

Echocardiography in Pulmonary Arterial Hypertension: from Diagnosis to Prognosis

Eduardo Bossone, MD, PhD, Antonello D'Andrea, MD, PhD, Michele D'Alto, MD, Rodolfo Citro, MD, Paola Argiento, MD, PhD, Francesco Ferrara, MD, Antonio Cittadini, MD, PhD, Melvyn Rubenfire, MD, and Robert Naeije, MD, PhD, *Milan, Salerno, and Naples, Italy; Ann Arbor, Michigan; Brussels, Belgium*

Pulmonary arterial hypertension is most often diagnosed in its advanced stages because of the nonspecific nature of early symptoms and signs. Although clinical assessment is essential when evaluating patients with suspected pulmonary arterial hypertension, echocardiography is a key screening tool in the diagnostic algorithm. It provides an estimate of pulmonary artery pressure, either at rest or during exercise, and is useful in ruling out secondary causes of pulmonary hypertension. In addition, echocardiography is valuable in assessing prognosis and treatment options, monitoring the efficacy of specific therapeutic interventions, and detecting the preclinical stages of disease. (*J Am Soc Echocardiogr* 2013;26:1-14.)

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Pulmonary hypertension (PH) is a hemodynamic and pathophysiologic condition defined as an increase in mean pulmonary artery pressure (MPAP) of ≥ 25 mm at rest as assessed by right-heart catheterization (RHC). It can be found in multiple clinical conditions with distinct pathogenetic and clinical features, such as pulmonary arterial hypertension (PAH) and left-heart, lung, and thromboembolic diseases (Table 1).^{1,2} In particular, PAH is characterized by the presence of precapillary PH due to relative blood flow obstruction proximal to the lung capillary bed and increased pulmonary vascular resistance (PVR). This results in right ventricular (RV) pressure overload, ultimately leading to right-heart failure and death. PAH has an estimated prevalence of 30 to 50 cases per million individuals, affects women more frequently than men, and can be idiopathic, heritable, drug or toxin induced, or associated with other medical conditions, such as congenital heart disease (CHD), connective tissue disease, human immunodeficiency virus infection, portal hypertension, schistosomiasis, and chronic hemolytic anemia (Table 2).³

Given the nonspecific symptoms and subtle physical signs, particularly in the early stages, a high clinical index of suspicion is necessary to detect the disease before irreversible pathophysiologic changes occur. In this regard, transthoracic echocardiography, by providing direct and/or indirect signs of elevated pulmonary artery pressure (PAP), is

an excellent noninvasive screening test for patients with symptoms or risk factors for PH, such as connective tissue disease, anorexigen use, pulmonary embolism, heart failure, and heart murmurs. It may also provide key information on both the etiology and the prognosis of PH.⁴⁻⁶

In this review, we discuss the diagnostic and prognostic role of echocardiography in PAH.

PULMONARY HEMODYNAMICS IN THE ECHOCARDIOGRAPHY LAB

Table 3 lists Doppler echocardiographic indices for the evaluation of patients with clinical suspicion of PH.⁷⁻²⁶ Doppler echocardiography enables the reliable estimation of PAP, because in the absence of pulmonary flow obstruction, tricuspid regurgitation (TR) peak velocity (TRV) and RV outflow tract acceleration time have linear positive and negative correlations, respectively, with systolic PAP (SPAP) and MPAP measured by RHC.^{7-12,15-20,27} Furthermore, peak early diastolic and end-diastolic velocities of pulmonary regurgitation correlate significantly with MPAP and pulmonary artery end-diastolic pressures.^{17,18}

PVR may be estimated by dividing TRV (in meters per second) by the time-velocity integral of the RV outflow tract (in centimeters).^{21,22} The rationale for this method is based on the recognition that PVR is directly related to pressure changes and inversely related to pulmonary flow. This approach may have utility in distinguishing high PAP due to increased pulmonary blood flow (as occurs in hyperthyroidism, anemia, and obesity) from PH due to elevated PVR. An estimate of PVR may also be valuable for identifying patients with clinically worsening and severe PAH with no change or a decrease in MPAP as a consequence of progressive decrease in RV ejection fraction and stroke volume ($PVR = MPAP - \text{pulmonary artery occlusion pressure}/\text{cardiac output [CO]}$). TRV is used in daily practice to determine RV systolic pressure, which is considered equal to SPAP in the absence of pulmonary outflow tract obstruction and/or pulmonic valve stenosis. This is done by calculating the systolic transtricuspid gradient using the modified Bernoulli equation (as simplified by Hatle *et al.*)⁹ and then adding

From the Department of Cardiac Surgery, IRCCS Policlinico San Donato, Milan, Italy (E.B.); the Department of Cardiology and Cardiac Surgery, University Hospital "Scuola Medica Salernitana," Salerno, Italy (E.B., R.C.); the Department of Cardiothoracic Sciences, Monaldi Hospital, Second University of Naples, Naples, Italy (A.D., M.D., P.A.); the Department of Internal Medicine and Cardiovascular Sciences, University "Federico II," Naples, Italy (F.F., A.C.); the Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan (M.R.); and the Department of Physiology, Faculty of Medicine Erasme Academic Hospital, Université Libre de Bruxelles, Brussels, Belgium (R.N.).

Reprint requests: Eduardo Bossone, MD, PhD, FCCP, FESC, FACC, Via Principe Amedeo, 36, 83023 Lauro (AV), Italy (E-mail: ebossone@hotmail.com).
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Abbreviations

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|---|
| CCB = Calcium channel blocker |
| CHD = Congenital heart disease |
| CO = Cardiac output |
| IPAH = Idiopathic pulmonary arterial hypertension |
| LV = Left ventricular |
| MPAP = Mean pulmonary artery pressure |
| PAH = Pulmonary arterial hypertension |
| PAP = Pulmonary artery pressure |
| PCWP = Pulmonary capillary wedge pressure |
| PH = Pulmonary hypertension |
| PVR = Pulmonary vascular resistance |
| RAP = Right atrial pressure |
| RHC = Right-heart catheterization |
| RT3DE = Real-time three-dimensional echocardiography |
| RV = Right ventricular |
| SPAP = Systolic pulmonary artery pressure |
| TR = Tricuspid regurgitation |
| TRV = Tricuspid regurgitation peak velocity |
| 2D = Two-dimensional |
| WHO = World Health Organization |

an assumed or calculated right atrial pressure (RAP).⁹⁻¹² Several studies have shown modest to good correlations between estimated RV systolic pressure and invasively measured pressures ($R = 0.57-0.93$), suggesting that technical and biological variability are not negligible. This variability is further reflected in the sensitivity (0.79–1.00) and specificity (0.60–0.98) for diagnosing or ruling out PH.²⁸⁻³¹ However, to avoid false-positives, it is important to be aware that the resting physiologic range of SPAP is dependent on age and body mass index and may be as high as 40 mm Hg in older (age > 50 years) or obese (body mass index > 30 kg/m²) subjects.³² The age-related increase in SPAP is more common in patients with diabetes and is likely due to pulmonary artery noncompliance or abnormal left ventricular (LV) diastolic filling pressures occurring with aging and systemic hypertension. An increase in SPAP has a negative impact on survival.³³ Moreover, it should not be overlooked that SPAP is a flow-dependent variable, such as in anemia and hypothyroidism, as a TRV of 3 m/sec is easily achieved in normal subjects at rest after dobutamine infusion.³⁴

A few aspects must be kept in mind to ensure accurate estimates of SPAP. Because velocity measurements are angle dependent, TRV should be taken from multiple views (and off

context of the clinical scenario, searching for other “concordant clinical and echocardiographic signs” of pressure overload (Table 3).

