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Review Article

A diagnostic algorithm for pulmonary hypertension due to left heart disease in resource-limited settings: can busy clinicians adopt a simple, practical approach?

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Abstract

Pulmonary hypertension (PH) has progressively moved from an orphan disease to a significant global health problem with a major disease burden in limited-resource countries, where over 97% of patients live. The aetiologies of PH differ between high- and low-income nations, but PH due to left heart disease is credited to be the most frequent contemporary form. Although a straightforward diagnosis of PH requires the use of right heart catheterisation (RHC), access to equipment for RHC is a deterrent. Furthermore, the risk associated with RHC limits its uptake to a selection of specialised centres. Moreover, the rigour and clinical reasoning for diagnosis in clinical medicine is rapidly changing and revealing that PH can complicate a diverse range of medical conditions needing other explorations. In this article, we provide for the busy clinician, a simplified diagnostic algorithm for PH that is relevant for making a correct early diagnosis and limiting the impact of PH.

Keywords: pulmonary hypertension, diagnostic algorithm, left heart disease

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Pulmonary hypertension (PH) is an elevation of the pressure in the arteries of the lungs, resulting from a variable combination of increased pulmonary vascular resistance, pulmonary blood flow and pulmonary venous pressure.¹ This definition applies irrespective of the underlying aetiology of PH, which includes a range of medical conditions such as chronic infectious diseases, and lung and left heart diseases. Pulmonary arterial hypertension (PAH), a specific type of PH, exclusively affects the pulmonary arterial circulation, resulting in increased pulmonary vascular resistance, and ultimately in right heart failure (HF) and reduced life expectancy.

Over the last century, significant progress in the diagnosis and management of PH has moved this condition from an orphan disease to a multidisciplinary and now acknowledged major global health problem. In 2010, it was estimated that PH affects more than 25 million individuals worldwide.^{2,3} The ultimate diagnosis is still based on right heart catheterisation (RHC). Aetiologies of PH differ between high- and low-income nations, but left heart disease (LHD) has progressively been credited to be the most common cause of PH in contemporary clinical settings.^{4,5}

Despite these improvements in understanding PH aetiologies, the condition is still diagnosed at an advanced stage in a significant proportion of patients, due to poor medical awareness and the paucity of symptoms in the early stages of the disease.⁶ This has negative impacts on subsequent quality of life and

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survival.⁷ The American College of Cardiology/American Heart Association⁸ and the European Society of Cardiology/European Respiratory Society⁷ guidelines have each provided a regularly updated diagnostic algorithm, based on prevalent aetiologies of PH as well as availability of several diagnostic tests, and especially, RHC in high-income countries.

This algorithm may not apply or may be difficult to implement in low-income countries where human and financial resources more than just science often influence the diagnostic approach. In sub-Saharan Africa (SSA), given the additional high and increasing prevalence of chronic and endemic risk factors of PH, which are almost specific to the region, such as chronic infectious diseases (HIV, tuberculosis and schistosomiasis), hypertensive heart disease, peripartum cardiomyopathies and rheumatic heart disease,⁹ a clear diagnostic approach to PH due to LHD (PHLHD) is of particular importance. Furthermore, the high cost, low availability and scarcity of expertise for RHC limit its utility in this part of the world and justify the interest in a more pragmatic algorithm.

Based on the experience and evidence from the Pan-African Pulmonary Hypertension Cohort (PAPUCO) study, we previously developed an algorithm,¹⁰ and herein suggest a four-step diagnostic approach for PHLHD in low-resources settings. These steps include (1) clinical evaluation to detect predisposing conditions for PHLHD, (2) assessment with chest X-ray (CXR) and electrocardiogram (ECG) to uncover the presence of PHLHD, (3) confirmation of the presence of PHLHD using Doppler echocardiography (echo), and (4) exploration of differential aetiologies of PHLHD and classification of the type of PH.

Step 1: clinical evaluation and detection of a predisposing condition

Data from the PAPUCO study¹¹ showed that PH should be suspected in any African patient with otherwise unexplained shortness of breath, fatigue, palpitations, cough, dizziness and/or signs of right ventricular dysfunction and right heart failure. Two-thirds of patients are likely to present in World Health Organisation functional class (WHO FC) III or IV and one-third may not walk further than 300 metres on a six-minute walk test. Clinical examination may reveal a systolic murmur (57%) or a loud P2 (41%). These clinical observations are largely similar for men and women.

