Section A -Research paper

Diagnosis of Pulmonary Hypertension: Review Article

Mohammed Awad Mohammed[1] , Mohammad Abdalla Eltahlawi [1], Maruwan Abdulwanis Mohammed[2], Lamiaa Gaber Zake[1], Walid I.M. Elgendy[1]

[1] Chest Department Faculty of Medicine , Zagazig University, Egypt

[2] Chest Department Faculty of Medicine, Omar Al-Moktar University , Libya

Corresponding Author: Maruwan Abdulwanis Mohammed

Email: ma.mohamed23@medicine.zu.edu.eg

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Abstract:

Pulmonary hypertension (PH) is classified into 5 clinical subgroups according to 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines,PH affects approximately 1% of the global population, and over half of patients with heart failure may be affected. The Preliminary tests in patients with symptoms and physical findings suggestive of PH include blood tests, immunology ,electrocardiography, chest radiography, pulmonary function tests ,6MWD and Transthoracic echocardiography is used to estimate the probability of PH. All patients with suspected PH without confirmed left-sided heart or lung diseases, should have Right-sided heart catheterization is essential for accurate diagnosis and classification.

Keywords: Pulmonary hypertension**,** Preliminary tests**,** Right-sided heart catheterization**.**

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Introduction:

Pulmonary hypertension (PH) is a chronic progressive disease that has remained challenging since the first World Symposium meeting in 1973. This meeting opened the era of ground breaking discoveries about the disease's pathophysiology and various treatment options. In this review, we aim to summarize the latest evidence regarding the disease, its definition, classification and diagnosis **(1)**.

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) of 20 mm Hg or greater at rest, confirmed by right-sided heart catheterization. While there are many causes of PH, While there are many causes of PH, it is almost always associated with deteriorating symptoms and increased mortality, regardless of the underlying disease. Pulmonary hypertension affects approximately 1% of the global population,upto10% of individuals older than 65years, and at least 50% of patients with heart failure (HF) **(2).**

Hemodynamic definitions of pulmonary hypertension (PH) that take into account more than just the pulmonary artery pressure (PAP) measured during right heart

catheterization (RHC) are likely to be more useful in clinical practice. This is because they have implications for prognosis and factors in this regard are pulmonary vascular resistance and pulmonary capillary wedge pressure**(3)**.

treatment, and can help in further categorizing the disease. The two important

TABLE(1) Haemodynamic definition of pulmonary hypertension 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines(4)

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units. Some patients present with elevated mPAP (>20 mmHg) but low PVR (⩽2 WU) and low PAWP (⩽15 mmHg); this haemodynamic condition may be described by the term 'unclassified PH' (see text for further details).

TABLE(2) Clinical classification of pulmonary hypertension 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines(4)

GROUP 1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.1.1 Non-responders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable[a]
1.3 Associated with drugs and toxins[a]
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn
GROUP 2 PH associated with left heart disease
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction[b]
2.2 Valvular heart disease
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
GROUP 3 PH associated with lung diseases and/or hypoxia
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with mixed restrictive/obstructive pattern
3.4 Hypoventilation syndromes
3.5 Hypoxia without lung disease (*e.g.* high altitude)
3.6 Developmental lung disorders
GROUP 4 PH associated with pulmonary artery obstructions
4.1 Chronic thrombo-embolic PH
4.2 Other pulmonary artery obstructions[c]
GROUP 5 PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders[d]
5.2 Systemic disorders[e]
5.3 Metabolic disorders[f]
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis

