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Screening strategies for pulmonary arterial hypertension

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KEYWORDS

Pulmonary arterial
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Diagnosis

Pulmonary arterial hypertension (PAH) is rare and, if untreated, has a median survival of 2-3 years. Pulmonary arterial hypertension may be idiopathic (IPAH) but is frequently associated with other conditions. Despite increased awareness, therapeutic advances, and improved outcomes, the time from symptom onset to diagnosis remains unchanged. The commonest symptoms of PAH (breathlessness and fatigue) are non-specific and clinical signs are usually subtle, frequently preventing early diagnosis where therapies may be more effective. The failure to improve the time to diagnosis largely reflects an inability to identify patients at increased risk of PAH using current approaches. To date, strategies to improve the time to diagnosis have focused on screening patients with a high prevalence [systemic sclerosis (10%), patients with portal hypertension assessed for liver transplantation (2-6%), carriers of mutations of the gene encoding bone morphogenetic protein receptor type II, and first-degree relatives of patients with heritable PAH]. In systemic sclerosis, screening algorithms have demonstrated that patients can be identified earlier, however, current approaches are resource intensive. Until, recently, it has not been considered possible to screen populations for rare conditions such as IPAH (prevalence 5-15/million/year). However, there is interest in the use of artificial intelligence approaches in medicine and the application of diagnostic algorithms to large health-care data sets, to identify patients at risk of rare conditions. In this article, we review current approaches and challenges in screening for PAH and explore novel population-based approaches to improve detection.

Introduction

Pulmonary arterial hypertension (PAH) is a rare, cardiopulmonary disease with insidious onset and usually rapid disease progression.^{1,2} Common symptoms of PAH, such as breathlessness and fatigue, are non-specific and patients

frequently delay seeking medical advice.³ Although disease awareness amongst healthcare professionals has improved, patients frequently experience significant delays between initial symptom onset and a confirmed PAH diagnosis.³ The time to diagnosis can be compounded in elderly patients by the presence of comorbidities.⁴⁻⁶ Consequently, many patients have advanced disease at diagnosis⁷ with 1-year mortality rates of up to 15% for patients with idiopathic, familial, or toxin- or drug-induced PAH⁸⁻¹² and up to 30% for systemic sclerosis-associated PAH (PAH-SSc).¹³

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Reducing the time to diagnosis is important. It may lessen the emotional impact of uncertainty in patients, the number of investigations performed and allow treatment at an earlier stage where therapies may be more effective.^{8,12-17} This may be achieved by systematic screening of at-risk populations.^{14,18} There are a number of tools including, clinical assessment, blood biomarkers, imaging, and exercise testing that can be utilized in screening programmes to improve the detection of PAH.^{1,19-23}

In this article, we review the rationale for screening for PAH, currently available tools and approaches, and explore the challenges of improving the detection of PAH using novel methods.

Screening strategies for pulmonary arterial hypertension

Reasons to screen for pulmonary arterial hypertension

Over the last two decades, there have been significant advances in the treatment of PAH and a more than doubling of survival^{24,25} but the time from symptom onset to diagnosis remains unchanged at around 2 years.²⁶ A recurring theme of studies is the frequent interaction with healthcare services prior to diagnosis and missed opportunities for earlier diagnosis, particularly in patients with idiopathic PAH (IPAH).²⁷ Initial PAH symptoms are non-specific and include breathlessness on exertion, fatigue, chest tightness similar to angina, palpitations, dizziness, and ankle swelling in advanced disease.¹ Patients presenting with these symptoms are often investigated for other cardiac,

pulmonary, neurological, musculoskeletal, haematological, or age-related causes during multiple consultations with primary care and specialist physicians before PAH is diagnosed particularly in its idiopathic form (Figure 1).^{1,28}

In patients with systemic sclerosis (SSc), an early-detection screening programme for the identification of patients at greatest risk of developing PAH was compared with routine clinical practice.¹⁴ The results showed that all 16 patients (100%) in the early detection cohort were alive at 1 year compared with 12 out of the 16 (75%) who were diagnosed using routine clinical practice. The importance of early detection became more relevant over time with survival rates at 3, 5, and 8 years of 81%, 73%, and 64%, respectively, in the screening cohort compared with 31%, 25%, and 17%, respectively, in the non-screened cohort.¹⁴ Despite the small patient numbers and limitations such as lead time and length-time bias, these results provide a rationale for screening at-risk patient populations and diagnosing PAH at a stage when it may be more amenable to treatment.

Definition and principles for screening in pulmonary arterial hypertension

Screening can be defined as the systematic use of a test, or tests, in at-risk individuals to identify disease before symptom onset.³⁰ However, in practice, it is frequently extended to include mildly symptomatic patients or those with early disease. Years can elapse between symptom onset and diagnosis in PAH, so there is value in considering adoption of screening approaches to improve the detection of PAH in symptomatic patients, where PAH is rarely