In the presence of these symptoms, clinicians should actively inquire about predisposing conditions, which in the SSA context, include hypertension (42%), previous or concurrent tuberculosis (22 and 5%, respectively), indoor cooking/heating without a chimney (32%) and HIV infection (22% overall). In the PAPUCO study, there were no significant differences in the risk-factor profiles of men and women besides exposure to indoor cooking/heating without a chimney (more women), history of smoking (more men) and alcohol abuse (more men). Also, although being a traditional risk factor for PH, the endemicity of schistosomiasis was only related to one case. In some predisposing groups, such as sickle cell disease, PH signs and symptoms may often be subtle and may not be apparent for months as they are generally non-specific.

When the clinical evaluation is not suggestive of PH, the clinician should search for other causes of symptoms (e.g.

tuberculosis, chronic pulmonary disease, LHD, malignancy). On the other hand, as shown in Fig. 1, when step 1 is suggestive of PH, the patient should systematically undergo step 2, non-invasive investigations, which should include a CXR and ECG.

Step 2: the role of chest X-ray and electrocardiogram

Chest X-ray

In SSA where pulmonary tuberculosis and HIV-associated chronic lung diseases are common (e.g. recurrent pneumonia, pneumocystis pneumonia), CXR allows moderate to severe lung diseases to be reasonably excluded but also, abnormalities on CXR are frequent in PHLHD and after completion of TB treatment. In the PAPUCO registry, 59% of patients presented with cardiomegaly and 22% had prominent pulmonary arteries (Fig. 2A).

Other findings supportive of underlying cardiac disease include left atrial enlargement, mild to moderate pleural effusion and cephalisation. In other circumstances, the presence of central pulmonary arterial dilatation, which contrasts with 'pruning' (loss) of the peripheral blood vessels, is very suggestive of PH. Right atrial and right ventricular (RV) enlargement may be seen in more advanced cases.

Electrocardiogram

The diagnostic utility of ECG in patients with PH was investigated in a sub-study of the PAPUCO registry.¹¹ Our findings demonstrated that a normal ECG is very rare among patients with PH. Sinus tachycardia and left ventricular strain pattern were observed in around one-fifth of cases (Fig. 2B), but PH-specific abnormalities such as p-pulmonale (14%) and evidence of right ventricular hypertrophy (19%) were documented in less than one-quarter of cases.

The sensitivity of ECG criteria for right heart strain ranged between 6.2 and 47.7%, while specificity ranged between 79.3 and 100%. Negative predictive value ranged between 81.5 and 88.9%, and positive predictive value between 25 and 100%. Positive predictive value was lowest (25%) for right bundle branch block and QRS right-axis deviation ($\geq 100^\circ$) and highest (100%) for QRS axis $\geq +100^\circ$, combined with R/S ratio ≥ 1 or R in V1 > 7 mm.

In short, signs involving PH on ECG were highly indicative of disease, but a normal ECG would not exclude disease. Because ECG patterns focusing on the R and S amplitude in V1 and right-axis deviation had good specificity and negative predictive value, their presence should trigger further investigation with Doppler echo (Fig. 1).

Step 3: the key role of Doppler echocardiography

A transthoracic Doppler echo examination is the next and most appropriate course of study. Doppler echo provides several variables that correlate with right heart haemodynamics, including an estimate of right ventricular systolic pressure (RVSP), and can simultaneously uncover functional and morphological cardiac sequelae of PH, and assist in the identification of possible cardiac causes of PH.

The Doppler echo estimation of RVSP (Fig. 3A) is based on the peak velocity of the jet of tricuspid regurgitation (TR). TR velocity can be obtained by either a duplex imaging from the