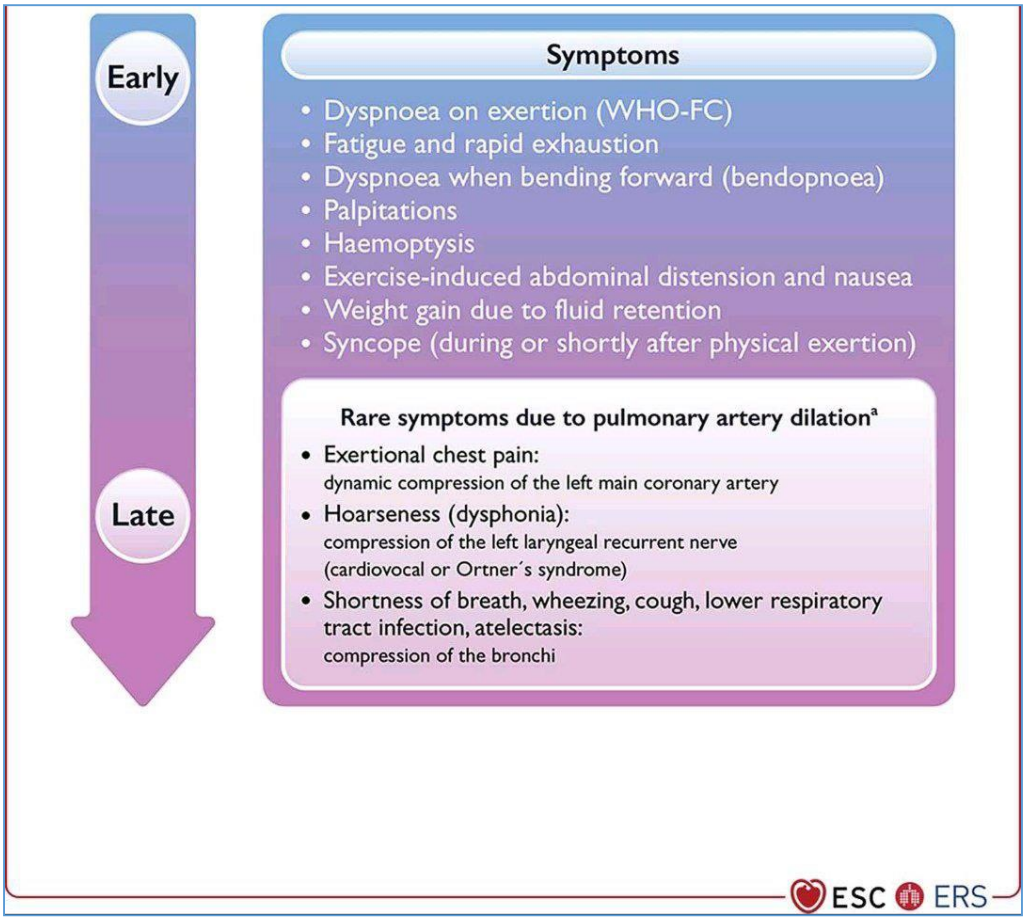
Preliminary Tests

1.Clinical presentation (5-7)

Symptoms of PH are mainly linked to right ventricle (RV) dysfunction, and typically associated with exercise in the earlier course of the disease. The cardinal symptom is dyspnea on progressively minor exertion. Other common symptoms are related to the stages and severity of the disease, and are listed in (Figure 1).

