

# Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Pulmonary arterial hypertension associated with connective tissue diseases

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**Abstract:**

The explosive growth of medical literature on pulmonary hypertension (PH) has led to a steady increase in awareness of this disease within the medical community during the past decade. The recent revision of the classification of PH is presented in the main guidelines.

Group 1 PH or pulmonary arterial hypertension (PAH) is a heterogeneous group and includes PH due to inheritable, drug-induced, and toxin-induced causes and to such underlying systemic causes as connective tissue diseases, human immunodeficiency viral infection, portal hypertension, congenital heart disease, and schistosomiasis.

Systemic sclerosis (SSc) is an autoimmune multisystem disorder, which affects over 240 persons per million in the United States.<sup>[1]</sup> Its manifestations are not confined to the skin but may also involve the lungs, kidneys, peripheral circulation, musculoskeletal system, gastrointestinal tract, and heart.

The outcome of PAH associated with SSc is worse when compared to other subtypes of PAH.

In this review, we summarize available information about the pulmonary vascular and cardiac manifestations of SSc with special emphasis on their prognostic implications as well as the peculiarity of their detection.

**Key words:**

pulmonary arterial hypertension, connective tissue disease, systemic sclerosis, right ventricular failure, Saudi association for pulmonary hypertension guidelines

Pulmonary arterial hypertension (PAH) is caused by a remodeling of precapillary arterioles leading to a progressive increase in pulmonary vascular resistance and right ventricular (RV) failure, which is a cause of significant morbidity and eventually the cause of death in patients afflicted with this syndrome.<sup>[2-5]</sup> PAH is typically diagnosed by right heart catheterization (RHC) when the mean pulmonary arterial pressure is  $\geq 25$  mmHg in the absence of elevation of the pulmonary arterial wedge pressure (PAWP). PAH includes a heterogeneous group of clinical entities sharing similar pathological changes that have been subcategorized as idiopathic PAH (IPAH), heritable PAH, and PAH associated with other diseases such as connective tissue diseases (CTD), including systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD), portopulmonary hypertension, and PAH-related to HIV infection, drugs, and toxins.

The exact mechanisms involved in the pathogenesis of PAH remain vastly unknown

but are likely to involve significant alterations in endothelial function,<sup>[6]</sup> an understanding of which has led over the past two decades to targeted therapy for this disease.<sup>[7]</sup> In addition to endothelial dysfunction, there are several lines of evidence implicating autoimmunity in the development of the pulmonary vascular changes, including the presence of circulating autoantibodies,<sup>[8]</sup> pro-inflammatory cytokines (e.g., IL-1 and IL-6),<sup>[9]</sup> and association of PAH with auto-immune diseases and CTD such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and MCTD. The pathologic pulmonary vascular lesions SSc-associated PAH (SSc-APAH) are indistinguishable from those of IPAH (with the exception of a higher prevalence of veno-occlusive disease in SSc-APAH).<sup>[10]</sup> although it is now quite clear that the two diseases have quite divergent outcomes and response to therapy.<sup>[3]</sup> Survival is significantly worse in SSc-APAH compared to IPAH despite the use of modern medical therapy.<sup>[11-13]</sup> While there are serologic and pathologic features suggestive of inflammation in both IPAH and SSc-APAH, inflammatory pathways and autoimmunity are

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likely more pronounced in SSc-APAH, perhaps explaining clinical discrepancies between the two syndromes.<sup>[11,12]</sup> Other connective tissue diseases such as SLE, MCTD, and to a lesser extent rheumatoid arthritis (RA), dermatomyositis, and Sjogren's syndrome, can also be complicated by PAH and will be discussed separately in this review.

### Scleroderma

SSc is a heterogeneous disorder characterized by dysfunction of the endothelium, dysregulation of fibroblasts resulting in excessive production of collagen, and abnormalities of the immune system.<sup>[14]</sup> Progressive fibrosis of the skin and internal organs is a pathologic hallmark of the disease resulting in major organ damage and failure explaining the high morbidity and early death. Genetic and environmental factors are thought to contribute to host susceptibility in the context of autoimmune dysregulation.<sup>[15]</sup> Whether presenting in the limited or diffuse form, SSc is a systemic disease with the propensity to involve multiple organ systems such as the gastrointestinal tract, the heart, kidneys and lungs.<sup>[16]</sup> Pulmonary manifestations include PAH, interstitial fibrosis, and increased susceptibility to lung neoplasms.

The use of a standard classification system for SSc has allowed more accurate estimates of incidence and prevalence of SSc, which vary according to geographic location, supporting a role for environmental factors in disease pathogenesis.<sup>[17]</sup> Prevalence of SSc ranges from 30-70 cases per million in Europe and Japan<sup>[18-20]</sup> to ~240 cases per million in the United States.<sup>[17]</sup> Incidence varies similarly by geographic area, with the highest rates found in the US (~19 persons per million per year).<sup>[21]</sup>

### Scleroderma-associated PAH

The prevalence of PAH in SSc patients, when the diagnosis is based on rigorous RHC for assessment of filling pressures, is about 8-14%.<sup>[22,23]</sup>

