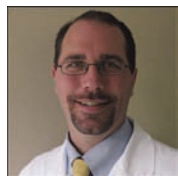


Screening for Pulmonary Arterial Hypertension



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Screening for disease before the arrival of symptoms is an intuitive cornerstone of preventive medicine and good clinical practice in many cases. However, screening is not appropriate for all conditions. Disease, test, and treatment should all be considered when developing a rational approach to screening.¹⁻⁴ Specifically, screening may be warranted if the target disease has significant morbidity and mortality. Testing in specific populations should be able to detect early disease, have relatively low risk, and a low rate of pseudo-disease detection (including both false positive results and true disease which naturally regresses). Lastly, treatments should be more effective if employed early.^{5,6} This article reviews the available literature addressing these key aspects of screening for pulmonary arterial hypertension (PAH).

MORBIDITY AND MORTALITY IN PAH

Morbidity and mortality related to PAH are improving. The Patient Registry for the Characterization of Primary Pulmonary Hypertension (National Institutes of Health [NIH] Registry), which enrolled participants between 1981 and 1985, reported a 68%, 48%, and 34% 1-, 3-, and 5-year survival respectively.^{7,8} The recent Spanish pulmonary hypertension registry (REHAP) reported improved 1-, 3-, and 5-year survival of 87%, 75%, and 65% respectively.^{9,10} The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) reported a 1-year survival of 91%.^{11,12} Some of this improvement is likely attributable to variability in PAH etiologies included in the registries and the proliferation of echocardiography, which may contribute to a lead-time bias and improved detection of indolent disease.^{13,14} Despite these potentially confounding factors, the magnitude of improvement in long-term observational study and meta-analysis of short-term results¹⁵⁻¹⁷ suggests that mortality over the last 2 decades is likely improving in the setting of current therapies.

While outcomes may be improving, these recent studies continue to highlight the high morbidity and mortality of PAH.

In addition to the individual burden of disease, PAH has a high societal cost. A conservative estimate of costs related to pulmonary hypertension suggested that patients with PAH incur charges 4 times higher per month than age-matched controls. Of these charges, nearly half of the attributable cost was related to inpatient hospitalization.^{18,19} Effective screening and treatment of PAH may benefit both the patient and community through improved survival and decreased hospitalization.

EARLY DETECTION OF PULMONARY HYPERTENSION

The classic paradigm of screening is to detect early disease in an at-risk population. This forms the bedrock of screening in diseases such as colon cancer and cervical cancer where the goal is to detect the predisease state.^{20,21} Detection of early PAH through measurement of pulmonary arterial pressure is limited by the large flow volume reserve of the pulmonary vascular bed. More than half of the cross-sectional area of the pulmonary arterial tree can be occluded before a clinically evident rise in pulmonary artery pressures is detectable.^{22,23} This suggests that the current World Health Organization (WHO) hemodynamic PAH definition actually describes advanced disease.^{24,25}

Despite the absence of a clearly defined

and detectable preclinical state that reliably progresses to PAH, earlier diagnosis may be feasible. The NIH Registry identified a median time from symptom onset to right heart catheterization of 1.3 years.³⁶ This improved marginally in the REVEAL cohort to 1.1 years³⁷; however, 21.1% of patients had a delay in PAH diagnosis of greater than 2 years from the first PAH-attributable symptom.³⁸ These reports suggest that improved detection with an aggressive screening protocol may shorten diagnosis delays by 1-2 years for many individuals.