In this regard, the European Society of Cardiology guidelines for the diagnosis and treatment of PH suggest to consider (1) PH unlikely for TRV ≤ 2.8 m/sec, SPAP ≤ 36 mm Hg (assuming RAP of 5 mm Hg), and no additional echocardiographic signs of PH; (2) PH possible for TRV ≤ 2.8 m/sec and SPAP ≤ 36 mm Hg but the presence of additional echocardiographic signs of PH or TRV of 2.9 to 3.4 m/sec and SPAP of 37 to 50 mm Hg with or without additional signs of PH; and (3) PH likely for TRV > 3.4 m/sec and SPAP > 50 mm Hg with or without additional signs of PH.²

ECHOCARDIOGRAPHIC FEATURES IN PULMONARY ARTERIAL HYPERTENSION

Figure 1 and Table 3 describe echocardiographic features in PAH. Because of chronic RV pressure overload, at the time of diagnosis, most patients present with enlarged right-side chambers, RV hypertrophy, increased interventricular septal thickness, an abnormal interventricular septum/posterior LV wall ratio (>1), and reduced global RV systolic function. Furthermore, the abnormal pressure gradient between the left and right ventricles results in shape distortion and motion of the interventricular septum (“flattening”), which persists throughout the cardiac cycle.³⁵ As a consequence, the left ventricle appears D-shaped, with reduced diastolic and systolic volumes but preserved global systolic function.⁶ Pericardial effusion and mitral valve prolapse have also been described in patients with PAH; the former may be a manifestation of impaired venous and lymphatic drainage secondary to elevated RAP, and the latter is related to a small left ventricle and the possible involvement of valve leaflets affected by associated connective tissue disorders.³⁷

At the time of definitive diagnosis, most patients with PAH show at least moderate TR, with SPAP ≥ 60 mm Hg. TR is usually caused by tricuspid annular dilation, altered RV geometry, and apical displacement of the tricuspid leaflets. The degree of TR cannot be used as a surrogate for the degree of PAP elevation.³⁸

Significant pulmonic valvular regurgitation is common in PAH. Pulsed-wave Doppler interrogation of the RV outflow tract usually reveals an acceleration time of <100 msec, which reflects abnormal MPAP.^{6-8,20} Finally, as a result of altered RV-LV interaction, LV diastolic dysfunction may be characterized by a marked dependence of LV filling on atrial contraction.^{39,40}

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transesophageal echocardiography should be considered in the following circumstances: (1) to confirm and assess congenital systemic-to-pulmonary shunts, (2) to assess the severity and contribution of mitral valve disease, (3) to characterize a right-sided intracardiac mass not well visualized with transthoracic echocardiography or other imaging techniques, and (4) to guide interventional procedures, such as balloon atrial septostomy.³⁶

EXERCISE-INDUCED PULMONARY HYPERTENSION: LOOKING BEYOND THE SCENE

The pulmonary circulation is a high-flow, low-pressure, low-resistance system. PVR is approximately one tenth of comparable systemic

axis if necessary), searching for the best envelope and maximal velocity. Additionally, the use of color flow Doppler is recommended to obtain the best alignment between regurgitant flow and the Doppler signal. From the apical position, the transducer must be angled more medially and inferiorly from the mitral valve signal. Although TR is present in >75% of the normal adult population, in case of a trivial regurgitant jet and a suboptimal continuous-wave Doppler spectrum, the injection of contrast agents (agitated saline, sonicated albumin, air-blood-saline mixture) may be required to achieve clear delineation of the jet envelope.^{35,36} Potential overestimation of Doppler velocities should be taken into account because of contrast artifacts. Furthermore, in severe TR with a large color flow regurgitant jet, the peak velocity may not reflect the true RV–right atrial pressure gradient because of early equalization of RV pressure and RAP. Thus, it is recommended to gather technically adequate TR signals and to consider SPAP values in the

Table 1 Hemodynamic definitions of PH

| Definition | Characteristics | Clinical group(s)* |
|------------------------------|---|--|
| PH | MPAP \geq 25 mm Hg | All |
| Precapillary PH | MPAP \geq 25 mm Hg PCWP \leq 15 mm Hg CO normal or reduced [†] | 1. PAH 3. PH due to lung disease 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms |
| Postcapillary PH | MPAP \geq 25 mm Hg PCWP > 15 mm Hg CO normal or reduced [†] | 2. PH due to left-heart disease |
| Passive | TPG \leq 12 mm Hg | |
| Reactive (out of proportion) | TPG > 12 mm Hg | |

TPG, Transpulmonary pressure gradient (MPAP – mean PCWP).

Values are measured at rest. Reproduced with permission from Galiè *et al.*²

*As defined in Table 2.

[†]High CO can be present in hyperkinetic conditions, such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anemia, hyperthyroidism, and so on.

values. In healthy subjects, moderate exercise induces mild increases in PAP that are linear with CO and decreases in PVR secondary to the dilation of compliant small vessels and/or the recruitment of additional vessels in the upper portion of normal lungs.⁴¹⁻⁴³

In elite athletes, substantial increases in PAP have been shown to occur during intense exercise as a result of marked increases in pulmonary blood flow along with increases in LV filling pressure.^{44,45} This “physiologic counteraction” may cause an impairment of the integrity of the pulmonary blood-gas barrier (pulmonary capillary “breaking stress”), with the development of exercise-induced pulmonary hemorrhage.^{45,46} Reported upper normal limits of Doppler-derived SPAP during exercise are <40 to 45 mm Hg in normal healthy individuals and <55 to 60 mm Hg in highly trained athletes.^{8,45,47,48} It is worth noting that PVR varies from one subject to another. Accordingly, the increase in PAP as a function of CO during exercise is quite variable as well, with reported slopes of PAP as a function of flow ranging from 0.5 to 2.5 mm Hg/L/min.^{49,50} There has been recent suggestion that steep increases in PAP may be a limiting factor for exercise capacity because of persistent limitations in RV output.^{49,51} Competitive athletes who exercise at high levels of CO and PAP because of an intrinsically steep pressure-flow relationship may be exposed in the long term to RV remodeling and subsequent arrhythmias.⁵²

