Pulmonary Hypertension Associated with Connective Tissue Disease

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Abstract

Pulmonary hypertension (PH) is common in most forms of connective tissue disease (CTD); the prevalent type of PH depends on the particular CTD. Thus, pulmonary arterial hypertension (PAH) is dominantly associated with scleroderma, while post-capillary PH is most common in rheumatoid arthritis and lung disease-associated PH is typically found in myositis and sarcoidosis.

Considerable expertise is required to identify, diagnose, and manage CTD-PH, as the primary physicians providing the majority of care for this population, rheumatologists, need a good working knowledge of CTD-PH, its rather subtle presentation, and how to access the necessary investigations to screen for and identify patients with PH. The role of the rheumatologist does not stop at diagnosis; in some conditions such as lupus, optimizing immunosuppression is key to the management of PH, and unlike simple idiopathic PAH, the natural history of CTD-PH is often punctuated by complications of the CTD rather than just events due to progression of PH or therapy-related adverse events.

The aim of this article is to provide an overview of all forms of CTD-PH, and to provide an easy reference source on current best practice.

Keywords

- pulmonary hypertension
- pulmonary arterial hypertension
- screening
- WHO group
- risk assessment tools
- NTproBNP
- SSc PAH

Pulmonary hypertension (PH) or elevated pressures in the pulmonary circulation is a relatively common abnormality with multiple potential causes,[1] including "back pressure" from left heart disease, hypoxic lung disease, vascular obstruction due to thromboembolism, and a small-vessel vasculopathy of the lung or pulmonary arterial hypertension (PAH). Unlike PH, PAH is relatively rare affecting around 1/15,000 of the population in the United Kingdom.[2] Elevation of pulmonary pressures (PH) is most often suspected on the basis of echocardiography. Typically, PH has been reported as likely if the tricuspid velocity (TV) exceeds 2.7 m/s (estimated systolic pulmonary artery pressure: 35–40 mm Hg), but this is an extremely inaccurate method of assessing pulmonary pressures and reliance on this single measure leads to both over- and under-diagnosis of PH.[1] While an echocardiogram can point to the suspicion of PH, invasive catheterization is required to confirm or refute the diagnosis in most cases and to get to an accurate diagnosis in all cases. That said even catheterization cannot in isolation define the type of PH apart from separating group 2 PH (left heart disease-associated PH) from all other subtypes.[1]

To fully resolve the cause of PH, one requires:

- *Imaging of the heart* (echocardiography or cardiac magnetic resonance [CMR] scanning);
- *Full lung function testing* (including gas transfer);
- *Imaging of lung perfusion* (ventilation/perfusion scanning at a minimum);
- *Assessment of the pattern and severity of pressure elevation and its relationship to flow* (cardiac catheterization with flow determined by thermodilution, direct Fick, or CMR);
- *Imaging of the lung parenchyma* (high-resolution computed tomography [HRCT] scanning)
- *Assessment for portal hypertension* (abdominal ultrasonography); and
- *Serological analysis* for human immunodeficiency virus, liver disease, autoantibodies, and at times more detailed analysis (e.g., for schistosomiasis).

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Table 1 Prevalence of PH subtypes in connective tissue diseases

WHO group	Group 1	Group 2	Group 3	Group 4	Group 5
Type	PAH	Post capillary PH	Hypoxia or lung disease-associated PH	Thromboembolic PH	Uncertain mechanism or multifactorial
Pathology	Vasculopathy affecting pulmonary arterioles (<200 μm)	Elevated left atrial pressure with/ without secondary pulmonary venous and arterial changes	Alveolar destruction or hypoxic vasoconstriction with/ without secondary vasculopathy	Vascular occlusion usually intraluminal	Multiple contributory pathologies
Typical	SSc, SLE	RA, SSc	Sarcoidosis, DM, PM, SSc	APS, SLE	Sarcoidosis
Unclear frequency	MCTD, Sarcoidosis, DM/PM, Sjogren's	DM/PM, EGPA		Behçet's disease	SSc
Rare	RA			SSc	

Abbreviations: APS, antiphospholipid syndrome; DM, dermatomyositis; EGPA, eosinophilic granulomatosis with polyangiitis; MCTD, mixed connective-tissue disease; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PM, polymyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

The main reason testing is so extensive is that it is not practicable to directly visualize the main site of pathology in PAH, thus PAH is diagnosed by excluding all other causes of PH.

When assessing PH in the setting of connective tissue disease (CTD), the same tests are required, but the probability of finding a particular type to PH depends on the precise CTD in each individual patient. ►**Table 1** outlines the most likely causes of PH according to the CTD subtype. Thus, PAH as well as left heart and lung PH are all common in systemic sclerosis (SSc), PAH is rare in rheumatoid arthritis (RA), while in group 2 (left heart) PH is common.[3,4]

The treatment of PH in CTD depends not only on the type of PH but also on the responsiveness of the CTD to disease-modifying therapy. Disease monitoring and prognosis is also dependent on the CTD and the type of PH in each case.

Definition and Classification of Pulmonary Hypertension

Important changes in the definition and subtyping of PH have been recommended at the sixth World Symposium on Pulmonary Hypertension (WSPH), some of which may have profound implications for epidemiology and indeed interpretation of previous work in this field,[5] if ultimately accepted in future guidelines.

