including glycogen storage diseases and Gaucher disease. PVOD: Pulmonary veno-occlusive disease; PCH: Pulmonary capillary hemangiomatosis; PCWP: Pulmonary capillary wedge pressure; PH: Pulmonary hypertension; PVR: Pulmonary vascular resistance; WU: Wood units; PAWP: Pulmonary arterial wedge pressure; mPAP: Mean pulmonary artery pressure.

PH associated with lung diseases. All PH groups may include both pre- and post-capillary components that contribute to PAP elevation. Elderly patients in particular may present with many causes that predispose them to PH. The primary classification should be based on the presumed predominant cause of pulmonary pressure elevation.

Epidemiology

PH is an important global health problem. All age groups can be affected. The current estimates suggest that the prevalence of PH is in 1% of the world population. The prevalence is higher in people over 65 years of age due to the presence of cardiac and pulmonary causes of PH. It is estimated that up to 10% of people over 65 years of age have PH. Globally, heart failure (HF) is the leading cause of PH. PH is present in up to 50% of patients with HF.[5] For these reasons, it should be expected that PH cases will be seen frequently in cardiology clinics. Lung disease, especially chronic obstructive pulmonary disease, is the second most common cause. The observed prevalence of PH in the UK has doubled in the past 10 years and is now 125 cases/million people. Regardless of the underlying condition, developing PH is associated with worsening symptoms and increased mortality. In developing countries, CHD, certain infectious diseases (schistosomiasis and human immunodeficiency virus), and high altitude represent important but understudied causes of PH.[1,5] Com-

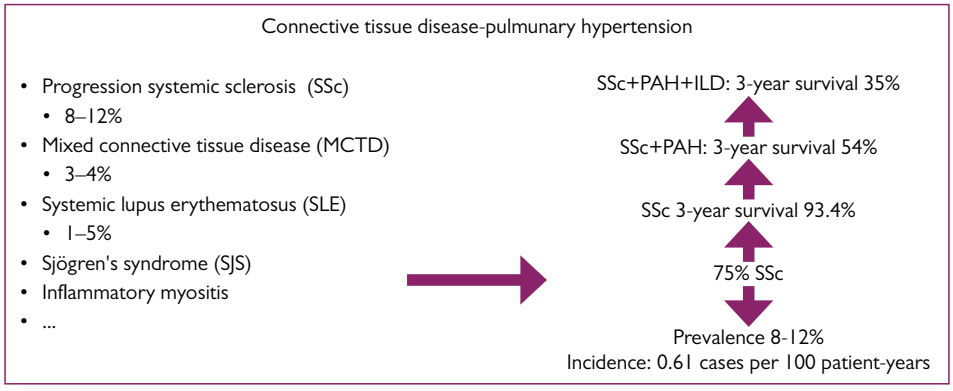

Figure 1. Pulmonary hypertension in connective tissue diseases. PAH cases developing in the course of SSc constitute 75% of CTD-related PAH cases. PAH may develop in 8–12% of all SSc cases, most commonly in the limited cutaneous involvement form. Created based on literature numbers 12 and 14.

PAH: Pulmonary arterial hypertension; ILD: Interstitial lung disease; CTD: Connective tissue diseases.

pared to PH, PAH is a more uncommon disease.[1,4] The incidence and prevalence of PAH are 6 and 48–55 cases/million adults, respectively, according to data from economically developed nations. It has been reported to predominantly affect younger individuals, mostly women. These data apply to HPAH, which currently affects women twice as often as men. However, recent data from the US and Europe show that PAH is now frequently diagnosed in older patients (i.e., those aged ≥65 years, who often have cardiovascular comorbidities, resulting in a more equal distribution between genders). In most PAH articles, IPAH was the most common subtype (50–60% of all cases), followed by PAH associated with connective tissue diseases (CTD), CHD, and portal hypertension (porto-PH) (Table 1).[6]

PAH Associated with CTD

Connective tissue disease-associated PAH (CTD-PAH) is the second most common cause of PAH after IPAH. Systemic sclerosis (SSc) is the most common CTD complicated by PAH, accounting for approximately 75% of cases of CTD-PAH. Up to 8–12% of SSc patients may develop PAH over time. PAH is a leading cause of death in SSc and is associated with a worse prognosis than IPAH. According to a French study from 2009, SSc-PAH has an incidence of 0.61 cases per 100 patient-years.[7,8]

In addition, PAH can be found in 1–5% of patients with systemic lupus erythematosus (SLE) and approximately 3–4% of those with mixed connective tissue disease (MCTD). Rarely, PAH has also been reported in primary Sjögren's syndrome, idiopathic inflammatory myopathies, and rheumatoid arthritis (Fig. 1). Data on the prevalence of PAH in CTDs other than SSc are much less reliable due to the lack of echocardiographic scans and left heart catheterization-based studies, which have been recommended only for SSc (Fig. 1).[4]

CTD-PAH is the second most common type of PAH in Western countries after IPAH. SSc, especially its limited variant, represents the main cause of CTD-PAH in Europe and the USA (SLE seems to be more prominent in Asia).[7,8]

Pathogenesis of PAH in CTD

Current data suggest that endothelial dysfunction and autoimmunity appear to be the most important mechanisms for CTD-PAH.[4,9]

Endothelial Dysfunction

As in IPAH, endothelial dysfunction plays a key role in the pathogenesis of CTD-PAH. Impaired production of vasoactive mediators and increased production of vasoconstrictors and proliferative mediators affect vascular tone and promote vascular remodeling. There are three pathways involved in endothelial dysfunction:

Endothelin-1 (ET-1)

ET-1 is an endogenous peptide produced by vascular endothelial cells and is one of the most potent vasoconstrictors and smooth muscle cell (SMC) mitogens. ET-1 appears to be particularly involved in the pathogenesis of CTD-PAH. ET-1 is overexpressed in the plasma and lung tissue of patients with SSc-PAH and SLE-PAH, and its expression rate is inversely correlated with survival in PAH. Agonistic ET-1 type A receptor antibodies (anti-ETAR) are more prevalent in SSc-PAH/CTD-PAH than in other forms of PAH and have been suggested to be useful predictors and prognostic biomarkers for SSc-PAH. ET-1 activates 2 endothelin receptor isoforms (type-A [ETA] and type-B [ETB]) of SMCs in vessels and induces vasoconstriction. Furthermore, ETB receptors are mainly involved in the scavenging of ET-1 and can cause vasodilation through the release of NO and prostacyclin from endothelial cells. On the other hand, the endothelin receptor antagonists (ERAs) bosentan, ambrisentan, and macitentan have been found useful and recommended for the treatment of PAH. For people with PAH in the WHO functional class II and III, ERAs are likely to increase exercise capacity, improve WHO functional class, prevent deterioration in the WHO functional class, and cause favorable changes in cardiopulmonary hemodynamic variables compared to placebo. However, they are less effective in reducing dyspnea and mortality. The combined use of ERAs and phosphodiesterase inhibitors may provide greater benefit in PAH, but this needs to be confirmed in future studies.[10]

