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Diagnosis and Differential Assessment of Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is diagnosed by various investigations that are essential for making the diagnosis, and by additional tests to clarify the category of pulmonary hypertension (PH). A diagnostic algorithm can guide the evaluation of PH, but like all guidelines the algorithm can be modified according to specific clinical circumstances. Most patients are diagnosed as the result of an evaluation of symptoms, whereas others are diagnosed during screening of asymptomatic populations at risk. Right heart catheterization (RHC) must be performed in patients with suspected PH to establish the diagnosis and document pulmonary hemodynamics. Before initiation of medical therapy, assessment of acute vasoreactivity (during catheterization) is necessary to determine the appropriate therapy for an individual patient. An acute response is generally defined as a decrease in mean pulmonary arterial pressure of at least 10 mm Hg with the mean pulmonary arterial pressure decreasing to 40 mm Hg or below, accompanied by a normal or high cardiac output. After PAH is diagnosed, disease severity should be assessed in order to accurately determine risk:benefit profiles for various therapeutic options. Useful tools to predict outcome include functional class, exercise capacity, pulmonary hemodynamics, acute vasoreactivity, right ventricular function, as well as brain natriuretic peptide, endothelin-1, uric acid, and troponin levels. Repeating these tests serially on treatment is useful for monitoring the response to a given therapy. Close follow-up at a center specializing in management of PH is recommended, with careful periodic reassessment and adjustment of therapy. (J Am Coll Cardiol 2004;43:40S–47S) © 2004 by the American College of Cardiology Foundation

The diagnosis of pulmonary hypertension (PH) involves two stages: detection (determining the cause of a patient's symptoms, or to detect the presence of pulmonary arterial hypertension [PAH] in a high-risk patient) and characterization (determining the specific clinical context of the PH, including causal factors, associated diseases or substrates, hemodynamic perturbations and their localization, and sequelae).

DETECTION

Symptom evaluation. Symptoms that suggest PH are exertional dyspnea, fatigue or weakness, angina, syncope, peripheral edema, and abdominal distension (Fig. 1). Exertional intolerance is quantitated with the World Health Organization (WHO) classification (Table 1).

Screening. Periodic assessment of patients with an underlying predisposition may be warranted to introduce therapy at an early stage, or to initiate more aggressive surveillance to detect progression. Screening for the presence of PAH using Doppler echocardiography is advisable when risk is sufficiently high to justify the expense (i.e., when diagnosis could lead to further evaluation and/or change in management). This currently includes individuals with: 1) a known genetic-mutation–associated PAH or a first-degree relative with idiopathic pulmonary arterial hypertension (IPAH); 2) scleroderma spectrum of disease; 3) patients with congenital heart disease and systemic-to-pulmonary shunts; or 4) portal hypertension undergoing evaluation for orthotopic liver transplantation (1). Other potential PAH substrates do not warrant routine screening (e.g., previous use of appetite suppressant, HIV infection, other connective tissue disorders, obstructive pulmonary disease, or high-altitude residence because of the infrequency and/or low likelihood of altering treatment at a presymptomatic stage).

Incidental discovery. The clinical significance and natural history of asymptomatic or mild PAH is unclear; thus, the implications for further assessment and/or treatment when discovered incidentally, as a result of screening or during evaluation of nonspecific symptoms, remain uncertain. Moreover, the criterion of clinically significant PH when detected under these circumstances by Doppler echocardiography, which in itself is an isolated estimate of right ventricular systolic pressure (RVSP), is not precisely defined. Commonly used definitions of PH are a pulmonary artery systolic pressure (PASP) >35 mm Hg or mean >25 mm Hg at rest or mean >30 mm Hg with exercise. However, PASP >40 mm Hg is present in 6% of otherwise normal individuals older than 50 years and 5% with a body mass index (BMI) >30 kg/m^2 (2).

In general, any degree of PH should prompt an attempt to define or exclude possible causes, because it may be the first evidence of a modifiable substrate. However, the

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Abbreviations and Acronyms

BMI = body mass index
CI = cardiac index
CTEPH = chronic thromboembolic pulmonary hypertension
ECG = electrocardiogram
IPAH = idiopathic pulmonary arterial hypertension
PA = pulmonary artery
PAH = pulmonary arterial hypertension
PASP = pulmonary artery systolic pressure
PH = pulmonary hypertension
RAP = right atrial pressure
RHC = right heart catheterization
RVSP = right ventricular systolic pressure
TTE = transthoracic Doppler echocardiography
V̇/Q̇ = ventilation–perfusion

severity of PH and the reliability of the measurement should temper the aggressiveness of the evaluation. Confirmation by right heart catheterization (RHC) is warranted before embarking on extensive evaluation for an underlying cause or considerations of prognosis or treatment.