Previous assessments based on echocardiographic measurements have overestimated the real prevalence of SSc-APAH<sup>[24-27]</sup> and should not be relied upon for establishing the diagnosis and initiating treatment given the inaccuracy of the Doppler signal in assessing true right ventricular systolic pressure<sup>[28]</sup> and the fact that, if pressure is indeed elevated, other diagnoses such as pulmonary venous hypertension cannot be excluded with certainty. However, it is likely that SSc-APAH remains overall under-diagnosed as suggested by the lower than expected prevalence of the disease in the few registries available.<sup>[29-31]</sup>

The vascular structural (intimal hyperplasia, fibrosis, and occlusion) and functional (endothelial activation, vasoreactivity and disorganized angiogenesis) abnormalities seen in SSc lead to widespread clinical manifestations such as Raynaud's phenomenon, digital ulcers, pulmonary-renal disease, renal crises, and PAH. The prevalence of these complications is variable with nearly 100% of SSc patients having evidence of Raynaud's phenomenon,<sup>[32]</sup> 5% developing acute renal crises,<sup>[33]</sup> and an estimated 7 to 13% developing PAH as diagnosed by right heart catheterization (RHC).<sup>[34]</sup>

It has become increasingly apparent that the disease course and responsiveness to therapeutic interventions in SSc-APAH are different from that observed in other forms of PAH, e.g. idiopathic pulmonary arterial hypertension or (IPAH). In

retrospective cohort studies, the risk of death was higher in SSc-APAH patients when compared with those with IPAH.<sup>[35]</sup> In addition, unlike IPAH patients whose mortality rate has probably improved with modern therapies, the survival rate of SSc patients remains relatively poor.<sup>[36]</sup> In a retrospective cohort study, Girgis *et al* compared the long-term outcomes of first-line bosentan monotherapy in 19 patients with IPAH and 17 patients with SSc-APAH. Functional class improved in 58% of IPAH patients compared with only 25% of SSc-APAH patients and overall survival at 1 and 2 years was 100% and 100% *versus* 87% and 79% for IPAH and PAH-SSc patients, respectively.<sup>[37]</sup>

The reasons for the substantial prognostic differences between IPAH and SSc-APAH are poorly understood. They might be in part explained by comorbid scleroderma disease features (such as interstitial lung disease) and age-related factors secondary to the later onset of PAH in SSc,<sup>[38]</sup> although age alone was not thought to be a predisposing factor for increased mortality in one study.<sup>[32]</sup> It has also been suggested that esophageal dysmotility, gastroparesis and small bowel malabsorption that are common in SSc may contribute to altered absorption and metabolism of oral PAH-specific therapy, thereby leading to sub-therapeutic concentrations of these medications in the sera.

### Pathophysiology

More details about the pathophysiology of the RV and pulmonary vascular disease in Scleroderma is discussed in the review (Pulmonary Vascular Disease in Scleroderma) in the current issue of the Journal.

There are early vascular changes in SSc, which include gaps between endothelial cells, cellular apoptosis, endothelial activation with expression of cell adhesion molecules, inflammatory cell recruitment, a procoagulant state, and remodeling of the small vessels with intimal proliferation and adventitial fibrosis leading to vessel obliteration.<sup>[39-42]</sup> The extent of these vascular lesions in vital organs such as the lungs, kidneys and heart defines the prognosis of patients with SSc.<sup>[43]</sup>

Specific endothelial injury is reflected by increased levels of soluble vascular cell adhesion molecule (sVCAM-1),<sup>[44]</sup> disturbances in angiogenesis reflected by increased levels of circulating vascular endothelial growth factor (VEGF),<sup>[45,46]</sup> and presence of angiostatic factors.<sup>[45,47]</sup> Increased VEGF, may be a consequence of increased angiogenesis or profound disturbances in signaling in SSc. Dysregulated angiogenesis in SSc-APAH, exemplified by the upregulation of VEGF, a glycoprotein with potent angiogenic and vascular permeability-enhancing properties, is a predominant pathological feature of the disease and is a logical candidate for therapeutic targeting.

### Autoantibodies

Several antibodies are frequently found in SSc-APAH such as antifibrillar antibodies (anti-U3-RNP)<sup>[48]</sup> and the poorly characterized anti-endothelial antibodies (aECA), which correlate with digital infarcts.<sup>[49]</sup> Antibodies to fibrin-bound tissue plasminogen activator in CREST patients<sup>[50]</sup> and in IPAH patients with HLA-DQ7 antigen,<sup>[51]</sup> and anti-topoisomerase II- $\alpha$  antibodies, particularly in association with HLA-B35 antigen,<sup>[52]</sup> have been reported in SSc-APAH. aECA antibodies which can activate endothelial cells, induce the expression of

adhesion molecules, and trigger apoptosis, are thought to play a role in the pathogenesis of PAH.<sup>[53]</sup>

Fibroblasts are essential components of the pulmonary vascular wall remodeling in PAH and are found in the remodeled neointimal layer in both SSc-APAH and IPAH. In that regard, the detection of anti-fibroblast antibodies in the serum of SSc and IPAH patients<sup>[54,55]</sup> has significant pathogenic importance since these antibodies can activate fibroblasts and induce collagen synthesis, thus contributing potentially directly to the remodeling process. Antibodies from sera of patients with SSc induce a pro-adhesive and pro-inflammatory response in normal fibroblasts.<sup>[55]</sup> Antifibroblast antibodies from sera of IPAH and SSc-APAH patients have distinct reactivity profiles<sup>[56]</sup> and react with fibroblast proteins involved in regulation of cytoskeletal function, cell contraction, cell and oxidative stress, cell energy metabolism and in different key cellular pathway.<sup>[57]</sup>

Taken together, particularly in light of the positive response to immunosuppressive therapy for some patients with PAH associated with SLE and MCTD,<sup>[58]</sup> these studies suggest that inflammation and autoimmunity play a major role in the pathogenesis of PAH, perhaps more specifically in CTD-associated PAH.