A number of investigators have reported subsets of patients with pathologic SPAP responses during exercise and normal SPAP at rest; this is referred to as exercise-induced PH (Table 4).^{48,53-64} Recently, using invasive maximum cardiopulmonary exercise testing, Tolle *et al.*⁶⁵ carefully phenotyped a large cohort of patients with exercise-induced PAH. In particular, they showed that at maximum exercise, oxygen uptake was lowest in resting PAH, intermediate in exercise-induced PAH, and highest in normal subjects, whereas MPAP and PVR followed the opposite pattern. These findings suggest that exercise-induced PAH is a mild, intermediate physiologic stage of PAH, with greater vasodilator reserve and less severe degrees of pulmonary vascular disease.⁶⁶ However, exercise-induced PAH is rarely considered because of the lack of specific symptoms or signs. Exercise Doppler echocardiographic evaluation should be performed in patients with modest changes in exercise capacity with no other identifiable causes, particularly in asymptomatic or mildly symptomatic subjects at high risk for PAH (i.e., first-degree relatives with PAH,

carriers of the PAH gene, patients with human immunodeficiency virus infection, and patients with connective tissue diseases). Although exercise Doppler echocardiography has been proved to be a safe and viable screening tool for detecting a pulmonary hypertensive response to exercise in high-risk patients, it remains technically demanding and requires considerable experience. It should also be emphasized that the optimal exercise protocol (treadmill vs supine, upright, or semirecumbent bicycle) has not been established. Importantly, data derived during or after bicycle exercise should not be applied to posttreadmill or recumbent exercise stress echocardiography, because each protocol is characterized by different loading conditions. However, in the assessment of PH, exercise must be dynamic (cycling or walking) rather than resistive (handgrip, weight lifting). Resistive exercise should be avoided because it results in decreased venous return during the Valsalva maneuver and little change in maximal oxygen uptake and CO but increased systemic vascular resistance and an eventual increase in intrathoracic pressure, each of which may contribute to elevated MPAP at any given level of flow.⁶⁷ A resistive component at high levels of dynamic exercise may spuriously increase MPAP at given levels of CO. Although the results of MPAP on exercise are often expressed for a given workload, results of exercise hemodynamics might be better expressed in MPAP as a function of flow (e.g., millimeters of mercury per liter) rather than as a function of workload, given that the mechanical efficiency of muscle contraction varies from one subject to another.⁶⁸ Recently, Argiento *et al.*,⁵⁰ in a series of 113 healthy volunteers (mean age, 37 ± 13 years; range, 19–63 years; 57 women [50%]) reported exercise flow-corrected upper limits of normal for MPAP of 34 mm Hg at a CO of <10 L/min, 45 mm Hg at a CO of <20 L/min, and 52 mm Hg at a CO of <30 L/min. All subjects underwent exercise echocardiographic testing on a semirecumbent cycle ergometer with workload increments of 20 to 30 W every 2 min until the maximum tolerated before the onset of dyspnea and/or leg pain. Echocardiographic measurements were taken during the last minute of each workload.

Thus, at present, semirecumbent exercise appears to be more suitable than treadmill exercise for reliable and reproducible Doppler echocardiographic recordings, given that measures are obtained during both exercise and recovery.^{47,50,69} Furthermore, the full physiologic range of PAP response to exercise should be defined in

Table 2 Updated clinical classification of PH (Dana Point, 2008)

| |
|--|
| 1. PAH |
| 1.1. Idiopathic |
| 1.2. Heritable |
| 1.2.1. BMPR2 |
| 1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia) |
| 1.2.3. Unknown |
| 1.3. Drug and toxin induced |
| 1.4. Associated with |
| 1.4.1. Connective tissue diseases |
| 1.4.2. HIV infection |
| 1.4.3. Portal hypertension |
| 1.4.4. Congenital heart disease |
| 1.4.5. Schistosomiasis |
| 1.4.6. Chronic hemolytic anemia |
| 1.5. Persistent PH of the newborn |
| 1. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis |
| 2. PH due to left-heart disease |
| 2.1. Systolic dysfunction |
| 2.2. Diastolic dysfunction |
| 2.3. Valvular disease |
| 3. PH due to lung disease and/or hypoxia |
| 3.1. Chronic obstructive pulmonary disease |
| 3.2. Interstitial lung disease |
| 3.3. Other pulmonary diseases with mixed restrictive and obstructive patterns |
| 3.4. Sleep-disordered breathing |
| 3.5. Alveolar hypoventilation disorders |
| 3.6. Chronic exposure to high altitude |
| 3.7. Developmental abnormalities |
| 4. Chronic thromboembolic pulmonary hypertension |
| 5. PH with unclear and/or multifactorial mechanisms |
| 5.1. Hematologic disorders: myeloproliferative disorders, splenectomy |
| 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis |
| 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders |
| 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis |

ALK1, activin receptor–like kinase type 1; BMPR2, bone morphogenetic protein receptor type 2; HIV, human immunodeficiency virus. Reproduced with permission from Simonneau *et al*.³

relation to age, gender, body mass index, and level of physical training. Well-designed longitudinal studies are warranted to investigate the natural history of exercise-induced PAH and whether preclinical treatment can prevent the development of more severe forms of pulmonary vascular disease in susceptible persons.^{70,71} Exercise-induced PAH remains a fascinating clinical condition and exercise Doppler echocardiography a versatile tool “to look beyond the scene” of otherwise unexplained effort dyspnea.

ECHOCARDIOGRAPHY AND PROGNOSIS

PAH is a progressive disease with a relatively poor prognosis even in the modern era (reported overall survival rates are 87% [95%

CI, 84%–90%], 76% [95% CI, 73%–80%], and 67% [95% CI, 63%–71%] at 1, 2, and 3 years, respectively).⁷² The natural history is heterogeneous and influenced mostly by “treatability” and/or “reversibility” of the underlying etiology, with systemic sclerosis and portopulmonary hypertension having the worst and CHD the best prognosis (neonatal right ventricles may also adapt better to increased PVR).^{1,2,73,74}

Before treatment, patients with suspected PAH should have confirmation of the diagnosis by exclusion of other causes of PH with RHC and/or left-heart catheterization, including both Fick and thermodilution estimates of CO. Although PAH is common in systemic sclerosis, about 50% of patients with PH will exhibit significant LV diastolic dysfunction and elevated LV end-diastolic pressure. Pulmonary capillary wedge pressure (PCWP) and pulmonary artery occlusion may be inaccurate in patients with more than mild to moderate PH. A careful and comprehensive prognostic evaluation in patients with PAH should include indices of impaired clinical status (World Health Organization [WHO] functional classes I–IV), exercise capacity as measured by standardized 6-min hall walk or cardiopulmonary exercise test, biomarkers such as B-type natriuretic peptide, renal function, Doppler echocardiography, and possibly magnetic resonance imaging. Each of these can correlate with gold-standard findings on cardiac catheterization. All of these parameters are indicators of significant right-heart dysfunction and are associated with unfavorable outcomes (death or lung transplantation) in patients with PAH.² Echocardiographic predictors of prognosis include pericardial effusion, indexed right atrial area, the degree of septal shift toward the left ventricle in diastole, tricuspid annular plane systolic excursion, pulmonary vascular capacitance, and RV Doppler index (Tei index or RV myocardial performance index) (Table 5).^{14,37,75–82} In a series of 53 patients with PAH (38 women; mean age, 45 ± 14 years), at a mean follow-up of 2.9 years, the RV Doppler index, a measure of global RV function, was a strong predictor of adverse outcomes on univariate and multivariate regression analysis.⁷⁷

