REVIEW

A new era in the management of pulmonary arterial hypertension related to scleroderma: endothelin receptor antagonism

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Evidence suggests that endothelin may have a fundamental role in scleroderma pathogenesis, including pulmonary arterial hypertension (PAH)—a leading cause of death in patients with scleroderma. Development of a new class of drug, endothelin receptor antagonists, heralds an improved outlook for patients with scleroderma and related diseases. Heightened vigilance towards early detection of PAH in scleroderma and a multidisciplinary approach to diagnosis and treatment may improve clinical outcomes for these patients.

Managing collagen vascular diseases is challenging, requiring multiple treatment strategies and a multidisciplinary approach. The management of scleroderma (also known as systemic sclerosis) is no exception, with the primary physician (such as a rheumatologist, internist, or dermatologist) encountering a variety of disease manifestations throughout its clinical course.

Current treatment options for scleroderma predominantly aim at alleviating symptoms, rather than modifying the disease, while research continues to strive for a better understanding of the disease pathogenesis.[1] Vascular injury appears to be an underlying precursor of scleroderma, with autoimmune and proliferative disturbances contributing to the pathophysiological changes.[2 3] The diverse detrimental effects of these underlying causes are apparent in the resulting multisystem damage. Pulmonary arterial hypertension (PAH) is a serious complication of scleroderma, with a wide prevalence depending on the method chosen for its detection (echocardiography or right heart catheterisation). Recent publications suggest that a prevalence of higher than 15% is unlikely.[4 5] As one of the leading causes of mortality in scleroderma,[2] the vascular pathogenesis seen in the development of PAH, as an independent or secondary disease, shares similar properties of vascular injury and consequences with the overall disease state of scleroderma.[3]

The identification of endothelin as a major influencing factor in many of the body's physiological processes has led to an increased understanding of mechanisms affecting both health and disease.[6] Endothelin is now recognised as having a fundamental role in the vascular dysfunction seen in collagen vascular diseases, such as scleroderma, in addition to a strong correlation with disease severity and prognosis in PAH.[3 6] The introduction of endothelin receptor antagonists (ERAs) as a therapeutic option brings hope of a proactive treatment to target the pathophysiology involved in PAH related to scleroderma, in addition to providing symptomatic relief.[6 7]

SCLERODERMA: DEFINITION

Scleroderma is a chronic disease resulting from primarily vascular, in addition to autoimmune and proliferative, disturbances. The reported prevalence of scleroderma varies, with an occurrence of 30.8 to 286 cases per million (in Mayes[8]). A recent evaluation of the prevalence in the Detroit area (USA), based on a capture-recapture analysis showed a prevalence estimate of 276 cases per million adults.[8] Women are more likely to be affected (3:1–6:1), with an average age at diagnosis of 40–50 years, or younger. Survival at 5–6 years has been reported as between 34% and 76%, with an increased mortality rate of up to fourfold that of the general population.[9–13] More recent reports, however, suggest that in unselected populations survival is higher than initially thought.[4 14]

The disease is classified based on early presentation and progression of symptoms. Classification is specified as diffuse scleroderma, limited scleroderma, or limited cutaneous scleroderma—more commonly referred to as the CREST syndrome. The characteristics of CREST syndrome are defined by the presence of at least three out of five of the following predominant symptoms: Raynaud's phenomenon, sclerodactyly, subcutaneous calcification, oesophageal hypomotility, and telangiectasia. Tables 1 and 2 outline the definition of these various disease states.[15–17]

An understanding of the pathogenesis of scleroderma is still incomplete. Microvascular dysfunction, endothelial cell injury, and increased collagen synthesis all occur from an early stage of the disease. Treatment is aimed at the underlying disease processes of the vascular and immune systems and the arrest of fibrosis.[1 2]

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Abbreviations: CCBs, calcium channel blockers; ERA, endothelin receptor antagonist; FVC, forced vital capacity; ILD, interstitial lung disease; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; TLCO, carbon monoxide transfer factor; VSMC, vascular smooth muscle cells

Table 1 Preliminary clinical criteria for systemic sclerosis (scleroderma)*[15]

Major criterion	Proximal scleroderma: skin changes characterised by tightness, thickening, and non-pitting induration, proximal to the metacarpophalangeal or metatarsophalangeal joints, affecting other parts of the extremities, face, neck or trunk (thorax or abdomen), usually bilateral and almost always including sclerodactyly
Minor criteria	Sclerodactyly Digital pitting scars of fingertips or loss of substance of the distal finger pad Bibasilar pulmonary fibrosis

One major or two minor criteria are required for confirmation of the presence of scleroderma.
*ARA Scleroderma Criteria Cooperative Study (SCCS).