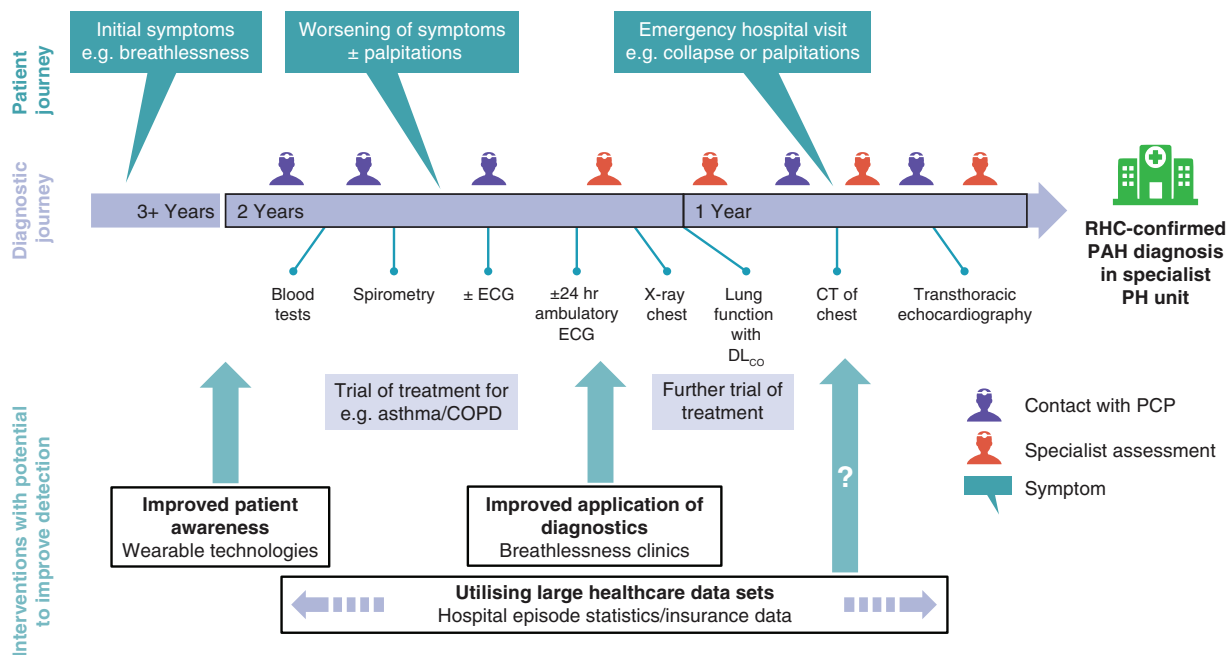


Figure 1 Schematic representation of a typical patient journey prior to pulmonary arterial hypertension diagnosis. Patients frequently delay seeking medical advice following the onset of symptoms and have multiple interactions with primary care and specialist physicians once they do.²⁷⁻²⁹ Typical investigations and their timing are shown and the potential for deployment of interventions to improve detection are indicated by light blue arrows. COPD, chronic obstructive pulmonary disorder; CT, computed tomography; DL_{co}, pulmonary diffusing capacity for carbon monoxide; ECG, electrocardiogram; PAH, pulmonary arterial hypertension; PCP, primary care physician; PH, pulmonary hypertension; RHC, right heart catheterization.

Box 1 Points for consideration in the development of a PAH screening programme

Which patients are considered to be most at risk of developing PAH?

Is the patient population to be screened completely asymptomatic?

Will early detection and/or treatment result in tangible clinical improvements in outcomes?

Is the screening associated with any risks?

How frequently should screening be performed?

What is the potential for false positive results (specificity vs. sensitivity)?

How cost-effective is the screening?

Will the screening, particularly those identifying putative genetic markers, have any emotional impact on the patient?

considered in the initial differential diagnosis. Ideally, a screening test should have high sensitivity and specificity, be reproducible, non-invasive, inexpensive, easily accessible and able to be performed in settings where results can be acted upon with further confirmative testing, or specific treatment.

Several important questions need to be considered in the conceptualization of a screening programme in order to maximize the benefit-risk ratio for each patient (Box 1).

Whom to screen: relevant at-risk populations

Screening is not feasible in all asymptomatic at-risk patients, so it is essential that the appropriate target populations are selected. Evidence-based recommendations for screening and diagnosis of PAH are currently only available for PAH associated with connective tissue diseases (CTDs)³¹ and state that patients with SSc, mixed CTD or other CTDs with scleroderma features should be screened for PAH. However, the prevalence of PAH in patients with CTDs other than SSc may be too low to justify wholesale screening of asymptomatic patients, using current approaches. In systemic lupus erythematosus, where the prevalence of PAH is thought to be ~1% and therefore considerably lower than SSc, the potential benefits of screening are currently being investigated.³² Other patient groups with a high prevalence of PAH include individuals with congenital heart disease, portal hypertension, HIV infection, or a genetic pre-disposition to PAH.³³

Heterozygous mutations of the gene encoding bone morphogenetic protein receptor type II (*BMPR2*) account for ~80% of familial PAH/heritable PAH (FPAH/HPAH) cases and between 10% and 20% of sporadic cases^{1,34,35}; patients with *BMPR2* mutations are younger and have more severe disease at diagnosis and are at an increased risk of death or lung transplantation compared with those without *BMPR2* mutations.³⁶ Therefore, genetic screening is potentially of considerable benefit, although the emotional impact on patients and family members found to have PAH-associated

mutations needs to be considered. The imminent results of the DELPHI-2 study (NCT01600898) evaluating multimodal PAH screening in asymptomatic *BMPR2* mutation carriers, are eagerly awaited. Future family studies in patients with confirmed FPAH/HPAH such as the UK National Cohort Study of Idiopathic and Heritable Pulmonary Arterial Hypertension (NCT01907295) could help establish the risk of developing PAH based on genotype.³⁷ However, such studies are restricted by relatively small patient numbers and the time required to accumulate data. One genotype-phenotype correlation study has revealed a non-*BMPR2* genetic trait associated with a pulmonary hypertensive response to exercise and hypoxia in relatives of patients with IPAH or FPAH/HPAH.²² Further studies are required to ascertain the viability of identification of this and other genetic traits to predict the development of PAH.

