

Pulmonary Hypertension in Patients With Connective Tissue Disease

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Abstract

Pulmonary hypertension (PH) is common in patients with connective tissue diseases (CTDs), particularly in systemic sclerosis. PH often heralds a poor prognosis. Unfortunately, there can be a significant delay between onset of this condition and establishment of diagnosis of PH in patients with CTDs. In recent times, improved diagnostic tools have aided in early diagnosis and have been shown to improve survival. The treatment approach in PH associated with CTDs is essentially similar to treatment of pulmonary arterial hypertension (PAH) alone. Notwithstanding, PH therapy is less efficacious in patients with CTDs than in patients with other forms of PAH. Although survival of patients with PH associated with CTDs has improved in the modern treatment era, it still remains low. Lung transplantation is a viable option for patients not responding to medical therapy. Research is ongoing, focusing on underlying mechanisms of CTD-associated PH for better targeted therapy.

Keywords: Pulmonary Hypertension; Connective Tissue Disease; Interstitial Lung Disease; Systemic Sclerosis

Introduction

PH is an incurable condition with high mortality and morbidity. It eventually leads to right ventricular hypertrophy followed by dilation, right ventricular failure, and death. PH is fairly prevalent in CTDs and it portends a poor prognosis. It can be seen in all forms of CTDs, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), mixed connective tissue disorders (MCTDs), Sjogren syndrome (SS), inflammatory myopathies, and most conspicuous in systemic sclerosis or scleroderma (SSc). The characterization of PAH (SSc-PAH) features dominantly in most published literature of CTD-PH. Unfortunately, there is a striking paucity of data in the published literature across the other CTDs. Therefore, the key characterizations of CTD-PAH, are mostly extrapolated from the evidence reported in SSc patients.

Definition and classification

PAH is defined, according to WHO criteria, as resting mean pulmonary artery pressure (mPAP) \geq 25 mm of Hg and pulmonary capillary wedge pressure (PCWP) \leq 15 mm of Hg, obtained by right heart catheterization [1]. In 2013 an updated clinical classification of PAH was published (Table 1) [1]. CTD-PAH has been listed as a subgroup within Group 1 PAH. Moreover, given the systemic nature of CTDs, CTD-PH may span WHO Groups 1 through 4 and often is considered "multifactorial," with features of several groups. For example, CTD-PH can occur in the setting of left heart diseases (Group 2) or secondary to pulmonary embolism (Group 4). The development of PH is a well-recognized complication of interstitial lung diseases (ILD, Group 3). In addition, pulmonary veno-occlusive disease (PVOD) is an uncommon but important determinant of CTD-PH, which is characterized by intimal proliferation and fibrosis of the intrapulmonary veins and venules [2].

<p>1. Pulmonary arterial hypertension (PAH)</p> <p>1.1 Idiopathic PAH</p> <p>1.2 Heritable PAH</p> <p>1.2.1 BMPR2</p> <p>1.2.2 ALK-1, Endogolin, SMAD9, CAV1, KCNK3</p> <p>1.2.3 Unknown</p> <p>1.3 Drugs and Toxins-induced</p> <p>1.4 Associated with:</p> <p>1.4.1 Connective tissue disease</p> <p>1.4.2 HIV</p> <p>1.4.3 Portal hypertension</p> <p>1.4.4 Congenital heart diseases</p> <p>1.4.5 Schistosomiasis</p> <p>1.5 Persistent pulmonary hypertension of newborn</p> <p>1.6 Secondary to pulmonary venoocclusive disease; Pulmonary capillary hemangiomatosis</p> <p>1' Pulmonary venoocclusive disease/pulmonary capillary hemangiomatosis</p>
<p>2. Pulmonary hypertension due to left heart disease</p> <p>2.1 Systolic dysfunction</p> <p>2.2 Diastolic dysfunction</p> <p>2.3 Valvular heart disease</p> <p>2.4 Congenital/acquired/left heart inflow/outflow tract obstruction, congenital cardiomyopathies</p>
<p>3. Pulmonary hypertension due to lung diseases and/or hypoxia</p> <p>3.1 Chronic obstructive pulmonary disease</p> <p>3.2 Interstitial lung disease</p> <p>3.2 Mixed restrictive and obstructive pulmonary disease</p> <p>3.4 Sleep-disordered breathing</p> <p>3.5 Alveolar hypoventilation</p> <p>3.6 Chronic high altitude exposure</p> <p>3.7 Developmental anomalies</p>
<p>4. Chronic thromboembolic pulmonary hypertension (CTEPH)</p>
<p>5. Pulmonary hypertension due to multifactorial unclear mechanisms</p> <p>5.1 Hematologic disorders (eg, myeloproliferative diseases, chronic hemolytic anemia, splenectomy)</p> <p>5.2 Systemic disorders (eg, sarcoidosis, langerhans cell histiocytosis, lymphangioleiomyomatosis)</p> <p>5.3 Metabolic disorders (eg, glycogen storage diseases, thyroid disorders)</p> <p>5.4 Others (eg, fibronising mediastinitis, chronic renal failure, segmental PH)</p>