Table 2 Criteria for the diagnosis of scleroderma[16]

lSSc	Raynaud's phenomenon (objective documentation) plus any one: Scleroderma-type nailfold capillary pattern Scleroderma selective autoantibodies Raynaud's phenomenon (subjective only) plus both: Scleroderma-type nailfold capillary pattern Scleroderma selective antibodies
lcSSc	Criteria for lSSc plus: Distal cutaneous changes
dcSSc	Criteria for lSSc plus: Proximal cutaneous changes

lSSc, limited scleroderma; lcSSc, limited cutaneous scleroderma (also known as CREST: calcinosis, Raynaud's phenomenon, oesophageal involvement, sclerodactyly, and telangiectasia); dcSSc, diffuse cutaneous systemic sclerosis (scleroderma).

PULMONARY ARTERIAL HYPERTENSION

PAH is a life threatening disease, with progressive pathophysiological deterioration of the cardiopulmonary vasculature, leading to vascular remodelling, pulmonary arterial vasoconstriction, and in situ thrombosis.[6 7] This results in an increase in pulmonary vascular resistance, with right heart failure and, ultimately, death. PAH can occur as idiopathic PAH (previously named primary pulmonary hypertension) of unknown origin, or in relation to an existing disease, such as connective tissue diseases, particularly scleroderma.[6 18 19]

PAH is defined as a mean pulmonary arterial pressure (mPAP) >25 mm Hg at rest or >30 mm Hg during exercise with a normal pulmonary artery wedge pressure.[20 21] Despite the gravity of the disease, detection remains elusive until the later stages, owing to the non-specific nature of its symptoms. Dyspnoea on exertion remains the primary symptom, with disease progression characterised by increasingly impaired exercise capacity, fatigue, and worsening dyspnoea. Syncope, chest pain, jugular vein extension, and oedema generally indicate the development of right heart failure(fig 1, table 3).[18–22]

> ''Preclinical symptoms of PAH can be mistaken for lack of fitness''

Diagnosis of PAH is through the exclusion of other diseases. Pulmonary function testing, including measurement of carbon monoxide transfer factor (TLCO), chest *x* ray examination, laboratory testing for underlying diseases, and ECG, are all employed to elucidate signs of PAH or to detect a separate underlying cause.[17 21 23] The UK[21] and World Health Organisation (WHO)[23] recommendations of widespread use of Doppler echocardiography in the assessment of non-specific cardiovascular signs and symptoms have led to occasional observations of mildly increased right ventricular systolic pressure. Where tricuspid regurgitant velocity on Doppler echocardiography is detected above 3 m/s, the patient is considered to be at high risk of pulmonary hypertension.[23] Right heart catheterisation, the definitive diagnostic test for PAH, confirms the disease through haemodynamic measures indicative of a compromised cardiopulmonary circulation, such as a raised mPAP and pulmonary vascular resistance. Early diagnosis of PAH is essential to optimise treatment and improve prognosis.[6 13 23 24]

SCLERODERMA AND ENDOTHELIN

Endothelin, a potent vasoconstrictor and fibrogenic peptide first noted in 1988,[25] is emerging as having a crucial role in a wide range of body processes. In health it has a vital role in vascular tone, mitogenesis, and neurohormonal activation. In disease, endothelin is a key pathogenic mediator, influencing

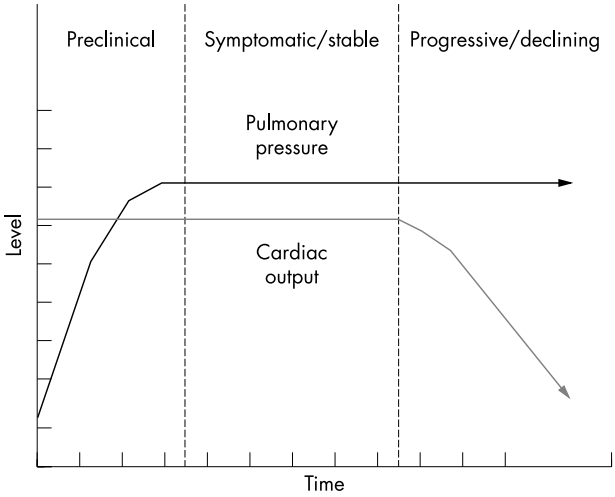

Figure 1 PAH: pathogenesis occurs before clinical symptoms.[22] Reproduced, with permission of Elsevier Science from Rich.[22]

