Screening, Early Detection, and Diagnosis of Pulmonary Arterial Hypertension: ACCP Evidence-Based Clinical Practice Guidelines

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This chapter reviews early detection, diagnosis, and screening of patients at risk for pulmonary arterial hypertension (PAH). We performed a comprehensive review of published studies to provide an evidence-based analysis, including an assessment of the sensitivity and specificity of the methods used clinically to detect and diagnose PAH. Each of the diagnostic methods and strategies are examined, including those that are utilized for the confirmation of conditions associated with PAH. Novel diagnostic techniques and future directions for the field are then considered to complete this chapter. The summary evidence tables can be viewed on-line at http://www.chestjournal.org/content/vol126/1_suppl/.

Substantial technical progress has occurred for many of the diagnostic methods discussed, primarily those methods that assess cardiac structure or estimate pulmonary artery pressures. Since PAH does not become manifest until the pulmonary vascular disease is advanced, even mild elevations in pulmonary arterial pressure reflect diffuse and extensive vascular damage. Changes in right ventricular function and structure, which can be assessed by noninvasive diagnostic methods, occur even later in the clinical course of PAH. Accordingly, there is a need for the development of an early detection approach that will require the identification and validation of biomarkers or other noninvasive and easily obtainable methods and strategies for the confirmation of conditions associated with PAH.
able parameters to assess the intrinsic vascular process at a presymptomatic or early symptomatic stage.

**HISTORICAL PERSPECTIVE**

The development of cardiac catheterization provided the first method to diagnose and confirm PAH, and was the pivotal diagnostic method for 3 decades after the first clinical description of idiopathic PAH (IPAH) in the early 1950s. Although cardiac catheterization is still necessary for disease confirmation in patients with suspected pulmonary hypertension (PH), in the current era it rarely reveals unsuspected new findings. The technical advances in noninvasive thoracic and cardiac imaging over the recent few decades enable the physician to strongly suggest a diagnosis of PH before confirmation by cardiac catheterization.

Echocardiography with Doppler ultrasound is the most portable and widely available technology among the noninvasive imaging methods. Echocardiography provides both estimates of pulmonary artery pressure and an assessment of cardiac structure and function. These features justify its application as the most commonly used screening tool in patients with suspected PAH.

**EVALUATION OF PAH**

Assessment of PAH is based on a logical sequence of determining whether there is a risk of PAH being present, whether PAH is likely to be present based on initial, noninvasive evaluation, clarifying the underlying etiology of PAH in an individual patient, and delineating the specific hemodynamic profile, including the acute response to vasodilator testing. The schema for patient evaluation using this approach is provided in Figure 1, and is expanded in the text.

**GENETIC SCREENING FOR MUTATIONS THAT CAUSE PAH**

Mutations in the bone morphogenetic protein receptor II (BMPR2) gene have been identified in approximately 50% of patients with familial PAH (FPAH) and 25% of patients thought to have sporadic IPAH. Other FPAH families demonstrate linkage to the same chromosomal region, 2q32, where BMPR2 resides, but the responsible mutations have not been identified. Confirmation of linkage of any FPAH locus, other than 2q32, has not been reported to date. FPAH is inherited in an autosomal dominant manner with incomplete penetrance. Since penetrance may be as low as 10 to 20%, most individuals with the mutation never acquire the disease although they may still transmit the mutation to their progeny. In FPAH families, the siblings or children of FPAH patients or of obligate heterozygotes have an overall risk of 50% of inheriting the gene, with a 20% penetration, yielding an estimated risk of 10% of acquiring the disease. The age of onset of FPAH is broad, ranging from 1 to 74 years. There is an unexplained tendency for FPAH to develop at earlier ages in subsequent generations, a phenomenon termed genetic anticipation. This appears to have a biological basis (yet undiscovered), rather than being the result of ascertainment bias.

The process of testing and counseling individuals for genetic mutations should be performed as part of a comprehensive program that includes discussion of the risks, benefits, and limitations of the test results. For genetic testing and counseling, molecular testing for the mutation should only be performed in a clinically approved and certified molecular genetics laboratory (Clinical Laboratory Improvement Act 1988 certified).

The molecular confirmation of the mutation and testing of specific asymptomatic individuals is usually performed in FPAH families in whom a specific BMPR2 mutation has been previously identified. If the mutation creates or deletes a recognition site for a restriction enzyme, then a polymerase chain reaction test will determine whether or not individuals in that family harbor the mutation. If the individual does not have the mutation, the risk of FPAH is no different from the general population. A subject who possesses the mutation has a 10 to 20% lifetime risk of acquiring FPAH.

**Linkage Analysis**

Linkage analysis may clarify the genetic status of at-risk relatives for families in whom a specific BMPR2 mutation has not been identified. Samples from multiple family members, including at least two affected individuals from different generations, are necessary to perform linkage analysis. The accuracy of linkage analysis can be >99%, and is dependent on the location of informative genetic markers in the patient’s family and the accuracy of the clinical diagnosis of FPAH in affected family members. Linkage analysis should be used with caution unless the specific family is large enough to be genetically informative and the BMPR2 marker alleles can be shown to cosegregate with the FPAH phenotype in that family. Genetic counseling for family members at risk for FPAH is complicated due to decreased penetrance, variable age of onset, and inherent limitations of linkage studies.

**Gene Sequencing**

Mutations causing FPAH have been identified in all but 1 of 13 exons among the 130,000 bases that
comprise BMPR2. When the mutation in a specific FPAH family is not known and the specimens available from that family are insufficient to conduct linkage, sequencing of the entire coding region is possible, but requires sequencing of several thousand bases. It is informative only if a functional mutation is identified.

**Prenatal Testing**

Prenatal testing for FPAH has not been reported, but it is feasible using mutational analysis or linkage in at-risk pregnancies, if the disease-causing mutation has been identified in affected family members, or if linkage has been established in a large geneti-
cally informative family prior to prenatal testing. Prenatal testing is controversial, especially for conditions such as FPAH that do not affect intellect and have effective treatments. Differences in perspective may exist among medical professionals and families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is needed.

Genetic Testing in Families of Patients With Sporadic IPAH

Because the identification of a genetic mutation in a patient with IPAH has significant implications for all bloodline relatives, molecular testing for mutations may soon become a “standard of care.” At present, however, only a positive result is informative, since a negative test finding for mutations in a sporadic patient has limited value. The value of genetic testing in sporadic IPAH families will likely increase as additional mutations linked to familial IPAH are identified.

Hereditary hemorrhagic telangiectasia (HHT) is a condition associated with mucocutaneous telangiectases causing recurrent epistaxis and GI bleeding, and arteriovenous malformations of the pulmonary, hepatic, and cerebral circulations. Pulmonary arteriovenous malformations can cause significant right-to-left shunts leading to systemic hypoxemia, paradoxical embolism, stroke, and cerebral abscesses, and reduced pulmonary vascular resistance. However, pulmonary hypertension has also been reported to occur in some individuals with HHT. Heterogeneous defects in components of the transforming growth factor-β receptor complex, including endoglin and activin receptor-like kinase 1 (ALK1) have been implicated in the autosomal dominant vascular dysplasia of HHT. Five families with HHT were identified with coexistent probands with FPAH, each with unique ALK1 mutations. It is not known whether specific mutations are responsible for both HHT and FPAH, or whether more complex genetic and environmental interactions facilitate the development of FPAH in individuals with ALK1 mutations. The clinical role for genetic testing for ALK1 mutations in patients or families with HHT and FPAH has not yet been determined.

