



Epidemiology Screening Diagnosis and Treatment of Systemic Sclerosis-Associated Pulmonary Arterial Hypertension

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Abstract

Systemic sclerosis (SSc) is a very rare rheumatologic disorder with systemic involvement including pulmonary, gastrointestinal, renal and musculoskeletal complications. Pulmonary hypertension is an important manifestation of SSc with multiple etiologies, including pulmonary arterial hypertension (PAH), left heart dysfunction, interstitial lung disease and chronic thromboembolic disease. PAH is present in 7-12% of SSc patients and is a leading cause of death in this population with a 2-year mortality of >60%. Routine screening for pulmonary hypertension is warranted in this group and results in earlier detection and initiation of therapy, which may result in improved outcomes. PAH treatment includes use of prostanoids, endothelin receptor antagonists, and/or phosphodiesterase-5 inhibitors/guanylate cyclase stimulators as monotherapy or in combination. This review will consider the multiple etiologies of pulmonary hypertension in SSc and address the epidemiology, clinical manifestations, screening guidelines, diagnostic considerations, current treatment and prognosis of SSc-associated PAH.

Introduction

Systemic sclerosis (SSc) is a heterogeneous rheumatologic connective tissue disorder mediated by an autoimmune response resulting in inflammation, fibrosis and vascular dysfunction [1]. Diagnostic findings include thickened skin of the hands and fingers, telangiectasias, fingertip ulcers or lesions, abnormal nailfold capillaries, Raynaud's phenomenon and positive autoimmune antibodies [2]. Within the spectrum of scleroderma, SSc is distinct by its involvement in multiple internal organ systems including pulmonary, cardiovascular, gastrointestinal, musculoskeletal and renal [1,3-7].

Pulmonary hypertension is a common complication of SSc, which can have multiple etiologies. The World Health Organization (WHO) categorizes pulmonary hypertension into five groups based on etiology: pulmonary arterial hypertension (PAH) (group 1), pulmonary hypertension secondary to left heart disease (group 2), chronic lung disease and/or hypoxia (group 3), chronic thromboembolic disease (group 4) and unclear or multifactorial etiology (group 5); pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis (group 1') are also recognized as rare etiologies of pulmonary hypertension [8]. SSc can cause cardiac ventricular diastolic and systolic dysfunction, interstitial lung disease, increased risk of thromboembolism and it is also associated with pulmonary veno-occlusive disease, thus accounting for WHO groups 2-4 and 1' pulmonary hypertension, respectively [8-11]. WHO group 1 PAH in SSc patients is a result of pulmonary arterial fibrosis, perivascular inflammation and intimal hypertrophy [6]. This is the most common cause of pulmonary hypertension in this group and will be the primary focus of this paper [12].

Epidemiology

SSc is a very rare disease with an estimated prevalence and incidence of 7-489 per million and 0.6-122 per million per year, respectively [13]. Despite its presence in only 7-12% of patients with SSc [8], PAH is a leading cause of death in this population [12] with a 2-year mortality ranging from 64-89% [14,15].

