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REVIEW

State-of-the-Art Review: Echocardiography in Pulmonary Hypertension

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Pulmonary hypertension is a progressive and often fatal disease that frequently presents with dyspnoea on exertion and results in increased right ventricular afterload and right ventricular failure. Although cardiac catheterisation is required for a formal diagnosis, transthoracic echocardiography (TTE) has a central role as a screening tool in those with symptoms and those at risk for developing pulmonary vascular disease. Echocardiographic techniques can be employed to estimate pulmonary artery pressure and resistance, right atrial pressure as well as to derive indirect information about right heart structure and function. Potential causes for pulmonary hypertension may also be identified such as congenital heart disease or left ventricular diastolic dysfunction. An increasing body of evidence has demonstrated the important prognostic utility of echocardiographic data in pulmonary hypertension and highlighted the potential for TTE to help clinicians understand whether treatment responses have been adequate or an escalation in therapy is necessary, as therapeutic options continue to expand for patients with pulmonary arterial hypertension. Although traditional echocardiographic techniques only allow surrogate measures of right ventricular systolic function due to the complex shape of the chamber, newer techniques have enabled three-dimensional assessment of the right ventricle to assess right ventricular volume and contractility. This review will discuss traditional methods as well as newer echocardiographic methods in the setting of pulmonary hypertension.

Keywords Right ventricle • Ultrasound • Congenital heart disease

Introduction

Pulmonary hypertension is a progressive and often fatal disease that frequently presents with the non-specific symptom of dyspnoea on exertion. It results from an increase in pulmonary artery pressure that may be related to a multitude of causes [1]. Pulmonary hypertension results in increased right ventricular afterload that may ultimately lead to right ventricular failure. Although cardiac catheterisation is required for a formal diagnosis, transthoracic echocardiography (TTE) is usually the investigation that first suggests increased pulmonary pressure and thus has a central role as a screening tool in those with symptoms and those at risk for developing pulmonary vascular disease. Furthermore, it is non-invasive and widely available.

Echocardiographic techniques can be employed to estimate pulmonary artery pressure and resistance, right atrial pressure as well as to derive indirect information about right heart structure and function which has important prognostic implications. Possible causes such as left heart or congenital heart disease may also be identified on TTE. Numerous echocardiographic measures have been shown to be predictive of clinical outcome in patients with pulmonary hypertension and are also useful to monitor treatment response and as adjunctive evidence for clinical deterioration that may warrant escalation in therapy. Although the most commonly utilised echocardiographic measure to assess for pulmonary hypertension is the peak velocity of the tricuspid regurgitation continuous wave Doppler jet there are many other echocardiographic indices that can also provide important

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clinical information. This review will discuss traditional methods as well as newer echocardiographic methods in the setting of pulmonary hypertension.

Pulmonary Hypertension Definition and Classification

Pulmonary hypertension is defined by a mean pulmonary artery pressure ≥20 mmHg measured at cardiac catheterisation. Pulmonary arterial hypertension (Group 1,3,4 and 5 – see Table 1) is further characterised by a pulmonary artery wedge pressure ≤15 mmHg and in contrast, post-capillary pulmonary hypertension is diagnosed when pulmonary artery wedge pressure is >15 mmHg. The updated Clinical Classification of Pulmonary Hypertension [2] is also shown in Table 1. In the current era, Group 2 (pulmonary hypertension due to left heart disease) is the most common type. Transthoracic echocardiography can provide important clues that are suggestive of raised left ventricular filling pressure to help guide clinical classification.

Table 1 Updated Clinical Classification of Pulmonary Hypertension [2].

Pulmonary Hypertension Group	Examples
Group 1	Idiopathic PAH
Pulmonary Arterial	Heritable PAH
Hypertension	Drug or Toxin induced
	PAH associated with other diseases:
	Scleroderma
	HIV
	Portal hypertension
	Congenital heart disease
Group 2	Myocardial disorders:
Pulmonary	Systolic dysfunction
Hypertension due	Diastolic dysfunction
to Left Heart	Congenital cardiomyopathy
Disease	Inflow/Outflow disorders:
	Valvular heart disease
	Congenital LV inflow or outflow obstruction
Group 3	COPD
Pulmonary	Interstitial lung disease
Hypertension due	Sleep disorders
to Lung Disease	Chronic hypoxia
Group 4	Chronic Pulmonary
Pulmonary	Thromboembolic Disease (CTEPH)
Hypertension due	
to pulmonary	
artery obstructions	
Group 5	Haematologic disorders:
PHT with	Myeloproliferative disorders
multifactorial cause	Chronic haemolytic anaemia
	Sarcoidosis
	Glycogen storage disorders
	Chronic renal failure

Abbreviations: PAH, pulmonary arterial hypertension; PHT, pulmonary hypertension; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency viruses; LV, left ventricular.

Estimating Pulmonary Pressure and Resistance With Echocardiography

Although cardiac catheterisation is required for a formal diagnosis, echocardiography is the cornerstone of screening tools for pulmonary hypertension. An understanding of the echocardiographic features that may be suggestive of increased pulmonary pressure, beyond a simple pulmonary artery systolic pressure estimation (usually derived from the tricuspid regurgitation jet), is essential for clinicians dealing regularly with dyspnoeic patients because early in the disease process, the echocardiographic abnormalities may be subtle and an overt increase in estimated pulmonary pressure may not be obvious on TTE. Of note, the recent definition of pulmonary hypertension has recently been lowered from a mean of 25 mmHg to 20 mmHg [2]. It is likely that the cut-points used to identify patients who are likely to have pulmonary hypertension will be lowered as more research becomes available that incorporates the new definition.

