

How to Proceed in a Multimodality Analysis for the Diagnosis and Risk Stratification of Pulmonary Hypertension?

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Pulmonary hypertension (PH) is a complex multiorgan system disease defined as mean pulmonary artery pressure (mPAP) ≥ 20 mmHg. The etiologies related to pathological changes in pulmonary vasculature leading to PH are wide. Hemodynamic categorization considers precapillary PH, represented by pulmonary arterial hypertension (PAH), pulmonary vascular resistance (PVR) ≥ 3 Woods units (WU), and pulmonary arterial wedge pressure ≤ 15 mmHg. Postcapillary PH, represented by left heart disease, involves PVR ≥ 3 WU and pulmonary arterial wedge pressure ≥ 15 mmHg. Clinical categorization considers 5 groups. Incidence per group is not well known; however, group 2 (associated with left heart disease) is the most common cause of PH. PAH (group 1) is still a highly devastating condition causing limited quality of life and high mortality, mostly related to right ventricle (RV) failure. Group 3 refers to PH associated with lung diseases and or hypoxia. Group 4 corresponds to PH associated with pulmonary artery obstructions, and group 5 to PH with unclear and or multifactorial mechanisms.¹ Currently, the diagnostic algorithm for PH considers a 3-step approach, from clinical suspicion by first-line physicians considering vital signs, functional class, etc.; non-invasive RV parameters by transthoracic echocardiography (TTE), cardiac magnetic resonance imaging (CMRI), computed tomography (CT), and pulmonary vascular assessment by ventilation perfusion (V/Q) scan. For diagnostic confirmation, however, right heart catheterization is necessary, preferably in PH centers.^{2,3}

In PH, a multimodality approach involves the use of multiple diagnostic tests to evaluate the various aspects of the disease, from suspecting to determining its etiology.⁴ It provides a comprehensive assessment for prognosis and can assist in guiding treatment decisions and evaluating response to therapy.

Transthoracic echocardiography

TTE is considered a highly useful, inexpensive, safe, and available imaging modality for initial approach to differential diagnosis of PH. Although a normal TTE does not rule out diagnosis, it decreases the likelihood of PH. Neither CT nor

CMRI are part of the initial line of PH; however, in selected patients they can provide additional information before proceeding to right heart catheterization.^{1,2}

It is important to be familiar with normal ranges of RV size and function.^{5,6} TTE showing right heart structure and function abnormalities increases suspicion of PH.⁷ It also allows detection of left heart (systolic and diastolic dysfunction, valvular heart disease) and congenital heart disease as potential causes of PH.⁸ RV function surrogates such as RV fractional area change, right atrial size, pericardial effusion, tricuspid annular plane systolic excursion (TAPSE), systolic pulmonary artery pressure (SPAP)/TAPSE ratio, and eccentricity index are recommended in follow-up and assessment of therapy response.⁹ However, it is important to note that these surrogates should be interpreted in the context of other clinical and imaging parameters, as they are not standalone diagnostic tools. Doppler can be used to estimate the possibility of PH by measuring tricuspid regurgitant jet velocity (TR) and calculating SPAP using the modified Bernoulli equation. When no TR is present or the signal is inadequate, pulmonary acceleration time can be used to calculate mPAP obtained from pulse wave Doppler signal of pulmonary flow. Pulmonary artery diastolic pressure can be estimated if pulmonary regurgitation is present. The velocity at end-diastole is converted into a pressure gradient, adding the estimated right atrial pressure to the resulting value. Finally, both left ventricle and RV output can be calculated.⁹ In clinical practice, differentiating acute, chronic, and chronic acute PH can be challenging (Table 1).

The following recent advances in echocardiography have improved our understanding and ability to better characterize RV dysfunction in PH:

1. Three-dimensional echocardiography (3DE) can provide detailed information on the size and function of the RV. It has been demonstrated that 3DE is more accurate than 2-dimensional echocardiography in assessing RV function in PH.
2. Speckle tracking echocardiography (STE) can be used to quantify RV free-wall strain, which is a measure of how much the RV is able to contract and relax. RV strain has demonstrated to be both a sensitive marker of RV dysfunction and a predictor of clinical outcomes and death in patients with PH.
3. Real-time 3DE makes it possible to acquire rapid information on RV volumes, RV stroke, and RV ejection fraction, as well as RV strain and strain rate. It is especially useful in assessing RV function in dynamic tests, such as exercise.
4. Contrast-enhanced echocardiography (CEE) improves the visualization of the cardiac chambers. CEE can be used to detect the presence of a clot, a mass, or other abnormalities.

Keywords

Pulmonary Hypertension; Diagnosis; Risk Factors

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Table 1 – Differentiating acute, chronic, and chronic acute pulmonary hypertension

Echocardiographic parameter	Acute	Chronic	Chronic acute
Dilated right ventricle	Yes	Yes	Yes +++
Hypertrophied right ventricle	Absent	Present	Present
Tricuspid regurgitation	Present	Present	Present
Pulmonary regurgitation	+ to ++	+++ to ++++	+++ to ++++
Pulmonary pressure	MPAP < 40 mmHg	Supra-systemic SPAP	Supra-systemic SPAP
Right ventricle hypokinesis	Severe	Late finding	Severe to very severe
Paradoxical septal motion	Present	Present (marked)	Present (severe)
Dilated pulmonary artery	Not common	Frequent	Very frequent

MPAP: mean pulmonary artery pressure; SPAP: systolic pulmonary artery pressure.