PH has to date been defined as a mean pulmonary artery pressure of greater than or equal to 25 mm Hg (mean pulmonary arterial pressure [mPAP] $\geq$ 25 mm Hg), and it is now recognized that this figure was arbitrarily chosen as clearly distinct from the normal level (mPAP: 14 mm Hg). Over the past few years evidence has accumulated to suggest that mPAP $>$ 20 mm Hg is pathological, and it has been proposed to change the definition of PH to an mPAP $>$20 mm Hg and that of precapillary PH (pre-PH) to mPAP $>$ 20 with a pulmonary vascular resistance (PVR) of $\geq$ 3 Wood's units (WU).

The evidence supporting this change comes from diverse sources, relying heavily on evidence gathered in CTD-PAH.

First, analysis of the normal pulmonary pressures in over 1,000 individuals has shown that the normal mPAP is 14 $\pm$ 3.3 mm Hg—so 20.6 mm Hg represents 2 standard deviations above normal.[6]

Second, two studies have demonstrated a substantial risk of progression of PH among patients with scleroderma and mPAP $>$ 20 mm Hg, with around one-third progressing to an mPAP $\geq$ 25 mm Hg over 3 years.[7,8]

Third, patients with a substantial burden of residual clot in the pulmonary arteries have significant effort limitation despite normal resting pressures and are improved by surgery or balloon pulmonary angioplasty.[9]

The implications of this new definition are less profound than one might think. In the DETECT study of 466 patients at increased risk of PH, 145 (31%) had mPAP $\geq$ 25 mm Hg (of whom 87 had PAH). Of the 321 with mPAP $<$ 25, 79 had mPAP of 21 to 24, potentially expanding the number with PAH very substantially.[10] However, on analyzing this population, lung disease or left heart disease was present and therefore the most likely explanation in 137, among the remainder only 36 had an mPAP of 21 to 24 of whom only 5 had a PVR $\geq$ 3WU.[11]

Just to add to the confusion, to date this is simply a consensus proposal and has yet to be formally adopted by any guidelines committee; so for the foreseeable future, the definition of PH remains mPAP $\geq$ 25 mm Hg, with this recommendation as simply a potential cause of controversy.

Considerable clarification on the issue of left heart disease associated PH has been proposed. It is now clear that patients with left heart PH (postcapillary PH) are very unlikely to benefit from advanced therapies and in some cases are clearly worsened by such treatment.[12] In recognition of this it is no longer recommended that referral to a PH center should be undertaken where the diagnosis is clear.[12] This includes most patients with reduced systolic function (ejection fraction $<$ 40%), significant valve disease, and heart failure with preserved ejection fraction (HFpEF, as evidenced by substantial left ventricular hypertrophy, left atrial enlargement or Doppler parameters, or clear clinical phenotype—obese, hypertensive, diabetic patients. for example). It is however recognized that in the setting of CTD modest left heart abnormalities can coexist with pulmonary vasculopathy.[12]

Less progress has been made on the issue of lung disease PH, here it is merely recognized that in the presence of substantial lung disease, mild PH should not be treated with advanced therapies.[13] Our recommendation is that in the setting of lung disease in patients with CTD, one should not assume a vasculopathic driver unless the lung pathology is mild (<20% lung fibrosis, <5% emphysema by volume), or where more severe, the lung pathology should be documented as stable while there has been clear worsening of effort tolerance and the hemodynamics severe (mPAP $\geq$ 35 mm Hg, PVR $\geq$ 4WU).

One point of relevance to CTD-PAH is the recognition of the importance of gas transfer (diffusing capacity of the lungs for carbon monoxide [DLCO] or TLCO) in identifying patients with pulmonary venoocclusive disease (PVOD) and lung disease associated PH.[13] A DLCO of $\leq$ 50% is strongly associated with these conditions, thus helping to differentiate idiopathic PAH (IPAH) from PVOD and lung disease-associated PH. Unfortunately, since gas transfer is also reduced in CTD-PAH, especially SSc-PAH, this threshold is not useful in CTD-PAH. Among this population a gas transfer $\leq$30% is however more suggestive of a process other than a vasculopathy driving elevation of pulmonary pressures.[14]

Screening for PAH

The role of screening for "early" PAH is now recognized. The best evidence for a planned screening program exists in the SSc spectrum of diseases.[15] This should start with lung function testing; where the DLCO exceeds 60%, evidence is limited, but it is recommended that a multimodal approach is taken combining forced vital capacity (FVC)/DLCO > 1.8 and/or N terminal prohormone of brain natriuretic peptide (NTproBNP) more than double the normal among those with a DLCO of 60 to 80%, while for those with normal DLCO—echocardiography using the European Society of Cardiology (ESC)/European Respiratory Society (ERS) table—combining TV or estimated pulmonary arterial systolic pressure (PASP) with the evaluation of the right heart for signs of elevated afterload.[15]

Where the DLCO is $\leq$60% the evidence-based approach is to use the DETECT app, which combines independently predictive parameters to optimize identification of those with PAH. To work effectively one needs at least five of the following six parameters: electrocardiography (ECG) axis; antibody status; presence or absence of telangiectasia; serum urate; NTproBNP; and FVC/DLCO.[10] The value of repeating the DETECT score on multiple occasions is not known, so the default at present is to monitor on follow-up and to use the FVC/DLCO and NTproBNP as outlined above. The United Kingdom consensus position is to monitor the variable aspects of the DETECT protocol (ECG axis, urate, NTproBNP, and DLCO) for significant changes and re-catheterize if these suggest progression.[16]

There are no convincing data to support screening in other CTDs—a study is currently underway to see if a screening program can be developed for systemic lupus erythematosus (SLE) where there is less certainty that the frequency of PH is sufficient to render such a program useful.[17] Screening clearly should not be used in RA or Sjogren's syndrome where the prevalence is far too low to justify such effort.