Table 1: Updated clinical classification of pulmonary hypertension 2013.

(Adapted from Simonneau, et al. "Updated clinical classification of pulmonary hypertension". *Journal of the American College of Cardiology*. 62.25 (2013): D34-41).

Epidemiology

Pulmonary arterial hypertension can complicate all variants of CTD, especially SSc. The prevalence of pulmonary hypertension in systemic sclerosis (SSc-PH) is reported between 7.85% and 12% [3]. In the REVEAL registry, most of the patients with SSc-PH had limited cutaneous (63%) disease; however, recent studies suggest prevalence is similar in diffuse cutaneous involvement as well [5,6]. PH is more commonly associated with certain clinical risk factors (Table 2) [3,4]. The possibility of a genetic influence due to endogolin gene polymorphisms has been described in a small study of patients with SSc-PH [7].

<p>SSc-PH</p> <ul style="list-style-type: none"> • Limited SSc • Late age of SSc onset • Long-standing disease • Presence of telangiectasia • Severe Raynaud disease <p>SLE-PH</p> <ul style="list-style-type: none"> • Female sex • Raynaud’s disease • Digital gangrene • Renal disease • Cutaneous vasculitis/livedo reticularis <p>MCTD-PH</p> <ul style="list-style-type: none"> • Raynaud disease

Table 2: Clinical risk factors for development of CTD-PAH.

Other CTDs: The prevalence of SLE-PH varies widely, from 0.5% to 43% depending on the method of detection, although PAH is typically modest [8]. A more accurate estimation of 10.8% of asymptomatic PH has been reported in patients with SLE [9]. Presence of PH in SLE is not related to the severity or duration of illness. It can be the presenting manifestation of SLE, but studies reveal a mean delay of 4.9 ± 3.7 years between diagnosis of SLE and manifestation of PH [10]. Overall, PH is a rare complication in patients with RA. PH in these patients is most commonly due to ILD with or without associated pulmonary vasculitis, in which case prognosis is grim. Unlike SLE, there is a possible correlation between duration of illness and presence of PH in RA. It has also been rarely reported in undifferentiated connective tissue disorders and Still’s disease [11]. PH is the most serious complication of MCTD, reported in between 8% and 50% of patients with MCTD [4]. It is more commonly associated with scleroderma pattern nailfold capillary abnormalities in MCTD patients [4]. Few cases of PH have been reported in inflammatory myopathies and antisynthetase syndrome with positive antiJo-1 antibody and mild ILD [12].

Data from the REVEAL registry show that overall, CTD-PH patients are older (mean age 57 years), are predominantly women, and are African American (except patients with SSc-PH, who are usually white) [5]. A higher prevalence of CTD-PH is also seen in women of childbearing age, and pregnancy is a risk factor for developing SLE-PH [13].

Diagnostic criteria

The diagnosis of PH in the setting of CTD is often difficult. Patients should be referred to providers with expertise in this field. These patients may present with typical symptoms or PH may be an incidental finding during testing or because they belong to a high-risk population (eg, SSc). PAH can be a presenting manifestation of CTD, so all patients with PAH should be screened for CTDs.

The clinical symptoms of PH are generally nonspecific, such as progressive breathlessness, fatigue, and functional limitations, which are worse due to concomitant musculoskeletal involvement associated with CTDs. Patients may also present with presyncope/syncope, chest pain, non-productive cough, or ankle edema. Physical examination generally identifies a loud P2 due to increased pulmonary artery pressure and a right ventricular heave, suggesting right ventricular hypertrophy. Additionally, there may be an apical mid diastolic rumble and a left parasternal holosystolic murmur, both increasing with inspiration due to dilated pulmonary artery and tricuspid regurgitation, respectively. Patients can develop signs of right heart failure, such as elevated jugular venous pressure showing prominent V wave with rapid y descent, right-sided S3 and/or S4, tender pulsatile hepatomegaly, ascites, and peripheral edema. Most of these patients also have resting tachycardia and cardiac cachexia.