The low percentage of asymptomatic patients with portal hypertension (between 2% and 6%) or HIV (~0.5%) who develop PAH, means wide-scale screening is currently not cost-effective.^{38,39} However, because of the risks associated with surgery in PAH, it is logical to offer PAH screening in patients with portal hypertension referred for liver transplantation. Few epidemiological studies have been carried out in patients with CTD other than SSc. In congenital heart disease, the prevalence of PAH is high, particularly in unrepaired post-tricuspid lesions (ventricular septal defect and patent ductus arteriosus).⁴⁰ No specific evidence-based guidelines currently exist for screening for PAH in congenital heart disease although these patients should be managed in specialist centres and at-risk patients evaluated.

Pulmonary arterial hypertension diagnostic tools currently used to screen for pulmonary arterial hypertension

The joint European Society of Cardiology/European Respiratory Society guidelines have identified several key diagnostic tests that could be used for screening.¹

Echocardiography

Doppler transthoracic echocardiography (TTE) is recommended whenever PAH is suspected and has the highest level of evidence of current tests used to screen for PAH.¹ A recent study including 313 492 patients undergoing echocardiography demonstrated that TTE is widely used and has the potential to identify patients at a population level. Importantly, even mild elevations of systolic pulmonary artery pressure (PAP) were associated with a poor outcome.⁴¹ The tricuspid regurgitation velocity (TRV) is an important TTE parameter, allowing an estimate of the systolic PAP. Although higher TRV values are associated with an increased probability of PAH, systolic PAP estimations in an individual patient may be inaccurate.⁴²

Other echocardiographic parameters associated with PAH include, but are not limited to, measurements from the ventricles (e.g. flattening of the interventricular septum), the pulmonary artery (e.g. reduced right-ventricular outflow tract acceleration time), or increases in inferior vena cava diameter or right atrium area.^{1,43} Evidence from the DETECT study,¹⁸ which included a wide range of echocardiographic variables in its screening model, has

suggested that TRV and right atrial area are the key echocardiographic parameters that should be assessed in selection of SSc patients for right heart catheterization (RHC) referral. Despite limitations such as challenges in image acquisition particularly in chronic lung disease, it is widely available and frequently used in the assessment of unexplained breathlessness.

Pulmonary function tests

The majority of patients with PAH have decreased lung diffusion capacity for carbon monoxide (DL_{CO}).¹ Significant reductions in DL_{CO} are frequently seen in asymptomatic patients subsequently diagnosed with PAH-SSc and is considered a robust predictor of the disease.^{44,45} In particular, a DL_{CO} of <60% can be used to enrich for a population at higher risk of PAH.¹⁸ Approximately 75% of patients with IPAH, particularly older patients or those with an increased tobacco exposure, have a reduced DL_{CO} .^{46,47} However, a normal DL_{CO} does not exclude a diagnosis, particularly in patients with FPAH/HPAH where DL_{CO} can be preserved.¹ A recent study evaluating cardiopulmonary abnormalities in newly diagnosed patients with pulmonary hypertension demonstrated that abnormalities of DL_{CO} correlated with World Health Organization (WHO) functional class (FC) although reductions in exercise capacity were more sensitive than DL_{CO} for the detection of pulmonary hypertension in asymptomatic patients in WHO FC I.⁴⁸ A parameter calculated from pulmonary function tests (PFTs) is the forced vital capacity/ DL_{CO} ratio (both expressed as percentage of the predicted values). In SSc, a ratio ≥ 1.8 suggests more pronounced reduction of gas transfer when compared with lung volume, and by inference higher likelihood of pulmonary vascular disease. This parameter is part of the algorithm derived from the Australian Scleroderma Cohort Study (ASCS).⁴⁹

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) allows discrimination between the metabolic, cardiovascular, and pulmonary components of exercise intolerance.⁵⁰ However, it requires expertise and specialist facilities, currently limiting its use, and as such it is not currently recommended as a screening tool for PAH.^{1,2,51,52} The typical CPET findings in patients with PAH include reductions in peak rate of oxygen consumption (VO_2), ratio of oxygen consumption to heart rate (O_2 pulse), work rate, anaerobic threshold, and an increase in the ratio of minute ventilation to CO_2 production (V_E/V_{CO_2} slope) and the ratio of dead space to tidal volume (V_D/V_T).⁵³⁻⁵⁵ Dumitrescu *et al.*⁵⁶ recently investigated the utility of CPET in early detection of PAH in 173 SSc patients, who also underwent RHC, and found peak VO_2 to be the most accurate parameter for diagnosis with values above 18.7 mL/kg/min excluding PAH in all patients (i.e. a negative predictive value of 1.0; 100% of patients with values exceeding this threshold did not have PAH). In addition, a nadir V_E/V_{CO_2} ratio of >45.5 had a positive predictive value of 1.0.⁵⁶ A cross-sectional study of patients with echocardiographic findings suggestive of PH also demonstrated the value of measuring peak VO_2 and V_E/V_{CO_2} slope to aid early detection of PAH.⁵⁷ The PH patients (18 PAH and 9 CTEPH) had lower peak VO_2 , compared with non-PH patients ($n = 61$; 877 vs. 1254 mL/min, respectively)

and multivariable logistic regression analyses identified V_E/V_{CO_2} slope and anaerobic threshold as independent predictors of PH.⁵⁷ Further investigation into the role of CPET in early detection of PAH and standardization of the technique is required to support its recommendation in clinical practice.

