

Diagnosis, Assessment, and Treatment of Non-Pulmonary Arterial Hypertension Pulmonary Hypertension

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The 4th World Symposium on Pulmonary Hypertension was the first international meeting to focus not only on pulmonary arterial hypertension (PAH) but also on the so-called non-PAH forms of pulmonary hypertension (PH). The term “non-PAH PH” summarizes those forms of PH that are found in groups 2 to 5 of the current classification of PH, that is, those forms associated with left heart disease, chronic lung disease, recurrent venous thromboembolism, and other diseases. Many of these forms of PH are much more common than PAH, but all of them have been less well studied, especially in terms of medical therapy. The working group on non-PAH PH focused mainly on 4 conditions: chronic obstructive lung disease, interstitial lung disease, chronic thromboembolic PH, and left heart disease. The medical literature regarding the role of PH in these diseases was reviewed, and recommendations regarding diagnosis and treatment of PH in these conditions are provided. Given the lack of robust clinical trials addressing PH in any of these conditions, it is important to conduct further studies to establish the role of medical therapy in non-PAH PH. (J Am Coll Cardiol 2009;54:S85–96) © 2009 by the American College of Cardiology Foundation

Previous international meetings on pulmonary hypertension (PH) have focused predominantly on pulmonary arterial hypertension (PAH), a form of PH that is usually severe but overall quite rare. The 4th World Symposium was the first to assign a working group to address in detail the so-called non-PAH forms of PH, that is, those forms of PH that are encountered in patients with chronic

obstructive pulmonary disease (COPD), interstitial lung disease (ILD), left heart disease (LHD), venous thromboembolism, and other conditions. It is a paradox in the field of PH that one of the less common forms, that is, PAH, has been extensively studied, whereas fewer data are available on other types of PH, many of which are far more common. At the same time, drugs with proven efficacy in PAH (1–3) are being increasingly used in other forms of PH, despite the virtual absence of clinical trials supporting this approach.

Pulmonary hypertension in chronic lung disease subsumes COPD, ILD, and other diffuse parenchymal lung diseases such as sarcoidosis, connective tissue disease, or pulmonary Langerhans cell histiocytosis. Space limitation prevents a discussion of the rarer diseases, such as sarcoidosis and pulmonary Langerhans cell histiocytosis, which are often associated with clinically relevant PH (4).

Epidemiology, Features, and Importance of PH in COPD

The prevalence of PH in COPD depends on the population under study, the definitions applied, and the tools used to evaluate patients (5). Most hemodynamic studies have been

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Abbreviations and Acronyms

| | |
|------------------------|--|
| BNP | = brain natriuretic peptide |
| COPD | = chronic obstructive pulmonary disease |
| CT | = computed tomography |
| CTEPH | = chronic thromboembolic pulmonary hypertension |
| DLCO | = diffusion capacity of the lung for carbon monoxide |
| ERA | = endothelin receptor antagonist |
| FEV₁ | = mean forced expiratory volume in 1 s |
| ILD | = interstitial lung disease |
| IPF | = idiopathic pulmonary fibrosis |
| LHD | = left heart disease |
| LV | = left ventricular |
| mPAP | = mean pulmonary artery pressure |
| PAH | = pulmonary arterial hypertension |
| PCWP | = pulmonary capillary wedge pressure |
| PDE-5 | = phosphodiesterase-5 |
| PEA | = pulmonary endarterectomy |
| PH | = pulmonary hypertension |
| PVR | = pulmonary vascular resistance |
| RCT | = randomized controlled trial |
| RHC | = right heart catheterization |
| RV | = right ventricular |
| SPAP | = systolic pulmonary arterial pressure |
| TR | = tricuspid regurgitation |

performed in patients with advanced disease. Three recent studies have provided data in large series of patients, the majority of them in the Global initiative for chronic Obstructive Lung Disease (GOLD) IV stage. In 1 study among 120 patients with severe emphysema (mean forced expiratory volume in 1 s [FEV₁], 27% predicted) undergoing evaluation for lung volume reduction surgery (6), the incidence of PH, defined as a mean pulmonary artery pressure (mPAP) >20 mm Hg, was 91%, although in the majority of patients (86%), it was in the mild-to-moderate range (mPAP 20 to 35 mm Hg). Only 5% of the patients showed an mPAP >35 mm Hg. The correlation between mPAP and lung function was weak (FEV₁, $r^2 = 0.11$ and PaO₂, $r^2 = 0.03$). The mPAP was more closely related to pulmonary capillary wedge pressure (PCWP) ($r^2 = 0.32$), which was mildly elevated in the majority of patients, suggesting the presence of diastolic left ventricular (LV) dysfunction in advanced COPD. However, gas trapping with elevated intrathoracic pressures may be an alternative explanation for the increased PCWP.

In a retrospective analysis of pulmonary hemodynamic studies in 998 COPD patients (7), 27 patients had severe PH, defined as an mPAP ≥ 40 mm Hg. Of the 27, 16 had alternative explanations for PH. Among the remaining 11 (1.1% of the whole group), COPD was the only identifiable cause of PH. This subset of patients had only moderate airway obstruction

(FEV₁ 50% predicted), but at the same time, they showed severe hypoxemia, hyperventilation, and a very low diffusion capacity of the lung for carbon monoxide (DLCO). The survival time of these patients was much shorter than in the other patients. These findings indicate that there is a subset of COPD patients with “out of proportion” PH sharing some clinical features with idiopathic PAH.