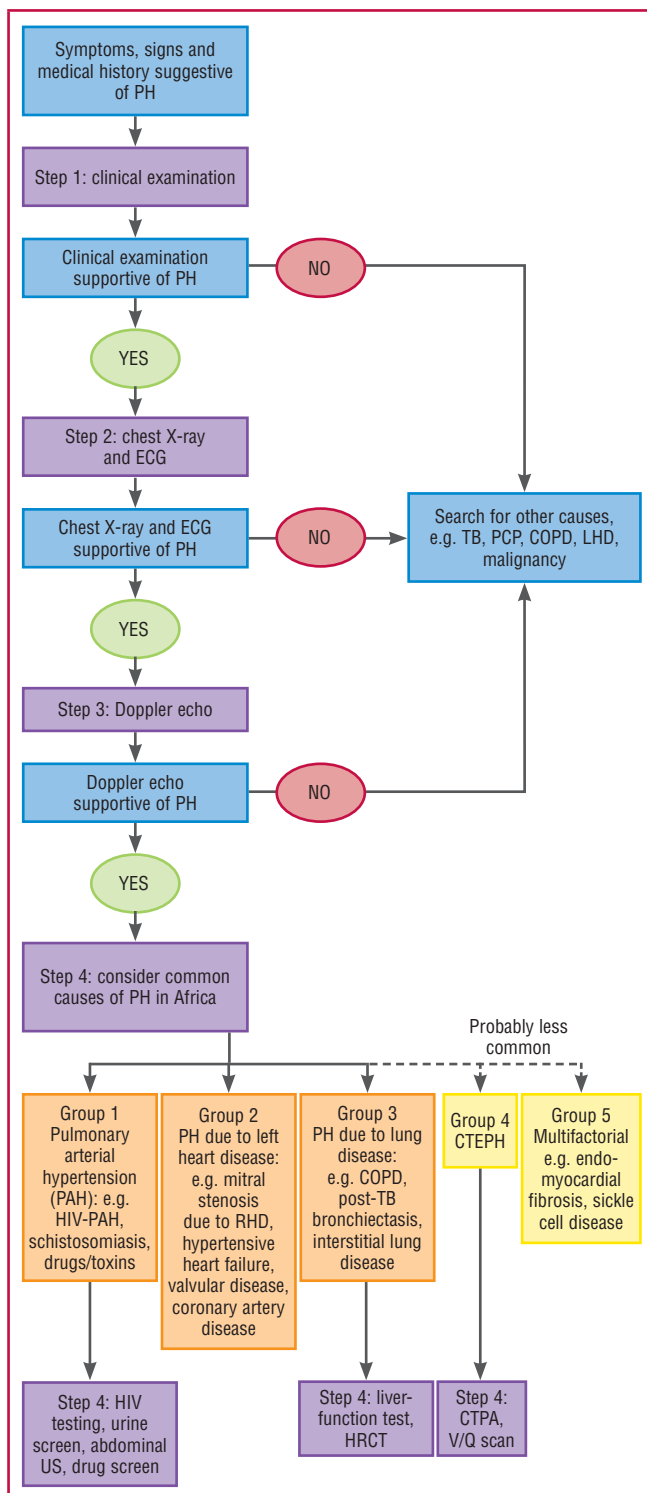


Fig. 1. Diagnostic algorithm to diagnose pulmonary hypertension due to left heart disease in low-resource settings, as evidenced from the PAPUCO study. PH, pulmonary hypertension; TB, tuberculosis; PCP, pneumocystis pneumonia; COPD, chronic obstructive pulmonary disease; LHD, left heart disease; Doppler echo, Doppler echocardiography; US, ultrasound; LFT, liver-function tests; HRCT, high-resolution computerised tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, CT pulmonary angiography; V/Q, ventilation/perfusion lung scan.