2. Patients with IPAH should be advised about the availability of genetic testing and counseling for their relatives. Level of evidence: expert opinion; benefit: intermediate; grade of recommendation: E/A.

Echocardiographic Screening of Asymptomatic Subjects at Risk for PAH

Few reports have evaluated echocardiography for screening asymptomatic patients with PAH, since the incidence of disease is low and Bayesian analysis would predict a large number of false-positive test results. Furthermore, health insurers may not reimburse the expense of testing “asymptomatic” individuals. Finally, whether establishing an early diagnosis of PAH (such as in a presymptomatic phase of FPAH) improves outcome is unknown, although it unquestionably has important emotional and social implications.

In some individuals, pulmonary artery pressure may be normal at rest but increase to abnormally high levels during conditions of increased blood flow such as during exercise. The significance of this response is not clear: it may reflect an early phase of the development of overt disease or may indicate a chronic, but stable pulmonary circulatory functional limitation. A false-positive result due to measurement error caused by large swings in intrathoracic pressure during exercise might also be contributory. Exercise echocardiography to detect asymptomatic gene carriers was reported to have a sensitivity of 87.5% and specificity of 100% in two large German families with FPAH, but independent confirmation of these studies is not available.

Clinical History

Presenting Symptoms

Patients with PAH generally present with a spectrum of symptoms attributable to impaired oxygen transport and reduced cardiac output. Although PAH may be asymptomatic, particularly in its early stages, exertional dyspnea is the most frequent presenting symptom, and was present in 60% of patients in the National Institutes of Health (NIH) prospective cohort study of patients with PPH. Dyspnea is eventually present in virtually all patients as the disease progresses. Fatigue, weakness, or complaints of general exertion intolerance are also common complaints. As PAH progresses, dyspnea may be present at rest. Anginal chest pain or syncope are each reported by approximately 40% of patients during the course of the disease. Since the symp-
toms of PH are nonspecific, the initial evaluation of patients with these symptoms is often appropriately directed at diagnosing or excluding more common conditions. In the absence of an identifiable explanation, however, pulmonary vascular disease should be considered as a cause for these symptoms, particularly unexplained dyspnea.

**Symptoms of Related Conditions**

Since PH may be associated with a variety of comorbid conditions, symptomatic evidence of a related illness should be considered. Orthopnea and paroxysmal nocturnal dyspnea suggest elevated pulmonary venous pressure and pulmonary congestion due to left-sided cardiac disease. Raynaud phenomenon, arthralgias, or swollen hands and other symptoms of connective tissue disease in the setting of dyspnea should raise the possibility of PAH related to connective tissue disease. A history of snoring or apnea provided by the patient’s partner warrants evaluation for sleep-disordered breathing as a potential causative or contributory factor.

**Symptoms of Disease Progression**

Leg swelling, abdominal bloating and distension, anorexia, plethora, and more profound fatigue develop as right ventricular dysfunction and tricuspid valve regurgitation (TR) evolve. A qualitative assessment of activity tolerance is useful in monitoring disease progression and response to treatment. The World Health Organization classification of functional capacity, an adaptation of the New York Heart Association (NYHA) system, has been useful in this regard (Table 1).

**Table 1—World Health Organization Classification of Functional Status of Patients With PH**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Patients with PH in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with PH 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.</td>
</tr>
<tr>
<td>III</td>
<td>Patients with PH 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.</td>
</tr>
<tr>
<td>IV</td>
<td>Patients with PH 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.</td>
</tr>
</tbody>
</table>

**Family and Personal Medical History**

Because of the recognized genetic component of PAH, inquiry into whether other family members have had symptoms or an established diagnosis of PAH or a history of connective tissue disease may lead to early recognition of clinical disease. Potential toxic exposures should be explored, such as a history of use of appetite suppressants, toxic rapeseed oil, or chemotherapeutic agents (including mitomycin-C, carmustine, etoposide, cyclophosphamide, or bleomycin). Known or suspected exposure to HIV infection should be explored. Although a history of pulmonary embolism or deep vein thrombosis in a patient with diagnosed or suspected PAH requires a meticulous search for unresolved chronic thromboembolic disease, chronic thromboembolic PH (CTEPH) may occur even in the absence of a recognized history of venous thromboembolism.

**Physical Examination**

Signs of PH on physical examination are subtle and often overlooked. Although no rigorous analysis of the sensitivity and specificity of findings on physical examination has been performed, experience suggests that the likelihood of PAH is increased when certain findings are present. For example, an accentuated pulmonary component of the second heart sound audible at the apex is noted in > 90% of patients with IPAH, reflecting increased force of pulmonary valve closure due to elevated pulmonary artery pressure. Other signs of increased pulmonary artery pressure include the following: (1) an early systolic ejection click due to sudden interruption of pulmonary valve opening, (2) a midsystolic ejection murmur caused by turbulent transvalvular pulmonary flow, (3) a palpable left parasternal lift produced by the impulse of the hypertrophied high-pressure right ventricle, (4) a right ventricular S4 gallop (audible in 38%), and (5) a prominent jugular “a” wave suggesting high right ventricular filling pressure.

Physical signs of more advanced disease include the diastolic murmur of pulmonary regurgitation and the holosystolic murmur of TR, which is audible at the lower left sternal border and augmented with inspiration. TR can also be detected by an elevated jugular venous pressure with accentuated V waves, hepatojugular reflux and a pulsatile liver. A right ventricular S3 gallop (audible in 23%), marked distension of the jugular veins, pulsatile hepatomegaly, peripheral edema (32%), and ascites are indicative of right ventricular failure. Low BP, diminished pulse pressure, and cool extremities are ominous.
signs since they indicate the presence of a markedly reduced cardiac output and peripheral vasoconstriction.

The physical examination may also provide insights into etiology. Cyanosis suggests right-to-left shunting, severely reduced cardiac output, or a marked impairment in intrapulmonary gas transfer. Cyanosis is noted in 20% of patients with IPAH. Digital clubbing is a rare finding in IPAH, and its presence should raise the possibility of congenital heart disease or pulmonary veno-occlusive disease. Rales, dullness, or decreased breath sounds point to pulmonary congestion, fibrosis, or effusion, respectively; and fine rales, accessory muscle use, wheezing, or prolonged exhalation imply pulmonary parenchymal or airway disease. Obesity, kyphoscoliosis, and enlarged tonsils represent possible causes for a hypoventilatory disorder. Scleroderma skin changes or other rashes, nail-fold capillary abnormalities, arthritis, and other stigmata are suggestive of an underlying connective tissue disorder. Peripheral venous insufficiency or obstruction warrants investigation for venous thrombosis and pulmonary thromboembolic disease.

**ECG**

PAH results in right ventricular hypertrophy and right-heart dilation. Since these processes produce ECG abnormalities, the ECG may provide a signal of hemodynamically significant PH. Right ventricular hypertrophy and right-axis deviation on ECG are seen in 87% and 79%, respectively, of patients with IPAH. ECG findings suggestive of PAH are as follows: (1) right-axis deviation; (2) a tall R wave and small S wave with R/S ratio > 1 in lead V1; (3) qR complex in lead V1; (4) rSR pattern in lead V1; (5) a large S wave and small R wave with R/S ratio < 1 in lead V3 or V6; or (6) S1, S2, S3 pattern. ST-T segment depression and inversion are often present in the right precordial leads. Right atrial enlargement is manifested as a tall P wave (≥ 2.5 mm) in leads II, III, and aVF and frontal P-axis of ≥ 75°.

