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# Pulmonary Hypertension in Systemic Sclerosis

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Additional information is available at the end of the chapter

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## Abstract

The main cause of death in systemic sclerosis is interstitial lung disease, followed by pulmonary hypertension (PH). Pulmonary hypertension is the result of microvasculopathy which is caused by a disrupted healing process of endothelin damage and is featured by vasoconstriction, proliferation of arterial wall, inflammation, and fibrosis. Reclassification of pulmonary hypertension has led to five distinctive groups. In systemic sclerosis, patients may suffer from pulmonary artery hypertension (PAH, group 1), pulmonary hypertension due to interstitial lung disease (group 3), cardiac disease (group 2), and/or thromboembolic pulmonary hypertension (group 4). Patients endure declining performance during exercise, but symptoms may be variable and nonspecific. Diagnosis is made by right heart catheterization. To select patients for this invasive procedure, several screening tools are discussed, including N-terminal pro-brain natriuretic peptide levels, uric acid levels, spirometry and diffusing capacity for carbon monoxide (DLCO), echocardiography (ECG), and the DETECT algorithm. Depending on features such as disease duration, presence of anti-centromere antibodies, and DLCO, three different flow charts for screening are presented. Based on pathophysiology, several medical treatments have been developed like prostanoids, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and stimulation of the nitric oxide pathway. Combination therapy as well as lung transplantation and supportive therapy is discussed.

**Keywords:** systemic sclerosis, pulmonary hypertension, DETECT algorithm, pharmaceutical treatment (prostanoids, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, nitric oxide pathway)

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## 1. Pulmonary hypertension

Pulmonary hypertension (PH) is a progressive disease characterized by an elevated pulmonary arterial pressure and pulmonary vascular resistance. As a consequence of the elevated

pulmonary arterial pressure, patients are at risk of right ventricular failure and death. PH is classified in five distinctive groups with similar pathophysiology, patient characteristics, and treatment options. It can occur as a complication in patients with systemic sclerosis, and as such, it is the second main cause of death after pulmonary fibrosis in patients with systemic sclerosis. The estimated 3-year survival among patients with PH associated with systemic sclerosis is approximately 55% compared with 95% in those patients without PH [1]. The diagnosis of pulmonary arterial hypertension is defined at right heart catheterization (RHC) by a mean pulmonary arterial pressure (mPAP) of  $\geq 25$  mmHg. RHC should be performed in all patients in whom PH is suspected. Early diagnosis and, subsequently, treatment of PH are of utmost importance since they improves survival rates.

### 1.1. Epidemiology

In patients with systemic sclerosis, approximately 10% develop pulmonary arterial hypertension as a complication of the disease [2, 3]. Prior to the availability of disease-specific PH therapies, the median survival for PH in patients with systemic sclerosis was 1 year following diagnosis [4]. A meta-analysis accomplished in 2013 with the inclusion of 22 studies representing 2244 patients with systemic sclerosis-associated PH showed that the current pooled survival rates after 1, 2, and 3 years are respectively 81% (95% confidence interval [95% CI] 79–84%), 64% (95% CI 59–69%), and 52% (95% CI 47–58%) [5]. To note, the prognosis of PH associated with systemic sclerosis is substantially worse than patients with idiopathic pulmonary artery hypertension (PAH) [6]. PH is generally considered a late complication of the disease, but in fact, it can occur at any time following the diagnosis. In a study from Hachulla et al. [7], PH was diagnosed  $6.3 \pm 6.6$  years after the first non-Raynaud symptom of systemic sclerosis. It was also shown that patients with early-onset PH were older at systemic sclerosis diagnosis than patients with late-onset PH (mean age,  $58.0 \pm 12.5$  vs  $46.6 \pm 12.9$  years), and that, early-onset PH was more severe than late-onset PH, with a lower cardiac index and greater total pulmonary resistance. Despite these differences, the mortality however was comparable between the early-onset and late-onset PH groups. In general, patients with limited cutaneous systemic sclerosis are considered to be at greater risk of PH than patients with diffuse cutaneous systemic sclerosis [8, 9]. In these studies, however, the diagnosis of PH was not always based on right heart catheterization but by Doppler echocardiography. In a retrospective cohort analysis from Nihtyanova et al. [10], it was found that the prevalence of RHC confirmed PH was similar in diffuse cutaneous systemic sclerosis (7%) and limited cutaneous systemic sclerosis (8%).

### 1.2. Classification of pulmonary hypertension

The classification of PH went through a series of changes since the first classification was proposed in 1973 by the World Health Organization (WHO) [11]. This first meeting was organized due to the epidemic of the aminorex-induced PAH. Before this date, there was little knowledge of PH, and there were no effective drugs available resulting in a survival prognosis of several years. Despite the fact that PH was an orphan disease, significant interest from scientists with collaborative effort from the pharmaceutical industry resulted in studies focusing on pathophysiology, molecular biology, epidemiology, and clinical trials.

Prompted by the attained scientific insights, the second world symposium on PH was held in Evian, France. Here, in 1998, the 'Evian' classification was proposed which consisted of five categories which shared pathophysiology, clinical patient characteristics, and pharmacological treatment options [12]. Five years after the Evian conference, the third world symposium on PH was held in Venice where several changes were made to the Evian classification. At this time, there were already three classes of drugs effective in the treatment of PH (prostanoids, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors), and a specific treatment algorithm was proposed [13]. At the fourth world symposium on PH held in Dana Point, California, the Evian-Venice classification composition was refined, and a few modifications, reflecting new scientific knowledge, were added. The last world symposium on PH was held in Nice, France, in 2013. At that moment, several worldwide experts were divided into 12 task forces, each with a specific topic related to PH [14]. The task force responsible for the clinical classification proposed to include the individual categorization of the persistent PH of neonates, the addition of congenital diseases in groups 2, 3, and 5, and the shifting of PH associated with chronic hemolytic anemia from group 1 to group 5 [15]. **Table 1** shows the last updated clinical classification of pulmonary hypertension proposed in 2015 [16].