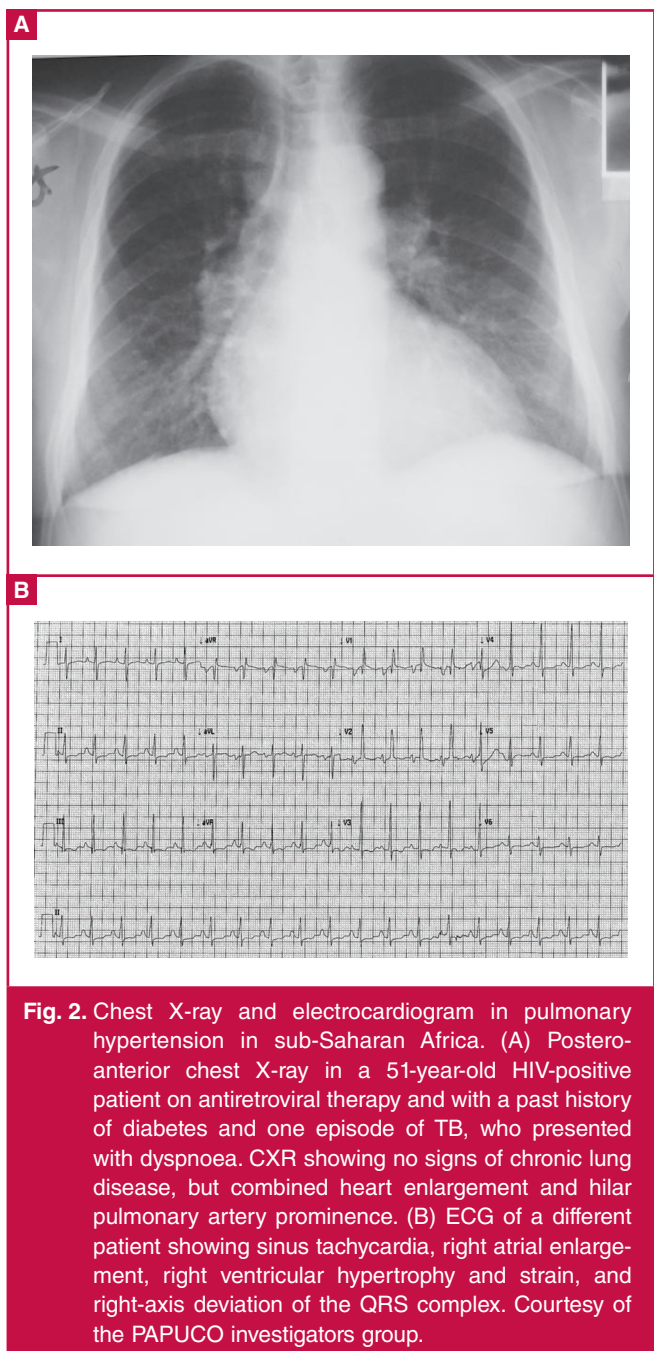


Fig. 2. Chest X-ray and electrocardiogram in pulmonary hypertension in sub-Saharan Africa. (A) Postero-anterior chest X-ray in a 51-year-old HIV-positive patient on antiretroviral therapy and with a past history of diabetes and one episode of TB, who presented with dyspnoea. CXR showing no signs of chronic lung disease, but combined heart enlargement and hilar pulmonary artery prominence. (B) ECG of a different patient showing sinus tachycardia, right atrial enlargement, right ventricular hypertrophy and strain, and right-axis deviation of the QRS complex. Courtesy of the PAPUCO investigators group.

right ventricular inflow view, parasternal short-axis view at the basal level, para-apical four-chamber view, apical four-chamber view, or even the subcostal view. The TR maximal instantaneous gradient (TR MIG) is frequently automatically calculated and displayed on the screen (Fig. 3A) when the maximal TR velocity is measured. Otherwise it is easily calculated using the simplified Bernoulli equation:¹²

$$TR\ MIG = 4\ (TR\ velocity)^2$$

Bernoulli's equation then allows for the estimation of the RVSP,¹² taking into account right atrial pressure (RAP):

$$RVSP = TR\ MIG + RAP.$$

RAP is estimated from the inferior vena cava (IVC) calibre and respiratory collapsibility (Table 1, Fig. 3B). In the absence of pulmonary stenosis and acute right HF, the estimated RVSP is assumed to equal the pulmonary artery systolic pressure.