The ECG, however, lacks sufficient sensitivity to serve as a screening tool for the detection of significant PAH. The sensitivities of right-axis deviation (a mean frontal plane QRS axis > 100°) and right ventricular hypertrophy (frontal plane QRS > 50, R/S-wave ratio in V1 > 1 and R wave in V1 > 0.5) were only 73% and 55%, respectively, in a population of 61 patients with IPAH or PAH due to connective tissue disease in whom the mean pulmonary artery pressure (mPAP) was > 50 mm Hg. Specificity was also low (70% for both criteria), and 8 of the 61 patients had normal ECG findings despite the presence of severe PAH. In patients with limited or diffuse scleroderma, right atrial enlargement or right ventricular hypertrophy were not observed more frequently in those with PH (defined as an echocardiographic systolic pulmonary artery pressure [sPAP] > 30 mm Hg) compared with those without PH. However, the average sPAP in the 12 patients with PH was only 43 ± 18 mm Hg (± SD), and only 2 patients had values > 50 mm Hg.

Certain features of the ECG in patients with an established diagnosis of PAH may have prognostic value. A P-wave amplitude in lead II of ≥ 0.25 mV is associated with a 2.8-fold greater risk of death over a 6-year follow-up period, and each additional 1 mm of P-wave amplitude in lead III corresponds with a 4.5-fold increased risk of death.

**Recommendation**

3. In patients with a suspicion of PAH, ECG should be performed to screen for a spectrum of cardiac anatomic and arrhythmic problems; it lacks sufficient sensitivity to serve as an effective screening tool for PAH, but contributes prognostic information in patients with known PAH. Quality of evidence: low; benefit: small/weak; strength of recommendation: C.

**Chest Radiography**

The chest radiograph (CXR) may disclose abnormal anatomic features due to the presence of PAH. Although most patients with asymptomatic PAH have normal CXR findings, the accuracy of the CXR in detecting PAH is unknown. An index has been described based on the ratio of the summed horizontal measurements of the pulmonary arteries from midline to their first divisions divided by the transverse chest diameter. All 50 patients with a sPAP < 30 mm Hg, and 10 of 100 patients with a sPAP > 45 mm Hg had an index ≤ 0.38. Additionally, the patients with high pulmonary flow due to intracardiac shunts but without PH also had an index of ≤ 0.38.

General radiographic signs that can be taken as suggestive of PH are enlarged main and hilar pulmonary arterial shadows, with concomitant attenuation of peripheral pulmonary vascular markings (“pruning”). These features were present in most IPAH patients in the NIH Registry. However, the absence of pruning should not be interpreted as excluding IPAH. Right ventricular enlargement is evidenced by impingement of the anteriorly situated right ventricular silhouette into the retrosternal clear
space on the lateral CXR. The CXR is also useful in defining coexistent conditions related to PH, such as pulmonary venous congestion (pulmonary venous hypertension, pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis), hyperinflation (COPD), or kyphosis (restrictive ventilatory disease). Common findings in CTEPH are cardiomegaly (86%), right ventricular enlargement (68%), mosaic oligemia (68%), right descending pulmonary arterial enlargement (55%), chronic volume loss (27%), atelectasis or effusion (23%), and pleural thickening (14%). Other studies report high (27%), atelectasis or effusion (23%), and pleural thickening (14%).

Once PAH is suspected based on the presenting features, screening examination, or incidental discovery during evaluation of apparently unrelated problems, further evaluation is intended to characterize the type of PH and establish its severity. The goal of this approach is to determine prognosis and establish an appropriate treatment strategy. As with assessment strategies for many diseases, this is a hierarchical process beginning with tests that are less invasive and complex but also less specific, followed by more specific, albeit more complex, tests that are performed based on need.

**Evaluation of the Patient With Suspected PAH**

sPAP is considered equal to right ventricular systolic pressure (RVSP) in the absence of pulmonic valve stenosis or outflow tract obstruction. An estimate of RVSP can be obtained using Doppler echocardiography by calculating the right ventricular/right atrial pressure (RAP) gradient during systole, approximated by the modified Bernoulli equation as $4v^2$, in which $v$ is the velocity of the tricuspid jet in meters per second. RVSP is derived by adding the RAP to the gradient ($RVSP = 4v^2 + RAP$). The RAP that is used in this calculation is either a standardized value or an estimated value based on echocardiographic characteristics of the inferior vena cava, or the vertical height of the jugular venous pulse on physical examination.

The reliability of Doppler echocardiographic techniques in detecting and quantifying PAH is pivotal in evaluating its usefulness as a diagnostic procedure and especially as a screening tool. A number of published studies have addressed this issue.

TR jets are analyzable in 39% to 86% of patients. At least 10 studies have reported correlation coefficients between RVSP estimated from TR and hemodynamic right-heart catheterization values. One study of 51 patients found a relatively poor correlation between these two measurements ($r = 0.31$). Nine studies reported statistically significant correlations ($r = 0.53, 0.57, 0.95, 0.78, 0.85, 0.76, 0.93, 0.90, and 0.89$, respectively). These studies incorporated a total of 500 patients with IPAH and PAH due to connective tissue disease, portopulmonary hypertension, and congenital heart disease, but also included patients with normal or minimally abnormal pulmonary pressures.

Pulmonary diastolic pressure can also be estimated by Doppler echocardiography and correlates well with invasive measurements ($r = 0.92$). The severity of PH has also been assessed from right ventricular outflow patterns and time intervals. Parameters include pre-ejection period, acceleration and deceleration, relaxation, and contraction times. These may be especially useful when TR and pulmonic valve regurgitation jets are not present or quantifiable.

Seven studies primarily including PAH due to congenital heart disease (n = 300) describe the estimation of pulmonary arterial pressures using right ventricular outflow patterns or time intervals using M-mode or Doppler echocardiography. Three of these studies were performed predominantly in pediatric populations. Six of the seven studies found correlations as high as $r = 0.92$ using a variety of time intervals including acceleration, right ventricular ejection time (RVET), and pre-ejection period, alone or in combinations. Deceleration time (DT) of the transmural flow velocity may be influenced by PH, but this may be complicated in the setting of left-heart disease. Total pulmonary resistance correlated with DT ($r = -0.70$) in one study of 26 patients in whom left-heart disease was excluded. It was the only independently significant variable in a multivariate analysis; DT was also correlated with the left ventricular deformity index ($r = -0.74$).

Although many studies have reported correlation coefficients as the measure of accuracy, another
relevant analysis is to compare the magnitude of difference between the echo estimate and the true value as measured by right-heart catheterization. In studies reporting such data, the mean differences ranged from 3 to 38 mm Hg. In one study, echocardiography underestimated \( sPAP \) by a mean of 11 mm Hg: the underestimation of \( sPAP \) was > 20 mm Hg in 31% of all patients studied. Two studies suggested that the discordance between estimated and true pulmonary artery pressure is greatest when \( sPAP \) is > 100 mm Hg.

The sensitivity and specificity of Doppler echocardiography estimated \( sPAP \) in predicting PAH ranges from 0.79 to 1, and 0.6 to 0.98, respectively. Most of these studies were relatively small, however, with the number of subjects ranging from 17 to 55. Table 1 shows RVSP estimations using TR velocity, summarizing an evidence-based comprehensive review of 11 studies that compared echocardiographically estimated RVSP to pulmonary artery pressure measured directly by invasive catheterization techniques. All but one of these studies showed a statistically significant correlation between estimated and directly measured \( sPAP \).