Blood biomarkers

Biomarker studies to screen for PAH are at an early stage of development and the majority of studies highlighting a potential role for blood biomarkers have been conducted in enriched populations of patients with suspected or confirmed PAH diagnoses.^{20,58-60} Of the current proposed blood biomarkers, only brain natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), and serum urate are included in currently used screening algorithms.^{18,49} Pulmonary hypertension causes an increase in myocardial wall stress resulting in the release of NT-pro-BNP (the inactive pre-cursor of BNP), from cardiomyocytes.^{61,62} Blood concentration of this peptide has been shown to be a useful biomarker for PAH,^{1,23,63} particularly in PAH-SSc, although it may not identify patients with mild disease.⁴⁹ Elevated NT-pro-BNP blood levels can also occur in patients with conditions such as left ventricular dysfunction and advanced renal insufficiency, so care is needed to eliminate any other potential source of the abnormality before further assessments are undertaken. A small number of studies have demonstrated that serum urate levels^{64,65} are elevated in patients with PAH, and reflect disease severity.⁶⁴ Serum urate is the final product of purine degradation and elevated levels are thought to reflect impaired oxidative metabolism occurring as a consequence of tissue ischaemia.⁶⁶ In the DETECT study, elevated levels were predictive of PAH.¹⁸

The diagnostic and prognostic value of blood biomarkers in asymptomatic subjects or specific at-risk populations needs further research but they have the potential to play an important role in screening programmes, given the simplicity of blood testing.

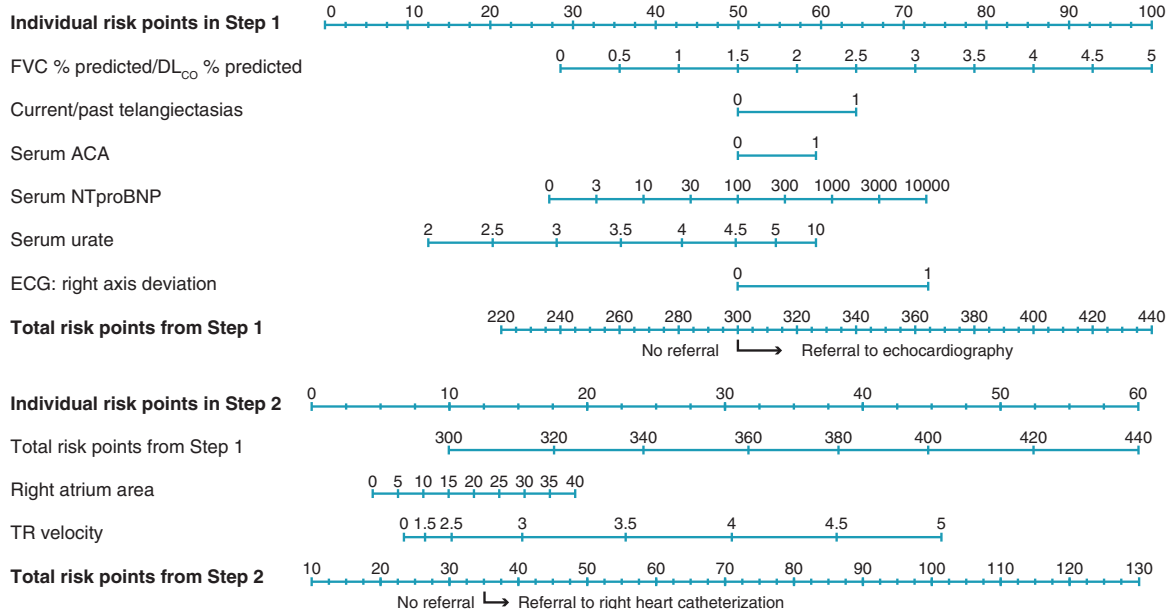
Electrocardiography

Since 1995, an electrocardiography-based mass screening system for general paediatric heart disease has been implemented in Japan. Between 2005 and 2012, the screening detected a unique subpopulation of paediatric patients with IPAH or HPAH associated with advanced pulmonary haemodynamics at rest in subjects with no obvious right heart failure.⁶⁷ Although the screening failed to identify early stage PAH it did improve disease detection. In patients with SSc screened for PAH in the DETECT study, the presence of right axis deviation aided discrimination between patients with and without PAH and is incorporated in the screening algorithm.¹⁸

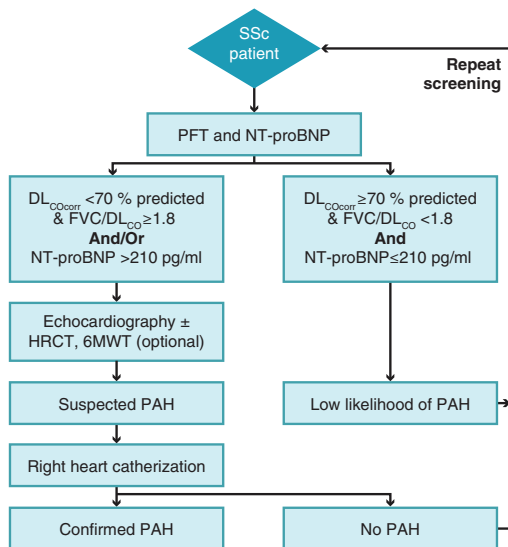
Current screening algorithms

The development and validation of screening algorithms to help identify patients with PAH is of considerable clinical importance. However, validated screening algorithms for PAH currently only exist for patients with SSc (Figure 2) and there is limited guidance for other patient groups (Table 1).