Detection assessment. Components of assessment to detect PAH include the *physical examination* (e.g., left parasternal lift, accentuated pulmonary component of S2, pansystolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency, right ventricular S3, jugular vein distension, hepatomegaly, peripheral edema, ascites, cool extremities), chest X-ray, electrocardiogram (ECG), and Doppler echocardiogram. Findings of central pulmonary arterial and/or right ventricular enlargement on *chest X-ray* suggest the presence of PAH. Additional clues to possible associated diseases should be considered, such as pulmonary venous hypertension—for example, septal lines and pleural effusions (pulmonary venous hypertension due to left heart filling abnormality, pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis); hyperinflation (chronic obstructive pulmonary disease); or kyphosis (restrictive pulmonary disease). Marked asymmetry of the enlarged central pulmonary arteries may be a clue to chronic thromboembolic disease.

The *ECG* may provide suggestive or supportive evidence of PAH by demonstrating right ventricular hypertrophy and strain, and right atrial dilation. Right ventricular hypertrophy on ECG is present in 87% and right axis deviation in 79% of patients with IPAH (3). The ECG has inadequate sensitivity (55%) and specificity (70%) to be a screening tool for detecting significant PAH (4).

Transthoracic Doppler echocardiography (TTE) estimates PASP and can provide additional information about the cause and consequences of PH. The PASP is equivalent to RVSP in the absence of pulmonary outflow obstruction. The RVSP is approximated by measurement of the systolic regurgitant tricuspid flow velocity v and an estimate of right atrial pressure (RAP) applied in the formula: RVSP = $4v^2$ + RAP. The RAP is either a standardized value, or an

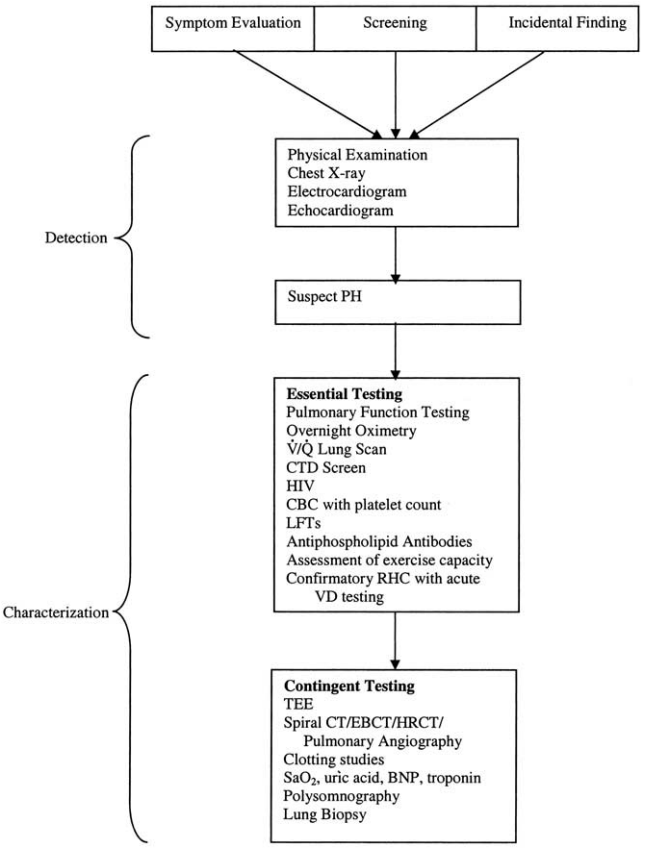

Figure 1. Guidelines for evaluating pulmonary hypertension. Abbreviations: BNP = brain natriuretic peptide; CBC = complete blood count; CT = computerized tomography; CTD = connective tissue disease; EBCT = electron beam computerized tomography; HIV = human immunodeficiency virus; HRCT = high-resolution computerized tomography; LFTs = liver function tests; PH = pulmonary hypertension; RHC = right heart catheterization; SaO_2 = systemic arterial oxygen saturation; TEE = transesophageal echocardiography; VD = vasodilator; V̇/Q̇ = ventilation/perfusion.

estimated value from characteristics of the inferior vena cava (5) or from jugular venous distension. Tricuspid regurgitant jets can be assessed in 39% to 86% of patients. Careful Doppler examination by experienced sonographers yields quantifiable tricuspid regurgitant signals in 74% of cases (6). Most studies report a high correlation (0.57 to 0.93) between TTE and RHC measurements of PASP (7). Reported sensitivity of TTE-estimated PASP for detecting PAH ranges from 0.79 to 1.00 (7–9) and specificity from 0.60 to 0.98. However, these figures are strongly influenced by the value used to define PH.

