Chapter

Advances in Management of Pulmonary Hypertension Associated with Systemic Sclerosis

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Abstract

Pulmonary hypertension is a well-known complication of systemic sclerosis. Patients with systemic sclerosis may develop a pulmonary arteriopathy characterized by vascular remodeling, increased pulmonary vascular resistance, and right ventricular failure. Pulmonary hypertension may also arise in systemic sclerosis as a consequence of interstitial lung disease or left ventricular dysfunction. Vascular remodeling is more prevalent than other forms of pulmonary hypertension in systemic sclerosis. The pathogenesis of pulmonary vascular remodeling in this disease state is not completely understood; however, there is evidence of a complex process involving genetic susceptibility, risk factors, vascular injury, and endothelial dysfunction. In those patients with pulmonary arterial hypertension, survival prognosis is extremely poor if the diagnosis is delayed or goes undetected and untreated. In recent years, a number of disease-targeted therapies have been developed that improve functional capacity, hemodynamics, and survival. Early detection and treatment with one or more targeted therapies are essential to improving survival when systemic sclerosis is complicated by pulmonary arterial hypertension.

Keywords: pulmonary arterial hypertension, systemic sclerosis, endothelin, nitric oxide, prostacyclin

1. Introduction

Systemic sclerosis (SSc) is a multisystem, autoimmune disease characterized by excessive collagen deposition and fibrosis of the skin and internal organs. The autoimmune process may affect the lungs with the development of interstitial fibrosis, pulmonary hypertension, or both. Pulmonary hypertension (PH) may result from a pathologic process of remodeling in the pulmonary arteries, in which case it is referred to as pulmonary arterial hypertension (PAH). Pulmonary hypertension may also arise secondary to interstitial fibrosis with chronic hypoxemia or myocardial fibrosis with postcapillary pulmonary hypertension. Pulmonary arterial hypertension associated with systemic sclerosis (SSc-PAH) represents the second most common cause of PAH after the idiopathic form of the disease (iPAH). Pulmonary arterial hypertension is associated with a progressive rise in pulmonary vascular resistance that can result in right ventricular failure and death. Patients with SSc-PAH have higher mortality than the idiopathic form of PAH or PAH associated with other diseases, such as congenital heart disease. While there is a

reasonable amount of information available pertaining to SSc-PAH, much of what we know about PAH in general comes from investigations of the idiopathic form of the disease. The current chapter will review current knowledge about PAH in the patient with systemic sclerosis and contrast it with information that distinguishes SSc-PAH from the idiopathic form of PAH.

2. Epidemiology

The prevalence of systemic sclerosis-associated PAH is reported to be between 5 and 15% of patients with systemic sclerosis [1–3]. There is wide variability in reported prevalence rates which range from as low as 3.7% [4] to as high as 43% [5]. This variability is in large part due to methods used to establish the diagnosis of pulmonary hypertension. While some prevalence studies base reported findings on echocardiography, others confirm diagnosis with right heart catheterization. Right heart catheterization (RHC) is the gold standard for accurate diagnosis of pulmonary hypertension and for distinguishing pulmonary arterial from postcapillary hypertension. Prevalence rates are consistently lower when diagnosis is determined by right heart catheterization [6]. In a meta-analysis, Yang et al. found 12 studies reporting the prevalence of PAH in SSc ranging from 3.6 to 32% with a pooled prevalence of 13%. Five of the 12 studies confirmed the diagnosis of PAH with right heart catheterization yielding a pooled prevalence estimate of 8.2%, while the pooled prevalence estimate from seven studies relying on echocardiography was 18% [7]. Even when pulmonary hypertension is diagnosed by right heart catheterization, some patients in cohort studies may refuse to undergo catheterization, thus affecting true prevalence [8].

The prevalence of pulmonary hypertension in systemic sclerosis depends on the phenotypic form of systemic sclerosis and the pathophysiologic mechanism behind the development of PH. The Australian Scleroderma Cohort Study (ASCS) of 232 patients identified PH in 10.1% of patients with diffuse scleroderma and in 12.7% of those with the limited form of the disease [9]. Prevalence of SSc-PAH consistently exceeds interstitial lung disease-PH (ILD-PH) or postcapillary-PH (PC-PH). Evaluation of PH subtypes in the ASCS cohort revealed 83.6% with PAH, 2.2% with ILD-PH, and 7.8% with PC-PH. The DETECT study, which was designed to develop an algorithm for detection of PAH in SSc, included 145 patients all of whom underwent right heart catheterization revealing 19% with PAH, 6% with ILD-PH, and 6% with PC-PH [10]. An Italian cohort of 867 consecutive SSc patients included 69 patients confirmed to have pulmonary hypertension with point prevalence for PAH 3.7%, PH secondary to ILD 1.4%, and postcapillary-PH 1.3% [4]. The lower prevalence of PH in the Italian cohort study raised speculation that ethnic factors might influence the prevalence of PH in SSc.

Prevalence of SSc-PAH appears to depend on other factors, such as duration of systemic sclerosis, gender, and ethnicity. Observations in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) study suggested patients who were female, Caucasian, or suffering with limited cutaneous scleroderma were more likely to have PAH [11]. Additionally, a reduction in DLCO below 55% predicted was noted in 79% of patients with SSc-PAH compared to 55% of patients with SSc alone. Other authors have observed a greater chance of developing SSc-PAH in male patients age 47 or older [12], patients with SSC more than 10 years [13], and those with DLCO <55% [14]. Iudici suggested that systemic sclerosis patients of Italian descent may be less likely to develop pulmonary hypertension based on observations that prevalence rates were substantially lower than those reported in Anglo-Saxon patients [4].

3. Pathophysiology

3.1 WHO classification of pulmonary hypertensive diseases

The World Health Organization (WHO) has classified pulmonary hypertension into five distinct groups on the basis of the primary pathophysiologic mechanism leading to elevated pulmonary artery pressure (**Table 1**) [15]. In a generic sense, pulmonary hypertension is diagnosed when mean pulmonary artery pressure (mPAP) ≥ 25 mmHg is measured by pulmonary artery catheterization. Patients classified as WHO Group 1 develop an arteriopathy of the small precapillary pulmonary arteries characterized by endothelial proliferation, smooth muscle layer hypertrophy, in situ thrombosis, and formation of plexiform lesions (**Figure 1**). Pulmonary arterial hypertension is defined more specifically as a mPAP ≥25 mmHg and also a capillary wedge pressure (CWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units (WU) [16]. Those in WHO Group 2 have elevated pulmonary artery pressure with a postcapillary origin typically related to left heart disease or dysfunction. WHO Group 3 pulmonary hypertension is a consequence of chronic hypoxia and attendant vasoconstriction as seen in chronic lung diseases, such as pulmonary fibrosis or emphysema. The fourth WHO Group constitutes those with pulmonary vascular obstruction, most often due to chronic thromboembolic disease. Finally, WHO Group 5 is a group of patients with pulmonary hypertension of mixed etiologies that do not fit within the other categories.

3.2 Histopathology

Patients who develop the characteristic vasculopathy of WHO Group 1 PAH experience a progressive rise in pulmonary vascular resistance resulting from the gradual occlusion of smaller vessels by cellular hyperproliferation, thrombosis, and plexiform lesion formation that obstruct blood flow. The resulting rise in resistance to blood flow through the pulmonary circulation causes right ventricular strain with initial compensation and hypertrophy. Eventually the rising resistance overwhelms the right ventricle resulting in its failure.

Pulmonary hypertension as it occurs in the scleroderma spectrum of diseases can develop by virtue of one or more mechanisms and can be classified as WHO Group 1 with the characteristic features of a precapillary arteriopathy, as WHO Group 2 when scleroderma affects myocardial physiology, or as WHO Group 3 if the patient primarily suffers from interstitial fibrosis and hypoxemia. Patients with systemic sclerosis may have complex forms of pulmonary hypertension involving more than one of these mechanisms. Treatment is dependent on the mechanism or mechanisms behind rising pulmonary vascular resistance, so it is important to carefully establish the root cause, or causes, for pulmonary hypertension in this patient population. Pulmonary arterial hypertension is the most common form of pulmonary hypertension to affect patients with systemic sclerosis. Therefore, this chapter's focus is primarily on the pathogenesis of pulmonary arterial hypertension. While other mechanisms leading to pulmonary hypertension in this group will be reviewed, the development of SSc-PAH is a devastating complication, and the greatest body of information available pertains to the WHO Group 1 type of arteriopathy.