### Genetic factors

Polymorphisms involving the bone morphogenetic protein receptor-2 (*BMPRII*) are present in over 80% of heritable IPAH<sup>[59-60]</sup> and up to 25% of sporadic cases of IPAH.<sup>[61-63]</sup> Additional candidate genes have been proposed to influence the pathogenesis of PAH.<sup>[64]</sup> Polymorphisms of the activin-receptor-like kinase 1 (*ALK1*) gene, another member of the TGF  $\beta$  receptor superfamily, have been reported in patients with hereditary hemorrhagic telangiectasia (HHT) and PAH.<sup>[64]</sup> However, to date *BMPR2* mutations have not been identified in two small cohorts of SSc-APAH patients.<sup>[65,66]</sup>

Candidate genes associated with SSc have been reported in different populations and include a variant in the promoter of monocyte chemoattractant protein-1 (*MCP-1*);<sup>[67]</sup> two variants in *CD19* (-499G>T and a GT repeat polymorphism in the 3'-UTR region);<sup>[68]</sup> a promoter and coding polymorphism in *TNFA* (*TNFA*-238A>G, *TNFA* 489A>G);<sup>[69]</sup> a variant in the promoter of the *IL-1* alpha gene (*IL1A* -889T);<sup>[70,71]</sup> and a 3-SNP haplotype in *IL10*.<sup>[72]</sup> A genome-wide association analysis provided evidence for association to multiple loci in a Native American population.<sup>[73]</sup>

Recently, an association between an endoglin gene (*ENG*) polymorphism and SSc-related PAH was identified. Wipf and colleagues demonstrated a significant lower frequency of the 6bINS allele in SSc-APAH patients as compared to controls or patients with SSc but no PAH.<sup>[74]</sup> Endoglin, a homodimeric membrane glycoprotein primarily present on human vascular endothelium, is part of the TGF- $\beta$  receptor complex. The functional significance of the *ENG* polymorphism in SSc patients remains to be determined.

More detailed information about the genetic factors can be found in the review of "genetic of Pulmonary Hypertension" in this issue of the journal.

Thus, there is compelling data supporting a genetic basis for SSc. However, aside from the few examples cited above,

the genes relevant to the pathogenesis and poor outcome associated with SSc-APAH have not been identified, and their definition will require robust, well-characterized large patient populations to provide adequate power for analysis.

### Clinical Features

Risk factors for the development of PAH in SSc patients include late-onset disease,<sup>[75]</sup> an isolated reduction in  $DL_{CO}$ , an FVC %/DLCO % ratio greater than 1.6,<sup>[76,77]</sup> or a combined decreased  $DL_{CO}$ /alveolar volume with elevation of serum N-terminal pro-brain natriuretic peptide levels, (Figure).<sup>[78,79]</sup>

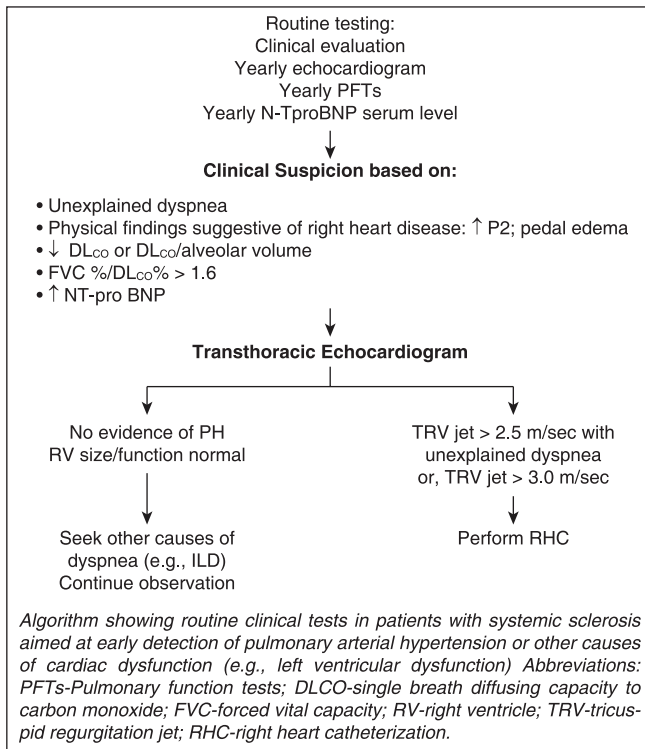
Typically, patients with SSc-APAH are predominantly women, have limited sclerosis with predominantly anticentromere antibodies, are older and have seemingly less severe hemodynamic impairment compared to IPAH patients.<sup>[12]</sup> Clinical symptoms are non specific, including dyspnea, functional limitation which may be more severe than in IPAH due not only to older age but also to frequent involvement of the musculoskeletal system in these patients. SSc-APAH patients also tend to have other organ involvement such as renal dysfunction and intrinsic heart disease. Indeed patients with SSc (even in the absence of PAH) tend to have depressed RV function as well as left ventricular systolic and diastolic dysfunction.<sup>[80-82]</sup> Like IPAH patients, SSc-APAH patients have severe RV dysfunction already at time of presentation but have more severely depressed RV contractility compared to IPAH patients.<sup>[83]</sup>

