Pulmonary Hypertension Associated with Connective Tissue Disease

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Stephen C. Mathai and Laura K. Hummers

Introduction

Pulmonary hypertension (PH) is a chronic disease of the pulmonary vasculature characterized by pulmonary vascular remodeling; leading to increased pulmonary vascular resistance (PVR) that ultimately causes right ventricular dysfunction, failure, and death [1]. PH can develop in association with many different diseases and can result from processes that primarily affect systems distinct from the pulmonary vasculature, such as the heart, lung parenchyma, liver, and kidneys, in addition to processes that affect the pulmonary vasculature directly, such as thromboembolism [2]. Patients with connective tissue disease are at particularly high risk for the development of PH not only related to the involvement of the aforementioned organ systems, but also to the possibility of direct pulmonary vascular involvement in the absence of thromboembolism, known as pulmonary arterial hypertension (PAH) [3]. The presence of PH in any form is nearly uniformly associated with increased morbidity and mortality. Unfortunately, patients with CTD-associated PH have variable response to therapy and tend to have poorer survival compared to PH patients without CTD. The reasons for the increased risk of development of PH, attenuated response to therapy, and poorer outcomes are poorly understood.

S.C. Mathai, M.D., M.H.S. (✉)
Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 1830 East Monument Street, 5th Floor, Baltimore, MD 21205, USA
e-mail: smathai4@jhmi.edu

L.K. Hummers, M.D., Sc.M.
Department of Medicine/Rheumatology, Johns Hopkins University School of Medicine, 5200 Eastern Avenue, Suite 4000, Mason F. Ford Building, Center Tower, Baltimore, MD 21224, USA

Definition and Classification of Pulmonary Hypertension

According to the most recent consensus guidelines, pulmonary hypertension is defined hemodynamically as a mean pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg [2]. Thus, right heart catheterization (RHC) is required to diagnose PH as mPAPs cannot be directly measured by echocardiography. In hemodynamic terms, PH is often divided into pre-capillary and post-capillary disease based upon measurements; namely, if the PVR is greater than 3 Wood units and the pulmonary capillary wedge pressure (PCWP) is less than or equal to 15 mmHg, pre-capillary PH is present. If the PCWP is greater than 15 mmHg, post-capillary PH is present. This results from elevated left atrial pressures passively transmitted backwards into the pulmonary veins and arteries, leading to an elevated PAP with normal PVR and transpulmonary gradient (TPG, TPG = mPAP-PCWP, normal $\leq$12) [4]. So-called "mixed-PH" or "reactive PH" refers to mixed pre- and post-capillary PH in which chronic elevation

P.F. Dellaripa et al. (eds.), *Pulmonary Manifestations of Rheumatic Disease: A Comprehensive Guide*,
DOI 10.1007/978-1-4939-0770-0_11, © Springer Science+Business Media New York 2014

Table 11.1 Clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension (PAH)
(a) Idiopathic PAH (IPAH)
(b) Heritable
(c) Drug-and toxin-induced
(d) Associated with (APAH)
– Connective tissue disease
– HIV infection
– Portal hypertension
– Congenital heart disease
– Schistosomiasis
1. Pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension owing to left heart disease
(a) Systolic dysfunction
(b) Diastolic dysfunction
(c) Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
(a) Chronic obstructive lung disease
(b) Interstitial lung disease
(c) Other pulmonary diseases with mixed restrictive and obstructive patterns
(d) Sleep disordered breathing
(e) Alveolar hypoventilation
(f) Chronic exposure to high altitude
(g) Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
(a) Hematologic disorders, chronic hemolytic anemias
(b) Systemic disorders
(c) Metabolic disorders
(d) Others

of the pulmonary venous pressure leads to pulmonary arterial vasoconstriction with pulmonary vascular remodeling [5]. Current guidelines further refine this classification and incorporate hemodynamic criteria with clinical and associated characteristics (Table 11.1).

Distinguishing between the various forms of PH is imperative to properly diagnose and treat the disease and to appropriately risk-stratify patients. The initial classification schema included only two groups: primary pulmonary hypertension and secondary pulmonary hypertension [6]. However, this schema and terminology has been abandoned in favor of the current classification system. As shown in Table 11.1, PH is divided into five groups, referred to as World Health Organization groups (WHO). PAH (WHO Group 1 disease) is defined hemodynamically by a mPAP greater than or equal to 25 mmHg with a PCWP less than or equal to 15 mmHg in the absence of chronic thromboembolic disease or other chronic respiratory disease. Included within this group is idiopathic PAH (IPAH), which was formerly known as primary pulmonary hypertension, and associated pulmonary arterial hypertension (APAH), which includes PAH related to CTD. Identifying Group I disease is particularly important as most of the current therapies for PH are approved only for use in this patient population [2, 7]. Group IV disease, PH related to chronic thrombotic or embolic disease, is also imperative to diagnose given the possibility of a surgical cure [8, 9]. Similarly, proper classification into the other WHO groups informs treatment strategies and management [10].

Because CTD in general can affect multiple organ systems, PH related to CTD can be associated with any of the five WHO groups (Fig. 11.1) [3, 11–18]. The most common CTDs associated with PH are listed in the figure and include mixed connective tissue disease (MCTD), polymyositis/dermatomyositis (PM/DM), rheumatoid arthritis (RA), Sjogren syndrome (SS), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc). The risk of development of PH of any form varies by underlying CTD; the risk of PAH in particular seems to be higher in certain CTDs such as SSc. Thus, recommendations for screening for PH in CTD vary by CTD. Further, the evaluation of patients with suspected CTD-PAH can slightly differ from evaluation for other forms of PAH. For instance, since patients with CTD-PAH rarely demonstrate a significant response to acute vasodilator testing during RHC and are even less likely to demonstrate a sustained response to calcium channel blocker therapy, routine acute vasodilator challenges during RHC are not recommended [2]. Similarly, treatment recommendations and treatment response also depend in part upon the underlying CTD.

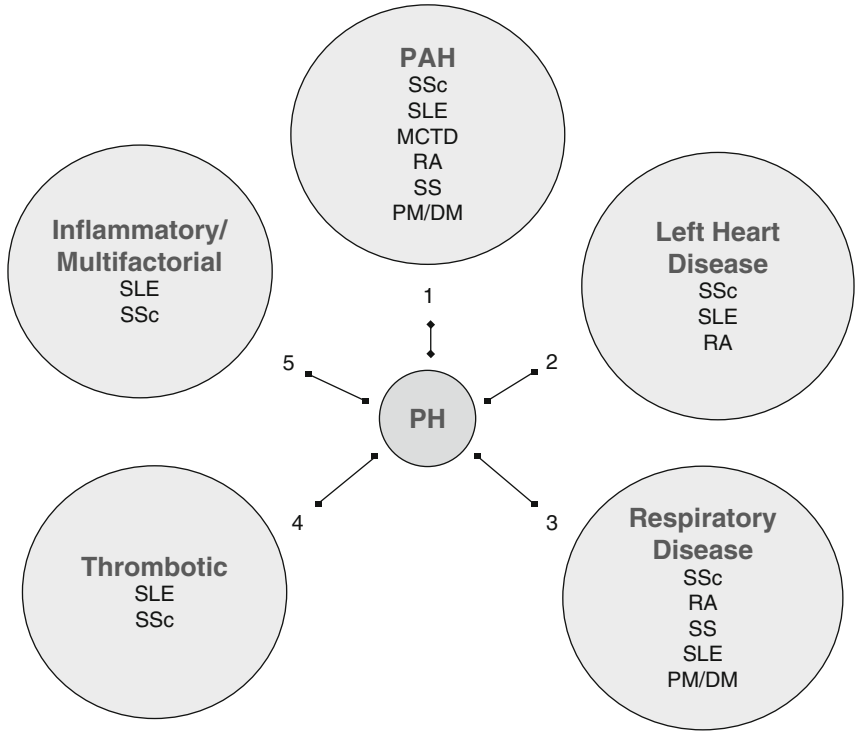

Fig. 11.1 Types of pulmonary hypertension in various connective tissue diseases

In general, the presence of PH complicating any of these CTDs is associated with a poorer prognosis [12, 19–23].

Pathophysiology and Pathobiology

The pathophysiology and pathobiology of pulmonary hypertension remain poorly understood. Further, there appears to be significant differences in the pathobiology of PAH compared to most other forms of PH, with notable distinctions between PAH and PH related to lung disease, for example [24–26]. However, given the substantial overlap between proposed mechanisms for CTD, ILD, and PAH, there may be commonality in the pathobiology that could be informative for therapeutic strategies [27].

PAH develops as a consequence of progressive remodeling of the small-to-medium sized pulmonary vasculature. Plexiform lesions, medial hypertrophy with muscularization of the arterioles, concentric intimal proliferation, and in situ thrombosis are the pathologic hallmarks of the disease (Fig. 11.2) [28]. While the exact mechanisms of this remodeling remain unclear, multiple factors are thought to be involved [2, 25]. Functionally, there is an imbalance between vasoactive mediators such as thromboxane A2 and endothelin-1 and vasodilatory factors such as prostaglandins and nitric oxide in the vascular endothelium. Pulmonary artery vasoconstriction ensues in tandem with cellular proliferation; increased shear stress on the vasculature propagates endothelial injury. With this, sympathetic activity and hypoxemia follow, leading to further pulmonary vasoconstriction and eventually in situ thrombosis. These changes in the pulmonary vasculature cause a progressive increase in PVR and right ventricular afterload. Compensatory mechanisms in the right ventricle (RV) initially maintain cardiac function, however, in the face of prolonged increased afterload, the RV decompensates and cardiac failure ensues.