In systemic sclerosis, patients may suffer from both pulmonary artery hypertension (PAH, group 1) and from pulmonary hypertension due to interstitial lung disease (group 3), cardiac disease (group 2), and/or chronic thromboembolic pulmonary hypertension (group 4). The diagnosis and evaluation of PH is through a series of testing including pulmonary function testing, such as the measurement of DLCO, chest X-ray, high resolution computed tomography (HRCT) scan, ECG, echocardiography, cardio-pulmonary exercise test, and laboratory testing, including antinuclear antibodies, and is always confirmed by the gold standard, a right heart catheterization.

### 1.3. Pathophysiology

PH is a hemodynamic abnormality of the pulmonary vasculature most often found in patients with heart and lung diseases. PH is also present in approximately 10% of the patients with systemic sclerosis [2, 3]. The consensus definition of PH, an mean pulmonary arterial pressure (mPAP) of  $\geq 25$  mm Hg, originates from the fifth world symposium on PH [17]. The normal physiological upper limit for mPAP is considered 20 mm Hg. The significance and prognosis is unknown so far in patients with a mildly elevated mPAP, that is a resting mPAP between 21 and 24 mmHg. In patients with systemic sclerosis for 3 years and 5 years after diagnosis of systemic sclerosis, respectively, 18.5% (95% CI 8.3–28.7) and 27.1% (95% CI 13.9–40.3) developed PH [18]. This implies that these patients should be carefully monitored.

PH may be due to abnormalities confined to the pulmonary arterial blood vessels (pre-capillary PH), to elevation of pulmonary venous pressure (post-capillary PH), to elevated resistance in the pulmonary capillary bed, to elevated cardiac output, or to a combination of these factors. Pre-capillary pulmonary hypertension is also called pulmonary arterial hypertension (PAH) and is considered one of the major clinical PH subtypes. In PAH, the hemodynamic hallmark states a normal pulmonary venous pressure measured as a pulmonary capillary wedge pressure (PCWP) of 15 mmHg or less and a high mPAP. As a consequence, the transpulmonary

## **1. Pulmonary arterial hypertension**

### **1.1. Idiopathic PAH**

### **1.2 Heritable PAH**

#### *1.2.1. BMPR2*

#### *1.2.2. ALK1, ENG, SMAD9, CAV1, KCNK3*

#### *1.2.3. Unknown*

### **1.3. Drug- and toxin-induced**

### **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*

#### *1.4.6. Chronic hemolytic anemia*

### **1.5. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**

#### *1.5.1. Idiopathic*

#### *1.5.2. Heritable*

##### *1.5.2.1. EIF2AK mutation*

##### *1.5.2.2. Other mutations*

#### *1.5.3. Drugs, toxins, and radiation induced*

#### *1.5.4. Associated with:*

##### *1.5.4.1. Connective tissue disease*

##### *1.5.4.2. HIV infection*

### **1.6. Persistent pulmonary hypertension of the newborn (PPHN)**

## **2. Pulmonary hypertension due to left heart disease**

### **2.1. Left ventricular systolic dysfunction**

### **2.2. Left ventricular diastolic dysfunction**

### **2.3. Valvular disease**

### **2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies**

### **2.5. Congenital/acquired pulmonary veins stenosis**

## **3. Pulmonary hypertension owing to lung disease and/or hypoxia**

### **3.1. Chronic obstructive pulmonary disease**

### **3.2. Interstitial lung disease**

### **3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern**

### **3.4. Sleep-disordered breathing**

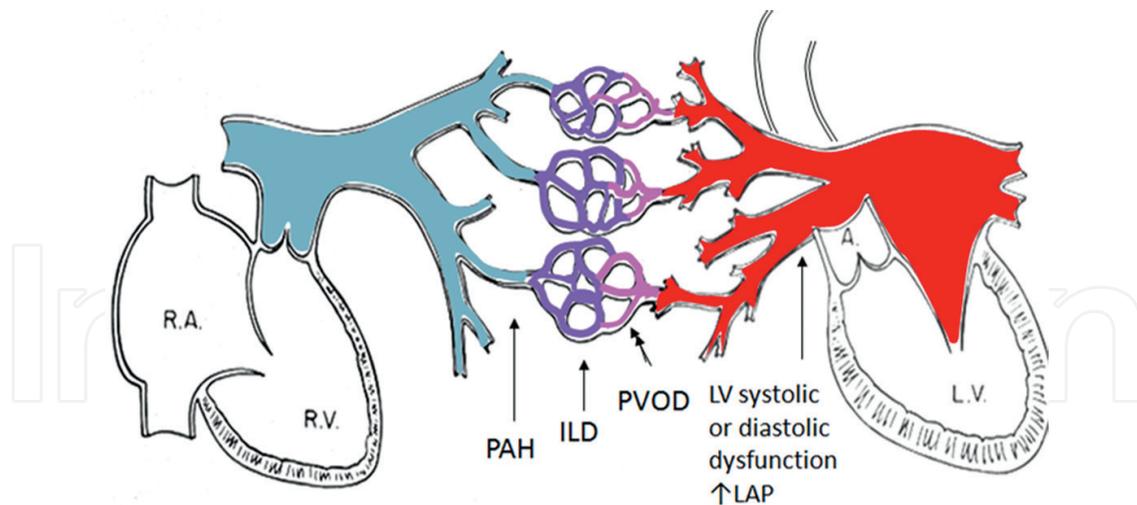
- 3.5. Alveolar hypoventilation disorders
  - 3.6. Chronic exposure to high altitude
  - 3.7. Developmental abnormalities
  - 4. Chronic thromboembolic pulmonary hypertension (CTEPH)**
    - 4.1. Chronic thromboembolic pulmonary hypertension
    - 4.2. Other pulmonary artery obstructions
      - 4.2.1. Angiosarcoma
      - 4.2.2. Other intravascular tumors
      - 4.2.3. Arteritis
      - 4.2.4. Congenital pulmonary arteries stenosis
      - 4.2.5. Parasites (hydatidosis)
  - 5. Pulmonary hypertension with unclear multifactorial mechanisms**
    - 5.1. Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
    - 5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioliomyomatosis, neurofibromatosis
    - 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
    - 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
- 