In addition, SSc- APAH patients tend to have more commonly LV diastolic dysfunction and a high prevalence of pericardial effusion (34% compared to 13% for IPAH).<sup>[12]</sup> In both groups, pericardial effusion portends a particularly poor prognosis.<sup>[12]</sup>

SSc-APAH patients also tend to have more severe hormonal and metabolic dysfunctions, such as high levels of N-terminal brain natriuretic peptide (N-TproBNP)<sup>[84]</sup> and hyponatremia.<sup>[85]</sup> Both N-TproBNP and hyponatremia have been shown, at baseline and with serial changes (for N- TproBNP),<sup>[84]</sup> to correlate with survival in PAH.<sup>[84,85]</sup>

### Early Detection

While IPAH is usually diagnosed late (patients presenting in WHO functional status III and IV), a population at risk for PAH such as SSc theoretically allows establishing measures for early detection. An algorithm for early detection of PAH may be helpful if based on a combination of symptoms and screening echocardiography [Figure 1] as exemplified by a recent large French registry where patients with SSc with tricuspid regurgitation velocity (TRV) jet by transthoracic echocardiography greater than 3 m/sec or between 2.5 and 3 m/sec if accompanied by unexplained dyspnea, were systematically referred for RHC.<sup>[22]</sup> Investigators were able to detect incident cases of SSc-APAH with less severe disease (as judged on hemodynamic data) compared to patients with known disease. Therefore, unexplained dyspnea should prompt a search for PAH in these patients, in particular in the setting of a low single breath  $DL_{CO}$  or declining  $DL_{CO}$  over time,<sup>[77]</sup> echocardiographic findings suggestive of the disease (elevated TRV jet or dilated RV or right atrium), or elevated levels of N-TproBNP, which can reflect cardiac dysfunction and have been found to predict



**Figure 1:** Algorithm for detection of PAH in patients with systemic sclerosis

the presence of SSc-APAH.<sup>[84]</sup> Systematic screening should allow detection of early disease and prompt therapy which may theoretically be beneficial from a prognostic standpoint.<sup>[86]</sup>

### Diagnostic Work up

ECG and chest X-ray together with clinical evaluation have a poor sensitivity and do not allow a prompt diagnosis at a pre-clinical stage, when therapeutics are supposed to be more effective. More elaborate techniques are becoming more available to accurately identify early perturbations of normal cardiac configuration and performance in patients with SSc.

#### Transthoracic echocardiography

Transthoracic echocardiography (TTE) is the most widely available semi-quantitative cardiac assessment modality. This non-invasive diagnostic tool gives estimates of elevated pulmonary artery pressures and of RV structural changes consistent with RV overload, such as ventricular dilatation and septal wall motion abnormalities. Overall, echocardiographic measures are useful in detecting RV and/or left ventricular (LV) dysfunction that usually occur in later disease stages, but are less helpful in identifying patients with early subtle cardiac involvement. Furthermore, unlike the LV, the non-invasive evaluation of the RV is hindered by its complex cavity geometry that does not lend itself to mathematical modeling. Additionally, there is poor endocardial definition and muscle fiber contraction occurs predominantly in the longitudinal direction and in a peristaltic fashion, which complicates estimations of RV ejection fraction and performance.<sup>[87]</sup> The appraisal of RV function is also difficult because of the interplay between intrinsic myocardial performance and right ventricular loading conditions.<sup>[88]</sup> Nevertheless, evaluation of overall RV

performance has recently been proposed in PAH with TTE measures that are not reliant on geometric measurements of the structurally intricate RV. This has allowed an earlier detection of cardiac alterations.

The Tei-index (or myocardial performance index), a mathematical quotient of isovolumetric contraction and relaxation time divided by ejection time, has been utilized as such a measure.<sup>[89]</sup> Patients with pulmonary hypertension have increased isovolumetric contraction and relaxation times and a decreased ejection time. In combination with standard TTE measures of pulmonary artery pressure, a Tei-index > 0.36 was found to be highly predictive of SSc patients with PAH based upon RHC.<sup>[90]</sup> It is important to note that the value of these parameters as outcome measures in clinical practice remains unknown.

Tricuspid annular systolic excursion (TAPSE) is another TTE method for the detection of global RV compromise that is independent of RV geometry. TAPSE is measured by the total displacement of the tricuspid annulus from end-diastole to end-systole. While prior studies demonstrated a strong relationship with RV ejection fraction, more recent investigations have shown that TAPSE scores can be influenced by RV and LV dysfunctions.<sup>[91]</sup> In PAH, TAPSE measurements have been shown to correlate with RHC parameters and to predict survival.<sup>[92]</sup> Preliminary studies suggest that PAH-SSc patients exhibit worse TAPSE measurements and worse prognosis compared to other patients with PAH.

Data related to Tei-indices and TAPSE scores for detection of global RV dysfunction and to the diagnosis and prognosis of PAH-SSc continue to accumulate. However, the utilization of these imaging studies as outcome measures in response to pharmacologic interventions has yet to be adequately evaluated. The studies available so far do not provide sufficiently detailed information regarding the components of RV structure and function to account for the disparity in the observed survival of PAH-SSc patients compared to other PAH patients.