Characteristic histopathologic features of pulmonary vascular remodeling observed in the patient with WHO Group 1 PAH are well-described and involve all layers of the pulmonary arterial vessels (**Figure 1A**) [17, 19, 21]. It is not uncommon for a similar process to affect the postcapillary venules in systemic sclerosis. A majority of patients will have in situ vessel thrombosis [18]. Flow-limiting

1. **Pulmonary Arterial Hypertension**

    1.1   Idiopathic
    1.2   Heritable
        1.2.1   BMPR2 mutation
        1.2.2   Other mutations
    1.3   Drug and toxin induced
    1.4   Associated with:
        1.4.1   Connective tissue disease
        1.4.2   Human immunodeficiency virus (HIV) infection
        1.4.3   Portal hypertension
        1.4.4   Congenital heart disease
        1.4.5   Schistosomiasis

1'. **Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis**

    1'.1   Idiopathic
    1'.2   Heritable
        1'.2.1   EIF2AK4 mutation
        1'.2.2   Other mutations
    1'.3   Drugs, toxins and radiation induced
    1'.4   Assoicated with:
        1'.4.1   Connective tissue disease
        1'.4.2   HIV infection

1''. **Persistant pulmonary hypertension of the newborn**

2. **Pulmonary Hypertension Due to Left Heart Disease**

    2.1   Left ventricular systolic dysfunction
    2.2   Left ventricular diastolic dysfunction
    2.3   Valvular heart disease
    2.4   Congenital/acquired left heart inflow/outflow tract obstruction and Congenital cardiomyopathies
    2.5   Congenital/acquired pulmonary vein stenosis

3. **Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia**

    3.1   Chronic obstructive pulmonary disease
    3.2   Interstitial lung disease
    3.3   Other pulmonary diseases with mixed obstructive and restrictive components
    3.4   Sleep-disordered breathing
    3.5   Alveolar hypoventilation
    3.6   Chronic high altitude exposure
    3.7   Developmental lung diseases

4. **Chronic Thromboembolic Pulmonary Hypertension and Other Pulmonary Artery Obstructions**

    4.1   Chronic thromboembolic pulmonary hypertension
    4.2   Other pulmonary artery obstructions
        4.2.1   Angiosarcoma
        4.2.2   Other intravascualar tumors
        4.2.3   Arteritis
        4.2.4   Congenital pulmonary arteries stenoses
        4.2.5   Parasites

5. **Pulmonary Hypertension With Unclear and/or Multifactorial Mechanisms**

    5.1   Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
    5.2   Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
    5.3   Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
    5.4   Other: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure

Table 1.
The World Health Organization classification of pulmonary hypertensive diseases.

pathologic features involving the intimal layer of the pulmonary arteries include eccentric or concentric intimal thickening and formation of plexiform or angiomatoid lesions (**Figure 1B**) [17, 19, 21]. There is excessive cell proliferation and
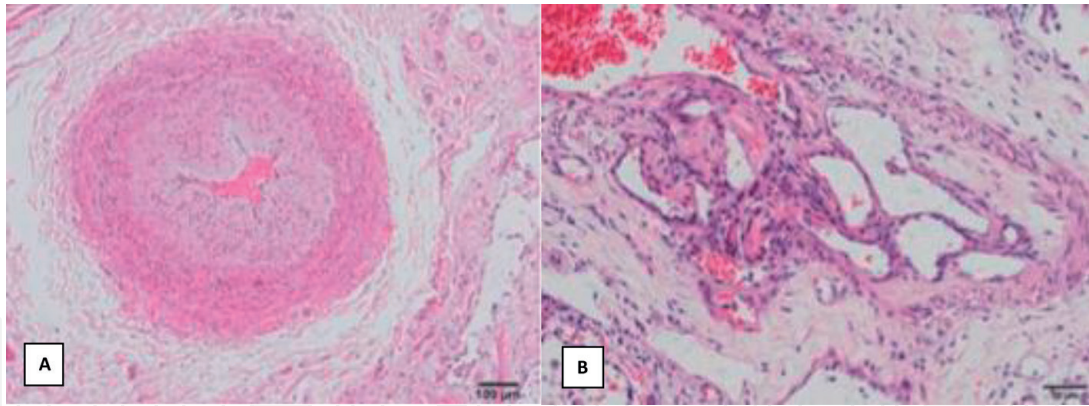
Figure 1.
Histopathology of vascular remodeling in pulmonary arterial hypertension. (A) Medial hypertrophy and cellular intimal thickening. (B) Fibrin thrombi in glomoid plexiform lesion. Reprinted by permission from Springer Nature: Ishibashi-Ueda and Ohta-Ogo [21]. Copyright 2017.

hypertrophy of the smooth muscle layer. Thickening of the adventitial layer, primarily due to collagen deposition, is also noted in these patients [17, 19–21].

Areas of eccentric intimal thickening may represent fibrotic organization of localized thrombi. This concept is supported by observations of myofibroblast infiltration and accumulation of mucopolysaccharides in these localized lesions along the vessel lumen [17]. Eccentric intimal lesions of this nature have been demonstrated in lung explants from patients with severe idiopathic PAH and those with the CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) variant of scleroderma [22]. Vascular resistance is also increased by concentric proliferation of the endothelial cell layer creating the well-described "onion skin" lesion that is thought to involve myofibroblasts and smooth muscle cells (SMC), as well as endothelial cells [23, 24]. Plexiform lesions consist of complex vascular networks with a myofibroblast core which distorts the vessel wall as it expands and extends into the lumen and the connective tissues surrounding the vessel [23]. A rosary of dilated channels may form an angiomatoid, or dilation, lesion and obstruct arterial flow [25]. Although specific mechanisms involved in intimal remodeling are yet to be defined with clarity, it is largely believed that the processes begin with endothelial injury and, in genetically susceptible individuals, result in endothelial proliferation, smooth muscle cell and myofibroblast migration, decreased apoptosis, and deposition of extracellular matrix [17, 18, 26].

Normally, the medial layer of muscularized arteries accounts for about 10–15% of the outer arterial diameter, while in iPAH, it may be 30–60% of the outside diameter [20, 27]. Thickening of the medial layer is largely due to cell hypertrophy; however, hyperplasia of the smooth muscle cells and accumulation of extracellular matrix also contribute to the shift in tunica media dimension [17, 28]. Nonmuscularized arteries may become muscularized with peripheral extension of proximal smooth muscle cell segments and pericyte differentiation into smooth muscle cells [19].

The adventitial layer is comprised of fibroblasts and extracellular matrix (ECM) components. While it accounts for roughly 15% of vessel diameter under normal circumstances, it may represent double that in the patient with PAH [17]. In addition to its role in providing structural support for the vessel, there is evidence that inflammatory cells and extracellular matrix components of the adventitia may serve a role in the regulation of cell activities in other layers [29]. Typical components of the pulmonary vascular ECM include elastin, collagens, fibronectin, tenascin, thrombospondin, growth factors, and matrix metalloproteinases and proteoglycans [30]. Normal vessel structural and functional integrity depend on a balance between ECM

deposition and degradation. Turnover is regulated by matrix metalloproteinases, adamalysins, serine elastase, and endogenous enzyme inhibitors [31]. In PAH excessive deposition of ECM contributes to vascular remodeling and decreased vessel wall compliance. Examination of the pulmonary vascular ECM in iPAH reveals prominent deposition of collagens I and III, enhanced collagen metabolism, alterations in proteoglycans and elastin, upregulation of tenascin C which is involved in intimal hyperplasia, and modification of fibronectin contributing to SMC proliferation and migration [32–35]. Scleroderma is a disease characterized by overproduction of ECM, although there have been no studies detailing ECM composition in SSc-PAH.

Studies comparing the pathologic features of iPAH to those with connective tissue disease- associated PAH (CTD-PAH), and specifically SSc-PAH, have highlighted both similarities and differences between the groups. In a study of lung explants from transplant recipients, Stacher et al. compared the features of vascular remodeling in patients with iPAH and CTD-PAH [36]. The investigators noted more pronounced morphologic changes in the smaller-sized and precapillary arteries in CTD-PAH. Plexiform lesions were noted with similar frequency but had a more scattered distribution in the patients with connective tissue disease. Histopathologic studies comparing these patient groups also reveal more active interstitial inflammation and fibrosis in systemic sclerosis and other connective tissue diseases [19, 36, 37]. In a study comparing tissue from 24 patients with SSc-PAH and 9 iPAH patients, Argula et al. noted fewer plexiform lesions and more interstitial cellularity and fibrosis in the SSc-PAH group, while there was little difference in intimal proliferation or arteriolar smooth muscle hypertrophy [37]. In contrast, Overbeek and colleagues found no plexiform lesions in a group of patients with limited cutaneous systemic sclerosis and PAH, while these lesions were present in 10 of 11 comparative iPAH patients [38]. Further intimal fibrosis and fibrosis of the pulmonary veins and venules were observed with significantly higher frequency in SSc-PAH. While there are similarities in the overall pattern of vascular remodeling in iPAH and SSc-PAH, differences are notable and suggest distinct pathogenetic mechanisms may be in play. Additionally, inflammation and fibrosis may have a greater role in SSc-PAH.

3.3 Pathogenesis

The coordinated mechanisms leading to vascular remodeling in PAH have been the subject of intensive investigation in recent years. It has been 18 years since Gaine proposed a theoretical model of the pathogenesis of PAH [18]. This model continues to serve as a basis for our basic understanding of the pathobiology of the disease and has been a platform for the development of approved therapies for WHO Group 1 PAH in use today. The model suggests a convergence of factors including genetic susceptibility, exposure to risk factors, vascular injury, and endothelial dysfunction leading to progressive remodeling of vasculature and rising pulmonary vascular resistance.

3.3.1 Genetic mutations

Evidence of a genetic basis for PAH was first reported in 2000 with the discovery of the bone morphogenetic protein receptor II (*BMPR2*) gene mutation in patients with heritable PAH [39, 40]. Mutation of this gene has been identified in at least 70–80% of cases of heritable PAH and 15–25% of sporadic iPAH [41]. *BMPR2* protein concentrations are decreased by 75% in lung tissue and endothelial cells from subjects with PAH [24]. Other gene mutations related to *BMPR2* and its downstream signaling pathway are now known including mutations in *ALK1*, *ENG*, and genes encoding components of the SMAD downstream signaling pathway [19, 41].

Mutations unrelated to the *BMPR2* signaling pathway have also been identified in a very small percentage of PAH patients and include *KCNK3*, which encodes a pH-sensitive potassium channel, and *CAV1*, which encodes a membrane protein, caveolin 1, which is essential for the formation of lipid rafts or caveolae [41]. While no link between the development of SSc-PAH and mutation of *BMPR2* has been established, other unique mutations have been identified in the systemic sclerosis population with PAH. For instance, a rare functional polymorphism in the *TLR2* gene, which promotes induction of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), is associated with the development of PAH in systemic sclerosis [42]. The development of diffuse cutaneous scleroderma, fibrosing alveolitis, and PAH has been linked to polymorphisms in *TNFAIP3*, which regulates the NF-kB inflammatory pathway [43]. Genetic variation in the promoter region of *UPAR*, the urokinase-type plasminogen activator receptor, has been associated with digital ulceration and PAH in scleroderma patients [44]. Clearly, there is evidence for genetic susceptibility to develop PAH in systemic sclerosis, although genetic mechanisms appear to differ from those associated with iPAH.