In a study of 215 patients with severe COPD (FEV₁ 24% predicted) who were candidates for lung volume reduction surgery or lung transplantation, PH, defined as an mPAP >25 mm Hg, was present in 50%, although it was mostly mild (mPAP 26 to 35 mm Hg) (8). In 9.8% of these patients, PH was considered moderate (mPAP 36 to 45 mm Hg), and in 3.7%, severe (mPAP >45 mm Hg). Cluster analysis identified a subset of patients with moderate impairment of airway function, high PAP, and severe arterial hypoxemia, further supporting the concept of the existence of a subgroup of COPD patients with moderate airflow obstruction and “out of proportion” PH.

The overall burden of PH in patients with COPD is substantial. If 1% of patients with advanced COPD have severe PH with mPAP >40 mm Hg (7), extrapolation from the U.S. or French prevalence figures on COPD suggests a prevalence of severe PH in COPD patients of 3 to 17 per million, similar to the prevalence of PAH (9). However, with an mPAP cutoff of 35 mm Hg rather than 40 mm Hg, the prevalence of out-of-proportion PH in advanced COPD increases by a factor of approximately 5 to 10. When all patients with mPAP >20 mm Hg are taken into account, the population-based prevalence of PH in COPD could be in the range of 100 to 150 per million.

The hemodynamic features of PH in COPD differ from those seen in PAH. In general, the degree of PH is low to moderate in magnitude, with mPAP rarely exceeding 35 to 40 mm Hg. Both right atrial pressure and PCWP tend to be normal or mildly elevated (10–13). The rate of progression of PH in COPD is slow, with an annual increase in mPAP of 0.4 to 0.7 mm Hg per year (14,15). Patients with COPD often develop right ventricular (RV) diastolic dysfunction with elevated RV filling pressures resulting in fluid retention and edema, especially during COPD exacerbations. Cardiac output in COPD is usually preserved and may increase during exacerbation episodes. Right ventricular forward failure, that is, low cardiac output as commonly seen in end-stage PAH, is exceedingly rare in COPD-associated PH, and death from right heart failure is a rarity in this group of patients.

Numerous studies have shown that the presence of even mild PH is of prognostic relevance in patients with COPD. A longitudinal 7-year study of 50 patients with COPD showed that survival was inversely related to pulmonary vascular resistance (PVR) (13). In a 15-year follow-up study with 200 patients (16), the presence or absence of PH was one of the strongest predictors of mortality. In a 1981 study of 175 patients with COPD (10), those with mPAP >20 mm Hg had shorter survival time than those in whom PAP was normal. A more recent study involving 84 patients receiving long-term oxygen therapy observed that mPAP was the best predictor of mortality (17). The 5-year survival rate was 36% in patients with mPAP >25 mm Hg, whereas in patients with mPAP <25 mm Hg the survival rate was 62%. In this study neither the FEV₁ nor the degree of hypoxemia or hypercapnia had prognostic value.

Epidemiology, Features, and Importance of PH in ILD

The term “ILD” summarizes a heterogeneous group of lung diseases with similar clinical, radiographic, and physiologic manifestations. The prevalence of PH in patients with ILD varies greatly as a function of the underlying disease and the diagnostic mode used to identify PH. The most extensive data have been published in idiopathic pulmonary fibrosis (IPF).

The incidence and prevalence of PAH in IPF remain unclear, with widely varying estimates. The differences reflect varying patient populations, varying underlying disease severity, and differing diagnostic modalities. In general, studies of patients undergoing assessment for lung transplantation have suggested a higher prevalence of PH. In one early study of ventricular dysfunction and tricuspid regurgitation (TR) in patients evaluated for lung transplantation, 50 of 77 IPF patients had echocardiographic evidence of RV dysfunction (18). Another study retrospectively identified an estimated systolic pulmonary arterial pressure (SPAP) >35 mm Hg in 84% of 88 patients and >50 mm Hg in 16% (19). The combination of emphysema in the upper lung zones and pulmonary fibrosis in the lower lobes on high-resolution computed tomography (CT) of the chest seems to be associated with a higher prevalence of PH (20,21). Echocardiographic data are difficult to interpret because the operating characteristics of echocardiography to estimate SPAP in patients with advanced lung disease seem to be quite poor (22).

Recent studies have used right heart catheterization (RHC) to accurately measure pulmonary pressures in IPF patients. Two retrospective analyses of IPF patients undergoing RHC reported PH (defined as mPAP >25 mm Hg) in 31.6% (23) and 33.9% (24) of the patients, respectively. In the United Network for Organ Sharing and the Organ Procurement and Transplant Network registries for IPF patients listed for lung transplantation between January 1995 and June 2004 (25), 2,525 of the 3,457 patients listed had RHC results available. Of these, 932 (37.0%) had an mPAP \geq 25 mm Hg, whereas 231 (9.1%) had an mPAP >40 mm Hg. Among 70 IPF patients evaluated prospectively (26), PH (resting mPAP >25 mm Hg) was detected in only 6 patients (8.1%) at baseline.

Several groups have emphasized the prognostic importance of PAH complicating IPF. Echocardiographically defined PH (SPAP >50 mm Hg) has been associated with impaired survival (19). Echocardiographically defined PH in IPF patients with superimposed emphysema negatively influences survival (20). In IPF patients undergoing RHC before listing for lung transplantation, the presence of PAH correlated linearly with mortality (23). In a prospective study, an mPAP >17 mm Hg was predictive of mortality (26).