**Table 1.** Updated clinical classification of pulmonary hypertension in 2015.

gradient is elevated as is the pulmonary vascular resistance. In post-capillary PH, also called pulmonary venous hypertension, the elevated PH is a consequence of an increased resistance to blood flow anywhere downstream from the pulmonary capillaries such as the pulmonary veins, left heart or even the systemic vasculature. This results in an elevated PCWP and most often normal transpulmonary gradient. The presence of solely a high cardiac output rarely results in marked PH since a healthy pulmonary vasculature is highly compliant. So the presence of PH in a situation with high cardiac output always suggests a pulmonary vascular defect.

In patients with systemic sclerosis, each of the PH subtypes may be present to different degrees. **Figure 1** provides a schematic view of the pulmonary vasculature and shows the anatomical location of the clinical subtypes of PH in patients with systemic sclerosis.

It is important to quantify each subtype in a patient, since it provides a prognosis for possible treatment effects. For example, PH associated with interstitial lung disease (ILD) has a worse prognosis compared to PAH in patients with systemic sclerosis [19–21]. A high mPAP in patients with systemic sclerosis can be due to proliferative pulmonary vasculopathy (PAH) featured by pulmonary artery vasoconstriction, proliferation of adventitia and intima wall, inflammation, and, ultimately, fibrosis. The PH may also be a consequence of the associated lung fibrosis due to prominent parenchymal destruction. The differentiation between PAH and pulmonary fibrosis-associated PH is sometimes difficult. In general, lung volumes



**Figure 1.** A schematic view of the pulmonary vasculature. RA: right atrium, RV: right ventricle, PAH: pulmonary arterial hypertension, ILD: interstitial lung disease, PVOD: pulmonary veno-occlusive disease, LV: left ventricle, LAP: left atrial pressure, and A: aorta.

(forced vital capacity (FVC) and/or total lung capacity (TLC)) below 60% of the predicted value indicate that PH is more likely to be associated with pulmonary fibrosis. When lung volumes (FVC and/or TLC) are above 70% of the predicted value, the PH is considered more likely to be due to PAH. For lung volumes between 60–70% of the predicted value, the cause is uncertain. Another cause of a high mPAP in patients with systemic sclerosis is pulmonary veno-occlusive disease (PVOD) [22]. This is thought to be the result of a more diffuse nature of the vascular lesions associated with systemic sclerosis and is located in the small venules of the vascular bed. Patients with PVOD often have more severe hypoxemia and a severe decrease in pulmonary diffusion capacity for carbon monoxide (DLCO). Indications for PVOD are typical radiological signs (lymph node enlargement, centrilobular ground glass opacities, and septal lines [23], hemoptysis, and severe hypoxemia). The diagnosis of PVOD is important since it may be harmful to prescribe pulmonary vasodilators since these vasodilators increase the risk for developing pulmonary edema. Also, post-capillary PH is seen in patients with systemic sclerosis, merely as a result of left ventricle diastolic dysfunction due to cardiomyopathy as indicated by an elevated PCWP > 15 mmHg [24, 25].

## 2. Diagnosis of pulmonary hypertension

### 2.1. Physical signs and symptoms

The first signs and symptoms of pulmonary hypertension are generally vague and nonspecific. Patients experience tiredness, fatigue, and shortness of breath when performing physical exercise or activities of daily living such as climbing stairs. These symptoms are often ascribed to having a low physical fitness. More severe symptoms such as feeling light headed during exercise, angina, syncope, and/or ankle edema only occur after extensive pulmonary vasculopathy have been developed. Also with physical examination, there are no specific abnormalities detected in patients with mild PH. Only when there is extensive pulmonary

vasculopathy resulting in right heart failure, there may be physical signs including a loud P2 cardiac sound, a right ventricle third sound, a murmur of tricuspid regurgitation, raised central venous pressure, and other signs of right heart failure such as an enlarged liver and ankle edema. The lack of symptoms until the PH is already advanced often results in a striking patient and doctor's delay for diagnosis and consecutively effective treatment. As a consequence, the majority of patients at diagnosis are in functional New York Heart Association/World Health Organization (NYHA/WHO) class III or IV (**Table 2**) [2, 26]. This is extraordinarily unfortunate since the prognosis is much worse in NYHA/WHO functional class III–IV compared to class I–II [27].

## 2.2. Screening for pulmonary hypertension

Patients with systemic sclerosis are at risk of developing pulmonary hypertension. Since the first signs and symptoms of PH are nonspecific and the prognosis of patients diagnosed and treated in less advanced stages is better than those diagnosed late, in recent years, several screening programs have been developed to detect PH as early as possible. Depending on features such as disease duration, results from pulmonary function tests, and echocardiography, three different flow charts will be discussed.