BMPR2 is a member of the transforming growth factor-beta (TGF-beta) superfamily of genes and normally functions to limit proliferation of smooth muscle cells and enhance endothelial cell survival by inhibiting apoptosis [45]. In contrast, TGF-beta is thought to promote SMC proliferation, matrix deposition, and alterations in endothelial cell growth [46, 47]. TGF-beta is known for fibrotic effects in several disease states, among which are systemic sclerosis [48]. Evidence from investigations of heritable PAH and preclinical models of SSc suggests that endothelial injury and consequent pulmonary vasculopathy may arise from an imbalance in TGF-beta/BMP signaling pathways [49–53]. For example, reduced BMPR2 receptor expression in heritable PAH correlates with increased activity of TGF-beta and its downstream signaling pathways. Reduction in BMPR2 levels in patients with systemic sclerosis also correlates with enhanced activity of TGF-beta and downstream SMAD2 and MAPK signaling pathways. Based on these observations, a theory has been advanced that heightened TGF-beta activity in systemic sclerosis might suppress BMP signaling pathways that serve to protect the endothelium [19].

In addition to the disruption created by structural remodeling in the pulmonary vessels, endothelial injury and dysfunction may lead to imbalances in production of mediators that affect vascular tone and platelet aggregation and further regulate cell proliferation. Immunochemical studies have demonstrated reduced levels of nitric oxide synthase and prostacyclin synthase in the pulmonary vascular endothelium [54, 55]. These enzymes are critical to the endogenous production of nitric oxide and prostacyclin, both of which have vasodilatory and antiproliferative effects. The production of thromboxane is increased leading to enhanced vasoconstriction and in situ thrombosis [56]. Vasoconstriction and cell proliferation are promoted by increased production of endothelin-1 by pulmonary endothelium [57]. Endothelin-1, survivin, and vascular endothelial growth factor (VEGF) have been found in plexiform lesions and may augment endothelial and smooth muscle cell proliferation while limiting cell apoptosis [57–59]. Levels of nitric oxide synthase, prostacyclin synthase, and tumor suppressors, such as caveolin-1, are reduced in the plexiform lesions [54, 55, 60]. The imbalances in production of vasoactive mediators have largely driven the development of treatments designed to counteract these imbalances and improve pulmonary vascular resistance.

3.3.2 Serotonin

The role of serotonin in the pathogenesis of PAH has been a topic of interest and investigation for several years. Serotonin is thought to promote vasoconstriction

and remodeling of pulmonary vessels by stimulating proliferation of SMCs and fibroblasts [61–63]. The induction of SMC proliferation may be affected by serotonin transporter activation of the platelet-derived growth factor-beta (PDGF-B) receptor [64]. In SSc patients, serotonin has been shown to induce ECM production by interstitial fibroblasts in a TGF-beta-dependent manner [65]. When a group of SSc-PAH patients were treated with ketanserin, a selective antagonist of S2 serotonergic receptors, a majority experienced reductions in pulmonary vascular resistance [66]. The serotonin pathway may hold promise for the development of new treatment approaches to SSc-PAH in the future.

3.3.3 Epigenetics

Epigenetic mechanisms affecting changes in cellular function in PAH have been a focus of more recent research. Epigenetic processes alter gene expression without effecting changes in DNA sequence. Epigenetic mechanisms may involve DNA methylation, modification of histone proteins, or RNA interference via microRNAs [67]. Extensive methylation of cytosine residues in the CpG dinucleotide sequences of the BMPR2 gene promoter region suppresses BMPR2 gene expression in SSc-PAH [68]. Elevated histone deacetylase levels have been noted in the lungs of PAH patients, and the inhibition of the deacetylase reduces proliferation of vascular fibroblasts and PDGF-stimulated SMC growth [69]. A number of microRNAs have been identified that influence cellular functions in hereditary and iPAH [19]. For instance, miR424 and miR503 normally suppress expression of fibroblast growth factor-2 (FGF-2); however, they are decreased in iPAH leading to an upregulation of FGF-2 expression [70]. These are just some representative examples of the growing knowledge of the role of epigenetic factors in PAH.

3.3.4 Cytokines and growth factors

The discovery of gene mutations involving the TGF-beta receptor family focused attention on the role of cytokines and growth factors in vascular remodeling of PAH. Observations of inflammatory cell infiltrates associated with vascular lesions and the presence of elevated cytokine levels in PAH have further supported a role for inflammation in this disease process. Lymphocytes, macrophages, dendritic cells, and mast cells have all been demonstrated on histopathologic examination of immune cell infiltrates in vascular lesions [17, 71, 72]. Elevated levels of several cytokines have been reported in iPAH including IL-1beta, IL-2, IL-4, IL-6, IL-8, IL-10, and IL-12p70, TNF-alpha, and chemokines CXC3L1, CCL2, and CCL5 [73–77]. The exact role of inflammation in the pathogenesis of PAH is unclear. Inflammation may reflect a consequence of hypoxia associated with PAH, as acute and chronic inflammation are known to occur in the setting of hypoxia. Alternatively, inflammatory mechanisms may be the drivers behind vascular cell injury and dysfunction. Macrophages are known to concentrate within and around advanced vascular lesions in iPAH and are thought to play a significant role in the remodeling process [78]. IL-6 produced by activated adventitial fibroblasts has been shown to induce a macrophage phenotype with proinflammatory and profibrotic characteristics [79]. Speculation about the role of immune dysregulation is supported by an observed deficiency of regulatory T cells in the lungs from iPAH patients [80]. In contrast to a deficiency of T-cell subpopulations, circulating autoantibodies and ectopic expansion of pulmonary lymphoid tissue in PAH patients suggest there is excessive B-cell activation [81]. PDGF has been implicated in the pathogenesis of PAH. Although originally discovered as a product of platelets, isoforms of this growth factor are also known to be secreted by macrophages,

endothelial cells, SMCs, and fibroblasts [82]. PDGF is a potent mitogen and chemoattractant for endothelial cells, smooth muscle cells, and fibroblasts. PDGF receptor-beta expression is more intense in small and postcapillary vessels in SSc-PAH than iPAH [83]. The PDGF receptor antagonist, imatinib, was investigated for treatment of PAH, and during the initial study phase, improvements in hemodynamics and exercise capacity were noted. However, the long-term extension study was terminated early due to severe and unexpected adverse events including intracranial hemorrhage, death, and other side effects [84].

3.3.5 Autoantibodies

Autoantibodies against endothelial cell antigens may promote pulmonary vascular remodeling, especially in SSc-PAH. The expression of anti-endothelial cell antibodies and target antigens has been confirmed in iPAH and SSc-PAH, although the role of these antibodies in the pathogenesis of PAH remains undetermined [85, 86]. Anti-endothelial cell antibody levels in serum of connective tissue disease patients with or without PAH were evaluated by Li and colleagues compared with control subjects [87]. While endothelial cell antibodies were detected at similar levels in connective tissue disease patients irrespective of whether PAH was present, one specific endothelial antibody subtype (anti-22kD) was only found in the patients with PAH. A second subtype (anti-75kD) was noted at significantly higher levels in patients with PAH. The investigators concluded that these subtypes of endothelial antibody might indicate a more specific risk for PAH in connective tissue diseases. Tamby also demonstrated the presence of serum immunoglobulin anti-fibroblast antibodies in patients with iPAH and SSc-PAH with distinct reactivity against target antigens [88]. While these observations imply immunosuppressive therapy should be a treatment option for SSc-PAH and possibly iPAH, there is no evidence to date that this approach is beneficial. A prospective, multicenter trial to evaluate the effect of rituximab on disease progression in subjects with SSc-PAH receiving concurrent standard medical therapy is currently ongoing.

3.3.6 Cancer similarities

Certain features of pulmonary vascular cell dysfunction in patients with PAH have led to the suggestion that vascular remodeling may represent a cancer-like process involving the cellular constituents of the pulmonary arteries. Investigators have reported evidence of proliferative, apoptosis-resistant, cancer-like behavior in endothelial cells, SMCs, and fibroblasts from subjects with PAH [89–91]. Specific observations leading to this concept include monoclonal expansion of endothelial cells from patients with iPAH when compared to patients with PAH associated with congenital heart disease, instability of short DNA microsatellite sequences within plexiform lesions, somatic chromosome abnormalities in the lungs of patients with PAH, persistent hyperproliferative and apoptosis-resistant state when endothelial cells are removed from their in vivo environment, and altered energy metabolism [92]. Enhanced proliferation of pulmonary vascular cells may be a consequence of excessive growth factor release from the ECM, alterations in growth factor production or receptor expression, and/or alterations in intracellular mitogenic signals [93–95]. Abnormal increases in key apoptotic factors including Bcl-xL, Bcl-2, and survivin have been reported in pulmonary vascular cells from PAH patients [58, 96, 97]. Although there is evidence of enhanced cell proliferation and resistance to apoptosis, vascular remodeling in PAH is distinguished from cancer in that there is no evidence that pulmonary vascular cells have the ability to reproduce in a clonal fashion without control.