Nitric Oxide (NO)

NO is a potent pulmonary vasodilator as well as an inhibitor of platelet activation and vascular SMC proliferation. In endothelial cells, activated NO synthase (NOS) produces NO by converting L-arginine to L-citrulline. Inducible NOS, one of the three known NOS isoforms, is activated by cytokines during inflammation. NO diffuses rapidly from the endothelium to SMCs, where its action is mediated through the activation of soluble guanylate cyclase (sGC) to produce cyclic guanosine monophosphate (cGMP). The intracellular concentration of cGMP is regulated *in vivo* by phosphodiesterase 5 (PDE5), which rapidly degrades cGMP to 5-GMP. cGMP is an important intracellular second messenger with relaxant and antiproliferative properties in pulmonary SMCs. Therapies aimed at increasing NO activity may be useful in the treatment of PAH. The type 5 cGMP phosphodiesterase inhibitors sildenafil and tadalafil have been found useful in the treatment of PAH. Riociguat is also an sGC stimulator that has shown antifibrotic, antiproliferative, and anti-inflammatory effects in preclinical models.[4,9]

Prostacyclin

Prostacyclin (PGI2) is a lipid mediator synthesized in endothelial cells from arachidonic acid by the enzymes cyclo-oxygenase and prostacyclin synthase. Once released, prostacyclin acts on the vasculature and platelets, mainly through activation of the enzyme adenylate cyclase, which converts adenosine triphosphate to cyclic adenosine monophosphate (cAMP). In vascular SMCs, cAMP mediates relaxation and reduces proliferation, vascular remodeling, and inflammation. Prostacyclin synthase is reduced in the lungs of PAH patients.

Autoimmunity

There is growing evidence that inflammation and autoimmunity may contribute to the onset and progression of PAH, particularly CTD-PAH. Infiltrating macrophages and lymphocytes, antinuclear antibodies (ANA), rheumatoid factor, and complement have been detected in the pulmonary vessels of patients with CTD-PAH. ANA and high levels of proinflammatory cytokines are detected in the serum of IPAH patients. Unexpectedly, elevated serum levels of interleukins 6, 8, 10, and 12 were more predictive of survival than hemodynamics or the six-minute walk test (6MWD) in a cohort of 21 PAH patients. Furthermore, IL-6 blockade has been shown to prevent chronic hypoxia-induced PH in mice by blocking the accumulation of Th17 cells and macrophages in the lungs. Data from animal models suggest that cytotoxic T cells may play a role in pulmonary arterial muscularization and B cells may promote pulmonary vascular injury and remodeling in PAH through the production of anti-endothelial cell antibodies.[4,9]

The pathogenesis of SSc-PAH involves damage to the vascular endothelium, inflammation, angiogenesis, and subsequent arterial obliteration. This process results in fibrosis leading to increased pulmonary artery pressure. Specifically, isolated PAH is more common in patients with limited SSc and is also closely associated with anti-fibrillarin (anti-U3-RNP) antibodies. Anti-fibrillarin antibodies are thought to influence pathogenesis through the upregulation of adhesion molecules and class II tissue-compatibility molecules present in pulmonary artery endothelial cells. Because this upregulation is associated with an increased risk of inflammatory vasculopathy.[11] The current evidence suggests that inflammation and autoimmunity are mainly involved in CTD-PAH other than SSc, at least in part reflecting differences in the overall pathogenesis between SSc and other CTDs. Actually, immunosuppressive medications have not really proven to be significantly efficient in SSc-PAH treatment, which may be due to endothelial dysfunction due to the vasoconstrictor/vasodilator imbalance observed in this condition. However, the possible contribution of inflammation and autoimmunity in determining the long-term prognosis of SSc-PAH patients cannot be definitively ruled out. Recent evidence suggests that active inflammation may also contribute to the pathogenesis of right ventricular dysfunction and failure, an important determinant of prognosis in PAH. Studies have shown that the accumulation of inflammatory cells such as macrophages and mast cells in the right ventricle is associated with maladaptive eccentric right ventricular remodeling. Patients with SSc-PAH have more impaired right ventricular function than those with IPAH despite similar afterloads; in particular, more inflammatory cells were found in the right ventricular tissue samples of SSc-PAH patients.[4,12]

In conclusion, autoimmunity does not seem to play a significant role in SSc-related PAH. Indeed, unlike previous examples of PAH with a CTD etiology, these patients do not respond to immunosuppressive treatments.

PAH occurs in 8–12% of SSc patients, with an even higher frequency in patients with limited cutaneous scleroderma. However, previous studies have excluded patients with concomitant pulmonary fibrosis. The European League Against Rheumatism (EULAR) Scleroderma Studies and Research database found isolated PAH associated with 9.2% of patients with limited scleroderma, compared with 5.8% of patients with diffuse scleroderma. Overall, the prevalence of SSc-induced PAH was found to range from 13 to 35% when diagnosed by an echocardiogram and 8–12% when diagnosed by RHC. However, it is important to note that the relatively recent change in the definition of PAH to include mPAP >20 will likely increase the prevalence of SSc-PAH.[13]

PH development in CTD patients is significant due to its impact on mortality. SSc-related PH cases constitute 75% of all CTD-originated PH cases. While the 3-year survival in SSc cases is 93.4% in general, this expectation decreases to 54% with the addition of PAH.[14] Moreover, if interstitial lung disease (ILD) and PAH are present together in the case of SSc, this expectation decreases to 35% (Fig. 1).