Estimating Pulmonary Pressure from the Tricuspid Regurgitation Profile

The most common TTE method for estimating systolic pulmonary artery pressure is continuous wave Doppler measurement of the right ventricular-right atrial pressure gradient reflected in the peak tricuspid regurgitation velocity (shown in Figure 1) which is then added to an estimated right atrial pressure utilising the modified Bernoulli equation: [3]

Pulmonary artery systolic pressure = 4 × (peak tricuspid regurgitation velocity)^2 + estimated right atrial pressure.

Accurate measurement requires an adequate amount of tricuspid regurgitation to record a well-defined spectral trace and careful alignment with the direction of regurgitant flow requiring assessment in multiple views including parasternal right ventricular inflow, basal short axis, apical long axis and subcostal. Off axis assessment may be required for eccentric jets. Agitated saline contrast may enhance the spectral trace in subjects with an inadequate tricuspid regurgitation envelope. Measurement errors can result in significant over or underestimation of the peak velocity. Even when measured accurately, the TTE estimate of pulmonary artery systolic pressure may vary significantly compared with the actual pressure measured at cardiac catheterisation [4] and so should be considered an estimation only. It is also important to note that while the definition of pulmonary hypertension is based upon the mean pulmonary artery pressure determined at cardiac catheterisation, the most commonly

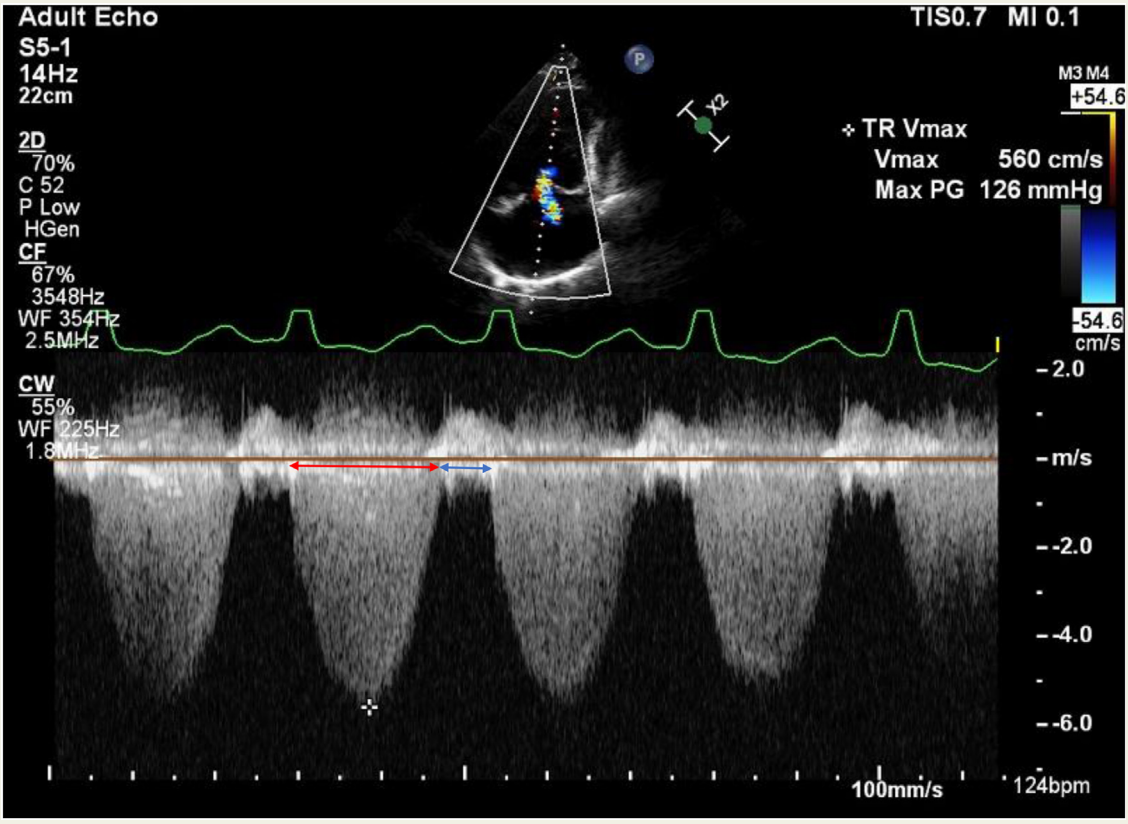

Figure 1 Measurement of the peak tricuspid regurgitation velocity which is added to right atrial pressure to estimate pulmonary artery systolic pressure.
a) This patient has severe pulmonary hypertension with systemic-level pulmonary pressure and prolonged systolic to diastolic duration ratio. The latter index quantifies the time in systole (marked with red line) relative to the time in diastole (marked in blue line) and suggests severe impairment in global right ventricular function in this patient.

reported TTE tricuspid regurgitation method provides an estimate of systolic pressure. Peak tricuspid regurgitation velocities that are considered suggestive of pulmonary hypertension are shown in Tables 2 and 3.

The estimated systolic pulmonary artery pressure can be used to estimate mean pulmonary artery pressure: [4]

Mean pulmonary artery pressure = 0.61 × (pulmonary artery systolic pressure) + 2

There are several factors that may confound the utility of the tricuspid regurgitation velocity to estimate pulmonary pressure. The right ventricular to right atrial pressure gradient will only be an accurate reflection of systolic pulmonary artery pressure in the absence of right ventricular outflow obstruction or pulmonary stenosis which is an especially important consideration in patients with congenital heart disease. In severe tricuspid regurgitation there is rapid pressure equalisation between the right ventricle and atrium that blunts the peak velocity profile. In the setting of severe right ventricular systolic dysfunction or low cardiac output, the estimated pulmonary pressure may not appear elevated even though pulmonary vascular resistance is high. This is because pulmonary vascular resistance is calculated by

Table 2 **Adapted from 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension [1].**

Peak tricuspid regurgitation velocity (m/sec)	Indirect evidence on transthoracic echo for pulmonary hypertension	Echocardiographic probability of pulmonary hypertension
≤2.8	No	Low
≤2.8	Yes	Intermediate
2.9-3.4	No	Intermediate
2.9-3.4	Yes	High
>3.4	Not required but usually present	High

Table 3 Summary Approach for Suspected Pulmonary Hypertension: Adapted from Celermajer and Playford [49].