Some patients with pulmonary vascular disease manifest PH only with activity, requiring assessment of pulmonary hemodynamics during exercise to establish this diagnosis. Several parameters in the resting Doppler echocardiogram (particularly TR velocity and right ventricular outflow tract velocity time integral at peak velocity) have been reported to distinguish exercise PH from normal PH in 96% of cases.

The probability of PH can be predicted in certain populations by Doppler echocardiographic criteria. In children with congenital heart disease who are assessed while receiving mechanical ventilation, right ventricular outflow mean acceleration, maximal deceleration, and rate-corrected pre-ejection period predicted the presence of PH (defined in that study as a mPAP ≥ 20 mm Hg and/or \( sPAP \) ≥ 30 mm Hg) with 91% accuracy when incorporated into a discriminant function. Among patients undergoing evaluation for orthotopic liver transplantation, the presence of a Doppler echocardiography-estimated \( sPAP \) > 40 mm Hg had a sensitivity of 63% and specificity of 98% for identifying patients with PH at right-heart catheterization (defined as a mPAP > 25 mm Hg with a normal pulmonary capillary wedge pressure, or an elevated pulmonary vascular resistance).

The yield of screening examinations depends not only on the sensitivity and specificity of the test employed, but also on the prevalence of disease (pretest probability) in the study population. False-positive test results will be more frequent when the prevalence of disease is lower, as in screening for presymptomatic disease in a population such as asymptomatic family members of patients with FPAH. Doppler echocardiography may underestimate \( sPAP \) in patients with severe PH, and overestimate \( sPAP \) in populations comprised mostly of subjects with normal pressures.

**Recommendations**

5. In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed as a noninvasive screening test that can detect PH, though it may be imprecise in determining actual pressures compared to invasive evaluation in a portion of patients. Quality of evidence: fair; benefit: substantial; strength of recommendation: A.

6. In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed to evaluate the level of RVSP, and to assess the presence of associated anatomic abnormalities such as right atrial enlargement, right ventricular enlargement, and pericardial effusion. Quality of evidence: expert opinion; benefit: intermediate; strength of recommendation: E/B.

7. In asymptomatic patients at high risk, Doppler echocardiography should be performed to detect elevated pulmonary arterial pressure. Quality of evidence: expert opinion; benefit: intermediate; strength of recommendation: E/B.

Risk groups warranting screening for PH include the following: patients with known genetic mutations predisposing to PH, first-degree relatives in a FPAH family, patients with scleroderma spectrum of disease, patients with portal hypertension prior to liver transplantation, and patients with congenital heart disease with systemic-to-pulmonary shunts.

**Evaluating Left Heart Disease, Systemic-to-Pulmonary Shunt, or Congenital Heart Disease as a Contributing Cause of PH**

Echocardiography provides direct evidence regarding left ventricular systolic and diastolic function and valvular function and morphology that can provide clues to causes of PH due to elevated pulmonary venous pressures. Left atrial enlargement, even in the absence of definite left ventricular dysfunction, should raise the possibility of elevated left-sided filling pressures that may contribute to pulmonary pressure elevation. Right-heart, and pos-
sibly left-heart, catheterization is required to determine the transpulmonary gradient, including ruling out left ventricular diastolic dysfunction. However, even in cases where the transpulmonary gradient is high, if the pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressures are also elevated, isolated pulmonary arteriopathy cannot be diagnosed.

Echocardiography provides the best initial and, in most cases, definitive assessment of possible congenital heart disease. The diagnosis of congenital heart disease often precedes or coincides with the discovery of PH. When PH is known or suspected in a patient without a specific causal diagnosis, an echocardiographic contrast (“bubble”) study using agitated saline solution is warranted to detect evidence of intracardiac shunting. This procedure is best suited for detecting right-to-left shunting (ie, shunt reversal). Some shunts, such as anomalous pulmonary venous return or pure left-to-right shunts, may be overlooked by contrast studies. If suspicion is high, or if a shunt is detected, transthoracic or transesophageal echocardiography may be warranted for best anatomic definition. Cardiac catheterization is required for accurate quantification of the shunt(s), as well as measurements of pulmonary arterial pressure and pulmonary vascular resistance that are necessary to assess the possibility of operative correction.

**Recommendations**

8. In patients with suspected or documented PH, Doppler echocardiography should be obtained to look for left ventricular systolic and diastolic dysfunction, left-sided chamber enlargement, or valvular heart disease. Quality of evidence: good; benefit: substantial; strength of recommendation: A.

9. In patients with suspected or documented PH, Doppler echocardiography with contrast should be obtained to look for evidence of intracardiac shunting. Quality of evidence: fair; benefit: intermediate; strength of recommendation: B.

**Evaluating Connective Tissue Disease or Other Risk Factors for PAH**

Early in the process of evaluating a patient with suspected or confirmed PH, a serologic assessment should be performed, in conjunction with appropriate observations on physical examination. Up to 40% of patients with IPAH have elevated antinuclear antibodies, and certain autoantibodies (ie, anti-Ku) have been identified in 23% of patients with IPAH.

**Scleroderma:** Although PAH has been observed in all of the connective tissue diseases, it occurs most frequently in systemic sclerosis. Eleven studies of patients with scleroderma reported a prevalence of PH, ranging from 4.9% (17 of 344 patients) to 38% (16 of 47 patients), with a mean from several studies of 16% (300 of 1,837 patients). In limited scleroderma, PH is the cause of death in up to 50% of patients who die of scleroderma-related complications. Isolated PAH is less common in diffuse scleroderma, and when present it is often seen with patients with the nucleolar antibody, anti-U3-RNP. The vasculopathy of most patients with scleroderma who acquire severe PAH is very similar to IPAH. They lack sufficient interstitial lung disease to account for the magnitude of elevation in pulmonary artery pressures. Furthermore pulmonary morphometric evidence suggests that PAH develops in these patients over a long period of time. Studies have shown that patients with scleroderma who are most likely to acquire isolated PAH (ie, in the absence of severe fibrosis) have the following characteristics: (1) long-standing limited scleroderma (CREST syndrome), (2) autoantibodies (including anti-centromere antibodies), (3) disease onset after menopause, and (4) anti-nuclear antibodies including U3RNP, B23 and Th/To, and U1RNP. Specific human leukocyte antigen associations have been noted in some, but not all, studies.

Patients with scleroderma and severe interstitial fibrosis may acquire PH, which is generally not as severe as those with PAH in the absence of fibrosis. However, there is a subgroup of patients who have a moderate amount of fibrosis and acquire PH out of proportion to the degree of fibrosis. These patients generally have an antinuclear antibody with a nucleolar pattern.