Assessment of PH in Chronic Lung Disease

Dyspnea and fatigue are symptoms of chronic lung disease as well as PH. Thus, patients with chronic lung diseases should be evaluated for PH when the symptoms are more severe than one would expect from lung function data, or when signs of right heart failure develop. Suspicion of PH should be high if clinical deterioration is not matched by a decline in pulmonary function. Profound hypoxemia, hyperventilation, and a low DLCO are indicators of PH.

Once PH is suspected, patients should be evaluated by Doppler echocardiography. A measurable TR velocity, however, is less likely to be observed in patients with COPD than in patients with PAH, ranging between 24% and 77% (27–29). Even if a TR jet is available, echocardiographic estimates of the PA pressure are often inaccurate, and both false-positive and -negative results have been reported. In 2 large series comparing echocardiographic data and findings from RHC in patients with chronic lung disease, the positive predictive values of echocardiography were 32% and 68%, respectively, and the negative predictive values were 93% and 67%, respectively (22,30). The results are somewhat better but still suboptimal in patients with ILD (22).

Plasma levels of brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) have also been evaluated as predictors of PH in patients with lung disease (31,32), but these biomarkers lack sensitivity, especially for milder forms of PH, and specificity, because elevated levels may also reflect LHD.

Given the limitations of echocardiography and biomarkers, RHC remains the standard for the diagnosis of PH. This is of particular relevance for patients who also suffer from some degree of LV dysfunction, which seems to be a common comorbidity and may contribute to the clinical features of cor pulmonale.

Treatment of PH in Patients With Chronic Lung Disease

It is self-evident that the underlying lung disease should be optimally treated according to relevant guidelines (33,34). Summarizing these recommendations is beyond the scope of this article. We will focus exclusively on the use of PH-targeted medication in patients with lung disease. So far, no large randomized controlled trials (RCTs) addressing the long-term effects of drugs targeting PH have been performed in patients with chronic lung disease. Patients with advanced lung disease, that is, those with total lung capacities <70% predicted and FEV₁/forced vital capacity ratios <50% to 60% have been excluded from RCTs in the field of PAH. There is not sufficient evidence showing that drugs approved for the treatment of PAH, that is, endothelin receptor antagonists (ERAs), phosphodiesterase-5 (PDE-5) inhibitors, and prostanoids, are safe and effective in patients with chronic lung disease-associated PH. This is

true for patients with advanced chronic lung disease and mild PH as well as for patients with severe PH in the setting of chronic lung disease, independent of its severity.

Any pulmonary vasodilator has the potential to worsen gas exchange in patients with chronic lung disease, and the effects of these drugs may vary substantially depending on whether the underlying disease has obstructive or restrictive features (35). Short-term studies have been performed in ILD patients with sildenafil (36), bosentan (37), and inhaled iloprost (38), and these drugs had no adverse effects on oxygenation. In contrast, unpublished data suggest that sildenafil may worsen oxygenation in patients with COPD and PH (39), and it has been shown that sildenafil can inhibit hypoxic pulmonary vasoconstriction (40). In another study in COPD patients, sildenafil did not improve stroke volume at rest or during exercise (41). A small RCT with bosentan in patients with COPD and mild PH found a significant deterioration of the PaO₂. At the same time, there was no improvement in exercise capacity, peak oxygen uptake, and health-related quality of life (42). All in all, much more evidence is needed before the use of PH-targeted drugs can be recommended for certain subpopulations of patients with chronic lung disease.

Working Group Recommendations for PH in Chronic Lung Disease (COPD, ILD, and Other Forms)

Diagnosis and assessment of PH in chronic lung disease

- In patients with chronic lung disease, the presence of PH should be suspected when the symptoms are more severe than expected based on lung function data, or when signs of right heart dysfunction are present. Profound hypoxemia, hyperventilation, or low DLCO values can be indicators of PH (E/A). (Please refer to Barst et al. [43] for an explanation of the evidence-based grading system.)
- Doppler echocardiography remains the most useful non-invasive tool for assessing the presence of PH in patients with chronic lung disease, but both false-positive and false-negative results are not uncommon (E/B).
- Biomarkers such as BNP or NT-proBNP need to be further evaluated. They seem to be useful screening tools for the presence of PH in patients with chronic lung disease, although they lack sensitivity and specificity (E/B).
- If the presence of PH is going to affect the management of a patient with chronic lung disease, confirmation by RHC is recommended (E/A).
- Patients with chronic lung disease and severe PH (i.e., mPAP >35 mm Hg and/or signs of right heart failure) should be referred to a center with expertise in PH (E/A).
- The use of RHC is strongly recommended in clinical trials studying patients with chronic lung disease and PH to categorize the patients under study and to identify subpopulations likely to benefit from PH-targeted drug therapy (E/A).

Treatment of PH in chronic lung disease

- The underlying lung disease should be optimally treated according to the respective guidelines, including the use of long-term oxygen therapy in patients with chronic hypoxemia (E/A).
- There is no sufficient evidence that the drugs currently used for PAH are safe and effective in patients with PH associated with chronic lung disease (E/A).
- Patients with PH and chronic lung disease should be treated in the setting of clinical trials whenever possible (E/A).
- PH in various lung diseases should be studied separately, because patients with COPD and PH may respond differently to medical therapy than patients with ILD and PH (E/A).
- Registries are needed to obtain data from patients with very rare conditions (E/A).
- The use of drugs currently approved for PAH in patients with chronic lung disease is not recommended until further data are available (E/B).