The range of RVSP among healthy controls has been well characterized. Among a broad population of male and female subjects ranging from 1 to 89 years of age, RVSP was reported as 28 ± 5 mm Hg (range 15 to 57 mm Hg). The RVSP increases with age and BMI (2). Athletically conditioned men also have higher resting RVSP. Defining the normal distribution of RVSP does not ipso facto define the point at which an elevated RVSP is clinically important or predictive of future consequences.

Mild PH is defined as a PASP of approximately 36 to 50

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Table 1. World Health Organization Classification of Functional Status of Patients With Pulmonary Hypertension

Class	Description
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

Adapted from Rich S. Primary pulmonary hypertension: executive summary. Evian, France: World Health Organization, 1998 (33).

mm Hg or a resting tricuspid reguritant velocity of 2.8 to 3.4 m/s. Possible explanations for mildly elevated PASP detected by echocardiography include 1) overestimation of the RVSP in a patient with true normal pulmonary pressure; 2) serendipitous observation of a rare transient pressure elevation in an otherwise healthy individual; 3) discovery of stable mild PH, possibly of long duration; or 4) discovery of early progressive PH in an individual with PAH. In addition, pulmonary artery pressure differences may be observed in different populations and conditions, including age, level of conditioning, exercise or stress. No clear guidelines are available that delineate normal from pathologic in all circumstances.

Pulmonary hemodynamics can also be estimated from the pulmonary regurgitant Doppler signal, right ventricular outflow patterns, and time intervals, including pre-ejection period, acceleration and deceleration times, and relaxation and contraction times.

CHARACTERIZATION: ESSENTIAL TESTS

Certain tests are essential if PH is suspected in order to characterize potential substrates, to determine severity and prognosis accurately, and to select treatment (Fig. 1). The *Doppler echocardiogram* provides essential information in addition to screening, as noted above, including estimation of baseline and follow-up PASP, estimated pulmonary vascular resistance, right ventricular size and function, semiquantitative right atrial size, left ventricular systolic and diastolic function, presence of prognostically relevant pericardial effusion, morphology and function of all cardiac valves, as well as patent foramen ovale, and intracardiac or intrapulmonary shunts (using "bubble" contrast techniques).

Pulmonary function testing will exclude or characterize the contribution of underlying airway or parenchymal disease. Although obstructive pulmonary disease with hypoxemia may be confirmed by testing, abnormalities occur in other types of PH. Approximately 20% of patients with chronic pulmonary embolism have restrictive parameters (i.e., lung volumes <80% predicted) but may have near normal diffusing capacity for carbon monoxide (DL_{CO}). The DL_{CO} of 20% of patients with limited systemic sclerosis is below normal; a DL_{CO} of <55% of predicted may be associated with future development of PAH.

Screening overnight oximetry will exclude significant obstructive sleep apnea/hypopnea.

Ventilation-perfusion ($\dot{V}/\dot{Q}$) lung scintigraphy is an indispensable component of assessment because chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially curable cause of PH. The $\dot{V}/\dot{Q}$ scans of patients with chronic pulmonary embolism generally show at least one segmental-sized or larger perfusion defect. Patients with PH who have normal $\dot{V}/\dot{Q}$ scans are unlikely to have chronic pulmonary embolism, and more likely to have IPAH. In three studies (10–12), $\dot{V}/\dot{Q}$ scanning showed sensitivity of 90% to 100%, with a specificity of 94% to 100% for distinguishing between IPAH and CTEPH. The $\dot{V}/\dot{Q}$ scans tend to correlate poorly with the severity of obstruction and to underestimate the degree of severity of large vessel obstruction. Scans consistent with thromboembolism may represent false positives, where the actual underlying pathology is pulmonary artery sarcoma, large vessel pulmonary vasculitis, extrinsic vascular compression, or pulmonary veno-occlusive disease.