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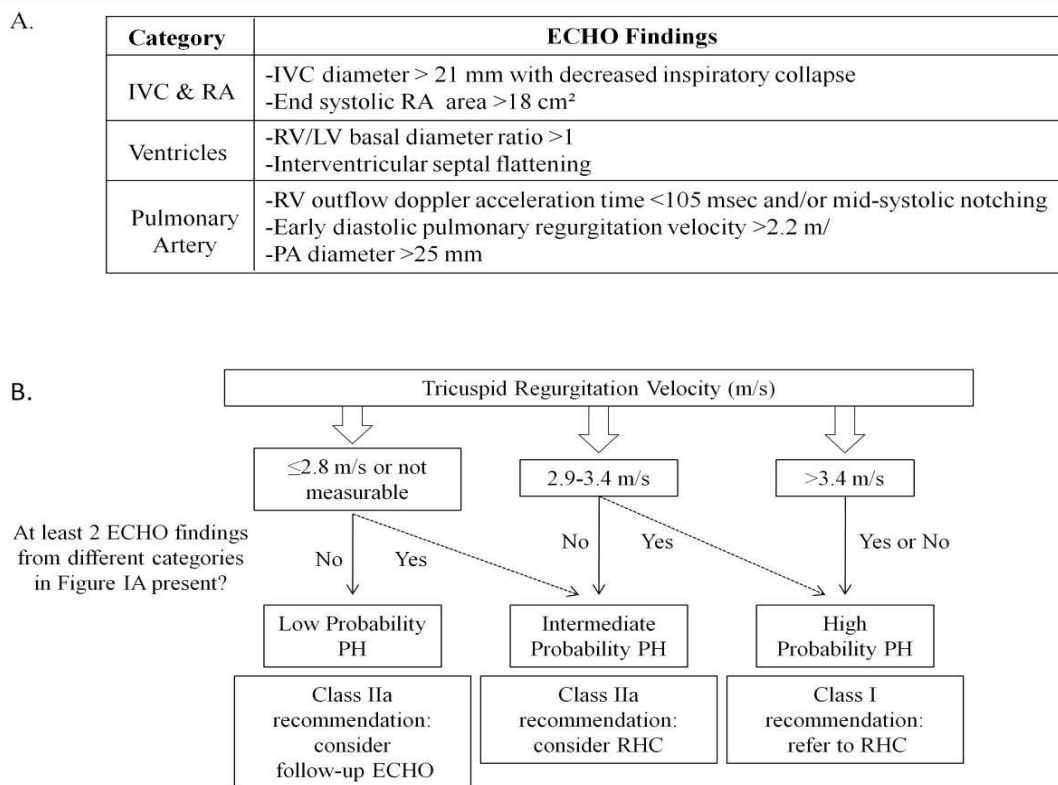


Figure 1: Algorithm to determine the probability of pulmonary hypertension. Adapted from the 2015 ESC/ERS pulmonary hypertension guideline [25]. (A) Echocardiography findings consistent with pulmonary hypertension, organized by anatomical category. (B) Algorithm based on tricuspid regurgitation velocity and echocardiography findings to determine probability of pulmonary hypertension and indications for follow up echocardiography vs. right heart catheterization. **Abbreviations:** IVC: Inferior Vena Cava; RA: Right Atrium; LV: Left Ventricle; PA: Pulmonary Artery; PH: Pulmonary Hypertension; ECHO: Echocardiogram; RHC: Right Heart Catheterization.

Risk Factors For The Development of PAH in Ssc Patients

Include: older age, post menopausal status, longer disease duration, diffusing capacity of carbon monoxide (DLCO) <50% predicted, limited cutaneous/CREST syndrome variant, telangiectasias, digital ulcers, positive anti-centromere, anti-U1-ribonucleoprotein and antiphospholipid antibodies and negative anti-Scl-70 antibody [16-18]. However, it is important to recognize that PAH can also affect patients with diffuse cutaneous involvement and can occur early in the disease course [16]. Hemodynamic findings associated with progression to PAH include: exercise-induced PAH, an annual increase in right ventricular systolic pressures by >3 mmHg per year, a mean pulmonary artery pressure (mPAP) between 21-24 mmHg and a transpulmonary gradient >11mmHg [16].