Clinical trial strategy for PH in chronic lung disease. It is unlikely that patients with end-stage lung disease are going to derive a substantial benefit from PH treatment. In contrast, patients with mild-to-moderate chronic lung disease but severe PH may be good candidates for clinical trials with drugs targeting the pulmonary vascular component. Because one would not expect all subpopulations of patients with chronic lung disease to respond similarly to PH medications, it is crucial that the patients under study be carefully evaluated and characterized: this will include the use of RHC to define the severity of PH and the hemodynamic profile.

A 2-step approach is recommended to evaluate drugs targeting PH in the setting of chronic lung disease.

- Step 1. Safety, proof-of-concept, and preliminary efficacy: important safety parameters include vital signs and blood gases (both PaO₂ and PaCO₂). Preliminary efficacy can be assessed by hemodynamics, exercise capacity (i.e., 6-min walk test), peak oxygen uptake, and ventilator efficacy measured during cardiopulmonary exercise testing, and improvement of oxygenation at rest and during exercise (E/A).
- Step 2. Long-term safety and efficacy: prevention of clinical worsening (i.e., morbidity and mortality), improvements in exercise capacity and quality of life (E/A).

Chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH results from obstruction of the pulmonary vascular bed by nonresolving thromboemboli. It has been estimated that there are 2,500 new cases of CTEPH each year in the U.S. (44). In a prospective study following survivors of acute pulmonary embolism, 3.8% of patients developed CTEPH within 2 years (45). However, up to 40% of patients with CTEPH have not had a clinically apparent acute pulmonary embolic episode (46–48). Sple-

nectomy, ventriculoatrial shunt for the treatment of hydrocephalus, chronic central intravenous lines, inflammatory bowel disease, and osteomyelitis seem to be risk factors for developing CTEPH (49). However, the absence of such a history does not rule out CTEPH. Novel interesting concepts are derived from the observation of abnormal (lysis-resistant) fibrinogen variants underlying clot nonresolution in CTEPH (50).

CTEPH differs from PAH by its major vessel involvement of the vascular remodeling process (51), which can be approached surgically by pulmonary endarterectomy (PEA); this has evolved over 4 decades to become the treatment of choice (52,53). The outcomes of PEA with regard to functional status, quality of life, hemodynamics, and RV function have been very favorable, including normalization of hemodynamics and exercise capacity in frequent cases. However, small vessel arteriopathy is variably present in CTEPH (54,55), and small vessel lesions are an important determinant of the outcome after PEA.

Diagnosis of CTEPH. The recommended strategy for diagnosis and evaluation of CTEPH is shown in Figure 1 (55).

The perfusion lung scan is the examination of choice for ruling out CTEPH. A normal or low-probability perfusion scan in a patient with PH effectively rules out CTEPH. Patients with operable CTEPH typically have at least 1 segmental or larger perfusion defect with normal or near-normal ventilation (56,57). However, the complete absence of perfusion to 1 lung should raise suspicion for other processes, such as malignancy, mediastinal fibrosis, congenital absence of the pulmonary artery, or vasculitis.

Contrast-enhanced chest CT findings in CTEPH include the following: chronic thromboembolic material within the central pulmonary arteries, increased bronchial artery collateral flow, variability in the size and distribution of pulmonary arteries, parenchymal abnormalities consistent with prior infarcts, and mosaic attenuation of the pulmonary parenchyma (55). Chest CT scanning is also useful in ruling out significant underlying fibrotic or emphysematous disease, obstructing tumors, mediastinal fibrosis, or lymphadenopathy that could mimic chronic thromboembolic disease. Although a negative CT scan does not rule out the diagnosis of CTEPH, new-generation multirow CT scanners are expected to provide improved diagnostic accuracy.

Pulmonary angiography is still considered the standard diagnostic tool in the evaluation of CTEPH. Characteristic angiographic findings include pouching, webs or bands with or without post-stenotic dilation, intimal irregularities, abrupt narrowing, or total occlusion of segmental or larger branches (58). When performed by experienced individuals, angiography is safe, even in patients with severe hemodynamic impairment (59).

Right heart catheterization for full hemodynamic assessment is mandatory in the workup of CTEPH. The presence of PH indicates a hemodynamic consequence of chronic thromboemboli. In addition, assessment of the degree of right-sided heart failure by measuring right atrial pressure,

cardiac output, and mixed venous O₂ saturation is important in determining severity of disease and risk from surgical intervention.

Other techniques with reported utility in evaluating CTEPH include pulmonary angiography (60), assessment of pulmonary artery pulse pressure and reflectance (61,62), and magnetic resonance imaging (63,64).

Treatment of CTEPH. Patients with CTEPH should receive lifelong anticoagulation adjusted to a target international normalized ratio between 2.0 and 3.0 to prevent recurrence of thromboembolic events. Figure 2 is a treatment algorithm for CTEPH.

SURGICAL THERAPY. The goal of PEA is to improve pulmonary hemodynamics, exercise capacity, symptoms, and survival. The procedure may be curative in appropriately selected patients. For details regarding patient selection and the procedure itself, please refer to the paper by Keogh et al. (65) in this issue of the *Journal*.