Entity	Measurements performed	Method	Abnormal	Interpretation
Is there pulmonary hypertension?	Right atrial pressure	IVC collapse from subcostal IVC long axis	>2.1 cm diameter <50% collapse with sniff	RA pressure >15 mmHg
	JVP height	Clinical assessment	Over 6 cm at 45 degrees	RA pressure >15 mmHg
	RA area	RV focussed apical 4-chamber view	>18 cm^2	Chronic RA pressure elevation
	RV-RA pressure difference	Maximum TR velocity from multiple views	>2.8 m/s	RVSP estimation: Dependent on age and BMI
	PASP	$RVSP = 4(TRV)^2$ + RA pressure	>40 mmHg (approx.)	Assumes no pulmonary stenosis: Dependent on age and BMI
	PA-RV pressure difference	Initial PR velocity	>25 mmHg	Mean PAP estimation
	PA-RV pressure difference	End PR velocity	>15 mmHg	Diastolic PAP estimation
	Pulmonary acceleration time	Duration of upstroke in pulmonary valve CW Doppler wave	<90 ms	Predicts PVR >3WU
Why is there pulmonary hypertension?	Groups 1, 3, 4 and 5 pulmonary hypertension	Pulmonary hypertension without signs of left heart disease		Investigation for underlying cause is required
	Group 1 due to Congenital Heart Disease	Describe exact location of defect in relation to arteries and other cardiac structures Determine the physiologic effects of the lesion using the Bernoulli equation Use traditional measures of pulmonary hypertension Assess volume and pressure effects on the right heart		PAH with Eisenmenger Syndrome PAH with left to right shunting, increased PVR but no Eisenmenger PAH with small defects PAH after corrective surgery
	Group 2 pulmonary hypertension: Left heart disease	Measure LV ejection fraction from parasternal and apical views	<50%	Left ventricular systolic dysfunction
		Measure diastolic function	E:E′ ratio >15	
		Measure biplane left atrial volume from apical views	LA volume >34 ml/m^2	Increased left ventricular filling pressures
		Measure LV mass using the area-length method	Males >104 g/m^2 Females >90 g/m^2	
		Assess for valvular disease	See text for details	
What are the consequences to the right heart?	RV shape	Visual assessment using parasternal short axis and apical 4-chamber views	PSAX: Ventricular septal systolic flattening Circular RV shape Apical 4-chamber: Rectangular RV shape Horizontal RV moderator band	Suggests RV pressure overload
	RV eccentricity index	Ratio of RV to LV dimension using mid ventricular PSAX view	>1.0	Suggests RV pressure overload
	RV dimensions	RV focussed 4-chamber view	>42 mm RV base >35 mm RV mid	

Table 3. (continued).

Entity	Measurements performed	Method	Abnormal	Interpretation
	RV wall thickness	RV free wall in subcostal 4-chamber view	>5 mm	RV hypertrophy is seen in chronic pressure overload
	RV fractional area change	RV focussed 4-chamber view	<35%	Impaired RV systolic function
	Tricuspid annular plane systolic excursion (TAPSE)	M-mode of lateral tricuspid annulus in RV focussed 4-chamber view	<17 mm	Impaired RV systolic function
	Tricuspid annular plane systolic velocity	Tissue Doppler imaging of lateral tricuspid annulus in RV focussed 4-chamber view	<10 cm/s	Impaired RV systolic function
	Right ventricular index of myocardial performance (RIMP)	$\frac{IVRT+IVCT}{ET}$ using PW Doppler (see text for explanation)	>0.44	Indicates both systolic and diastolic RV dysfunction
		Measure P-Q slope (see text for details)	Rise in RVSP >3 mmHg/L/min	

Abbreviations: RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; RIMP, right ventricular index of myocardial performance; JVP, jugular venous pressure; PASP, pulmonary artery systolic pressure; PA, pulmonary artery; IVC, inferior vena cava, RVSP, right ventricular systolic pressure; PSAX, parasternal short axis; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RA, right atrium; BMI, body mass index; WU, wood unit; CW, continuous wave.

dividing the transpulmonary pressure gradient by cardiac output. Conversely, high output states including normal physiological settings, such as pregnancy, may result in increased tricuspid velocities and pulmonary pressure but pulmonary vascular resistance is low.

More recently, the velocity time integral of the tricuspid regurgitation jet has been utilised to calculate the mean right ventricular to right atrial pressure gradient, which when added to right atrial pressure has been shown to be a fairly reliable estimate for mean pulmonary artery pressure [5].

Estimation of Mean and Diastolic Pulmonary Artery Pressure From the Pulmonary Regurgitation Profile

Approximately 10% of patients with pulmonary hypertension will have a significant degree of pulmonary regurgitation. The pulmonary artery diastolic pressure can be estimated from the end-diastolic velocity demonstrated on the spectral profile utilising the following modified Bernoulli formula:

Pulmonary artery diastolic pressure = 4 (end-diastolic pulmonary regurgitation velocity)^2 + right atrial pressure

Mean pulmonary artery pressure can be estimated from the early diastolic velocity when the spectral profile is adequate:

Mean pulmonary artery pressure = 4 (initial diastolic pulmonary regurgitation velocity)^2 + right atrial pressure

The pulmonary regurgitation spectral profile will not be accurate for assessing pulmonary artery pressure in the setting of pulmonary valve stenosis, pulmonary artery stenosis or severe pulmonary regurgitation.