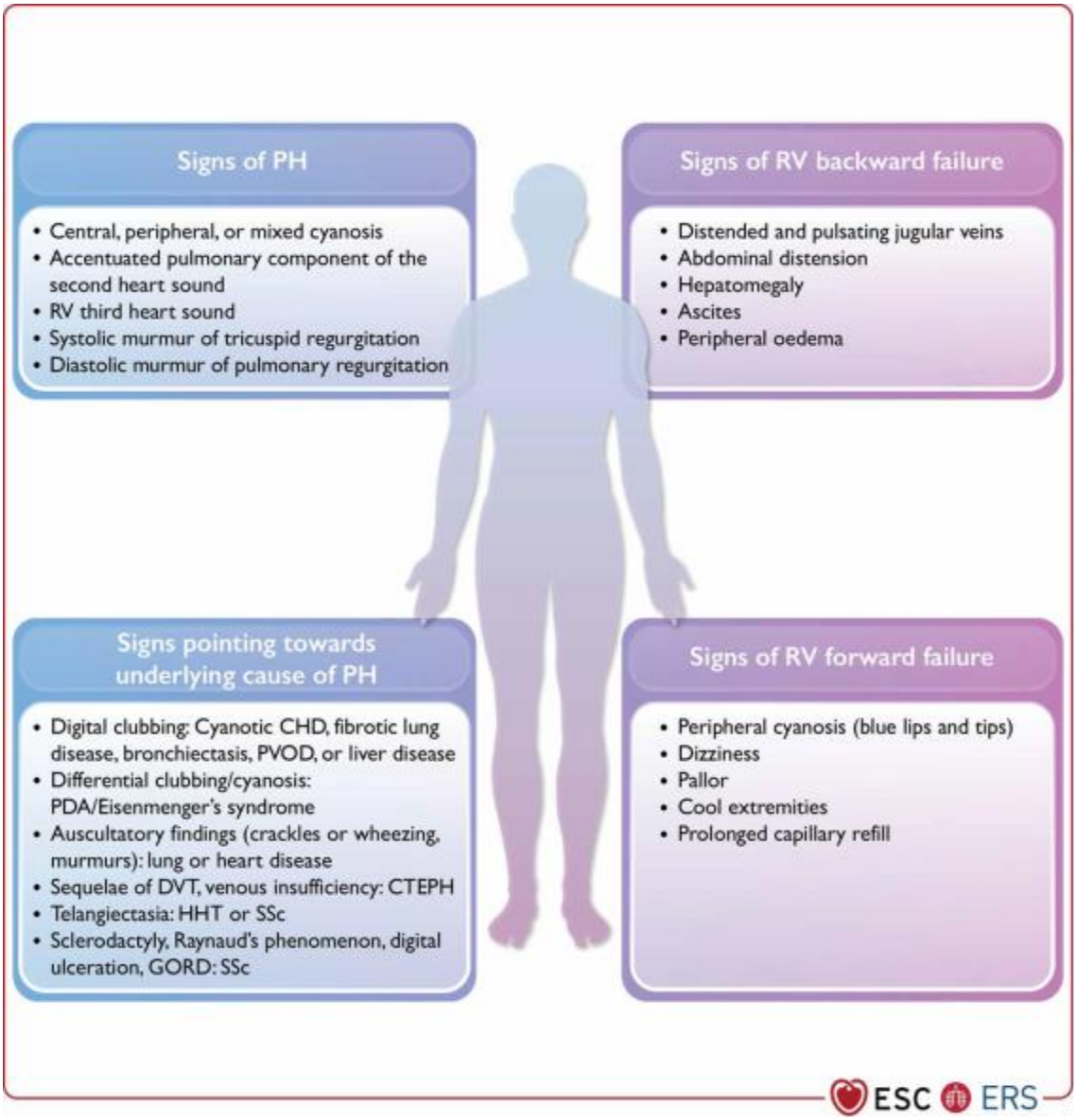
Potential clinical signs and physical findings are summarized in (Figure 2) Importantly, the physical examination ,Past history , family history and Drugs history as (Aminorex, Fenfluramine, Dexfenfluramine ,Toxic rapeseed oil ,Benfluorex, SSRIs, Phenylpropanolamine, Chemotherapeutic agents, Interferon, Amphetamines,Oral contraceptives estrogen, L-Tryptophan , Methamphetamines ,Cigarette smoking) may also be the key to identifying the underlying cause of PH.

figure(1) symptom pulmonary hypertension 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines(4)



Figure(2) signs of pulmonary

hypertension 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines(4)



FIGURE(2) Clinical signs in patients with pulmonary hypertension. CHD, congenital heart disease; CTEPH,chronic thrombo-embolic pulmonary hypertension; DVT, deep venous thrombosis; GORD, gastro-oesophagealreflux disease; HHT, hereditary haemorrhagic telangiectasia; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; RV, right ventricle; SSc, systemic sclerosis.