A detailed physical examination can suggest the presence of an underlying CTD, such as telangiectasias, digital ulcerations/pits, calcinosis, sclerodactyly and/or more proximal skin thickening, seen in scleroderma. The presence of a rash, alopecia, keratoconjunctivitis sicca, arthritis, and/or proximal muscle weakness are other clues in this regard. The incidence of Raynaud disease is higher in SSc-PAH and MCTD-PAH than in other forms of CTD-PH [5]. Most patients with SSc-PAH or SLE-PAH are functionally in Class III of the New York Heart Association (NYHA) classification at presentation; they often have dysfunction of other organs (eg, renal, cardiac) [3,4].

Chest radiography: The features of PH include central pulmonary artery dilation (right descending >1.6 cm and left descending > 1.8 cm) with peripheral pruning and relative oligemia, cor pulmonale with dilated right-sided chambers. In addition, chest radiographs may also show evidence of ILD, such as reticulation, infiltrates, and pulmonary venous congestion due to left heart diseases [14,15]. Presence of a pleural effusion on chest radiography strongly suggests right ventricular dysfunction in patients with SSc.

Electrocardiogram (ECG): ECG in patients with PH demonstrates right atrial enlargement, right ventricular hypertrophy, and right axis deviation in addition to rhythm abnormalities, most commonly supraventricular in origin. The low-voltage ECG may reveal pericardial effusion. ECG is abnormal in most patients with PAH, but is neither sensitive nor specific enough to be a screening tool [15].

Doppler echocardiogram: The transthoracic echocardiogram is the best screening tool to detect CTD-PH. PH is likely if the tricuspid regurgitant (TR) jet velocity is > 3.4 m/s and/or the systolic pulmonary artery pressure (SPAP) is > 50 mm of Hg. PH may also be possible if the TR jet velocity is 2.8 - 3.4 m/s and if the SPAP > 36 mm of Hg, if associated with other features such as increased dimensions of right heart chambers, increased right ventricular (RV) wall thickness, RV hypokinesis, dyskinesia of the interventricular septum, and dilation of the main pulmonary artery [16]. In general, the sensitivity and specificity of Doppler-estimated SPAP in predicting PH ranges from 0.79 to 1.0 and from 0.6 to 0.98, respectively [17]. However, SPAP measurement can be inaccurate in patients with advanced lung diseases [18]. Moreover, patients with SSc-PH often have disproportionately severe RV dysfunction, even without associated PH [19]. In background of ILD, a composite index of computed tomography-measured main pulmonary artery diameter and SPAP on echocardiogram predicts PH better than each single parameter alone [20]. On echocardiography, one should also look for other factors contributing to or complicating PH, such as left ventricular diastolic dysfunction or pericardial effusion, which are more common in patients with SSc.

Pulmonary function tests (PFTs): PFTs are necessary tools to identify PH, as suggested by a low lung diffusion capacity (DLco). A DLco < 60% of predicted together with a forced vital capacity (FVC)/DLco ratio > 1.6 is highly sensitive (70%) in predicting presence of PH in patients with SSc [17,21]. Data from the REVEAL registry suggests the FVC/DLco ratio is usually lower in other patients with CTD-PAH because of better preserved DLco in those patients. Unlike in SSc, the risk of developing PH does not correlate well with low DLco in patients with SLE [5].

Computed tomography (CT) of the chest: Patients with CTD usually undergo high-resolution CT of the chest to diagnose ILD or, polyserositis, and often undergo CT pulmonary angiogram (CTPA) to rule out any pulmonary thromboembolic disease. A ratio of main pulmonary artery to ascending aorta diameter greater than one (ie, MPA/AA > 1) on a chest CT strongly correlates with mPAP > 20 mm of Hg [22].

Ventilation perfusion (V/Q) scan: A V/Q scan may detect presence of CTEPH. However, its usefulness is limited due to matched perfusion defect expected in associated lung parenchymal involvement in CTDs. A CTPA would be more useful to detect concomitant or superimposed thromboembolic disease in that scenario. Moreover, an unmatched perfusion defect can also be seen in patients with PVOD.

Biomarkers: An elevated N-terminal pro-BNP (NT pro-BNP) level is a risk factor for development of CTD-PAH in occult diseases as well as a prognostic marker. A NT pro-BNP level > 240 pg/ml has a 90% specificity for detecting SSc-PAH. The serial changes in NT pro-BNP also correlate with survival in SSc-PAH [7]. However, it should not be viewed in isolation, as NT pro-BNP may remain elevated in other causes of CTD-related cardiac dysfunction or renal dysfunction as well.