#### Tissue doppler and doppler strain imaging

Tissue Doppler imaging (TDI) allows echocardiographic measurement of myocardial velocities for determination of global as well as segmental systolic and diastolic ventricular dysfunction. Although originally developed for the examination of the LV, application of this technique to the RV is gaining interest. TDI has many advantages over conventional Doppler when deriving time-dependent myocardial performance indices. However, its major drawback is that nonfunctioning segments are often not observed due to interdependence with functioning segments.<sup>[93]</sup> In contrast, Doppler strain imaging (DSI) allows for examination of segmental deformation regardless of normal surrounding segments.<sup>[93]</sup> Therefore, the addition of TDI and Doppler strain and strain rate imaging to standard TTE provides additional information; TDI detects abnormalities not shown on TTE, and DSI finds discrepancies not found on TDI. Strain and strain rate imaging are thus promising new sensitive and accurate modalities to evaluate SSc patients for early cardiac involvement.

#### Nuclear imaging

Nuclear imaging can be a good adjunctive method for evaluating cardiac complications even in the early stages

of SSc. Earlier studies investigating RV abnormalities using radionuclide imaging with <sup>99m</sup>Tc ventriculography showed a significant decrease in RV ejection fraction in SSc patients (with no evidence of PAH) when compared to controls.<sup>[94]</sup> Steen and colleagues followed 48 patients who had undergone cardiac evaluation, and found that thallium perfusion defect scoring was the single most powerful predictor of mortality and subsequent development of clinical cardiac disease in patients with either limited or diffuse scleroderma.<sup>[95]</sup> However, the clinical implications of these defects remain controversial.

### Cardiac MRI

Cardiac MRI is becoming the gold standard for non-invasive evaluation of RV structural changes; it allows accurate and reproducible measurements of ventricular dimensions, wall thickness, and myocardial mass without relying on geometric assumptions. It enables precise analysis of the different patterns of heart involvement in SSc by differentiating morphological, functional, perfusion and delayed contrast enhancement abnormalities. Compared to other imaging modalities, cardiac MRI detected significantly compromised RV function in a higher number of asymptomatic SSc patients.<sup>[96]</sup> The ventricular mass index, ratio of the right and left ventricular end diastolic mass, was found to correlate strongly with the mean pulmonary artery pressure in patients with SSc and may have a role in non-invasively excluding clinically significant PH in breathless SSc patients in whom echocardiographic screening has failed.<sup>[97]</sup>

Moreover, MRI provides imaging of the coronary arteries and assessment of the viability of the myocardium. It can also potentially be used as a guide for myocardial biopsy or ablation studies, when indicated, and as a mean for monitoring therapeutic effects. For instance, Wilkins *et al* were able to show significant improvement in cardiac MRI morphological alterations (i.e., decreased RV mass) with sildenafil as compared to bosentan therapy.<sup>[98]</sup> Taken together, these results suggest that MRI is a reliable and sensitive technique to diagnose heart involvement in SSc and identify potential mechanisms such as inflammation and fibrosis.

### Right heart catheterization

RHC remains the gold standard to evaluate RV hemodynamic changes following pressure overload. In patients with SSc, RHC is essential for diagnosing pulmonary hypertension, monitoring disease progression, and assessing the response to therapeutic interventions.

### Endomyocardial biopsy

The technique of endomyocardial biopsy is now recognized as an established and safe procedure that can significantly increase the frequency of detection of cardiac involvement in patients with SSc.

In addition, several investigators advocate the use of myocardial biopsies in this patients' population as a tool to exclude specific cardiac pathologies such as hydroxychloroquine toxicity and cardiac amyloid and to distinguish between inflammatory and fibrotic forms of heart involvement in SSc patients, distinctions that might lead to specific therapies. However, this diagnostic method is somewhat limited by its invasive nature and high rate of sampling errors, as suggested by its relatively low diagnostic yield compared with autopsy results.

## Prognosis

Patients with SSc-APAH have a worse prognosis compared to patients with other forms of PAH such as IPAH. Indeed, one-year survival rates for SSc-APAH patients range from 50-81%,<sup>[11,13,23,27,99]</sup> considerably lower than the estimated 88% one year survival for IPAH patients.<sup>[100]</sup> In all patients with SSc, PAH significantly worsens survival and is one of the leading causes of mortality in these patients.<sup>[17,99,101]</sup>

### PAH Associated with Other Connective Tissue Diseases

PAH can complicate any connective tissue disease, most frequently SSc as discussed above, but also SLE, MCTD, RA, or other diseases such as Sjogren's syndrome and dermatomyositis.

#### Systemic lupus erythematosus

Pulmonary vascular involvement is common in SLE and, like in SSc, there is evidence of endothelial dysfunction with an imbalance between vasodilators and vasoconstrictors. Endothelin levels are high in patients with SLE, particularly in those patients with pulmonary hypertension. Other factors contributing to pulmonary vascular derangement in SLE include recurrent thromboembolic disease, particularly in patients with a hypercoagulable state from antiphospholipid antibodies, which are present in up to 10% of patients with SLE,<sup>[102]</sup> pulmonary vasculitis, and parenchymal disease (e.g., interstitial lung disease, and the shrinking lung syndrome from myositis of the diaphragm). Combined vasculitis and chronic hypoxia are frequent contributing offenders in these syndromes. Finally, pulmonary venous hypertension may be a consequence of left ventricular dysfunction, myocarditis, or Libman Scahs endocarditis.