Genetic factors contribute to not only the predisposition to the development of PAH but also

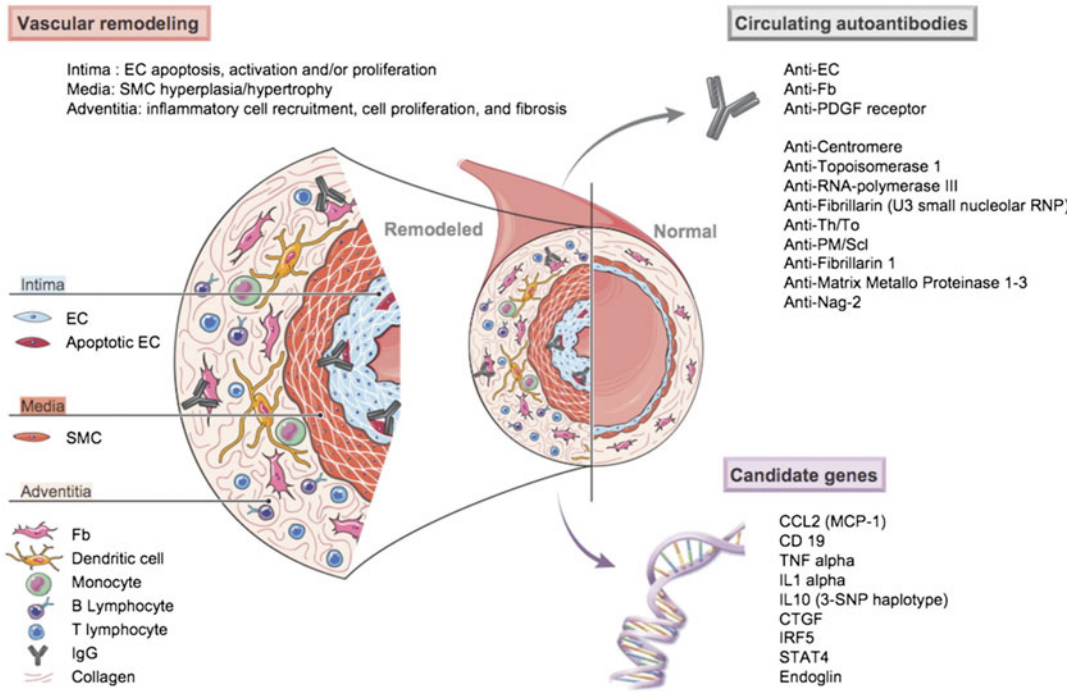

Fig. 11.2 Pulmonary vascular remodeling in CTD-PAH. This schematic features inflammatory mediators, cells, and mechanisms involved in the pulmonary vascular remodeling of SSc-PAH. Vascular changes affect all three layers (intima, media, and adventitia) of the pulmonary vessel and involve endothelial cell (EC) apoptosis, EC activation with increased expression of cell adhesion molecules, and inflammatory cell recruitment leading to vessel obliteration. A number of circulating auto-antibodies including classic autoantibodies, such as anti-centromere, anti-topoisomerase 1, anti-RNA-polymerase III, anti-fibrillarin (U3 small nucleolar ribonucleoprotein [RNP]), anti-Th/To, and antipolymyositis/scleroderma (PM/Scl), and more recently anti-fibrillarin 1, anti-matrix metalloproteinases (MMP) 1-3, anti-novel antigen(nag)-2 (non-steroidal anti-inflammatory drug-activated gene), and evidence that anti-fibroblast (Fb) antibodies, anti-EC antibodies (AECA), and anti-platelet derived growth factor (PDGF) receptor antibodies might exert a pathogenic role. An increasing number of candidate genes have been reported to be associated with SSc in different cohorts, including, among others, a variant in the promoter of chemokine (C-C motif) ligand 2 (monocytes chemotactic protein-1) (CCL2 [MCP-1]), two variants in cluster of differentiation 19 (CD 19), a promoter and coding polymorphism in tumor necrosis factor (TNF)-α, a variant in the promoter of IL-1α gene, a three-single-nucleotide polymorphism (SNP) haplotype in IL-10, a polymorphism in the connective tissue growth factor (CTGF) promoter region, the interferon regulatory factor 5 (IRF5) rs2004640 GT substitution, and the signal transducer and activator of transcription 4 (STAT4) rs 7574865 single nucleotide polymorphism. *SMC* smooth muscle cell. (Used with permission from Le Pavec J, Humbert M, Mouthon L, Hassoun PM. Systemic sclerosis-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2010; 181[12]: 1285-93)

may contribute to the progression of disease and disease severity. Specific mutations in the transforming growth factor-β (TGF-β) superfamily, involved in regulation of fibrosis and angiogenesis, have been described in PAH patients. Mutations of the bone morphogenic protein type II receptor (BMPR2) gene are highly prevalent in patients with the familial/hereditary form of PAH; a smaller proportion of patients without the familial/hereditary form of PAH also demonstrate mutations in this gene [29]. Other TGF-β pathways are associated with PAH; mutations in the type I TGF-β receptor, activin A receptor type-II like-1 (ALK-1), are found in patients with hereditary hemorrhagic telangiectasias who develop PAH [30]. Other more rare mutations in the downstream mediators of BMPR2 signaling have also been described [31]. In general, these

mutations in the BMPR2 pathway lead to loss of function or reduced expression [32]. While mechanistic studies of BMPR2 mutations show that these mutations are permissive but not necessary for the development of PAH, the genetic data to date suggest a role for BMPR2 in the maintenance of the pulmonary vasculature. Interestingly, there are limited data demonstrating mutations in the TGF-β pathway in PAH related to CTD. Two small studies failed to show BMPR2 mutations in cohorts of patients with SSc-PAH and CTD-PAH [33, 34]. However, another study reported an association between a mutation in endoglin, a glycoprotein present on vascular endothelium that is part of the TGF-β superfamily, and risk of PAH in a cohort of SSc patients with and without PAH [35]. Still, this association remains to be recapitulated in other cohorts and highlights the potential differences in pathogenesis and pathobiology between various forms of PAH.

Inflammation and autoimmunity are thought to play a central role in the development of PAH, both in the IPAH and in CTD-PAH [36, 37]. In human PAH, plexiform lesions have been found to contain macrophages, T lymphocytes, B lymphocytes, and dendritic cells [38]. Tertiary lymphoid follicles containing these cells have recently been identified in patients with IPAH, located adjacent to remodeled pulmonary arteries [39]. Circulating factors, including inflammatory mediators, such as macrophage inflammatory protein-1 α, interleukin (IL)-1, IL-6, and P-selectin are increased in IPAH. Involvement of inflammatory cells is also a prominent feature of pulmonary vascular remodeling in CTD-PAH [40].

Autoimmunity and subsequent immune dysregulation may lead to activation of pathogenic autoreactive B cells and T cells and thus may be involved in the pathobiology of PAH and in particular, CTD-PAH. In SSc in particular, a number of specific autoantibodies are found, including anti-centromere, anti-topoisomerase 1, anti-RNA-polymerase III, anti-fibrillarin (U3 small nucleolar ribonucleoprotein), anti-Th/To, and anti-polymyositis/scleroderma; these autoantibodies typically correlate strongly with particular clinical phenotypes including the presence of various forms of PH [41]. More recently, anti-fibrillarin 1, anti-matrix metalloproteinases 1-3, anti-novel antigen 2, and anti-fibroblast antibodies have been identified [42]. Anti-fibroblast antibodies, thought to be important mediators of fibroblast activation and thus collagen synthesis that contributes to vascular remodeling, have been found in the serum of both SSc-PAH and IPAH patients [43]. Anti-endothelial cell antibodies (AECA) and antibodies to fibrin-bound tissue plasminogen activator are also present in patients with SSc-PAH. AECA have been shown to activate endothelial cells, induce the expression of adhesion molecules, and trigger apoptosis; thus these antibodies may be implicated in the pathogenesis of PAH [44]. In a recent study, antibodies to angiotensin II type 1(AT1R) receptor and endothelin-1 type A (ET1R) receptors were found to be significantly elevated in the serum of patients with SSc when compared to other CTDs such as RA and SS; these levels were highest in patients with SSc-PAH and were strongly associated with risk of death [45]. Further, the authors showed AT1R and ET1R antibodies initiated canonic signaling mediated by ERK1/2 in vitro using microvascular endothelial cells, suggesting a potential link between autoimmunity, endothelial injury, and fibrosis and thus, a role in PAH pathogenesis. Taken together, these data support a role for autoimmunity in the development of PAH and may explain the higher prevalence of PAH in CTDs in general.