In all newly diagnosed patients with systemic sclerosis, it is advised to perform a yearly screening for PH. After performing a thorough history and physical examination, patients should undergo a series of tests including pulmonary function test (including FVC, TLC, and diffusion capacity for carbon monoxide (DCLO)), chest X-ray, HRCT scan, ECG, echocardiography, and laboratory testing including antinuclear antibodies and N-terminal pro-Brain Natriuretic Peptide (N-terminal pro-BNP). Since the gold standard for diagnosing PH is right heart catheterization (RHC) an algorithm is used to indicate which patients should subsequently undergo the invasive procedure of an RHC [2, 28]. An RHC is recommended for those patients with an FVC/DCLO higher than 1.6 and/or DCLO below 60% of predicted values for those who experience shortness of breath or have a N-terminal pro-BNP more than twice the upper limit of normal (**Figure 2A**). For the patients where the echocardiography shows right atrial or right ventricle enlargement, a tricuspid regurgitant jet velocity (TRJ) higher than 2.8 m/s or a TRJ between 2.5 and 2.8 m/s with shortness of breath, it is also strongly advised to perform an RHC (**Figure 2B**).

For those patients with systemic sclerosis and a disease duration of more than 3 years and a pulmonary DCLO below 60% of the predicted value, the DETECT algorithm as described in

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Class I: PH but no symptoms and no limitations in ordinary physical activity, for example, no shortness of breath when walking, climbing the stairs, and so on.

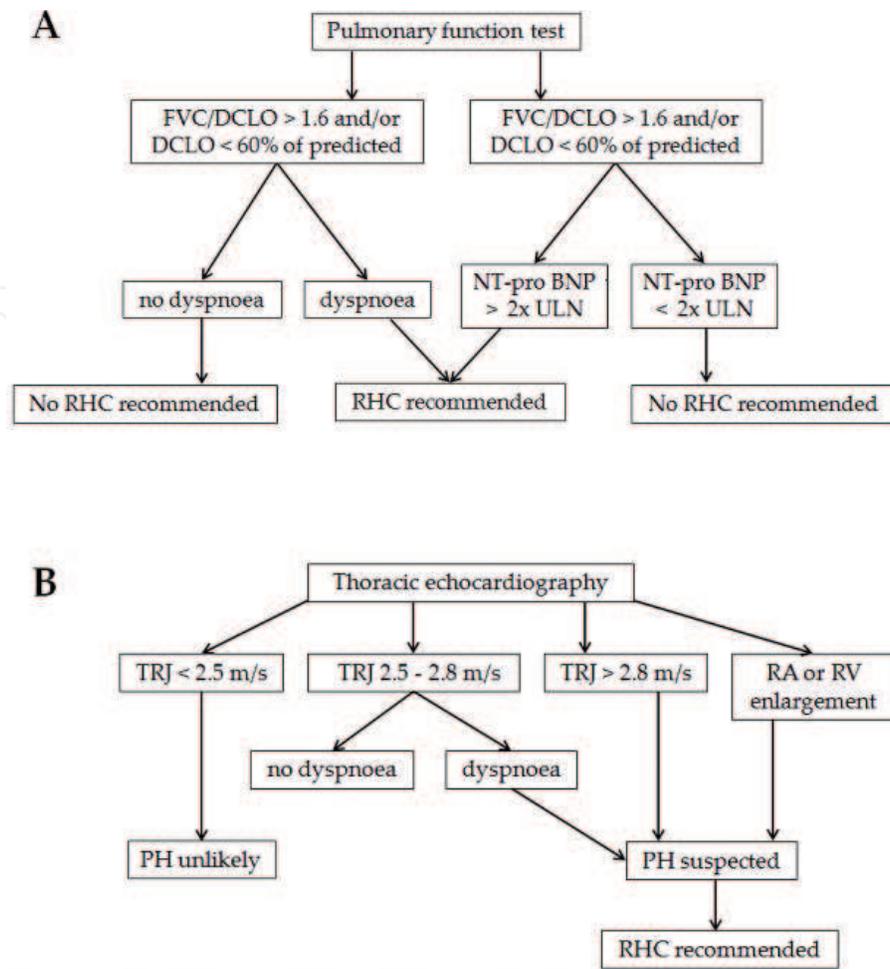
Class II: Mild symptoms (mild shortness of breath and/or angina) and slight limitations during ordinary activity.

Class III: Marked limitations in activity due to symptoms even during a less-than-ordinary activity, for example, walking short distances (20–100 m). Comfortable only at rest.

Class IV: Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

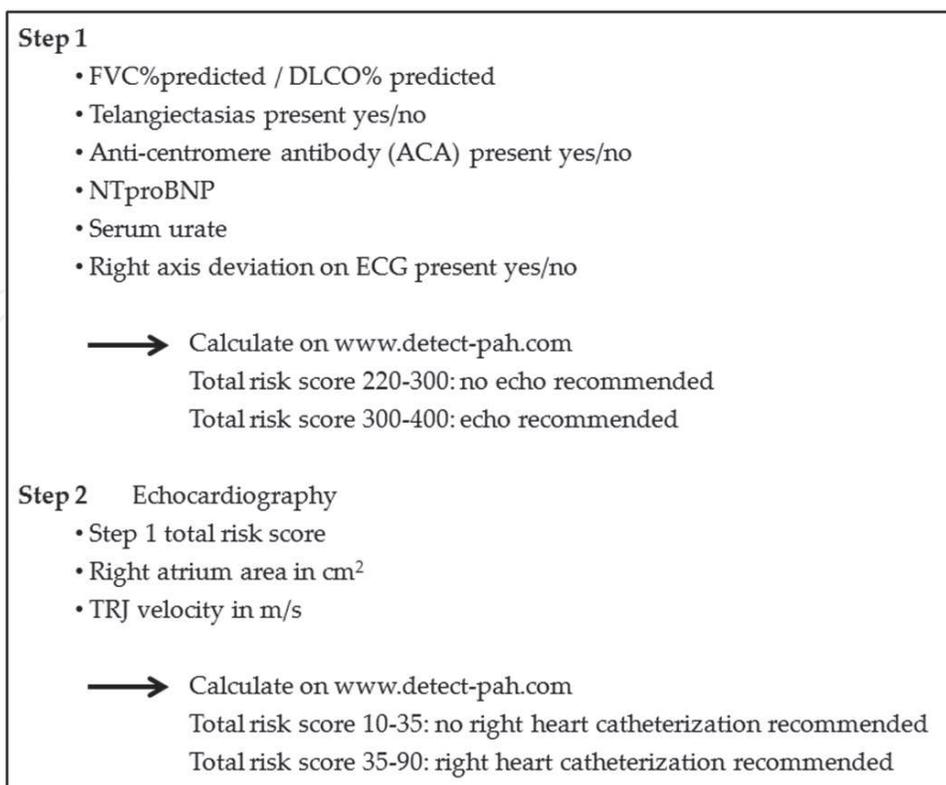
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**Table 2.** New York Heart Association/WHO functional class.