Risk factors for developing PAH caused by scleroderma include duration of disease or high age at the time of SSc diagnosis, presence of limited cutaneous SSc, low diffusing capacity for carbon monoxide (DLCO), presence of limited SSc subtype, anti-centromere antibody (ACA)-positive, and presence of telangiectasia. As men are thought to be more prone to develop PAH than women, risk stratification is necessary to help assess

Table 2. The World Health Organization functional classification of patients with pulmonary hypertension

Class	The World Health Organization functional class definition of patients with pulmonary hypertension
I	No limitations on ordinary physical activity; ordinary physical activity does not cause shortness of breath, fatigue, chest pain, or presyncope.
II	Mild physical activity limitation; no discomfort at rest; However, normal activity leads to increased shortness of breath, fatigue, chest pain, or presyncope
III	Significant activity limitation; no discomfort at rest but less than normal physical activity leads to increased shortness of breath, fatigue, chest pain, or presyncope
IV	Inability to perform physical activity at rest; there may be signs of right ventricular failure, symptoms increase with almost any type of physical activity

mortality rates of patients with PAH, taking into account factors such as symptoms of right HF, the World Health Organization Functional Class (WHO FC) (Table 2), and gender. Increased mortality is partly attributed to the difficulty of identifying PAH until disease progression becomes more severe.[11]

Risk factors for developing PAH caused by scleroderma include duration of disease or high age at the time of SSc diagnosis, presence of limited cutaneous SSc, low DLCO, presence of limited SSc subtype, ACA-positive, and presence of telangiectasia. As men are thought to be more prone to develop PAH than women, risk stratification is necessary to help assess mortality rates of patients with PAH, taking into account factors such as symptoms of right HF, WHO FC (Table 2), and gender. Increased mortality is partly attributed to the difficulty of identifying PAH until disease progression becomes more severe.[11]

Clinical Phenotypes of PH in Scleroderma

The precise phenotyping of PH in SSc remains challenging for clinicians in daily practice. Various and sometimes overlapping mechanisms have been proposed to explain PH in the presence of SSc. Indeed, SSc combines a diffuse vasculopathy, inflammation, autoimmunity, and fibrogenesis, leading to widespread fibrosis and vascular manifestations, and as a consequence, PH can be explained by pulmonary arterial vasculopathy (Group 1), pulmonary fibrosis (Group 3), or cardiac involvement (Group 2), as well as PVOD-like lesions (Group 1.5). The main problem is that there is no single group of PH and no single mechanism in SSc. However, while it may be difficult to distinguish the precise leading mechanism in a given patient, some may be combined to various degrees to explain the clinical presentation (Table 1). ILD, PVOD, and cardiac involvement can complicate the understanding and classification of SSc-PH and should be carefully considered in each patient. Further studies are needed to better understand the heterogeneity of SSc-PH and to better classify and treat these patients.[12,15]

Clinical Features and Diagnostic Approach of PAH Associated with CTD

The first signs and symptoms of PAH are often vague and non-specific. Patients experience fatigue, dyspnea on exertion, weakness, and dizziness. These symptoms are often attributed to the PAH itself or to having low physical fitness. More severe symptoms, such as presyncope, angina, and/or edema, only occur after diffuse pulmonary vasculopathy has developed. The diagnostic approach in patients with clinical suspicion of PAH should include physical examination, blood tests, pulmonary function tests (PFT) including forced vital capacity (FVC), DLCO, echocardiography, and high-resolution computed tomography (HRCT) scan of the chest. In the differential diagnosis of PAH, ventilation/perfusion lung scans should also be considered when necessary.

According to the recommendations in the European Society of Cardiology and the European Respiratory Society (ESC/ERS) 2022 guidelines for the diagnosis of PAH:[1]

- In SSc patients, an annual assessment of the risk of developing PAH is recommended.
- To identify asymptomatic patients with PAH, the DETECT algorithm is recommended in adult patients with SSc with a disease duration of >3 years, FVC ≥40%, and DLCO <60% (Fig. 2).
- RHC is recommended to exclude PAH in SSc patients with unexplained breathlessness after non-invasive evaluation.
- Consideration should be given to assessing the risk of PAH in patients with SSc based on echocardiograms or PFT and assessment of breathlessness in combination with BNP/NT-proBNP.
- In symptomatic patients with SSc, exercise echocardiography, cardiopulmonary exercise testing, or cardiac MRI may be considered to assist in RHC implementation decisions.

Although blood tests are generally not useful for the diagnosis of PAH, tests such as elevated N-terminal pro-BNP (NT-proBNP) levels may help to differentiate between forms of PAH and estimate prognosis. It is also useful to know the uric acid level for use in the DETECT algorithm. Special tests for the underlying CTD may also be required.

Pulmonary function tests are non-invasive and very informative tests that can be used in the diagnosis and follow-up of PAH. A mild restrictive pattern is detected in FVC with a marked decrease in DLCO. Therefore, the FVC/DLCO ratio will be higher than one. In a patient with SSc, FVC/DLCO follow-up performed under appropriate conditions and a ratio higher than one should be a warning for PAH. It should be kept in mind that compliance with these tests may decrease, especially in SSc patients due to decreased mouth opening.

Echocardiography shows an enlarged and hypertrophic right ventricle with signs of overpressure such as systolic septal flattening. Systolic, diastolic, and mPAPs can be estimated using the shape of the velocity curve of the regurgitation velocity and right ventricular outflow tract velocity of tricuspid regurgitation and pulmonary regurgitation. Together with echocardiographic estimation of right atrial pressure, cardiac index, and left atrial pressures, a fairly accurate impression of pulmonary hemodynamics can be obtained. Resting echocardiography in combi-