2.blood test and immunology (8)

The initial diagnostic assessment of patients with newly diagnosed PH aims to identify comorbidities and possible causes or complications of PH. Laboratory tests that should be obtained at the time of PH diagnosis include: blood counts (including haemoglobin) serum electrolytes (sodium, potassium),kidney function (creatinine, calculation of estimated glomerular filtration rate, and urea),uric acid, liver parameters

(alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, γ-glutamyltranspeptidase, bilirubin), iron status (serum iron, transferrin saturation, and ferritin) and BNP or NT-proBNP. In addition, serological studies should include testing for parasitic infection, hepatitis viruses and HIV.

Basic immunology laboratory work-up is recommended, including screening tests for anti-nuclear antibodies,anti-centromere antibodies, and anti-Ro. Screening for biological markers of antiphospholipid syndrome is recommended in patients with CTEPH. Additional thrombophilia screening is not generally recommended, unless therapeutic consequences are to be expected . Pulmonary arterial hypertension and other forms of severe PH can be associated with thyroid function disorders; hence, laboratory screening should include at least thyroid-stimulating hormone.

3.Chest Radiograph

Chest radiographs can be used to identify abnormalities in patients with pulmonary hypertension (PH). These abnormalities can include central pulmonary arterial dilatation, which is in contrast to the loss of peripheral blood vessels. In addition, an enlarged right ventricle (RV) or right atrium (RA), particularly in advanced cases, may be visible. A chest radiograph can also help in differential diagnosis by revealing changes that suggest the presence of lung disease or left heart disease. However, it is important to note that PH cannot be excluded if the chest radiograph appears normal. **(9)**

4.Electrocardiography (ECG)

Electrocardiography is a diagnostic tool used to measure the electrical impulses of the heart by attaching electrodes to the patient's skin. It can provide early indications of the presence of pulmonary hypertension (PH). ECG may detect abnormalities that suggest right atrial or ventricular dilatation, such as right bundle branch block (RBB), right axis deviation (RAD), RV hypertrophy, RV strain, P pulmonale, and QTc prolongation. RV strain is more sensitive for screening than RV hypertrophy, making it a better choice for early detection of PH.**(9)**

5.Transthoracic Echocardiography

Doppler transthoracic echocardiography involves taking a sonogram of the heart using an ultrasound probe placed on the patient’s chest. It is used to assess normal functioning of the heart and estimate the pressures in the right heart. One of the most important parameters of echocardiography is the tricuspid regurgitation velocity (TRV) that allows an estimate of the systolic pulmonary artery pressure (PAP), which was found to be associated with poor outcome if elevated by even mild levels. It can be used to determine the size and thickness of the right ventricle, which may get enlarged in patients with PH. Other echocardiographic parameters associated with PH include measurements from the pulmonary artery (e.g. reduced RV outflow tract acceleration time), ventricles (eg, RV/left ventricle basal diameter ratio > 1.0, flattening of the interventricular septum), or increases in inferior vena cava diameter or right atrium area **(10).**

Echocardiography to estimate the probability of PH.

The probability of PH is estimated by transthoracic echocardiography. The unique geometry of the right ventricle makes it challenging to obtain RV ejection fraction from 2-dimensional echocardiography, and therefore surrogate measures of RV function are used. Firstly, peak tricuspid regurgitation velocity (TRV) is measured by continuous-wave Doppler echocardiography, and pulmonary artery systolic pressure is estimated using the simplified Bernoulli equation. Next, TRV is classified as 2.8 m/s or less or not measurable, 2.9 to 3.4 m/s, or greater than 3.4 m/s. Echocardiographic signs suggestive of PH include RV/left ventricular (LV) basal diameter ratio of greater than 1.0, flattening of the interventricular septum, and pulmonary artery RV outflow Doppler acceleration time of less than 105 ms. According to the category of TRV and the presence or absence of echocardiographic signs, the patient can be assigned a low, intermediate, or high probability of PH **(10)**.