The pathobiology of other forms of pulmonary hypertension (non-PAH pulmonary hypertension) is less well characterized than for PAH. Patients with Group 2 PH (PH due to left heart disease) can have either passive PH (due solely to increased pressure downstream of the pulmonary arteries) or reactive/mixed PH (due to a combination of increased downstream pressure and structural and/or functional abnormalities of the pulmonary vasculature) [4]. Pathologically, pulmonary veins are enlarged, dilated, and thickened with pulmonary capillary dilatation, interstitial edema, alveolar hemorrhage, and enlarged lymphatics. Distal pulmonary arteries can show

evidence of medial hypertrophy, smooth muscle cell proliferation, and eccentric intimal lesions, without the classic plexiform lesions. Chronic elevation of pulmonary venous pressures leads to excessive production and accumulation of collagen IV in the extracellular matrix that leads to structural changes in the pulmonary vasculature from the capillaries to the arterioles and arteries [46]. Patients with CTD may be particularly prone to developing Group 2 PH due to high prevalence of diastolic or non-systolic dysfunction of the left ventricle; additionally, valvular disorders, particularly affecting the mitral valve, may also be present in certain CTDs and lead to increased pulmonary venous pressures [3].

Group 3 PH can result from several entities, including obstructive lung disease, restrictive lung disease, neuromuscular disease, or obstructive sleep apnea. Within this category, PH related to restrictive lung disease from interstitial lung disease is most commonly encountered clinically. While vascular obliteration related to parenchymal destruction can contribute to the development of PH in ILD, this mechanism is not thought to be sufficient to cause PH. While hypoxia clearly contributes to the development of PH related to ILD, there is a growing interest in commonalities in pathobiology between PH and ILD, and in particular, SSc related ILD (SSc-ILD), that may explain the frequent co-presentation of these two entities [27]. Endothelial apoptosis possibly due to circulating AECA and anti-fibrillarin antibodies represent the initial insult in the pathogenesis of SSc [47]. This process is followed by inflammation and dysregulated angiogenesis initially that ultimately progresses to obliterative vasculopathy with intimal proliferation. The same factors that lead to fibrosis in the vasculature may be influencing fibrosis in the interstitium, mediated by several pathways including the TGF-β superfamily, and factors such as the CXC chemokines, platelet-derived growth factor, and angiotensin II, among others [48–50]. Whether or not endothelial injury in SSc predisposes these patients to a higher risk of development of PH-ILD compared to other forms of ILD remains to be determined [51].

Characteristics of PH by CTD Type

Scleroderma

SSc is a heterogeneous disorder characterized by endothelial dysfunction, fibroblast dysregulation, and immune system abnormalities that lead to progressive fibrosis of the skin and internal organs [42]. Genetic and environmental factors in the setting of immune dysregulation are thought to contribute to host susceptibility [23]. More accurate estimates of the incidence and prevalence of SSc have resulted from the use of a standard classification system [52]. These estimates vary by geographic location, suggesting a role for environmental factors in the disease pathogenesis [53, 54]. For instance, the prevalence of SSc ranges from 30 to 70 cases per million in Europe and Japan to approximately 240 per million in the United States [55–58]. Incidence also varies by geographic location; the highest rates occur in the United States with approximately 19 cases per million per year.

Typically classified as limited or diffuse based upon extent of skin involvement, SSc of both subtypes can involve multiple organs, such as the heart, lungs, kidneys, and gastrointestinal tract [53]. Pulmonary hypertension in SSc may result from PAH, left heart disease, lung disease, chronic thromboembolic disease, and renal disease and thus fall into any of the five WHO classification groups of PH. In addition, various forms of PAH can develop in patients with SSc. In an autopsy series, Dorfmuller and colleagues described pulmonary veno-occlusive disease-like changes in the pulmonary venules and veins in 75 % of CTD patients with clinically diagnosed PAH [40]. While technically not PVOD, the authors surmised that these changes in the pulmonary veins of SSc patients may lead to similar responses to pulmonary vasodilator therapy as in PVOD. The classification (i.e., limited vs. diffuse) along with extended antibody profile have been associated with certain types of PH within the WHO group schema.

PAH occurs in about 8–14 % of patients with SSc when the diagnosis is based upon RHC

Table 11.2 Clinical risk factors for the development of PAH in SSc

Limited SSc
Late age of onset of SSc
Duration of SSc
Post-menopausal time period
Raynaud phenomenon
Number of telangiectasia
Severe digital ulcers
Decreased DL_{CO}
$FVC/DL_{CO} > 1.6$
Increased NT-proBNP
Antibody profile (anti-centromere, anti-U3 RNP)
Increasing RVSP >2 mmHg/year

[59, 60]. Higher estimates of PAH (up to 45 % in certain series) have overestimated the prevalence because the diagnosis has relied upon echocardiography and not RHC [61–64]. While echocardiography can be useful to suggest the presence of PH and to identify potential etiologies of PH (e.g., valvular disease, left ventricular dysfunction, congenital heart disease), echocardiography cannot establish the diagnosis of PH due to the inaccuracy of the Doppler signal in assessing true right ventricular systolic pressure and the frequent inability to obtain an adequate Doppler signal, particularly in CTD patients [65–67]. In a recent study of SSc patients who were at risk of developing PH based upon clinical characteristics including echocardiography findings, less than two-thirds of patients had RHC-confirmed PAH; around 15 % had Group II PH and 20 % had Group III PH [68]. However, despite the potential for over-diagnosis of PAH based upon the limitations of echocardiography; SSc-PAH is still likely to be under-recognized and underdiagnosed as suggested by the lower than expected prevalence of SSc-PAH in PH registries [69–71].

Risk factors for the development of PAH in SSc patients are varied and range from immutable patient characteristics to SSc-specific features to cardiopulmonary manifestations of developing pulmonary vascular disease (Table 11.2). Typically, PAH develops in women more frequently than men with SSc, however, men have poorer outcomes with a nearly fourfold increased risk of death [72]. Race may influence disease severity as blacks with SSc-PAH have poorer functional capacity, RV function, and more severe hemodynamics at diagnosis than whites [73]. Age also influences the risk of PAH. As shown by Schachna and colleagues, the risk of PAH increased over 20 % with every 10 years of age at onset of SSc and when dichotomized at 60 years of age, there was twofold increased risk of development of PAH for late onset rather than younger onset of SSc [74]. There may be effect modification between gender and age with respect to the risk of development of PAH; postmenopausal changes in estrogen levels may abrogate its cardioprotective effects and thus be linked to increased risk of development of PAH amongst older women [75, 76]. Duration of SSc has also been associated with risk of PAH [77].

SSc type may also be associated with risk of PAH. While historically, PAH has been associated with limited cutaneous SSc (lcSSc), more recent epidemiologic studies from France have suggested that patients with diffuse cutaneous SSc (dcSSc) may have a higher likelihood of developing PAH [59, 78, 79]. Still, these associations may be biased by the low prevalence overall of incident cases (only 8 total PAH cases out of 374 SSc patients followed for 3 years) and perhaps by differences in the overall prevalence of SSc by disease type since lcSSc is three to five times more prevalent than dcSSc in Western Europe [80]. Other disease-specific features of SSc that can be associated with the development of PAH include severe digital ischemia and higher number of telangiectasias [81, 82].

Decline in pulmonary function as assessed by pulmonary function testing has also been associated with the risk of development of PAH. Isolated decreases in diffusing capacity of carbon monoxide (DLCO) in lcSSc patients portends an increased risk of PAH; a retrospective study identified patients with SSc-PAH had significantly reduced DLCO almost 5 years prior to establishing the diagnosis of PAH [81]. Other parameters, such as a forced vital capacity (FVC) to DLCO ratio of greater than 1.6 and a DLCO to alveolar volume (VA) ratio of less than 70 % have been demonstrated to predict the presence of PAH [81, 83].

Screening and Early Detection

Because SSc patients are at high risk of developing PAH, routine screening for this disease has been recommended by several medical societies [2, 84]. However, the frequency of screening, type of test selected, and patient characteristics vary by screening program. Since some of the recommendations include patient symptoms as an indicator for screening, these programs actually represent early detection algorithms rather than true screening programs [85]. However, employing early detection algorithms can effectively identify patients with PAH earlier in the disease course [59, 86]. When compared to a cohort of patients identified with PAH in routine practice, employment of an algorithm based upon echocardiographic findings (tricuspid regurgitant (TR) jet velocity ≥2.5 m/s) in combination with patient symptoms identified patients with less severe hemodynamic disease and less severe symptoms. Survival was also significantly better in this small cohort of patients compared to those who underwent routine clinical evaluation [86]. However, reliance solely upon echocardiography as a screening tool has significant limitations, with both high false positive and false negative rates [87]. Incorporation of other tools, such as symptoms, PFTs, and serum biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) may potentially enhance the effectiveness of early detection strategies [59, 83]. A recent multinational study employed a two-step algorithm incorporating PFT parameters, serum biomarkers, clinical characteristics (presence of telangiectasias), and EKG findings to generate a risk score to determine the need for echocardiography [88]. Subsequent findings on echocardiography (right atrial enlargement, TR jet ≥2.5 m/s) in combination with Step 1 score determined the need for RHC. Using this algorithm, the false negative rate for PAH was 4 % compared to nearly 30 % false negative rate when employing the European Society of Cardiology/European Respiratory Society guidelines for screening in this population [87]. A recent consensus statement on the screening and early detection of PAH in CTD endorsed this algorithm for SSc patients with DLCO <60 % predicted and >3 years duration of SSc (from first non-Raynaud's symptom) while recommending yearly PFTs and echocardiography in all SSc patients [89].