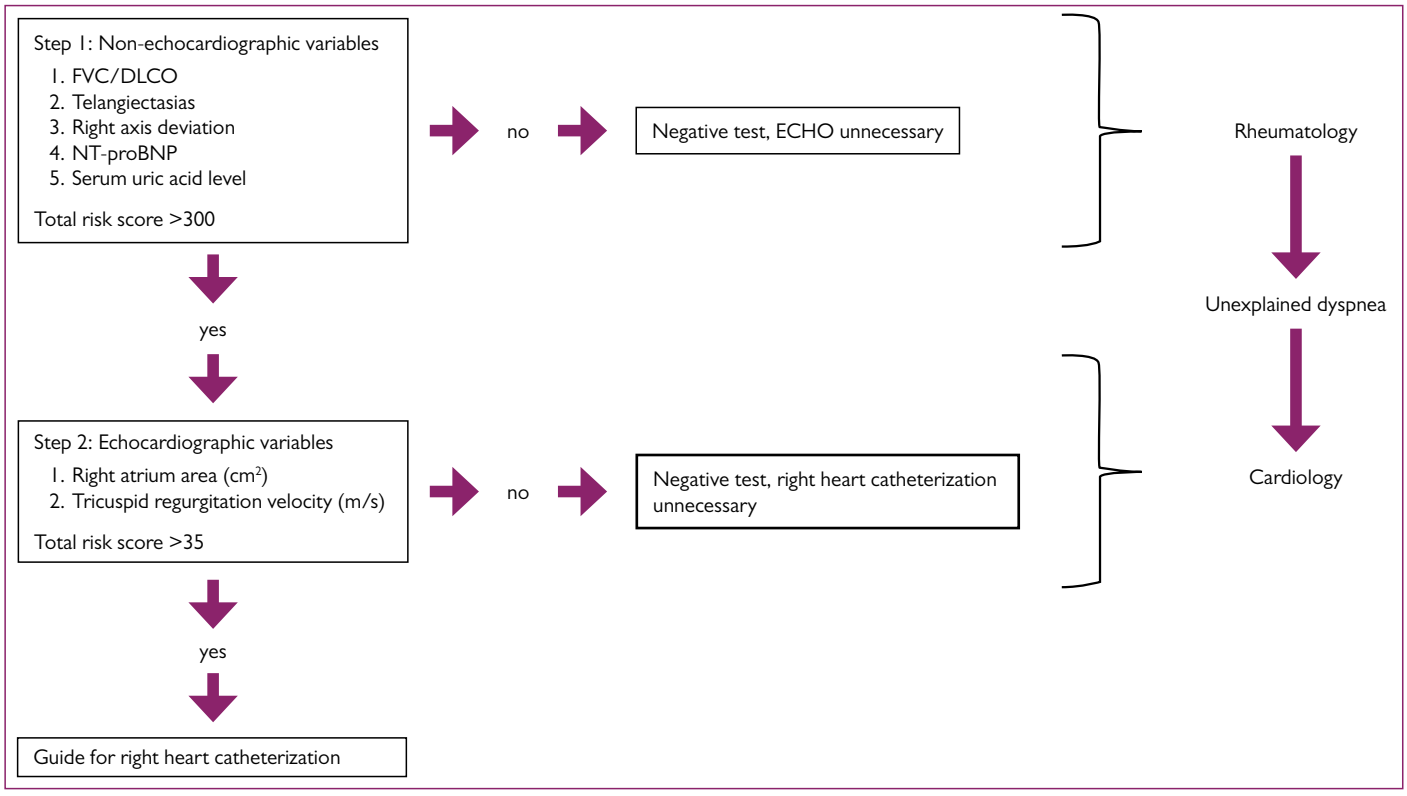

Figure 2. Components and implementation of the DETECT algorithm. The aim is to evaluate the patient with non-invasive methods before RHC and to identify those at high risk for PAH. Adapted from literature no:17.

FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide; ECHO: Echocardiography; RHC: Right heart catheterization.

nation with other tests is recommended as a screening test in asymptomatic SSc patients, followed by an annual evaluation. In other CTDs, screening for PH is not recommended in the absence of suggestive symptoms, whereas echocardiography should be performed in the presence of symptoms.[1]

Chest radiography is often the first investigation in the evaluation of a patient with dyspnea or other symptoms suggestive of PH. It is widely used because of its relative ease of access and low cost. Chest radiography can provide clues to both the presence of PH and the underlying cause. Chest X-ray findings in patients with PAH may include:

i. Dilatation of the main and central pulmonary arteries, i.e., right interlobar pulmonary artery >16 mm in men and >15 mm in women
ii. Narrowing of the branches of the peripheral and pulmonary arteries, commonly referred to as "pruning"
iii. Increased ratio of the pulmonary artery to the pulmonary vein.

Chest X-ray features suggestive of group 2 PH may include cardiomegaly with enlargement of the left-sided spaces, valvular calcification, and pulmonary venous congestion. In group 3 PH, chest radiography may reveal lung parenchymal pathologies such as interstitial fibrosis, bronchiectasis, or diffuse emphysema.[16]

While HRCT scanning is the primary imaging modality for the evaluation of the lung parenchyma, CT pulmonary angiography allows non-invasive evaluation of the pulmonary arteries. The advantages of CT include excellent spatial resolution, extended field of view, and the ability for multiplane reconstruction.[16] Dilatation of the main pulmonary artery is a sensitive and specific finding in PH. A main pulmonary artery diameter >2.9 cm has a specificity of 89% for PH. A ratio of the diameter of the main pulmonary artery to the ascending aorta >1.0 is an additional sensitive marker of PH. A dilated right or left pulmonary artery >1.8 cm is also indicative of PH and a predictor of mortality (Fig. 3). In chronic PH, mural calcification, increased vascular remodeling, tortuosity, and pruning of peripheral branches are classically described features. However, these CT findings are somewhat limited by their low negative predictive value. In addition, patients with parenchymal lung pathology without PH may also have some of the above features.[1,16]

However, the gold standard for diagnosing all forms of PH is a RHC performed as described in the European College of Cardiologists guidelines. How do we make the decision for RHC? Various algorithmic approaches can be used for this purpose, which has been developed from the many clinical, laboratory, and imaging data mentioned above. The DETECT algorithm, the algorithm developed in the "Evidence-based detection of PAH in SSc: The DETECT study" by Coghlan et al., is one of the most popular algorithms and is also recommended by ESC/ERS (Fig. 4).[1,17] A slightly more practical algorithm for similar risk calculation has also been suggested by the Australian Scleroderma Interest Group.[18] Furthermore, an algorithm based on echocardiography data was proposed in the French recommen-

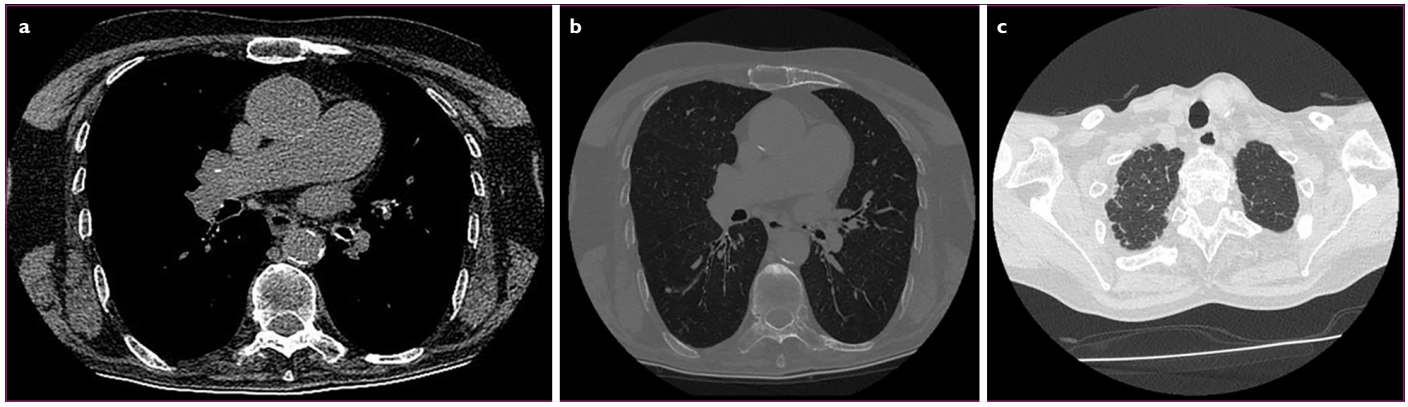

Figure 3. HRCT images of a patient with pulmonary hypertension: (a) Note the widening in diameter of the pulmonary artery. (b) Interlobular, septal, and intralobular thickening, subpleural bundling, and (c) Interlobular, septal and intralobular thickening, micronodules are observed.