The presence of elevated pulmonary artery systolic pressure by this method, however, is neither specific to nor predictive of the hemodynamic subgroup or classification of PH, nor does it provide insight into the nature of changes in pulmonary vascular resistance (PVR), pulmonary artery wedge pressure (PAWP), or cardiac output. In addition, several other transthoracic echocardiographic parameters can indicate the probability of PH **(11)**.

Common abnormal measurements of the right side of the heart in PH include tricuspid annular plane systolic excursion of less than 17 mm, RV systolic tissue Doppler velocity of less than 10 cm/s measured at the lateral tricuspid annulus, and RV ejection fraction of less than 45%. With cardiac magnetic resonance imaging and the presence of late gadolinium enhancement, reduced pulmonary arterial distensibility, and retrograde flow have a high predictive value for identification of PH, although no single measurement can exclude PH **(12)**.

Roles of echocardiography in the diagnosis and assessment of PH

Echocardiography has several additional roles in the assessment of PH. For example, an echocardiogram can be used to predict the probability of elevated PVR with normal PAWP or to detect occult postcapillary PH **(13)**.

Signs suggesting pulmonary hypertension due to left sided heart disease (PH-LHD) include LV ejection fraction less than 50%, E/é ratio (ratio between early mitral inflow velocity and mitral annular early diastolic velocity) greater than 15, LA volume index greater than 34 mL/m2, LV mass index greater than 104 g/m2 in males and greater than 90 g/m2 in females, and evidence of valvular heart disease **(11)**. Conversely, high pulmonary arterial pressures accompanied by a small LA volume are strongly suggestive of PAH. An algorithm to estimate the probability of PH-LHD has been proposed **(14)**.

Echocardiographic parameters reported to predict survival in patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) include tricuspid regurgitation velocity (TRV), tricuspid annular plane systolic excursion, pulmonary artery dilatation, moderate to severe tricuspid

regurgitation, RV functional area change, pericardial effusion, and myocardial performance index **(15)**.

6.Pulmonary Function Tests

Pulmonary function tests in PH patients assess the amount of air the lungs can hold, the amount of air moving in and out, and the lungs ability to exchange oxygen. Through the measurement of total lung capacity (TLC), forced expiratory volume (FEV), forced vital capacity (FVC) and lung diffusion capacity for carbon monoxide (DLCO) **(3)**.

7.6MWT

Two 6MWTs were performed according to the official European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines on subsequent days using a 30 m straight walking course using cones as turnaround points. Use of walking aids (cane, rollator, etc.) was allowed during the 6MWTs and patients were instructed to take all usual medications. Patients were instructed to walk as far as possible and the distance walked (6MWD) was registered after each test. All tests were supervised by a trained and qualified technician who walked behind the patient, providing them with standardized phrases for encouragement every minute and informing them about the remaining time of the test. Patients were permitted to stop (if required) during the test, but were instructed to resume walking once they were able to. Heart rate (beats/min) and oxygen saturation (SpO_2) as measured by pulse oximetry were assessed before, during and at the end of the 6MWTs and perceived dyspnea and leg fatigue (modified Borg scale; range 0-10) were assessed at the start (at rest) and at the end (at peak exertion) of the test. Oxygen supplementation was used if required, and oxygen desaturation during the 6MWT was defined as a drop of ≥4% in SpO_2 and an end-SpO_2 of <88% **(16)(17).**

8.Ventilation/Perfusion Scan

Ventilation/perfusion scan (V/Q scan) is performed using radioactive material that is inhaled as well as injected (via a blood vessel) into the lungs. This produces a picture of air and blood flow in the lungs that may reveal the presence of blood clots within the lungs. The doctor will review the images that are produced to evaluate the health of the lungs. The V/Q scan is useful for differential diagnosis for excluding chronic thromboembolic pulmonary hypertension (CTEPH) that can be cured by surgical pulmonary thromboendarterectomy **(3)**.