Pulmonary regurgitation velocities suggestive of pulmonary hypertension are shown in Table 4.

Estimation of Pulmonary Artery Pressure Using Pulmonary Acceleration Time

The acceleration time measured from the pulsed Doppler profile of the pulmonary valve shortens as pulmonary vascular resistance increases. An acceleration time of <90 milliseconds (ms) is strongly suggestive of pulmonary hypertension and pulmonary vascular resistance greater than 3 Wood units [6]. Mean pulmonary artery pressure may also be estimated from the pulmonary acceleration time: [7]

Mean pulmonary artery pressure = 90 − (0.62 × pulmonary acceleration time) if acceleration time <120 ms

The shape and size of the pulmonary pulsed wave Doppler profile may also be informative. In addition to the steepened acceleration time, as pulmonary hypertension progresses a mid-systolic notching may be visible. Later, as stroke volume falls, the overall area of the envelope diminishes.

Estimation of Right Atrial Pressure

As outlined above, an estimate of right atrial pressure is necessary in order to calculate pulmonary pressure using the valve regurgitation methods. Right atrial pressure is also an important indicator of right ventricular diastolic pressure

Table 4 Summary of abnormal right heart measurements in pulmonary hypertension [1,8].

Measurement	Abnormal
TR velocity	>2.8 m/s
PASP	>40 mmHg
PR initial velocity	>2.2 m/sec
RV basal diameter	>42 mm
RV mid diameter	>35 mm
RVOT PSAX distal diameter	>27 mm
RA end-systolic area	>18 cm^2
TAPSE	<17 mm
RV S′	<10 cm/s
Pulsed Doppler RIMP	≥0.44
Tissue Doppler RIMP	≥0.55
FAC (%)	<35%
3D right ventricular assessment:	
End diastolic volume	≥87 ml/m^2 (male); ≥74 ml/m^2 (female)
End systolic volume	≥45 ml/m^2 (male); ≥36 ml/m^2 (female)
Ejection fraction	<45%
RV subcostal wall thickness	>0.5 cm

Abbreviations: PASP, pulmonary artery systolic pressure; RV, right ventricle; RVOT, right ventricular outflow tract; PSAX, parasternal short axis; RA, right atrium. TAPSE, tricuspid annular plane systolic excursion; S′, systolic tissue Doppler velocity measured at the lateral tricuspid annulus; MPI, myocardial performance index; FAC, fractional area change.

that increases as the right heart decompensates in advanced pulmonary hypertension. Haemodynamically important tricuspid valve disease may also cause increased right atrial pressure. Some laboratories choose an arbitrary constant right atrial pressure (such as 5 or 10 mmHg) to avoid variations in measurement. Current guidelines suggest using the inferior vena caval diameter and the degree of inspiratory collapse to estimate right atrial pressure (Table 1) [1,8]. Clinical estimation of the jugular venous pressure can be useful to substantiate the echocardiographic estimation of right atrial pressure. Right atrial dilatation may also be an important marker of raised right atrial pressure although volume loading from tricuspid regurgitation also needs to be taken into consideration.

Estimating Pulmonary Vascular Resistance

Pulmonary vascular resistance is determined by the following relationship:

Pulmonary vascular resistance = (Mean pulmonary artery pressure − mean left atrial pressure) ÷ cardiac output

Theoretically then, TTE derived measurements of mean pulmonary artery pressure and cardiac output might be employed to estimate pulmonary vascular resistance if left atrial pressure appears normal. At the present time, such calculations are not well validated and the clinical utility is unknown. A number of other equations have also been proposed to estimate pulmonary vascular resistance (PVR) and have been described in detail in a recent review [9].

Indirect Echocardiographic Evidence for Pulmonary Hypertension

The right ventricle has evolved to be a thin-walled, low pressure pump and thus is structurally quite unlike the left ventricle. It has a complex, roughly triangular shape, that wraps around the left ventricle so that is appears crescentic in short axis views. This anatomy makes two-dimensional echocardiographic assessment of volume and ejection fraction challenging as techniques such as Simpson's biplane cannot be employed. There are however, numerous methods that provide useful information about the right ventricle that provide important clinical data, albeit with some limitations. Early or in mild pulmonary hypertension, the right ventricle adapts to increased afterload with hypertrophy that reduces wall tension with preservation of volume and systolic function. As disease progresses, ventriculoarterial uncoupling develops which manifests as worsening right ventricular dilatation and declining stroke volume. A summary of abnormal TTE measurements in pulmonary hypertension is shown in Tables 3 and 4.

Right Ventricular Dimensions

Right ventricular dimensions are usually measured in the four-chamber view, rotating to ensure that the maximum width of the right ventricle is measured (''right ventricular focussed view''). A diameter greater that 42 mm at the base and 35 mm in the mid-right ventricle is considered dilated [10]. Body size and high levels of aerobic training may result in dimensions outside the normal range in the absence of important cardiovascular pathology.

The right ventricular end-diastolic area to left ventricular end-diastolic area or biventricular index is a more recently described index that also quantifies right ventricular dilatation, relative to the left ventricle. An index of ≥0.93 may be associated with increased risk of death in patients with pulmonary hypertension [11]; but at this time, normal ranges and degrees of abnormality are not established. Many labs apply this method informally to help grade the subjective degree of right ventricular dilatation and classify the right ventricle as severely dilated if it exceeds the left ventricular area in the apical four-chamber view. Causes of volume loading or cardiomyopathy should be considered if the degree of dilatation is out of proportion to the severity of pulmonary vascular disease.