The prevalence of PAH in SLE is unclear but is likely less than in SSc, affecting about 0.5- 14% patients with SLE in a large review of the literature encompassing over 100 patients.<sup>[103]</sup> The patients are predominantly female (90%), young (average age of 33 at time of diagnosis), and often suffer from Raynaud's phenomenon.

The pathological lesions are often indistinguishable from IPAH or SSc-APAH lesions, with intimal hyperplasia, smooth muscle cell hypertrophy, and medial thickening. Survival, which was quite poor (25-50% at 2 years) even compared to SSc-APAH in studies antedating specific PAH therapy, is now improved and estimated at 75%.<sup>[13]</sup>

#### Mixed connective tissue disease

Patients with MCTD have clinical features, which overlap between those of SSc, SLE, RA, and polymyositis. The exact prevalence of PAH in MCTD is unknown but is thought to be as high as 50%.<sup>[104]</sup> PAH in these patients may occasionally respond to immunosuppressive drugs.<sup>[58]</sup>

#### Rheumatoid arthritis

Both the prevalence and impact of PAH in patients with RA have not been well characterized but are thought to be relatively low compared to other CTD such as SSc, SLE and MCTD.

### Primary Sjogren's syndrome

Although primary Sjogren's syndrome (pSS) is a relatively common autoimmune disease with glandular and extra-glandular manifestations, it is very rarely complicated by PAH. In a recent review by Launay *et al* of patients with pSS and PAH,<sup>[105]</sup> the mean age at diagnosis of PAH of these almost exclusively female patients was 50 years. Patients had severe functional class (FC III and IV) and hemodynamic impairment. Standard therapy (with endothelin receptor antagonists, phosphodiesterase inhibitors or prostanoids) was typically ineffective despite an initial improvement. Some patients were reported to respond to immunosuppressive treatment. However, any conclusion regarding treatment is limited by the small size of this case report. Survival rate was low (66% at 3 years).

### Therapy for PAH Associated with CTD

More detailed information about specific drug therapy in the management of PAH can be about in the review (Specific Treatment For Pulmonary Arterial Hypertension) in this issue of the Journal. This section applies essentially to the treatment of patients with SSc-APAH, which represents the largest group of CTD-associated PAH patients in most clinical therapeutic trials.

Evidence of chronically impaired endothelial function,<sup>[106-108]</sup> affecting vascular tone and remodeling, is the basis for current PAH therapy. Vasodilator therapy using high dose calcium channel blockers is an effective long-term therapy for a minority of patients with IPAH who demonstrate acute and sustained vasodilation (*e.g.*, to NO or adenosine) during hemodynamic testing.<sup>[109,110]</sup> However, since most patients with CTD-associated PAH patients fail to demonstrate a vasodilator response to acute testing,<sup>[29]</sup> high dose calcium channel therapy is usually not indicated for these patients except at low dosage for Raynaud's syndrome.

### Anti-inflammatory drugs

Inflammation may play a significant role in PAH associated with CTD. In that respect, it is interesting to note that occasional patients with severe PAH associated with some forms of CTD (such as SLE, primary Sjögren's syndrome, and MCTD) have had dramatic improvement of their pulmonary vascular disease with corticosteroids and/or immunosuppressive therapy.<sup>[58]</sup> Unfortunately, this has not been the case for patients with SSc-APAH, whose PAH is usually notoriously refractory to immunosuppressive drugs.<sup>[58]</sup>

### Prostaglandins

Prostacyclin (epoprostenol) has potent pulmonary vasodilator, anti-platelet aggregating and antiproliferative properties,<sup>[111]</sup> and has proven effective in improving exercise capacity, cardiopulmonary hemodynamics, modified NYHA functional class, symptoms, as well as survival in patients with PAH when given by continuous infusion.<sup>[112-114]</sup> In SSc-APAH, continuous intravenous epoprostenol improves exercise capacity and hemodynamics,<sup>[115]</sup> compared to conventional therapy, and may have long-term beneficial effects<sup>[116]</sup> although a clear effect on survival in these patients there has yet to be demonstrated.

Treprostinil, an analogue of epoprostenol suitable for continuous subcutaneous administration, has modest effects

on symptoms and hemodynamics in PAH.<sup>[117]</sup> In a small study of 16 patients (among whom 6 had CTD related PAH), intravenous treprostinil improved 6 minute walk distance (6MWD), modified NYHA functional class, and hemodynamics after 12 weeks of therapy.<sup>[118]</sup>

Although the safety profile of this drug is similar to IV epoprostenol, required maintenance doses are usually twice as much as for epoprostenol. However, for patients with SSc-APAH and often severe and debilitating Raynaud's phenomenon, the lack of requirement of ice packing and less frequent mixing of the drug offer significant advantages.

Several reports of pulmonary edema in SSc-APAH patients treated with prostaglandin derivatives, both in acute and chronic settings, have raised the suspicion of increased prevalence of veno-occlusive disease in these patients,<sup>[119,120]</sup> and concern about usefulness of these drugs for this entity. Nevertheless, intravenous prostaglandin therapy remains an option for patients with CTD- APAH with modified NYHA class IV. Considering the frequent digital problems and disabilities that these patients often experience, this form of therapy can be quite challenging and may increase the already heavy burden of disease in these patients. In summary, both epoprostenol and treprostinil are FDA approved for PAH, but are cumbersome therapies requiring continuous parenteral administration with the attendant numerous adverse effects (*e.g.*, infection and possibility of pump failure),<sup>[121]</sup> which make these drugs less than ideal.