Isolated PAH in scleroderma is associated with a marked decrease in the diffusing capacity of the lung for carbon monoxide (DLCO) at the time of the diagnosis of PAH. Twenty percent of patients with limited scleroderma and an isolated decrease in DLCO acquired PAH within 5 years, and 35% of patients with a marked decrease in DLCO (<55% of predicted) will eventually acquire PAH, although only 5% of these patients acquire severe interstitial fibrosis. A case-control study compared DLCO in 105 patients with scleroderma and PAH to similar patients without PAH; patients with PAH had a very low DLCO (mean, 52% predicted) 5 years prior to the diagnosis of PAH. In contrast, the mean DLCO in control patients was >80% predicted. Fifteen patients and 20 patients with and without PAH, respectively, had serial measurements of DLCO over a 15-year period; PAH patients had a linear decrease in the DLCO, from 80% predicted 15 years before PAH to 45% predicted at the time of diagnosis of...
PAH. Measurements in control patients remained at approximately 80% predicted throughout the same time period. Other parameters such as ECG and CXR were not predictive of PAH.11,12,75,76

Elevations in pulmonary artery pressures have been noted in 5 to 40% of patients with connective tissue diseases.54 McGregor and colleagues55 observed 152 patients with serial echocardiograms; 20% of patients with sPAP > 30 mm Hg died of PAH within 2 years after the initial echocardiogram. Older men, those with a rapid rise in sPAP, or those with an initial sPAP > 60 mm Hg were at the greatest risk of dying from PAH.77 However, 65% of these patients did not have sPAP > 60 mm Hg after 3 years of follow-up. Subjects with PAH had sPAP of 34 mm Hg 4 years before acquiring severe PAH,71 compared with sPAP values averaging 29 mm Hg in the control subjects at a similar time point.

One study54 suggested that exercise echocardiography is a highly sensitive test for PAH in scleroderma, although few patients were evaluated. Morelli et al54 found that five of nine asymptomatic patients with scleroderma and a normal resting echocardiogram had a marked increase in estimated sPAP with exercise (up to 60 mm Hg), compared with no increase in estimated sPAP among the control subjects. Using continuous pulmonary artery pressure monitoring, Raeside et al78 found significant increases in pulmonary artery pressures during exercise in five patients with scleroderma. In the study of Morelli et al,54 patients with scleroderma and known PAH were found to have abnormal cardiopulmonary exercise test results, while the asymptomatic patients had normal exercise test results.

Other Connective Tissue Diseases: In mixed connective tissue disease, an overlap of scleroderma, systemic lupus erythematosus (SLE), and myositis associated with the anti-U1-RNP antibody, one long-term follow-up study found that PAH was the most common cause of death, occurring in 38% of patients.79 Elevated pulmonary artery pressures occur less frequently in SLE, rheumatoid arthritis,80,81 or polymyositis. As with PAH due to scleroderma, these patients have also had long-standing disease at the time of PAH diagnosis. Four investigations19,25,82,83 of patients with systemic lupus erythematosus reported a prevalence of PH that ranged from 4.3% (18 of 419 patients),19 to 43% (12 of 28 patients),82 with a mean of 7% (51 of 725 patients). One investigation80 of patients with rheumatoid arthritis identified PH in 21% (30 of 146 patients).

Anti-cardiolipin antibodies84,85 were associated with PAH in several series of patients with SLE, similar to the findings in some studies of CTEPH.90,97 In the study of Asherson et al,85 68% of the patients with SLE and PAH had antiphospholipid antibodies.

HIV: HIV infection is associated with an increased prevalence of PH, ranging up to 0.5%.88–91 The possibility of HIV exposure should be assessed with appropriate blood testing in all patients with unexplained PAH.

Other Associated Diseases and Abnormalities: Several epidemics of PAH have occurred over the past 30 years as a result of ingesting materials that are associated with an increased risk for PAH. Between 1967 and 1972, there was a marked increase in the incidence of PAH in Germany and Switzerland that was attributed to the widespread use of aminorex, an anorexic drug.92 The incidence of PAH markedly decreased once aminorex was withdrawn from the market. Many of the patients improved when use of the drug was discontinued. A similar rise in the incidence of PAH was observed due to the use of the fenfluramine anorexigen.93 There have been two other epidemics of a scleroderma-like illness in which PH became an acute, severe, and often fatal complication. The use of contaminated rapeseed oil in Spain in 1981 resulted in an epidemic of toxic oil syndrome, during which 20,000 people fell ill.94 PAH developed in approximately 2.5% of these patients, and 20% died. PAH as a late complication of the toxic oil syndrome did not occur. More recently, contaminated tryptophan caused the eosinophilic myalgia syndrome, which was clinically quite similar to toxic oil syndrome, including PAH as a severe complication.95

PH occurs in other diseases, such as sickle-cell disease96 and chronic liver and renal disease. Patients with sickle-cell disease often have an elevated pulmonary capillary wedge pressures even though Doppler echocardiography shows normal left ventricular systolic function. In a series of patients with end-stage renal disease, PAH was seen in 40% of 58 patients receiving hemodialysis, but not in those receiving peritoneal dialysis.97 Increased cardiac output (6.9 L/min vs 5.5 L/min) was seen in the patients with PAH, and the PAH reversed in patients who underwent kidney transplantation. Twelve investigations44,45,98–101 of patients with advanced liver disease, often undergoing evaluation for liver transplantation, reported a prevalence of PH ranging from 2% (10 of 507 patients)98 to 41% (9 of 22 patients).

Thyroid disease has also been suggested as a risk factor for PAH. Although it is unclear whether or not thyroid disease is causally related to PAH, its presence warrants further evaluation and treatment in the setting of PAH. Some other laboratory abnormalities may be present in PAH that, while not
indicative of coexistent diseases, may provide additional prognostic information (these are discussed in more detail in the “Prognosis” section of this Guideline). For example, uric acid levels are often elevated and correlate with mean RAP and mortality, and levels of brain natriuretic peptide, indicative of right ventricular pressure overload, correlate with both severity of right ventricular dysfunction and mortality.

**Recommendation**

10. **In patients with unexplained PAH, testing for connective tissue disease and HIV infection should be performed.** Quality of evidence: expert opinion; benefit: intermediate; strength of recommendation: E/A.

*Evaluating Thromboembolic Disease as an Etiology of PAH*

CTEPH is a potentially curable condition that should be considered in all patients with unexplained PH. Ventilation-perfusion (V/Q) lung scans of patients with CTEPH generally show one or more segmental-sized or larger mismatched perfusion defects. A normal V/Q scan makes CTEPH unlikely to be the cause of PAH. In three studies, V/Q scanning showed sensitivity of 90 to 100% with specificity of 94 to 100% in differentiating between IPAH and CTEPH. A retrospective review of V/Q scans among patients with angiographically or biopsy-confirmed IPAH found that none had a high-probability V/Q scan, and only 1 of 15 had any evidence of V/Q mismatch (intermediate probability of pulmonary embolism). Patchy, nonsegmental diffuse defects are less specific, but may be associated with thromboembolic disease. Perfusion scans tend to correlate poorly with the severity of obstruction, and to underestimate the degree of severity of large-vessel obstruction in CTEPH. Although negative scan results are highly specific for absence of thromboembolism, false-positive scan results may occur with pulmonary artery sarcoma, large-vessel pulmonary vasculitis, extrinsic vascular compression, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis.

A spectrum of abnormalities on CT scanning have been described in patients with CTEPH, including right ventricular enlargement, dilated central pulmonary arteries, 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. These are nonspecific findings, however, and their absence does not exclude the presence of surgically accessible disease (see the article on surgical treatment).

CT may have utility beyond addressing the simple question of whether or not thromboembolism is present. In patients with unilateral perfusion defects, CT may suggest alternative diagnoses, such as sarcoma, vasculitis, malignancy, and mediastinal fibrosis. CT may also be useful in evaluating the pulmonary parenchyma in patients with CTEPH and coexistent obstructive or restrictive lung disease, and in determining the extent of small-vessel involvement and likelihood of improvement after thromboendarterectomy.