HRCT: High-Resolution Computed Tomography.

dations for the treatment of scleroderma in individuals with appropriate clinical complaints and examination findings. They suggested that special attention should be given when DLCO <60% in cases of SSc diagnosed for more than 3 years. They also suggested using the DETECT algorithm.[19]

The components of the DETECT algorithm and how to implement it are summarized in Figure 2. Online calculators developed for such purposes are accessible, but unfortunately, it does not work outside of the US.[20]

PAH Treatment

Early diagnosis and early treatment of PH is essential to prevent functional deficits. ESC-ERS published its current guidelines on diagnosis and treatment in 2022. Early diagnosis and initiation of treatment before the development of organ damage has been reported as the basic approach. A treatment algorithm has been developed taking into account major randomized controlled trials with newly developed drugs. In addition, the treatment decision should be based on the patient's risk status and should be reviewed according to changes in risk status. The three-layer risk stratification used in the 2015 guideline was developed as a four-layer model in ESC-ERS 2022. Compared to the three-layer model, the four-layer model was more sensitive to changes in risk from baseline to follow-up, and these changes were associated with changes in the long-term risk of death. The main advantage of the four-layer model over the three-layer model is better discrimination within the intermediate-risk group, which in turn guides therapeutic decision-making. However, the three-layer model, which should be comprehensive and include echocardiographic and hemodynamic variables, for which thresholds for the four-layer model have not yet been established, is retained for the initial assessment, and the three-layer risk analysis is used in the first steps of the proposed treatment algorithm, (Fig. 4).[1]

In addition, many countries and organizations such as EULAR have similarly published treatment guidelines. The EULAR recommendations were published in 2017 as scleroderma treatment recommendations. More recent publications are included here.[21] The American College of Chest Physicians Recommendations, published in 2019, recommend taking non-pharmacologic measures such as vaccination, avoiding pregnancy, avoiding high altitudes that lower oxygen saturation below 91%, avoiding all non-essential surgical procedures, and performing a vasoreactivity test after systemic determination of disease severity, Initiate treatment with a calcium channel blocker in those with a positive test and determine treatment options according to subsequent developments and determine which drugs should be used in the next steps using the WHO FC for PAH. If the patient can use combination therapy, it recommends starting with combination therapy with ambrisentan and tadalafil.[22]

Although the French has some differences in their algorithmic approaches, they recommend treatment according to ESC-ERS 2022 recommendations.[19]

In a recent review by Pope et al. on the management of scleroderma, they used the REVEAL risk score for risk assessment, which Benza et al.[23] used in their study. In patients with SSc, the assessment of PAH, clinical evaluations, and risk stratification based on imaging data are used to guide treatment decisions. Risk is graded using the REVEAL 2.0 calculator and includes 14 variables (https://www.pahinitiative.com/hcp/risk-assessment/calculators). A REVEAL score ≤6 corresponds to low risk, a score of 7 or 8 corresponds to intermediate risk, and a score of ≥9 corresponds to high risk. It recommends oral combination therapy with endothelin receptor antagonist (ERA) and PDE5i in low-risk patients and combination therapy including intravenous prostacyclin analog and even lung transplantation in high-risk patients.[24]

According to the ESC-ERS 2022 recommendations, the outline of the treatment of CTD-PAH is as follows:[1]

- Treatment of PAH may differ according to the underlying CTD. For example, immunosuppressive therapy with a combination of glucocorticosteroids and cyclophosphamide may provide clinical improvement in PAH patients associated with SLE or MCTD but is not recommended in SSc-PAH.
- The choice of PAH treatment in the context of SSc and its systemic manifestations requires consideration of other vascular damage such as digital ulcers.