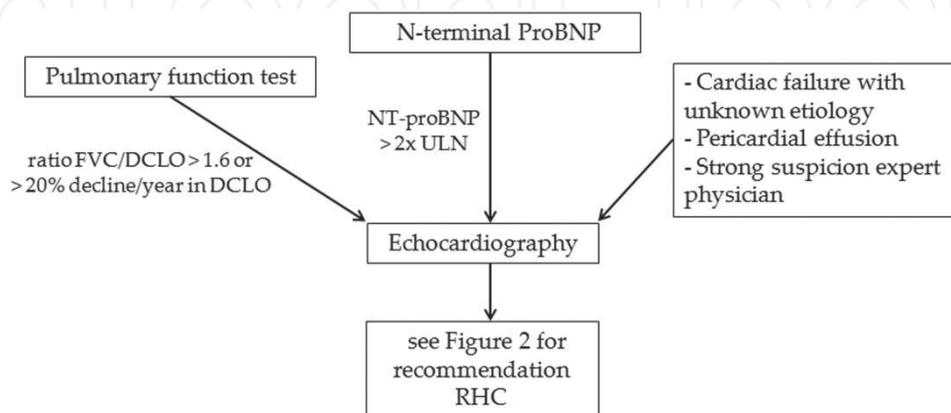
**Figure 2.** Recommendations when to perform a right-heart catheterization are shown. FVC: forced vital capacity, DCLO: diffusion capacity for carbon monoxide, NT-pro-BNP N-terminal pro brain natriuretic peptide, TRJ: tricuspid regurgitation jet, RA: right atrium, RV: right ventricle, PH: pulmonary hypertension, and RHC: right heart catheterization.

**Figure 3** is advised to be conducted yearly [29]. The objective of the DETECT study was to develop the first evidence-based detection algorithm for systemic sclerosis-associated PH. This algorithm would minimize the number of missed PH diagnoses while optimizing the use of diagnostic RHC by determining those patients with systemic sclerosis that will not benefit from catheterization. In the first step of the DETECT algorithm, six relatively simple assessments are used to determine which patients should be referred for an echocardiography. These assessments are a percentage of predicted FVC divided by the percentage of predicted DCLO, the presence of telangiectasia, the presence of anti-centromere antibodies, the serum level of N-terminal pro-BNP, the serum level of urate, and whether there are signs of right-axis deviation on ECG. The total risk score can be calculated at: <http://detect-pah.com>. In step 2, the step 1 prediction score and two echocardiographic variables, right atrium enlargement and TRJ velocity, determine which patients should subsequently be referred for an RHC. The results from the DETECT study showed that the algorithm recommended RHC in 62% of patients (referral rate) and missed 4% of PAH patients (false negatives). By comparison, when the European Society of Cardiology/European Respiratory Society guidelines were applied to these patients, 29% of diagnoses were missed while requiring an RHC referral rate of 40% [29].



**Figure 3.** DETECT algorithm in patients with systemic sclerosis with more than 3 years of disease duration and DCLO<60%.

For those patients with systemic sclerosis with a disease duration of more than 3 years and a pulmonary diffusion capacity for carbon monoxide (DCLO) above 60% of the predicted value, a yearly screening for PH is recommended by means of a pulmonary function test, including DCLO and, serum level of N-terminal pro-BNP [28–31]. **Figure 4** displays the flow chart and recommends an echocardiography when there is a decline of more than 20% in DCLO within 1 year, a FVC/DCLO ratio below 1.6, or a N-terminal pro-BNP serum level more than twice above the upper limit of normal. Depending on the results of the echocardiography, an RHC is



**Figure 4.** A flow chart for screening PH in patients with systemic sclerosis with more than 3 years of disease duration and DCLO > 60%.

recommended (**Figure 2B**). When there are signs of cardiac failure without a known etiology, signs of pericardial effusion, or a strong suspicion of PH (despite a normal or slightly elevated N-terminal pro-BNP and DCLO above 60% of predicted value), an echocardiography is recommended.