Certain auto-antibodies are associated with increased risk of developing PAH in CTD, illustrated in Table 3.

- **SSc-** Anti-Scl-70 antibody, nucleolar speckled ANA (U3RNP), topoisomerase antibody, endothelial cell antibody (aECA)
- **SLE-** Anti-cardiolipin antibody, anti-ribonuclear antibody (anti-RNP), aECA, rheumatoid factor (RA)
- **SS-** antiRo/SSA antibody, anti-RNP antibody, rheumatoid factor, hypergammaglobulinemia
- **Inflammatory myopathies-** antiJo-1 antibody
- **MCTD-** U1RNP antibody

Table 3: Autoimmune markers associated with high incidence of PAH in patients with CTDs.

Nailfold capillaroscopy: This simple testing method can identify patients with SSc, SLE, and MCTD who may be at increased risk of developing PAH [15].

Six-minute walk test (6MWT): The 6MWT is a simple, inexpensive, reproducible tool to follow disease progression and treatment response in patients with PAH. Exercise desaturation in 6MWT is a hallmark of presence of PAH in CTD patients. Nonetheless, concomitant musculoskeletal involvement makes it a less reliable diagnostic parameter [23].

Right heart catheterization (RHC): RHC is the gold standard for diagnosing PAH. It also helps to exclude Group 2 PAH by measuring elevated PCWP. Early mortality is strongly linked to an elevated pulmonary vascular resistance (PVR), if PAH is associated with ILD [24]. Interestingly, far fewer patients with SSc-PAH or SLE-PAH demonstrate vasoreactivity during RHC.

Initial screening tool: Despite a high prevalence of PAH causing complications in patients with CTD, diagnosis often gets delayed due to the inherent difficulty in detecting PAH in the context of other organ dysfunctions. The initial screening recommendation has conventionally been Doppler measurement of TR jet velocity in echocardiogram. Recently a consensus-based, evidence-driven recommendation has been published for early detection of CTD-PAH. It recommends screening for PAH in all patients with SSc, but in only symptomatic patients who have other CTDs (Tables 3, 4) [25].

<p>Detection algorithm:</p> <p>Step 1- If abnormal, an echocardiogram is recommended</p> <ul style="list-style-type: none"> • Past or current telangiectasia • PFTs with DLco • NT-proBNP • Presence of anti-centromere antibody • Right axis deviation in ECG • Serum urate <p>Step 2- If abnormal, referral for RHC is indicated</p> <ul style="list-style-type: none"> • TR jet velocity by echocardiogram • Right atrial area in echocardiogram
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Table 4: Initial screening evaluation to detect PH in patients with SSc.

PVOD: PVOD has been described in CTDs including SSc, SLE, RA, and MCTD. Clinically, patients with these conditions often have severe hypoxemia and pleural effusions. The chest CT shows smooth interlobular septal thickening, centrilobular ground glass opacities, pleural effusions, enlarged pulmonary arteries, and lymphadenopathy. Distinguishing PVOD from PAH may be difficult, but PVOD should be suspected in CTD-PAH with the above features in the absence of ILD, especially if patients are unresponsive or poorly responsive to PH-specific therapy [2].

Management

The management of CTD-PH involves a multipronged strategy. In general, patients with CTD-PH are less responsive to treatment than their counterparts. The initiation of PH-specific therapy is further complicated by their propensity to develop V/Q mismatch in the presence of ILD. The approach to treatment in these patients can be divided into general measures and PH-specific therapies, discussed in greater detail below.

General measures: Lifestyle modifications have an important role in management of CTD-PH. These include smoking cessation, reduced salt intake, and immunization against influenza and pneumococcal pneumonia. The WHO consensus document strongly recommends against women getting pregnant if they have any type of PH. However, no consensus exists regarding appropriate birth control methods. Many PH-specific drugs interact with oral contraceptive agents, and intrauterine devices can sometimes cause a vasovagal reaction, which is poorly tolerated by these patients. Women with PH who become pregnant should be appropriately counseled regarding morbidity risks and the possible termination of pregnancy. Those who elect to continue their pregnancy should be treated with PH-specific therapy and planned elective delivery [26].