RISK FACTORS

Older age of onset
Longstanding duration of disease > 5 years
Anti-centromere antibody
Anti-nuclear antibody nucleolar pattern
Anti-U1 RNP antibody
Absence of anti-Scl 70 antibody
DLCO < 60% predicted
FVC %predicted/DLCO %predicted > 1.6
Elevated N-terminal pro BNP

PAH GENETIC MUTATIONS

BMPR2 - bone morphogenetic protein receptor 2
ALK1 - activin receptor like kinase type 1
CAV1 - caveolin 1
ENG - endoglin
KKCNK3 - potassium channel super family K member 3
SMAD4 - acronym from fusion of *Caenorhabditis elegans*
SMAD9   *Sma* genes and the *Drosophila Mad*

SSC-PAH GENETIC MUTATIONS

TNFAIP3 - tumor necrosis factor alpha induced protein 3
TLR2 - Toll like receptor 2
uPAR - urokinase type plasminogen activator receptor
CAV1 - caveolin 1

ENDOTHELIAL DYSFUNCTION

Excessive endothelin-1 production
Deficiency of nitric oxide production
Deficiency of prostacyclin production
Excessive thromboxane production

SMOOTH MUSCLE CELL DYSFUNCTION

Impaired potassium channel ($K_{V1.5}$) function

OTHER PATHOGENETIC MECHANISMS

Inflammation, Cytokines and Growth Factors
        Inflammatory cell infiltrates in vascular lesions
        Elevated Interleukins 1 beta, 2, 4, 6, 8 10 and 12p70
        Elevated TNF- alpha, CXC3L1, CCL2, CCL 5
        PDGF
Epigenetic mechanisms
        DNA methylation
        Histone modification
        Micro RNAs
Autoantibodies
        Anti-endothelial cell antibodies
        Anti-fibroblast antibodies
Cancer-like cell characteristics
        Monoclonal expansion of endothelial cells in iPAH
        Unstable short DNA microsatellite sequences
        Somatic chromosome abnormalities
        Hyperproliferation/apoptosis resistance ex vivo
        Metabolic shift from glucose oxidation to glycolysis
Serotonin
        SMC and fibroblast proliferation

Table 2.
Summary of factors involved in pathogenesis of pulmonary arterial hypertension.

Endothelial cells, SMCs, and adventitial fibroblasts from patients with PAH are not only more proliferative and apoptosis-resistant but rely more on glycolysis for energy production [89, 98–100]. Mitochondria demonstrate a metabolic shift from glucose oxidation to uncoupled aerobic glycolysis similar to that described in cancer cells [101]. The glycolytic pathway increases NADPH production which in turn enhances antioxidant defenses while producing ribonucleotides for DNA synthesis. This shift in metabolism serves as a mechanism to support rapid cell proliferation.

3.3.7 Ion channels

Increased cytosolic calcium levels in SMCs of patients with PAH promote not only contraction but also hyperproliferation and apoptosis resistance [41]. Elevated cytosolic Ca^{+2} levels in PAH have been linked to downregulation of voltage-gated potassium channels, such as Kv1.5 [102]. Downregulation or dysfunction of voltage-gated potassium channels allows membrane depolarization and influx of calcium. Cytosolic calcium levels are further enhanced by impaired mitochondrial Ca^{+2} uptake. The resulting increases in intracellular calcium drive cells into the cell cycle, thus enhancing proliferation [103].

Research has certainly revealed that the pathogenesis of PAH is a very complex process, and our understanding of the mechanisms involved is far from complete. Knowledge of imbalances in endogenously produced vasomotor regulators has allowed the development of therapies that have improved quality of life and survival. However, it is apparent that PAH is not merely a disease of vasomotor dysfunction, but one that involves complex genetic mechanisms, cytokines, inflammation, and metabolic derangements (**Table 2**). While the progressive arteriopathy of iPAH and SSc-PAH shares many features, research has disclosed distinct differences in the pathogenesis of the two entities that may lead to more effective treatments for each in the future.

4. Screening and diagnosis

The majority of patients with SSc-PAH are diagnosed with PAH when the pulmonary arteriopathy is well established, while a small percentage is diagnosed at an early, asymptomatic stage [2]. Even when symptoms are present, the symptoms of PAH are nonspecific and may be attributed to other causes. Mortality is higher in patients with SSc-PAH than iPAH or PAH associated with other disease processes, such as congenital heart disease [104, 105]. An estimated 1-year survival of 84% for patients with iPAH contrasts with a 55% rate of survival at 1 year in SSc-PAH [106]. Patients with SSc-PAH have a higher mortality rate than those with non-scleroderma connective tissue disease-associated PAH [107]. Further, mortality is higher in patients with SSc- PAH than in systemic sclerosis patients without lung involvement or with lung involvement other than PAH [108]. In recent years, PAH and lung fibrosis have replaced scleroderma renal crisis as major causes of death in systemic sclerosis [109]. Pulmonary arterial hypertension accounts for about 30% of deaths in systemic sclerosis [109, 110]. Three-year survival rates of 70, 50, and 20% have been reported in treated SSc-PAH patients with WHO FC 1, FC 2, and FC 3 symptoms, respectively [107]. Earlier discovery of PAH in the systemic sclerosis patient may have an impact on these discouraging survival statistics. In a study by Humbert et al., the 1-, 3-, 5-, and 8-year survival rates in a cohort of SSc-PAH patients managed according to routine practice were 75%, 31%, 25%, and 17%, respectively, compared to survival rates of 100%, 81%, 73%, and 64%, respectively, in a group managed in a proactive detection program [111]. These data underscore the importance of consistently screening patients with systemic sclerosis for PAH.

Although experts agree on the importance of screening for SSc-PAH in order to detect vascular involvement at an earlier stage, there is less consensus on the most effective algorithm to confirm the presence of PAH. Several risk factors have been identified that signal the potential for the development of SSc-PAH (**Table 2**). Patients who are older and have long-standing SSc are at greater risk of developing PAH [1, 112]. The limited cutaneous form of SSc has historically been considered a risk for PAH; however the presence of diffuse cutaneous SSc has also been reported with similar prevalence [13, 113]. Anticentromere antibodies (ACA), anti-U1-ribo-nucleoprotein antibodies (RNP), and a nucleolar pattern of antinuclear antibody (nucleolar-ANA) are associated with an increased risk of SSc-PAH [114–117]. The absence of anti-Scl 70 has been associated with the development of PAH, while the presence of these autoantibodies is associated with the development of interstitial lung disease [14]. Symptoms that relate to PAH are nonspecific and typically relate to progressive right ventricular (RV) dysfunction. Common symptoms include shortness of breath, fatigue, weakness, chest pain, and syncope [118]. Physical findings suggesting PAH include an accentuated pulmonary component of the second heart sound, an RV third heart sound, a pansystolic murmur of tricuspid regurgitation, and a diastolic murmur of pulmonary regurgitation [16]. Jugular venous distension, hepatomegaly, ascites, edema, and cyanosis are findings in advanced disease. Certain findings on electrocardiogram, such as right axis deviation, RV hypertrophy, RV strain, and right bundle branch block, may point to a diagnosis of PAH. Electrocardiogram abnormalities are more likely to be found in severe PAH. A normal electrocardiogram does not exclude PAH. Plain chest radiography can also be helpful in diagnosing PAH if the X-ray demonstrates central pulmonary artery enlargement, pruning of the peripheral vessels, or enlargement of right heart chambers. A chest radiograph may be helpful in distinguishing other causes of PH if interstitial lung disease or pulmonary venous congestion is present. Similarly, pulmonary function tests can be very helpful in detecting airway disease or restrictive lung disease that could lead to WHO Group 3 PH. Pulmonary function testing in patients with SSc-PAH may reveal severe gas diffusion impairment. Mukerjee et al. noted that a DLCO <50% was 90% specific but only 39% sensitive in excluding a diagnosis of SSc-PAH [6]. A DLCO/VA <70% or FVC percent/DLCO percent >1.6 has been considered predictors for the development of SSc-PAH [119]. Pulmonary function testing and CXR or high-resolution CT scanning are helpful in distinguishing PAH from WHO Group 3 PH associated with ILD. Echocardiography has been considered a noninvasive alternative to RHC in determining the presence of SSc-PAH, although certain limitations are recognized. Factors affecting image quality have been noted to limit the ability to estimate pulmonary artery systolic pressure accurately in patients who were later confirmed to have PAH by RHC [120, 121]. Right heart catheterization is the gold standard for diagnosis of PAH and is required to confirm PAH. Right heart catheterization with saline volume challenge can be helpful in distinguishing WHO Group 2 PH due to abnormal left ventricular function in systemic sclerosis. Several algorithms have been proposed that rely on various combinations of symptoms, physical exam findings, biomarkers, PFTs, and findings on echocardiography to determine which patients warrant definitive study with right heart catheterization [10, 16, 120, 122, 123].

A screening algorithm including assessment of symptoms, Doppler echocardiography, and right heart catheterization was studied in a French prospective multicenter study by the Itinerair-Scleroderma Investigators Group that enrolled 599 patients with scleroderma [120]. The study was limited to patients without significant pulmonary function abnormalities. Patients with a velocity of tricuspid regurgitation (VTR) > 3 m/s regardless of symptoms and patients with a VTR 2.5–3 m/s with dyspnea were considered at risk for PAH and underwent right heart

catheterization (RHC). Right heart catheterization confirmed mild PAH in 18 of 33 patients suspected of having PAH based on symptoms and/or Doppler echocardiography. Twelve of the 33 patients did not have PAH, and 3 patients were confirmed to have left heart dysfunction. This algorithm allowed early detection of SSc-PAH; however a substantial number of patients undergoing RHC did not have PAH.

An alternative screening algorithm was suggested by the Australian Scleroderma Interest Group (ASIG) that employs N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and PFT data to predict the presence of PAH [122]. Data to develop this algorithm were collected from the Australian Scleroderma Cohort Study, a multicenter study of risk and prognostic factors for cardiopulmonary outcomes in systemic sclerosis. NT-proBNP levels from SSc patients with confirmed PAH were compared with a group at risk for PAH (systolic PAP $_{TTE}$ > 36 mmHg, hemoglobin corrected DLCO <50% predicted, and/or FVC/DLCO percent predicted ≥1.6), a group with ILD, and a group of controls with no evidence of cardiopulmonary complications. NT-proBNP levels were positively correlated with systolic PAP by transthoracic echocardiogram, mean PAP by RHC, pulmonary vascular resistance, and mean right atrial pressure. The authors proposed a model in which patients screened positive when NT-proBNP was ≥209.8 pg./ml and/or DLCO was <70.3% with FVC/DLCO ≥1.82. They noted a sensitivity of 100% with specificity 77.8% for SSc-PAH but acknowledged a need for prospective validation of the model.