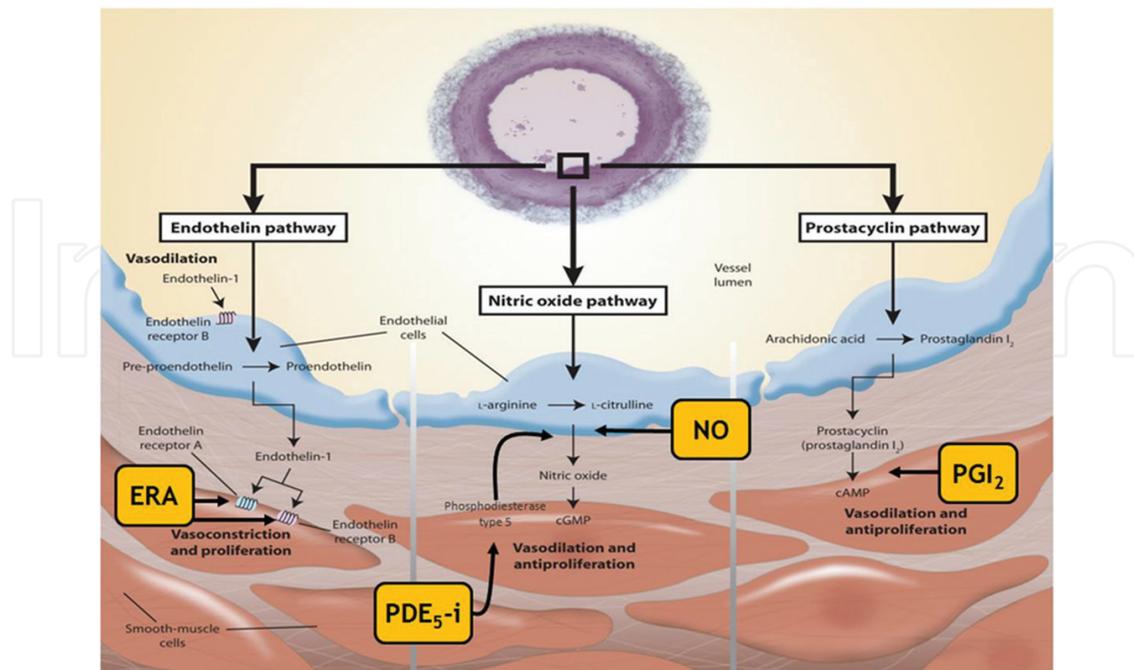
### 3. Treatment of pulmonary hypertension

The treatment of PH in patients with systemic sclerosis is a complex strategy which consists of a thorough evaluation of the severity of PH and the subsequent response to treatment. The treatment should be done by a team of experts in the field of rheumatology, cardiology, and pulmonary medicine and, in most countries, is restricted to highly specialized hospitals. Before treatment can be initiated, the NYHA/WHO group of PH should be defined in each patient. Vasoactive treatment is only indicated and reimbursed for NYHA/WHO group 1, PAH and NYHA/WHO group 4, and chronic thromboembolic pulmonary hypertension. The treatment strategy for PH can be divided into three main steps [16]. The first consists of general measures, supportive therapy, and referral to a specialized center. The second step includes the initiation of drugs approved for the treatment of PH. The final third step is related to the response to the initial treatment strategy and, in case of an inadequate response, the role of drug-combination therapy and lung transplantation. To note, the initial drug therapy, whether drug mono-therapy or drug-combination therapy for PH, depends on the NYHA/WHO functional class (**Table 2**). In patients with a severe disease (WHO functional class  $\geq$  III), there is a high-estimated 1-year mortality and consequently the urge for a more aggressive treatment strategy [27].

In the first treatment step, general measures should be discussed with patients with systemic sclerosis-associated PH. This includes the encouragement to be physically active within symptom limits and to avoid excessive physical activity that leads to distressing symptoms [32, 33]. The exercise training programs should be conducted in centers which have experience in the care for PH patients. Since PH patients are at risk to develop pneumonia [34], vaccination against influenza and pneumococcal pneumonia is recommended. Patients should also be instructed that when (elective) surgery is necessary, the anesthesiologist is familiar with their PH and when possible local anesthesia or an epidural is preferable [35]. Furthermore, pregnancy should be avoided. As PH has a severe impact on daily living and may be life threatening, psychological, social, and emotional support is advocated [36]. One of the recommendations for supportive therapy for PH in patients with systemic sclerosis is the use of diuretics in those patients who show signs of right heart failure and fluid retention [37]. Although there are no RCTs on the use of diuretics in PH, clinical experience of experts show clear benefits. Continuous long-term oxygen ( $O_2$ ) therapy is only recommended in PH patients when arterial blood  $O_2$  pressure is consistently below 8 kPa [38], as in patients with chronic obstructive pulmonary disease (COPD). There are no scientific data which suggest that long-term oxygen therapy is beneficial. The evidence for the use of oral anticoagulants in patients with PH is not proven [39] despite the high prevalence of vascular thrombotic events [40] and risk factors such as heart failure, immobility, and coagulation abnormalities [41]. The final recommendation for supportive therapy is iron substitution in those patients with systemic sclerosis-associated PH with known iron deficiencies [42].

The second step in the treatment of PH consists of treatment of the underlying cause or initiating vasoactive therapy if appropriate. In patients with NYHA/WHO group 2 PH, it is due to left heart disease, optimization of cardiac function, and/or valvular disease. In patients with PH associated with lung disease, NYHA/WHO group 3, specific treatment of the cause of this disease is mandatory. PH treatment includes the initiation of drug therapy according to the evidence-based treatment algorithm [16]. In 2012, Nickel et al. [43] showed that goal-orientated therapy, a treatment strategy that uses known prognostic indicators (NYHA/WHO functional class, N-terminal pro-BNP, cardiac index) as treatment targets resulted in better prognosis in the patients achieving these goals. Changes in these established prognostic indicators during the course of the disease provide important prognostic information. In contrast to other causes of PH, such as idiopathic PAH, there is no long-term favorable response to calcium-channel blockers in patients with systemic sclerosis associated-PH [44]. The three pathogenetic pathways targeted by drug therapy in patients with systemic sclerosis-associated PH are the endothelin pathway, the nitric oxide pathway, and the prostacyclin pathway as depicted in **Figure 5** [45].