Outcomes

Outcomes in SSc-PAH are poor. While a recent study from the multicenter observational PHAROS cohort reports improved overall survival in the SSc-PAH population with 3 year survival of 75 %, other modern era cohort studies have reported 3-year survival less than 60 % [17, 60, 70, 72, 90–93]. The improved survival in the PHAROS registry may reflect inclusion of patients with less severe disease as more than half of the subjects had NYHA functional class I or II disease at enrollment. Prior studies have also demonstrated that survival remains worse in SSc-PAH than in patients with the idiopathic form of PAH, despite seemingly less severe hemodynamic perturbations at diagnosis [91, 94]. However, as recent research has shown, traditional measures of hemodynamic derangements in PAH (e.g., RAP and CO) may not be the best metrics to assess disease severity or outcomes in SSc-PAH [93]. For example, in one cohort study of SSc-PAH and IPAH patients, NT-proBNP levels were significantly higher in the SSc-PAH population despite less severe hemodynamic impairment; this difference persisted when controlling for potential confounders such as age and renal function [95]. Since NT-proBNP is released from the ventricles in response to increased wall stress, the observation suggested that responses to increased afterload on the RV may differ between SSc-PAH and IPAH. In line with this, recent physiologic studies have shown depressed RV function for a similar afterload in SSc-PAH compared to IPAH [96, 97]. Using pressure-volume measurements in the RV, Tedford and colleagues demonstrated significantly lower contractility in SSc-PAH compared to IPAH patients, despite similar pulmonary vascular resistive and pulsatile loading characteristics as assessed by resistance-compliance relationships and arterial elastance measures [97]. These findings suggest intrinsic RV dysfunction may contribute to the clinical differences in presentation and outcomes

Table 11.3 Predictors of survival in PAH-SSc

Male gender[a]
Age[a]
NYHA functional class at diagnosis[a]
Increased NT-proBNP
Right atrial pressure[a]
Mean pulmonary artery pressure[a]
Cardiac index
Stroke volume index
Pulmonary vascular resistance
Renal function

[a]Variable association with survival in PAH-SSc

noted between SSc-PAH and IPAH. Table 11.3 shows predictors of outcomes in patients with SSc-PAH.

PH Related to ILD in SSc

SSc patients can also develop PH related to ILD. However, there are few data describing the prevalence of PH in SSc-ILD. While the presence of ILD in SSc in the absence of PH portends a poor prognosis, survival is even worse in SSc patients with combined ILD and PH [12, 23, 70, 98]. In a cohort of 59 SSc-PH patients, 20 of whom had significant ILD (defined as a TLC <60 % predicted or TLC between 60 and 70 % predicted combined with moderate to severe fibrosis on high resolution CT of the chest), survival was significantly worse in the SSc-ILD cohort with 1-, 2-, and 3-year survival rates of 82 %, 49 %, and 39 % compared to 87 %, 79 %, and 64 % in the PH alone group, respectively ($p<0.01$) [12]. Presence of ILD portended a fivefold increased risk of death compared to PAH. Similar 3-year survival rates (47 %) were noted in another cohort of 47 SSc-PH-ILD patients [98].

Mixed Connective Tissue Disease

Patients with MCTD have clinical features of several connective tissue diseases including SSc, SLE, rheumatoid arthritis, and polymyositis. Symptoms include polyarthritis, myositis, sclerodactyly, Raynaud's phenomenon, esophageal dysmotility; less commonly serositis, rash, telangiectasias, and pigmentation abnormalities can be found. The characteristic laboratory feature is presence of antibodies to uridine-rich (U1) RNP polypeptides. While several diagnostic classification schemas for this disease have been proposed, all require the presence of U1-RNP antibodies [99]. These U1-RNP antibodies are also implicated in the pathogenesis of PAH by inducing endothelial cell activation and damage, perhaps in association with AECA [100, 101].

While renal involvement in MCTD is less common than with SLE or SSc, lung involvement may be more common than either entity [102–104]. Lung disease in MCTD can manifest as parenchymal disease, pulmonary vascular disease, or both [15, 21]. In one single center series of 201 subjects with MCTD, over 50 % of patients had ILD; whereas nearly 24 % were reported to have PAH. However, this is likely an over-estimate of the prevalence of PAH given that the diagnosis was established by echocardiography using a non-standard definition of PH (right ventricular systolic pressure estimate greater than 25 mmHg). Further, the proportion of patients with PH-ILD in this study was not reported. Other cohort studies have provided estimates of the prevalence of PAH in MCTD ranging from 19 % to as high as 50 %; however, some of these studies were either single-center studies or defined PAH based upon echocardiographic findings alone [103, 105, 106]. A recent study from a Norwegian prospective registry of patients with MCTD suggested a much lower prevalence of PAH, with only 5/147 patients with PH and just 2/147 with PAH [15]. However, since this was an observational study without a specific screening protocol for PH, this is likely an underestimate of the prevalence of PH and PAH. For example, while all patients underwent a screening echo at the time of enrollment, only 64 % of patients underwent a repeat echo during a mean follow-up period of nearly 6 years. Thus, it is likely that incident cases were missed during the study follow-up. Therefore, a reliable estimate of both PAH and PH-ILD in MCTD remains to be defined.

Another potential contributor to pulmonary vascular disease may be more common in MCTD than SSc. In the prior study by Gunnarsson and colleagues, the authors report a remarkably high

proportion of patients who develop thrombosis, both arterial (6.4 %) and venous (19.9 %) [107]. Whether these patients with venous thrombosis developed chronic thromboembolic disease and PH is unknown. Interestingly, anti-endothelial cell and anti-cardiolipin antibodies were frequently found in patients who developed thrombotic events, suggesting a possible common pathway for pulmonary vascular disease. This finding alone reinforces the importance of a thorough evaluation for chronic PE in MCTD patients with possible PH.

The REVEAL registry included 52 patients with MCTD-PAH and thus has added to our understanding of the particular characteristics of this disease [17]. These patients tended to be younger at enrollment than SSc-PAH patients (49.4 ± 16.1 vs. 61.8 ± 11.1 years, respectively). While there was no difference in gender distribution between MCTD-PAH and SSc-PAH, a higher proportion of MCTD-PAH patients were black and Hispanic. Serum biomarkers such as brain natriuretic peptide and creatinine were both significantly lower in the MCTD-PAH group compared to the SSc-PAH group. Interestingly, while there were no differences in spirometry or lung volume measurements between these groups, diffusion capacity for carbon monoxide (DLCO) was significantly higher in the MCTD-PAH group. On echocardiography, MCTD-PAH patients had less evidence of left ventricular systolic dysfunction; invasive hemodynamics did not significantly differ between groups, except for right atrial pressure that tended to be lower in the MCTD-PAH cohort.

Screening and Early Detection

In the REVEAL registry, nearly 70 % of patients with MCTD-PAH had functional class III symptoms at the time of diagnosis, highlighting the delay in diagnosis in this patient population [17]. A recent consensus statement suggests that MCTD patients with features of SSc should undergo the same screening protocol as patients with SSc alone to potentially mitigate the delay in diagnosis of PAH [89]. Whether this strategy will be effective in the early detection of PH in this population remains to be determined.

Outcomes

PAH is likely the most common cause of death in patients with MCTD. In a cluster analysis that divided patients into three groups based upon clinical features and antibody profiles, patients with either "PAH" (defined by echocardiography) or predominantly vascular involvement (thrombosis) had significantly poorer survival than the group with predominantly ILD and the group with predominantly articular manifestations [107]. PAH was the most common cause of death in both the vascular cohort (72 %) and in the overall cohort (50 %). Two recent cohort studies have reported outcomes in RHC-proven MCTD-PAH. In a national registry from the United Kingdom, survival in MCTD-PAH ($n = 28$) was similar to the survival observed in the SSc-PAH cohort ($n = 259$), at 1 year (83 % vs. 77 %) but perhaps better at 3 years (66 % vs. 47 %) [70]. In the REVEAL registry, 1-year survival did not differ between MCTD-PAH and SSc-PAH (88 % vs. 82 %) [17]. However, when compared to other forms of CTD-PAH, such as SLE-PAH, survival was worse in the MCTD-PAH cohorts in both studies.

Systemic Lupus Erythematous

SLE is also a multisystem disease that can affect the lungs and lead to several forms of pulmonary vascular disease including PH-ILD, PAH, and CTEPH. In addition, PH can result from SLE-associated cardiomyopathy or from renal failure requiring hemodialysis and placement of arteriovenous fistulas [108]. Thus, PH in SLE can also be classified in any of the five PH categories (Fig. 11.1).