Epidemiology

Scleroderma

The reported prevalence of PH in scleroderma is dependent on the rigor of the diagnostic technique used (catheterization vs. echocardiography), whether one relies on symptoms or an active screening approach, the accuracy of the screening approach used, and the duration of the disease in the population studied. Recent studies have all included right heart catheter for diagnosis; however, the required pretest probability before the definitive test is performed has varied, as has the compliance with the screening protocol, which is often not reported. As shown above, the change in definition of PAH at the recent WSPH will only have a modest impact on the prevalence (►**Table 2**).

Larger more recent studies suggest a prevalence of 10% or more among populations with a disease duration exceeding 10 years. Both Nihtyanova et al[20] and Morrisroe et al[21] have assessed the incidence of PH among their populations and reported an incidence of 1 to 2% per annum. There is a consistent trend toward more PAH in the limited SSc (lSSc) population with slightly more postcapillary or lung disease-associated PH in those with diffuse SSc (dSSc). The DETECT study using catheterization in all patients is clearly the only completely reliable study to date; however, two-thirds of SSc patients had a DLCO > 60% and were excluded from the study. This threshold was chosen on the basis of the findings in the Itineraire study that PAH was much less frequent in that population (prevalence: 1.2 vs. 8%).[22] Thus, to compare findings in this study to other studies, one should divide the prevalence by 3/7, suggesting that around 15% of lSSc and 7% of dSSc of an unselected SSc population of 11-year duration would have PAH.

Systemic Lupus Erythematosus

Considerable uncertainty continues around the prevalence of PH in SLE, with multiple mainly small, echo-based studies suggesting a prevalence between 0.5 and 17.5%. SLE-PAH exceeds SSc-PAH in Asian populations; this appears to be only partly explained by the greater prevalence of SLE in those countries. However, the only available reliable data on prevalence within populations come from Western countries. For example, Condliffe et al[23] found only 35 patients with SLE precapillary PH in the United Kingdom between 2001 and 2006, of whom 28 had PAH. Given a prevalence of SLE of 0.1%,[24] this represents a prevalence of precapillary PH among SLE patients of less than 1/1,000. Similar conclusions can be drawn from the low prevalence of SLE-PAH in France[25] and the United States.[26] Such analyses are limited by the exclusion of postcapillary PH and thromboembolic PH which may contribute to many of the estimates of PH prevalence in the literature.

Table 2 Prevalence of SSc PH and PAH in recent studies

Study	Population	Disease duration	Screening protocol	lSSc PH %	dSSc PH %	lSSc PAH %	dSSc PAH %
Vonk et al (2009)[18]	654	9.1 y	Various	10%		?	?
Avouac et al (2010)[19]	1,165	13 y	TV > 2.8 m/s DLCO < 50% Dyspnea? Cause	5.2%	6.3%	4.5%	1.4%
Nihtyanova et al (2014)[20]	398	13 y	TV > 2.5 m/s; DLCO < 50% or fall 20%; Dyspnea? Cause	24%	18%	17%	10%
Coghlan et al (2014)[10]	408	11.4 y	RHC			36%[a]	16%[a]
Morrisroe et al (2017)[21]	1,636	14.6 y	sPAP > 40; DLCO < 50% with FVC > 85% or fall >20%; Dyspnea? Cause			12.7%[b]	10.1%[b]

Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; dSSc, diffuse SSc; FVC, forced vital capacity; lSSc, limited SSc; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; sPAP, systolic pulmonary arterial pressure; SSc, systemic sclerosis; TV, tricuspid velocity.
[a]Coghlan et al (2014)[10] (DETECT study) preselected a high-risk subgroup (DLCO < 60%), all patients were catheterized—the whole study comprised 466 patients but the detailed report excluded 12% of patients with PH other than PAH—the breakdown in terms of limited versus diffuse was not reported.
[b]Morrisroe et al (2017)[21] (ASIG) reported the prevalence of PH at 14.2% without a breakdown of disease subtype.

Other CTDs

The prevalence if PH in mixed CTD (MCTD) is quite difficult to pin down; confusion between overlap CTDs where SSc overlap syndromes contribute to very high rates of PH and more pure forms of MCTD—ribonucleoprotein (RNP) positive without features diagnostic of another CTD[27]—makes estimates unreliable. In most other conditions data are limited; however, in the case of RA, it is clear that the prevalence of PAH is identical to that seen in the general population.[21,28] Importantly these studies do not address the issue of postcapillary PH which is common in RA, as there is a strong association with HFpEF and RA,[3] explaining the much higher prevalence reported in the literature based on echocardiography alone.[29]

Diagnostic Group of PH Associated with CTD

While in most studies SSc-PAH or abnormalities of the small pulmonary arteries has dominated, there are exceptions with left heart disease[30] or PVOD (pulmonary venous abnormalities) dominating in some.[31] In terms of left heart disease, it is clear that a degree of abnormality of the left heart is extremely common in SSc,[32] so if highly sensitive and unproven techniques such as fluid loading[29] are used to label individuals as having postcapillary PH, then it is possible to ascribe most PH in SSc to left heart disease. When it comes to more standard assessments, generally less than 15% of SSc-PH is thought to be due to left heart disease.[10] PVOD is also important and undoubtedly more common in SSc when compared to IPAH; if one considers a transplant population where one focuses on those failing despite therapy, then the prevalence approaches 50%,[30] but in a standard PH population this represents less than 15% of those initially labelled as PAH.[33] In terms of lung disease PH, this is more difficult as it depends on the enthusiasm for catheterizing those with obvious lung disease, how small airways disease and emphysema are diagnosed, and how one treats extent of pulmonary fibrosis. Our approach is to consider anyone with a DLCO of <30% as likely to have a lung disease contribution to PH; we accept that <20% pulmonary fibrosis extent on HRCT is unlikely to cause PH,[34] unless there is associated emphysema,[35] and that if extent of emphysema exceeds 5%, then it is difficult to label someone as having a pure vasculopathy.