vasoconstriction, fibrosis, vascular hypertrophy, and inflammation. Endothelin is secreted from endothelial cells and has two known receptor subtypes—ET_A, found predominately on vascular smooth muscle cells (VSMC), induces a vasoconstrictor effect, while ET_B, found on endothelial cells and VSMC, has both a vasoconstrictor and vasodilator effect.[6] Endothelin dysfunction is increasingly acknowledged as having a fundamental role in the pathogenesis of cardiovascular, vascular, pulmonary, and renal diseases, while speculation continues to grow of its potential impact in some cancers.[2 6 25]

Given the activation of endothelial cells in some collagen vascular diseases, dysfunctional endothelin activity is now recognised as an important contributor to this disease area.[2 6] Both clinical and preclinical investigations have exposed raised endothelin levels in primary and secondary Raynaud's phenomenon, systemic lupus erythematosus, and other collagen vascular diseases.[2]

In the case of scleroderma, raised circulating endothelin levels have been demonstrated[26] and in one study correlated with cardiac hypertrophy.[27] Endothelin has been implicated in vasoconstrictor and profibrotic activity and the increased extracellular matrix substances seen in the dermis and internal organs of patients with scleroderma.[2 28] Endothelial cell damage leading to increased endothelin production may influence early stage disease, such as the manifestation of Raynaud's phenomenon, and sustained increase in

Table 3 Clinical manifestations of PAH: primary symptom is dyspnoea*[23]

Preclinical	Symptomatic	Declining
Few symptoms manifest, or are mistaken for lack of fitness	Increasing dyspnoea on exertion Decreasing exercise tolerance Fatigue	Dyspnoea at rest Severe impairment of exercise tolerance Hypoxaemia Syncope Chest pain Oedema Right heart failure.
WHO class I	WHO class II–III	WHO class IV

*Adapted from the WHO Functional Assessment of PAH.[23]

endothelin levels may play an important part in later stage organ fibrosis. Endothelin plasma levels are raised in the lung tissue of patients with scleroderma with pulmonary disease, including PAH, and a correlation of this increase with the severity and prognosis of PAH supports the evidence surrounding endothelin dysfunction.[2 6 18 29 30]

SCLERODERMA AND PULMONARY ARTERIAL HYPERTENSION

PAH related to scleroderma is now one of the leading causes of mortality in this disease.[2] Historically the median survival was only 1 year after diagnosis of PAH.[31] More recent reports show that though the prognosis remains poor in comparison with idiopathic PAH,[32 33] the median survival in PAH associated with scleroderma is more than 3 years[5]; however, these were screened patients. A recent publication showed that the 5 year cumulative survival of SSc related PAH was 10% compared with 80% in a control population of patients with SSc without PAH.[34] With the improved management of renal crisis in scleroderma, pulmonary manifestations of the disease, including PAH, have emerged as the major contributors to morbidity and mortality in these patients.[34 35] The prevalence of PAH in patients with scleroderma appears to be no higher than 15%.[4 5] However, histopathogical evidence of pulmonary arteriopathy is found in up to 50–65% of patients with limited scleroderma, suggesting that much greater numbers may be at risk of developing PAH if followed up for long enough.[13 18 31]

> ''Screening of patients with scleroderma is essential so that PAH can be detected early''

PAH in limited scleroderma typically presents later in the disease when other symptoms such as Raynaud's phenomenon are well established. In diffuse scleroderma, pulmonary hypertension development is generally seen after the establishment of interstitial lung disease (ILD), although PAH and ILD can appear as independent manifestations of scleroderma related disease.[6 23] Regardless of the onset of PAH, it appears that injury due to vascular, inflammatory, and profibrotic abnormalities occurs from early stage disease, when clinical symptoms are not apparent. Screening for PAH in the high risk scleroderma group is imperative for early detection and effective treatment, as survival in late stage disease is recorded at less than 50% despite treatment intervention.[6 13 24 36]