Right Ventricular Hypertrophy

Right ventricular hypertrophy develops in response to increased right ventricular afterload in pulmonary hypertension and may be an early sign of disease, in the absence of

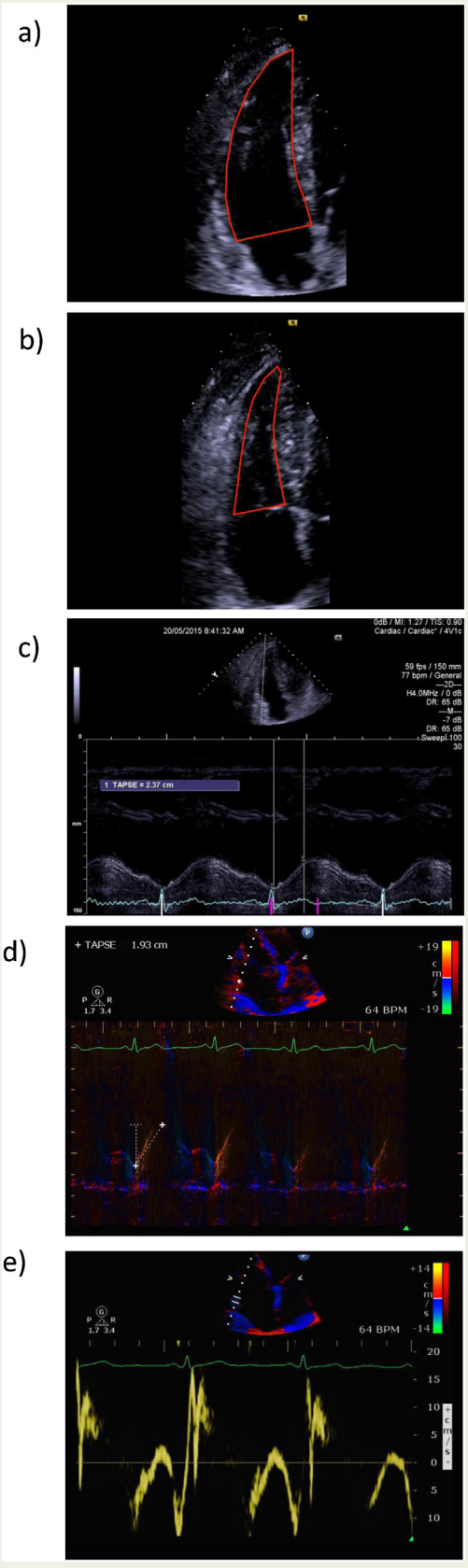

Figure 2 Measurement of right ventricular (RV) function from an RV-focussed apical 4-chamber view.

Reproduced with permission from Celermajer and Playford [49].
a and b) End-diastolic and end-systolic areas are measured by tracing the endocardial border in diastole and systole respectively. The fractional area change is the ratio of the change in area and end-diastolic area.
c and d) Tricuspid annular plane systolic excursion is the distance the lateral tricuspid annulus travels in systole, measured using M-mode or M-mode performed during color-coded tissue Doppler imaging.
e) Systolic function can also be measured using tissue Doppler systolic descent velocities of the tricuspid annulus (S′).

other obvious pathophysiology. Ideally, right ventricular wall thickness should be measured in diastole in the subcostal view although the parasternal window may sometimes be the only option. A wall thickness >5 mm is considered abnormal [8].

Right Ventricular Systolic Function

Subjective assessment of overall right ventricular ejection fraction is prone to inter-observer variability. Incorporating other quantitative measures of ventricular systolic function is prudent, especially for serial monitoring and prognostication. In the absence of an accurate two-dimensional echocardiographic method to assess right ventricular ejection fraction, the fractional area change (FAC) is commonly calculated as a surrogate with <35% considered representative of systolic dysfunction [1]. The FAC is defined as (end-diastolic area − end-systolic area)/end-diastolic area × 100 and has been shown to correlate with three-dimensional right ventricular volumetric assessment [12]. An example, obtained by tracing the endocardial border beyond trabeculations, is shown in Figure 2a and b.

Because FAC only assesses the ventricle in one plane, other measures of right ventricular systolic function should also be assessed. Tricuspid annular plane systolic excursion (TAPSE) measures right ventricular longitudinal shortening and is another surrogate of systolic function obtained using M-mode of the lateral tricuspid annulus from the four-chamber view (Figure 2c and d). Systolic dysfunction is likely when TAPSE is <17 mm. The right ventricular S′ velocity is measured from the peak systolic tissue Doppler velocity of the same region (Figure 2e). A velocity <10 cm/sec is suggestive of systolic dysfunction. Both of these methods, assess a small section of the right ventricle and so, although useful in most patients, some subjects will demonstrate relative sparing of the basal segments of the ventricle and thus the TAPSE and S′ may appear relatively normal. It is therefore important that these results are incorporated into an overall assessment of function that considers all the information available.