Another issue we have noted is that the proportion of PH due to conditions other than PAH is greater in mild PH when compared to severe PH.[7]

The need for precision and rigor in diagnosis has led us to developing a very complex diagnostic algorithm—outline below (►**Fig. 1**).

Finally, the recent recommendation of diagnosing PAH in the group currently labelled as borderline (mPAP: 21–24, with a PVR ≥ 3WU) creates further issues; we know that 30% of this population will progress to standard PH over 5 years.[7] However, a significant proportion will progress to Group2 or 3 PH rather than PAH, creating further concerns when it comes to treatment of this novel population.[8]

As outlined in ►**Table 1**, the forms of PH prevalent in other CTDs vary considerably. The only point worth noting here is that chronic thromboembolic PH (CTEPH) is relatively uncommon in SSc, prevalent in antiphospholipid syndrome (APS), and relatively common in SLE. In Behçet's pulmonary artery aneurysms may thrombose leading to a form of CTEPH where surgical intervention is not indicated.

General Management of CTD-PH

All forms of CTD-PH are associated with a worse prognosis and significant effort limitation, the details of management

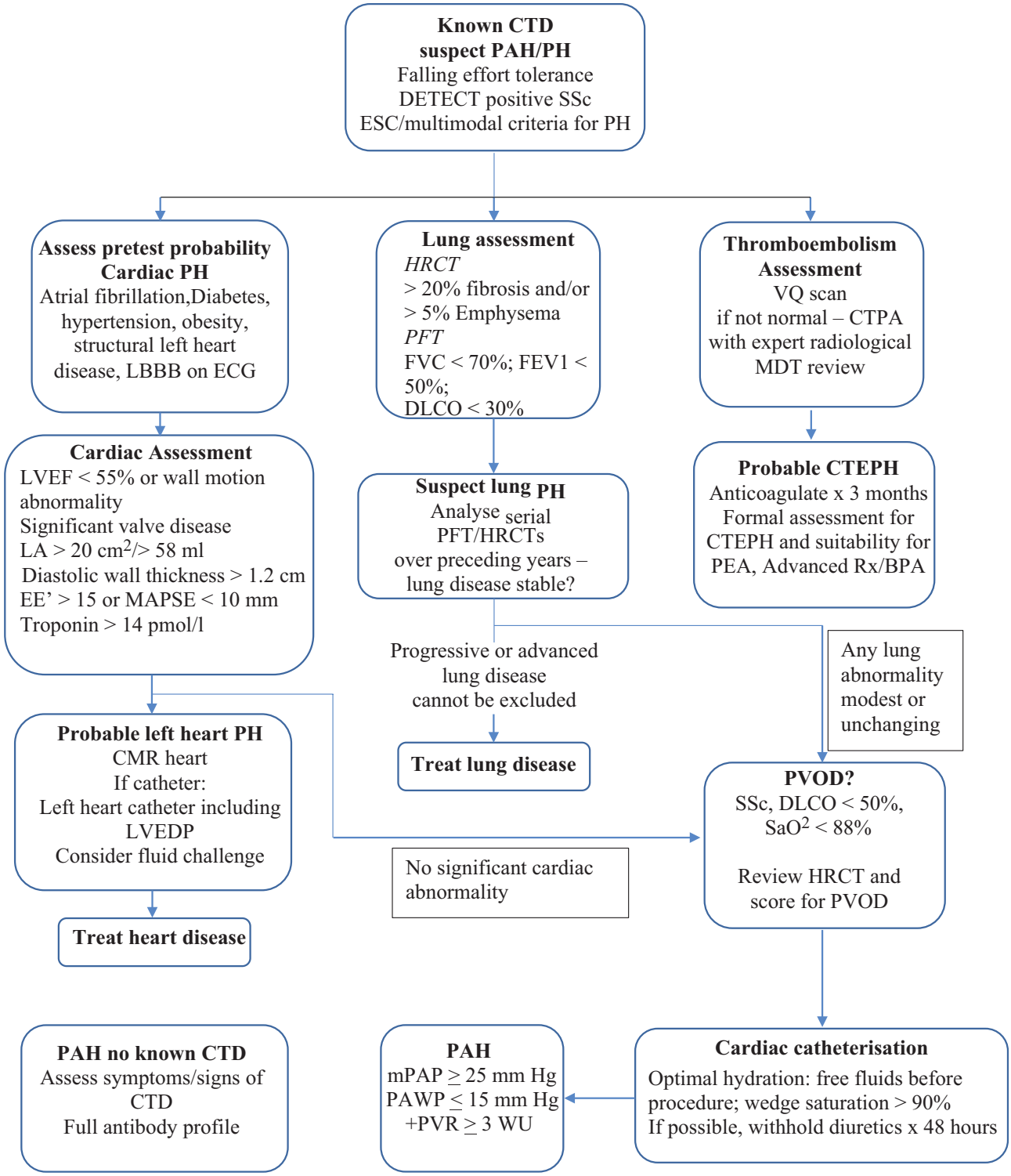

Fig. 1 Diagnostic algorithm for CTD-PH. CTD, connective tissue disease; PH, pulmonary hypertension. LBBB, left bindle branch block; PFT, pulmonary function test; CTEPH, chronic thromboembolic pulmonary hypertension; PAWP, pulmonary artery wedge pressure.