A DETECT



B Australian Scleroderma Interest Group



C ItinerAIR Sclérodemie algorithm

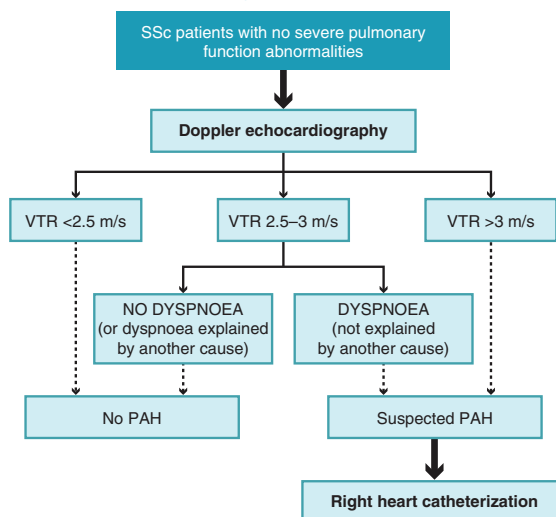


Figure 2 Summary of three approaches to screen for SSc-PAH, including that of the DETECT study (A),¹⁸ that of the Australian College of Physicians (B),⁴⁹ and the ItinerAIR Sclérodemie algorithm (C).⁴⁵ ACA, anticentromere antibody; DL_{co}, pulmonary diffusing capacity for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography (of lung); NTproBNP, N-terminal pro-brain natriuretic peptide; PFT, pulmonary function test; TR, tricuspid regurgitant jet; VTR, peak velocity of tricuspid regurgitation. Figure 2A reproduced from *Annals of the Rheumatic Diseases*, Coghlan *et al.*¹⁸ with permission from BMJ Publishing Group Ltd. Figure 2B reproduced from *Arthritis Res Ther*, Thakkar *et al.*⁴⁹ by permission from BioMed Central Ltd.: Springer Nature, under the CC-BY-2.0 license (2013) <https://creativecommons.org/licenses/by/2.0/>. Permission is granted for reproduction of Figure 2C from Hachulla *et al.*⁴⁵ *Arthritis Rheum*. John Wiley and Sons. Copyright © 2005 by the American College of Rheumatology.

Since the initial French study demonstrating the ability of a screening regimen based on echocardiography and symptoms to identify patients with SSc with milder haemodynamic disease,¹⁴ a number of PAH screening approaches have been proposed. The DETECT algorithm is a highly sensitive, two-step, non-invasive prediction score, which can be used to screen for SSc-PAH in at-risk adults (SSc >3 years; DL_{co} <60% predicted).¹⁸ This DETECT study performed RHC in all patients and could therefore assess missed PAH diagnoses (false negatives) not provided by

previous studies. This study proposes a two-step approach to assessing patients with SSc for PAH. In Step 1, patients undergo a series of six tests, including clinical assessment for the presence of telangiectasia, PFTs, electrocardiogram, and serum biomarkers (anticentromere antibody, NT-pro-BNP, and uric acid) to identify those requiring further assessment by TTE (Step 2). Those with a high-risk score should then be referred for a RHC (Figure 2A). The ASCS⁴⁹ has also assessed a non-invasive screening algorithm for PAH based on NT-pro-BNP levels and lung function

Table 1 Risk factors for PAH and screening recommendations from guidelines

Risk factor	Recommendations	Screening in asymptomatic individuals?	Guideline society
Systemic sclerosis	Echocardiogram yearly \pm biomarkers/PFTs or DETECT algorithm	Yes	ACC/AHA ESC/ERS
<i>BMP2</i> -mutation carriers and first-degree relatives of patients with familial PAH	Annual NT-proBNP and PFTs \pm echocardiography	Yes	ASIG
	Echocardiogram yearly	Yes	ACC/AHA
Systemic sclerosis	Echocardiogram yearly	Yes	ACC/AHA ESC/ERS
Portal hypertension	Echocardiogram if liver transplantation considered	Yes	ACC/AHA ESC/ERS
Congenital heart disease	Echocardiogram and right heart catheterization at time of diagnosis; consider repair of defect	No	ACC/AHA
HIV infection	Echocardiogram only if symptomatic	No	ACC/AHA ESC/ERS
Previous anorexigen use	Echocardiogram only if symptomatic	No	ACC/AHA

ACC, American College of Cardiology; AHA, American Heart Association; ATS, American Thoracic Society; ASIG, Australian screening interest group; ESC, European Society of Cardiology; ERS, European Respiratory Society; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PFT, pulmonary function test.
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parameters (Figure 2B). This algorithm had sensitivity, specificity, positive, and negative predictive values for the detection of PAH of 94.1%, 54.5%, 61.5%, and 92.3%, respectively. The ASCS algorithm showed significantly improved diagnostic accuracy compared with the use of PFTs or NT-pro-BNP alone and has a potential advantage of not using TTE. It must, however, be underscored that TTE in SSc is not exclusively performed for PAH screening but also provides important information on left, right, valvular, and pericardial parameters. Algorithms combining PFTs and echocardiography to screen for PAH in SSc also exist.⁶⁹ It has been suggested that approaches combining a number of modalities are more robust as screening tools than approaches solely reliant on the use of a single modality. Compared with screening approaches based on TTE alone, DETECT identified patients with PAH-SSc with less severe haemodynamic disease and significantly reduced the rate of missed PAH diagnoses (4% vs. 29% based on mean PAP \geq 25 mmHg) and reduced healthcare resource usage. DETECT was also able to identify patients with PAP $>$ 20 mmHg,¹⁸ which is relevant given the recent recommendations from the World Symposium to consider this threshold as the upper limit of normal value.³³

Guidance on when and for whom to consider screening of PAH in patients with portal hypertension or congenital heart disease is detailed in a separate review in this supplement,⁷⁰ but it is also important to note that screening algorithms/methods should be tailored to the at-risk population concerned.⁶⁸ Patients considered for correction of CHD with prevalent systemic-to-pulmonary shunts should be screened for PH by means of RHC; the presence of PAH and the magnitude of pulmonary vascular resistance elevation is associated with significant risk after CHD correction.⁷¹ Patients considered for liver transplantation

should be screened for PH by echocardiography followed by RHC if needed, as the presence of PAH is associated with significant mortality risk after transplantation.^{1,2} Research is ongoing to improve PAH screening in these at-risk populations, and this includes studies on the utility of a new echocardiographic parameter, pulmonary arterial stiffness, and in HIV⁷² and CHD populations.⁷³ Further research is needed to guide screening in at-risk populations, particularly trials of screening algorithms for PAH as currently, there is only a body of evidence for PAH-SSc, which we focus on here.