Cardiac magnetic resonance imaging

CMRI easily provides complete information about RV structure and function in patients with suspected or confirmed PH with high sensitivity and specificity in measuring RV mass index, RV diameters, RV thickness, RV free-wall motion, end-diastolic volume, end-systolic volume, stroke volume, and RV ejection fraction. CMRI can also provide information on the size and structure of pulmonary arteries and the blood flow through the lungs. It is more accurate than TTE in the assessment and follow-up of patients with PH, but it is a more time-consuming, higher cost, and less available technique. CMRI does not expose the patient to radiation; however, it can be difficult to perform in claustrophobic patients, and renal function should be checked before the test. Outside of PH centers, it is not widely used in diagnostic approach.⁴ Both TTE and CMRI play important roles in disease assessment, risk stratification, and evaluation of therapeutic intervention.

Computed tomography

CT provides detailed information about the pulmonary vasculature, lung parenchyma, and cardiac structure. Thus, information on the size and structure of the pulmonary arteries (PA) and the blood flow through the lungs can be obtained, identifying the presence of blood clots or other abnormalities. Accordingly, it is useful in the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) and can also identify distal obstructions, narrowing of the PA and their branches and distal stenosis. Additionally, it identifies pouch-like defects, intimal irregularities, PA webs or bands, and enlargement of bronchial arteries due to collateral blood supply, which is of prognostic significance, as these patients have better postsurgical evolution. CT can also detect underlying lung disease, such as interstitial lung disease or emphysema, which also contributes to PH.¹⁰ Currently, CT is a readily available technique, but patients are exposed to ionizing radiation and in some cases requires the administration of contrast dye.

Ventilation perfusion scan

Finally, V/Q scan evaluates the probability of blood clots in pulmonary vasculature. It involves the injection of a

radioactive tracer and the inhalation of a radioactive gas in order to investigate if there is a V/Q mismatch, indicating the presence of a blood clot in wedge-shaped perfusion defects with normal ventilation. Due to its high sensitivity, V/Q scan is the test of choice when screening patients with suspected CTEPH. A normal V/Q scan practically excludes the probability of CTEPH. Importantly, complete absence of perfusion in one lung should raise the possibility of other conditions different to CTEPH, such as vasculitis, malignancy and fibrosing mediastinitis. One of the drawbacks of V/Q scan is the high number of non-diagnostic or indeterminate tests, as well as underestimation of central vascular obstruction and its incapacity to differentiate pulmonary veno-occlusive disease and fibrosing mediastinitis.⁴ In clinical practice, V/Q scan seems to be underutilized, even though it is part of the current recommendations for suspicion of PH due to its high sensitivity and specificity.

In summary, advances in echocardiography have improved our ability to consider pulmonary pressure probability and to characterize RV dysfunction. TTE RV function surrogates are practical parameters, especially in follow-up. STE, 3DE, real-time 3DE, and CCE are all useful modern modalities that can provide more detailed information on RV function or dysfunction in PH. CMRI, CT, and V/Q scanning are useful imaging modalities in the diagnosis and risk stratification of PH. These techniques can help to guide treatment decisions and to improve clinical outcomes in this patient population. Every imaging modality has advantages and disadvantages (Table 2). Technique selection will be based on the clinical scenario and individual patient needs. According to findings, it is important to consider consultation with a health care professional who specializes in PH, avoiding unnecessary delays that could impact patient's health. Artificial intelligence will be available in the near future and will allow faster, reliable assessment of both RV and left ventricular volume, ejection fraction, mass, and global and segmental function. These advances will certainly be of major significance in patients with PH.

Table 2 – Imaging modalities in pulmonary hypertension: advantages and disadvantages

Imaging modality	Advantages	Disadvantages
Echocardiography	First choice, widely available Easily repeatable - monitoring Heart rhythm independent Pulmonary pressure calculation 2D, 3D, RT3D, ST, CEE Low cost No radiation	Operator dependent Acoustic window dependent Pulmonary pressure underestimation Pulmonary pressure overestimation
Cardiac magnetic resonance imaging	Acoustic window independent Complete RV structure and function Pulmonary circulation evaluation Myocardial tissue characterization Low intra-interobserver variability High quality images	Not widely available Technically limited in arrhythmias Contraindicated in renal failure Secondary renal damage in few cases Caution in claustrophobic patients High cost
Computed tomography	Acoustic window independent RV quantification Lung parenchyma assessment Mediastinum assessment Useful in CTEPH	Radiation exposure Contrast use Not for monitoring High cost
V/Q lung scan	Pulmonary vascular assessment Good for CTEPH screening High sensitivity and specificity	Non-specific findings High number of non-diagnostic tests Not for monitoring Radiotracer use High cost

2D: two-dimensional echocardiography; 3D: three-dimensional echocardiography; CEE: contrast-enhancement echocardiography; CTEPH: chronic thromboembolic pulmonary hypertension; RT3D: real-time three-dimensional echocardiography; RV: right ventricle; ST: speckle tracking echocardiography; V/Q: ventilation perfusion.

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