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Review Article

Pulmonary Hypertension in Connective Tissue Disorders

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Abstract

Pulmonary hypertension (PH) is common in 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 pulmonary hypertension in connective tissue diseases. In recent times, improved diagnostic tools have aided in early diagnosis and has been shown to improve survival. The treatment approach in PH associated with CTDs is essentially similar to pulmonary arterial hypertension. Notwithstanding, the PH therapy is less efficacious here than other forms of pulmonary hypertension. Although the survival has improved in 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 mechanism of connective tissue disease associated pulmonary hypertension 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 CTD and it portends a poor prognosis. It can be seen in all forms of CTDs such as systemic lupus erythromatosus (SLE), rheumatoid arthritis (RA), mixed connective tissue disorders (MCTD), sjogren's syndrome (SS), inflammatory myopathies, and most conspicuous in systemic sclerosis or scleroderma (SSc). The characterization SSc related PH (SSc-PH) 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-PH, are mostly extrapolated from the evidence reported in SSc patients.

Definition and classification

PH is defined, according to WHO criteria, as resting mean pulmonary artery pressure (mPAP) ≥ 25 mm of Hg and pulmonary wedge pressure (PCWP) ≤ 15 mm of Hg, obtained by right heart catheterization [1]. In 2013 an updated clinical classification of PH was published (Table 1) [1]. Connective tissue disease associated pulmonary hypertension (CTD-APAH) has been enlisted as a subgroup within Group 1 pulmonary hypertension (PAH). Moreover, given the systemic nature of connective tissue diseases, CTD-PH may span WHO groups 1 through 4 and often is considered "multifactorial" with features of several groups. For examples, CTD-PH can occur in the setting 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].

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

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 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, majority of the patients of SSc-APAH 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 genetic influence due to endogolin gene polymorphisim have been described in SSc- PAH in a small study [7].

Systemic Sclerosis associated PH • Limited SSc • Late age of onset of SSc • Long standing disease • Presence of telangiectasia • Severe Raynaud's phenomenon
SLE related PH • Female sex • Raynaud's disease • Digital gangrene • Renal disease • Cutaneous vasculitis/livedo reticularis
MCTD related PH
Raynaud's phenomenon

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

Other CTDs: The prevalence of PH in SLE (SLE-PH) varies widely from 0.5% to 43% depending on the method of detection, although PH is typically modest [8]. A more accurate estimation of 10.8% of asymptomatic PH has been reported in 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 RA. PH in RA 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 (UCTD) and juvenile still's disease [11]. Pulmonary hypertension is the most serious complication of MCTD, reported between 8% and 50% [4]. It is more commonly associated with scleroderma pattern nail fold capillary abnormalities in MCTD patients [4]. Few cases of PAH have been reported in inflammatory myopathies (PM-DM) and antisynthetase syndrome with positive antiJo-1 antibody and mild ILD [12].

Data from REVEAL registry reveals that overall CTD-APAH patients were older (mean age 57 years), predominantly women and of African-American origin except SSc-PH who are mostly of Caucasian decent [5]. A higher prevalence of CTD-APAH is also seen in women of child bearing age and specifically, pregnancy is a risk factor for developing SLE-PH [13].

Diagnostic criteria

The diagnosis of PH in 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 incidental finding during testing or as they belong to high risk population (e.g. SSc). PH can be a presenting manifestation of CTDs and all patients with PAH should be screened for CTDs.

The clinical symptoms are generally non-specific like progressive breathlessness, fatigue and functional limitations, which are however worse due to concomitant musculoskeletal involvement in CTDs. Patients may also present with presyncope/syncope, chest pain, non-productive cough or ankle edema. The physical examinations 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 in inspiration due to dilated pulmonary artery and tricuspid regurgitation respectively. The patients can develop signs of right heart failure like 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. Also, most of the patients have resting tachycardia and cardiac cachexia.

A detailed physical examination can suggest the presence of an underlying CTD, for example 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's phenomenon is higher in SSc and MCTD associated PH than other forms of CTD-APAH [5]. Majority of patients with SSc or SLE associated PAH are functionally in NYHA class III at presentation; they often have other organ dysfunctions like renal and cardiac [3,4].

Chest X-ray: 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 X-ray may also show evidence of interstitial lung diseases such as reticulation, infiltrates as well as pulmonary venous congestion due to left heart diseases [14,15]. Presence of a pleural effusions on chest X-ray strongly suggests RV dysfunction in patients with SSc.