MEDICAL THERAPY. Although surgical intervention with PEA is the preferred treatment in appropriate candidates, pharmacotherapy may be beneficial in certain contexts: 1) in patients with predominantly distal disease that is not surgically accessible; 2) when surgery is contraindicated because of prognostically significant comorbidity; 3) in patients who are at high risk because of extremely poor hemodynamics before PEA (bridging to PEA); and 4) in patients with persistent or residual PH after PEA (54).

Patients with inoperable disease or with persistent or recurrent PH after PEA. Elevation of PVR out of proportion to what is attributable to mechanical thrombus obstruction is occasionally seen and signals a significant and in some cases inoperable extent of peripheral vasculopathy. High PVR is associated with poor outcome in terms of both survival and persistent PH. In addition, approximately 10% to 15% of patients show persistent or residual PH after PEA surgery, with or without concomitant diminished functional capacity; these individuals may benefit from adjunctive medical treatment (66).

Several open-label studies with prostanoids, ERAs, and PDE-5 inhibitors have been performed in patients with CTEPH, and most suggest hemodynamic and clinical improvement (67-70). Some open-label studies suggest improved survival with medical therapies compared with historical controls (71,72). However, only 1 large RCT has so far been performed in patients with inoperable CTEPH: the BENEFIT (Bosentan Effects in inOperable Forms of chronic Thromboembolic pulmonary hypertension) study (73). This first randomized controlled study in inoperable CTEPH patients showed that treatment with bosentan significantly reduced PVR and NT-proBNP at week 16, but the 6-min walk distance remained unchanged, and there was no treatment effect on time to clinical worsening. Further studies are required to determine whether medical therapy offers a substantial benefit in various CTEPH populations.

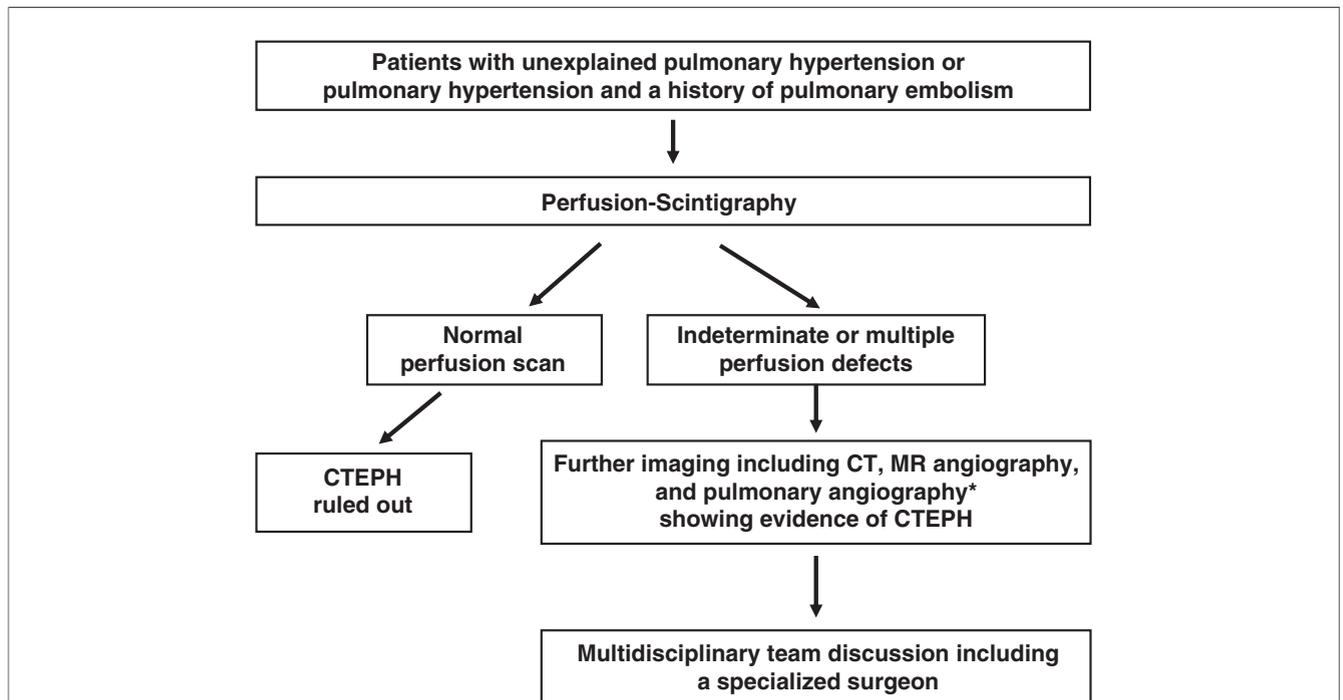


Figure 1 Diagnostic Imaging Algorithm for CTEPH

*Pulmonary angiography is usually performed in conjunction with right heart catheterization and should be performed at centers experienced with chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary endarterectomy. Modified, with permission, from Hoeper et al. (54). CT = computed tomography of the chest; MR = magnetic resonance.

Pre-PEA bridging therapy. The concept of introducing medical treatment as a therapeutic bridge between CTEPH diagnosis and PEA was initially proposed for continuous intravenous epoprostenol (74,75). A significant proportion of CTEPH patients undergoing PEA are hemodynamically unstable in the pre-operative period, to the point where risks from surgery in general are significantly heightened. Under these circumstances, effective medical therapy may improve pre-operative hemodynamics and stability, furthering post-operative stability. On the other hand, delay in surgery may be detrimental. Thus, the use of medical therapy and the timing of surgery should be discussed with the surgeon to make sure that risks are balanced.