A third screening algorithm was employed in the DETECT study, a multinational, cross-sectional investigation of factors in SSc patients that could serve to detect PAH at an earlier stage [10]. A broad range of variables (112 in total) pertaining to standard demographic and clinical characteristics, serum tests, electrocardiography, and echocardiography were examined in patients with a diagnosis of systemic sclerosis for more than 3 years, a predicted DLCO <60%, and a predicted FVC ≥ 40%. About 466 patients underwent RHC and 87 (19%) were confirmed to have WHO Group 1 PAH. Univariate and multivariate analyses were used to select the variables with best discriminatory power for predicting PAH. These variables

Resting echocardiography is recommended as a screening test in asymptomatic patients with systemic sclerosis.

A combined approach (including biomarkers, PFTs and echocardiography) should be considered to predict PH in systemic sclerosis.

Initial screening using the stepwise DETECT algorithm may be considered in adult systemic sclerosis patients with > 3 years disease duration and a DLCO < 60% predicted.

Annual screening with echocardiography, PFTs and biomarkers may be considered in patients with systemic sclerosis.

Systemic sclerosis patients with a mean PAP ranging from 21 to 24 mmHg should be closely monitored, because of a higher risk of PAH.

Exercise echocardiography is not recommended to predict PH in high risk populations.

Adapted from: Galie N, Humbert M, Vachiery J-L et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016; 37(1): 67-119

Table 3.
2015 ESC/ERS recommendations for pulmonary arterial hypertension screening in systemic sclerosis.

were incorporated in a two-step algorithm. Six non-echocardiographic variables were used in Step 1 to recommend echocardiography (FVC % predicted/DLCO % predicted, current/past telangiectasias, serum anti-centromere antibody, NT-pro BNP, serum urate, ECG with right axis deviation), and a decision to recommend RHC in Step 2 was based on right atrial area and velocity of tricuspid regurgitation (VTR). Complete Step 1 data were available for 356 patients. About 52 patients did not meet Step 1 criteria for referral to echocardiography. Of these, two patients (4%) were determined to be false PAH negative. Complete Step 2 data were available for 267 patients. About 69 patients did not meet Step 2 criteria for referral to RHC. Of these, one patient was determined to be false PAH negative. Of the 198 patients referable for RHC, 69 were true PAH positive. The overall sensitivity of this algorithm was 96% with a specificity of 48%, a 62% rate of referral for RHC, and a 4% false PAH negative rate.

Summary recommendations for PAH screening in systemic sclerosis from the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension are summarized in **Table 3**. The guidelines support a combined approach incorporating biomarkers, PFTs, and echocardiography for baseline screening in patients with systemic sclerosis. Annual screening with these indicators should be considered for all patients with systemic sclerosis. Systemic sclerosis patients with a mean PAP from 21 to 24 mmHg should continue to be monitored closely for progression. Exercise echocardiography has been used for early detection of PAH in systemic sclerosis [124, 125]; however the ESC/ERS do not recommend this approach. A summary diagnostic algorithm is provided in **Figure 3**.

5. Treatment

As understanding of the pathogenesis of PAH has evolved over the past two decades, a number of medical therapies have been developed that improve exercise capacity, hemodynamics, quality of life, and survival. Treating PAH has become a complex exercise now that there are multiple agents that can be employed alone or in various combinations. It is important to remember that PAH is a progressive disease process, and any treatment plan requires ongoing monitoring and adjustment if treatment goals are not being met. Although far fewer patients with PAH require lung transplantation in the era of targeted medical therapy, there are those who progress even on maximal medical therapy leaving transplantation as their last viable option.

The treatment of pulmonary arterial hypertension involves not only selection of appropriate agents for inclusion in a treatment plan but an ongoing process of assessment of patient characteristics that should determine the selection of medications. The concept of using a risk assessment tool to aid selection of appropriate agents for treatment was introduced in 2006 based on studies showing correlation between clinical characteristics of disease and survival [104]. For instance, 6 MW, FC, and certain hemodynamic measures were shown to directly correlate with prognosis. These findings were used to develop a tool to evaluate a patient's risk of early death. Patients could be categorized as low or high risk of rapid progression to death, and treatment agents could be selected based on the level of risk in order to modify the course of disease and extend survival. This concept further evolved with the development of a risk calculator using data from the American REVEAL Registry [126, 127]. The REVEAL Registry was a 3-year longitudinal registry of 2967 WHO Group 1 PAH patients with data collected pertaining to the clinical characteristics, evaluation, treatment, and outcomes. Data from this registry was used to develop a user-friendly algorithm to determine a patient's risk of demise in the short term. Most recently,

the ESC/ERS further refined the characteristics used to assess risk of progression in PAH and presented criteria that classified patients as low, moderate, or high risk of progression to near-term death (**Figure 2**). Using the ESC/ERS risk assessment algorithm, patients categorized as low risk have an estimated 1-year mortality <5%. Those within the intermediate-risk group have an estimated 1-year mortality of 5–10%, and those in the high-risk group have an estimated 1-year mortality >10%.

5.1 Risk assessment

Following the accurate diagnosis of PAH (**Figure 3**), a careful assessment of severity of disease should be completed before deciding on specific treatment options. This assessment is critical at the outset of treatment, but it remains an important part of ongoing patient management. Given that PAH can progress rapidly, even on therapy, it is necessary to complete a reevaluation of severity of illness and risk stratification periodically several times a year. If patients show signs of deterioration in their clinical parameters, treatment plan adjustments are in order.

5.1.1 Functional capacity

Assessment of the severity of illness begins with an understanding of symptoms and functional capacity. Patients who present symptoms, such as shortness of breath, fatigue, or edema, that have developed and worsened over a short period of time are at higher risk of early death. Further, those with overt signs of right heart failure, such as edema, ascites, cyanosis, or syncope, are in a high-risk group requiring urgent attention. The World Health Organization functional class (FC) is a valuable indicator of severity of illness and has been shown to correlate with survival [128, 129]. Patients are classified in four groups (FC 1–4) based on degree

Determinant of prognosis	Low Risk <5%	Intermediate Risk 5-10%	High Risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional [a]	Repeated [b]
WHO functional class	I, II	III	IV
6 MW distance	> 440 m	165-440 m	< 165 m
Cardiopulmonary exercise testing	Peak VO_2 > 15 ml/min/kg (> 65% predicted) VE/VCO_2 slope <36	Peak VO_2 11-15 ml/min/kg (35-65% pred) VE/VCO_2 slope 36-44.9	Peak VO_2 <11 ml/min/kg (< 35 % predicted) VE/VCO_2 slope $\geq$45
NT-proBNP level	BNP < 50 ng/l NT-proBNP <300 ng/l	BNP 50-300 ng/l NT-proBNP 300-1400 ng/l	BNP > 300 ng/l NT-proBNP >1400 ng/l
Imaging by echocardiogram or cardiac MRI	RA area <18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mmHg CI > 2.5 l/min/m^2 SvO_2 >65%	RAP 8-14 mmHg CI 2.0-2.4 l/min/m^2 SvO_2 60-65%	RAP >14 mmHg CI < 2.0 l/min/m^2 SvO2 < 60%

ESC/ERS= European Society of Cardiology/European Respiratory Society; WHO= World Health Organization; 6 MW= 6 minute walk; VO_2= oxygen consumption; VE/VCO_2 = ventilatory equivalents for carbon dioxide; NT-proBNP= N-terminal pro brain natriuretic peptide; BNP= brain natriuretic peptide; MRI= magnetic resonance imaging; RA= right atrium; RAP= right atrial pressure; CI= cardiac index; SvO_2= mixed venous oxygen saturation
[a] occasional syncope with brisk or heavy exercise or occasionally orthostatic syncope
[b] repeated episodes of syncope regardless of activity level

Adapted from Galie N, Humbert M, Vachiery J-L et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016; 37(1): 67-119.