Newer echocardiographic techniques have evolved that are being increasingly incorporated into clinical practice. Three-dimensional echocardiography enables accurate

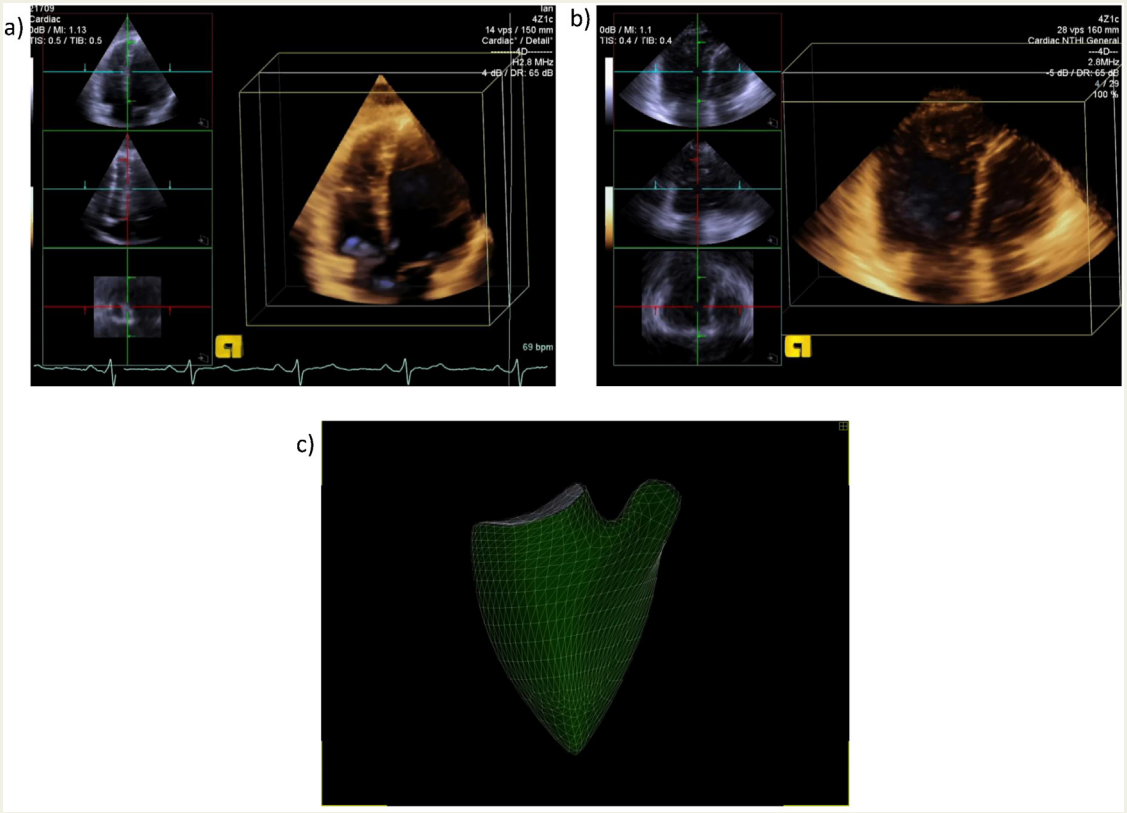

Figure 3 Multiplane reconstruction of the right heart.
Images have been acquired in the setting of a) normal haemodynamics and b) severe pulmonary arterial hypertension demonstrating a severely dilated ventricle. By 3D surface rendering c), the internal contour of the right ventricle is mapped and used to calculate ventricular volumes.

volumetric assessment of the right ventricle using either summation of discs (see Figure 3) or surface modelling and is the most accurate echocardiographic measure of right ventricular systolic function [13] however adequate data acquisition is challenging in patients with suboptimal TTE windows and adequate expertise in data acquisition and analysis are essential. In the ''summation of discs'' method, the right ventricular endocardial border is traced in several views. The software algorithm then slices the three-dimensional shape into a serious of slices of fixed height to calculate the volume. For surface modelling, a software program fits the ventricle that has been traced or demarcated in numerous two-dimensional views, into a three-dimensional model using a proprietary algorithm. Normative data are available for this methodology and the normal right ventricular ejection fraction using these methods is $\geq$45% [8]. Recent data reported the three-dimensional right ventricular ejection fraction had a stronger correlation with directly mean pulmonary artery pressure than traditional measured of right ventricular systolic function [14].

Strain imaging to assess the right ventricle is an evolving area. Strain is defined as the percentage change in the myocardial deformation and strain rate describes the rate of deformation. These parameters are measured using tissue Doppler or speckle tracking. There is some data to suggest that right ventricular strain has prognostic relevance in the setting of pulmonary hypertension (see Prognosis below) but the most important type of deformation (circumferential, longitudinal or area strain) and normative values are not well-established. At present, most of the data in this area has investigated global longitudinal strain [15–19]. Area strain, a measure of relative area change that incorporates longitudinal and circumferential strain, holds promise as a useful clinical tool [20].

Right Ventricular Global Performance

Measures of right ventricular global performance reflect both diastolic and systolic function. The right ventricular index of myocardial performance is a measure of overall (systolic and diastolic) ventricular function and is calculated by adding the right ventricular isovolumic contraction time to the isovolumic relaxation time and dividing the total by the ejection time using pulsed wave Doppler or tissue Doppler. The upper reference limit is 0.40 by pulsed Doppler and 0.55 with tissue Doppler [8]. This method is not widely used in routine clinical practice.

Another easily measurable parameter that reflects global ventricular performance is the systolic to diastolic duration ratio (shown in Figure 1) that simply compares the time in systole and diastole recorded from the continuous wave

Doppler profile of the tricuspid regurgitation jet. A higher systolic to diastolic duration ratio has been shown to be associated with worse right ventricular systolic function, haemodynamics, functional capacity and clinical outcomes in the setting of paediatric pulmonary hypertension [21] and to clinical outcomes in Eisenmenger's syndrome [22]. In children, a ratio >1.4 is associated with an especially poor prognosis [21]. Specific cut-points are not established in the setting of adult pulmonary hypertension but a diastolic time that is much shorter than systolic time is generally a worrying sign when in normal sinus rhythm.