Blood tests for evaluation of PAH include antinuclear antibody (ANA) titer to screen for connective tissue disease, HIV serology, complete blood count with platelet count, liver function tests, and antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies). Although 40% of patients with IPAH have positive but low ANA titers (≥1:80 dilutions) (13), patients with a substantially elevated ANA and/or suspicious clinical features require further serologic assessment and rheumatology consultation.

Assessment of exercise capacity is a key part of the evaluation of PH. The goals of exercise testing vary under different clinical circumstances, and they determine the specific testing modality to employ. These objectives include: searching for alternative or contributory reasons for symptoms (e.g., myocardial ischemia); determining maximal exercise tolerance; characterizing comfortable activity level (functional capacity) of the patient; obtaining predictive data; establishing a baseline measure of exercise capacity and following the response to therapy; assessing the interaction of the circulatory and ventilatory systems; or attempting to discover abnormal pulmonary hemodynamic responses to exercise before clinically evident PH at rest.

The most commonly used exercise tests for PH are the 6-min walk test (6MWT) and cardiopulmonary exercise testing with gas exchange measurements. Other options include exercise testing in conjunction with noninvasive Doppler echocardiographic assessment of RVSP, and exercise testing in conjunction with RHC.

The *6MWT*, developed for evaluation of congestive heart failure (14), is predictive of survival in IPAH and also correlates inversely with WHO functional status severity, moderately with baseline cardiac output and total pulmonary resistance (but not mean pulmonary arterial pressure), and strongly with peak exercise oxygen consumption (V_{O_2}), peak oxygen pulse, and minute ventilation–carbon dioxide output slope (V_E-V_{CO_2} slope) in IPAH. Arterial oxygen desaturation >10% during the 6MWT increases mortality risk 2.9 times over a median follow-up of 26 months (15).

Cardiopulmonary exercise testing is discussed in more detail elsewhere in this Supplement. Consistent observations in PAH are reduced peak V_{O_2}, peak work rate, the ratio of V_{O_2} increase to work rate increase, anaerobic threshold, peak oxygen pulse, and increased V_E-V_{CO_2} slope. These observations indicate that the mechanism(s) of exercise limitations in PAH include V/Q mismatching, lactic acidosis at a low work rate, arterial hypoxemia, and inability to adequately increase stroke volume and cardiac output (16).

Exercise Doppler echocardiography has been utilized to evaluate RVSP responses with exercise. In healthy men, tricuspid regurgitant velocity increases from an average of 1.72 m/s at baseline to a peak of 2.46 m/s at mid-level exercise and to 2.27 m/s at peak exercise (240 W); in trained athletes the baseline value is 2.25 m/s and increases to 3.41 m/s at peak exercise (17). As with invasive exercise studies, the criteria for an abnormal response are not well established.

Right heart catheterization is required to confirm the diagnosis of PAH. Cardiac output, determined by thermodilution or Fick (with measured oxygen consumption) during RHC is also required to calculate pulmonary vascular resistance. Pulmonary arterial hypertension is defined by a mean pulmonary artery pressure (mPAP) >25 mm Hg at rest or >30 mm Hg with exercise; in PAH, pulmonary capillary wedge pressure or left ventricular end diastolic pressure is ≤15 mm Hg and pulmonary vascular resistance is >3 units. The RHC also characterizes intracardiac shunting, and it establishes pulmonary venous pressure. An elevated pulmonary capillary wedge pressure supports the presence of left heart disease or pulmonary vein obstruction, though a normal pulmonary capillary wedge pressure does not rule out pulmonary veno-occlusive disease.

Hemodynamic measurements have been used to estimate the natural history of IPAH in an individual patient. The probability of survival P(t) one, two, or three years after diagnosis can be estimated as $P(t) = \{H(t)\}^{A(x,y,z)}$, where $H(t) = \{0.88 - 0.14t + 0.01t^2\}$, $A(x,y,z) = e^{(0.007325x + 0.0526y - 0.3275z)}$, t = years, x = mPAP (mm Hg), y = mRAP (mm Hg), and z = cardiac index (CI) (l/min/m^2) (18). Other logistic regression equations have been reported to predict survival or death within one year.