Prevalence estimates of PH in SLE vary widely, from 0.0005 to 14 % of patients [19, 109–118]. Much of this variance in estimates can be attributed to the definition of PH and the method of detection employed. For example, three of the studies that employed RHC to diagnose PH utilized non-standard definitions of PH (mPAP >30 mmHg (one study) and mPAP >40 mmHg (two studies)) [19, 109, 110]. Furthermore, since screening protocols for PH are not recommended

based upon the relative rarity of PH in the SLE population, only symptomatic patients undergo evaluation for PH. Thus, while it appears that the prevalence of PH in SLE is lower than that in other CTDs such as SSc and MCTD, the true prevalence may be significantly higher.

Patients who develop the disease tend to be young (average age around 30 at diagnosis) and often have Raynaud's phenomenon. On average, patients have SLE for nearly 5 years prior to the development of PAH [119]. Risk factors for the development of PAH related to SLE are not well described, but one retrospective cohort study that used echo to define PH (defined as a RVSP ≥35 mmHg) found that blacks were more likely to have PH. Further, patients with longer disease duration, peripheral nervous system involvement, and with pericarditis were more likely to have PH [118]. The authors also found patients with anti-smooth muscle antibodies and anticardiolipin antibodies were more likely to develop PH.

Outcomes

As expected, outcomes in SLE patients with PH are worse than for those without PH. While prior studies reported median survival for SLE-PAH patients ranging from 2 to 3 years, a more recent cohort study from the United Kingdom reported a 3-year survival of 75 % [19, 70, 113, 120]. PAH also appears to be a common cause of death in several cohorts from Korea and China, however, it is a rare cause of death in North American and European cohorts [121, 122]. These differences between cohorts suggest possible ethnic differences in the impact of PH on outcomes in SLE but remain to be confirmed or explained. In a recent systematic review of factors associated with outcomes in SLE-PAH, Johnson and colleagues found both PH-specific and SLE-specific parameters predicted survival [117]. Higher mPAP at diagnosis was associated with poorer outcomes. Vascular manifestations of SLE in particular, such as Raynaud's phenomenon, pulmonary vasculitis, thrombosis, thrombocytopenia, and presence of anti-cardiolipin antibodies, portended a poorer prognosis. Interestingly, neither lupus disease activity nor nephritis was associated with poorer outcomes.

Sjogren Syndrome

Sjogren syndrome (SS) is a chronic inflammatory disease characterized by lymphocytic infiltration of exocrine glands and extra-glandular tissues. The disease can present as primary disease or in association with other CTDs like RA or SSc. Up to 0.4 % of the general population has SS; the vast majority are women in the fourth and fifth decades of life [123]. While the sicca syndrome (xerophthalmia and/or keratoconjunctivits sicca and xerostomia) is most commonly present in patients with SS, extra-glandular involvement of the lungs is common, typically manifesting as ILD. Various types of ILD have been described in SS, including lymphocytic interstitial pneumonia, non-specific interstitial pneumonitis, usual interstitial pneumonitis, and organizing pneumonia [124].

In contrast, PAH is rare in SS; in fact, only 43 known cases of RHC-confirmed SS-PAH are reported in the literature. Relatively large cohort studies have estimated the prevalence of PH around 20 %, however, neither study distinguished between PH related to ILD and PAH and RHC was not used to establish the diagnosis [22, 125]. Thus, the true prevalence remains unknown. However, in the largest case series of patients with SS associated PH Launay and colleagues describe characteristics of patients with this disease, noting that these patients were more likely to have Raynaud's phenomenon, vasculitis, and ILD [14]. Antibody profiles suggested associations with anti-Ro and RNP antibodies; hypergammaglobulinemia was also noted to be more frequent in SS patients with PAH. Survival in this cohort was poor with 1- and 3-year survival at 73 % and 66 % respectively, similar to survival seen in patients with PAH-SSc.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterized by a symmetric, inflammatory polyarthritis that leads to joint destruction. RA is more prevalent than most other CTDs occurring in 40 out of 100,000 persons in the US.

Women in the US have a nearly 4 % lifetime risk of developing RA [126]. Extra-articular disease affects multiple organs including the skin, eyes, hematologic system, and kidneys; importantly, cardiopulmonary involvement is common. There is a high risk of coronary artery disease, myocardial infarction, heart failure, and sudden death compared to age-matched persons without RA [127]. Pulmonary manifestations include interstitial lung disease, rheumatoid nodules, airways disease with bronchiolitis obliterans and organizing pneumonia. Additionally, pleural disease with effusion, empyema, bronchopleural fistula, or pyopneumothorax is fairly common, occurring in up to 20 % of patients [128]. Lung disease may also result from disease-modifying antirheumatic drugs, with complications such as pneumonitis, fibrosis, obliterative bronchiolitis, infection, and bronchospasm, amongst others [129].

Pulmonary hypertension in RA has been reported in association with left heart disease, interstitial lung disease, and chronic thromboembolic disease [130, 131]. Isolated pulmonary hypertension, that is, PH in the absence of overt left heart disease, ILD, and chronic thromboembolic disease, has been infrequently reported in the literature [132–142]. In these case reports, PH has been attributed to pulmonary vasculitis [132, 135, 136, 138], hyperviscosity syndromes [134], and PAH [133, 137]. In a few of these studies, RHC was performed, confirming the diagnosis of PAH. Further, lung tissue obtained either by biopsy or at autopsy in these patients demonstrated some classic features of PAH, including intimal proliferation, medial hypertrophy, and even plexiform lesions in the small pulmonary arterioles [132, 135, 137]. In the UK registry, only 12 RA-PAH patients were identified while in the REVEAL registry, 28 cases of RHC-proven RA-PAH were included [17, 70]. When compared to patients with SSc-PAH in the REVEAL cohort, RA-PAH patients tended to be younger (54 ± 15.8 vs. 61.8 ± 11.1 years). Raynaud's phenomenon was less likely to be present (3.6 % vs. 32.6 % of the cohort); renal insufficiency was less frequent, and BNP levels were significantly lower. Functional class at baseline, 6 min walk distance, and hemodynamics were similar between RA-PAH and SSc-PAH patients. Similar to the findings seen in the MCTD-PAH cohort in the REVEAL registry, while spirometry and lung volumes were similar when compared to SSc-PAH, diffusing capacity was higher in the RA-PAH cohort. Survival in the RA-PAH cohort was significantly better than the SSc-PAH cohort with 1-year survival at 96 % vs. 82 % in the SSc-PAH cohort (p-value = 0.01).

Polymyositis/Dermatomyositis

Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory myopathies that are characterized by proximal muscle weakness. DM has characteristic skin manifestations though clinical features of both DM and PM vary among affected individuals. The estimated prevalence of these diseases varies from 5 to 22 per 100,000 persons with an annual incidence of 2 per 100,000 [143, 144]. PM/DM are both multisystem disorders with the potential to affect the heart, GI tract, and lungs; there is also an increased rate of malignancy, particularly with DM [145]. The most common pulmonary manifestation of PM/DM is interstitial lung disease, occurring in about 10 % of patients, though respiratory symptoms such as dyspnea and orthopnea can also arise from muscle weakness affecting the diaphragm [146].

Pulmonary hypertension appears to be a rare complication of PM/DM and if present, may be related to underlying ILD [18]. In the UK registry, only seven patients (2 % of the entire CTD-PAH cohort) with PM/DM-PAH were identified; there were no cases of PM/DM-PAH in the REVEAL registry [17, 70]. No clinical demographic or hemodynamic characteristics of these patients were reported in the UK registry; however, the 1- and 3-year survival was 100 % for these patients, suggesting better outcomes for PM/DM-PAH compared to other CTD-PAH.

Treatment

With improved understanding of PAH, novel therapies targeting select pathways in the putative pathogenesis have been developed. These therapies focus on the chronically impaired

endothelial function that affects pulmonary vascular tone and remodeling. Further, recent studies identifying aberrant proliferation of endothelial and smooth muscle cells and increased secretion of growth factors have drawn investigators to compare PAH to a neoplastic process and have paved the way for trials of antineoplastic agents in PAH [147–151].

Randomized clinical trials of novel therapeutics for PAH have included patients with various forms of CTD-PAH, although the majority of patients enrolled likely have SSc (Table 11.4). Sub-group analyses in the CTD-PAH cohorts of these studies have only been intermittently reported [152–156]. Given the differences in demographic and hemodynamic characteristics between CTD-PAH types, the results from these clinical trials are unlikely to be generalizable to all forms of CTD-PAH and thus should be interpreted with caution in most cases. Still, the PAH therapies discussed next are commonly used in all forms of CTD-PAH although the evidence base for diseases other than SSc is minimal.