Chemical or exercise stress-testing is able to detect subclinical coronary artery disease and a similar paradigm has been considered in PAH.²⁶⁻²⁸ Characteristic PAH anomalies during cardiopulmonary exercise testing (CPET) include decreased ventilatory efficiency, desaturation, reduced end-tidal carbon dioxide, blunted increase in stroke volume/oxygen pulse, and a low anaerobic threshold. These changes can reliably differentiate PAH patients from subjects without elevated pulmonary pressures and can potentially refine prognosis in patients with known pulmonary hypertension.²⁹⁻³¹

Exercise-induced pulmonary hypertension (EIPAH) in patients without resting PAH has been advocated as an early form of PAH. In EIPAH an individual has a resting pulmonary pressure that fails to meet criteria for PAH, but with exercise pulmonary pressures rise inappropriately. EIPAH was formerly defined as a mean pulmonary arterial pressure of greater than 30 mm Hg with exercise, but this

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definition was abandoned and a formal cut-point is not currently codified.³² In support of EIPAH as early disease, patients with EIPAH have a 6-minute walk distance, pulmonary vascular resistance, cardiac output, and maximal oxygen uptake that are intermediate between those of normal patients and patients with resting PAH.^{33,34} Despite this, 2 factors limit the clinical adoption of EIPAH as an early form of PAH. First, the rise in pulmonary pressures during exercise appears to increase with age, and there are no established reference ranges for abnormal pulmonary arterial pressures during exercise.³⁵ Second, descriptions of the natural history of EIPAH are lacking. Before EIPAH could be used effectively as a tool for early detection, the likelihood of asymptomatic or minimally symptomatic individuals with EIPAH to progress to PAH would need to be determined.

Alternatively, genetic screening represents a mechanism for detecting individuals with increased risk to develop PAH. Bone morphogenetic protein receptor type II (BMPR2) mutations have been reported in 6%-40% of patients diagnosed with idiopathic PAH and in >70% of patients diagnosed with familial PAH.¹⁵ PAH-associated BMPR2 mutations, however, have a modest penetrance of 20%. While patients with these genotypes certainly represent an at-risk population, identification of a mutation is insufficient to reliably diagnose future PAH, as it would result in an 80% false positive rate.¹⁵

Although right heart catheterization is required to definitively diagnose PAH, transthoracic echocardiography with Doppler is the currently accepted screening test for PAH.³⁹ It is important to recognize the limitations of transthoracic echocardiography, including the potential for inaccurate estimates of pulmonary arterial pressure and misclassification of borderline cases.⁴⁰ Despite these limitations, there currently is not an alternative test with a better balance of cost, availability, operating characteristics, and risk profile. Alternative screening tests that have been considered but are less sensitive or specific than echocardiography include brain-natriuretic peptide, forced vital capacity/diffusing lung capacity, and CPET. While studies looking at combinations of

tests are lacking, combinations may improve predictive value of screening when considered in addition to echocardiography.⁴¹

EARLY INTERVENTION IN PULMONARY HYPERTENSION

While survival in the current era of targeted PAH therapy appears to have improved, the importance of timing in therapy initiation is less well established. WHO functional class is thought to worsen over time as disease progresses and is recognized as a predictor of prognosis in PAH.^{12,18,42-44} Consensus guidelines by the European Respiratory Society and others have targeted WHO class II disease as a therapy goal believed to lead to improved prognosis.⁴⁵ This target is rooted in the observations that WHO class I/II tends to be associated with improved survival, PAH therapy improves WHO

functional class, and patients on therapy whose functional class improves tend to have a survival advantage.^{46,47} These associations may have several limitations. Lead-time bias is likely present, in which earlier diagnosis provides the impression of improved survival despite negligible impact on the natural history of the disease. In addition, the association between improvement in WHO functional class and survival following treatment may reflect the heterogeneity of underlying disease rather than efficacy of treatment, similar to the prognostic value of a vasodilator challenge.⁴⁸ These associations do not provide solid evidence regarding the proper timing of treatment in PAH.

Improved prognosis with early rather than late therapy is crucial to advocating for screening over symptom-directed diagnosis and treatment (Figure 1). Two studies have specifically addressed the