Figure 2.
ESC/ERS risk assessment in pulmonary arterial hypertension (estimated risk for 1-year mortality).
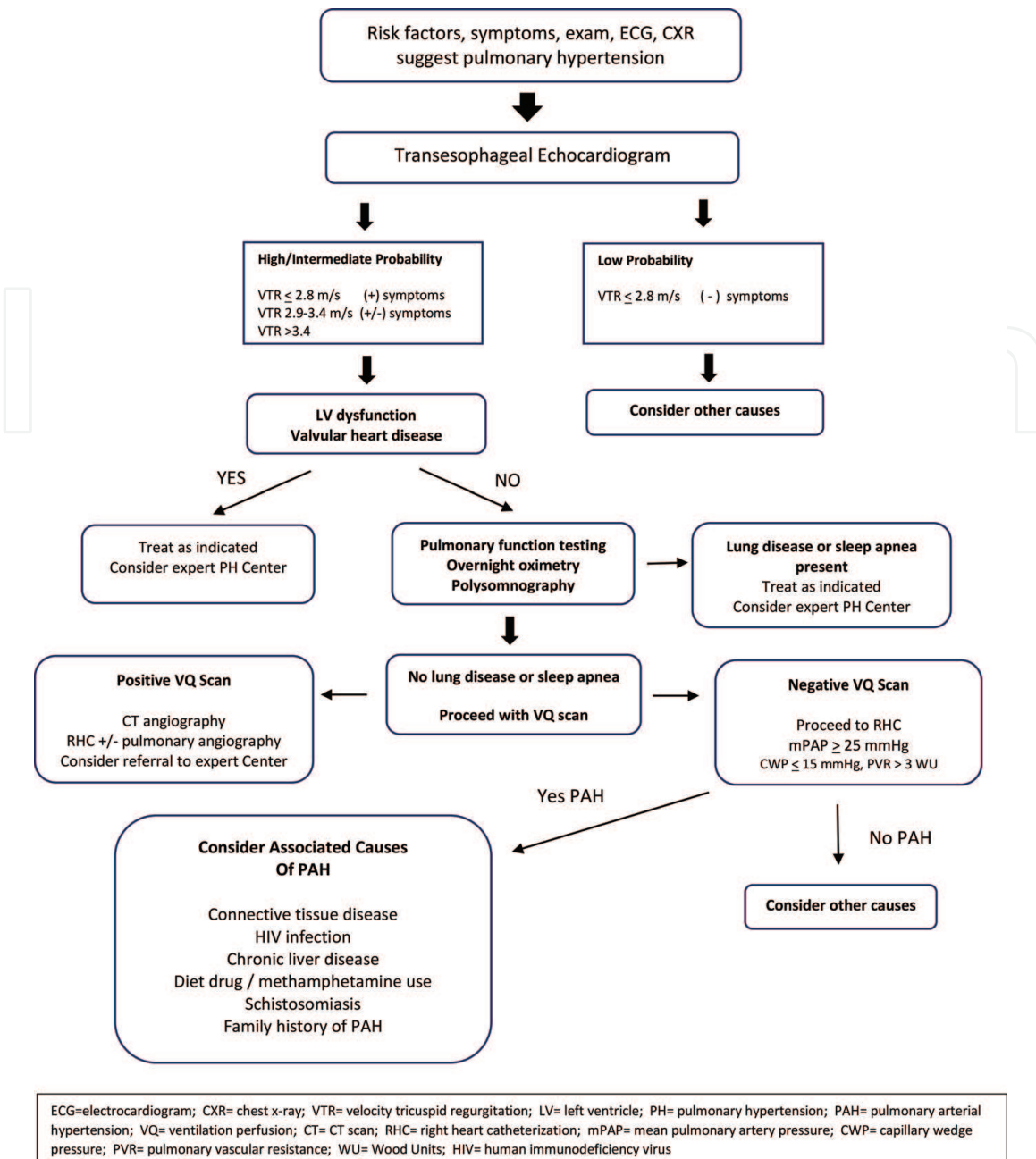
Figure 3.
Algorithm for the diagnosis of pulmonary arterial hypertension.

of functional impairment (**Table 4**). Patients who have FC 3 or 4 functional impairment are considered high risk; a goal of any treatment plan is to achieve FC 1 or 2 functional capacity [16]. Although functional class has been shown to correlate well with survival prognosis, it is a subjective measure of symptoms which is subject to interpretation by the healthcare provider [130]. Another important indicator of illness severity is the 6 min walk (6 MW) test [131]. The 6 MW test is a submaximal exercise test that is easy to perform in the outpatient or inpatient setting. The 6 MW test has been shown to correlate with survival and has served as a primary endpoint in the majority of clinical investigations leading to today's therapeutic options [132, 133]. Six-min walk distance has been shown to correlate with pulmonary pressures and represent a direct predictor of mortality in SSc-PAH [131]. The ESC/ERS Guidelines suggest that patients who can ambulate >440 m have better survival prognosis and are an appropriate goal to target when making treatment decisions [16]. The 6 MW test does have limitations with its reliability being challenged by factors such as age, gender, weight, comorbid conditions, and the individual's

Class	Funtional capacity
I	Patient with pulmonary hypertension but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or syncope.
II	Patient with pulmonary hypertension resulting in slight limitation of physical activity. Patient is comfortable at rest. Ordinary physical activity results in fatigue or dyspnea, chest pain or syncope.
III	Patient with pulmonary hypertension resulting in marked limitation of physical activity. Patient is comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain or syncope.
IV	Patient with pulmonary hypertension resulting in inability to carry on any physical activity without symptoms. Patient with signs of right heart failure. Dyspnea and/or fatigue may occur even at rest.

Table 4.
The World Health Organization (WHO) functional class.

motivation. Cardiopulmonary exercise testing (CPET) is often employed to evaluate exercise capacity in this population. CPET can provide important information about general exercise capacity, as well as more detailed information about gas exchange, ventilation, and cardiac function during exercise. Patients with PAH will demonstrate exercise limitation characterized by low end-tidal partial pressure of carbon dioxide (pCO_2), high ventilation equivalents for carbon dioxide (VE/VCO_2), low oxygen pulse (VO_2/HR), and low peak oxygen uptake (peak VO_2) [134, 135]. These parameters have been included in the ESC/ERS risk assessment algorithm. Peak VO_2 > 15 ml/min/kg or greater than 65% predicted and a VE/VCO_2 slope < 36 portend a more favorable prognosis and represent goals of targeted therapy [136].

5.1.2 Echocardiography and hemodynamics

Echocardiography is not only a valuable screening tool for detecting the presence of pulmonary hypertension, but it plays a role in assessing severity of illness and response to treatment. The measurement of pulmonary artery pressure (PAP) by echocardiography is not a reliable prognostic indicator, nor does it accurately reflect progression or improvement in pulmonary vascular resistance [121, 128]. The absence of tricuspid regurgitation and/or poor image quality limits the ability to determine systolic PAP by echocardiography in 20–39% of patients [121]. The value of echocardiography in assessing severity of illness lies in measurement of chamber sizes, assessment of right ventricular (RV) function, and the presence or absence of pericardial effusion which is considered a reflection of RV failure. A complete echocardiographic assessment in the PAH patient would include description of right atrial (RA) and RV dimensions, measurement of tricuspid regurgitant velocity, left ventricular (LV) eccentricity index, and RV contractility [137, 138]. RV contractility can be determined from RV longitudinal systolic strain/strain rate, RV fractional area change, Tei index, or tricuspid annular plane systolic excursion (TAPSE) [137, 139]. Echocardiography with exercise may provide useful information about RV function. An increase in estimated PAP by >30 mmHg during exercise indicates better RV reserve associated with better long-term outcome and is considered an

independent marker of prognosis in PAH [140]. A right atrial area < 18 cm^3 with no evident pericardial effusion are indicators for favorable prognosis or treatment outcome [16]. Additional information about prognosis or treatment effect can be gained from right heart catheterization and hemodynamic measurements. As in the case of echocardiography, PA pressure is of little value. Cardiac index, RA pressure, and mixed venous oxygen saturation have been shown to have the greatest prognostic significance [128, 129]. Goals of therapy that are associated with favorable prognosis include CI ≥ 2.5 L/min/m^2, RA pressure < 8 mmHg, and SvO2 > 65% [16].

5.1.3 Biomarkers

There are a number of biomarkers of vascular dysfunction, inflammation, cardiac function, and tissue hypoxia that have been investigated as a specific marker for pulmonary vascular remodeling [141–144]. Of these, brain natriuretic peptide (BNP) and NT-proBNP are used in clinical practice and research [145–147]. These biomarkers reflect ventricular wall stress, as seen in volume overload and ventricular contractile dysfunction, and serve as surrogate indicators of myocardial dysfunction [122, 148]. Either marker is considered an acceptable choice for assessing severity of illness. BNP has slightly better correlation with pulmonary vascular hemodynamics and is less likely to be affected by renal function, while NT-proBNP appears to be a stronger predictor of prognosis [149]. Compared to BNP, NT-proBNP is more sensitive to early increases in systolic PAP as measured by echocardiography [150]. BNP levels below 50 ng/L or NT-proBNP levels below 300 ng/L are associated with a more favorable prognosis [16].

5.1.4 Monitoring

Implementation of the prognostic indicators outlined in **Figure 2** is variable among centers providing expert care for patients with PAH. After a treatment plan is established, patients will typically be reevaluated every 3–4 months depending on stability of their disease. During early phases of treatment or times when therapy targets indicate a need to alter the treatment plan, patients are often seen more frequently. It is not practical to perform all of the measures listed in **Figure 3** at every visit. In the outpatient setting, clinicians tend to rely on assessment of symptoms, physical exam findings, FC, 6 MW distance, and BNP or NT-proBNP levels to determine severity of disease at any given point in time. This information may be supplemented periodically with echocardiography or cardiopulmonary exercise testing. Right heart catheterization is performed initially at diagnosis and in some centers yearly thereafter or in the event condition deteriorates in those patients with high-risk features. In other centers repeat hemodynamic measurements are obtained less frequently and typically if there is an indication the patient's condition is progressing.

Once the diagnosis is established and severity of illness is defined, decisions about disease-targeted therapy can be made. Available targeted therapies exert clinical benefit via the nitric oxide, endothelin, or prostacyclin pathways which were discussed earlier in this chapter. There are several options that affect each of these pathways. The choice of therapy for any given patient will depend on severity of illness and may be further influenced by side effects, safety issues, and in some cases economic and social support factors.

5.2 Phosphodiesterase 5 inhibitors

The phosphodiesterase 5 (PDE-5) inhibitors effect smooth muscle relaxation and inhibit proliferation and inflammatory mechanisms by augmenting cyclic

guanosine monophosphate (cGMP) activity in pulmonary vascular smooth muscle. As noted earlier in this chapter, patients with PAH have been shown to have deficient nitric oxide synthase activity in the pulmonary vasculature leading to a deficiency of nitric oxide production [54]. Nitric oxide is produced by the pulmonary endothelium and catalyzes the production of cGMP in nearby smooth muscle cells. PDE-5 degrades cGMP, thus limiting its effect on smooth muscle cells. The phosphodiesterase 5 inhibitors sildenafil and tadalafil block the degradation of cGMP, thus permitting beneficial cGMP effects to continue.