9.Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (MRI) is an accurate and reliable method that helps assess multiple cardiac parameters including RV size and function, cardiac output (CO), stroke volume, and pulmonary artery distensibility **(9)**.

10.Abdominal ultrasound

An abdominal ultrasound examination should be part of the comprehensive diagnostic work-up of patients with newly diagnosed PH, particularly if liver disease is suspected. A major objective is to search for liver disease and/or portal hypertension ,or portocaval shunt (Abernethy malformation). During the course of the disease, patients with PH may develop secondary organ dysfunction mainly affecting the liver and kidneys**(18).**

Confirmatory Test(Gold standard)

Right Heart Catheterization(pulmonary artery catheterization)

Under current guidelines, right heart catheterization (RHC) is a gold standard test for confirming the diagnosis of PH before any PH treatment is initiated. RHC is used to measure PAP, left ventricular filling pressure, and CO. It can also evaluate pulmonary hypertension due to left heart disease, assess the severity of pulmonary hypertension, and identify the subset of patients who respond favorably to acute vasodilators such as nitric oxide (these patients respond favorably to treatment with high-dose calcium channel blockers/CCBs). The patients who respond favorably to acute vasodilator testing and are treated with CCBs should be followed closely for safety and efficacy with a complete reassessment including RHC after 3 to 4 months of therapy **(9)**.

Right heart catheterization is commonly performed by accessing the common femoral vein in the leg, the internal jugular vein in the neck, or the antecubital veins in the arm. In the leg, the femoral vein becomes the external iliac vein and then drains into the inferior vena cava, draining into the right atrium. The cephalic vein in the arm drains into the subclavian vein, which then drains into the right atrium. In the neck, the internal jugular vein joins the subclavian vein and forms the brachiocephalic vein. Brachiocephalic veins from both sides drain into the superior vena cava, which drains into the right atrium. Antecubital venous access has been associated with shorter procedure time and lower chances of significant hematomas **(19)**.

Indications (20) (21).

- Suspected cardiogenic shock
- Evaluation of a patient with dyspnea to diagnose or exclude pulmonary hypertension, constrictive pericardial disease, restrictive cardiomyopathy, heart failure with a preserved ejection fraction
- Determine response to vasodilator therapy in pulmonary hypertension
- Cardiac tamponade
- Intracardiac left-to-right shunt quantification
- Guiding fluid management and hemodynamic monitoring of patients after surgery or complicated myocardial infarction, heart failure, shock
- Adult congenital heart disease
- Evaluation for cardiac transplantation
- Surveillance status post-cardiac transplant
- Post cardiac transplant with new or worsening symptoms suggestive of graft rejection
- Pre-implantation assessment of left ventricular assist devices
- Post-implantation optimization after left ventricular assist device placement
- In valve disease when there are discrepancies between clinical presentation and non-invasive diagnostic testing .

Contraindications (19)

Absolute contraindications include right-sided endocarditis, right-sided tumor, or thrombus. Relative contraindications