### Endothelin receptor antagonists

In randomized, placebo-controlled trials, bosentan therapy was shown to have a beneficial effect on functional class, 6MWD, time to clinical worsening, and hemodynamics in PAH.<sup>[122,123]</sup> Roughly one fifth of these patients consisted of SSc- APAH patients while a large majority had a diagnosis of IPAH. In a subgroup analysis, there was a non-significant trend towards a positive treatment effect on 6MWD among the SSc-APAH patients treated with bosentan compared to placebo.<sup>[123]</sup> At most, bosentan therapy prevented deterioration in these patients. This less than optimal effect of therapy in patients with SSc-APAH is unclear but may be related to the severity of PAH at time of presentation, as well as other factors such as, hypothetically, more severe RV and pulmonary vascular dysfunction, as compared to patients with other forms of PAH (*e.g.*, IPAH).

In a recent analysis of patients with CTD-APAH (*e.g.*, patients with lupus, overlap syndrome, and other rheumatological disorders) included in randomized clinical trials of bosentan, there was a trend toward improvement in 6MWD and improved survival compared to historical cohorts.<sup>[124]</sup> Single center experience suggests that long-term outcome of first-line bosentan monotherapy is inferior in SSc-APAH compared to IPAH patients, with no change in functional class and worse survival in the former group.<sup>[125]</sup> Since Endothelin-1 (ET-1) appears to play an important pathogenic role in the development of SSc-APAH, contributing to vascular damage and fibrosis, inhibiting ET-1 remains a rational therapeutic strategy in these patients.

As an example of mechanistic effect, in a small study of 35 patients with SSc (10 of whom had SSc-APAH), bosentan

treatment appeared to reduce endothelial cell (as determined by endothelial soluble serum factors such as ICAM-1, VCAM-1, P-selection and PECAM-1) and T cell subset (assessed by expression of lymphocyte function-associated antigen-1, very late antigen-4, and L-selectin on CD3 T cells) activation.<sup>[126]</sup> Aside from improving pulmonary hypertension, ET-1 receptor antagonists (specifically bosentan) cause significant reductions in the occurrence of new digital ulcerations without, however, healing preexisting ulcers.<sup>[127]</sup>

In an effort to target the vasoconstrictive effects of endothelin while preserving its vasodilatory action, selective endothelin-A receptor antagonists have been developed.

A large placebo-controlled, randomized trial of ambrisentan, the only currently FDA-approved selective endothelin receptor antagonist, improved 6MWD in PAH patients at week 12 of treatment, however, the effect was larger in patients with IPAH compared to patients with CTD-APAH (range of 50-60 meters versus 15-23 meters, respectively).<sup>[128]</sup> Ambrisentan is generally well tolerated although peripheral edema (in up to 20% of patients)<sup>[128]</sup> and congestive heart failure have been reported.

### Phosphodiesterase inhibitors

Sildenafil, a phosphodiesterase type V inhibitor that reduces the catabolism of cGMP, thereby enhancing the cellular effects mediated by nitric oxide, has become a widely used and highly efficacious therapy for PAH. The pivotal SUPER trial demonstrated that sildenafil therapy causes an improvement in the 6MWD in patients with IPAH and CTD-APAH or pulmonary hypertension associated with repaired congenital heart disease (patients were predominantly FC II or III) at all three doses tested (20, 40, and 80 mg, given three times a day).<sup>[129]</sup> The current FDA-recommended dose is 20 mg three times a day since there were no significant differences in clinical effects and time to clinical worsening at week 12 between all doses tested. In a post-hoc subgroup analysis of 84 patients with PAH related to CTD (forty-five percent of whom had SSc-APAH), data from the SUPER study suggest that sildenafil at a dose of 20 mg improved exercise capacity (6MWD), hemodynamic measures, and functional class after 12 weeks of therapy.<sup>[130]</sup> However, there was no effect for the dose of 80 mg three times a day on hemodynamics in this subgroup of patients with CTD-related PAH.<sup>[130]</sup> For this reason and because of the potential of increased side-effects (such as bleeding from arterio-venous malformations) at high doses, a sildenafil dosage of 20 mg three times a day is recommended for SSc-APAH patients (and perhaps patients with PAH associated with other forms of CTD) as standard therapy. Higher doses are occasionally attempted in case of limited response. The impact of long-term sildenafil therapy on survival in these patients remains to be determined.

Finally, tadalafil, another phosphodiesterase inhibitor, has now been shown to be effective for PAH,<sup>[131]</sup> although subgroup analysis has not been performed yet and thus its effects on CTD-APAH remain unclear. Tadalafil has the advantage over sildenafil of single daily dosage.

### Combination therapy

It is now a common practice to add drugs when patients fail to improve on monotherapy. Adding inhaled iloprost to patients

receiving bosentan has been shown to be beneficial in a small, randomized trial.<sup>[132]</sup> Combination therapy is mechanistically appealing and anecdotally efficacious as these drugs target separate, potentially synergistic pathways.<sup>[133]</sup> Several multicenter trials are now exploring the efficacy of various combinations of two oral drugs or one oral and one inhaled drug. The published results of the PACES trial demonstrate that adding sildenafil (at a dose of 80 mg three times a day) to intravenous epoprostenol improves exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life.<sup>[134]</sup> About 21% of these patients had CTD, including 11% with SSc-APAH. Although no specific subgroup analysis is provided, improvement was apparently mainly in patients with IPAH.