Clinical Manifestations

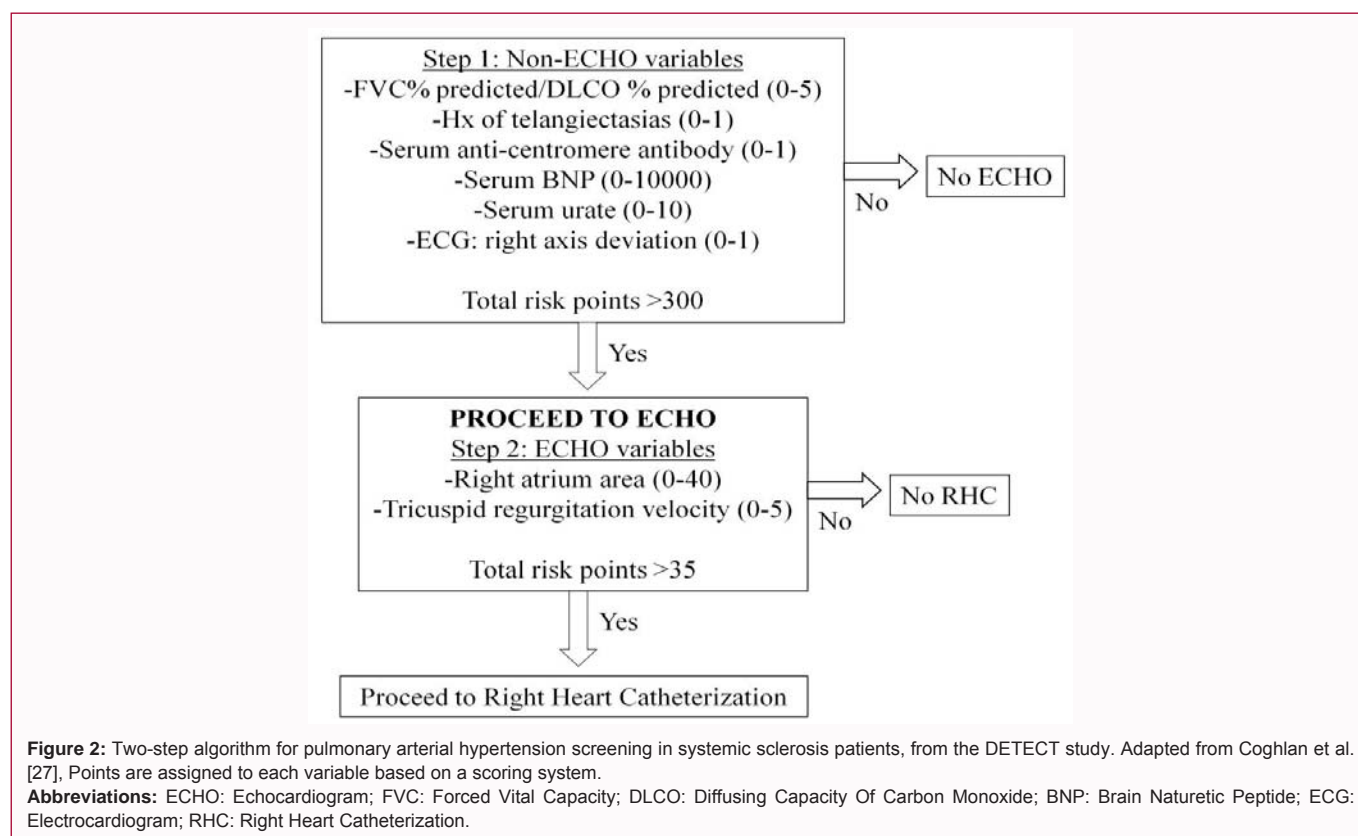
Many SSc patients with PAH remain asymptomatic for a prolonged period until they have reached the advanced stages of disease with right heart failure. Symptoms are nearly indistinguishable from patients with idiopathic PAH (IPAH) and initially include dyspnea on exertion, lethargy, fatigue and later progress to chest pain, presyncope/syncope, edema, and rest symptoms as right heart failure develops [19,20]. Clinical signs include elevated jugular venous pressure, hepatomegaly, peripheral edema, ascites, cool extremities, pronounced pulmonary component of the second heart sound, pansystolic murmur of tricuspid regurgitation, diastolic murmur from pulmonary insufficiency and/or right ventricular fourth heart sound [21]. These patients may also have signs and symptoms related to other organ involvement in SSc including characteristic dermatologic

changes, gastrointestinal reflux, dysphagia, diarrhea, arthritis, muscle weakness, acute renal injury, severe hypertension and calcinosis [1,7].