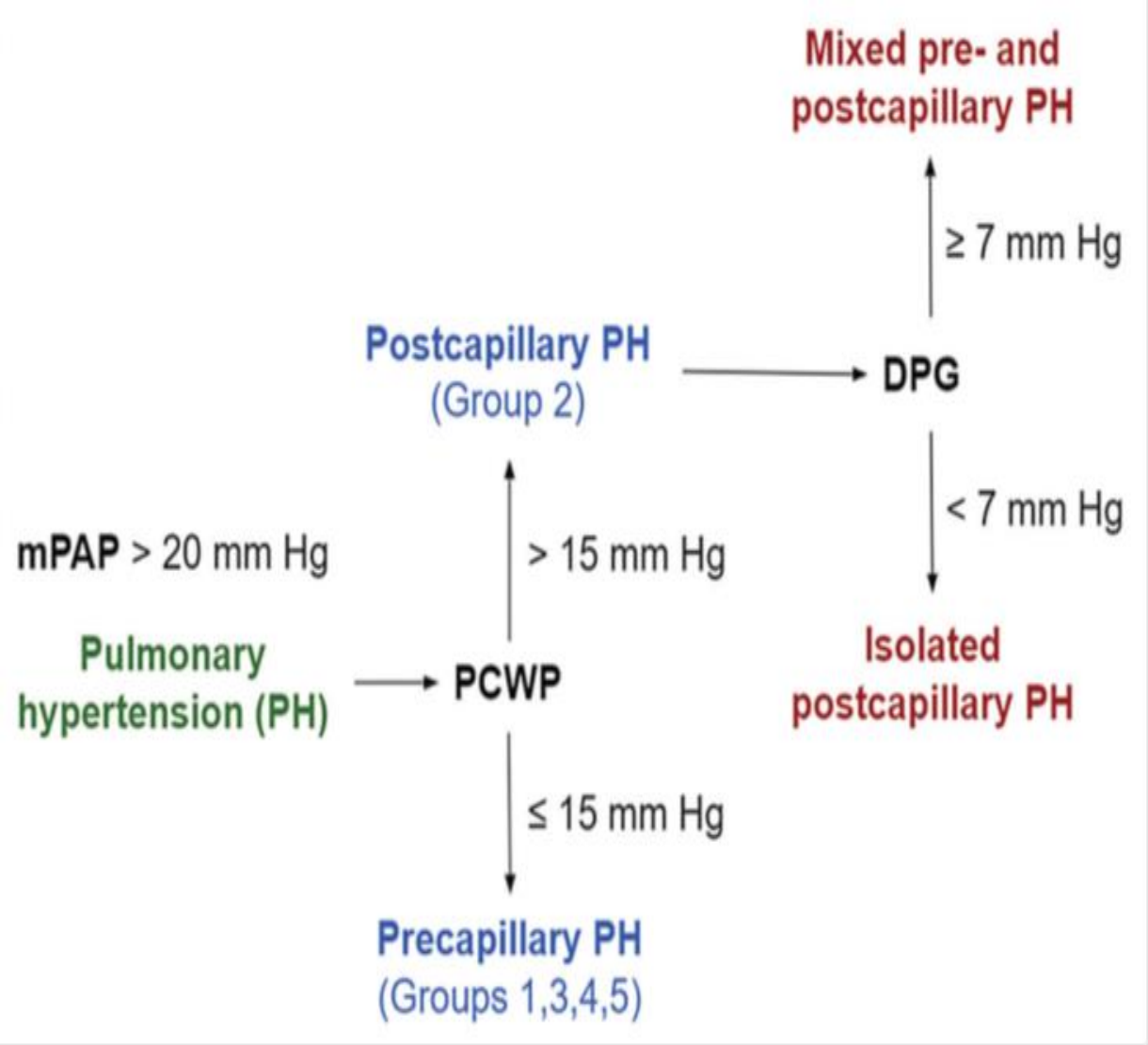
include severe coagulopathy or bleeding diathesis. Appropriate caution should be exercised in the setting of arrhythmias, left bundle branch block to avoid provoking dysrhythmias

Right heart catheterization to diagnose and classify pulmonary hypertension

The purpose of RHC is to confirm the diagnosis of PH (class I, level of evidence C), determine its severity, identify the etiology to guide management (class I, level of evidence C), and assess vasoreactivity of the pulmonary vasculature (class IIa, level of evidence C). Given the significant impact hemodynamic measurements have on the management of PH, all patients with PH should undergo a RHC, especially since the procedure itself has very low morbidity (1.1%) and mortality (0.055%). Right heart catheterization allows for accurate measurement of right atrial (RA) and ventricular (RV) pressures, pulmonary artery pressure (PAP) and mean PAP (mPAP), pulmonary capillary wedge pressure (PCWP), and venous oxygen saturation from the pulmonary artery (PA), as well as superior vena cava (SVC), inferior vena cava (IVC), RA, and RV oxygen saturations if a shunt is suspected **(10)**.