Table 11.4 Inclusion of CTD-PAH patients in pivotal trials of PAH therapy

	CTD-PAH (*n*, overall %)	Type of CTD (*n*, % CTD)
Epoprostenol	111 (100 %)	lcSSc: 77 (69 %)
		dcSSc: 14 (13 %)
		Others: 20 (18 %)
Oral treprostinil	110 (19 %)	NR
Oral treprostinil add-on	92 (26 %)	NR
SC treprostinil	90 (19 %)	lcSSc: 20 (22 %)
		dcSSc: 25 (28 %)
		SLE: 25 (28 %)
		MCTD: 17 (19 %)
		Overlap: 3 (3 %)
Inhaled treprostinil	77 (33 %)	NR
Inhaled iloprost (AIR)	35 (17 %)	NR
Inhaled iloprost + bosentan	NR	NR
Beraprost	13 (10 %)	NR
Vardenafil (EVOLUTION)	20 (30 %)	NR
Tadalafil (PHIRST)	95 (29 %)	NR
Sildenafil + epoprostenol (PACES)	55 (21 %)	SSc: 31 (56 %)
		SLE: 14 (25 %)
		Other: 10 (18 %)
Sildenafil (SUPER)	84 (30 %)	SSc: 50 (60 %)*
		SLE: 19 (23 %)
		MCTD: 8 (10 %)
		SjS: 4 (5 %)
		RA: 1 (1 %)
Bosentan (EARLY)	33 (18 %)	SSc: 15 (46 %)
		SLE: 11 (6 %)
		MCTD: 3 (9 %)
		SjS: 1 (3 %)
		Other: 1 (3 %)
Bosentan (Study 351 + BREATHE)	66 (27 %)	SSc: 52 (78 %)
		SLE: 8 (12 %)
		Overlap: 4 (6 %)
		UCTD: 2 (3 %)
Bosentan + epoprostenol (BREATHE-2)	6 (18 %)	SSc: 5 (83 %)
		SLE: 1 (17 %)
Ambrisentan (ARIES 1 + ARIES 2)	136 (35 %)	NR
Sitaxsentan (STRIDE-1)	42 (24 %)	SSc: 19 (45 %)
		SLE: 15 (36 %)
		MCTD: 7 (17 %)

General Measures

Despite a lack of specific data for PAH of any form, consensus guidelines recommend the use of supplemental oxygen in patients who are hypoxic (peripheral oxygen saturation <90 %) at rest or with exercise, largely based upon extrapolation of data from chronic obstructive lung disease [2, 157, 158]. In addition, diuretics are recommended for the management of volume overload and for right heart failure. Digoxin may also be useful for the management of refractory right heart failure complicated by atrial arrhythmias. Exercise, and in particular, pulmonary rehabilitation, may also be beneficial as demonstrated in a clinical trial of prescribed exercise in a population of patients with IPAH [159]. In this study, both quality of life and exercise capacity as assessed by the 6MWT were significantly improved in patients who completed a specific exercise program, with rather large effect sizes. Similar results were demonstrated in a smaller observational study of CTD-PAH [160].

Anticoagulation

Anticoagulation is recommended in the treatment of IPAH based primarily upon retrospective, observational data showing improved survival in patients on warfarin therapy [2]. However, no such data exists for CTD-PAH. Despite the potential for increased risk of gastrointestinal bleeding due to vascular ectasias that may be common in certain forms of CTD, the current guidelines recommend therapy with oral anticoagulation in those without contraindications, particularly in those patients with more advanced disease who are receiving continuous intravenous therapy.

Immunosuppression

As discussed previously, inflammatory and immunological mechanisms are likely involved in the pathogenesis of both CTD and PAH. Given this potential commonality in pathobiology, anti-inflammatory agents have been employed in various types of CTD-PAH. However, there are no randomized clinical trials in patients with CTD-PAH to support its use in this patient population. Still, several case series have suggested efficacy in certain populations within CTD-PAH. In the report by Jais and colleagues, 23 patients with either SLE- or MCTD-associated PAH were treated with combination therapy including cyclophosphamide and glucocorticoids; nearly half of the SLE-PAH and MCTD-PAH patients demonstrated clinical improvement in functional capacity and hemodynamics [161]. However, the 6 SSc-PAH patients included in the cohort did not demonstrate response to immunosuppression. Still, these patients did experience improvement in these parameters once PAH-specific therapy was initiated. Other investigators have reported improvements in functional capacity, hemodynamics, and in certain cases, in expected survival, with immunosuppressant therapy [162–164]. Randomized clinical trials are needed to better understand the role of immunosuppressant therapy in patients with CTD-PAH, and in particular, in SSc-PAH in whom disease is often refractory to such interventions.

Prostaglandins

Prostacyclin is an endogenous vasodilator that inhibits platelet aggregation via activation of cyclic adenosine monophosphate. Exogenous prostanoids increase production of prostacyclins which in turn restores the balance between vasoconstrictors such as thromboxane A2 and vasodilators. The synthetic prostacyclin epoprostenol was the first drug approved for therapy for PAH and to date, remains the only therapy that has been shown to improve survival in a randomized clinical trial of PAH patients [165]. Epoprostenol has also been studied in patients with SSc-PAH [166]. However, while there were statistically significant improvements in exercise capacity and hemodynamics, no survival benefit was found. Still, this medication is considered the most efficacious for the treatment of PAH and thus, is used in patients with severe disease.

There are several important factors related to drug delivery and side effects that must be carefully considered prior to initiation of intravenous epoprostenol. Since the half-life of this medication is only 2–3 min, it must be delivered via continuous infusion through a tunneled catheter. Further, IV epoprostenol is only stable at room temperature for 8 h and thus must be kept cold to maintain its integrity. Recently, a room temperature stable formulation was approved for commercial use. Side effects are common and include headache, jaw pain, nausea, diarrhea, leg pain, heel pain, and flushing. Systemic hypotension is also common. These side effects can be dose-limiting in certain patients. Several reports of pulmonary edema in patients with SSc-PAH who were treated both acutely and chronically with prostaglandin derivatives raise the suspicion of occult pulmonary veno-occlusive disease and highlight the risks of therapy in these patients [167, 168].

Use of IV epoprostenol in patients with CTD-PAH seems to vary from use in IPAH patients. A recent study reporting the 15-year experience at the University of Michigan found that significantly fewer SSc-PAH patients received IV prostacyclins compared to IPAH patients in the cohort (38.5 % vs. 55.3 %, $p = 0.02$) despite nearly 80 %

of the SSc cohort demonstrating severe PAH (WHO functional class III/IV) [94]. We have a similar experience at our center, with less than 45 % of class III/IV SSc-PAH patients on IV prostacyclin therapy. This is in part related to patient factors including limited manual dexterity in our SSc population due to sclerodactyly and digital ulcers (DU); historically, the need for the use of cold packs also precipitated Raynaud's exacerbations and contributed to lower utilization in this patient population. However, this rate of use in severe PAH patients parallels use across the United States as shown in the REVEAL registry, where only 43 % of patients (all PAH types) who died were receiving IV prostacyclin therapy at the time of death [169].

There are several other formulations of prostacyclin analogues that are currently available for use in the treatment of PAH and have been studied in CTD-PAH. Iloprost is formulated in both intravenous and inhaled versions, though only the inhaled form is approved for therapy of PAH in the USA. IV iloprost has been studied in CTD patients without PAH for treatment of peripheral vascular complications and shown to improve exercise capacity and hemodynamics compared to baseline values; however no specific data exist in patients with CTD-PAH [170, 171]. Studies of inhaled iloprost in various forms of PAH, including CTD-PAH, have demonstrated significant improvements in functional class, exercise capacity, and hemodynamics compared to placebo [172].

Treprostinil is another prostacyclin analogue that is chemically stable at room temperature and is available in IV, subcutaneous (SC) and inhaled forms; trials with an oral form of treprostinil are currently underway. Similar to IV epoprostenol, IV treprostinil must be delivered via a central catheter and continuous infusion pump. The SC formulation is also delivered via continuous infusion, but through a needle placed in the subcutaneous space. Ninety patients with various types of CTD-associated PAH were included in the large randomized clinical trial of SC treprostinil (Table 11.4). The response in this subset, as reported by Oudiz and colleagues, suggested clinical efficacy, with improvements in dyspnea scores, functional capacity, and hemodynamics, though the change in 6MWD between treatment and placebo groups was of marginal statistical significance (25 m, $p=0.055$) [153]. Although patients with CTD-PAH were included in the TRIUMPH study investigating the addition of inhaled treprostinil to bosentan or sildenafil and significant improvement in functional capacity was found, no subgroup analyses on CTD-PAH patients were reported [173].

Endothelin Receptor Antagonists

Endothelin-1 (ET-1) is a potent vasoconstrictor that regulates vascular tone and cell proliferation in the pulmonary vasculature; perturbations in ET-1 balance are thought to contribute to the pathogenesis of PAH [174]. Further, ET-1 also may have a role in the pathogenesis of SSc contributing to vascular damage and fibrosis as prior studies have identified relationships between ET-1 levels and disease severity [175]. Thus, ET-1 remains an attractive target for therapy in CTD-PAH and SSc-PAH in particular.