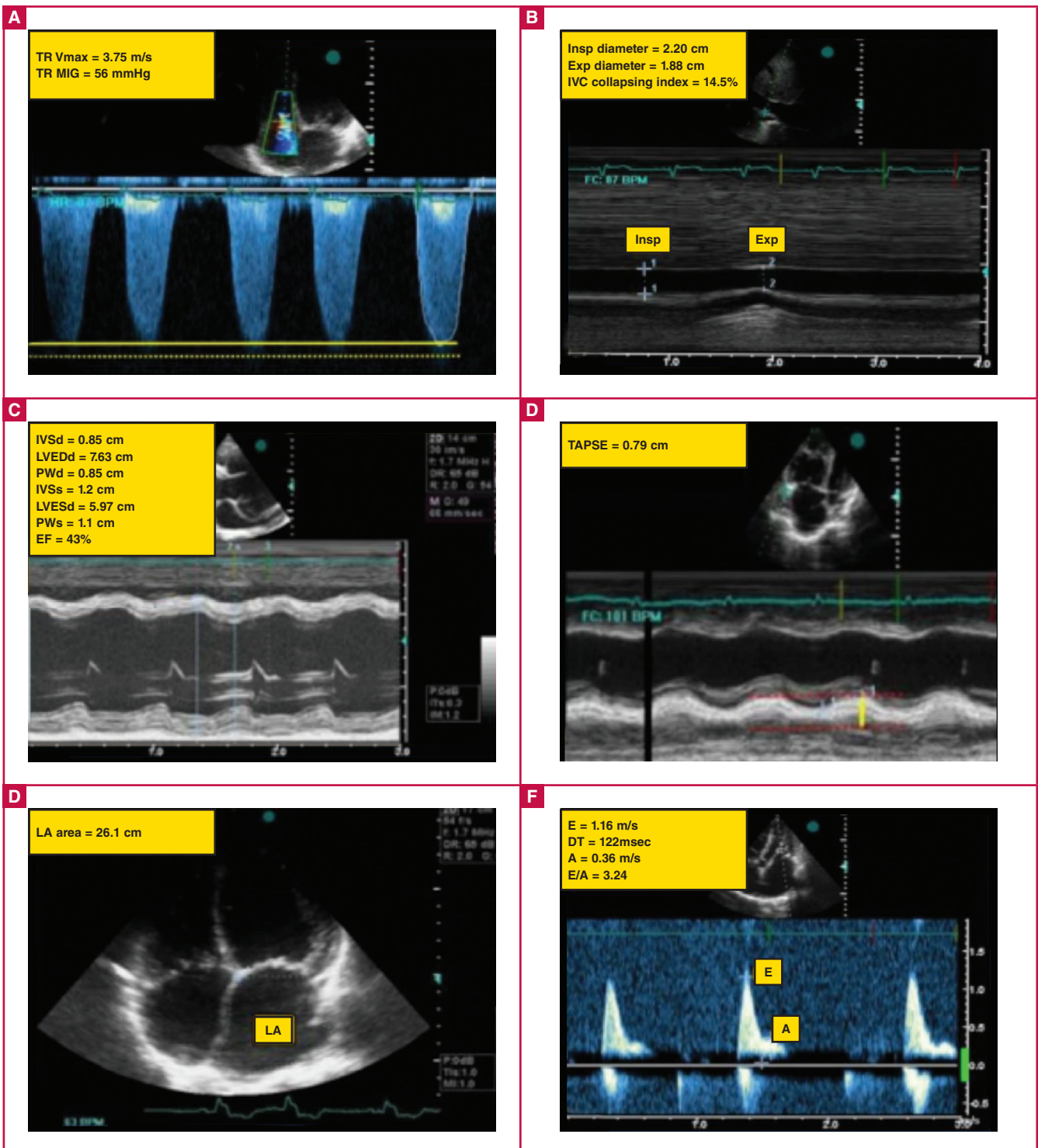


Fig. 3. Echocardiographic evaluation in patients with pulmonary hypertension in sub-Saharan Africa. Measurement of pulmonary pressure is based on identification of the tricuspid regurgitant (TR) jet and using continuous-wave Doppler to obtain the maximum instantaneous right ventricular–right atrial gradient, as indicated by the solid yellow line (A). The yellow dotted line indicates measurement of over-gained (shaggy) signals with significant overestimation in the gradient. TR Vmax indicates TR maximal velocity, TR MIG, TR maximal instantaneous gradient. (B) Right atrial pressure is estimated from the inferior vena cava (IVC) calibre and respiratory collapsibility. ins, inspiration, exp, expiration. (C) shows measurements of the ejection fraction using the Teicholz formula; IV(D/S) indicates interventricular septum (diastole/systole), LVED(S)d: left ventricular end-diastolic (systolic) diameter, PWd(s): posterior wall in diastole (systole). (D) indicates the measurement of the tricuspid annular plane systolic excursion (TAPSE) in a patient with right heart failure. (E) A visual assessment of right cardiac cavities in apical four-chamber view showing dilated heart cavities. (F) indicates a restrictive mitral Doppler pattern in the same patient. Modified from thesis 'Predicting pulmonary hypertension and outcomes in patients with left heart disease'. <http://hdl.handle.net/11427/16533>.

Table 1. Estimation of right atrial pressure from inferior vena cava calibre and respiratory collapsibility. Adapted from Beigel *et al.*¹²

Estimated RAP (mmHg)	IVC diameter (cm)	IVC collapse with inspiration (sniff)
5	< 2.1	> 50%
10	< 2.1	< 50%
15	≥ 2.1	> 50%
20	≥ 2.1	< 50%

RAP, right atrial pressure; IVC, inferior vena cava.