NONCONVENTIONAL ECHOCARDIOGRAPHY

The accuracy of conventional two-dimensional (2D) echocardiography in delineating RV structure and function is challenged by several factors, including (1) the asymmetric and complex pyramidal shape of the right ventricle, along with its retrosternal location; (2) limited definition of the endocardial surface; and (3) marked load dependence of many functional indices.^{83–86} Emerging ultrasound techniques, namely, Doppler tissue imaging, strain imaging, and real-time three-dimensional echocardiography (RT3DE), may provide additional information (Figure 2).^{87–90}

Doppler Tissue Imaging

Doppler tissue imaging of the mitral and tricuspid annulus has been extensively applied to assess LV and RV function in many cardiac diseases, including CHD, heart failure, and PH.^{91–95}

According to the current American Society of Echocardiography guidelines on right-heart assessment, basal RV free wall S' < 10 cm/sec should be considered a marker of RV dysfunction, particularly in young adults (no sufficient data exist in the elderly).^{8,96,97}

Specifically, Ruan and Nagueh,⁹⁸ in a series of 70 patients with idiopathic PAH (IPAH), demonstrated that lateral mitral annular velocities can reliably predict the presence of normal or reduced mean PCWP, ruling out “de facto” a left-heart etiology. In addition, tissue Doppler analysis of systolic and diastolic myocardial velocities may

Table 3 Doppler echocardiographic indices for the evaluation of patients with clinical suspicion of PH^{7,8}

| Key indices (cutoff) | Additional indices (cutoff) | Complementary indices (cutoff) | Research tools |
|--|---|--|--|
| Pulmonary hemodynamics | | | |
| SPAP = $4 \times TRV^2 + RAP$ ⁹⁻¹² (TRV > 2.8–2.9 msec: SPAP 36 mm Hg) | MPAP = TVI _{TR} + RAP ¹³ (≥25 mm Hg) | AT _{RVOT} (<100 msec) log ₁₀ (EPSPAP) = $-0.004(PAAT)$ + 2.1 ¹⁵ | PVCAP = SV/4 × (TRV ² – PRV ²) ¹⁴ (<0.8 mL/mm Hg predicts mortality in PAH patients) |
| RAP = IVC size and collapsibility ¹⁶ (>2.1 cm, collapse < 50%: RAP 15 mm Hg) | | RV IVRT' (by DTI; >65 msec: SPAP > 40 mm Hg; <59 msec: RAP > 8 mm Hg) | |
| MPAP = $4 \times PRV^2 + RAP$ ^{17,18} (≥25 mm Hg) | MPAP = $0.61 \times SPAP + 2$ mm Hg ¹⁹ | MPAP = $90 - 0.62 \times AT_{RVOT}$ ²⁰ MPAP = $79 - 0.45 \times AT_{RVOT}$ | |
| DPAP = $4 \times (PRV ED)^2 + RAP$ PVR = TRV/TVI _{RVOT} (cm) × 10 + 0.16 ²¹ (>0.2: PVR > 2 WU; <0.15: normal PVR) | PVR = SPAP/(HR × TVI _{RVOT}) ²² (>0.076: indexed PVR > 15 RU) | FVE _{RVOT} ²³ (midsystolic “notch”) | |
| PCWP = $1.9 + 1.24 \times E/E'$ ²⁴ (E/E' >15: PCWP > 15 mm Hg) | LAVi ²⁵ (>31 mL/m ²) | | |
| Impaired RV systolic function | | | |
| TAPSE (<16 mm) | Tei index: (IVRT + IVCT)/ET (>0.40 by PW Doppler; >0.55 by DTI) | | 3D RV EF (<44%) |
| RV FAC (<35%) | | | RV LPSS ²⁶ (≥–19%) |
| S'-wave velocity by DTI (<10 cm/sec) | | | |

AT, Acceleration time by PW Doppler; DPAP, diastolic PAP; DTI, Doppler tissue imaging; ED, end-diastole; EF, ejection fraction; EPSPAP, estimated peak SPAP; FAC, fractional area change [(end-diastolic area – end-systolic area)/end-diastolic area × 100]; FVE, Doppler flow velocity envelope; HR, heart rate; ET, ejection time; IVC, inferior vena cava; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LAVi, left atrial volume index (increases the accuracy for estimation of PCWP when E/E' is 8–13 in the gray zone); LPSS, longitudinal peak systolic strain; PAAT, pulmonary artery acceleration time; PRV, peak pulmonary regurgitation velocity; PSAX, parasternal short-axis; PVCAP, pulmonary vascular capacitance; PW, pulsed-wave; RA, right atrial; RVOT, RV outflow tract; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion (M-mode echocardiography); 3D, three-dimensional TVI, time-velocity integral.

Indirect 2D echocardiographic signs include RV hypertrophy (RV wall thickness > 5 mm from the subcostal view), RV dilation (diameter > 42 mm at the base, >35 mm at the midlevel, longitudinal > 86 mm), RA dilation (area > 18 cm², minor-axis dimensions > 44 mm, major-axis dimensions > 53 mm), RVOT dilation (PSAX distal diameter > 27 mm at end-diastole), systolic flattening of the interventricular septum, LV eccentricity index (>1 in systole ± diastole), and pericardial effusion.

track the improvement in RV function (at the septum and RV free wall levels) and LV filling (at the lateral mitral annular level) in response to long-term targeted therapy.^{4,24,98,99}

Two-Dimensional Strain

Despite the lack of reproducibility and the paucity of data, ventricular strain and torsion analysis (an easily obtained, cost-effective, objective, angle-independent, noninvasive technique) has been implemented to assess regional and global RV function as well as the impact of RV pressure overload on ventricular interdependence and relative LV performance.^{87-90,100-115}

Puwanan *et al.*¹¹⁶ using 2D speckle-tracking echocardiography in a series of 44 patients with precapillary PH (88% with PAH), demonstrated that chronic RV pressure overload directly affects RV longitudinal systolic deformation and interventricular septal and LV geometry. Furthermore, they noted a decreased LV torsion along with an impairment of segmental longitudinal and circumferential strain that was greater for the interventricular septum than for the LV free wall.

In a cohort of 80 patients with PAH, Sachdev *et al.*⁸² reported significantly decreased RV longitudinal peak systolic strain ($-15 \pm 5\%$) and strain rate ($-0.80 \pm 0.29 \text{ sec}^{-1}$). Furthermore, RV free wall strain worse than -12.5% was found to be associated with a greater

degree of clinical deterioration within 6 months, and it also predicted 1-year, 2-year, 3-year, and 4-year mortality (unadjusted 1-year hazard ratio, 6.2; 95% CI, 2.1–22.3). After adjusting for age, sex, PH cause, and functional class, patients had a 2.9-fold higher rate of death per 5% absolute decline in RV free wall strain at 1 year.

Recently, Haecck *et al.*²⁶ in a series of 142 patients with PH of different etiologies (53 [37%] with PAH), observed that RV longitudinal peak systolic strain (≥–19%) was significantly associated with worse New York Heart Association functional class, lower tricuspid annular plane systolic excursion, and all-cause mortality (37 patients died during a median follow-up period of 2.6 years) (Figure 3).