Regular monitoring for PAH related to scleroderma is a required element of disease management, as all patients with scleroderma are at risk of developing PAH. A decreased TLCO, with little or no associated reduction in lung volumes on pulmonary function testing, may be indicative of the presence, or high risk, of PAH.[24 34] A decreasing TLCO (<60% of predicted) with normal forced vital capacity (FVC >75% of predicted) has been reported to be an excellent predictor of the subsequent development of PAH in scleroderma.[34 37] However, in a screened population, 26% of patients with proven PAH had a TLCO of >60%, and 30% of patients with a low TLCO did not meet the criteria for PAH at catheterisation. Jugular vein extension, loud pulmonary second heart sound, and a left parasternal heave indicate late stage PAH, as do ECG irregularities such as peaked P wave or right ventricular strain. Baseline and annual Doppler echocardiography, as recommended by the WHO and UK PAH guidelines, facilitate early detection of PAH in this patient group (tables 4 and 5).[21 22] Right heart catheterisation confirms the diagnosis and shows the consequence of disease activity in both the right and left heart (mPAP >25 mm Hg at rest/mPAP >30 mm Hg with exercise with a normal pulmonary artery wedge pressure).[21 23 24 34]

Necropsy evidence discloses a much higher presence of PAH related to scleroderma than detected clinically[31] and highlights the fact that PAH remains undiagnosed in the majority of affected patients. However, when a screening protocol (echocardiography and lung function testing) followed by right heart catheterisation was used the prevalence of PAH associated with SSc was only 12% in 722 patients over 4 years.[5] Thus, either not all pulmonary vasculopathy leads to clinical disease or there is a prolonged phase of progressive vascular damage which will eventually lead to PAH. However, early diagnosis before significant damage occurs may greatly improve prognosis, if an effective treatment is available for clinical application.[20 24]

CURRENT AND FUTURE TREATMENT OPTIONS FOR PULMONARY ARTERIAL HYPERTENSION

Without an effective treatment that can act on both the cause and symptoms of PAH related to scleroderma, routine screening is of minimal value.[13] To date, treatment options have been limited owing to a lack of randomised, placebo controlled trial evidence of efficacy and survival benefit. In addition, treatments had potentially damaging effects owing to the nature of the underlying collagen vascular disease.[7]

Anticoagulant treatment has been shown to significantly improve survival in idiopathic PAH[38] and is also recommended in PAH related to scleroderma.[39] Supportive oxygen

Table 4 Haemodynamic assessments of PAH by echocardiography*[21 23]

Tricuspid regurgitant velocity
Right ventricular ejection time
Right ventricular dimensions
Right ventricular volumetric data
Right ventricular index of myocardial performance
Timing of mid-systolic deceleration of right ventricular ejection

*WHO and UK PAH guidelines recommend baseline and annual echocardiograms for patients with scleroderma.[21 23]

Table 5 Clinical signs of PAH which has progressed (cardiac specific)[42]

Increased intensity of the second heart sound (P_2)
Transmission of the P_2 to the cardiac apex
Increase in jugular venous pressure
Signs of tricuspid regurgitation
Pulmonary ejection sounds and pulmonary insufficiency murmur
Right ventricular S_3 gallop (signifies right ventricular failure)
Systolic pulsation over the second left intercostal space (signifies dilated pulmonary artery)

treatment may alleviate moderate hypoxia, while the use of diuretics and digitalis, under close monitoring, has benefit in some patients.[39] Calcium channel blockers (CCBs) have proven efficacy in a minority (<6%) of patients with primary pulmonary hypertension who respond both to an acute vasodilator test, and exhibit persistent responsiveness to CCB treatment when recatheterised after 3 months of treatment.[38 40] However, in PAH related to scleroderma, where a non-vasoreactive response (<3% exhibiting the 20% fall in mPAP required to support a trial of CCBs)[5 40] due to significant vascular injury is common, use of these agents is limited.[39 41] Indeed, vasodilator treatment can be detrimental, exacerbating scleroderma-type symptoms such as gastric reflux and oesophageal motility,[6 7] and has the potential to damage heart function, owing to a negative inotropic effect.[42] Lung transplantation continues to be a treatment option, most commonly in late stage, severe PAH. The generally last line placement of this intervention is primarily because of the lack of available heart-lung donor organs.[21] The survival at 1 and 3 years is similar for patients with idiopathic ILD and with overall indications (PAH, ILD, or both) related to scleroderma (63.5% *v* 70.6% at 1 year and 58.2% *v* 55.8% at 3 years).[43]