Diastolic Function

The simplest way to assess right ventricular diastolic pressure is to estimate right atrial pressure, as described above. Other parameters are also employed, albeit less frequently and are similar to the methods employed to assess left ventricular diastolic function including tricuspid inflow velocities measured with pulsed Doppler and lateral tricuspid annular velocities with tissue Doppler (see Table 4). An E/E′ ratio ≥4 may be suggestive of increased right atrial pressure [23]. Diastolic flow predominance in the hepatic veins (measured with pulsed Doppler) may also be suggestive of right ventricular diastolic dysfunction.

Pericardial Effusion

The presence of a pericardial effusion in the setting of pulmonary hypertension is a poor prognostic marker [24], except perhaps in Eisenmenger's syndrome [9,22]. The development of a pericardial effusion likely reflects a marked increase in right atrial pressure because the pericardial lymphatics drain, via the coronary sinus to the right atrium. In our experience, the effusion may resolve with optimisation of pulmonary hypertension therapy. Occasionally, another cause may underlie the effusion, and thus, if a patient does not have an important derangement in right heart haemodynamics other aetiologies should be entertained such as autoimmune involvement of the heart and/or pericardium in the setting of scleroderma.

Ventricular Septal Motion

The interventricular septal wall motion provides important information about the relationship between right and left ventricular pressure. If the systolic pressure difference between the two ventricles becomes attenuated, the interventricular septum becomes flattened creating a D-shaped left ventricle and a more rounded right ventricle during systole in the parasternal short axis views. This can be quantified using the right ventricular eccentricity index that is measured in the parasternal short axis view by measuring the ratio of the left ventricular anteroposterior diameter and the septolateral diameter. A right to left ventricular ratio of >1.0 is highly suggestive of right ventricular pressure loading [25].

If right ventricular diastolic pressure approaches or exceeds the left ventricular diastolic pressure, such as in the setting of right ventricular failure or right heart volume loading, isolated diastolic interventricular flattening may be evident.

Right Ventricular End-Systolic Remodelling Index

This recently described parameter, the right ventricular end-systolic remodelling index, is simply a ratio of the end-systolic right ventricular free wall length (from apex to tricuspid annulus) to the septal length and provides additional quantitative information about the degree of adverse right ventricular remodelling. A remodelling index <1.35 is at the upper limits of normal and suggests adequate right ventricular adaptation. An index between 1.35 and 1.70 suggests adverse remodelling. An index ≥1.7 suggests severe adverse remodelling in the setting of pulmonary hypertension [26].

Identification of Likely Causes and Specific Disease-Group Considerations

As outlined in Table 1, pulmonary hypertension is generally classified into one of five groups. It is important that potential contributors to pulmonary hypertension are sought at echocardiography because of the important implications for diagnosis and management.

Congenital Heart Disease

The presence of an intracardiac or pulmonary venous shunt as a contributor to right heart dilatation and pulmonary hypertension should be considered in all patients being assessed for pulmonary hypertension. Transthoracic echocardiography views that usually demonstrate secundum atrial septal defects most clearly are the parasternal short axis and subcostal views. Careful assessment with and without colour on these regions is essential, however, atrial septal defects, especially sinus venosus-type may be easily missed with TTE. "Out of proportion" right ventricular dilatation should prompt a more detailed search for a shunt lesion such as anomalous pulmonary venous return. Transoesophageal echocardiography, chest computed tomography (CT) or cardiac magnetic resonance imaging (CMR) may sometimes be required to delineate anatomy.

Due to major advances in care there has been enormous growth in the population of adults living with complex congenital heart disease in recent decades. A large proportion of these patients either have or are at risk for pulmonary hypertension.

Pulmonary arterial hypertension complicating congenital heart disease can be broadly classified into five categories:[2]

1 Eisenmenger's syndrome that develops in the setting of a large left to right shunt that has resulted in a severe increase in pulmonary vascular resistance and reversal of the shunt from right to left.
2 Pulmonary hypertension with a large left to right shunt and high pulmonary vascular resistance that has not progressed to Eisenmenger physiology.
3 Pulmonary hypertension after corrective surgery such as late closure of a large ventricular septal defect or

overshunting from a surgically created systemic to pulmonary artery shunt.
4 Pulmonary hypertension due to raised left heart disease (eg. supramitral ring, hypoplastic left ventricle) sided filling pressure or pulmonary venous obstruction.
5 Small septal defects or shunts where the natural history of pulmonary hypertension resembles idiopathic pulmonary hypertension and the contribution of the congenital defect is unclear.

Echocardiography has a pivotal role in screening and diagnosis in this group. The identification of pulmonary hypertension in the setting of a congenital heart defect should prompt referral to an expert Congenital Heart Disease Centre [27], as management decisions can be highly complex and inappropriate management decisions are frequently made when these patients are managed in a non-expert setting [28]. Transthoracic echocardiography is utilised to define intracardiac and great vessel anatomy and estimate the haemodynamic burden using the traditional methods described above. Of note, estimation of Qp:Qs using echocardiography is generally inaccurate and should not be relied upon to guide management decisions.

There are numerous important pitfalls to consider if an increased tricuspid regurgitation velocity has been identified in a patient with a congenital heart defect. Some of the important considerations are:

1 Right ventricular outflow tract obstruction, pulmonary valve obstruction and/or pulmonary artery obstruction will all increase right ventricular systolic pressure. The degree of right heart outflow obstruction needs to be taken into consideration when deciding the significance of an increased right ventricular systolic pressure or peak tricuspid regurgitation velocity. Pulmonary valve and pulmonary artery obstruction also invalidates the utility of the pulmonary regurgitation jet and acceleration time to assess for pulmonary hypertension.
2 A significant left to right shunt increases flow across the tricuspid and pulmonary valves and so pressures may seem high although the resistance is not abnormally increased when corrected for flow.
3 The jet of a perimembranous ventricular septal defect is often directed in a very similar direction to the tricuspid regurgitation jet and differentiating the two jets may be very difficult.
4 Some patients with complex congenital defects have a systemic right ventricle (a right ventricle that pumps to the systemic circulation such as a Mustard-type repair for transposition or congenitally corrected transposition of the great arteries) and thus the tricuspid regurgitation jet reflects the systemic blood pressure rather that the pulmonary pressure.