Working Group Recommendations for CTEPH

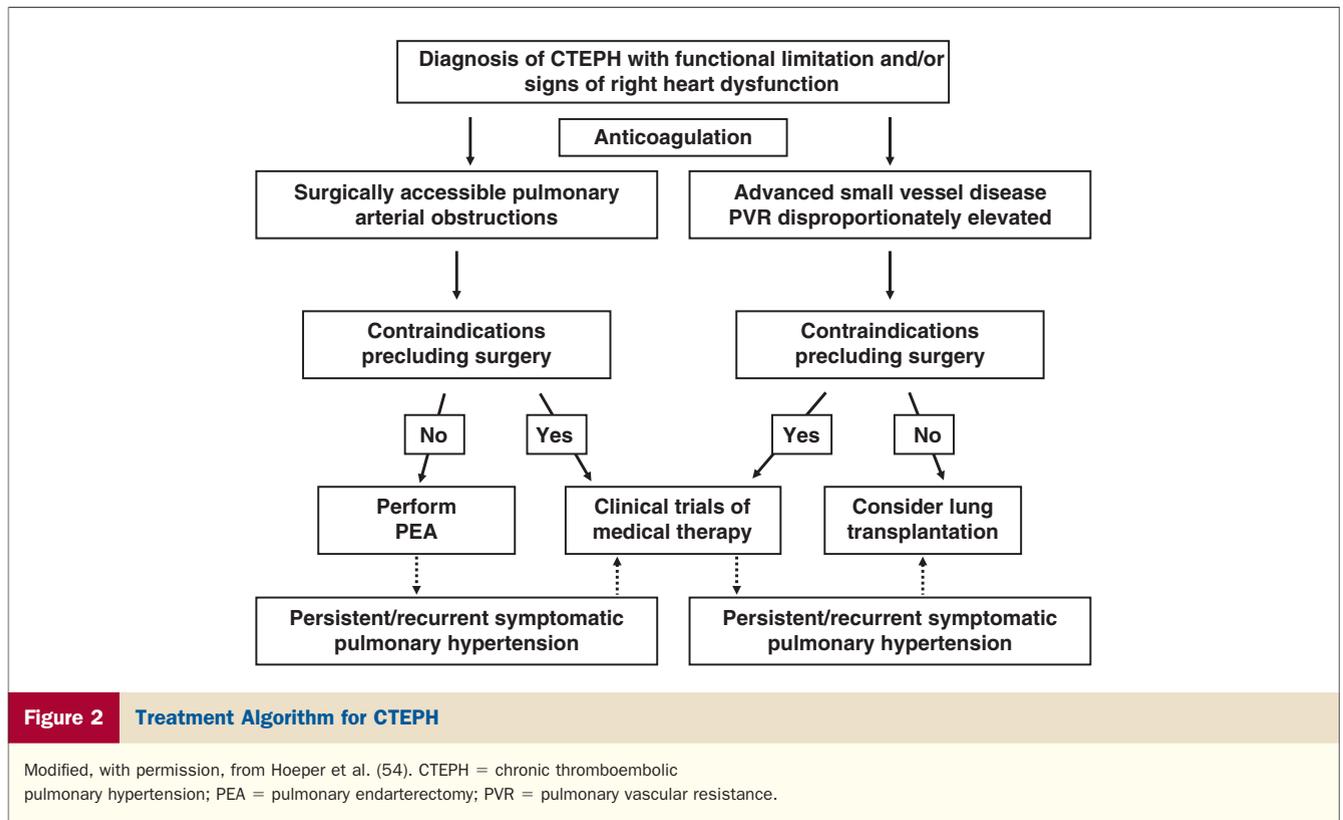
Diagnosis and assessment of CTEPH

- Perfusion scintigraphy should be performed in all patients with unexplained PH because a normal or near-normal perfusion pattern virtually excludes CTEPH (E/A).
- Patients with a history or findings suggesting CTEPH should be evaluated at a center with expertise in this condition. A surgeon experienced in PEA surgery should be available at this center, or a close collaboration with such a surgeon should exist (E/A).
- Pulmonary angiography to assess operability should be performed at the center where surgery would be per-

formed or at centers with an established cooperation with a surgical center (E/A).

Treatment of CTEPH

- Surgical PEA is the preferred treatment of CTEPH because it is potentially curative (E/A).
- The decision of whether or not a patient is a candidate for PEA surgery should involve a multidisciplinary team that includes at least 1 surgeon with substantial experience in this procedure (E/A).
- In severely compromised patients with surgically accessible disease but for whom surgery must be delayed, pre-operative medical therapy with prostanoids, ERAs, or PDE-5 inhibitors may be used to improve hemodynamics and clinical performance before surgery, but this approach needs to be adjusted with the responsible surgeon (E/B).
- Patients with predominantly peripheral (i.e., inoperable) disease may be candidates for medical therapy and should be considered for enrollment in clinical trials whenever possible (E/A).
- Preliminary data suggest that drugs currently approved for PAH may have beneficial effects in patients with CTEPH, but as long as there are no robust data from RCTs, the decision of whether or not to treat CTEPH



patients with these drugs should be restricted to centers experienced in the management of this disease (E/B).