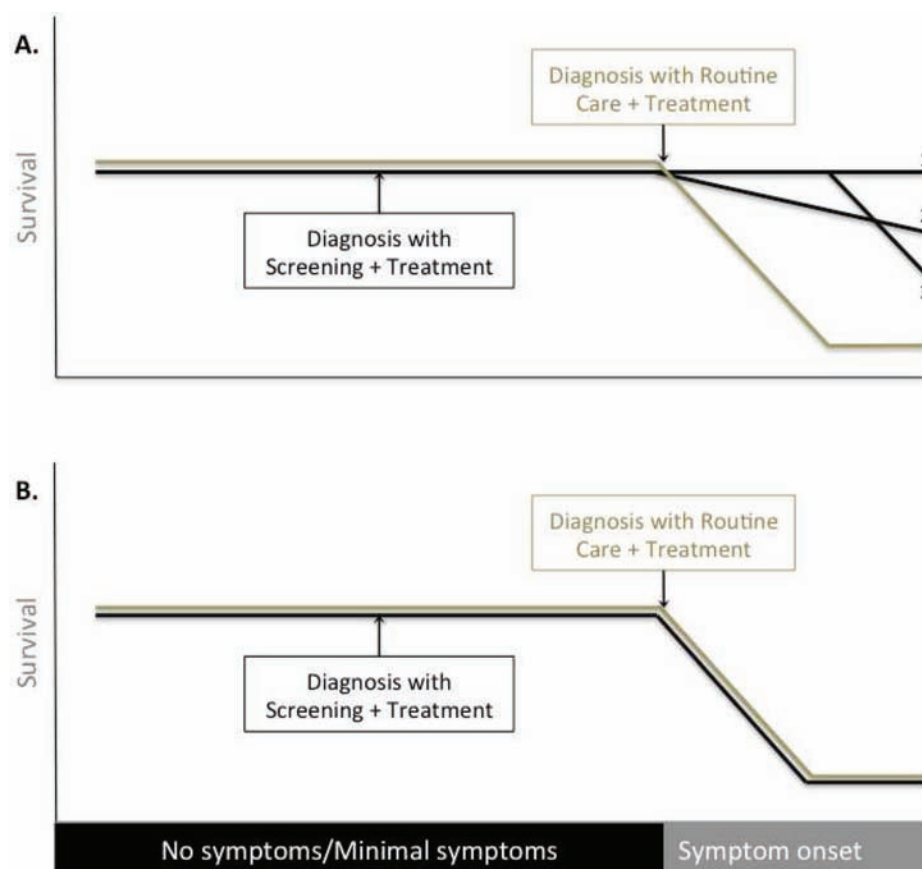


Figure 1: Potential effects of screening on disease course. (A) Effective screening where earlier detection and treatment can: 1, prevent disease; 2, change the rate of decline; 3, delay disease onset. (B) Ineffective screening program where earlier detection and earlier treatment have no advantage over detection with routine care and treatment.

Table 1: Positive and Negative Predictive Value of Doppler-Echocardiography* Using Published Test Characteristics for the Detection of Pulmonary Hypertension Stratified by Prevalence of Disease in the Screened Population

Population	Test Characteristics (%)		Positive/Negative Predictive Value (%)			
			For prevalence of			
	Sensitivity	Specificity	1%	5%	10%	20%
Meta-analysis ⁵⁹	83	72	3/100	13/99	25/97	43/94
Cardiac disease ¹	89	46	2/100	8/99	15/97	29/94
Idiopathic pulmonary fibrosis ⁵	58	87	4/100	19/98	33/95	53/89
Emphysema ⁷	60	74	2/99	11/97	20/94	37/88
Liver disease ⁹	97	77	4/100	18/100	32/100	51/99

*The systolic pulmonary artery pressure cutoff on echocardiogram was 32-50 mm Hg in the meta-analysis, 40 mm Hg in cardiac disease/idiopathic pulmonary fibrosis/emphysema, and 50 mm Hg in liver disease.

differential impact of early vs late therapy on the natural history of PAH. One study actively screened systemic sclerosis patients and found that active screening and earlier treatment were associated with improved survival.⁴⁹ This does not compellingly make the case for screening and early treatment. As the authors acknowledge, the screened cohort had a better WHO functional class at baseline and improved survival could represent either lead-time bias or length-time bias (a selection bias in which otherwise undetected indolent disease skews survival in a screening program).⁴⁹

The Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Hypertension (The EARLY study) sought to minimize lead-time and length-time bias by randomizing patients with WHO class II PAH to bosentan or placebo for 6 months. The EARLY study found improved pulmonary vascular resistance, lower rates of clinical worsening, and a lack of decline in functional parameters in the bosentan group.⁵⁰ This study represents the best evidence supporting early treatment, but further information is needed. Specifically, the differential impact of early vs delayed treatment on survival and long-term disease stability is not yet known. Subjects in the EARLY study were on average greater than 2 years from diagnosis, and the range of 6-minute walk distances suggest that impairment was not trivial in many participants.