Eletrocardiogram (ECG): ECG 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 be seen with pericardial effusion. ECG is abnormal in majority of the patients but not sensitive nor specific as 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 systolic 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 dilated main pulmonary artery [16]. In general, the sensitivity and specificity of doppler estimated SPAP in predicting PH ranges from 0.79 to1.0 and 0.6 to 0.98 respectively [17]. However, SPAP measurement can be inaccurate in patients with advanced lung diseases [18]. Moreover, SSc-PH often have disproportionately severe RV dysfunction, even without associated PH [19]. In background of ILD, a composite index of CT scan 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 or complicating PH such as LV diastolic dysfunction or pericardial effusion that are more common in patients with SSc.

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

CT scan of Chest: Patients with CTD usually undergo high-resolution CT scan of chest to diagnose presence of interstitial lung disease, polyserositis and often CT pulmonary angiogram (CTPA) to rule out any pulmonary thromboembolic disease. A ratio of main pulmonary artery to ascending aorta diameter greater than one (MPA/AA > 1) in CT scan strongly correlates with mPAP > 20 mm of Hg [22].

Ventilation perfusion (V/Q) scan: 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 PVOD.

Biomarkers: An elevated N-terminal pro-BNP (NT pro-BNP) level is a risk factor for development of CTD-PH in occult diseases as well as a prognostic marker. A NT pro-BNP level > 240 pg/ml has a 90% specificity for detecting SSc-PH. The serial changes in NT pro-BNP also correlate with survival in SSc- PH [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.

The presences of certain auto-antibodies are associated with increased risk of developing PH in CTD, illustrated in table 3.

• **SSc-** anti Scl70 antibody, Nucleolar speckled ANA (U3RNP), Topoisomerase antibody, endothelial cell antibody (aECA)
• **SLE-** Anti-cardiolipin antibody, anti-ribonuclear antibody (anti-RNP), aECA, rheumatoid factor (RA)
• **Sjogren syndrome-** antiRo/SSA antibody, anti-RNP antibody, RA, hypergammaglobulinemia
• **Inflammatory myopathies**- antiJo-1 antibody
• **MCTD**- U1RNP antibody

Table 3: *Auto-immune markers associated with high incidence of PH in CTD patients.*

Nalifold Capillaroscopy: It can identify those at high risk of developing PH later in SSc, SLE and MCTD patients [15].

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

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

Initial screening tool: Despite a high prevalence of PH complicating CTD patients, diagnosis often gets delayed due to the inherent difficulty in detecting PH in 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-PH. It recommends screening for PH in all patients with scleroderma but in only symptomatic patients in other CTDs (Tables 3, 4) [25].

Detect algorithm:

Step 1- If abnormal, an echocardiogram is recommended

- Past or current telangiectasia
- PFTs with DLco
- NT-proBNP
- Presence of anti-centromere antibody
- Right axis deviation in ECG
- Serum urate

Step 2- if abnormal, referral for RHC is indicated

- TR jet velocity by echocardiogram
- Right atrial area in echocardiogram

Table 4: *Initial screening evaluation to detect PH in SSc patients.*

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

Management

The management of CTD-PH involves a multipronged strategy. In general CTD-PH patients are less responsive to treatment than their counterpart. The initiation of PH-specific therapy is further complicated by their propensity to develop V/Q mismatch in presence of interstitial lung disease. The approach to treatment in these patients can be divided into General measures and PH-specific therapies.

General Measures: The life-style recommendations have an important role in management of CTD-PH. That includes smoking cessation, reduced salt intake, immunization against influenza and pneumococcal pneumonia. The WHO consensus document strongly recommends against pregnancy in any form of PH. There however is no consensus regarding appropriate birth control methods. Many PH specific drugs interact with oral contraceptive agents; the intrauterine devices can sometimes cause vasovagal reaction, which is poorly tolerated by these patients. Patients with PH who become pregnant should be appropriately counseled for termination of pregnancy. Those who choose to continue should be treated with PH-specific therapy and planned elective delivery [26].

These patients are prone to suffer from anxiety and depression, often need a psychosocial support. Prospective clinical trial has shown that exercise training program as an ad-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 in CTD-PH is unclear as patients are at increased bleeding risk from intestinal telangiectasia. There are no data supporting anticoagulation in 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 (CCB) are usually not recommended as PH specific therapy as patients with CTD-PH rarely demonstrates vasoreactivity in RHC and it may precipitate right heart failure due to negative chronotropic action. However many of them will be on low dose CCB to treat Raynaud's syndrome.

Endothelin receptor (ET) antagonists are potent pulmonary vasodilator and anti- smooth muscle mitogen of pulmonary vasculature. Bosentan and Macitentan are non-selective ET-1 antagonist whereas Ambrisentan is a selective ETA1 receptor antagonist. Studies have shown they are less efficacious in CTD-PH than other form of PH. However, this does not preclude their use in CTD-PH; in fact half of the CTD-PH patients in REVEAL registry are on ET-1 antagonist [5]. Peripheral edema and congestive heart failure has been reported with use of ET-1 antagonists. This class of drug carries a boxed warning of contraindication in pregnant women due to teratogenic effect.