Screening

In SSc patients there is often a delay in diagnosing pulmonary hypertension and active screening can result in early detection and initiation of treatment, which is associated with improved outcomes [22-24]. Thus, the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension recommend annual screening for pulmonary hypertension with echocardiography (ECHO), DLCO and serum brain natriuretic peptide (BNP) in patients with SSc [25]. Although ECHO can detect elevated pulmonary artery pressures and diastolic and/or systolic dysfunction, and is considered the first-line imaging modality to screen for pulmonary hypertension, it lacks sensitivity for detecting mild cases of pulmonary hypertension. Additionally, there are no specific cutoffs for right ventricular systolic pressures and this variable must be considered in conjunction with associated findings, such as right ventricular hypertrophy or dilation and interventricular systolic/diastolic septal flattening, to determine the probability of pulmonary hypertension and indication for right heart catheterization (RHC) [26]. (Figure 1) outlines the algorithm developed by the 2015 ECS/ERS pulmonary hypertension guidelines for determining probability of pulmonary hypertension and indications for ECHO and RHC.

These guidelines also acknowledge use of the 2-step algorithm (Figure 2) developed by the DETECT study for patients with a DLCO <60% and a disease duration of >3 years. The algorithm uses a scoring



system based on the patients calculated percent predicted forced vital capacity/percent predicted DLCO ratio, a history of telangiectasias, serum anti-centromere antibody, serum BNP, serum urate and the presence of right axis deviation on electrocardiogram (ECG) to determine indications for obtaining an ECHO. Right atrial area and tricuspid regurgitation velocity calculated by ECHO are used to determine appropriateness of referral for RHC. This strategy was established to decrease the number of screening ECHOs obtained in low risk patients and the number of patients referred for RHC. The study found that the two-step DETECT screening algorithm had similar or better sensitivity and specificity than the ESC/ERS pulmonary hypertension guidelines when screening for PAH in this population [27].

Although exercise-induced pulmonary hypertension is not a classification in the current guideline, several studies have demonstrated an abnormal increase in mPAP or right ventricular systolic pressure with exercise in patients with normal resting pressures [18,28,29]. Additionally, it has been shown that pulmonary hypertension provoked by exertion predicts progression to resting pulmonary hypertension. Thus, exercise ECHO can be useful to identify early disease in high risk patients with symptoms during exercise.

Diagnosis

Based on data from the aforementioned screening tests, patients are referred for RHC, which is the gold standard for diagnosing pulmonary hypertension. PAH is defined as a resting mPAP \geq 25 mmHg, pulmonary capillary wedge pressure (PCWP) \leq 15 mmHg and pulmonary vascular resistance $>$ 3 Wood units. A mPAP between 21-24 mmHg is considered borderline pulmonary hypertension. An elevated mPAP and PCWP suggest a diagnosis of WHO group 2 pulmonary hypertension. The pulmonary vascular resistance and

diastolic pressure gradient (defined as the difference between the diastolic PAP and PCWP) can be utilized to further differentiate between a diagnosis of WHO group 2 pulmonary hypertension that is independent of, or in combination with, a diagnosis of PAH, as both diagnoses can be seen in patients with SSc [25]. (Figure 3) outlines the diagnostic approach to differentiate between the various causes of pulmonary hypertension based on these hemodynamic parameters.