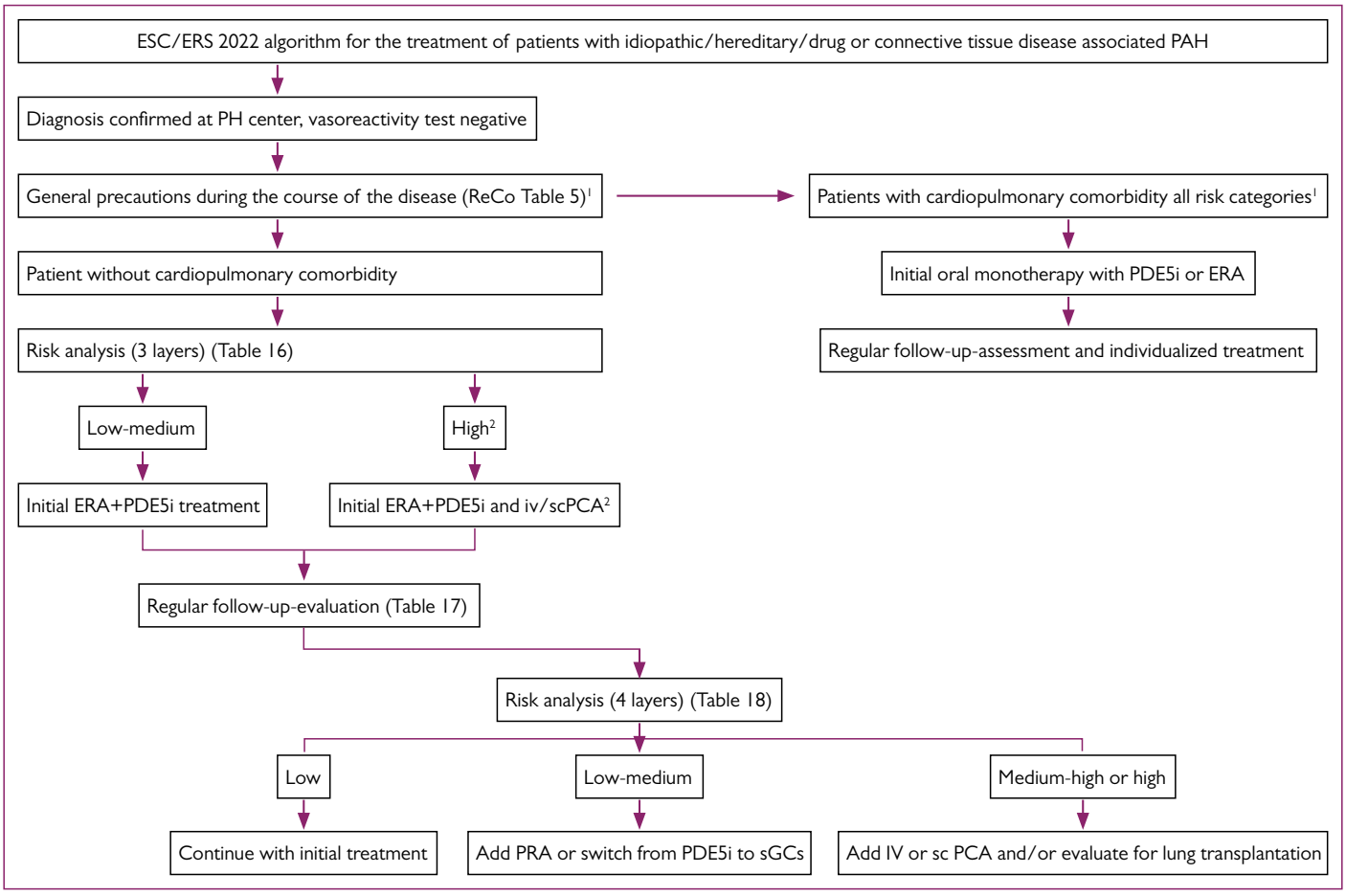

Figure 4. Evidence-based pulmonary arterial hypertension treatment algorithm for patients with idiopathic, hereditary, drug-associated, and connective tissue disease-related pulmonary arterial hypertension, summarizing the ESC/ERS recommendations. Recommendation Table 5, Tables 16-18 are tables from the ESC/ERS 2022 guideline and are available in the guideline. The grades of recommendations can also be followed in the same guidelines.[1]

ESC/ERS: European Society of Cardiology and the European Respiratory Society; PDE5i: Phosphodiesterase 5 inhibitors; ERA: Endothelin receptor antagonist; scPCA: Subcutaneous ProstaCyclin Analogue; sGCS: Soluble Guanylate Cyclase Stimulator.

- Patients with SSc and other CTDs may also have ILD and/or HF with preserved ejection fraction (HFpEF) and this needs to be taken into account when starting PAH treatment.
- In SSc, the long-term risk/benefit ratio of oral anticoagulation is unfavorable due to the increased risk of bleeding, whereas Vitamin K antagonists are recommended in CTD-PAH with a thrombophilic predisposition (e.g., antiphospholipid syndrome).
- The presence of connective tissue disease should not be considered a primary contraindication for lung transplantation.
- In patients with PAH, it is recommended to assess disease severity with a panel of data from clinical evaluation, exercise tests, biochemical markers, echocardiography, and hemodynamic assessments.
- Achieving and maintaining a low-risk profile with optimized medical therapy is recommended as a treatment goal in PAH patients.
- For risk stratification at the time of diagnosis, it is recommended to use a three-layer model (low, intermediate, and high risk), taking into account all available data, including hemodynamics.
- For risk stratification during follow-up, it is recommended to use a four-layer model (low, medium-low, medium-high, and high risk) based on WHO FC, 6MWD, and BNP/NT-proBNP; additional variables are considered if necessary.
- In patients with certain PAH etiologies and comorbidities, optimization of therapy should be considered on an individual basis, recognizing that a low-risk profile is not always achievable.
- It is recommended that the treatment and follow-up of PAH patients be performed in centers with experience in this field.

Non-pharmacologic Strategies

Patients with SSc-PAH should be counseled not to smoke tobacco and cannabis; receive vaccinations such as pneumococcal, influenza, and COVID-19; exercise regularly as tolerated; and discuss contraception. Hypoxia may develop in the end stage of PAH and if the patient is hypoxic, they need oxygen therapy. If a patient with SSc and PH is severely hypoxic, the cause of hypoxia (such as PVOD, ILD, or pulmonary embolism) should be investigated. Patients with SSc and PH with right ventricular overload and fluid re-

tention should be advised to follow a salt-poor diet. High altitudes that reduce oxygen saturation to less than 91% should be avoided.

In general, pregnancy is dangerous for the mother with SSc-PAH because of increased CO and the possibility of worsening hypoxia, so it should be avoided. Fetal mortality is also high. Patients should be thoroughly warned about this and educated about appropriate contraceptive methods. If at all possible, adoption and surrogacy should be taken into consideration for women with PAH who want to become parents. However, women with PAH who are contemplating or who become pregnant are advised to seek immediate counseling at an experienced PH center to facilitate genetic counseling and shared decision-making and to provide psychological support to patients and their families as needed. It is important to discuss the prognosis with patients and support and care personnel (such as social workers and nurses) and palliative care may need to be provided.[1,22,24]

Pharmacologic Therapies

Currently accepted drug groups for the treatment of PAH are calcium channel blockers (CCB), ERA, phosphodiesterase-5 inhibitors, sGC stimulators, and prostacyclin analogs. There is no indication for the use of CCBs in the treatment of SSc-related PAH because patients are mostly unresponsive to NO (negative acute vasoreactivity test).

Subgroup analyses of PAH-SSc patients enrolled in RCTs with monotherapy or combination therapy of ERAs, PDE5i, sGC stimulators, prostacyclin receptor agonists, epoprostenol, and prostacyclin analogs showed positive effects compared to placebo. In some of these trials, the magnitude of response in the PAH-SSc subgroup was lower than in the IPAH subgroup. In a 3-month randomized controlled trial of continuous IV epoprostenol in SSc-PAH patients, epoprostenol treatment improved exercise capacity, symptoms, and hemodynamics. However, a retrospective analysis showed that IV epoprostenol had a better impact on survival in IPAH compared with SSc-PAH. The choice of PAH treatment in the context of SSc and its systemic manifestations requires consideration of other vascular damage, such as digital ulcers.[1,22,24]

CCB

CCBs consist of three different subgroups: Benzothiazepines (e.g., diltiazem), dihydropyridines (e.g., amlodipine and nifedipine), and phenylalkylamines (e.g., verapamil). The CCBs predominantly used in PAH are nifedipine, diltiazem, and amlodipine. Amlodipine and felodipine are increasingly used in clinical practice because of their long half-life and good tolerability.