Prostanoids are synthetic analogue of prostacycline PGI2 available as intravenous (epoprostenol, treprostinil), subcutaneous (treprostinil), inhalation therapy (iloprotst, treprostinil) and new oral agent (treprostinil). These drugs significantly improves exercise capacity, 6MWD, functional class and pulmonary hemodynamics [17,28]. The significant side effects include 'Flu-like illness', jaw and leg pain, diarrhea, headache, dizziness, flushing, palpitation, tremor and hypotension besides 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 (PDE-5) inhibitors prevent degradation of cGMP and potentiates vascular smooth muscle dilatation via maintaining of Nitric oxide (NO). Sildenafil and Tadalafil are the two common drugs belonging to this group. They offer a potential advantage being orally administered and better tolerated. One clinical trial with Sildenafil demonstrated improved 6MWD, mPAP and PVR in SSc patients [17,29]. The retinal hemorrhage has been reported with Sildenafil and concomitant use of anticoagulant, when daily dose of Sildenafil exceeds 60 mg. These drugs are also associated with serious events such as myocardial infarction, stroke, transient ischemic attacks, seizures and should be avoided in patients taking nitrate preparations. Notwithstanding, the low cost, ease of administration and tolerability makes it the preferred first-line agent to treat CTD-PH. Riociguat, a guanylate cyclase stimulator increasing production of NO, has a great potential for use in CTD-ILD associated PH, is currently being investigated [30].

Inflammation and immunological mechanism plays a vital part in initiation and progression of CTD-APAH. Small studies have suggested that immunosuppressive therapy with combined cyclophosphamide and corticosteroids was associated with clinical improvement in PH due to SLE, MCTD and SS in terms of WHO functional class, 6MWD and mPAP [31]. Reports also suggest that pulmonary arterial hypertension in SLE may improve with Rituximab therapy [32]. SSc patients with PAH have not shown any benefit with immunosuppressive therapy to date, but rituximab is currently under investigation for SSc associated PAH [33].

The goals of PH-therapy are described in table 5 [3]. Combination therapy is being increasingly used in CTD-PH patients, around 40% CTD-APAH patients were using combination therapy in REVEAL registry [5]. It is generally reserved in those who fail monotherapy or with disease progression. The intravenous drugs are generally recommended for treatment of PH in patients with advanced NYHA functional class, in those with low cardiac index or when oral therapy fails.

• NYHA functional class- I or II
• Normal or near-normal RV size in 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/m^2

Table 5: *Goals of PH therapy.*

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

Prognosis

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

- older people > 60 years,
- Male gender,
- Advanced NYHA functional
- Severely reduced DLco (< 39%)
- Low arterial oxygen tension
- Decreased 6MWD
- Elevated PVR and RAP
- Presence of pericardial effusion and poor kidney function

Table 6: *Predictors of mortality in SSc related PH.*

Conclusion

PH is a fatal complication of CTD, especially in systemic sclerosis patients. It is now more commonly recognized with other CTD as well, due to increased awareness and utilization of various screening tools. Unfortunately PH therapy is not as beneficial in CTD-PH as in other form of PH. Notwithstanding, aggressive immunosuppressive therapy needs to be employed in CTD-PH patients other than SSc. The systemic sclerosis patients and those failing immunosuppression in other CTD, may benefit from PH-specific therapy. Overall prognosis still remains grim and for most patients candidacy for lung transplantation should be evaluated.

Key Points

- Pulmonary hypertension (PH) is increasingly becoming a well-recognized entity of connective tissue diseases (CTD). It is seen in diverse spectrum of connective tissue disorders, most notably in systemic sclerosis (SSc).
- Presence of PH heralds a poor prognosis in these patients.

- Low DLco and FVC/DLco > 1.6 and elevated NT pro-BNP are risk factors for development of PH in SSc patients.
- Measurement of TR jet velocity is the most valuable non-invasive test to detect PH in CTD.
- CTPA and cardiac MRI is a useful screening tool for detection as well.
- 6 minute walk test distance (6MWD) is not a reliable marker in CTD patients unlike other PH patients.
- More recently, valuable screening tools have been deployed for early detection of this complication.
- PH-specific therapy, in general, is less efficacious in CTD related PH than many other form of PH. Inhaled prostanoids and oral sildenafil are the options, when PH-specific therapy is needed
- Aggressive immunosuppression to control disease inflammation and PH, should be instituted sooner than later in CTD-PH other than SSc
- Survival after lung transplant in CTD related PH (CTD-PH) is comparable to other chronic lung diseases but with significant morbidity related to CTD and associated gastroesophageal reflux.

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