Importantly, a vasodilator study should be performed whenever PAH is discovered or confirmed during RHC in patients in whom symptoms and/or disease severity warrant treatment. All patients in whom vasodilator treatment is to be initiated require hemodynamic monitoring for detection of either beneficial or detrimental effects of acute treatment. Uncontrolled studies have suggested that long-term administration of calcium-channel blockers (CCB) prolongs survival in the rare subset of responsive patients compared with unresponsive patients. Unfortunately, no clinical or hemodynamic parameters exist that can predict acute and/or chronic responses to CCB in PAH patients. It is generally accepted that patients who may benefit from long-term CCB can be identified by an acute vasodilator challenge performed during RHC; that is, a sustained benefit from CCB treatment is seen in patients in whom, during acute vasodilator testing, mPAP decreases ≥10 mm Hg to reach a mPAP ≤40 mm Hg with a normal or high cardiac output (19). Owing to the potential risk of severe life-threatening hemodynamic compromise occurring with acute vasodilator challenge with CCB, acute vasodilator testing should be done using a safe, potent, and short-acting vasodilator with limited side effects to identify with accuracy those patients who may benefit from long-term CCB therapy.

The acute pulmonary effect of short-acting vasodilators (e.g., intravenous epoprostenol, inhaled nitric oxide [NO], intravenous adenosine, or inhaled iloprost) predicts the hemodynamic response to long-term CCB. Thus, the efficacy of the short-acting drug has been used to determine whether chronic CCB treatment should be initiated. However, with novel oral and inhaled therapeutic agents combining vasodilatory and antiproliferative properties now available (e.g., endothelin receptor antagonists, prostacyclin analogues, and phosphodiesterase type 5 inhibitors), the usefulness of invasive testing for pulmonary vasoreactivity in selecting optimal treatment is now less clear. Although it is reasonable to believe that patients who respond to intravenous epoprostenol, inhaled NO, intravenous adenosine, or inhaled iloprost will respond to such oral or inhaled therapies, no study has evaluated the acute and chronic responses to these drugs in vasoreactive patients.

The abrupt development of pulmonary edema during acute vasodilator testing suggests the presence of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis and is a contraindication to chronic vasodilator treatment.

CHARACTERIZATION: CONTINGENT TESTS

Certain tests are *contingent* on the presentation and results of essential testing (Fig. 1). They may not be necessary in all patients. *Transesophageal echocardiography* (TEE) provides important data that may alter treatment in up to 25% of patients. Useful in the detection of intracardiac shunts, especially atrial septal defects, TEE can also detect central pulmonary emboli including chronic thromboemboli causing PAH, with a reported sensitivity of 80% (20), and up to 96%, with a specificity of 88%, in patients with documented severe central acute or chronic thromboembolism (21).

Additional imaging may be required if the V̇/Q̇ scan is

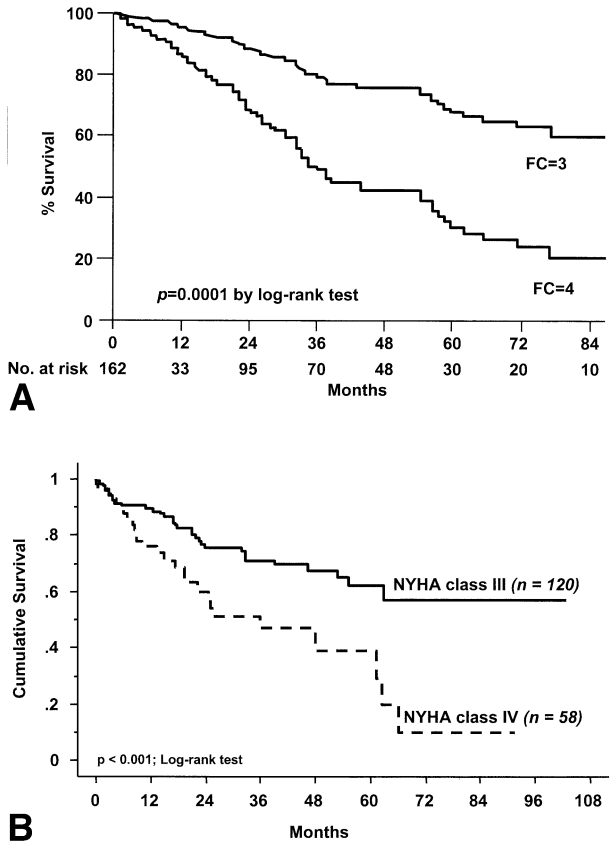

Figure 2. (A) Long-term (7-year) survival in patients with idiopathic pulmonary arterial hypertension (IPAH) based on functional class (III vs. IV) at the time of epoprostenol initiation. p = 0.0001 by log-rank test (30). **(B)** Survival in patients with IPAH treated with intravenous epoprostenol according to New York Heart Association (NYHA) functional class. Estimated percentages of survival for patients in NYHA functional class IV at baseline **(dashed line)** were 76%, 60%, and 47% at one, two, and three years, respectively, as compared with 90%, 76%, and 71% for patients in NYHA functional class III at baseline **(solid line)** ($p < 0.001$ by the Cox-Mantel log-rank test) (32).