Endothelin receptor antagonists (ERA) block ET receptors on vascular smooth muscle thereby promoting vasorelaxation in the pulmonary vasculature. Bosentan, a dual competitive ET receptor antagonist, was the first agent developed in this class. In the BREATHE-1 study, significant improvements in functional class, 6MWD, time to clinical worsening (TTCW), and hemodynamics were found in PAH subjects receiving bosentan compared to placebo. Almost a third of these subjects in this trial had CTD-PAH. In a subgroup analysis of this study, CTD-PAH patients, most of whom had SSc-PAH, did not exhibit a significant improvement in 6MWD; however, subjects in the treatment arm were less likely to experience deterioration. These findings were similar to observations from our experience with initial therapy with bosentan; when compared to IPAH patients, SSc-PAH patients had less robust response to therapy with no change in FC, poorer survival, and a higher incidence of side effects [176]. However, in a multicenter observational study of initial therapy with

bosentan in a cohort of 53 CTD-PAH patients (80 % with SSc-PAH), after 48 weeks of therapy, a larger proportion of patients experienced an improvement in FC than a decline (27 % vs. 16 %), but the majority experiencing no change in FC (57 %) [156]. Further, 1-year survival was 92 %; improved when compared to historical controls, however, no improvement in health-related quality of life was noted. In a sub-group analysis of randomized clinical trials of bosentan in which CTD-PAH subjects were included, trends towards improvement in 6MWD and improved survival compared to historical controls were found [154]. However, this cohort included patients with various forms of CTD-PAH and thus may not accurately reflect the experience of a particular group within the CTD population. Bosentan has also been studied in the management of Raynaud's and digital ulcers (DU), but a recent meta-analysis suggests that while the number of new DU are reduced in SSc patients on bosentan, there is no effect on healing of existing DU [177]. Thus, bosentan therapy seems to stabilize and in some cases, improve symptoms and functional capacity in patients with CTD-PAH, but may not improve quality of life or other vascular complications of CTD such as DU. There may also be improvement in 1-year outcomes compared to historical controls, but this has not been evaluated in a prospective, randomized study.

Ambrisentan is another ERA with a high selectivity for ETA vs. ETB receptors (>4,000-fold). This selectively may target the vasoconstrictive effects of endothelin while preserving the vasodilatory action that is mediated by ETB receptors, however, the clinical relevance of this degree of selectivity is unknown. In large, randomized, double-masked, placebo-controlled clinical trials of PAH, patients receiving ambrisentan demonstrated significant improvement in 6MWD and a significant reduction in TTCW [178]. In the CTD-PAH subgroup, initially there was improvement in 6MWD, but by the end of the study at 24 weeks, no differences compared to baseline were found. In the long-term extension study, 124 of the 383 subjects (32 %) included had CTD-PAH, however, the type of CTD was not reported [179]. In this observational study, 1- and 2-year survival for CTD-PAH patients was 91 % and 83 % respectively; however, since nearly 20 % of subjects were on combination therapy with other PAH-specific medications at 2 years, the long-term effects of ambrisentan alone cannot be determined accurately. In another observational study that included 40 CTD-PAH patients who were either treatment-naïve or on background therapy with other PAH-specific medications, no significant improvement in 6MWD was noted after 24 weeks of therapy with ambrisentan. Still, in each of these studies, ambrisentan was well tolerated; however, nearly 33 % of patients experienced worsening lower extremity edema with initiation of therapy.

Macitentan is a tissue-targeting ERA that has been shown in vivo to remain active in local tissue environments leading to longer functional half-life than other ERAs [180]. A recent randomized, double blind, placebo controlled trial of macitentan at 3 and 10 mg demonstrated a significantly reduced risk of morbidity/mortality compared to placebo with 45 % reduction in the 10 mg group with a 30 % reduction in the 3 mg group [181]. In this study, 30.5 % of PAH patients had CTD-related disease; however, no data on specific effects in this population have been published to date. Macitentan was well tolerated, with no difference in lower extremity edema between the placebo and treatment arms.

Side effects with ERA are common and include peripheral edema, headache, dyspnea, upper respiratory tract infection, nasal congestion, fatigue, and nausea. ERAs may also cause hepatotoxicity. However, due to differences in formulation between bosentan, ambrisentan, and macitentan, there is no increased risk of liver dysfunction over placebo with ambrisentan and macitentan and thus, monthly monitoring for hepatotoxicity is not required for these agents, but is for bosentan [182]. Further, decreases in hemoglobin can occur and require monitoring. ERAs are teratogenic and thus pregnancy is a formal contraindication; further, due to drug–drug interactions, estrogen/progesterone contraception is not a reliable form of contraception in the presence of bosentan.

Phosphodiesterase Inhibitors

Phosphodiesterase type 5 inhibitors (PDE5I) inhibit the degradation of cyclic guanosine monophosphate (cGMP), a second messenger released by soluble guanylate cyclase (sGC) in response to nitric oxide (NO) stimulation. NO is a potent vasodilator that also inhibits platelet aggregation and vascular smooth muscle cell proliferation; deficiency of NO is thought to be an integral part of the pathogenesis of PAH [183]. By slowing the breakdown of cGMP, PDE5I enhance vascular smooth muscle cell dilation.

The expression and activity of PDE5 is considerably elevated in the lung and pulmonary vascular smooth muscle cells and is thus an attractive therapeutic target for treatment of PAH. Several agents initially used to treat erective dysfunction have been studied as therapy for PAH. Sildenafil was the first agent studied in a large, randomized clinical trial of PAH. In the SUPER study, subjects were randomized to 20, 40, or 80 mg of sildenafil three times a day or placebo [184]. Compared to placebo, there was a significant improvement in the primary outcome (6MWD) at all doses at the end of the 12-week study. Secondary outcomes, such as hemodynamics, also demonstrated significant improvement between groups, but no significant differences in dyspnea or TTCW were noted between groups. A sub-group analysis of CTD-PAH subjects in the SUPER study showed statistically significant improvements in 6MWD with the 20 and 40 mg doses (42 m, 95 % CI 20–64 m, $p<0.01$ and 36 m, 95 %CI 14–58, $p<0.01$, respectively) [156]. In addition, functional class improved with each dose, but a higher proportion of patients in the 40 and 80 mg dose groups experienced improvement compared to the 20 mg group (40 % and 42 % vs. 29 %, respectively). Hemodynamic improvements with all treatment doses were also noted. Based upon the conglomeration of data, the FDA approved dose of sildenafil for the treatment of PAH is 20 mg TID, though some clinicians advocate higher doses in practice.

Tadalafil is another PDE5I that has been studied for the treatment of PAH. Tadalafil has a distinct chemical structure compared to sildenafil that leads to differences in selectivity for the PDE5 enzyme and in its pharmacokinetics [185]. Since tadalafil has a 17.5 h half-life, it can be administered once daily. In the PHIRST study, a double-blind, placebo-controlled trial of once daily tadalafil in either treatment naïve or patients on stable bosentan therapy, significant improvement in 6MWD was noted at the highest dose studied (40 mg daily) [186]. Further, improved TTCW and quality of life in the treatment arm was noted, though there was no significant improvement in functional class or in dyspnea. In CTD-PAH subjects, there was a dose-dependent improvement in 6MWD, with a placebo-adjusted improvement of 49 m (95 %CI 15–83) in the 40 mg group compared to placebo.

In general, PDE5I are well tolerated. Common side effects include flushing, headache, nasal congestion, myalgias, and gastrointestinal upset. Given some homology between PDE5 and PDE6 which is predominantly in the retina and integral in the phototransduction cascade, there is a potential for visual side effects, including light sensitivity, blue-greenish or blurred vision. Importantly, a recent study in patients on chronic therapy with PDE5I reported that sildenafil is well tolerated from an ocular perspective [187]. The authors' practice is to have patients undergo evaluation by an ophthalmologist prior to initiation of PDE5I therapy and then follow up on a yearly basis while on therapy to monitor for potential ocular problems.

Riociguat is a sGC stimulator that sensitizes sGC to low levels of bioavailable NO and leads to increased cGMP synthesis through NO-independent mechanisms [188]. This mechanism of action offers a potential benefit over PDE5I since PDE5I depends upon bioavailability of NO and NO is relatively deficient in PAH [189]. Thus, sGC stimulation by riociguat may be more effective in increasing NO bioavailability.

Two recent studies of riociguat in PH have been completed, one in PAH and one in CTEPH. PATENT-1 investigated the efficacy and safety of riociguat in PAH patients who were either treatment naïve or on background therapy with another

PAH-specific medication [190]. The primary outcome of change in 6MWD at 12 weeks was met, with a 36 m improvement in the treatment group compared to placebo (95 % CI 20–52 m, $p<0.01$). Interestingly, significant improvements in 6MWD of nearly similar magnitude were noted in both treatment naïve patients and in those on background therapy. Statistically significant improvements in secondary outcomes, including functional class, TTCW, quality of life, dyspnea, NT-proBNP, and hemodynamics were also found. No data regarding efficacy in CTD-PAH subjects, who comprised 25 % of the study cohort, has been published to date. Side effects were generally mild and riociguat had a favorable safety profile.