Further, when diagnosing PAH in SSc patients it important to evaluate for other pre-capillary causes of pulmonary hypertension such as interstitial lung disease, thromboembolic disease or other rare causes [8]. Thus, pulmonary function tests (PFTs) and computed tomography (CT) of the chest are also indicated in the complete pulmonary hypertension workup. In regard to PFTs, the DLCO is usually decreased to 40-70% of predicted in PAH; a decreased total lung capacity or findings consistent with restrictive physiology can indicate a diagnosis of interstitial lung disease [19]. CT of the chest may also reveal findings suggestive of PAH [30], interstitial lung disease or pulmonary venoocclusive disease and/or capillary hemangiomatosis [31-33]. Ventilation/perfusion (VQ) lung scan is also indicated in the evaluation of patients with pulmonary hypertension as it is the imaging method of choice to assess for chronic thrombo-embolic pulmonary hypertension (WHO group 4) [25], which is also rarely associated with SSc [26]. Cardiac magnetic resonance imaging may also provide diagnostic and prognostic information as it is currently the most accurate imaging modality to assess right ventricular morphology, size and ejection fraction and to identify myocardial fibrosis, commonly seen in SSc [26]. It is also noteworthy that multiple etiologies of pulmonary hypertension with varying degrees of severity can occur in patients with SSc. Data from RHC, ECHO, PFTs, CT of the chest, cardiac magnetic resonance imaging and VQ scan must be integrated to reach this clinical conclusion.

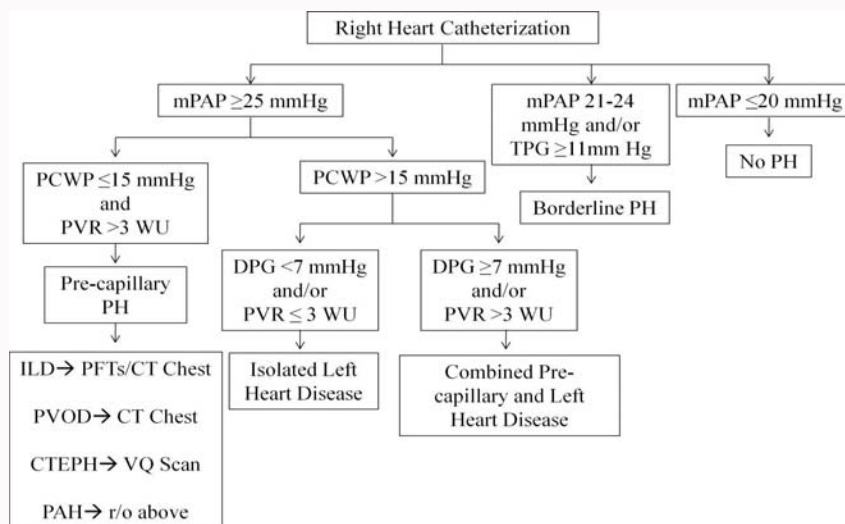


Figure 3: Algorithm for the diagnosis of various etiologies of pulmonary hypertension in systemic sclerosis patients. Adapted from the 2015 ESC/ERS pulmonary hypertension guideline [25].

Abbreviations: mPAP: mean pulmonary arterial pressure; mmHg: millimeters mercury; TPG: Transpulmonary Gradient; PCWP: Pulmonary Capillary Wedge Pressure; PVR: Pulmonary Vascular Resistance; WU: Wood Units; DPG: Diastolic Pressure Gradient (Diastolic Pulmonary Arterial Pressure - Pulmonary Capillary Wedge Pressure); ILD: Interstitial Lung Disease; PFT: Pulmonary Function Tests; CT: Computed Tomography; PVOD: Pulmonary Veno-Occlusive Disease; CTEPH: Chronic Thromboembolic Pulmonary Hypertension; VQ: Ventilation-Perfusion; PAH: Pulmonary Arterial Hypertension; PH: Pulmonary Hypertension.

Immunologic testing, which is indicated in the diagnosis of SSc, is important when diagnosing concomitant PAH as several antibodies may have prognostic implications. For example, anti-U1-ribonucleoprotein positivity has been associated with improved survival in this patient population [6].

Treatment

General considerations

As there are no comprehensive disease modifying therapies in SSc, treatment is directed toward specific organ system complications. Although multiple studies show that patients with SSc-associated PAH are less responsive to PAH therapy than those with IPAH [12], the 2015 ESC/ERS pulmonary hypertension guidelines recommend the same treatment algorithm for both [25]. However, routine vasoreactivity testing during RHC, which is utilized in other patients with PAH, is not recommended in connective tissue disease-associated PAH [25] because <1% of these patients have long-term response to calcium channel blockers [34]. With the exclusion of calcium channel blockers, three classes of drugs have been identified in the treatment of SSc-associated PAH: prostanoids, endothelin receptor antagonists and phosphodiesterase-5 inhibitors/guanylate cyclase stimulators. Supportive therapy with supplemental oxygen and diuretics, including aldosterone antagonists, can be used for symptom control in these patients; however, there are no controlled trials to support the use of these interventions [25].