Unmet needs and future directions

The development and implementation of PAH screening algorithms for patients with SSc has shown that patients with PAH can be diagnosed with less severe haemodynamic disease.^{14,18,49} However, patients with SSc represent less than 25% of the total PAH population and there remains a large unmet need. The improvements in diagnosing PAH in SSc have required a large commitment and investment from both the rheumatological and pulmonary hypertension communities. Although the DETECT study reported that its use resulted in overall reductions in healthcare resource usage,¹⁸ an assessment of the ASCS algorithm⁷⁴ suggested that annual rescreening of patients could result in potentially unnecessary invasive and costly RHC procedures. Even though both algorithms have been shown to be adept at early identification of PAH-SSc, full cost-effectiveness studies of both algorithms along with greater validation, a better understanding of optimal screening frequency and the best use of the algorithms are required. More research is required to identify patients with SSc who are at low risk of developing PAH. In addition, long-term

outcomes of the screened populations need to show benefits of early PAH detection, as previously suggested with a screening approach based on combining TTE with a symptomatic assessment.¹⁴

The success of screening algorithms in patients with SSC is encouraging and underlines the importance of developing algorithms that are suitable for use in other patients at risk of developing PAH. However, a large proportion of PAH patients do not belong to an 'at-risk' population and the identification of these mildly symptomatic patients remains a challenge. Currently, timely diagnosis in these patients relies on a systematic approach to the investigation of these patients in both the primary and secondary care settings. The only study to investigate the impact of a 'traditional' screening tool on PAH detection in a general, unselected population is a recent nationwide study of electrocardiography-based mass screening in Japanese schools.⁶⁷ Electrocardiography-based screening for the early detection of various cardiovascular diseases has been mandatory in Japanese schools since 1995 but Sawada *et al.* were the first to investigate the impact of this established system on PAH detection. In this retrospective observational study of paediatric patients with IPAH or hereditary PAH (HPAH) who were newly diagnosed between 2005 and 2012, 28 (41%) children were detected by the electrocardiography-based screening. Compared with patients in whom PAH was detected by other means (the non-screening group), the screening group had milder clinical symptoms (greater proportion in WHO FC I/II and longer 6MWD) yet both groups had established PAH (mean PAP of ~60 mmHg, mean pulmonary vascular resistance index of ~20 Wood units·m², mean cardiac index of ~3 L/min/m²).⁶⁷ This indicates that this screening programme detected a unique subpopulation of IPAH/HPAH patients but did not achieve 'true' earlier detection, since elevated PAP is a relatively late event in PAH development. It remains unclear whether the screening group benefited from being diagnosed and whether this method is suitable as a large-scale screening strategy for PAH.⁷⁵ There are also novel screening methods on the horizon that may allow large-scale screening in a cost-effective manner. These would have the potential to dramatically improve early detection of PAH and are discussed in the next section.

Diagnostic tools that could be used to screen for pulmonary arterial hypertension

Blood-based biomarkers

The use of blood-based biomarkers to screen for PAH is attractive as blood sampling is straightforward and can be easily deployed at a population level. The current approach to blood-based biomarkers has relied primarily on the identification of biomarkers that reflect the impact of the disease process on cardiac function rather than focusing on biomarkers that reflect pulmonary vasculature abnormalities. Elevated NT-pro-BNP levels are only observed in patients with PAH and cardiac impairment, whereas proteomic, metabolomic, and microRNA approaches to biomarker identification may have the potential to aid earlier diagnosis. MicroRNAs are stable and readily detected in plasma and multiple studies have shown they are dysregulated in patients with PAH^{76,77} with circulating levels

predicting survival in the cases of miR-150⁷⁸ and miR-140-5p⁷⁹ for example. Proteomic and metabolomic analyses have also identified a combination of nine circulating proteins associated with a high risk of mortality, independent of other clinical assessments⁸⁰ and 62 metabolites prognostic for PAH, with modified transfer RNA and altered bioenergetics related to survival.⁸¹ The addition of further blood-based markers to existing screening algorithms, such as DETECT,¹⁸ and risk stratification strategies, such as the REVEAL risk score calculator,^{23,82} should be explored and prospective biomarker studies undertaken.

Volatile organic compounds

Detectable in exhaled breath, volatile organic compounds (VOCs) have been proposed as non-invasive biomarkers for diseases such as cancer, and more recently for PAH.⁸³⁻⁸⁵ Significant alterations of the exhaled VOCs among PAH patients have been identified, both when compared with controls or patients with other respiratory diseases, suggesting exhaled breath analysis has a potential non-invasive medical application in the field of PAH.⁸⁴ A large explorative study (SNOOPY2) in patients with confirmed and suspected pulmonary hypertension (PH) has recently been completed (NCT02782026) and results should be presented in late 2019.