5.2.1 Sildenafil

Sildenafil has been shown to improve symptoms, exercise capacity, and hemo-dynamics in patients with PAH including those with connective tissue disease (CTD) [151, 152]. It is available as an oral agent prescribed at 20 mg tid. This drug is generally well tolerated with most common side effects including headache, flushing, nausea, and nasal congestion, all resulting from vasodilation. The use of nitroglycerin is contraindicated in patients taking sildenafil due to a risk of severe hypotension when these drugs are used in combination. Safety during human pregnancy has not been studied; however no fetal harm has been noted in animal studies.

5.2.2 Tadalafil

Tadalafil has also proven to have beneficial effects on symptoms, exercise capacity, hemodynamics, and time to clinical worsening in a large randomized clinical trial involving 405 PAH patients including 95 with connective tissue disease [153]. Tadalafil's greatest benefit was realized at a dose of 40 mg daily. The drug is well tolerated with side effects and precautions similar to sildenafil.

5.2.3 Vardenafil

Vardenafil is a third agent within the PDE-5 inhibitor class that demonstrated significant advantage when comparing 6 MW distance, cardiac index, mean PA pressure, and pulmonary vascular resistance in patients treated with vardenafil 5 mg twice daily or placebo [154]. The long-term effects of vardenafil in PAH have not been evaluated, and the drug has not been approved for the treatment of PAH in the United States.

5.3 Soluble guanylate cyclase stimulators

While the phosphodiesterase 5 inhibitors promote vasodilation and limit proliferation by preventing the degradation of cGMP, the soluble guanylate cyclase (sGC) stimulator riociguat interacts directly with guanylate cyclase to stimulate production of cGMP [54].

5.3.1 Riociguat

Riociguat is the only member of this family in use to date. Riociguat was studied in two randomized clinical trials, one focused on patients with PAH (PATENT 1) and included those with CTD [155] and the other patients with chronic thromboembolic pulmonary hypertension (CTEPH) [156]. Significant improvements were observed in exercise capacity, FC, time to clinical worsening, and hemodynamics. Subgroup analysis of the PATENT 1 trial specifically

evaluating benefit in CTD-PAH revealed improvements in 6 MW, FC, pulmonary vascular resistance, and cardiac index [157]. Riociguat is an oral therapy with maximum daily use of 2.5 mg tid. Side effects are similar to those seen with the PDE-5 inhibitors. In addition, riociguat can induce systemic hypotension and has been linked to an increased risk of bleeding. It is teratogenic and contraindicated in pregnancy. Females of childbearing age are required to participate in a Risk Evaluation and Mitigation Strategy (REMS) program and undergo monthly pregnancy testing in addition to practicing careful contraceptive measures. This drug should not be used with nitroglycerin or PDE-5 inhibitors due to the risk of severe hypotension.

5.4 Endothelin receptor antagonists

Excessive levels of endothelin 1 produced by pulmonary vascular endothelial cells have been implicated in the vasoconstriction and cell proliferation seen in PAH [57, 158, 159]. Endothelin binds with two G protein-coupled receptors, type A and B, located on the smooth muscle cell surface and thereby promotes its physiologic effects. Type A receptors mediate vasoconstriction, cell growth, and inflammation, while type B receptors mediate opposing effects including vasodilation and natri-uresis while inhibiting proliferation and inflammation.

5.4.1 Bosentan

Bosentan was the first targeted oral therapy developed to treat PAH and is prescribed with a bid dosing schedule. Bosentan has been investigated in patients with iPAH, PAH associated with CTD, and Eisenmenger syndrome [160–162]. The drug interacts with both type A and B receptors to effect improvements in exercise capacity, FC, time to clinical worsening, hemodynamics, and echocardiographic variables [163]. About 10% of patients treated with bosentan in clinical trials developed reversible elevations in liver transaminases. Monthly monitoring of liver function tests is required for patients using bosentan. Other side effects that can be seen are fluid retention and anemia. Further, this drug is teratogenic and contraindicated during pregnancy. Females of childbearing age who use bosentan must enroll in a Risk Evaluation and Mitigation Strategy (REMS) program and are required to undergo monthly pregnancy testing. They should be counseled to avoid pregnancy with careful contraceptive practices if sexually active. It is important to note that hormonal contraceptive effectiveness is reduced by bosentan. It is also important to note that cyclosporine and glyburide may increase bosentan levels and increase the risk of liver toxicity.

5.4.2 Ambrisentan

Ambrisentan is a selective endothelin type A receptor blocker which is available as an oral therapy prescribed for once daily use. This drug has been studied in one pilot and two randomized clinical trials demonstrating improvements in symptoms, exercise capacity, time to clinical worsening, and hemodynamics in patients with iPAH, CTD-PAH, and HIV-associated PAH [164, 165]. The risk of liver function abnormalities is minimal, and monthly liver function testing is not required for patients using ambrisentan; however its use is not recommended in patients with moderate to severe liver dysfunction. Ambrisentan use can be complicated by the development of edema and anemia. Like bosentan, ambrisentan is teratogenic and contraindicated during pregnancy. All of the precautions relating to use in females of childbearing age noted for bosentan are also true for ambrisentan.

5.4.3 Macitentan

Macitentan is the most recent endothelin 1 antagonist available to PAH patients as a once daily oral therapy. Like bosentan, macitentan is a dual endothelin receptor blocker. In contrast to bosentan and ambrisentan, the benefits of macitentan were realized in a large event-driven investigation involving 742 patients treated for an average of 100 weeks [166]. Macitentan significantly reduced time from initiation to a composite endpoint of worsening PAH, initiation of intravenous or subcutaneous prostanoid therapy, atrial septostomy, lung transplantation, or death. The study population included a significant proportion of patients on background therapy who also experienced significant benefit. Macitentan is well tolerated and, as with other endothelin antagonists, may be associated with fluid retention or anemia. Again, this drug is teratogenic and contraindicated during pregnancy. Patients using this drug should follow the same risk reduction recommendations as noted with bosentan and ambrisentan.

5.5 Prostacyclin analogues

A deficiency of prostacyclin activity characterizes the dysfunction of the third major pathway involved in the development of PAH. Prostacyclin is produced by the pulmonary endothelium, and its bioactive effects include vasodilation of the pulmonary vascular bed, inhibition of platelet aggregation, and cell proliferation [167]. A reduction of prostacyclin synthase expression has been recognized in pulmonary arteries from patients with PAH and is thought to be the central focus of dysfunction in this pathway [55]. The prostacyclin analogues are available as oral, inhaled, or systemically administered disease-targeted therapies.

5.5.1 Epoprostenol

Epoprostenol is available for use as a continuous intravenous (IV) infusion. Epoprostenol has a short half-life of 3–5 min. The original formulation was unstable at room temperature after about 8 h and required considerable effort to maintain at cooler temperatures. A newer formulation of the drug is now available that has extended room temperature stability. Treatment is initiated at a dose of 2–4 ng/kg/min and titrated upward to reach clinical therapy targets. Patients experience tachyphylaxis with the continuous infusion, therefore requiring intermittent dose escalation over time. The maximum beneficial dose of epoprostenol is typically 40 ng/kg/min, although titration may go beyond this point. Epoprostenol has been shown to improve symptoms, exercise capacity, and hemodynamics in FC 3 and 4 patients with iPAH and SSc-PAH [168–170]. Side effects with epoprostenol can be pronounced and may include jaw pain, nausea, diarrhea, flushing, and headache. There is a risk of catheter-related complications including infection and thrombosis. Epoprostenol can cause hypotension when used with other antihypertensives and may increase risk of bleeding when used in patients taking anticoagulants or antiplatelet agents. Epoprostenol has been used during pregnancy without evidence of fetal harm to date. Given the short half-life of epoprostenol, an infusion of this drug should not be discontinued abruptly due to the risk of rebound pulmonary vasoconstriction and death.

5.5.2 Treprostinil

Treprostinil is an analogue of epoprostenol available in systemic, inhaled, and oral formulations. The systemically infused form of treprostinil is stable at

room temperature, has a half-life of 3–4 h, and can be administered by continuous subcutaneous (SC) or IV infusions. Dosing typically begins with 1–2 ng/kg/min with gradual dose escalation to achieve clinical target goals. Side effects are similar to epoprostenol. Additionally those patients using the subcutaneous formulation may experience significant infusion site pain. Several topical analgesic preparations are available that can successfully control local infusion site pain. As is the case with epoprostenol, patients develop tachyphylaxis requiring dose escalation to maintain clinical benefit. The usual effective dose is 20–80 ng/kg/min, although dosing can extend well beyond this range. Treprostinil was first studied in its continuous SC formulation. A randomized clinical trial of 470 patients treated with SC treprostinil, including 17% CTD patients, revealed improvements in exercise tolerance and hemodynamics [171, 172]. Dose titration was limited by side effects, including infusion site pain, and as such benefits were noted in those patients achieving higher doses >13.8 ng/kg/min. Later treprostinil was approved for use as a continuous IV infusion. Treprostinil can be administered in an inhaled formulation with a specialized nebulizer four times daily. This formulation is very well tolerated with most commonly reported effects including mouth soreness, cough, and headache. Tachyphylaxis does not develop due to intermittent dosing. Some patients may notice recurrence of PAH symptoms as effect wanes between treatments. In a randomized clinical trial of inhaled treprostinil added to background therapy with bosentan or sildenafil, there were improvements in 6 MW, NT-proBNP levels, and quality of life measures [173]. More recently, treprostinil has been offered in an oral formulation that is taken by either bid or tid scheduled dosing. Although intermittent dosing is employed in the treatment of patients with oral treprostinil, dose escalation over time helps achieve and maintain clinical target goals. The use of oral treprostinil can be complicated by significant gastrointestinal side effects, such as nausea, anorexia, and diarrhea. In a randomized clinical trial of treatment-naïve PAH patients, oral treprostinil use was associated with improvement in 6 MW distance [174]. Treprostinil can cause hypotension when used with other antihypertensives and may increase risk of bleeding when used in patients taking anticoagulants or antiplatelet agents. Parenteral and inhaled treprostinil safety during pregnancy has not been studied in humans but did not lead to fetal harm in animals, and as such they have Category B designations. Oral treprostinil has been associated with adverse fetal effects in animal studies and is designated Category C. Continuous IV therapy carries a risk of catheter-related complications including infection and thrombosis. Oral treprostinil use is contraindicated in patients with Child-Pugh Class 3 hepatic impairment. Treprostinil should not be discontinued abruptly due to the risk of rebound pulmonary vasoconstriction and death.