In the treatment algorithm outlined by the 2015 ESC/ERS pulmonary hypertension guidelines, patients with WHO functional class II-III symptoms should be started on initial monotherapy or combination therapy with the aforementioned three classes of drugs, while initial therapy in those with WHO functional class IV symptoms should be a combined regimen, including an intravenous prostanoid. If clinical response is inadequate, double or triple sequential combination therapy is advised [25]. Finally, listing for lung transplant is the ultimate therapeutic approach for persistent failure to respond to maximum medical therapy. Tools to assess

clinical response include symptoms, signs of right heart failure, WHO functional class, 6 minute walk test (6MWT), cardiopulmonary exercise testing, Borg dyspnea score, hemodynamic parameters on RHC, ECG and serum BNP [25].

While most trials evaluating PAH treatment use the above tools to assess outcomes, four landmark trials have provided longer term data on mortality and have radically changed PAH treatment in the last decade. These include the GRIPHON [35], SERAPHIN [36], PATENT-2 [37], and AMBITION [38] trials which evaluated use of selexipag, macitentan, riociguat and the upfront combination of ambrisentan and tadalafil, respectively. These trials, in addition to other studies, will be discussed individually below. However, in order to increase relevance, only studies with $\geq 20\%$ of the cohort with connective tissue disease-associated PAH will be considered [6].

Prostanoids

Prostanoids were the first agents approved for the treatment of PAH. These drugs stimulate cAMP, resulting in pulmonary and systemic vasodilation [16]. Badesch et al reported improved exercise capacity and hemodynamic measures in patients with SSc-associated PAH who received IV epoprostenol for 12 weeks [39]. However, this study did not show survival benefit, which was demonstrated in a subsequent report by the same group. The survival rates for 1-, 2-, 3- and 4-years were 71%, 52%, 48%, and 48%, respectively, which are higher than historically reported outcomes in similar patient populations [40]. Other investigations have found similar outcomes in patients treated with treprostinil [41] and iloprost [42]. Finally, the GRIPHON trial revealed that use of selexipag, an oral selective prostacyclin-receptor agonist, compared to placebo resulted in a lower composite primary outcome of death or complication related to PAH [35].

Endothelin receptor antagonists

Endothelin receptor antagonists, which act by interfering with the vasoconstrictive effects of the receptor, have demonstrated promising clinical results in the treatment of SSc-associated PAH

[16]. In the BREATHE-1 trial, treatment with bosentan for 16 weeks prevented deterioration in performance on the 6-MWT in the SSc-associated PAH group and improved performance in the IPAH group [43]. Denton et al. [44] and Launay et al. [45], found that treatment with bosentan resulted in improved or stabilized functional class and higher survival rates compared to historically reported data for patients with connective tissue disease-associated PAH. In the ARIES-1 and ARIES-2 trials, PAH patients treated with ambrisentan had improved exercise capacity, functional class and Borg dyspnea score with prolonged time to clinical worsening at 12 weeks [46]. Finally, in the SERAPHIN trial, treatment with macitentan was associated with reduced morbidity and mortality in patients with PAH; however, the majority of patients had IPAH and subgroup analysis of SSc patients are in progress [37].