depend on the precise diagnosis. All however are benefited by supportive measures, including diuretics for the management of fluid overload, respiratory rehabilitation to improve management of respiratory distress and to improve effort tolerance, psychological support, and later involvement of palliative care services.[1] The role of anticoagulation in CTD-PH is limited to those with a proven thromboembolic component or in the presence of atrial fibrillation, as there is no clear evidence of benefit and a signal for harm in the setting of SSc-PAH.[36,37] In PAH the only possible signal for benefit is in IPAH.[36] Oxygen supplementation has clear prognostic benefits in the setting of chronic obstructive pulmonary disease with hypoxemia, and while recommended in the setting of chronic hypoxia and PAH, there is no evidence base for symptomatic or prognostic benefit.[1] One exception is obesity hypoventilation-associated PH where the use of

noninvasive ventilation is associated with improved prognosis and symptoms.[38] Intuitively as hypoxia causes pulmonary vasoconstriction, most centers will offer long-term oxygen therapy to those with PH and hypoxia. Finally, it is common to offer oxygen supplementation during flights for those that become symptomatic on exposure to 15% oxygen or where hypoxemia is documented—again without clear evidence of benefit.[1]

All forms of CTD-PH are associated with limited tolerance of major physiological stresses such as pregnancy, major illnesses, and operative procedures. In almost all cases adequate contraceptive measures should be advised, with termination in the event of pregnancy in those with significantly elevated pulmonary pressures despite therapy.[1] Intermediate and high-risk operations should be avoided unless necessary, where necessary these should be planned with the PH team, to ensure optimal pre- and peri-operative management of right ventricular function, using spinal anesthesia where possible, and often with invasive monitoring of central venous pressure.[39,40] Early mobilization postoperation is essential with early aggressive management of any complications, especially infection. In general, if the mPAP is <35 mm Hg with a cardiac index, >2.5 patients will get through major surgery.

Clear exceptions to the general proscription in respect of operations exist, for example thromboendarterectomy for chronic thromboembolic disease and lung transplantation for PAH. Another major exception is valvular heart disease-associated PH, here relief of the hemodynamic stress of stenosis or incompetence more than compensates for the risk associated with PH.

CTD-PAH

The efficacy of advanced therapies for CTD-PAH in particular in scleroderma has been reported to be "attenuated," the magnitude of increase in 6-minute walk distance (6MWD) is lower, the quality of life benefits less, and the frequency of side effects greater[41] in most studies when compared to IPAH. In the meta-analysis published by Rhee et al looking at individual patient level data from the pivotal trials, the magnitude of benefit certainly is lower in CTD-PAH in general; however, the benefit in terms of 6MWD is the same in SSc-PAH as in IPAH.[42] The difference being that among those with IPAH treated patients experienced an increase in 6MWD, while in SSc-PAH those receiving placebo had a very substantial reduction in 6MWD.

The recent outcome trials show a very different story to the previous impressions. In these trials the magnitude of benefit in terms of reduction of morbidity/mortality events or clinical failure end-points was essentially identical between the CTD/SSc-PAH populations and the IPAH populations.[43] Among patients receiving combination therapy in these trials, event rates were almost identical between IPAH and CTD/SSc-PAH populations. Further, while adverse event rates were higher in the CTD/SSc-PAH patients, there was no disproportionate impact of therapy on these rates. Thus, in the GRIPHON trial,[44] while those on selexipag had a significant burden of prostanoid side effects, the relative burden of side effects was identical between active-treatment and placebo patients whether they had IPAH or CTD-PAH. The GRIPHON trial is the only trial to include a sufficient number of patients with SLE-PAH, to allow retrospective evaluation of this subpopulation, as with SSc-PAH the magnitude and direction of benefit are identical to those seen in the whole population, though the numbers included meant that unlike SSc-PAH, the confidence intervals exceed 1.[42] In the AMBITION trial,[45] the relative side-effect burden was equally reduced in the combination therapy arm (ambrisentan plus tadalafil), irrespective of the underlying diagnosis. A comprehensive list of pivotal trials where subanalysis for the SSc-PAH population has been performed was recently published by our group.[46]

We may therefore safely conclude that therapy is beneficial in SSc-PAH further that combination therapy is necessary in most patients with SSc-PAH as the majority have an intermediate or high-risk status. The evidence also supports the use of these agents in other CTDs, though we have much less convincing data for conditions other than SSc-PAH.

While in SSc-PAH we focus on advanced PH therapies, there is convincing, if observational, data to support the use of immunosuppression in those with SLE-PAH and to a lesser extent with MCTD-PAH.[47] The high early mortality observed in SLE-PAH in historic data[22] has disappeared with early aggressive immunosuppression, and clinical experience shows that when lupus is well controlled, right ventricular tolerance of elevated pulmonary pressures is similar to that observed in IPAH.