Exercise testing

There are limited data on the natural history of early pulmonary vascular disease since patients usually present with advanced disease.⁷ However, it is generally accepted that the development of exercise-induced PH precedes resting PH. Studies using exercise echocardiography have demonstrated that patients at risk of developing PAH, such as relatives of patients with hereditary PAH or IPAH, have an exaggerated rise in systolic PAP in response to exercise.^{22,86} In addition, patients with exercise pulmonary hypertension in the setting of systemic sclerosis have an increased risk of going on to develop PAH.⁵⁶ Cardiorespiratory exercise testing can also be used to identify the cause of breathlessness and increasingly is deployed in specialized breathlessness clinics. Patients with PAH have characteristic abnormalities reflecting a cardiac limitation to exercise associated with increased dead space ventilation and hyperventilation. Although CPET provides a large amount of physiological information it is time-consuming to perform and requires significant expertise, meaning its deployment is limited to carefully selected at-risk groups. A study of 895 patients with Group 1 to Group 5 PH demonstrated that 89% of asymptomatic (WHO FC I) patients, 93% of patients with mild breathlessness (WHO FC II), and 100% of patients in WHO FC III and IV walked <80% of their predicted exercise capacity using an incremental field walking test (incremental shuttle walking test); this test would be more suited to screening large populations.⁴⁸

Imaging investigations

There continue to be significant advances in imaging technologies and also a lag between reporting of evidence demonstrating the diagnostic value of imaging and its

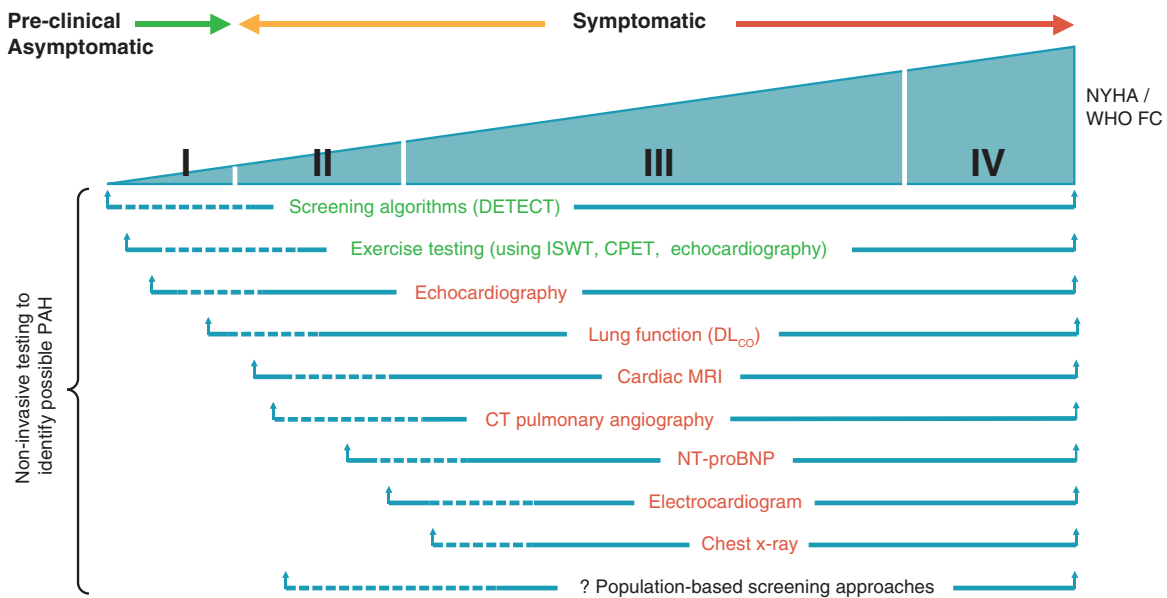


Figure 3 Schematic representation of proportion of patients presenting in each World Health Organization functional class and the non-invasive tools available to assess for pulmonary arterial hypertension in these patients. The range marked by the arrows represents the potential for each diagnostic tool to diagnose pulmonary arterial hypertension at different levels of disease severity. CPET, cardiopulmonary exercise testing; CT, computed tomography; DL_{CO} , pulmonary diffusing capacity for carbon monoxide; ISWT, incremental shuttle walking test; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; WHO FC, World Health Organization functional class.

implementation in clinical practice.⁸⁷ Consequently, there is a significant potential diagnostic dividend that may be realized to aid earlier diagnosis of PAH. Many features of pulmonary hypertension visible on a computed tomography (CT) scan performed for the assessment of unexplained breathlessness are frequently not reported by radiologists or recognized by physicians. Pulmonary artery enlargement, elevated pulmonary artery to aortic ratio, right ventricular dilation, elevated right ventricular to left ventricular ratio, and abnormalities of lung perfusion, such as centrilobular ground glass, which are observed in PAH,⁸⁸ could potentially be assessed using artificial intelligence (AI) approaches. Machine learning (ML) approaches have been shown to improve automation and quantification of some imaging parameters, particularly in magnetic resonance imaging.⁸⁹ There is a lot of interest in the application of these approaches to more scalable imaging techniques, such as CT, where the application of tensor-based approaches such as those used in facial recognition software could be used to recognize patterns consistent with a diagnosis of pulmonary hypertension.

Healthcare utilization behaviour

While there is optimism regarding the potential to identify early pulmonary vascular disease in SSC, until recently this was not the case for IPAH. However, a number of investigators have recently studied the patient journey and have postulated that a patient with IPAH may exhibit a particular pattern of behaviour prior to diagnosis that could potentially be used to diagnose IPAH earlier.²⁷ The DELAY study used a combination of health records and quantitative and qualitative interviews²⁸ and demonstrated that patient-driven delay, multiple general practitioner and hospital visits occur prior to specialist referral. A similar pattern has

also been observed in a large descriptive cross-sectional study of 567 patients with pulmonary hypertension.²⁹ A recurring theme is a significant delay between symptom onset and seeking medical advice and there is interest in the use of wearable technologies and ML approaches to these large complex datasets to develop AI algorithm approaches that can alert patients and doctors to changes in daily levels or patterns of activity. The Sheffield Pulmonary Hypertension Index project²⁷ aims to develop a predictive algorithm based on routinely collected healthcare utilization data to reduce the time to IPAH diagnosis. In this study, 127 815 adults with pulmonary hypertension were identified from a national healthcare data set; it was determined that 589 of these patients had probable IPAH. The incidence and demographics of these probable IPAH patients were similar to the reported literature. In a separate cohort of 864 patients with confirmed IPAH, data could be linked with NHS Hospital Episode Statistics in 98.6% of cases and these patients had an average of 18 hospital contacts in the 3 years prior to diagnosis.²⁷ Importantly, these data have a complexity and richness that has the potential to facilitate an earlier diagnosis by identifying a 'fingerprint' that may be deployed to detect patients at risk of IPAH. Further work to develop, validate and, if successful, deploy such approaches is required.