Despite the recognition that further study is needed to definitively establish the role of timing in therapeutic efficacy,

the EARLY study, observational data, and a sound pathophysiologic rationale cautiously support systematic early treatment.

HIGH-RISK POPULATIONS IN WHOM SCREENING FOR PULMONARY HYPERTENSION MAY BE APPROPRIATE

The prevalence of disease in an at-risk population that warrants screening is not fixed and should take into account the merits of early intervention and the costs and morbidity of testing. By comparison with other fatal diseases, the prevalence of disease in the target population ranges from 0.6%-1.0% in breast cancer to 2%-4% in colon and lung cancer.³ High-risk groups that warrant screening may therefore be best considered from the perspective of predictive value of the test. Predictive values require knowledge of both disease prevalence and test characteristics. Using published reports of the sensitivity and specificity of Doppler echocardiography to identify PAH, we constructed a table of predictive values based on hypothetical prevalence of disease (Table 1). In the case of mammography screening guidelines, the positive predictive value (PPV) was used to determine when screening was effective. A PPV <4% was felt inadequate to justify screening; however, a PPV of 9% was felt sufficient to justify mammography.⁵¹ To achieve a PPV >4% using echocardiography, the prevalence of PAH in the target population must be ~1%. To achieve a PPV of 9%, the prevalence of PAH in the target population should be closer to 5% (Table 1).

WHO Diagnostic Group 1 Populations at Risk for PAH

The following groups have a PAH prevalence that would justify screening by echocardiography: known carriers of a disease causing BMPR2 mutation, immediate family members of patients with familial PAH who have not undergone genetic testing, systemic sclerosis, candidates for liver transplant, and patients with hereditary hemorrhagic telangiectasia (Table 2). Patients with congenital heart disease represent a heterogeneous population based on underlying anatomy and type of repair. As such, uniform recommendations cannot be applied to this group. Other patient populations associated with PAH, including HIV and anorexigen users, appear to lack threshold levels of prevalence to recommend routine asymptomatic screening given the current test characteristics of echocardiography.

The children of patients with familial PAH and a known BMPR2 mutation have a 50% chance of having the disease gene. Genetic testing of family members may be useful to obviate future screening, as failure to find the BMPR2 mutation identified in the index patient appears to reduce the risk of PAH closer to population levels.¹⁵ A positive test, however, does not change screening recommendations over that suggested in familial PAH with unknown genetics. Patients with familial PAH who have not been tested and those with a known mutation should consider asymptomatic echocardiographic screening yearly per the American College of Cardiology Foundation (ACCF)/

Table 2: Prevalence of Pulmonary Hypertension in Possible High-Risk Screening Cohorts

High-Risk Population	Reported Prevalence of Pulmonary Hypertension
Obstructive sleep apnea ¹¹	17%-70%
Idiopathic pulmonary fibrosis ⁶⁰	>30%
BMPR2 mutation ¹³	Penetrance 20%
Hereditary hemorrhagic telangiectasia ²²	16%
First-degree relative with BMPR2 mutation or 2 relatives with PAH ^{15,17}	10%
Systemic sclerosis ¹⁸	8%-12%
Candidates for liver transplant ²⁰	4%-6%
Acute pulmonary embolus ²⁴	1%-3%
Sickle cell disease ^{26,28}	0.5%-30%
HIV infection ²⁹	0.5%
Anorexigen/stimulant use ^{42,61}	0.005%

American Heart Association (AHA) guidelines or every 3 to 5 years per a review of genetics in PAH by Austin et al.^{15,42}