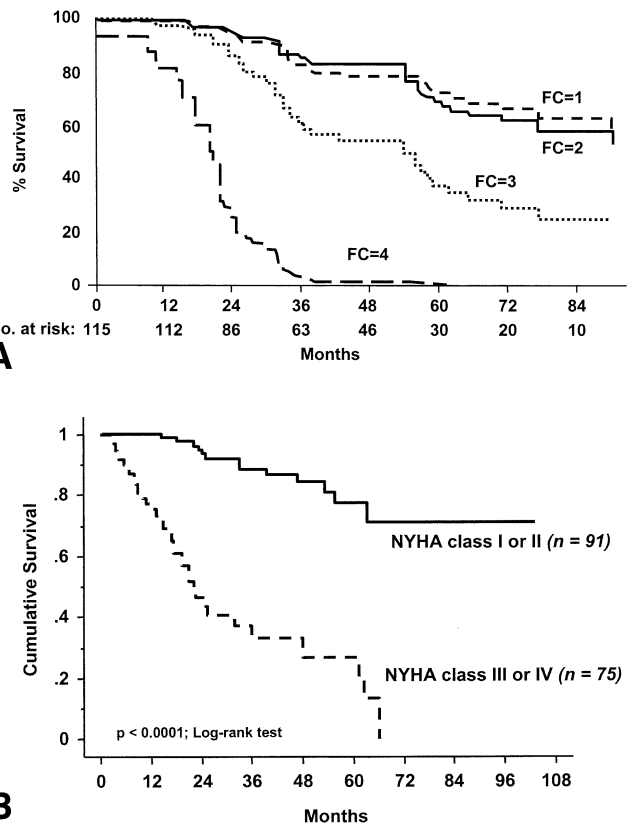

Figure 3. (A) Subsequent survival in patients with idiopathic pulmonary arterial hypertension (IPAH) stratified by functional class after 1 year epoprostenal treatment 1: $p < 0.001$ for functional class III vs. functional class IV and for functional class III vs. functional class I and functional class II (30). **(B)** Survival in patients with IPAH treated with intravenous epoprostenol according to New York Heart Association (NYHA) functional class. After three months of treatment with epoprostenol, survival rates for patients reclassified in NYHA functional class I or II **(solid line)** were 100%, 93%, and 88% at one, two, and three years, respectively, as compared with 77%, 46%, and 33% for patients persisting in NYHA functional class III or IV **(dashed line)** ($p < 0.001$ by the Cox-Mantel log-rank test) (32).

suggestive of chronic pulmonary embolism. *Chest computerized tomography* (CT) provides supportive noninvasive evidence, but if negative it should not obviate the use of pulmonary angiography. A mosaic pattern of lung attenuation in a noncontrast CT scan raises the possibility of chronic thromboembolism. Contrast-enhanced *spiral (or helical) CT* or *electron-beam CT* (EBCT) can visualize central chronic pulmonary thromboemboli. The CT features of chronic thromboembolic disease are complete occlusion of pulmonary arteries, eccentric filling defects consistent with thrombi, recanalization, and stenoses or webs.

The sensitivity of spiral CT for detecting central pulmonary embolism is >85% to 90%. Though sensitivity for detecting distal emboli is lower, detection rates of up to 97% for distal emboli (compared with high probability V̇/Q̇ scans or angiography) have been reported (20). Specificity is also 90%, with occasional misclassification of IPAH as being CTEPH (20).

The EBCT signs of pulmonary vein obstruction (e.g., pulmonary veno-occlusive disease) are smooth thickening of interlobular septa, peribronchovascular cuffing, and alveolar ground-glass opacification.

High-resolution CT provides detailed views of the lung parenchyma during evaluation of PH or hypoxia and aids in the diagnosis of pulmonary fibrosis. Diffuse bilateral thickening of the interlobular septae and the presence of small, centrilobular, poorly circumscribed nodular opacities suggest pulmonary capillary hemangiomatosis; diffuse central ground-glass opacification and thickening of interolobular septa suggest pulmonary veno-occlusive disease.