CT scanning measurements that correlate with severity of PAH include the cross-sectional area of the pulmonary artery, the diameter of the main pulmonary artery, the ratio of the diameter of the artery to the bronchus, the ratio of the diameter of the pulmonary artery to the pulmonary vein, and the ratio of the main pulmonary artery to the aortic diameter, and the presence of pericardial thickening or effusion. Although such observations may be useful in noninvasively adding weight to a diagnosis of PH and an assessment of severity, they do not replace Doppler echocardiography or invasive measurements in the diagnostic scheme for PAH.

CT scanning may be useful in exploring potential etiologic factors and discriminating between PAH conditions. For example, a ground-glass, mosaic attenuation pattern in the lower lobes is suggestive of pulmonary veno-occlusive disease.

MRI techniques can delineate anatomic abnormalities of the pulmonary arteries, including the presence of chronic thromboemboli. In one report, the MRI diagnosis of chronic pulmonary thromboembolism matched the V/Q diagnosis in 92% of cases. Preliminary evidence suggests that contrast-enhanced, three-dimensional magnetic resonance angiography may permit the detection of central chronic thromboembolic material, and may be equivalent to digital angiography to the level of the segmental arteries.

MRI is also able to noninvasively visualize right ventricular chamber size, shape, and volume; myocardial thickness and mass; and the presence of fat or edema. Abnormalities in these parameters may provide noninvasive clues to the presence of PH: mPAP correlates linearly with MRI-measured right ventricular wall thickness, inferior vena cava diameter, and main pulmonary artery diameter. MRI-measured RVSP and right ventricular diastolic volume are significantly increased and left ventricular end-diastolic volume are decreased in patients with IPAH. Right ventricular mass in patients with IPAH correlates with mPAP (r = 0.75). MRI also
can yield an mPAP estimate based on regression analysis of the measured dimensions of the main pulmonary artery and mid-descending thoracic aorta: mPAP = 24 × main pulmonary artery/aorta dimension + 3.7 (r = 0.7, p < 0.01).136 Velocity-encoded cine MRI stroke volume measurement has demonstrated a high correlation (r = 0.90) with that obtained by thermodilution techniques, and a ratio of MRI-measured maximal change of pulmonary inflow rate during ejection over acceleration volume correlates with pulmonary vascular resistance (r = 0.89).137 Since right ventricular pressure overload and enlargement affect left-heart filling and function, it is not surprising that MRI indices of left-heart structure and function also correlate with the severity of PAH. For example, pulmonary artery pressures are correlated with MRI-derived left ventricular end-diastolic volume, left ventricular stroke volume, and acceleration time/ejection time.138

Doppler echocardiography can also provide information that may help differentiate between CTEPH and IPAH. In a retrospective, unblinded study139 of 35 patients known to have either CTEPH (19 patients) or IPAH (16 patients), Doppler echocardiography-derived pulmonary pulse pressure normalized by sPAP or mPAP separated these two groups with a sensitivity of 0.95 and specificity of 1.00. Cutoff values were 0.77 and 1.35 for pulse pressure/mean pressure, respectively.

At present, pulmonary angiography remains the diagnostic procedure of choice for the evaluation of suspected CTEPH. Accordingly, a clinical suspicion of CTEPH based on V/Q scan results warrants pulmonary angiography for definitive diagnosis, even when the CT or MRI fails to demonstrate evidence of CTEPH.

**Recommendations**

11. In patients with PAH, V/Q scanning should be performed to rule out CTEPH; a normal scan effectively excludes a diagnosis of CTEPH. Quality of evidence: low; benefit: substantial; strength of recommendation: B.

12. In patients with PAH, contrast-enhanced CT or MRI should not be used to exclude the diagnosis of CTEPH. Quality of evidence: low; benefit: negative; strength of recommendation: D.

13. In patients with PAH and a V/Q scan suggestive of CTEPH, pulmonary angiography is required for accurate diagnosis and best anatomic definition to assess operability. Quality of evidence: expert opinion; benefit: substantial; strength of recommendation: E/A.

**Evaluating Hypoxic Lung, Ventilatory, or Parenchymal Disease as a Cause of PH**

Pulmonary function testing is a necessary part of the initial evaluation of all patients with PH, primarily to exclude or characterize the contribution of underlying airway or parenchymal lung disease. In IPAH and CTEPH, approximately 20% of patients have a restrictive defect, defined as a reduction in lung volumes to < 80% of predicted.5,107 In one study,140 one half of the 79 patients with IPAH had FVC values < 80%. In CTEPH, a mild-to-moderate restrictive defect is thought to be due to parenchymal scarring from prior infarcts.141,142 The DLCO is mildly reduced, to approximately 60 to 80% of predicted, in both IPAH and CTEPH.143 While there is no clear correlation between the severity of PH and the magnitude of reduction in DLCO, there is a strong correlation between DLCO and peak oxygen uptake, peak work rate, and NYHA class.140 Arterial hypoxemia is often present, and is due to V/Q mismatch and/or mixed venous hypoxemia resulting from a low cardiac output. The degree of arterial hypoxemia is often mild to moderate; when hypoxemia is severe, it is usually indicative of right-to-left intracardiac or intrapulmonary shunts.

Twenty percent of patients with systemic sclerosis have an isolated reduction in DLCO.144 When the reduction in diffusion is severe (< 45 to 55% of predicted), it may portend the future development of PH in the limited cutaneous form of the disease.57,74 In a cohort of patients with systemic sclerosis, a baseline DLCO < 45% of predicted was associated with a cumulative probability of acquiring PH (defined as Doppler echocardiographic sPAP > 40 mm Hg) during 15 years of follow-up of 0.75, compared to 0.48 in patients with less severe reductions of DLCO.56 Among patients with systemic sclerosis, DLCO correlates inversely (r = 0.60) with invasively measured sPAP.22 As noted previously, a fall in DLCO in a patient with scleroderma and normal lung volumes is suggestive of the early development of PAH.

Patients with CTEPH often have a widened alveolar-arterial gradient for oxygen on arterial blood gas analysis,108 due to similar mechanisms present in IPAH. In all forms of PAH, desaturation during exercise is primarily related to the inability of the right ventricle to augment cardiac output, resulting in further depression of mixed venous oxygen saturation. On occasion, right-to-left shunting through a
patent foramen ovale during exercise may also contribute to desaturation in PAH.

An assessment of the adequacy of oxygenation is warranted in PAH, even when resting oxygen saturation is unremarkable. Measurement of oxygen saturation during exercise may disclose desaturation that may be attenuated by supplemental oxygen therapy. Nocturnal oximetry may disclose sleep-disordered breathing with repeated episodes of desaturation (see section on sleep-disordered breathing). Nocturnal hypoxemia occurs in >75% of patients with IPAH independent of more severe ventilatory disturbances.145

**Lung Biopsy:** Open or thorascopic lung biopsy carries a substantial risk of morbidity and mortality in the setting of PH.146 Additionally, the histopathologic findings in the small pulmonary arteries are nonspecific and may not differentiate between CTEPH, PAH due to a variety of causes, and IPAH.147 On rare occasions, however, histopathologic evaluation may establish a diagnosis of active vasculitis, granulomatous pulmonary disease, pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, interstitial lung disease, or bronchiolitis. Nevertheless, since the likelihood of altering the clinical diagnosis based on a pathologic examination is low and the risk is high, routine performance of a lung biopsy to establish a diagnosis of PAH or to determine its cause is discouraged.