- Amlodipine: Start with 5 mg daily and increase to 15–30 mg daily (single or double dose).
- Diltiazem: Start with 60 mg twice daily, may take 120–360 mg twice daily.
- Felodipine: Start with 5 mg daily and increase to 15–30 mg daily (single or double dose).

They have no place in the treatment of SSc-PAH patients. Other groups of PAH patients who respond favorably to acute vasoreactivity testing may respond favorably to treatment with CCBs. <10% of patients with IPAH, HPAH, or drug-associated PAH respond; acute vasodilator response does not predict a favorable long-term response to CCBs in patients with other forms of PAH. Patients without a vasoreactivity study or with a negative test should not be started on CCBs due to potentially serious side effects (e.g., severe hypotension, syncope, and right HF) unless prescribed at standard doses for other indications (such as Raynaud). Because of the presence of Raynaud's phenomenon in the majority of SSc patients, CCBs are frequently prescribed. However, in cases resistant to CCB treatment, digital ulcers, or PAH development, non-CCB treatments are needed. The comparatively high daily dosages of CCB that has been demonstrated to be efficacious in PAH should be gradually increased.[1,22,24]

Patients who meet the criteria for a positive acute vasodilator response and are treated with CCBs should be closely monitored for safety and efficacy and a full reassessment, including RHC, should be performed 3–6 months after treatment. Additional acute vasoreactivity testing should be performed during reassessment to detect persistent vasodilator response; this suggests that the dosage of CCBs could be increased. Patients with a satisfactory chronic response present with the WHO FC I/II and marked hemodynamic improvement (ideally mPAP <30 mmHg and PVR <4 WU) during CCB therapy. In the absence of a satisfactory response, additional PAH treatment should be initiated. In some cases, a combination of CCBs with approved PAH-specific drugs may be necessary due to clinical worsening with attempts to discontinue CCBs, (Fig. 4).[1]

The most common side effects of CCB drugs are systemic hypotension and peripheral edema which may require treatment modification.

ERA

PAH is associated with elevated levels of endothelin 1 (ET-1), a potent vasoconstrictor and mitogen; however, it remains unclear whether elevated ET-1 levels are the cause or consequence of PAH. ET-1 acts through two receptor subtypes, ET receptor types A and B. ET-1 causes vasoconstriction and proliferation in smooth muscle cells by binding to ET type A and B receptors and increases NO and prostacyclin production by binding to ET type B receptors. ET-1 binding to endothelin receptors A and B on PA smooth muscle cells promotes vasoconstriction and proliferation. Endothelin B receptors are mostly expressed on pulmonary endothelial cells and contribute to vasodilation through acceleration of prostacyclin and NO production and clearance of ET-1. However, selective blockade of endothelin A receptor alone or non-selective blockade of both A and B receptors has been shown to show similar efficacy in PAH.[1,22,24] Three oral ERAs targeting this pathway are available: Bosentan, ambrisentan, and masitentan. Bosentan and masitentan are non-selective ET-1 receptor antagonists, while ambrisentan is a selective type A ET-1 receptor antagonist.

ERA therapies require regular monitoring of liver enzymes and hemoglobin levels due to the risk of hepatotoxicity and anemia. It is uncertain to know in advance which ERA will be most effective in an individual.

Toxicity studies in animals have demonstrated severe teratogenic effects of ERA, particularly craniofacial malformations; Yet, a 2019 systematic review of 39 cases exposed to ERA during pregnancy found no fetal congenital problems, and it is currently contraindicated.[1,25]

Ambrisentan

Ambrisentan is an oral ERA that preferentially blocks the endothelin A receptor. Approved dosages in adults are 5 mg and 10 mg daily. It has been shown to be effective in PAH patients in terms of symptoms, exercise capacity, hemodynamics, and time to clinical deterioration. While an increased incidence of peripheral edema has been reported with the use of ambrisentan, there has been no increase in the incidence of abnormal liver function.

Bosentan

Bosentan is an oral ERA that improves exercise capacity, WHO FC, hemodynamics, and time to clinical deterioration in PAH patients. Studies in SSc-PAH patients have shown that bosentan can improve exercise capacity and hemodynamics (pulmonary artery pressure and pulmonary vascular resistance).[26] The approved target dose in adults is 125 mg twice daily. Dose-related increases in liver transaminases may occur in 10% of treated patients (may be reversible after dose reduction or discontinuation of treatment). Therefore, liver function tests should be performed monthly in patients receiving bosentan. Due to pharmacokinetic interactions, bosentan may render hormonal contraceptives unreliable and may decrease serum levels of warfarin, sildenafil, and tadalafil.[1,22,24]

Prostacyclin Analogs

Prostacyclin (also known as prostaglandin I2) is a vasodilator and inhibits platelet aggregation. Prostacyclin levels are reduced in patients with PH. Prostacyclin analogs bind to the prostacyclin receptor, leading to an increase in cAMP, resulting in vasodilation, antiproliferative, and antithrombotic effects. Prostacyclin analogs evaluated for the treatment of PAH and approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) include epoprostenol (administered intravenously), iloprost (inhaled), beraprost (orally administered) and treprostinil (inhaled or chronically subcutaneously administered), and the orally active selective prostacyclin receptor agonist selexipag.

Epoprostenol has a short half-life, requiring continuous intravenous administration. Challenges include the need to aseptically reconstitute the drug, the need for an indwelling central venous catheter, and side effects; for these reasons, the use of epoprostenol is generally reserved for the treatment of advanced disease. Selexipag is an oral selective prostacyclin receptor agonist with effects comparable to those of endogenous prostacyclin. Oral selexipag is easier to use than continuous intravenous or subcutaneous prostacyclin analogs and patients do not experience rebound if discontinued abruptly compared with epoprostenol, but its use is dependent on access and reimbursement.[24]

PDE5 inhibitors and Guanylate Cyclase Stimulators

Stimulation of sGC by NO results in the production of the intracellular second messenger cGMP. This pathway is controlled by a negative feedback loop through the degradation of cGMP by different phosphodiesterases, among which subtype 5 (PDE5) is abundantly expressed in the pulmonary vasculature.[1,22,24]

Sildenafil

Sildenafil is an orally active, potent, and selective inhibitor of PDE5. PAH patients treated with sildenafil have shown favorable results on exercise capacity, symptoms, and/or hemodynamics. The approved dose of sildenafil is 20 mg orally 3 times daily. Most side effects of sildenafil are mild to moderate and are mainly due to vasodilation (headache, flushing, and nosebleeds).