Patients with PH are prone to anxiety and depression, and often need psychosocial support. A prospective clinical trial has shown that an exercise training program as an add-on to medical therapy is highly effective in improving exercise capacity, quality of life, and short-term survival in these patients [27]. The role of anticoagulation therapy in patients with CTD-PH is unclear, as patients are at increased risk of bleeding from intestinal telangiectasia. There are no data supporting anticoagulation in patients with CTD-PH unless they have CTEPH or atrial fibrillation. Other supportive therapies, such as diuretics, digoxin, and oxygen to maintain oxygen saturation above 90%, should be utilized as appropriate.

PH-specific therapy: Calcium channel blockers (CCBs) are usually not recommended as PAH-specific therapy, as patients with CTD-PAH rarely demonstrate vasoreactivity in RHC, and their use may precipitate right heart failure due to negative chronotropic action. However, many patients with CTD-PAH take low-dose CCBs to treat Raynaud disease.

Endothelin receptor (ET) antagonists are potent pulmonary vasodilators and anti-smooth muscle mitogens of pulmonary vasculature. Bosentan and macitentan are non-selective ET-1 antagonists, whereas ambrisentan is a selective ETA1 receptor antagonist. Studies have shown they are less efficacious in CTD-PAH than in other forms of PAH. However, this does not preclude their use in patients with CTD-PAH; in fact, half of the CTD-PAH patients in the REVEAL registry are on an ET-1 antagonist [5]. Peripheral edema and congestive heart failure have been reported with use of ET-1 antagonists, and this class of drug carries a boxed warning of contraindications in pregnant women due to teratogenic effects.

Prostanoids are synthetic analogues of prostacycline PGI₂, available as intravenous (epoprostenol, treprostinil), subcutaneous (treprostinil), inhalation therapy (iloprost, treprostinil), and oral agents (treprostinil). These drugs significantly improve exercise capacity, 6MWD, functional class, and pulmonary hemodynamics [17,28]. The significant adverse effects include flu-like illness, jaw and leg pain, diarrhea, headache, dizziness, flushing, palpitation, tremor, and hypotension, in addition to the risk of indwelling catheter infection. Epoprostenol can reduce furosemide clearance and potentiate digoxin toxicity with concomitant use. These therapies require complex maintenance and follow-up, which should be conducted in specialized PH centers.

Phosphodiesterase 5 inhibitors prevent degradation of cyclic guanosine monophosphate and potentiates vascular smooth muscle dilatation via maintaining of nitric oxide. Sildenafil and tadalafil, the two most common drugs belonging to this group, they offer the advantages of being orally administered and better tolerated. One clinical trial of sildenafil demonstrated improved 6MWD, mPAP, and PVR in patients with SSc [17,29]. Retinal hemorrhage has been reported in patients taking sildenafil and anticoagulants simultaneously if the daily dose of sildenafil exceeds 60 mg. These drugs are also associated with serious events such as myocardial infarction, stroke, transient ischemic attacks, and seizures, and should be avoided in patients taking nitrate preparations. Notwithstanding, the low cost, ease of administration, and tolerability makes them the preferred first-line agents to treat CTD-PAH. Riociguat, a guanylate cyclase stimulator that increases nitric oxide production, has a great potential for use CTD-PAH and ILD-PAH, and is currently being investigated [30].

Inflammation and immunological mechanisms play a vital part in the initiation and progression of CTD-PAH. Small studies have suggested that immunosuppressive therapy with combined cyclophosphamide and corticosteroids was associated with clinical improvement in patients with SLE-PAH, MCTD-PAH, and SS-PAH in terms of WHO functional class, 6MWD, and mPAP [31]. Reports also suggest that PAH in patients with SLE may improve with rituximab therapy [32]. To date, immunosuppressive therapy has not been shown to be beneficial in patients with SSc-PAH; however, investigations are currently underway to examine the effect of rituximab in this patient population. [33].

The goals of PAH therapy are described in Table 5 [3]. Combination therapy is being increasingly used in patients with CTD-PAH, with roughly 40% of patients in the REVEAL registry were using some form of combination therapy [5]. It is generally reserved in those for whom monotherapy fails, or in patients with disease progression. Intravenous drugs are generally recommended for treatment of PAH in patients with advanced NYHA functional class, in those with low cardiac index, or in those for whom oral therapy fails.

- NYHA functional classification: Class I or Class II
- Normal or near-normal RV size on echocardiography
- 6MWD > 380 - 440 m
- Normal BNP/NT pro-BNP
- Cardiopulmonary exercise testing showing peak oxygen consumption >15 ml/min/kg
- Pulmonary hemodynamics- Right atrial pressure <8 mm of Hg, Cardiac index >2.5-3 l/min/m²

Table 5: Goals of PAH therapy.