However, further studies in larger populations are needed to confirm the incremental prognostic value of strain-based measures over other well-established invasive and noninvasive predictive parameters of mortality, considering the variety of PH etiologies and their underlying pathophysiologic mechanisms.¹⁻³

RT3DE

Accurate volume analysis independent of RV size and shape, without foreshortened views and geometric assumptions, ensures the superiority of RT3DE over conventional echocardiographic methods in

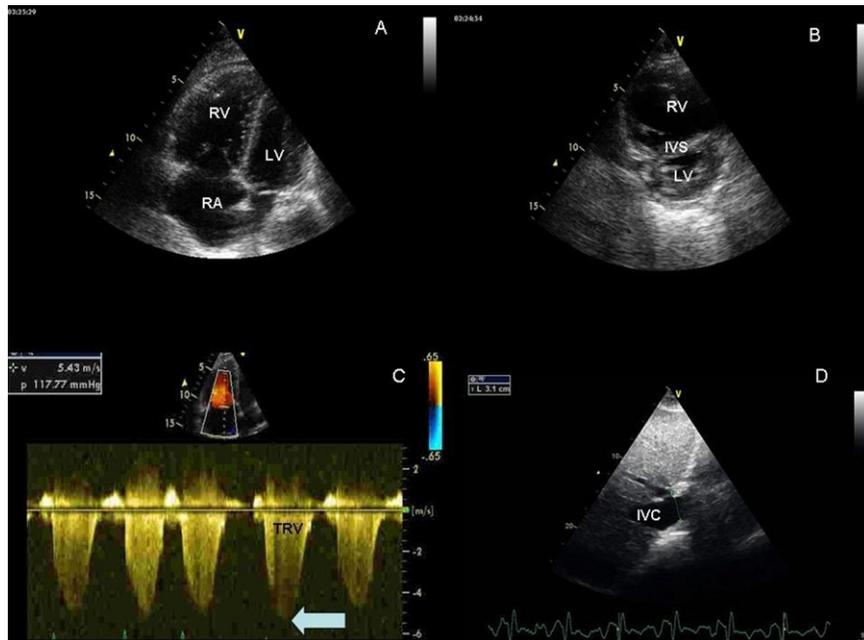


Figure 1 A young patient with IPAH. **(A,B)** Apical four-chamber and parasternal short-axis views, showing severe right ventricular enlargement and dislocation of the interventricular septum (IVS) toward the left ventricle (LV). **(C)** Doppler tracing of TR, showing severe PH (TRV >5 m/sec) (arrow). **(D)** Dilated inferior vena cava (IVC) from the subcostal view. RA, Right atrium; RV, right ventricle.

the assessment of RV function.^{8,117-119} Compared with cardiac magnetic resonance, RV volumes calculated from RT3DE showed significantly better agreement and lower intraobserver and interobserver variability than those calculated from 2D echocardiography.¹²⁰⁻¹²² On the basis of current evidence, the combination of conventional 2D and Doppler methods with RT3DE can be recommended for the evaluation of RV function in various clinical settings. Grapsa *et al.*,¹²³ in a homogeneous cohort of 60 consecutive patients with PAH, demonstrated that RV remodeling (relative changes in mass, volumes, and ejection fraction) can be comprehensively assessed with both RT3DE and cardiac magnetic resonance without intravenous contrast agents. Each imaging modality provided a significant degree of accuracy and reproducibility, with cardiac magnetic resonance being more reproducible for measurements of ejection fraction and RV mass. The use of intravenous contrast agents can further improve RV visualization, particularly in smaller right ventricles. In addition, RT3DE enables unique views to better understand specific causes of PH (i.e., septal defects, complex congenital pathology, left-sided valvular or ventricular heart disease) and to investigate RV functional and morphologic changes.¹²⁴⁻¹²⁷ In this regard, Grapsa *et al.*¹²⁷ evaluated 141 consecutive patients with PH (55 with PAH, 32 with chronic thromboembolic disease, and 34 with PH secondary to mitral regurgitation) using RT3DE and demonstrated that different causes of PH may lead to diverse RV remodeling, regardless of RV systolic pressures at rest. They found that patients with PAH had more dilated, hypertrophied, and poorly functioning right ventricles compared with those with other forms of PH. This may be explained by the inability of the right ventricle to adapt to the silent, prolonged, irreversible, and pathophysiologic alterations of pulmonary vessels (vasoconstriction, cell proliferation, and thrombosis) observed in PAH.¹²⁸ It should be also underlined that in patients with PAH, the degree of right-heart dilation and dysfunction is a key determinant of adverse clinical outcomes.^{1,2,14,77-82,129}

Finally, the capability to complement RV assessment with geometric data on tricuspid valve tenting in TR secondary to PH confirms the

unique value of RT3DE to comprehensively address right-heart structure and function in patients with PAH.^{127,130}

SCREENING FOR PULMONARY ARTERIAL HYPERTENSION: THE PIVOTAL ROLE OF ECHOCARDIOGRAPHY

The substantial time delay from symptom onset to definite diagnosis in PAH remains an unresolved issue. This has relevant clinical implications, especially when considering the better prognosis and response to treatment with early detection of the disease (WHO class I or II, 6-min walk distance > 450 m, normal or mildly increased B-type natriuretic peptide, no evidence of right-heart failure). Regular echocardiographic screening of patients at high risk for PAH or with unexplained symptoms of fatigue or dyspnea is essential and provides an overall good sensitivity and specificity.^{1,2,4}

As discussed, symptomatic (WHO classes II–IV) and asymptomatic (WHO class I) patients at high risk for PAH, with exercise-induced PH or transthoracic echocardiographic findings suggestive of or consistent with PH should undergo RHC (the gold standard), and possibly left-heart catheterization, to confirm the diagnosis and direct treatment. In asymptomatic subjects at high risk for PAH (those with known genetic mutations, first-degree relatives in a familial PAH family, patients with systemic sclerosis, patients with congenital shunts, patients with portal hypertension, or mildly symptomatic patients with human immunodeficiency virus infection), regular clinical and echocardiographic screening (at yearly intervals) is warranted to detect the disease at an early stage.^{1,2,4} An echocardiography-based diagnostic algorithm is shown in Figure 4. After an initial comprehensive clinical evaluation, the patient should undergo a resting or exercise transthoracic echocardiographic examination to detect direct and/or indirect signs of PH and to exclude left-heart disease or CHD. Additional imaging and diagnostic laboratory tests should be considered when secondary causes of PH are suspected on clinical grounds. Finally, it is important to realize that PAH accounts for