Tadalafil

Tadalafil is a PDE5i administered once daily. Tadalafil at doses up to 40 mg per day was administered to 406 PAH patients in an RCT, and the patients' exercise ability, symptoms, hemodynamics, and time to clinically worsen all improved. The side effect profile was similar to that of sildenafil.

Riociguat

Riociguat is a guanylate cyclase stimulator. Whereas PDE5 potentiates the NO-cGMP pathway by slowing cGMP degradation, sGC stimulators increase cGMP production by directly stimulating the enzyme both in the presence and absence of endogenous NO. In a randomized controlled trial involving 443 patients with PAH treated with riociguat up to 2.5 mg 3 times daily, 44% and 6% had prior treatment with ERAs or prostacyclin analogs, respectively, showed favorable results in terms of exercise capacity, hemodynamics, WHO FC and time to clinical deterioration, with an adverse effect profile similar to that of PDE5is. Oral riociguat is approved in Europe for the treatment of PAH associated with connective tissue disease. It is contraindicated in cases of idiopathic pulmonary fibrosis[1,22,24] PDE5 inhibitors and sGC stimulators should not be combined with each other and with nitrates as they may cause systemic hypotension.

Combination oral therapy with an ERA and a PDE5i is often first-line treatment in SSc-PAH (Fig. 4). In the past, monotherapy with a single oral agent was initially recommended, but at present, this approach is only recommended in selected low-risk patients (REVEAL risk score ≤6). Any ERA can be combined with a PDE5 inhibitor. For example, in the AMBITION trial, combination therapy with ambrisentan and tadalafil in PAH patients led to a significantly lower risk of clinical failure events compared to ambrisentan monotherapy or tadalafil monotherapy (hazard ratio [HR] 0.50, 95% confidence interval [CI] 0.35–0.72; p<0.001).[27] *Post hoc* analyses of the SSc-PAH subgroup showed a reduction in treatment failure with combination therapy compared with single-agent therapy (HR 0.44, 95% CI 0.22–0.89) 112. Similarly, combining masitentan with sildenafil or tadalafil improved efficacy compared with monotherapy. An alternative medication from the same class may be used if a medication causes intolerance or is contraindicated.

Two agents with a similar mechanism of action should not be combined. It should be considered that bosentan may increase the metabolism of sildenafil and cause a decrease in the plasma concentration of sildenafil; therefore, this combination may not be preferred. The combination of a PDE5 inhibitor with the sGC stimulator riociguat is not recommended due to the increased risk of hypotension. Patients with functional class IV (the most severe patients) may be considered for a triple combination therapy consisting of an ERA, a PDE5 inhibitor, and a prostaglandin analog (Fig. 4). Treatment is often modified according to various targets such as NT-proBNP, 6MWD, pulmonary artery hemodynamics, and functional class (for dyspnea). There is a trend to start with treatment with two PAH-specific drugs and add a third if the patient has poor prognostic factors.[1,22,24]

Other Treatments

Almost 40% of PAH patients are iron deficient. Although widely studied, the mechanisms linking PAH and iron deficiency remain unclear.

Iron deficiency is defined as serum ferritin <100 μg/L or serum ferritin 100–299 μg/L and transferrin saturation <20% in PAH patients. The underlying pathologic mechanisms are complex. Iron deficiency in PAH patients is associated with impaired myocardial function, aggravated symptoms, and increased risk of death. Based on these data, regular monitoring of iron status (serum iron, ferritin, transferrin saturation, and soluble transferrin receptors) is recommended in patients with PAH.[28]

Connective tissue disease should not be considered a primary contraindication for lung transplantation. This has been extensively studied, recommending a multidisciplinary approach that optimizes the management of SSc before, during, and after surgery. Double lung or heart-lung transplantation may be considered in SSc and PH patients with end-stage lung disease, especially in patients whose disease progresses despite treatment. Lung transplantation is performed to prolong survival and improve quality of life. The survival rate after transplantation has improved over time and is estimated to be 93% at 1 year after transplantation. Other surgical options may include right-to-left shunting or atrial septostomy, which is rarely done, as in cases of severe right HF while awaiting transplantation.[22]

Prognosis

Despite available targeted therapies, survival in SSc-PAH has remained low. Early data reported a 3-year survival rate of only 52% in SSc-related PAH. More recent studies have reported 3-year survival rates of 56–75% in SSc-PAH. This was again lower than in many other causes of PAH. SLE-PAH studied in a nationwide cohort study in France had better survival, with 3-and 5-year overall survival rates of 89.4% and 83.9%, respectively. This study found that the risk factors for death were renal involvement and high PVR. In 2 other cohort studies, the presence of anti-U1RNP antibodies was found to be a protective factor for survival.[12] ILD is seen in 25–50% of SSc patients, most prominently in DSSc patients. In the association of ILD and PAH, 3-year survival decreases to 35%.[29]

Conclusion

PAH may develop in connective tissue patients, most commonly in SSc patients. The presence of PAH significantly affects the quality of life and survival, especially in scleroderma patients. Early diagnosis and treatment before the development of organ damage is the golden rule in the treatment of PAH. The diagnosis is primarily made by RHC in the presence of complaints such as unexplained dyspnea and syncope that develop in the presence of an underlying CTD such as SSC, which increases the risk of PAH, in the light of the data obtained from tests such as electrocardiogram, echocardiography, PFT, DLCO.

When planning treatment, pharmacological therapies are used in addition to non-pharmacological measures.

Drug selection should be made by considering the other characteristics of the patient. CCB is not recommended except for Raynaud. Combination oral therapy with an ERA and a PDE5 inhibitor is often the first-line treatment in SSc-PAH. During follow-up, treatment can be changed according to the patient's clinical and laboratory data and risk analysis. Patients in functional class IV (the most severe patients) may be considered for a triple combination therapy consisting of an ERA, a PDE5 inhibitor, and a prostaglandin analog. Patients are risk-analyzed into three-layer risk categories at the start of treatment and, if necessary, a four-layer risk analysis is performed at follow-up to determine the treatment context. Treatment is determined and followed according to the ERS/ESC 2022 guideline and other guidelines, which are often developed in the light of this guideline. Lung transplantation should not be ruled out in cases resistant to these treatments.

Despite the current advances, the prognosis in patients with PH is still poor and patients should be followed and treated in experienced centers specialized for PH.

Disclosures

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