Patients for whom medical therapy fails should be referred for consideration for lung transplantation. Concomitant involvement of other organs is not an absolute contraindication for lung transplantation, but places them at increased risk of post-transplant complications [34]. Non-pulmonary organ involvement with regards to gastroesophageal reflux (and esophageal dysmotility), cardiac dysfunction, and chronic kidney disease may complicate the evaluation and candidacy of lung transplantation in patients with CTD. Hence, these patients should be properly screened, particularly for gastroesophageal reflux diseases and renal dysfunction. However, the scant data available suggest the short-term morbidity and mortality as well as long-term survival in patients with SSc and other CTDs are similar to those of patients with chronic lung conditions who undergo lung transplantation [35,36].

Prognosis

The presence of PH is an important predictor of mortality in patients with CTDs. Although the survival in patients with CTD-PAH has improved in the modern treatment era, it still remains disappointingly low. Patients with SSc-PAH have the worst prognosis of all types of CTD-PAH; in fact, patients with SSc are 3 times more likely to die with PAH than without PAH [37]. Data from the PHAROS registry show cumulative 1-, 2-, and 3-year survival rates of 93%, 88%, and 75%, respectively, in patients with SSc-PAH, in spite of early detection and PAH-specific therapy [21]. The predictors of mortality in SSc-PAH are described in Table 6 [3]. The adverse prognosis is further compounded by coexisting ILD, with a 5-fold increase in mortality [38]. Although most published cohorts of CTD-PAH involved patients with SSc, limited data suggests similar outcomes in other CTDs. Nearly half of the deaths in patients with MCTDs are attributed to PAH, whereas patients with MCTDs without PAH have excellent prognoses [4]. The outcomes of RA-PAH and MCTD-PAH are similar. In a small series of SS-PAH patients, 3-year survival was 66%. On the contrary, PAH related to inflammatory myopathies has a much better outlook, with 3-year survival approaching 100%, although cases are few and far between.

<ul style="list-style-type: none"> • Older age (ie, > 60 years) • Male sex • Advanced NYHA classification functional status • Severely reduced DLco (ie, < 39%) • Low arterial oxygen tension • Decreased 6MWD • Elevated PVR and right atrial pressure • Presence of pericardial effusion and poor kidney function

Table 6: Predictors of mortality in patients with SSc-PAH.

Conclusion

PH is a fatal complication of CTD, especially in patients with SSc. It is now more commonly recognized in other CTDs as well, due to increased awareness and utilization of various screening tools. Unfortunately, PAH therapy is not as beneficial in patients with CTD-PAH as it is in other form of PH. Notwithstanding, aggressive immunosuppressive therapy needs to be employed in patients with CTD-PAH (but not in patients with SSc-PAH). Patients with SSc and patients with other CTDs for whom immunosuppressive regimens fail may benefit from PAH-specific therapy. Overall prognosis still remains grim, and for most patients, candidacy for lung transplantation should be evaluated.

Key Points

- Pulmonary arterial hypertension (PAH) is becoming an increasingly well-recognized entity of connective tissue diseases (CTDs). It is seen in a diverse spectrum of CTDs, most notably, in systemic sclerosis (SSc).
- The presence of PAH heralds a poor prognosis in patients with CTDs.

- Low lung diffusion capacity and forced vital capacity/lung diffusion capacity > 1.6 and elevated NT pro-BNP are risk factors for development of PAH in patients with SSc.
- Measurement of tricuspid regurgitant jet velocity is the most valuable noninvasive test to detect PAH in patients with CTD.
- Computed tomography pulmonary angiography and cardiac magnetic resonance imaging are useful screening tools for PAH detection as well.
- The 6-minute walking distance test is not a reliable marker in patients with CTDs, unlike in other patients with PAH.
- More recently, valuable screening tools have been deployed for early detection of this complication.
- PAH-specific therapy, in general, is less efficacious in patients with CTD-PAH than for patients with other forms of PAH. Inhaled prostanoids and oral sildenafil are options, when PAH-specific therapy is needed.
- Aggressive immunosuppression to control disease inflammation and PAH should be instituted sooner rather than later in patients with CTD-PAH (other than SSc-PAH).
- Survival after lung transplantation in patients with CTD-PAH is comparable to survival of transplantation for other chronic lung diseases, but with significant morbidity related to CTDs and associated gastroesophageal reflux disease.

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