Combination Therapy

Given the potential for synergistic effects between the available PAH therapies that target separate pathways involved in the pathogenesis of the disease, combination of therapies from different classes commonly occurs in clinical practice, though the evidence base for this practice is limited. As discussed previously, several therapies have been studied in clinical trials that enrolled a proportion of subjects on background PAH therapy with an agent from a different class than the drug of interest. Several on-going trials are examining the efficacy of combination therapy, including COMPASS (sildenafil and bosentan) and AMBITION (tadalafil and ambrisentan). In addition, there is an on-going investigator-initiated observational study of tadalafil and ambrisentan in treatment naïve SSc-PAH patients, which is nearing completion (clinicaltrials.gov identifier NCT01042158). Other completed studies examining the impact of combination therapy have demonstrated mixed results. In BREATHE-2, a study of adding bosentan or placebo to IV epoprostenol failed to achieve the primary endpoint of improvement in total pulmonary resistance on RHC and in secondary endpoints such as improvement in 6MWD [191]. Interestingly, the authors attribute the lack of clinical response in this study to a higher proportion of SSc-PAH patients in the treatment arm citing less robust response to therapy in general in the SSc-PAH population. In PACES, where subjects on IV epoprostenol therapy were randomized to sildenafil 80 mg TID or placebo, there were significant improvements in exercise capacity, TTCW, quality of life, and hemodynamics. However, only 17 % of the cohort had CTD-PAH and thus, no conclusions regarding the efficacy of this combination in this population can be drawn.

At our center, we have found poorer response to combination therapy in SSc-PAH compared to IPAH patients [192]. Although the addition of sildenafil to bosentan monotherapy improved functional class and 6MWD in IPAH subjects, no such effect was found in the SSc-PAH subjects. Furthermore, there were significantly more side effects in the SSc-PAH group, including hepatotoxicity. Drug–drug interactions have been described between bosentan and sildenafil and may be of clinical significance, particularly in the SSc-PAH population [193].

Novel Therapies

Recent insights into the pathobiology of PAH that emphasize the aberrant proliferation of endothelial and smooth muscle cells have led investigators to study anti-neoplastic agents that target these processes. In experimental models of PH, inhibition of proliferation and increased apoptosis of smooth muscle cells with the addition of various tyrosine kinase inhibitors (TKI) improved hemodynamics, reversed vascular remodeling, and improved survival [194, 195]. Several case reports of the TKI imatinib, a dual platelet-derived growth factor and vascular endothelial growth factor inhibitor, suggested utility in patients with PAH, including one patient with SS-PAH and one with PVOD [150, 196–199]. However, several large clinical trials of imatinib demonstrated mixed results and ultimately, the drug was not approved for use in PAH [148, 149]. In addition, the TKI dasatinib has recently been reported to induce PAH [200]. This is thought to be related to the wide-ranging targets of dasatinib, including Src kinase, that may be implicated in the development of PAH [201].

A multi-center study of the anti-neoplastic agent, rituximab, in PAH-SSc patients is ongoing. Rituximab is a chimeric monoclonal antibody against the B-cell surface protein CD20. Based upon pre-clinical data suggesting integral involvement of B-cells in SSc pathogenesis and in PAH pathogenesis, a Phase II clinical trial for the evaluation of rituximab in SSc-PAH was initiated and currently enrolling subjects [202]. The primary outcome of this trial is change in PVR at 24 weeks.

PH-Specific Therapy in PH-ILD-CTD

As discussed previously, patients with CTD often develop PH related to concomitant ILD and this may be more common in SSc compared to other CTDs. While treatment of PH-ILD with PAH-specific medications is appealing from a therapeutics standpoint, differences in the mechanism of development of PH in the presence vs. absence of ILD may influence the response to specific pulmonary vasodilator therapy. Hypoxic vasoconstriction, one of the predominant mechanisms of development of PH in ILD, is also an important regulator of ventilation perfusion (VQ) matching in the presence of parenchymal lung disease. Currently, all commercially available PAH medications work by causing pulmonary vascular dilation; thus, it is highly likely that addition of such medications would worsen VQ matching by releasing appropriate hypoxic vasoconstriction. Still, given the high prevalence of pulmonary vascular disease in SSc, there may be a population of patients with some degree of ILD who will respond to PAH-specific therapy (Fig. 11.3). Unfortunately, identification of these patients is challenging.

Several investigators have reported their experience with off-label use of PAH-specific therapies in SSc patients with PH-ILD. Le Pavec and colleagues recently reviewed the response to PAH-specific therapy in 70 SSc patients with PH-ILD who were treated with various PAH-specific therapies [203]. After a mean follow up of 7.7 years, there were no changes in functional class, 6MWD, or hemodynamics when compared

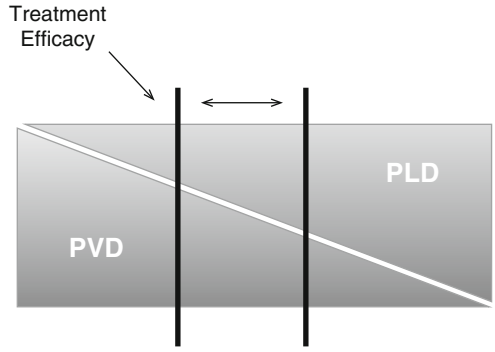

Fig. 11.3 Contributors to pulmonary hypertension in CTD and response to pulmonary vasodilator therapy. While clinically pulmonary hypertension in CTD is commonly attributed to either pulmonary vascular disease or parenchymal lung disease, typically, there are components of both contributing to elevated pulmonary pressures as demonstrated in this figure. Efficacy of pulmonary vasodilator therapy seems to be greatest in patients with predominantly pulmonary vascular disease, however, the "threshold" proportion of parenchymal lung involvement (represented here by the red lines) for which efficacy of these therapies can be demonstrated remains to be determined

to baseline values. One-, 2-, and 3-year survival rates were 71 %, 39 %, and 29 % respectively. In multivariable analyses, worsening of oxygenation with initiation of therapy and deterioration of renal function were associated with risk of death. There are few studies examining the response to PAH-specific therapies in PH-related to other forms of CTD.

Lung Transplantation in CTD-Related Pulmonary Hypertension

Many centers consider CTD to be relative contraindication to lung transplantation due to concerns about gastroesophageal reflux leading to bronchiolitis obliterans syndrome, renal impairment complicating management of immunosuppressive and antimicrobial agents commonly employed post-transplantation that are often nephrotoxic, and extrapulmonary organ involvement. Based upon these concerns, less than 2 % of all lung transplantation worldwide between 1995 and 2010 occurred in patients with underlying CTD [204]. However, as shown by several

investigators, outcomes for CTD patients do not appear to be significantly different from patients with either IPAH or ILD in isolation [205–207]. Thus, lung transplantation should be considered for patients with severe PH who are failing therapy.

Response to Therapy in CTD-PAH

In general, clinical trials of PAH-specific therapies for the treatment of PAH have shown a blunted response in CTD-PAH, and in particular, SSc-PAH. For instance, a systematic review of treatment effect of PAH therapies in CTD-PAH using data from the pivotal clinical trials of these agents demonstrated a non-significant improvement in exercise capacity in the CTD population with smaller effect size estimates [208]. However, the presence of comorbidities and confounding factors in CTD-PAH may limit the interpretation of the currently employed outcome measures for clinical trials of therapeutics in PAH. As shown in Table 11.5, several CTD-specific factors may influence the measures of response to therapy, including concomitant ILD, left ventricular diastolic dysfunction, musculoskeletal disease, and gastrointestinal disease. In an attempt to mitigate these limitations of outcome measures in CTD-PAH trials, a Delphi consensus study convening experts from multiple subspecialties involved in the care of patients with SSc and PAH recommended a set of core outcome measures be utilized in clinical trials of SSc-PAH therapies; these measures encompassed domains such as cardiopulmonary hemodynamics, exercise testing, dyspnea, medication adherence, quality of life, and survival [209]. Recent expert opinion has suggested using TTCW as a primary outcome measure with focus on disease-specific measurement of clinical worsening (i.e., distinguishing between CTD-related and PAH-related clinical worsening) and stratifying patients by disease type and functional class at randomization [210].

Conclusions and Future Directions

Pulmonary hypertension commonly complicates CTD and is invariably associated with high morbidity and mortality. Unfortunately, despite heightened awareness for this entity in CTD patients, PH is often under-recognized in CTD. Further, while specific pulmonary vasodilator therapy has been shown to improve symptoms, quality of life, and survival in other forms of PAH, the response to therapy has been attenuated in patients with CTD-associated disease in general. However, currently employed markers of disease severity and outcome measures are inadequate for CTD-related PH and thus, identification and validation of measures relevant to CTD-associated disease is imperative. Additionally, therapies targeting pathways specific to CTD are currently under investigation and may provide directed therapy for this devastating complication of CTD.

Table 11.5 Disease-specific considerations in CTD-associated PH

Domain	Tool	Application to CTD-PAH
Hemodynamics	RHC, Echo	Group II and III disease confound assessment
Exercise testing	6MWD	Musculoskeletal disease/deconditioning
Dyspnea	Borg dyspnea	Non-PAH causes for dyspnea (ILD, anemia, etc.)
Adherence with therapy	Adverse events	Concomitant medications for CTD may interact
Pharmacodynamics	Bioavailability	Different due to GI motility, malabsorption
Quality of life	SF-36/CAMPHOR	Extra-pulmonary involvement affects QOL
Global state	Survival	Poorer survival overall compared to IPAH

Adapted with permission from Denton CP, Avouac J, Behrens F, Furst DE, Foeldvari I, Humbert M, et al. Systemic sclerosis-associated pulmonary hypertension: why disease-specific composite endpoints are needed. Arthritis Res Ther 2011;13(3):114

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