Phosphodiesterase-5 inhibitors and Guanylate cyclase stimulators

Phosphodiesterase-5 inhibitors, such as sildenafil and tadalafil, inhibit the hydrolysis of cGMP which increases nitric oxide concentration, resulting in vasodilatation, anti-proliferation and pro-apoptotic effects on pulmonary vasculature. Riociguat is a guanylate cyclase stimulator which has similar effects [16]. In a subgroup analysis of the SUPER-1 trial, sildenafil treatment for 12 weeks enhanced exercise capacity, WHO functional class and hemodynamic parameters in patients with connective tissue disease-related PAH [47]. In a double blind placebo controlled trial, treatment with tadalafil improved exercise capacity and health related quality of life and decreased clinical worsening at 16 weeks [48]. Jing et al. [49], found that treatment with vardenafil resulted in improved exercise capacity and hemodynamic function at 12 weeks. The PATENT-2 [37] trial reported that treatment with riociguat improved exercise capacity, pulmonary vascular resistance, WHO functional class, time to clinical worsening and Borg dyspnea score at 12 weeks.

Combination therapy

Several investigators have reported clinical outcomes with combination therapy of the above drug classes. In a recently published prospective multicenter study, the combination of ambrisentan and tadalafil for 36 weeks in treatment-naive patients with SSc-associated PAH resulted in improved functional class, exercise capacity and hemodynamics, including increased right ventricular ejection fraction [50]. Combination therapy in the AMBITION trial with these two agents compared to either as monotherapy after 24 weeks resulted in a more satisfactory clinical response, improved exercise capacity and lower rates of clinical failure defined as death, hospitalization for worsening PAH, disease progression, or unsatisfactory long term clinical response [38]. However, the addition of bosentan to sildenafil was not superior to placebo in reducing mortality or morbidity but did marginally improve exercise capacity [51]. A prior study demonstrated that addition of sildenafil to IV epoprostenol improved hemodynamics, exercise capacity, time to clinical worsening and health related quality of life at 16 weeks [52]. In Tapson et al. [53] and Mc Laughlin et al. [54], the addition of oral or inhaled treprostinil to an endothelin antagonist and/or phosphodiesterase inhibitor had insignificant clinical results.

Anticoagulation

The clinical results of anticoagulation in patients with SSc-associated PAH has had inconsistent effects with various studies demonstrating improved [55] or worse [56] survival while others have reported no benefit or harm [57,58]. Based on these outcomes

the current ESC/ERS pulmonary hypertension guidelines provides a class IIb recommendation to consider anticoagulation in connective tissue disease-associated PAH patients on an individual patient basis [25].

Prognosis

Patients with PAH related to SSc have a grave prognosis, which is more unfavorable than those with IPAH. However, during the first decade of this century, survival rates have improved to a median of approximately 5 years in a 2011 study, nearly five-fold higher than reported in 1996. Furthermore, the 1-, 2-, and 3-year survival rates reported in 2011 were 81, 72 and 64%, respectively, which is over 1.5 times higher than in 1996 [12]. This decrease in mortality is likely related to both advances in PAH therapy, earlier diagnosis and timelier initiation of therapy due to screening for PAH in the SSc population [12,22-24].

The prognostic indicators for survival in these patients include: advanced age, male gender, poor functional class and exercise ability, decreased DLCO, antibody positivity, increased right atrial pressures and signs of right heart failure [12,16]. With lung transplantation, 3-year survival rates were 46-79% in 7 observational studies which is similar to that in patients with IPAH undergoing lung transplantation [16].

Future Considerations

Several reports have identified increases in cytokines and other inflammatory markers including interleukin, tumor necrosis factor-alpha, adhesion molecules, endothelial growth mediators and von Willebrand factor in patients with SSc-associated PAH; these markers afford new areas of investigation and potential targets for therapy [16,59,60]. In addition, immunosuppressive therapy is under investigation [6].

Conclusion

PAH is a relatively common and potentially fatal complication of SSc requiring screening for detection as patients are often asymptomatic until development of advanced disease. Because SSc is a heterogeneous disorder with diverse manifestations, diagnosis may be delayed. Thus, PAH screening should be considered in patients with features suggestive of a connective tissue disorder. SSc-associated PAH has a dire prognosis with only modest responsiveness to therapy compared to IPAH and early detection and initiation of therapy are critical.

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