In a smaller one center clinical trial, adding sildenafil to patients with IPAH or SSc-APAH after they failed initial monotherapy with bosentan, demonstrates that combination therapy improved the 6MWD and FC in IPAH patients. The outcome in patients with SSc-APAH was less favorable, although combination therapy may have halted clinical deterioration. In addition, there were more side effects reported in the SSc-APAH compared to the IPAH patients, including hepatotoxicity that developed after addition of sildenafil to bosentan monotherapy.<sup>[135]</sup>

### Anticoagulation

Based essentially on retrospective data showing a survival advantage,<sup>[109,136]</sup> anticoagulation is routinely recommended in the treatment of IPAH patients. However, the role of anticoagulation in other forms of PAH, in particular in CTD-APAH is much less clear.

Theoretically, there is potential for increased bleeding in patients with CTD, particularly with SSc where intestinal telangiectasia may be common. In the author's experience, less than 50% of SSc-APAH patients started on anticoagulation remain on therapy long-term because of bleeding complications (e.g., often related to occult bleeding in the gastrointestinal tract), which are often difficult to diagnose.

### Tyrosine kinase inhibitors

The finding that there is pathologically aberrant proliferation of endothelial and smooth muscle cells in PAH, as well as increased expression of secreted growth factors such as VEGF and bFGF, has caused a shift in paradigm in treatment strategies for this disease as some investigators have likened this condition to a neoplastic process reminiscent of advanced solid tumors.<sup>[137]</sup> As a result, anti-neoplastic drugs have been tested in experimental models.<sup>[138,139]</sup> However, the results of a double-blinded, placebo-controlled, randomized phase III trial (IMPRES) have recently published and have created a major concern about the effectiveness of this drug, as despite the fact that patients treated with imatinib experienced better exercise tolerance (the primary endpoint) and significant improvement in hemodynamics, the time to clinical worsening and mortality were not different between the 2 groups. Furthermore, side effects profile, mainly cerebral hemorrhage, was another major concern in imatinib-treated patient.<sup>[140]</sup> Whether these new anti-neoplastic drugs with anti-tyrosine kinase activity will have a role in SSc (where there is evidence for both dysregulated proliferation and increased expression

of growth factors such as VEGF)<sup>[141]</sup> or in IPAH remains to be determined. Interestingly, a single case report suggests significant improvement of right ventricular function with imatinib treatment in a SSc-APAH patient. Also of note is that imatinib is being investigated for SSc-related interstitial lung disease.<sup>[142]</sup>

### Lung transplantation

Lung transplantation (LT) is typically offered as a last resort to patients with PAH who fail medical therapy. CTD is not an absolute contraindication to LT; however, patients with CTD-APAH frequently suffer from associated morbidity and organ dysfunction other than the lung, which places them at a significantly increased risk for LT. Motility disorder of the esophagus and gastroesophageal reflux in patients with SSc significantly enhance the post-operative potential of aspiration and damage to the recipient lung. For these reasons, patients with SSc-APAH are often denied LT consideration. However, if properly screened and approved for LT, patients with SSc experience similar rates of survival 2 years after the procedure compared with patients who receive LT for pulmonary fibrosis or IPAH.<sup>[133]</sup> In addition, a recent retrospective study suggests that the 1-year survival rate is similar for SSc patients (transplanted for respiratory failure related to PAH or interstitial lung disease) compared to patients with IPF although acute rejection appears to be more common for the former group.<sup>[144]</sup>

### Conclusion

In summary, pulmonary hypertension is a common complication of CTD, particularly SSc where it carries a very poor prognosis. Despite modern therapy for PAH, survival of patients with CTD-APAH remains unacceptably low. Possible reasons include an increased prevalence of pulmonary veno-occlusive lung disease in SSc-APAH patients, or more severe vascular lesions affecting not only proximal and distal pulmonary vessels but also the heart (such as inflammatory myocarditis) in CTD. Thus, a better understanding of the underlying pathophysiology affecting the heart and pulmonary vessels in CTD is needed for better targeted therapy. Whether specific anti-inflammatory agents or drugs targeting tyrosine kinase activity will have any role in CTD-APAH is unclear at this time but needs to be explored.

Heart involvement is a serious complication of SSc. It is often clinically occult and its detection depends on the sensitivity of the diagnostic method used. The etiology of cardiac involvement seems to be multifactorial, since different degrees of inflammation, fibrosis and vascular abnormalities have all been observed. Another important contributing factor is the presence of systemic and/or pulmonary hypertension that may overwhelm the ventricular compensatory mechanisms. In recent years, it has become evident that early diagnosis of scleroderma heart disease is fundamental for appropriate management of this patient population. For this reason, significant progress needs to be made in the development of simple, yet reliable, markers of cardiac function. However, major challenges remain in validating current assessment strategies in large and well-designed clinical studies, and determining longitudinally the effect of early therapeutic interventions. Furthermore, a better understanding of the

fundamental cellular and molecular mechanisms that govern the adaptation of the right heart to its increased load may provide an explanation for the accelerated RV failure and less robust response to drug therapy observed in SSc patients. This will also allow exploration of novel treatment paradigms with potential positive impact on the quality of life and life expectancy of this patient population.

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