Optimizing Treatment in CTD-PAH

A number of risk assessment tools have become available over the past decade that help to discriminate those at low risk (annual risk < 5%) from those at high risk (>10% annual risk).[1] The first and most comprehensively evaluated is the REVEAL score.[48] While providing a very accurate assessment of individual risk, it is not particularly user-friendly and includes many components that are either insensitive of change or not modifiable in response to therapy. More recently scores based on the ESC/ERS guidance have become available. Of particular relevance to daily life is the French groups system based on the presence of three non-invasive criteria (functional class 1 or 2, 6MWD > 440 m, and BNP < 50 ng/L or proBNP < 300 ng/L). The presence of at least one low-risk criterion is associated with an excellent 5-year survival.[49] The model appears to suggest that the presence of at least one low-risk criterion in IPAH patients is associated with low-risk status (<5% annual mortality), while the absence of any low-risk criterion was associated with a high-risk status (>10% annual mortality). While this model has not been prospectively validated to date in the SSc-PAH population, we have assessed it in a group of over 200 patients with SSc-PAH at the Royal Free Hospital and the presence of two or three low-risk features is associated with a low-risk status, while the absence of any low-risk features is associated with a very high risk (20% annual mortality), the presence of only a single low-risk parameter confers an intermediate risk profile (5–10% annual mortality). As expected, the bias in the scleroderma population was heavily

weighted toward the high-risk end of the spectrum (140 or 222 patients were high risk at baseline). This suggests that while the hemodynamics in SSc are less advanced than seen in IPAH at diagnosis,[24] the right ventricular tolerance is poorer, so the need for early combination therapy, and a move to intravenous (IV) therapy if less than two low-risk features are achieved within the first few months.

Another useful scoring system proposed by the French group included invasive parameters.[48] In essence counting the number of low-risk features from the following: functional class (1 or 2), 6MWD (>440 m); RA pressure < 8 mm Hg, or cardiac index > 2.5 L/min/m^2. This model has been tested by the John Hopkins[50] group in SSc and those with 3 or 4 low risk features are low risk, 0 or 1 are high risk, while 2 low risk features confer an intermediate range. Testing this score in over 300 of our SSc patients, we come to the same conclusion. However, again we note that 40% of patients are either high risk (13% annual mortality) or very high risk (20% annual mortality).

The implementation of such scoring systems should help focus treatment efforts on those most in need of rapid escalation of therapy. As with most data in CTD-PAH, we are forced to generalize from data largely gathered in SSc-PAH to other forms of CTD-PAH.

Postcapillary CTD-PH

The second major group is left heart disease-associated PH. The advice from the most recent world symposium is that invasive investigation is not required where the probability of postcapillary PH is high, so patients with severe valve lesions and poor systolic function as seen particularly in SLE will not require catheterization just because TV or estimated PASP is elevated—even if very high.[12]

There is more room for confusion when it comes to HFpEF, as is often seen in scleroderma and sarcoidosis. HFpEF should be suspected when the left atrium is enlarged (>20 cm^2, or >60 mL), there is left ventricular hypertrophy (wall thickness ≥ 1.2 cm), or the EE' is significantly abnormal, >14. Other clues include atrial fibrillation, hypertension, diabetes or obesity—especially if these are combined.[12] In the general population one can almost discount the possibility of PAH when there is evidence of left ventricular diastolic dysfunction; however, in CTD (especially RA and SSc) a more nuanced approach is required. In patients with a CTD, mild PH (TV < 3.4 m/s, est. PASP < 50 mm Hg + RA pressure, without septal flattening or severe right ventricular [RV] dilation [RV diam. > LV]) can be safely attributed to postcapillary PH where there is clear evidence of a left heart abnormality, usually left atrial enlargement with or without atrial fibrillation. Where CTD-PH is more severe particularly if there is septal flattening, excluding a coexistent vasculopathy in the presence of—but not driven by elevated diastolic pressures—is more difficult and catheterization may be necessary.

Discriminating postcapillary PH from precapillary PH in the setting of left heart disease requires a fastidious approach to data acquisition and analysis.[42] Patients should be allowed free fluids before catheterization to avoid dehydration, diuretics should be withheld where possible, and if this is not possible, the possibility of artificially reducing the wedge pressure should be kept in mind. The option to move to left heart catheterization should a borderline wedge be obtained (PAWP: 12—15 mm Hg, or inability to confirm that the wedge saturation exceeds 90%). Finally, consideration should be given to fluid challenge (500 mL NaCl over 5 minutes) if dehydration may be contributing to an apparently normal diastolic pressure.

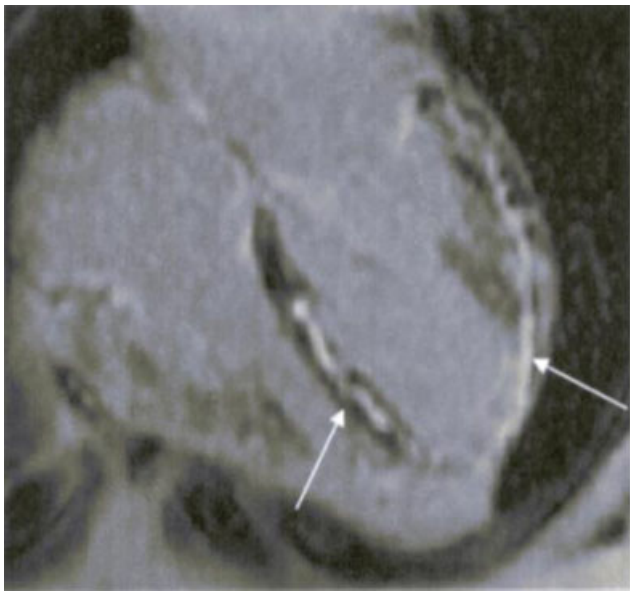

Fig. 2 Midwall fibrosis on a CMR scan of a patient with severe scleroderma cardiac involvement (*arrows*). CMR, cardiac magnetic resonance.

Where doubt exists, for example a wedge pressure of 14 mm Hg in a patient on significant diuretics or where there is atrial fibrillation or a large left atrium, CMR scanning can be particularly helpful (►**Fig. 2**). The presence of significant midwall fibrosis or elevated T1/T2 levels indicates the presence of a significant nonischemic burden of myocardial tissue that is not myocyte-based—either inflammatory or fibrotic.[51]

Management of Postcapillary CTD-PH

Clearly in the setting of reversible or treatable cardiac disease, this should be the priority. Thus, SLE-related valvular heart disease should be managed surgically where appropriate[52]; of note in scleroderma, aortic stenosis often progresses more rapidly[53] than in normal patients and valve replacement significantly reduces left heart filling pressures. Ankylosing spondylitis is another CTD that is frequently associated with aortic regurgitation and may lead to postcapillary PH.