Non-WHO Group 1 Populations at Risk for Pulmonary Hypertension

Among patients with acute pulmonary embolus, the subsequent prevalence of chronic thromboembolic pulmonary hypertension may justify screening based on a PPV >4%. However, a single ventilation-perfusion scan at 3 months is superior to repeated echocardiography in the long-term exclusion of chronic thromboembolic pulmonary hypertension.⁴²

The prevalence of pulmonary hypertension in patients with idiopathic pulmonary fibrosis may also meet the threshold for screening. However, while sildenafil may increase 6-minute walk distance in idiopathic pulmonary fibrosis, it has not been shown to modify the natural history of this disease and asymptomatic screening is not warranted currently.⁵² Likewise, the prevalence of pulmonary hypertension in severe chronic obstructive pulmonary disease (COPD) has been reported from 30%-70% depending on the modality of diagnosis (echocardiography or catheterization) and the severity of COPD in the studied population.^{53,54} No effective treatment exists for pulmonary hypertension in COPD and screening primarily informs prognosis, surgical risk, and transplant priority, so screening should be limited to these settings.⁵⁴

The prevalence of pulmonary hypertension associated with obstructive sleep apnea (OSA) has been reported between 17% and 70%; however, these studies largely used a mean pulmonary artery pressure definition of >20 mm Hg and were retrospective cohorts with a strong risk for a selection bias.^{11,55} OSA is relatively common and the severity of pulmonary hypertension is most often mild and stable. These observations warrant caution before advocating widespread screening.¹¹ Significant heterogeneity in reports of PAH prevalence in sickle cell disease,^{26,28} alongside the suggestion of harm with treatment argue that screening in this population is likely not warranted at this time despite current recommendations for the same.⁵⁶

Some populations with increased risk of PAH still lack threshold levels of prevalence to condone routine screening of asymptomatic patients. The use of history, physical findings, and basic clinical results to enrich the frequency of disease and target screening in lower prevalence groups warrants further study.

TIMING OF SCREENING

There is scant evidence on appropriate screening frequency. Guidelines exist which represent common-sense practical recommendations. These suggest yearly screens for PAH in patients with systemic sclerosis, although interval development of symptomatic PAH between yearly screenings has been well described and

some advocate for screening every 6 months.^{42,57,58} Echocardiography is variably recommended between 1 and 5 years in patients with a known BMPR2 mutation or untested first-degree relatives of a patient with familial PAH.^{15,42} Screening at the time of liver transplant consideration is recommended and is commonly performed on a yearly basis while listed for transplant.⁴² Yearly screens for PAH in sickle cell disease are recommended in the ACCF/AHA 2009 guidelines.⁴² Given the debate surrounding PAH in sickle cell disease that has arisen since the publication of these guidelines, this recommendation may need to be revisited.^{26,56}

CONCLUSION

The combination of disease, test, and treatment can accurately identify appropriate targets for screening. PAH clearly has the associated morbidity and mortality to be considered as a target disease for screening. While the optimal test for asymptomatic PAH is not established, systematic screening with echocardiography may decrease endemic delays in diagnosis. Definitive evidence that early treatment of PAH is superior to later treatment is limited. Preliminary work, most notably the EARLY study and a sound rationale, supports the use and further study of treatment early in the course of PAH. Based on these factors, there is moderate but not strong evidence to support routine screening for PAH in high-risk populations. Current screening recommendations suggest a role for screening in familial PAH, systemic sclerosis, candidates for liver transplantation, and patients with hereditary hemorrhagic telangiectasia.

While the balance of evidence appears to support screening and early start of therapy, ongoing research should continue to address the following questions:

- Is early treatment more efficacious than late treatment?
- What is the optimal screening interval?
- What is the natural history of EIPAH? Are there other ways of detecting disease before patients meet current PAH diagnostic criteria?

- (d) Should patients with OSA or sickle cell disease be screened?
- (e) Do combinations of imaging, functional, and lab markers improve the sensitivity and specificity of PAH detection over echocardiography alone?

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