> ''Current treatment options are limited and in some patients may have damaging effects''

Prostacyclin treatment, delivered through continuous intravenous infusion (epoprostenol), has demonstrated efficacy in patients with severe PAH (both idiopathic and related to scleroderma). However, continuous intravenous infusion leads to a variety of administration related complications, in addition to the requirement for dose escalation with chronic treatment. Prostacyclin analogues (such as treprostinil, iloprost, beraprost) are under investigation, with the aim to alleviate some of these problems through differing administration routes. Efficacy reports in idiopathic PAH and PAH related to scleroderma vary with these agents,[44–47] though all have shown some benefit indicated by improvement of the 6 minute walk test—an assessment shown to correlate with prognosis.[48] Additionally, subcutaneous treprostinil and inhaled iloprost had additional benefit for haemodynamic measures and symptom relief. These agents may prove useful, as an alternative over the more cumbersome delivery of epoprostenol, in the treatment of PAH. More data with groups of patients with identified scleroderma related PAH are required, to determine the future roles of these agents in this specific disease.[45–47] Of the other available treatment options, inhaled iloprost has recently obtained European approval but only in idiopathic PAH. In addition, sildenafil may be another option in scleroderma. However, it is not currently approved and there are no studies testing the compound in a scleroderma population.

When viewed in this context, the emergence and recent commercial availability of the oral ERA, bosentan (Tracleer), offers a viable, effective treatment option. Evolving data indicate that the antagonism of endothelin at both its known receptor sites may significantly and positively impact on the successful management of a variety of diseases, including PAH related to scleroderma.[6]

ENDOTHELIN RECEPTOR ANTAGONISM: ROLE IN THE TREATMENT OF PAH RELATED TO SCLERODERMA

The rationale for treatment with an ERA is seen in the presence of raised endothelin levels in the dermis and internal organs of patients with scleroderma[2 28] and, specifically for scleroderma related PAH, the increase in endothelin plasma levels in lung tissue and bronchoalveolar fluid of these patients.[5 29] Additionally, the fundamental role of endothelin in fibrotic, mitogenic, and VSMC proliferative activity, as well as its vasoconstrictor properties, lend support to a treatment that may potentially arrest the underlying disease processes.[6 7]

Bosentan is the first ERA approved in the EU and USA for the treatment of primary pulmonary hypertension and PAH related to collagen vascular diseases such as scleroderma, in patients with grade III WHO functional class. With an affinity for the two endothelin receptors (ET_A and ET_B) and a convenient, oral administration, bosentan has demonstrated significant efficacy in decreasing mPAP and other haemodynamic measures, improving exercise capacity, and delaying the disease progression of PAH.[49–51] Furthermore, in animal models and an echocardiographic subanalysis of patients with PAH receiving bosentan, evidence of reversed ventricular remodelling, improved right ventricular function, and improved cardiac output were observed.[42 52]

A subgroup of patients with PAH related to scleroderma (n = 47) were included in a double blind, placebo controlled, multicentre trial of PAH related to collagen vascular diseases and idiopathic PAH (n = 213).[49 50 53] Patients were randomised 2:1 to receive either bosentan (125 mg or 250 mg twice a day) or placebo. A positive treatment effect was seen, in both idiopathic PAH and PAH related to scleroderma, for the primary end point of improved exercise capacity, as measured by a 6 minute walk test. In patients with idiopathic PAH, bosentan significantly improved walk distance, in comparison with the distance walked by the placebo group. For the scleroderma subgroup, bosentan appeared to stabilise the disease, compared with a decline in functional ability seen with patients receiving placebo. The mean treatment effect in PAH related to scleroderma was 36.8 m on the 6 minute walk test in favour of bosentan. Additionally, bosentan delayed the time to clinical worsening and reduced dyspnoea in patients with either idiopathic PAH or PAH related to scleroderma. These results need to be confirmed in a larger group of patients with scleroderma. Treatment was well tolerated and routine liver monitoring ensured an acceptable safety profile.[49 53] The main adverse event of the bosentan treatment is a moderate and usually transient increase of liver aminotransferases (aspartate aminotransferase and/or alanine aminotransferase): 9% in the BREATHE-1 study.[49] Liver function tests must be performed before starting treatment, then monthly and 2 weeks after any dose increase. Severe hepatitis was never described with bosentan.