Table 4 PAP response to exercise in patients at high risk for PAH

| Study | Associated disease | n | Age (y) | Height (cm) | Weight (kg) | Exercise protocol | RAP estimate (mm Hg) | Baseline SPAP (mm Hg) | Peak SPAP (mm Hg) |
|--|----------------------------|-----------------|-------------|-------------|-------------|------------------------------------|------------------------|------------------------------|------------------------------|
| Himelman <i>et al.</i> (1989) ⁵³ | COPD | 36 (15 female) | 32–80 | | | Supine bicycle (10 or 25 W/2 incr) | From IVC | 46 ± 20 (ctrl 22 ± 4) | 83 ± 30 (ctrl 31 ± 7) |
| Oelberg <i>et al.</i> (1998) ⁵⁴ | Asymptomatic ASD | 10 (4 women) | 52.9 ± 11.2 | 167 ± 7 | 82 ± 20 | Upright bicycle (10 W/2 incr) | From IVC | 31 ± 8 (ctrl 17 ± 8) | 51 ± 10 (ctrl 19 ± 8) |
| Grünig <i>et al.</i> (2000) ⁵⁵ | HAPE-S | 9 men | 45 ± 8 | 182 ± 8 | 82 ± 9 | Supine bicycle (25 W/2 incr) | Fixed value (5 mm Hg) | 28 ± 4 (ctrl 27 ± 4) | 55 ± 11 (ctrl 36 ± 3) |
| Grünig <i>et al.</i> (2000) ⁵⁶ | Relatives of IPAH cases | 52 | | | | Supine bicycle (25 W/2 incr) | Fixed value | 24 ± 4 (NR); 23 ± 3 (AR) | 37 ± 3 (NR); 56 ± 11 (AR) |
| Collins <i>et al.</i> (2006) ⁵⁷ | Scleroderma | 51 (49 women) | 53.9 ± 12.0 | | | Treadmill (5.9 ± 1.9 METs) | Fixed value (10 mm Hg) | 24 ± 8 | 38 ± 12 |
| Alkotob <i>et al.</i> (2006) ⁵⁸ | Scleroderma | 65 (56 women) | 51 ± 12 | | | Treadmill (1 to 13.4 METs) | Fixed value (5 mm Hg) | 25 ± 8 | 39 ± 8 |
| Kiencke <i>et al.</i> (2008) ⁵⁹ | HAPE-S | 10 | 33 ± 2 | | | Supine bicycle | | 19 ± 4 (ctrl 17 ± 3) | 23 ± 6 (ctrl 11 ± 5) |
| Steen <i>et al.</i> (2008) ⁶⁰ | Scleroderma | 54 (51 women) | | | | Treadmill (85% pred max HR) | Fixed value (10 mm Hg) | 34.5 ± 11.5 | 51.4 |
| Grünig <i>et al.</i> (2009) ⁴⁸ | Relatives of IPAH patients | 291 (125 women) | 37 ± 16 | 169 ± 9 | 69 ± 15 | Supine bicycle (25 W/2 incr) | From IVC | 20.7 ± 5.4 (ctrl 20.4 ± 5.3) | 39.5 ± 5.6 (ctrl 35.5 ± 5.4) |
| Reichenberger <i>et al.</i> (2009) ⁶¹ | Scleroderma | 33 (31 women) | 54 ± 11 | | | Supine bicycle (30 W/2 incr) | From IVC | 23 ± 8 | 40 ± 11 |
| Möller <i>et al.</i> (2010) ⁶² | ASD and VSD | 44 (25 female) | 17.5 ± 3.3 | 167 ± 8.8 | 59 ± 11 | Supine bicycle (25 W/2 incr) | From IVC | 20.7 ± 5.3 (ctrl 21.8 ± 3.6) | 37 (24–76) (ctrl 39 [17–63]) |
| Kovacs <i>et al.</i> (2010) ⁶³ | Connective tissue disease | 52 (42 women) | 54 ± 11 | 167 ± 8 | 69 ± 12 | Supine bicycle (25W/2 incr) | From IVC | 27 ± 5*; 23 ± 3†; 23 ± 3‡ | 55 ± 10*; 29 ± 8†; 30 ± 7‡ |
| D'Alto <i>et al.</i> (2011) ⁶⁴ | Systemic sclerosis | 172 (155 women) | 51.8 ± 21.5 | 163 ± 9 | 66 ± 14 | Supine bicycle (25W/2 incr) | From IVC | 26.2 ± 5.3 (ctrl 20.6 ± 3.7) | 36.9 ± 8.7 (ctrl 25.9 ± 3.3) |

AR, Abnormal response to exercise; ASD, atrial septal defect; COPD, chronic obstructive pulmonary disease; ctrl, controls; HAPE-S, high-altitude pulmonary edema susceptible; HR, heart rate; incr, increments; IVC, inspiratory collapse of the inferior vena cava; NR, normal response to exercise; VSD, ventricular septal defect.

*Exercise SPAP > 40 mm Hg.

†Exercise SPAP < 40 mm Hg, peak oxygen uptake < 75%.

‡Exercise SPAP < 40 mm Hg, peak oxygen uptake > 75%.

Table 5 Echocardiographic prognostic predictors in patients with PAH

| Study | Patients | Age (y) | Etiology | Treatment | Echocardiographic indices | Follow-up (median) | Outcome |
|--|---------------|---------|---|----------------------------------|---|--------------------|-----------------------------|
| Eysmann <i>et al.</i> (1989) ⁷⁵ | 26 (18 women) | 40.8 | PPH | Vasodilators* | Pericardial effusion | 19.7 mo | Death |
| Hinderliter <i>et al.</i> (1997) ⁷⁶ | 79 (57 women) | | PPH | PGI | Pericardial effusion | 1 y | Death, lung transplantation |
| Yeo <i>et al.</i> (1998) ⁷⁷ | 53 (38 women) | 45 ± 14 | PPH | CCBs | Tei index [†] ≥ 0.83 | 2.9 y | Death, lung transplantation |
| Raymond <i>et al.</i> (2002) ⁷⁸ | 81 (59 women) | 40 ± 15 | PPH | PGI | Pericardial effusion, RA area index (5 cm ² /m) | 1 y | Death, lung transplantation |
| Forfia <i>et al.</i> (2006) ⁷⁹ | 63 (52 women) | 55 ± 15 | IPAH, SSc, CTD, RD, CTEPH | PGI, ERA, PDE5-i inhibitors | TAPSE < 1.8 cm | 19.3 mo | Death |
| Mahapatra <i>et al.</i> (2006) ¹⁴ | 54 (41 women) | 44 ± 11 | PPH | PGI, ERA, CCBs | PVCAP | 49.3 mo | Death |
| Brierre <i>et al.</i> (2010) ⁸⁰ | 79 (36 women) | 61.4 | IPAH, anorexigens, SSc, IDD, portal hypertension, HIV, RD, CTEPH, sarcoidosis | ERA, PGI, PDE5-i inhibitors, PEA | MPAP ≥ 49 mm Hg, DPAP ≥ 29 mm Hg, abnormal EDSC, IVC diameter [‡] , Tei index [†] ≥ 0.98, TAPSE [§] , pericardial effusion | 12 mo | Death |
| Ghio <i>et al.</i> (2011) ⁸¹ | 72 (52 women) | 52 ± 16 | IPAH | According to current guidelines | RV diameters (>36.5 mm) | 38 mo | Death |
| Sachdev <i>et al.</i> (2011) ⁸² | 80 (61 women) | 56 ± 14 | PAH | According to current guidelines | RV free wall strain per absolute 5% decrease | 24 mo | Death |

CCB, Calcium channel blocker; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; DPAP, diastolic PAP as measured from pulmonary regurgitant flow; ERA, endothelin receptor antagonist (bosentan); EDSC, end-diastolic septal curve, defined as abnormal if convex toward the right ventricle on the two-dimensional parasternal short-axis view; HIV, human immunodeficiency virus; IDD, immune dysfunction disease; IVC, inferior vena cava; PDE5-i, phosphodiesterase type 5 inhibitor (sildenafil); PEA, pulmonary endarterectomy; PGI, prostacyclin and analogues (epoprostenol, iloprost, treprostinil); PPH, primary PH; PVCAP, pulmonary vascular capacitance; RA, right atrial; RD, respiratory disease; SSc, systemic sclerosis (scleroderma); TAPSE, tricuspid annular plane systolic excursion.