Endothelin (ET-1) is a peptide produced by endothelial cells which have vasoconstrictive and proliferative effects and is a mediator of vascular hypertrophy and fibrosis. In patients with PH, ET-1 concentrations are elevated and correlated with indices of disease severity [46]. There are two distinct receptor isoforms in the pulmonary vascular smooth muscle cells, the so-called endothelin receptor type A and B. Blocking of these ET-1 receptors by endothelin receptor antagonists (ERAs) has shown to exert beneficial effects on WHO functional class, improved hemodynamics, and an increased time to clinical worsening [47–50]. There are no head-to-head studies comparing the three available ERAs (ambrisentan, bosentan, and



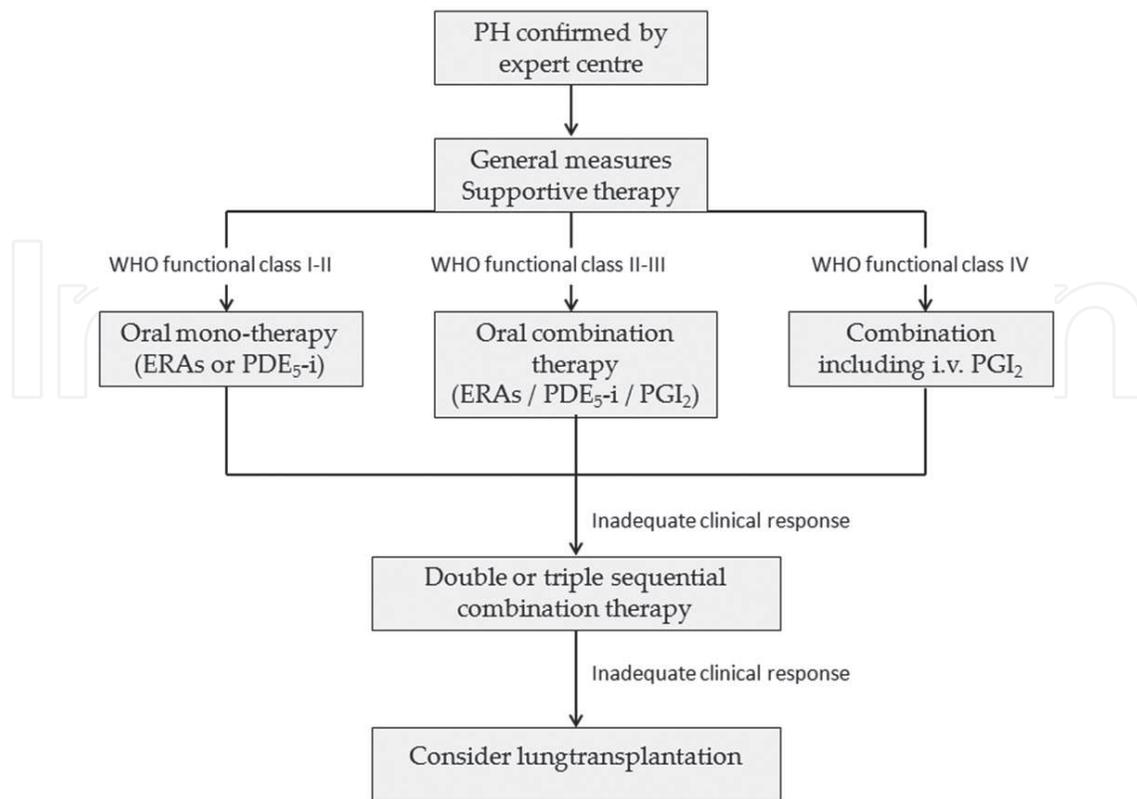
**Figure 5.** Targeted medical therapy for pulmonary arterial hypertension based on the endothelin pathway, nitric oxide pathway, and prostacyclin pathway. Adapted from Humbert et al. [45]. ERA: endothelin receptor antagonist, PDE<sub>5</sub>-I: phosphodiesterase type 5 inhibitor, NO: nitric oxide, and PGI<sub>2</sub>: prostacyclin derivatives.

macitentan), and they are considered to have similar efficacy. The most serious side effect of ambrisentan and bosentan, but not Macitentan, is liver toxicity which was found to be dose dependent and reversible. Monthly liver function assessment is therefore recommended.

The second pathway targeted by drug therapy in patients with systemic sclerosis associated-PH is the nitric oxide (NO) pathway. NO stimulates guanylate cyclase in vascular smooth muscle cells to convert guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which ultimately decreases intracellular calcium levels and thereby promotes vascular smooth muscle relaxation [51, 52]. As such, NO is considered a powerful vasodilator. In the pulmonary vasculature, phosphodiesterase type 5 (PDE<sub>5</sub>) degrades cGMP. As a consequence, inhibition of PDE<sub>5</sub> by PDE<sub>5</sub> inhibitors (PDE<sub>5</sub>-i) results in vasodilation through the NO/cGMP pathway. At the moment, there are two registered PDE<sub>5</sub>-i for PH called sildenafil and tadalafil. Both sildenafil [53, 54] and tadalafil [55] have shown beneficial effects such as an improved exercise capacity and prolonged time to clinical worsening in RCTs after 12 weeks of treatment. The soluble guanylate cyclase stimulator, called riociguat, enhances cGMP production and has also shown favorable results on exercise capacity, hemodynamics, NYHA/WHO functional class, and, time to clinical worsening in patients with PH [56].