Pulmonary angiography is required to confirm CTEPH and assess operability. Chronic thrombi appear different from acute thrombi and occur in highly variable locations, often incorporated into and retracting the vessel wall. Obstructions can take the form of bands or webs, sometimes with post-stenotic dilation. Irregular intimal surface, rounded or pouch-like termination of segmental branches, luminal narrowing of the central vessel, and odd-shaped

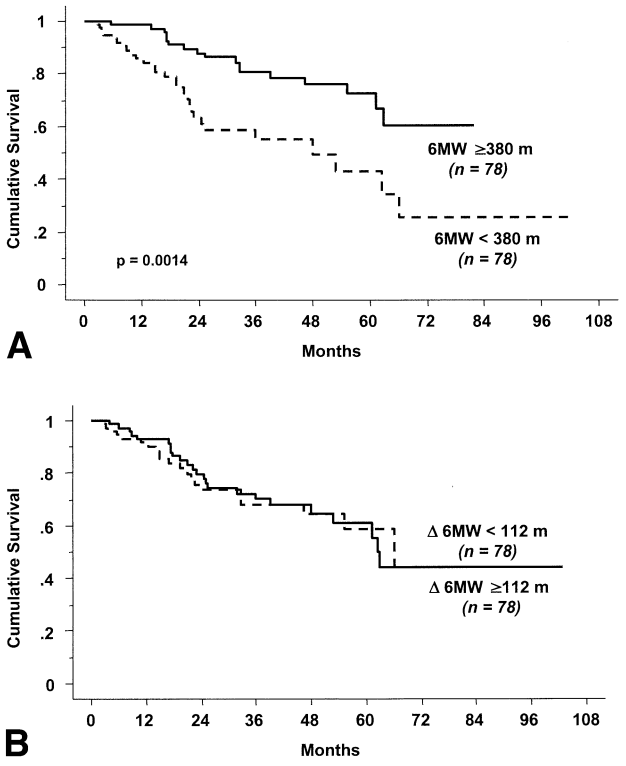

Figure 4. (A) Kaplan-Meier survival estimates in 156 patients with idiopathic pulmonary arterial hypertension (IPAH), according to the results of the 6-min walk (6MW) test performed after three months of epoprostenol therapy. Survival rates for patients walking >380 m during the 6MW test (corresponding to the median value) **(solid line)** were 99%, 88%, and 81% at one, two, and three years, respectively, as compared with 86%, 64%, and 56% for patients walking <380 m **(dashed line)** ($p = 0.0005$ by the Cox-Mantel log-rank test). **(B)** Kaplan-Meier survival estimates in 156 patients with IPAH, according to the change in the 6MWT between baseline and three months of epoprostenol therapy. No difference in survival was demonstrated in patients who improved their 6-min walk distance to >112 m (corresponding to the median value) **(solid line),** as compared with those who did not **(dashed line)** ($p = 0.86$ by the Cox-Mantel log-rank test) (32).

pulmonary arteries all may indicate the presence of chronic pulmonary embolism.

For patients with known or suspected CTEPH, further evaluation of a potential *clotting diathesis* is warranted (bleeding time, coagulation Factors VIII, VII, II, and V, von Willebrand factors, Protein C and S). Factor V Leiden mutation (the most common cause of activated protein C resistance) has been implicated as high risk for idiopathic venous thromboembolism, though not specifically in pulmonary embolism or CTEPH. Serum viscosity, serum protein electrophoresis, and Hgb electrophoresis may be helpful under certain circumstances.

Additional blood tests may provide prognostic data. *Arterial blood gas* or *oximetry* measurements showing desaturation may signal abnormal gas exchange, right-to-left shunting, ventilation/perfusion mismatching, interstitial fibrosis, other parenchymal lung disease, or hypoventilation. Failure to normalize with high FiO_2 oxygen inhalation supports a component of right-to-left shunting. Arterial blood gas measurement or oximetry during exercise may disclose desaturation requiring supplemental oxygen treatment to improve exercise capacity. Overnight oximetry may disclose disordered sleep with frequent desaturations and may be the first clue to sleep apnea sufficient to cause or contribute to PH. Nocturnal hypoxemia occurs in >75% of IPAH patients independent of the occurrence of apneas or hypopneas (22).

Hyperuricemia occurs with high frequency in patients with PH and correlates with hemodynamic abnormalities (e.g., right atrial pressure) and mortality in IPAH (23).

Brain natriuretic peptide (BNP) is elevated in right ventricular pressure overload and correlates with severity of right ventricular dysfunction and mortality in PAH (24).