5.5.3 Iloprost

Iloprost is a stable analogue of prostacyclin that is also available in IV, inhaled, or oral formulations. Oral iloprost has not been evaluated for use; however, both the IV and inhaled forms have been used in Europe, and the inhaled form has been approved for use in the United States. The inhaled formulation is administered with a specifically designed handheld and portable nebulizer device. This form of iloprost is used by nebulization 6–9 times a day at a dose of 2.5–5 ug/inhalation. The effect lasts from 30 to 90 min. The intermittent dosing eliminates the development of tachyphylaxis. Improvements in symptoms, exercise capacity, and pulmonary vascular resistance were observed in a clinical trial in which iloprost was compared with placebo in patients with PAH and CTEPH [175]. The effect of IV iloprost was noted to be similar to epoprostenol in a small group of patients with PAH and CTEPH [176]. The inhaled drug is well tolerated with most frequent side effects

being cough, flushing, and jaw pain. Inhaled iloprost can cause hypotension and should be avoided or used cautiously in patients with relative hypotension.

5.6 Prostacyclin receptor agonist

The development of the prostacyclin receptor agonist class of disease-targeted therapies represents a new approach to treating PAH. Although the prostacyclin receptor agonism of this new class is similar to that of prostacyclins, the receptor interaction is selective for the IP receptor. The established prostanoid receptors in the human pulmonary artery are the IP, EP_3, and TP receptors. The IP receptor mediates vasodilation and inhibits proliferation, while the EP_3 and TP receptors may promote vasoconstriction and cell proliferation [177–179].

5.6.1 Selexipag

Selexipag is a selective IP receptor agonist that is structurally distinct from prostacyclin with an active metabolite that is 37-fold more potent. Selexipag is prescribed for oral BID dosing beginning with 200 mcg bid and titrating to a maximal dose of up to 1600 mcg bid. The target treatment dose for individual patients is determined by the development of side effects limiting further dose escalation. Selexipag reduced the risk of reaching a composite morbidity and mortality (worsening PAH resulting in need for atrial septostomy or lung transplantation, initiation of parenteral prostanoid therapy or chronic oxygen therapy, hospitalization for PAH, other indication of disease progression, or death) by 40% in a large placebo-controlled, event-driven trial including 1156 patients [180, 181]. At baseline, 80% of patients were being treated with stable doses of an endothelin blocker, a PDE-5 inhibitor, or both. A subgroup analysis of 334 patients with connective tissue disease-associated PAH (170 SSc, 82 systemic lupus, 82 mixed or other) revealed a similar 41% reduction in risk of the composite morbidity and mortality events [182]. Further the treatment effect was consistent regardless of background PAH treatment or connective tissue disease subtype. Commonly reported side effects include headache, nausea, diarrhea, flushing, myalgia, and arthralgia.

5.7 Combination therapy

Despite observations from clinical trials that individual therapeutic agents can improve exercise capacity, time to clinical worsening, and hemodynamics, pulmonary arterial hypertension remains a progressive disease that is difficult to control. The progressive nature of this disease process in patients treated with monotherapy has fostered the practice of combining agents to limit progression. One approach has been the sequential addition of agents affecting the three known pathophysiologic pathways. In this approach an agent affecting one of the pathways is chosen to begin monotherapy and if clinical response is inadequate, one or more agents affecting the other pathways are added until desired clinical benefit is achieved. Upfront combination therapy has become a more contemporary approach to managing pulmonary arterial hypertension. This approach to treating PAH was conceived from experience with the treatment of other disease states, such as cancer or congestive heart failure, with agents affecting multiple mechanisms of disease upfront. The upfront combination approach gained momentum with the AMBITION trial which demonstrated a 50% reduction in composite morbidity/mortality events in patients treated with an upfront combination of tadalafil and ambrisentan compared to either agent as monotherapy [183]. This benefit was also recognized in a subgroup analysis of patients with CTD-PAH and SSc-PAH [184].

Hemodynamics, RV structure and function, and overall functional status were significantly improved in SSc-PAH patient treated with the upfront combination [185]. Investigations of several newer treatments for PAH, such as riociguat, macitentan, and selexipag, have included significant proportions of patients on background therapies and have demonstrated added improvements in exercise capacity, functional class, and time to clinical worsening [155, 166, 181]. These studies have fueled the impetus to include recommendations for combination therapy in contemporary treatment guidelines [16, 186].

5.8 Nonmedical treatment options

Medical therapy can improve activity tolerance, hemodynamics, and quality of life and can even improve survival prognosis; however, in some cases PAH will progress even with aggressive medical therapy. Nonmedical options may include balloon atrial septostomy and/or lung transplantation. Atrial septostomy may be beneficial in FC 4 patients with right heart failure or severe syncopal symptoms who are progressing on maximal medical therapy [187]. Atrial septostomy is also a consideration as a bridge to lung transplantation when medical therapy fails. An interatrial right-to-left shunt may decompress the right heart chambers and ultimately improve oxygen transport despite an observed oxyhemoglobin desaturation [188]. Atrial septostomy is not recommended in end-stage patients with mean RAP >20 mmHg and a resting room air saturation below 85% [187, 188]. Lung transplantation is also an option for patients with end-stage SSc-PAH failing medical therapy. In some centers, patients with SSc-PAH may not be offered lung transplantation due to the risk of aspiration pneumonia related to esophageal disease. However, studies have shown that survival after lung transplantation is similar in patients with SSc-PAH and other transplant indications [189]. There has been increasing interest in stem cell therapy as a treatment option for PAH. Although animal models have shown some promise, stem cell therapy is not currently a viable option for treatment of human PAH [190].

5.9 Treatment algorithm

The poor survival prognosis associated with SSc-PAH and the availability of multiple disease-targeted treatment options have fostered the development of algorithms to guide the treatment decision process. Both the American College of Chest Physicians [186] and the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the ESC/ERS [16] have published guidelines to aid clinicians in the treatment of patients with PAH.

5.10 Supportive measures

In addition to a careful risk assessment, choice of appropriate disease-targeted agent, and close monitoring of treatment effect, there are severe supportive measures that apply in the management of the patient with SSc-PAH. Patients are not restricted from physical activity. Physical activity and supervised rehabilitation have been shown to improve exercise tolerance, reduce fatigue, and improve quality of life [191, 192]. The ESC/ERS Guidelines suggest that patients who are stable clinically should consider participation in a rehabilitation program at a center experienced with the management of PAH if possible [16]. Patients with SSc-PAH should be vaccinated against influenza and pneumococcal pneumonia. Pregnancy in patients with PAH is associated with a high mortality risk and should be avoided. If patients with PAH become pregnant, the high risk of complications

and pregnancy termination should be discussed. Some PAH treatments cause fetal harm, and patients are required to undergo monthly pregnancy monitoring when using such therapies. Riociguat and the endothelin antagonists are teratogenic. Patients using these targeted therapies should be carefully counseled about the risk of fetal harm and instructed to use at least two barrier methods of contraception while using these agents. In the event patients do become pregnant, they may continue PAH therapies that are not considered fetal toxic, such as the prostanoids, plan an elective delivery, and work closely with a high-risk obstetrical team and experienced pulmonary hypertension specialist throughout the pregnancy [193]. Patients with PAH are often overwhelmed by the physical limitations, financial burden, and social impact associated with PAH [194]. Screening for depression is helpful in identifying patients who could benefit from referral to appropriate services in the community where help is available to ease the psychosocial burden of this disease. Genetic counseling may be appropriate for select patients [195]. It is often helpful for the affected patient and at-risk family members to understand their mutation status in order to plan for the future. Genetic testing and counseling should involve a multidisciplinary team including pulmonary hypertension specialists, genetic counselors, geneticists, psychologists, and nurses. Elective surgery is not contraindicated but does carry an increased risk to the PAH patient. Patients with significantly impaired RV function are at highest risk and should undergo careful preoperative assessment [196–198]. Epidural anesthesia may be better tolerated [199]. Patients using oral therapies may require transition to an intravenous or inhaled form of therapy until able to take oral medications postoperatively.

6. Conclusions

Pulmonary arterial hypertension is a leading cause of death in patients with systemic sclerosis. While the pathogenesis of PAH in the patient with systemic sclerosis bears resemblance to that of idiopathic PAH, there are distinct differences in genetic predisposition, role of inflammation and autoantibodies, and pathologic manifestations of disease. Early detection is essential in preventing early demise from SSc-PAH. Several algorithms have been suggested for screening SSc patients for PAH. In general, it is recommended that annual screening with biomarkers, PFTs, and echocardiography be considered in any patient with systemic sclerosis, even if they are asymptomatic. There are a number of medical therapies available which have demonstrated benefit in SSc-PAH, as well as iPAH. The importance of regular monitoring and repeat risk assessment cannot be underemphasized. Lung transplantation may be an option for those patients who progress on maximal medical therapy. While the prognosis for SSc-PAH has certainly improved over the past two decades, continued research into the mechanisms of disease and development of new treatments will ensure further improvements in quality of life and survival in the future.

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