Figure 3 summarizes the potential of currently available non-invasive tools to identify patients at risk of PAH at different levels of disease severity.

New approaches to screening and detecting pulmonary arterial hypertension

How best to apply existing and new screening and diagnostic tools remains a major challenge in PAH, where

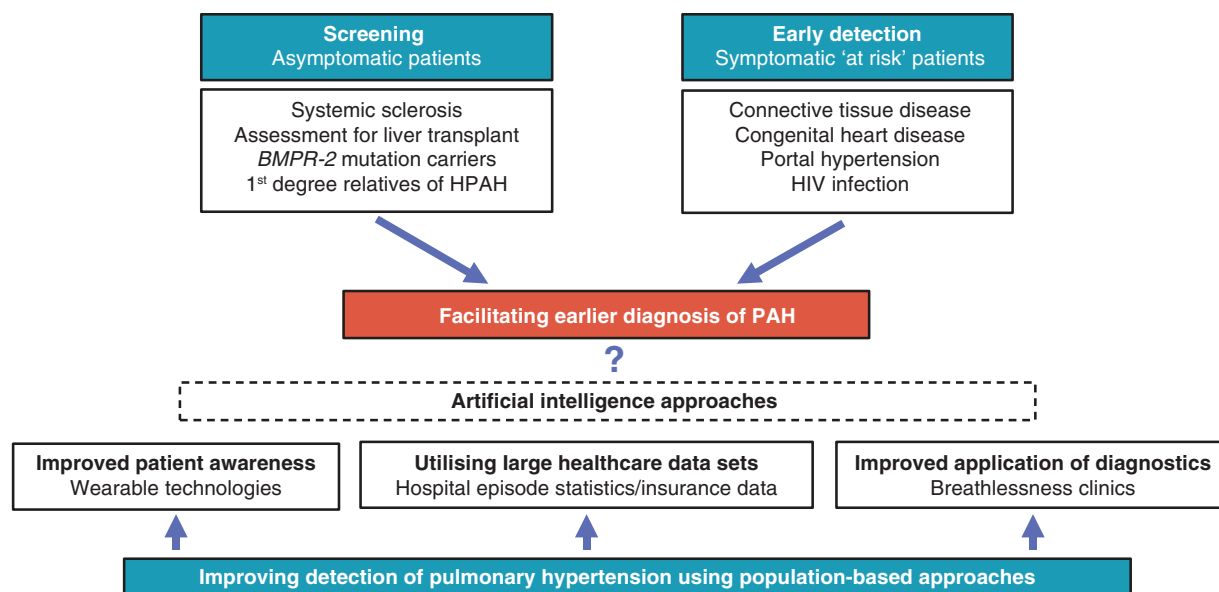


Figure 4 Summary of approaches to facilitate an earlier diagnosis of pulmonary arterial hypertension. Earlier diagnosis may be achieved by screening asymptomatic and at-risk patients and improving the detection of pulmonary hypertension by using population-based approaches to screening symptomatic patients where a diagnosis of pulmonary arterial hypertension may not be considered as an initial diagnosis. *BMPR-2*, bone morphogenetic protein receptor type 2 gene; HPAH, heritable pulmonary arterial hypertension; PAH pulmonary arterial hypertension.

approaches to screening and improved detection are required for both asymptomatic patients (e.g. systemic sclerosis) and symptomatic patients for whom a PAH diagnosis is rarely considered as an initial diagnosis (Figure 4).

Breathlessness clinics

As the majority of patients with PAH present with breathlessness, the development of specialist clinics, where diagnostic investigations are performed by experienced clinicians in a systematic and timely manner, could reduce the time-to-diagnosis and also potentially allow evaluation of aforementioned screening tools.

Application of algorithms to routinely collected large data sets to identify patients for further evaluation

The use of AI approaches to routinely collected data is an area of increasing interest. In many countries around the world, large and complex data sets on healthcare resource utilization exist. If predictive algorithms could be developed to identify patients at increased risk of PAH, the potential benefits could include opportunities to assess economic impact of diagnostic testing and treatment, without the potential lead-time bias that exists using current approaches. In addition, data from patients at an earlier stage of disease may yield new insights into early molecular mechanisms and highlight novel targets for drug development.

Conclusions

Despite evidence of the success of screening algorithms to facilitate earlier diagnosis of PAH in SSc, progress in diagnosing PAH earlier in other forms of PAH such as IPAH remains disappointing. The creation of screening algorithms

for patients at risk of SSc-PAH has increased the speed and specificity of diagnosis, potentially improving survival although the costs from screening remain significant. The development and validation of screening algorithms for PAH of other aetiologies is required if we are to realize similar improvements for a wider patient population. Screening for PAH in asymptomatic at-risk patients and the development of screening-based approaches in symptomatic patients where the diagnosis is rarely considered are required to improve detection rates and reduce the time to diagnosis. A number of novel screening tools and approaches provide hope to patients and physicians that the advances seen in treatment will also be seen in the diagnostic journey.

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