If the history and/or screening overnight oximetry is suggestive, *polysomnography* should be considered to assess a possible contributory role in PH. Up to 20% to 27% of patients with sleep apnea syndromes have PH (25). The degree of waking PH in obstructive sleep apnea is generally mild and reversible by six months of continuous positive airway pressures, i.e., CPAP (26). Open or thoracoscopic *lung biopsy* entails substantial risk of morbidity and mortality. Because of the low likelihood of altering the diagnosis, routine biopsy is discouraged. Under certain circumstances, histopathologic findings may provide useful information by excluding or establishing a diagnosis of active vasculitis, granulomatous pulmonary disease, pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, interstitial lung disease, or bronchiolitis (27).

ASSESSMENT OF PAH SEVERITY

After PAH is diagnosed, in order to assess risk:benefit profiles for various therapeutic options accurately, precise assessment of prognosis as a function of disease severity is required. Measurable descriptors of disease severity have several potential applications: 1) accurate comparison of patient populations, 2) precise characterization of a patient population for the purpose of homogeneous enrollment into clinical protocols, 3) valid comparison of baseline severity with post-treatment severity as a measurement of therapeutic efficacy, 4) valid comparison of post-treatment severity of similar patients on alternative treatment strategies, 5) accurate longevity prediction (or surrogate for survival in clinical studies), and 6) useful early prediction for timing of transplantation. The characteristics of ideal descriptor(s) of disease severity include: 1) easily performed assessment procedure, 2) reproducible results temporally and between centers, 3) high correlation with outcome of interest (e.g., survival), 4) low risk, 5) low expense, 6) low discomfort level, and 7) wide availability.

Various demographic and hemodynamic characteristics, as well as exercise capacity, acute pulmonary vasoreactivity, assessment of right ventricular function, neurohormonal levels (e.g., BNP [24], norepinephrine [28]), as well as endothelin-1 (29), uric acid (23), and troponin (31), correlate with survival. Some of these modalities may provide

prognostic information similar to that derived from invasive tests (e.g., cardiac catheterization) and may prove more useful and convenient in assessing treatment efficacy. These tools may also increase predictive accuracy when used in combination. Because many of these variables have been shown to correlate with one another, which parameter(s) will prove to be most useful for decision making and optimizing treatment (e.g., timing of transplantation) will require further study. It is important to remember that these tests evaluated IPAH patients and not patients with PAH related to connective tissue disorders, congenital systemic to pulmonary shunts, HIV infection, or portal hypertension. Thus, these parameters must be applied cautiously to PAH patients in whom comorbid factors might contribute to the overall outcome; for example, patients with PAH related to connective tissue disorders are known to have a worse prognosis than do IPAH patients, whereas patients with PAH related to congenital systemic to pulmonary shunts have a more slowly progressive course than do IPAH patients.

In addition to evaluating various parameters, such as functional class (32) or exercise capacity, at the time of diagnosis prior to initiation of medical therapy, repeating these parameters on treatment is useful in predicting outcome with a given therapy (e.g., epoprostenol). McLaughlin et al. (30) as well as Sitbon et al. (32) demonstrated that the baseline functional class in patients with IPAH treated with epoprostenol (i.e., before epoprostenol is started) is predictive of survival with epoprostenol (Fig. 2). In addition, patients' functional class on chronic intravenous epoprostenol is also predictive of outcome with continued epoprostenol (Fig. 3) (30,32). Additional survival parameters include: 1) right atrial size and pericardial effusion assessed by echocardiography; 2) exercise endurance assessed by the 6MWT, both at the time of diagnosis as well as on chronic medical therapy (e.g., epoprostenol); and 3) hemodynamics. It appears that although the baseline 6-min walk distance prior to epoprostenol treatment is useful as a parameter in predicting disease severity, once a patient is on epoprostenol, the actual 6-min walk distance on chronic epoprostenol is more predictive of survival than the change in 6-min walk distance with epoprostenol (Fig. 4) (32). By multivariate analysis in IPAH patients treated with epoprostenol, Sitbon et al. (32) reported that the only parameter independently predictive of outcome prior to starting epoprostenol is the presence of right heart failure; after three months of epoprostenol, persistence of functional class III or IV, mPAP <59 mm Hg and a drop in pulmonary vascular resistance $<30\%$ relative to baseline are associated with a poor prognosis.

In conclusion, evaluating disease severity as a function of: 1) end-organ consequences (e.g., right heart failure), 2) symptoms and functional limitation, and 3) markers of decreased survival is necessary for decision making to optimize the appropriate aggressiveness of PAH patients' care.

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