Calculated measurements performed during RHC include : (1) cardiac output (CO) and index (CI) by Fick equation or thermodilution, (2) systemic vascular resistance (SVR), (3) transpulmonary gradient (TPG), (4) diastolic pressure gradient (DPG), and (5) pulmonary vascular resistance (PVR). The CO and CI by Fick should be chosen over thermodilution if there is a suspected shunt since thermodilution may be inaccurate due to early circulation of the injectate. The shunt can be identified from a step-up in the venous oxygen saturations obtained from the SVC, IVC, RA, RV, and PA (also known as a shunt run) **(22)**.

Figure (3). Hemodynamic definitions of pulmonary hypertension (PH), including PH with left heart disease (23).



This is also seen with mixed pre- and post-capillary PH. The hemodynamic waveforms can also provide additive information. In the presence of RV failure, the RA pressure will be significantly elevated. When contracting against elevated RV diastolic pressures, a prominent *a* wave is seen on the RA tracing. The RA waveform may display prominent *v* waves, suggesting severe tricuspid regurgitation, which is often seen with PH. Large v waves are also visible with decreased RA compliance from chronic elevated pressure. Normally, the RV functions in a low-impendence, high-capacitance, low-pressure system. It can easily accommodate increases in volume but is exquisitely sensitive to changes in afterload. In the early stages of PH, RV function is normal and can pump against an increase in pulmonary vascular resistance. As the RV fails, RV end-

diastolic pressure rises. The RV waveform will show a sharp early diastolic dip followed by elevated and sustained diastolic pressure. A prominent *a* wave may also be seen, which reflects RV noncompliance **(24)**.

The PA systolic pressure (PASP) is elevated in PH and should equal the RV systolic pressure in the absence of pulmonic stenosis. PA diastolic pressure (PADP) is an indirect measurement of the LA pressure and LV end-diastolic pressure (LVEDP) in the absence of downstream pulmonary venous or mitral valve pathology. Thus, in postcapillary PH, PADP also will be elevated. While PCWP and LVEDP are often used interchangeably to describe left-sided filling pressures, it is important to understand that they both provide different information **(22)**.

The mean PCWP provides an integrated measure of the hemodynamic burden imposed by the left atrial (and indirectly LV) operating compliance on the pulmonary circulation. In contrast, the LVEDP is a surrogate measure of LV pre-load and LV diastolic operating compliance alone **(25)**.

The discrepancies between LVEDP-PCWP are particularly exaggerated in the presence of a large *v* wave as in mitral regurgitation or stiff LA syndrome, but also in mitral stenosis, pulmonary vein stenosis, and pulmonary veno-occlusive disease. Interestingly, the PCWP has been shown to have greater prognostic significance than LVEDP in patients with heart failure with preserved ejection fraction (HFpEF) and thus must always be measured accurately In fact, when trying to calculate pulmonary arteriolar resistance or evaluate the cause of dyspnea, clinicians should preferentially use the mean PCWP instead of the LVEDP **(26)**.

It is important to note that in the later stage of disease, severe PH with RV failure might demonstrate decreased PA pressures to near-normal levels and should not be mistaken for a lack of pathology. Rather, it is because the failing RV is unable to generate the expected pressures, and this is often accompanied by significantly elevated RA and RV end-diastolic pressures **(24)**.

As discussed earlier, a PCWP $\geq$ 15 mm Hg distinguishes between pre- and postcapillary PH. In cases of severe PH, hybrid tracings overestimating the wedge pressure are common. In such cases, PCWP can be confirmed with a wedge oxygen saturation (> 92%) or by measuring the LVEDP directly (assuming no mitral stenosis). To complete the baseline hemodynamic assessment, CO should also be measured. Cardiac output is normal in patients who are well compensated, but it decreases as RV failure worsens, so patients can develop cardiogenic shock. Regardless of the underlying cause of PH, RV failure ultimately leads to hemodynamic deterioration and death. Hence, RV dysfunction is a harbinger of mortality in patients with PH **(22)**.

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