HFrEF (heart failure with reduced ejection fraction) less commonly leads to PH, but can do so. In some situations preventing the development of heart failure is possible. Thus, in SLE myocarditis associated with flares may necessitate more aggressive immunosuppression than the systemic manifestations.[54] Also, eosinophilic granulomatous polyangiitis associated cardiac inflammation is best managed by aggressive immunosuppression in the early stages of the disease.[55] Finally, persistent troponin-positive scleroderma

"myocarditis" precedes systolic left ventricular (LV) dysfunction in a significant proportion of the relatively small number of SSc patients that develop systolic heart failure and appears responsive to immunosuppression with cyclophosphamide or mycophenolate.[56]

Once LV systolic dysfunction has developed, standard management with angiotensin converting enzyme (ACE) inhibitors and β-blockers (carvedilol tends to be well tolerated despite Raynaud's) is important. Adequate diuresis to reduce filling pressures is vital where PH has supervened.[57] In the presence of a significant "scar" burden (regional late gadolinium enhancement on CMR), an implantable cardioverter defibrillator (ICD) should be placed (consider cardiac resynchronization if there is left bundle branch block), as this is the population in which sudden death is prominent.[58]

HFpEF whatever its cause is commonly associated with PH. In sarcoidosis, left heart involvement frequently leads to HFpEF, and is strongly associated with dysrhythmias including ventricular tachyarrhythmias.[59] Steroids form an important part of the management of sarcoid cardiac involvement, but more powerful immunosuppressives may be required.[58] As with HFrEF above, substantial scar burdens can be an important marker of future arrhythmic events, and consideration of ICD implantation should be undertaken. While HFpEF is common in SSc and regional scarring is frequently found in these patients on CMR scanning, there are less convincing data for an association with lethal arrhythmias in this setting; however, we still advise Holter monitoring in this subgroup and recommend ICD implantation if there is >1,000 ventricular ectopy (VE) per day or documented nonsustained ventricular tachycardia.[60]

HFpEF is underdiagnosed and common in RA, and the cause is not determined; however, amyloid may play a role as may hypertension. There is even less clear evidence for the role of ICDs in this group, but standard management is important to improve quality of life.

In terms of managing PH in the setting of HFpEF, only diuretics have a proven role in management, but no other therapy has.[61] We recommend measuring BNP/NTproBNP regularly in these patients and aiming to normalize this as far as possible (generally at least halving), allowing for renal tolerance. Where available implantable pulmonary artery pressure monitoring would provide the best way of optimizing left-sided filling pressure by lowering pulmonary artery diastolic pressure toward normal over time.[62]

Atrial fibrillation is a common association with HFpEF both in the presence or absence of PH and anticoagulation should be recommended where the bleeding risk is not excessive. Finally, while there is little direct evidence, it makes sense to manage hypertension aggressively in patients with HFpEF, diuretics being the first-line therapy and vasodilators being introduced only after optimal diuretic management is in place as these agents tend to lead to fluid retention.

Lung PH in CTD

PH is most commonly seen with Interstitial lung disease (ILD) in the setting of CTD. ILD in SSc, lupus, sarcoidosis, and myositis is frequently associated with PH and is associated with a poor prognosis.[13] There is debate over the role of advanced therapies in the setting of lung PH; however, there is no convincing evidence of efficacy. The randomized controlled trials of PH therapies have not excluded patients with mild lung involvement.[1] All trials have accepted a FVC of 60 to 80% if no extensive lung disease on HRCT scanning, with no requirements for a preserved gas transfer, thus will have included patients with mild fibrosis, emphysema, and combined pulmonary fibrosis and emphysema (CPFE; ►**Fig. 3**).

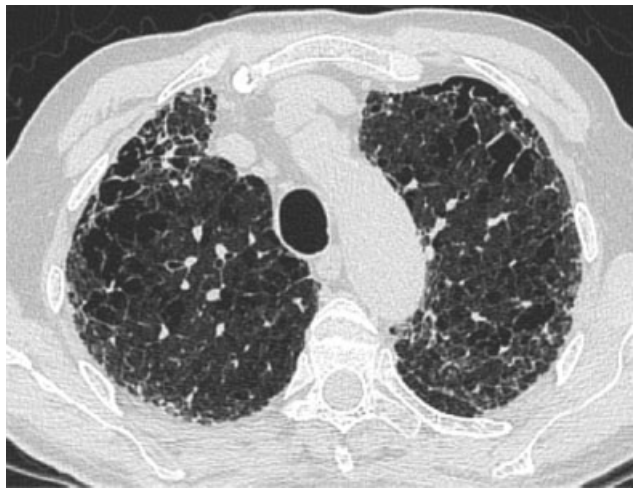

Fig. 3 HRCT scan showing combined fibrosis and emphysema in an ex-smoker with SSc and severe lung disease-associated PH. HRCT, high-resolution computed tomography; PH, pulmonary hypertension; SSc, systemic sclerosis.

On this basis, knowing that pulmonary vasculopathy is common in CTD, it is generally accepted that mild lung involvement should not lead to a diagnosis of lung PH. Nevertheless, data from IPAH show that even mild lung involvement is associated with a worse prognosis.[63] In the setting of lung PH, there is some suggestion of benefit in terms of hemodynamics,[13] but no convincing evidence of symptomatic or effort tolerance benefit.