**Recommendations**

14. In patients with PAH, testing of pulmonary function and arterial blood oxygenation should be performed to evaluate for the presence of lung disease. Quality of evidence: low; benefit: substantial; strength of recommendation: B.

15. In patients with systemic sclerosis, pulmonary function testing with Dlco should be performed periodically (every 6 to 12 months) to improve detection of pulmonary vascular or interstitial disease. Quality of evidence: fair; benefit: intermediate; strength of recommendation: B.

16. In patients with PAH, lung biopsy is not routinely recommended because of the risk, except under circumstances in which a specific question can only be answered by tissue examination. Quality of evidence: expert opinion; benefit: substantial; strength of recommendation: E/A.

**Assessing Severity and Prognosis of PAH**

Understanding the severity of disease is necessary to establish a prognosis and to determine the approach to therapy. Severity of PAH can be considered from several interrelated perspectives: (1) the degree of pulmonary pressure elevation; (2) the extent of end-organ damage, especially the right heart; (3) symptoms and functional limitation; and (4) markers implying a shortened survival.

**Degree of Pulmonary Pressure Elevation:** Although Doppler echocardiographic methodology may provide a proxy measurement of pulmonary hemodynamics by estimating right ventricular pressure, a more accurate value for pulmonary artery pressure obtained by right-heart catheterization is strongly advised. Right-heart catheterization also provides direct and accurate measurements of RAP, pulmonary venous pressure (pulmonary capillary wedge pressure), pulmonary blood flow, mixed venous oxygen saturation, and allows for the calculation of pulmonary vascular resistance.

Right-heart catheterization not only provides important indices of disease severity, but it also enhances the diagnostic process by excluding other etiologies such as intracardiac or extracardiac shunts and left-heart disease, and provides an assessment of the degree of right-heart dysfunction through measurement of RAP and cardiac output. It should be acknowledged that right-heart catheterization also has limitations: measurements are generally obtained only under resting conditions in the supine position, which may not be representative of hemodynamic responses to upright posture, activity, or sleep. Even under these static circumstances, measurements may vary. Prolonged measurement of pulmonary hemodynamics in a group of 12 patients with PAH found wide intrindividual spontaneous variability in pulmonary arterial pressure, by >20 mm Hg in some patients, and a mean coefficient of variability of 8% in the group.148 Nevertheless, right-heart catheterization remains the “gold standard” for pulmonary hemodynamic measurement and is a necessary component of the evaluation of PAH.

In the NIH Registry, which was performed prior to the era of effective therapies for IPAH, hemodynamic parameters were found to be predictive of survival in patients with conventional therapy.149 From these data, a formula was derived to predict survival. The probability of survival P(t) at 1, 2, or 3 years after diagnosis can be estimated as $P(t) = (H(t))^{A(x,y,z)}$, where $H(t) = (0.88 - 0.14t + 0.01t^2)$, $A(x,y,z) = e^{(0.007325x + 0.00526y - 0.3273z)}$, $t =$ years, $x =$ mean RAP (millimeters mercury), $y =$ mean cardiac index (liters per minute per meter squared). Survival determinants, including the impact of current therapies, are discussed in greater detail elsewhere in this Guideline.
Recommendations

17. In patients with suspected PH, right-heart catheterization is required to confirm the presence of PH, establish the specific diagnosis, and determine the severity of PH. Quality of evidence: good; benefit: substantial; strength of recommendation: A.

18. In patients with suspected PH, right-heart catheterization is required to guide therapy. Quality of evidence: low; benefit: substantial; strength of recommendation: B.

Extent of End-Organ Consequences: Right ventricular dysfunction is the eventual consequence of the pressure overload imposed by pulmonary vascular disease. Right ventricular hypertrophy is the adaptive result of pressure overload, and right atrial and right ventricular enlargement are the morphologic manifestations of progressive decompensation. These abnormalities are most efficiently assessed qualitatively or semiquantitatively by echocardiography. Other imaging techniques, such as CT or MRI scans, may add additional quantitative data, but their incremental clinical value has not been reported.

Right ventricular contractility is difficult to measure because it is difficult to apply geometric assumptions to the shape of this chamber during the cardiac cycle. Indirect indices of right ventricular function, however, have been investigated. Continuous wave Doppler echocardiographic measurement of TR jet velocity has been suggested as a means of noninvasively evaluating contractility (rate of rise in pressure) of the right ventricle. However, the rate of rise in right ventricular pressure varies with the level of PH, and is not an independent marker of right ventricular function. An alternative index of right ventricular function is the right ventricular index of myocardial performance. The total duration of systole, including right ventricular pre-ejection period, RVET, and isovolumetric relaxation period, is measured as the interval between cessation and reappearance of tricuspid diastolic flow detected by Doppler echocardiography. After subtraction of RVET, which is easily obtained from pulmonary artery flow velocity curve, the remaining time represents the total duration of systolic isovolumetric contraction time and diastolic isovolumetric relaxation time of the right ventricle. The index of (isovolumetric contraction time + isovolumetric relaxation time)/RVET reflects global right ventricular function, and is not substantially affected by heart rate, right ventricular pressure, right ventricular dilation, or TR. Additionally, this index correlates with symptoms and survival in patients with IPAH.

In one small study of 26 patients with IPAH, a short pulmonary flow acceleration time (< 62 ms) correlated with poor survival, while but peak TR velocity did not. Coronary sinus dilatation was found to correlate with RAP and size (but not with pulmonary artery pressure) among the 35 patients (81%) with CTEPH or IPAH in whom the coronary sinus could be visualized.

Symptoms and Functional Limitation: Symptomatic classification correlates with survival. Among untreated patients, NYHA class III or IV status was associated with a mean survival of 2.5 years and 6 months, respectively; NYHA class I or II status was associated with a mean survival of 5 years. The functional response to long-term treatment with IV epoprostenol sodium is also predictive of survival. Patients with NYHA class III or IV symptoms after 3 months of treatment have a 33% probability of survival for 3 years, whereas NYHA class I and II symptoms are associated with 88% probability of survival over the same period. Patients who are NYHA class III or IV after 17 ± 15 months of treatment (± SD) have a 35% and 0% probability of 3 year survival, respectively, compared to 89% for NYHA class I or II patients. Functional classification of patients with PH is now based on a modification of the NYHA system, and takes syncope into account as a marker of functional status. This classification was recommended by a PH task force of the World Health Organization in 1998, and is shown in Table 1.

Formal assessment of exercise capacity is an integral part of the evaluation of PH. The most commonly used exercise tests are the 6-min walk test; a standard treadmill exercise test utilizing a low-intensity, graduated exercise protocol; cardiopulmonary exercise testing with gas exchange measurement; exercise testing in conjunction with noninvasive Doppler echocardiographic assessment of pulmonary artery pressure; and exercise testing in conjunction with right-heart catheterization.