*CCBs, prazosin, hydralazine.

[†]Tei index = (isovolumic contraction time + isovolumic relaxation time)/ejection time.

[‡]Twenty or more millimeters with respiratory variation in IVC diameter <50%.

[§]As a continuous variable for each 1-mm decrease.

^{||}RV end-diastolic diameters (RV wall thickness ≤ 6.6 mm) in the parasternal long-axis view.

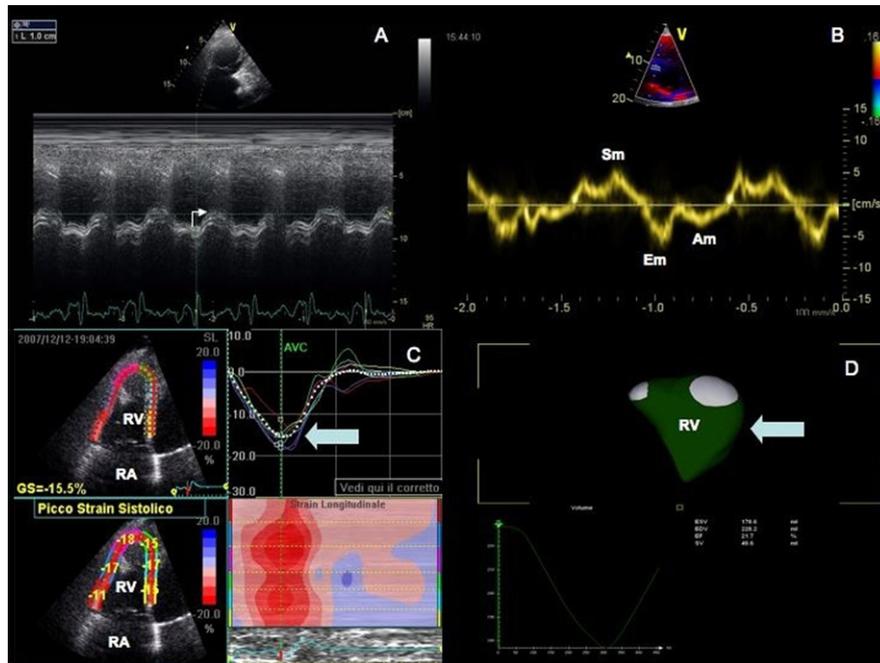


Figure 2 Impaired right ventricular function assessed by different echocardiographic techniques in a young patient with IPAH. **(A)** Standard M-mode echocardiography: severely reduced tricuspid annular plane systolic excursion (*arrow*). **(B)** Pulsed-wave Doppler tissue imaging of the right ventricular lateral wall: reduced myocardial systolic peak velocity (Sm) and both early (Em) and late (Am) diastolic peak velocities. **(C)** Right ventricular 2D speckle strain: impairment of global longitudinal strain (GS) (<16%), an index of right ventricular myocardial deformation, and of segmental myocardial deformation (see *arrow* showing longitudinal deformation curves of six right ventricular myocardial segments). **(D)** Dynamic three-dimensional tripartite Beutel model (*arrow*), showing a dilated right ventricle (RV) with depressed ejection fraction (22%). AVC, Aortic valve closure; RA, right atrium.

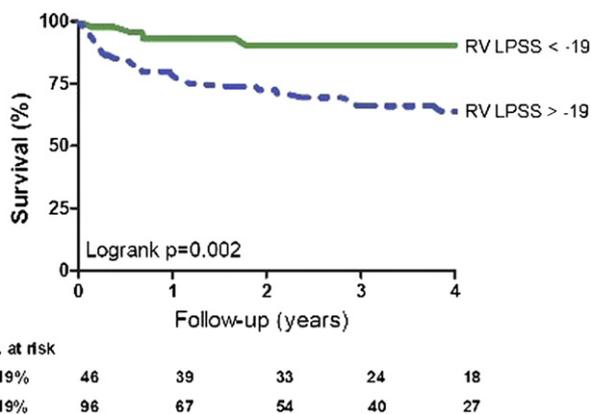


Figure 3 Kaplan-Meier survival curves in a PH population. Kaplan-Meier survival curve for patients with RV longitudinal peak systolic strain (LPSS) < -19% (*solid line*) and patients with RV LPSS ≥ -19% (*dotted line*). During a median follow-up period of 31.2 months (interquartile range, 10–50 months), 37 patients (26%) died. Patients with RV LPSS ≥ -19% had significantly worse survival than those with RV LPSS < -19%. Reproduced with permission from Haecck *et al.*²⁶

only 3% to 4% of all causes of PH, the vast majority being due to left-heart (78%–80%) and/or lung (10%–12%) diseases.²

RHC and Vasoreactivity Testing

RHC is required to confirm the diagnosis of PAH, to assess the severity of hemodynamic impairment, and to test the vasoreactivity of

the pulmonary circulation.² The procedure has very low morbidity (1.1%) and mortality (0.05%) rates if performed at experienced centers.¹³¹ It is usually performed through direct puncture of the right internal jugular vein or the right or left femoral vein. The following variables must be recorded during RHC: PAP (systolic, diastolic, and mean), RAP, PCWP, and RV pressure. CO must be measured in triplicate. Superior vena cava, pulmonary artery, and systemic arterial blood oxygen saturation should also be determined. These measurements are needed for the calculation of PVR. Satisfactory recording of PCWP is crucial for the differential diagnosis of PH due to left heart disease. PCWP > 15 mm Hg excludes the diagnosis of precapillary PAH. Rarely, left-heart catheterization may be required for direct assessment of LV end-diastolic pressure. The Fick method is mandatory in the presence of a systemic-to-pulmonary shunt.