Clinical trial strategy for CTEPH. There is no doubt that drugs used in PAH, such as prostanoids or PDE-5 inhibitors, improve hemodynamics in CTEPH. The question is whether administration of these drugs also improves meaningful clinical end points such as exercise capacity, quality of life, time to clinical worsening, and survival. At least 2 different scenarios require further investigation:

- Patients with operable disease but severe hemodynamic impairment (i.e., $PVR > \sim 1,000 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$): these patients have an elevated perioperative risk, and it is unclear whether a limited period of medical treatment to improve hemodynamics also improves outcome when compared with immediate surgery. This problem is extremely difficult to study because a blinded placebo-controlled study might be considered unethical. Thus, this question should be addressed in a carefully designed open study involving only centers with broad experience in the surgical and medical management of CTEPH patients (E/B).
- Patients with peripheral (inoperable) disease and those with persistent or recurrent PH after PEA surgery are good candidates for clinical trials. The questions that need to be answered are whether medical therapy improves exercise capacity and quality of life and whether it delays time to clinical worsening (E/A).

PH Associated With LHD

LHD is one of the most common causes of PH. It may be caused by chronic heart failure attributable to LV dysfunction of systolic or diastolic origin or by valvular diseases, predominantly mitral valve disorders (76). Up to 60% of patients with severe LV systolic dysfunction and up to 70% of patients with isolated LV diastolic dysfunction may develop PH, and the presence of PH is associated with a poor prognosis in these patient populations (77-79).

Pulmonary hypertension with $PVR > 2 \text{ mm Hg/l/min}$ (Wood units) has been reported in up to 50% of patients referred to transplant clinics (79). Pulmonary hypertension and RV dysfunction carry a poor prognosis for patients with chronic heart failure (80). In one study, the mortality rate after 28 months was 57% in patients with left heart failure and moderate PH, compared with 17% in patients without PH (81). Patients with a transpulmonary gradient $\geq 16 \text{ mm Hg}$ have an increased risk of post-operative RV failure after heart transplantation (82).

The pathogenesis of PH in LHD is complex. There is a passive (pulmonary venous) component in response to increased left atrial pressure (83). In some patients, a superimposed active component caused by pulmonary arterial vasoconstriction and vascular remodeling may lead to a further increase in PAP.

Table 1 Risk Factors Favoring Diagnosis of Diastolic Heart Failure

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|--|
| Clinical features |
| Age >65 yrs |
| Elevated systolic blood pressure |
| Elevated pulse pressure |
| Obesity |
| Hypertension |
| Coronary artery disease |
| Diabetes mellitus |
| Atrial fibrillation |
| Echocardiography |
| Left atrial enlargement |
| Concentric remodeling (relative wall thickness >0.45) |
| Left ventricular hypertrophy |
| Elevated left ventricular filling pressures (grade II to IV diastolic dysfunction) |
| Interim evaluation (after echocardiography) |
| Symptomatic response to diuretic drugs |
| Exaggerated increase in systolic blood pressure with exercise |
| Re-review of chest radiograph consistent with heart failure |

Diagnosis and assessment of PH associated with LHD

In many cases, the presence of LHD is obvious, given the patient's history and the echocardiographic findings. Sometimes, however, it can be extremely difficult to distinguish between PH caused by diastolic LV dysfunction and PAH. Risk factors of LV dysfunction are outlined in Table 1.

Echocardiographic findings suggestive of diastolic LV dysfunction include the presence of a dilated left atrium, atrial fibrillation, abnormal mitral inflow pattern, and LV hypertrophy (84). Although echocardiography provides important information, invasive measurements of PCWP or LV end-diastolic pressure may be required to document the presence of elevated LV filling pressures (84). However, resting PCWP and LV end-diastolic pressure can be normal despite LV diastolic dysfunction, especially when patients have been treated with diuretics. Exercise or volume challenge has been proposed to identify occult LV dysfunction, but these tools have not been fully standardized and require further evaluation. An elevated transpulmonary gradient (mPAP–mean PCWP) >12 mm Hg is suggestive of active PH, that is, a pre-capillary component of PH (84). Figure 3 depicts a suggested diagnostic strategy to discriminate between pulmonary arteriopathy and PH related to diastolic heart failure or “heart failure with normal ejection fraction.”

Vasoreactivity tests using compounds with inotropic and/or systemic and/or pulmonary vasodilator activities have been recommended in heart transplant candidates to determine whether this procedure is feasible in patients with LHD and PH. However, there is no internationally accepted standard protocol for this procedure, and the criteria for operability or nonoperability, respectively, need to be further evaluated and standardized.