To avoid errors in the measurement of RVSP, it is mandatory to observe some conditions, including accurate measurement of the IVC, avoiding measuring over-gained (shaggy) signals (Fig. 3A). If the heart rhythm is irregular, it is recommended that three to five consecutive cycles be measured and the mean of these cycles be recorded.

In patients with PH, Doppler echo also contributes to the evaluation of the RV systolic function through measurement of the tricuspid annular plane systolic excursion movement (TAPSE). TAPSE represents the distance of systolic excursion of the RV annular plane towards the apex. As shown in Fig. 3D, it is obtained using an M-mode cursor passed through the tricuspid lateral annulus in the four-chamber view and measuring the amount of longitudinal displacement of the annulus at peak systole.

In the PAPUCO registry,¹¹ Doppler echo findings showed that left ventricular (LV) function was moderately impaired overall (median LV ejection fraction 46%) (Fig. 3C). As expected, RVSP was markedly elevated (median value 58 mmHg), with concurrent moderate to severe right atrial (58%) and right ventricular (55%) hypertrophy a common feature. Only one-third of cases ($n = 69$; 33%) showed no evidence of right atrial or ventricular enlargement. Overall, 78 patients (37%) presented with a diagnosis of right HF based on TAPSE movement < 15 mm (Fig. 3D) plus one or more clinical signs of HF.

The LHD aetiology¹³ of PH is suggested by (1) presence of heart disease as suggested by a dilation in the cavities (Fig. 3E), presence of heart valve disease or abnormal contractility, and (2) arguments suggestive of an elevation of left ventricular filling pressure, such as left atrial dilation (Fig. 3E) or a mitral Doppler restrictive pattern (Fig. 3F). In the subgroup of patients with PHLHD,¹³ aetiologies were predominantly hypertensive HF with reduced or preserved ejection fraction, dilated and peripartum cardiomyopathy and rheumatic valvular heart disease. Left atrium size and TAPSE were predictors of RVSP in these patients, and RVSP predicted short-term hospitalisations but not mortality.

We therefore recommend that an estimated RVSP greater than 35 mmHg in SSA should warrant further evaluation for PH in patients with suggestive PH in step 1 and/or 2 (Fig. 1). Finally, Doppler echo can clearly help identify possible aetiologies of PH, and particularly PHLHD (Table 2), anticipating the contribution of other tests.

Step 4: other investigations

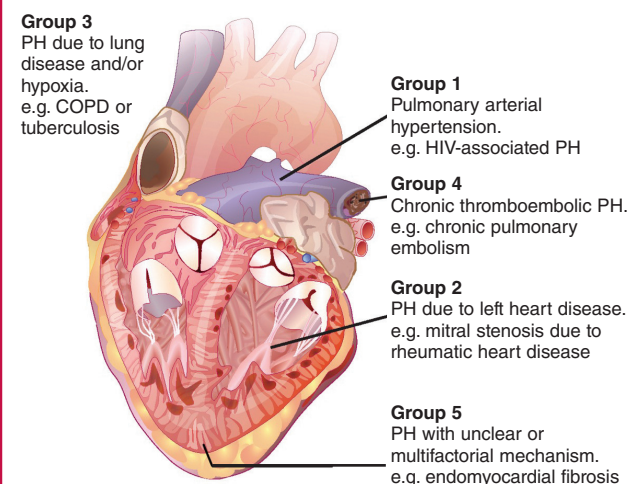
A careful selection of other tests can contribute to establishing a diagnosis of PH in patients residing in low-income countries such as SSA. The utilisation of these other investigations will depend on both the results of the above initial tests and the clinical context. Given the high burden of HIV/AIDS in the

Table 2. Possible causes of pulmonary hypertension identified by echocardiography with relevance to sub-Saharan Africa¹³