Vasoreactivity testing is strongly recommended at the time of RHC in IPAH, heritable PAH, and PAH associated with anorexigen use to identify patients who may benefit from long-term therapy with calcium channel blockers (CCBs; nifedipine, diltiazem, and amlodipine).^{132,133}

Acute vasodilator challenge should be performed only at experienced centers using short-acting and safe drugs with no or limited systemic effects, such as inhaled nitric oxide (the preferred agent). Alternatively, intravenous epoprostenol or adenosine may also be used, but with a risk for systemic vasodilator effects.²

A positive acute response is defined as a reduction in MPAP ≥ 10 mm Hg to reach an absolute value of MPAP ≤ 40 mm Hg with increased or unchanged CO.² Only about 10% of patients with IPAH will meet these criteria. Approximately half of IPAH-positive acute responders are also positive long-term responders to CCBs,⁴ and only in

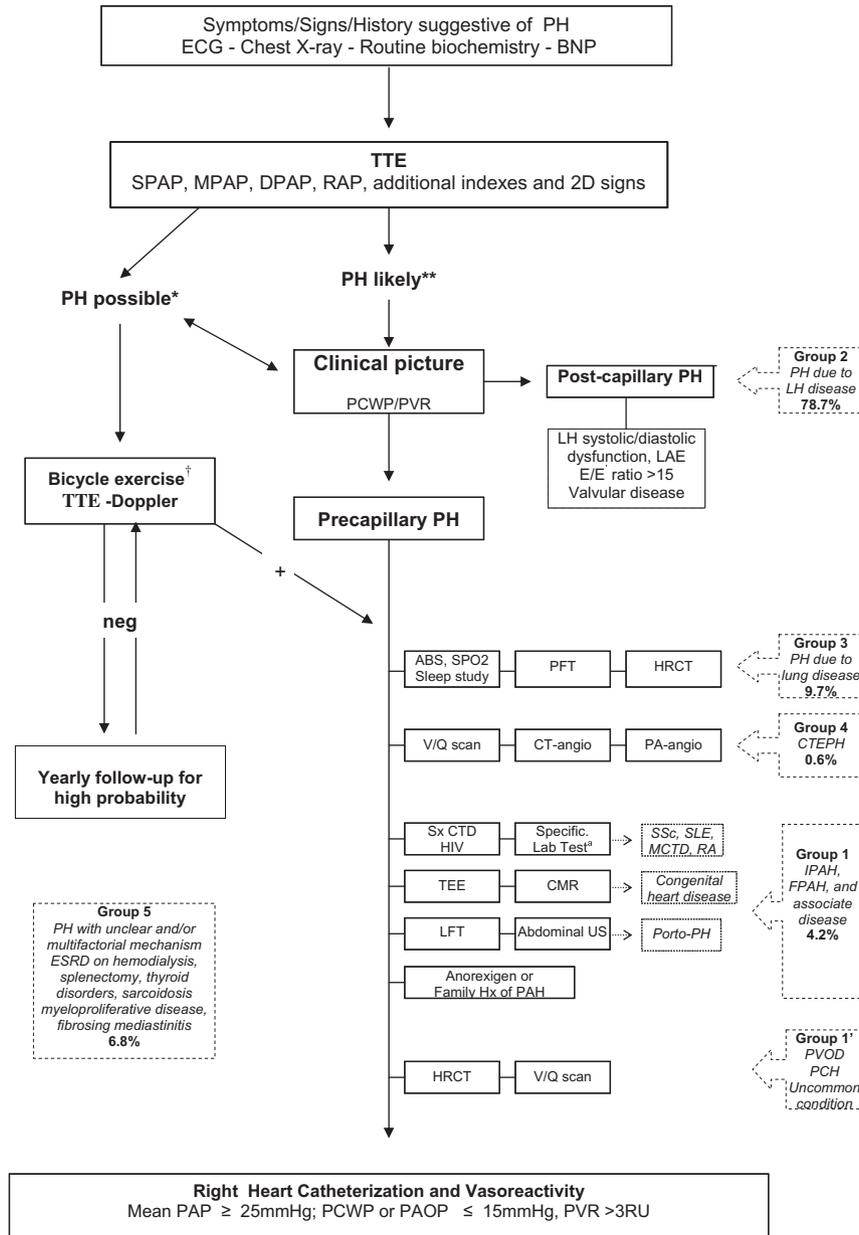


Figure 4 Role of echocardiography in the diagnosis of PAH. *ABG*, Arterial blood gases or saturation; *BNP*, B-type natriuretic peptide; *CMR*, cardiac magnetic resonance; *CT-angio*, contrast-enhanced computed tomographic pulmonary angiography; *CTD*, connective tissue disease; *CTEPH*, chronic thromboembolic PH; *DPAP*, diastolic PAP; *ECG*, electrocardiography; *ESRD*, end-stage renal disease; *Fam Hx*, family history; *FPAH*, familial PAH; *HIV*, human immunodeficiency virus; *HRCT*, high-resolution computed tomography; *LAE*, left atrial enlargement; *LFT*, liver function test; *LH*, left heart; *MCTD*, mixed connective tissue disease; *neg*, negative; *PA-angio*, pulmonary artery angiography; *PAOP*, pulmonary artery occlusion pressure; *PCH*, pulmonary capillary hemangiomatosis; *PFT*, pulmonary function test (spirometry, diffusing capacity of the lungs for carbon monoxide, overnight oximetry, polysomnography); *Porto-PH*, portopulmonary hypertension; *PVOD*, pulmonary veno-occlusive disease; *RA*, rheumatoid arthritis; *RU*, resistance units; *SLE*, systemic lupus erythematosus; *SPO₂*, saturation of peripheral oxygen; *Sx*, symptoms; *SSc*, systemic sclerosis; *TEE*, transesophageal echocardiography; *TTE*, transthoracic echocardiography; *US*, ultrasound; *V/Q*, ventilation/perfusion. ^aSpecific laboratory tests for thyroid function, immunology-rheumatology (antinuclear antibodies, C-reactive protein, Scl-70 antibodies), hematology, HIV, and schistosomiasis. *TRV ≤ 2.8 m/sec and SPAP ≤ 36 mm Hg but the presence of additional echocardiographic variables or TRV of 2.9 to 3.4 m/sec and SPAP of 37 to 50 mm Hg, with or without additional echocardiographic variables suggestive of PH. *TRV > 3.4 m/sec and SPAP > 50 mm Hg, with or without additional echocardiographic variables suggestive of PH. [†]Doppler upper limits: <40 to 45 mm Hg in healthy individuals, <55 to 60 mm Hg in highly trained athletes; MPAP 34 mm Hg at a CO of <10 L/min, 45 mm Hg at a CO of <20 L/min, and 52 mm Hg at a CO of <30 L/min.^{8,45,50}

these patients is the continuation of CCBs as a single therapy reasonable.

The effectiveness of acute vasoreactivity tests and long-term treatment with CCBs in patients with associated PAH is still debated. In particular, the use of CCBs is not recommended in patients with CHD-related PAH because of their negative inotropic and systemic vasodilator effects (with subsequent increase in right-to-left shunting).

Recent observations suggest that residual pulmonary vasoreactivity may be a valuable tool for the risk stratification of patients with CHD-related PAH.^{134,135}

Finally, acute vasoreactivity studies to identify patients with long-term favorable responses to CCBs are not recommended in clinical groups 2, 3, 4, and 5.

CONCLUSIONS

Echocardiography is a pivotal screening test in symptomatic patients at risk for PAH. As an imaging modality, it has the advantage of being widely available, cost effective, and safe. It also plays an important role in assessing outcomes, monitoring the efficacy of specific therapeutic interventions for PH, and detecting the preclinical stages of disease. Newer ultrasound techniques may provide key additional information in the assessment of right-heart structure and function.

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