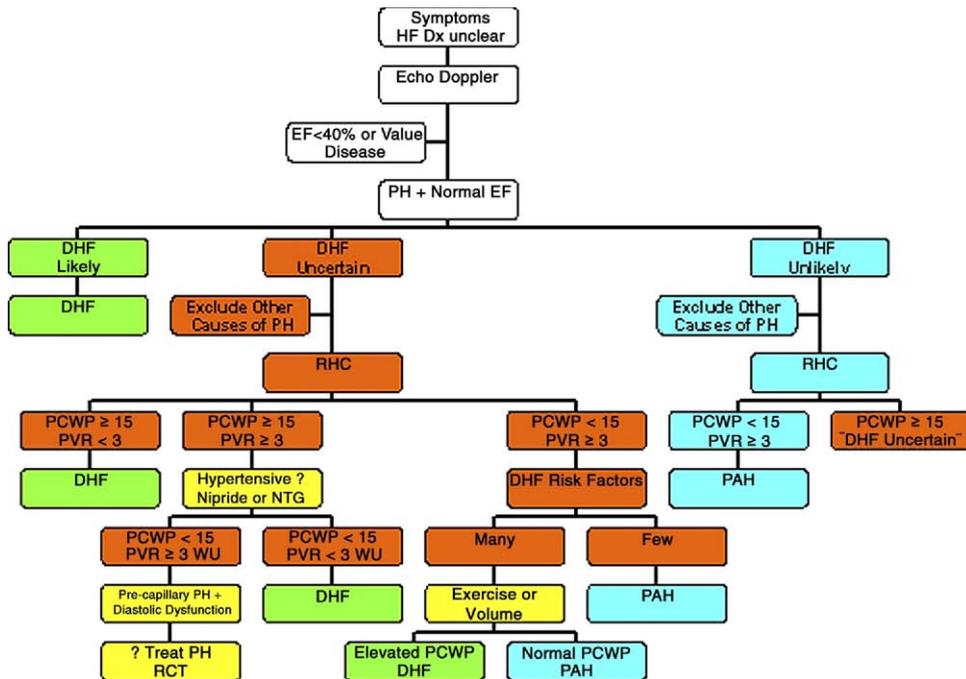


Figure 3 Diagnostic Approach to Distinguish Between PAH and PH Caused by Diastolic Left Heart Disease

See Table 1 for risk factors for diastolic heart failure. DHF = diastolic heart failure; Dx = diagnosis; EF = ejection fraction; HF = heart failure; NTG = nitroglycerine; OMT = optimized medical therapy; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; RHC = right heart catheterization; WU = Wood units.

Treatment of PH associated with LHD. Optimal correction of the underlying substrate is a necessary first step in management because treatment of LHD may decrease PH (85). Careful attention must be paid to optimize LV filling pressures (86). In valvular heart disease such as mitral stenosis, post-operative reduction of PCWP may lead to a rapid reduction of PAP in both passive and active PH (87). However, the reduction may be incomplete, despite the normalization of the PCWP, in cases with PH caused by chronic pathological obstructive changes. This component may require weeks to months to regress, even after successful valve surgery (87). In the majority of patients, an almost complete normalization of PH is expected.

There is an ongoing debate regarding whether drugs used in PAH, that is, ERAs, PDE-5 inhibitors, or prostanoids, may be useful in patients with LHD and PH, especially when PH becomes severe and dominates the clinical picture. Theoretical concerns about this approach include the possibility of causing pulmonary edema when pulmonary vasodilators are administered to patients with elevated LV filling pressures. This potentially adverse effect, however, may be offset when the concomitant treatments reduce LV afterload and LV filling pressures.

Virtually no data from long-term RCTs address the population of patients with LHD and PH. Inhaled nitric oxide and prostanoids exert favorable acute hemodynamic effects in these patients (88–90). However, it is of concern that a study of epoprostenol in heart failure showed a higher mortality in the active treatment group (91). Large trials with ERAs in patients with LHD have also failed to show beneficial long-term effects, although these trials did not look specifically at the subset of patients with LHD and PH (92,93). The PDE-5 inhibitor sildenafil improves systolic and diastolic LV function as well as systemic vasoreactivity in experimental models of heart failure, making it a promising agent for future studies in patients with LHD and PH (94,95). Results of recent small studies suggest that sildenafil may improve exercise capacity and quality of life in patients with PH caused by LHD (96–98). However, long-term data from carefully designed clinical studies are required before sildenafil can be recommended for patients with LHD and PH because there have been instances in which drugs used to treat left heart failure had positive effects on surrogate end points but decreased survival, as was the case with PDE-3 inhibitors (99,100).

Working Group Recommendations for PH Associated With LHD

Diagnosis and assessment of PH in LHD

- Left heart disease is one of the most common causes of PH. The presence of LHD is obvious in many patients, but it may be occult in others, especially when

isolated LV diastolic dysfunction is present. Features suggestive of LV diastolic dysfunction or diastolic left heart failure include an older age, atrial fibrillation, and an enlarged left atrium (E/A).

- Right and left heart catheterization may be required to distinguish between PAH and PH associated with LHD (E/A).
- In patients with elevated PCWP and an elevated transpulmonary gradient, reduction of LV afterload with nifedipine or other vasodilators is useful to identify an active pulmonary arterial component of PH (E/A).
- In patients with LHD and PH considered for heart transplantation, pulmonary vasoreactivity testing with inhaled nitric oxide or prostanoids may be used to assess reversibility and operability, although the criteria for operability or nonoperability require further evaluation (E/A).

Treatment of PH in LHD

- Treatment of LHD according to established criteria is the basis for a successful approach to patients with LHD and PH (E/A).
- Patients with end-stage heart failure and PH may be candidates for heart transplantation (in milder, largely reversible forms of PH) or heart–lung transplantation (if PH is severe and fixed) (E/A).
- The use of prostanoids, ERAs, and PDE-5 inhibitors in patients with LHD and PH is not recommended until robust data from long-term clinical trials are available (E/A).

Clinical trial strategy for PH in LHD. Drugs that reduce LV afterload as well as PVR may have beneficial effects in patients with moderate or severe PH in the setting of milder forms of heart failure or LV diastolic dysfunction with preserved ejection fraction. Short-term beneficial effects on hemodynamics and exercise capacity have been shown with several drugs, including PDE-5 inhibitors. These drugs need to be rigorously studied to assess long-term safety and efficacy in patients with LHD and PH and to identify subpopulations of patients most likely to derive a benefit. These trials should address morbidity and mortality end points to yield meaningful results (E/A).

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