The 6-min walk test was developed as an objective measure of exercise capacity in patients with congestive heart failure, and was modified from prior protocols used in patients with obstructive pulmonary disease. It proved to be reproducible, and correlated with other measures of functional status. The test was subsequently applied to the evaluation of patients with IPAH, and has been used as a primary end point in a number of clinical trials. An additional observation derived from these studies was that 6-min walk performance was predictive of...
survival in patients with IPAH. The 6-min walk distance in IPAH correlates inversely with NYHA functional status severity and pulmonary vascular resistance, and directly with baseline cardiac output, peak exercise oxygen consumption (VO₂), peak oxygen pulse, and the minute ventilation (VE)/carbon dioxide output (VCO₂) slope. In a multivariate analysis that included clinical, echocardiographic, and neurohumoral factors, the 6-min walk was the only independent predictor of survival in 43 patients with IPAH followed up for 21 ± 16 months (± SD). In addition, a > 10% fall in arterial oxygen saturation during 6-min walk testing predicted a nearly threefold higher mortality over a median 26 months of follow-up.

In specialized centers, cardiopulmonary exercise testing using cycle ergometry can be performed safely in adults and children with PH. In patients with IPAH, the results of cardiopulmonary exercise testing are abnormal in a pattern that helps explain the mechanism by which PAH produces symptoms. Reductions in peak VO₂, peak work rate, the ratio of VO₂ increase to work rate increase, anaerobic threshold, peak oxygen pulse, and increased VE/VCO₂ slope are typically seen and indicate that the exercise limitations in IPAH are due to both V/Q mismatching, and an inability to adequately increase stroke volume and cardiac output resulting in lactic acidosis at a low work rate and arterial hypoxemia. The VE/VCO₂ slope promptly decreases following thromboendarterectomy for CTEPH, reflecting improved ventilatory efficiency. In contrast, exercise capacity (peak VO₂) improves gradually over a longer period, reflecting ongoing peripheral adaptation.

Exercise and ambulatory invasive pulmonary hemodynamic measurements have been performed in patients with suspected PH and demonstrate marked pulmonary arterial pressure increases during exercise. However, the value of exercise hemodynamic studies in predicting outcomes remains uncertain.

Exercise noninvasive hemodynamic assessment using Doppler echocardiography has been utilized to evaluate pulmonary artery pressure responses in different patient populations with varying degrees of baseline PAH. In healthy men, TR velocity increases from an average of 1.72 m/s at baseline to a peak of 2.46 m/s at midlevel 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. As with invasive exercise studies, the degree of abnormal pressure response to exercise that may be reliably considered a cause of symptoms or have prognostic significance is not well established.

** Recommendation **

19. In patients with PAH, serial determinations of functional class and exercise capacity assessed by the 6-min walk test provide benchmarks for disease severity, response to therapy, and progression. Quality of evidence: good; benefit: intermediate; strength of recommendation: A.

** Summary **

A high level of suspicion is of paramount importance for the diagnosis of PAH, regardless of the underlying cause. Once suspected, a methodical workup using commonly employed diagnostic interventions allows both confirmation of the presence of PAH and elucidation of its etiology. Clarification of etiology is necessary to ensure that the proper therapeutic interventions are implemented. A diagnostic algorithm that is accepted among experienced centers (Fig 1) can guide the evaluation of PAH. Like all guidelines, the algorithm may be modified according to specific clinical circumstances. Most patients receive a diagnosis as a result of evaluation for symptoms, while some diagnoses are made during screening of asymptomatic populations at risk. Future developments may include refinement in noninvasive diagnostic studies, including imaging techniques and biomarkers that are not only specific for the presence of PAH but sensitive to changes in the clinical status and may therefore also be useful as markers of severity.

** Summary of Recommendations **

1. Genetic testing and professional genetic counseling should be offered to relatives of patients with FPAH. Level of evidence: expert opinion; benefit: intermediate; grade of recommendation: E/A.

2. Patients with IPAH should be advised about the availability of genetic testing and counseling for their relatives. Level of evidence: expert opinion; benefit: intermediate; grade of recommendation: E/A.

3. In patients with a suspicion of PAH, ECG should be performed to screen for a spectrum of cardiac anatomic and arrhythmic problems; it lacks sufficient sensitivity to serve as an effective screening tool for PAH, but contributes prognostic information in patients with known PAH. Quality of evidence: low; benefit: small/weak; strength of recommendation: C.
4. In patients with a suspicion of PAH, a CXR should be obtained to reveal features supportive of a diagnosis of PAH and to lead to diagnoses of underlying diseases. Quality of evidence: low; benefit: intermediate; strength of recommendation: C.

5. In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed as a noninvasive screening test that can detect PH, though it may be imprecise in determining actual pressures compared to invasive evaluation in a portion of patients. Quality of evidence: fair; benefit: substantial; strength of recommendation: E/B.

6. In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed to evaluate the level of right ventricular systolic pressure and to assess the presence of associated anatomic abnormalities such as right atrial enlargement, right ventricular enlargement, and pericardial effusion. Quality of evidence: expert opinion; benefit: intermediate; strength of recommendation: E/B.

7. In asymptomatic patients at high risk, Doppler echocardiography should be performed to detect elevated pulmonary arterial pressure. Quality of evidence: expert opinion; benefit: intermediate; strength of recommendation: E/B.

8. In patients with suspected or documented PH, Doppler echocardiography should be performed to look for left ventricular systolic and diastolic dysfunction, left-sided chamber enlargement, or valvular heart disease. Quality of evidence: good; benefit: substantial; strength of recommendation: A.

9. In patients with suspected or documented PH, Doppler echocardiography with contrast should be obtained to look for evidence of intracardiac shunting. Quality of evidence: fair; benefit: intermediate; strength of recommendation: B.

10. In patients with unexplained PAH, testing for connective tissue disease and HIV infection should be performed. Quality of evidence: expert opinion; benefit: intermediate; strength of recommendation: E/A.

11. In patients with PAH, V/Q scanning should be performed to rule out CTEPH; a normal scan result effectively excludes a diagnosis of CTEPH. Quality of evidence: low; benefit: substantial; strength of recommendation: B.

12. In patients with PAH, contrast-enhanced CT or MRI should not be used to exclude the diagnosis of CTEPH. Quality of evidence: low; benefit: negative; strength of recommendation: D.

13. In patients with PAH and a V/Q scan suggestive of CTEPH, pulmonary angiography is required for accurate diagnosis and best anatomic definition to assess operability. Quality of evidence: expert opinion; benefit: substantial; strength of recommendation: E/A.

14. In patients with PAH, testing of pulmonary function and arterial blood oxygenation should be performed to evaluate for the presence of lung disease. Quality of evidence: low; benefit: substantial; strength of recommendation: B.

15. In patients with systemic sclerosis, pulmonary function testing with DLCO should be performed periodically (every 6 to 12 months) to improve detection of pulmonary vascular or interstitial disease. Quality of evidence: fair; benefit: intermediate; strength of recommendation: B.

16. In patients with PAH, lung biopsy is not routinely recommended because of the risk, except under circumstances in which a specific question can only be answered by tissue examination. Quality of evidence: expert opinion; benefit: substantial; strength of recommendation: E/A.

17. In patients with suspected PH, right-heart catheterization is required to confirm the presence of PH, establish the specific diagnosis, and determine the severity of PH. Quality of evidence: good; benefit: substantial; strength of recommendation: A.

18. In patients with suspected PH, right-heart catheterization is required to guide therapy. Quality of evidence: low; benefit: substantial; strength of recommendation: B.

19. In patients with PAH, serial determinations of functional class and exercise capacity assessed by the 6-min walk test provide benchmarks for disease severity, response to therapy, and progression. Quality of evidence: good; benefit: intermediate; strength of recommendation: A.

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