These encouraging results offer hope of a more effective, convenient management option for patients with scleroderma related PAH. With the potential to delay and possibly reverse the disease process of PAH,[52 54] ERA treatment may, in time, ease the current grim prognosis that weighs so heavily on patients and physicians. Recent data in patients with idiopathic PAH treated with bosentan show an improvement of long term survival compared with the expected survival using the NIH equation, which depends

on mPAP, mean right atrial pressure, and cardiac index (96%, 89%, and 86% survival rate in the bosentan group at 1, 2, and 3 years *v* 69%, 57%, and 48% expected).[55] Whether similar improvements in the outlook of patients with scleroderma related PAH treated with bosentan occur is unclear as no large scale registry data are yet available. However, all patients treated in the UK and France are now being followed up using the TRAX registry system, thus substantial long term data on over 100 patients with scleroderma should be available within the next year. Investigations into endothelin and ERA treatment for other aspects of the scleroderma disease process suggest that it has stabilising, delaying, and modifying qualities—as seen in a recent study of bosentan treatment in scleroderma related digital ulceration.[56] Studies with bosentan are also being conducted in pulmonary fibrosis in scleroderma. ERA treatment may prove to be the crucial link in fundamentally managing endothelin related diseases, as the full potential of this therapeutic approach is disclosed.

Other ERA agents are currently being evaluated. Sitaxsentan (an ET_A specific antagonist) has already been studied in a double blind trial of 178 patients with PAH.[57] There was no statistically significant difference on a cardiopulmonary exercise test, which was the primary end point. However, the 6 minute walk test showed an improvement of 35 m with 100 mg/day. The results described above with bosentan and those seen with sitaxsentan refute the historical premise that ET_B blockade might be counterproductive. Ambrisentan another selective blocker is also currently being tested. Thus within a couple of years we should have more knowledge of how to exploit this important neurohormonal system which we believe is pathogenetically involved in many aspects of scleroderma.

CONCLUSION

Early detection of disease before significant microvascular damage occurs remains the key to optimising treatment efficacy in both scleroderma and PAH. With the availability of bosentan for the treatment of PAH related to scleroderma, diligence in annual screening for early echocardiographic and pulmonary signs of pathophysiological deterioration is a vital factor contributing to effective management and, potentially, disease minimisation. ERA treatment heralds an improved outlook for scleroderma and related diseases. With a multidisciplinary approach to diagnosis and treatment, the hope is that a significant, positive change in the clinical outcomes of these patients will be seen. With extensive experience in the USA and EU, bosentan appears to be effective and well tolerated in idiopathic PAH and in scleroderma related PAH.

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APPENDIX

Box 1 shows details of the early detection of scleroderma related PAH.

Box 1: Early detection of scleroderma related PAH: clinical applications

Baseline and annual echocardiography are recommended for patients with scleroderma, even in the absence of dyspnoea.

At each visit, assess the patient for signs of dyspnoea, especially on exertion.

- If dyspnoea present:
  - ECG, chest *x* ray examination, pulmonary functional tests (TLCO, FVC), pulmonary computed tomography scan to evaluate for lung fibrosis
  - Evaluate functional status through the 6 minute walk test
  - Refer for a Doppler echocardiogram, even if the patient has had one within the past 12 months—disease evolution may be rapid
- Qualitative assessments include:
  - Enlarged right atrium and ventricle
  - Right ventricular hypertrophy
  - D shaped left ventricular cavity with flattening of the interventricular septum in systole.
  - Diminished/absent atrial wave of pulmonary valve
  - Mid-systolic closure or notching of pulmonary valve
- Haemodynamic assessments of PAH by echocardiography:
  - Tricuspid regurgitant velocity
  - Right ventricular ejection time
  - Right ventricular dimensions
  - Right ventricular volumetric data
  - Right ventricular index of myocardial performance
  - Timing of mid-systolic deceleration of right ventricular ejection
- Diagnosis confirmation: right heart catheterisation:
  - mPAP and pulmonary artery wedge pressure
  - Pulmonary vascular resistance
  - Cardiac index
- Assess for late stage disease functional signs:
  - Increasing dyspnoea, progressing to dyspnoea at rest
  - Increasing fatigue
  - Decreasing exercise tolerance (assess by the 6 minute walk test).
  - Hoarseness (Ortner syndrome)—due to compression of the left recurrent laryngeal nerve by the enlarged pulmonary artery
  - Haemoptysis

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