Predisposing conditions for pulmonary hypertension
• Valvular disease [mitral (aortic) stenosis/regurgitation, prosthetic valve dysfunction]
• Left ventricular systolic dysfunction (including hypertensive heart failure, dilated cardiomyopathy, peripartum cardiomyopathy, myocardial infarction)
• Left ventricular diastolic function (including ischaemic heart disease, hypertensive heart disease, hypertrophic cardiomyopathy, Fabry's disease, infiltrative cardiomyopathies)
• Other obstructive lesions (coarctation, supravalvular aortic stenosis, sub-aortic membrane, cor triatriatum)
• Congenital disease with shunt [atrial (ventricular) septal defect, coronary fistula, patent ductus arteriosus, anomalous pulmonary venous return]
• Pulmonary embolus (thrombus in inferior vena cava, right-sided cardiac chamber, or pulmonary artery; tricuspid or pulmonic valve vegetation)
• Pulmonary vein thrombosis/stenosis
Findings that suggest specific disease entity
• Left-sided valve changes (systemic lupus erythematosus, anorexigen use)
• Intra-pulmonary shunts (hereditary haemorrhagic telangiectasia)
• Pericardial effusion (idiopathic pulmonary arterial hypertension, systemic lupus erythematosus, systemic sclerosis)

region as well as its contribution in the PAPUCO registry (22%), it is reasonable to screen all patients with PH for HIV. Other tests, such as abdominal ultrasound, liver-function test, high-resolution computerised tomography (CT), CT pulmonary angiography, ventilation/perfusion lung scan, and electrophoresis of haemoglobin will be guided by the clinical context. It is only after these steps have been completed and once a definitive diagnosis of PH has been reached and potential underlying co-morbidities or causes identified, that classification within an appropriate aetiological group must be considered (Fig. 4).

We acknowledge classification difficulties in SSA and other low-income countries, especially in the absence of RHC and other imaging studies. It is noticeable that in some patients, several mechanisms may be involved in the pathogenesis of PH in Africa. For example, the interaction between sickle cell disease-related haemolysis and HIV, chronic lung disease due to tuberculosis, schistosomiasis, and viral hepatitis could yield very complex multifactorial and unclear PH.

**Fig. 4. World Health Organisation classification of pulmonary hypertension with relevant examples for sub-Saharan Africa.¹**

Limitations of the suggested algorithm

It is important to acknowledge that a major limitation of our approach lies in the validity of RVSP for diagnosis of PH using Doppler echo. There is absolutely no doubt that RHC is the standard to accurately diagnose PH and determine its severity as well as its impact on right ventricular function. However, RHC is an invasive procedure, and it is expensive and not available in most low-resource settings where the majority of patients with PH are resident, particularly in SSA.

There is abundant literature on the validity of Doppler echo RVSP estimates in patients with left heart disease using RHC values as the gold standard. Lanzarini *et al.*¹⁴ reported a concordance correlation coefficient of 0.88 between RHC and RVSP, with ± 20 mmHg and 95% limits of agreement. In their study of Doppler echo evaluation of haemodynamics in patients with decompensated systolic HF, Nagueh *et al.*¹⁵ reported that Doppler echo identified patients with invasive systolic pulmonary artery pressure > 35 mmHg with 94% sensitivity and 90% specificity.

In an analysis of data from the ESCAPE trial, McClanahan and Guglin¹⁶ suggested that the accuracy of Doppler echo RVSP estimates in systolic HF might be inaccurate in the presence of right ventricular systolic dysfunction. However, at least two reasons could have explained this lack of accuracy: first, patients included in the ESCAPE trial¹⁶ were in acute HF and not haemodynamically stable; and second, echocardiography in ESCAPE was not protocol driven, and the time differential between RHC and RVSP evaluation using Doppler echo was widely variable. In view of the above and provided that patients are haemodynamically stable and a rigorous Doppler echo technique is used by experienced observers, it is acceptable and pragmatic to detect PH using Doppler echo estimates of RVSP, although we recommend a confirmation with RHC before any specific therapeutic action is required.

Finally, our recommendations are based on a single study. Ideally, such a practice algorithm, which is intended to provide clinicians with recommendations, should be based on systematic review of the available evidence, and an assessment of the benefits and harms of care options, with the intention of optimising patient care and outcomes. However, expert opinion remains a major part of all such practice guidelines,^{17,18} particularly when high-quality evidence is lacking, as is the case in SSA.

Conclusion

For the busy clinician, it is important to recognise the increasing burden of PHLHD in low-resource settings and be able to make an early diagnosis. Adopting a four-step diagnostic algorithm is recommended and the steps include: (1) a clinical evaluation, (2) CXR and ECG assessment, (3) Doppler echo, and (4) exploration of differential aetiologies before classification of the type of PH. This strategy will help manage the majority of patients in low-resource settings, especially those with various types of PHLHD, for which indications of RHC should be restricted to avoid unnecessary risk.

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