The final possible targeted pathway in the treatment of PH is the prostacyclin pathway. Prostacyclin is mainly produced by vascular endothelial cells and induces vasodilation of the vascular bed [57] and is a powerful inhibitor of platelet aggregation [58]. Prostacyclin exerts its effects by ultimately increasing the production of intracellular cyclic adenosine monophosphate (cAMP). Unfortunately, it has a very short half-life time of about 3 min. The introduction of stable analogues of prostacyclin with different pharmacokinetic properties but similar pharmacodynamic properties extended the clinical use of prostacyclins. Epoprostenol, a synthetic prostacyclin, has a short half-life time and requires cooling and continuous administration by means of an infusion pump and tunneled venous catheter. In an unblinded Randomized Controlled Trial (RCT), the effects of poprostenol on 111 patients with PH secondary to the scleroderma spectrum of disease showed an improvement in exercise capacity, cardiopulmonary hemodynamics, and a decrease in mPAP [59]. Serious side effects such as venous catheter infections, sepsis, and pump malfunction have been described and may lead to death. Iloprost is a chemically more stable prostacyclin analogue and can be administered intravenously or via inhalation. Both inhaled iloprost [60] and intravenous iloprost [61] have shown to improve exercise capacity and clinical symptoms. Treprostenil is an analogue of poprostenol with sufficient chemical stability to be administered without cooling. Both the subcutaneous administration and inhalation of treprostenil have shown beneficial effects in patients with PH [62, 63]. Recently, the first oral selective IP-prostacyclin receptor agonist selexipag was approved. In an event-driven study in 1156 patients, a 40% reduction of mortality and PH-associated complications were found in the selexipag-treated patients [64].

**Figure 6** shows the current treatment algorithm for systemic sclerosis associated-PH [16]. Initial drug therapy, whether drug monotherapy or drug-combination therapy for PH, depends on the NYHA/WHO functional class combined with determinants of a worse prognosis such as clinical signs of heart failure, syncope, N-terminal pro-BNP plasma levels above



**Figure 6.** A treatment algorithm for systemic sclerosis associated-PH. ERA: endothelin receptor antagonist, PDE<sub>5</sub>-I: phosphodiesterase type 5 inhibitor, and PGI<sub>2</sub>: prostacyclin derivatives.

300ng/l, echocardiographic signs of right atrial enlargement, 6-min walking distance, and/or low physical fitness levels (VO<sub>2</sub> peak oxygen consumption < 15 ml/min/kg).

### 3.1. Combination therapy

When initial drug monotherapy in PH patients with WHO functional class I–II fails or when patients with systemic sclerosis associated-PH at first diagnoses are already in WHO functional class II–IV, combination therapy can be applied. Because of the three possible targeted pathways (ET-1-, NO-, and prostacyclin pathway), this was thought to be an attractive option [65]. Combination therapy can be applied sequentially or upfront. Sequential therapy was the most widely used strategy; in case of an inadequate response to monotherapy, a second and subsequently a third drug can be added. Several trials have been conducted which evaluated the efficacy of drug combination therapy compared to monotherapy. A recent meta-analysis on 15 RCTs, with combination of PAH-specific therapies (upfront and sequential add-ons) compared with PAH-specific monotherapy, showed a risk reduction for clinical worsening of 17 versus 28%, respectively [66]. A similar outcome was observed by a meta-analysis from Fox et al. [67] on 18 RCTs. Combination therapy was associated with a reduction in non-fatal end points, an improved 6-min walking distance, improved functional class, and pulmonary hemodynamics. So far, the strongest scientific evidence has been found for the combination therapy of ambrisentan and tadalafil in PH

patients with NYHA/WHO functional class II and III [68]. Only recently, the effects of initial triple upfront combination therapy in patients diagnosed with PH has been evaluated [69]. Nineteen newly diagnosed NYHA/WHO functional class III/IV PAH patients initiated on upfront triple combination therapy (intravenous epoprostenol, bosentan, and sildenafil) were collected retrospectively. After 4 months' triple combination therapy, 18 patients significantly improved their 6-min walking distance and hemodynamics. Seventeen patients had improved to NYHA/WHO functional class I or II but most striking was the overall estimated survival of 100% after 1, 2, and 3 years [69].

### 3.2. Lung transplantation

When patients decline despite aggressive drug therapy and other interventions, lung transplantation can be considered. The first lung transplantation for pulmonary vascular disease was performed in 1982 at Stanford University by Dr. Reitz and colleagues [70]. The timing of transplantation is crucial and depends on several factors, including the cause of PH, stage of the disease, co-morbidities and suitability for operation, possible alternative treatments, and of course, availability of donors. Patients with systemic sclerosis were initially often denied transplantation because of concerns about the short- and long-term outcomes related to the extra-pulmonary manifestations of systemic sclerosis [71]. A systematic review performed by Khan et al. [72] addressed this issue and evaluated the survival of systemic sclerosis patients after lung transplantation. He identified seven observational studies reporting the results of approximately 185 patients with systemic sclerosis who underwent single-lung, double-lung, or heart-lung transplantation. The indication for lung transplantation was both ILD and/or PAH related. The results showed that post-transplantation survival ranged 69–91% at 30 days, 69–85% at 6 months, 59–93% at 1 year, 49–80% at 2 years, and 46–79% at 3 years. He concluded that the short-term and intermediate-term survival after lung transplantation were similar to patients with idiopathic forms of PAH and other causes of ILD requiring lung transplantation. So nowadays, systemic sclerosis is a widely accepted diagnosis for the potential necessary lung transplantation. Remarkable was the considerable variability in survival estimates. This is probably due to different selection criteria of patients and may also be related to survival differences across systemic sclerosis patients with PAH, ILD, or a combination of PAH and ILD. Future work should aim to prospectively study adults with systemic sclerosis as they are evaluated for lung transplantation in order to identify potentially modifiable risk factors that can improve transplant outcomes in this population [73].

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