Thus, there is very little evidence for advanced therapies where lung pathology is advanced, and a clear risk of aggravating hypoxemia. In addition, some advanced therapies appear to worsen outcomes in lung fibrosis[64,65] and bosentan when tested in a well-constructed trial in idiopathic pulmonary fibrosis-associated lung PH was clearly ineffective.[66]

Our policy is to accept the Goh criteria in CTD–PH, where there is less than 20% involvement on HRCT, we diagnose CTD-PAH, if "indeterminate" we diagnose CTD-PAH if FVC > 70%.[33] We will also treat as PAH if new PH is identified in a patient that has developed worsening dyspnea despite stable spirometry and HRCT extent of disease for at least 1 year, on condition that the PH is precapillary and severe (pulmonary arterial wedge pressure [PAWP] ≤ 15 mm Hg, mPAP > 35 mm Hg, PVR > 4 WU).[67] Special attention is paid to identifying CPFE in all patients with a DLCO < 40%, even modest emphysema in the presence of modest fibrosis ("indeterminate" or 10–20%) can produce severe lung-associated PH. Emphysema can occur even in the absence of smoking in SSc.[34]

Detailed management of pulmonary involvement in CTD is beyond the scope of this article, in terms of the PH element, management of hypoxemia and respiratory rehabilitation as well as dealing with fluid overload are advised, as outlined above under general management of CTD-PAH.

Chronic Thromboembolic PH

CTEPH needs to be excluded in all patients with PH for the very simple reason that this is the most curable form of PH.[68] Thus, every PH patient should have a negative nuclear medicine ventilation perfusion scan, where this is not unequivocally negative a CTPA should be performed, and analyzed by an expert in chronic thromboembolic disease. The reason for the latter requirement is that standard radiological reporting only assesses the presence or absence on intraluminal lesions, while in CTEPH it is important to assess for missing vessels and peripheral attenuation.[69] In APS, CTEPH is particularly likely to lead to PH (►**Fig. 4**), but thrombosed aneurysms in Behçet's disease should also be considered.

When present, the priority is a minimum of 3 months of effective anticoagulation to ensure all medically treatable lesions are dealt with[67]—in the case of APS this may require high levels of anticoagulation using warfarin to achieve an international normalized ratio (INR) of greater than 3.5.[70] Next, all treatable with definitive pulmonary endarterectomy should be identified[67] (generally this requires around six segmental vessels with proximal lesions). For those who on expert multidisciplinary team review are not appropriate for surgery, riociguat is of proven benefit[71]; there is supportive evidence also for macitentan in this population.[72] More recently, balloon pulmonary angioplasty offers a further treatment option for those unsuitable for surgery, and with a less than optimal response to medical therapy.[73]

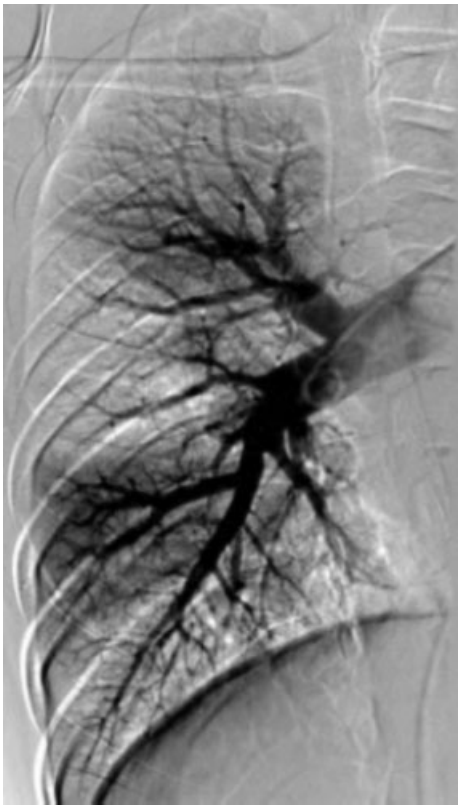

Fig. 4 Pulmonary angiogram showing distal chronic thromboembolic disease in a patient with APS and severe PH. Note absence of perfusion with attenuated vessels in the mid lobe and medial and mid lower lobe. APS, antiphospholipid syndrome; PH, pulmonary hypertension.

Pulmonary Venoocclusive Disease

PVOD is a particularly severe form of PAH associated with an extremely poor prognosis and poor response to therapy. PVOD should be considered when the gas transfer is low (<50%, or in SSc < 30%) or there is severe hypoxemia.[5] Currently the triad of interlobular septal thickening, centrilobular ground glass shadowing, and lymphadenopathy has supplanted lung biopsy as the method of "diagnosing" PVOD.[74] In those without CTD, genetics can help, biallelic EIF2AK4 mutations are strongly associated with PVOD. Among those with CTD, SSc has been identified as a subgroup particularly susceptible to PVOD,[30,32] when present the focus in on transplant assessment, diuretics to avoid pulmonary edema, and limited use of advanced therapies, with particular care in the use of prostanoids.[75]

Conclusion

CTD-PH comprises a complex and varied group of pathologies, and ensuring a correct diagnosis both in terms of the CTD and form of PH is the first pivotal step to optimal management. Management and monitoring require attention not only to the PH but also to the underlying CTD, and deterioration may be due to either the underlying CTD, progression of the PH, or worsening cardiac tolerance of afterload.

Conflict of Interest
Dr Coghlan has worked with Johnson & Johnson, GSK, Bayer & United Therapeutics to develop and bring to market novel therapies for pulmonary hypertension.

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