Previous surgical reports and clinical notes often provide crucial information to help properly characterise the situation from an echocardiographic perspective.

Left Heart Disease

Left heart disease is the cause for over two-thirds of pulmonary hypertension diagnoses. Left heart disease that has resulted in diastolic dysfunction and increased left ventricular filling pressure accounts for the majority of cases.

There may be important clues on TTE that are highly suggestive of raised left ventricular filling pressure (Group 2, see Table 1) which has important implications for management, inter alia, as patients with Group 2 pulmonary hypertension generally do not benefit (or can be harmed) from targeted pulmonary vasodilator therapy. Although the haemodynamics usually require confirmation with cardiac catheterisation, the TTE findings should also be taken into consideration. This is of particular significance in patients who have a pulmonary capillary wedge pressure (a surrogate for left atrial pressure measured during right heart catheterisation) measurement that does not seem consistent with the TTE. In this situation the left ventricular end-diastolic pressure should be measured directly to ensure the measurements are accurate and the patient is being correctly categorised.

The presence of left ventricular hypertrophy and/or left atrial dilatation are clues that left ventricular filling pressure may be increased. The presence of moderate or worse mitral or aortic valve disease is also often associated with raised left ventricular diastolic pressure.

A detailed discussion regarding the assessment of left ventricular diastolic function is outside the scope of this article and updated guidelines have recently been published [29]. In brief, left ventricular diastolic dysfunction may be graded and left atrial pressure can be estimated by incorporating measurements using pulsed wave Doppler of the mitral inflow and pulmonary veins combined with tissue Doppler assessment of the lateral and medial mitral annulus. An E/E′ >14 is suggestive of diastolic dysfunction [29]. Bowing of the interatrial septum from left to right is also suggestive of high left atrial (LA) pressure. Atrial arrhythmias or other causes of irregular heart rate or loss of atrioventricular synchrony may invalidate some of these methods.

Recently the echocardiographic pulmonary to left atrial ratio (ePLAR) has been proposed as a simple measure to help differentiate patients with elevated pulmonary vascular resistance from those with pulmonary hypertension due to left heart disease [30]. This index is calculated from the ratio of the peak tricuspid regurgitation velocity and the E/E′. In a large ''normal'' cohort, the mean ePLAR was 0.30 ± 0.09 m/sec. In patients with elevated pulmonary vascular resistance or Group 1 pulmonary hypertension, the mean ePLAR was 0.44 ± 0.22 m/sec in contrast to the left heart disease group (Group 2) who had lower values (0.20 ± 0.11 m/sec).

Lung Disease

There are not specific TTE features to help establish whether pulmonary hypertension is related to lung disease (Group 3 pulmonary hypertension) however there are several

important considerations in this group. The echocardiographic windows are frequently suboptimal related to lung hyperinflation, displacement of the heart and dyspnoea. There may also be marked respiratory variation in the Doppler traces related to large swings in intrathoracic pressure.

Acute Rises in Pulmonary Vascular Resistance

In suspected acute pulmonary embolism, the identification of new right ventricular dilatation and impairment with TTE may provide important clinical clues but should not delay treatment in an unstable patient. Right ventricular dysfunction has important implications for prognosis [31].

A large acute pulmonary embolism causes an abrupt increase in pulmonary vascular resistance that the right ventricle is not adapted to. This may result in an acute reduction in systolic function and classically, an increase in right ventricular size in the basal and mid regions. There may be relative sparing of the right ventricular apical region that has been labelled ''McConnell's sign''. In acute pressure overload the interventricular septum may bow to the left. Importantly, because of the reduction in right ventricular stroke volume (low flow) the peak tricuspid regurgitation velocity is usually not markedly increased.

Occasionally thrombus or tumour may be seen in the right heart, inferior vena cava or proximal pulmonary arteries. The presence of overt pulmonary hypertension demonstrated on TTE in the setting of acute pulmonary embolism suggests superimposed pulmonary hypertension from another cause or chronic thromboembolic pulmonary hypertension (Group 4). Right atrial dilatation and right ventricular hypertrophy are also suggestive of more chronic pressure loading.

Additional Echocardiographic Tools

Transoesophageal Echocardiography

Transoesophageal echocardiography has a role in a subset of patients with pulmonary hypertension in whom a congenital shunt is suspected such as atrial septal defect. It is usually not possible to exclude partial anomalous pulmonary venous connections with transoesophageal echocardiography. Transoesophageal echocardiography may assist in characterising the anatomy in left-sided valve disease or rarer intracardiac anomalies. Centres performing balloon atrial septostomy, usually utilise transoesophageal echocardiography (or intracardiac echocardiography) to help guide the proceduralist.

Agitated Saline Contrast

Agitated saline contrast may be administered via a peripheral vein (a bubble study) as a screening test to assess the degree of right to left shunting in patients who have hypoxaemia out of proportion to their degree of lung parenchymal and/or pulmonary vascular disease. If TTE is used, usually the apical four-chamber view is preferred, if adequate and the left heart chambers are carefully monitored for bubbles once they enter the right heart. The bubble study would be expected to be strongly positive if shunting (either via a patent foramen ovale, septal defect or pulmonary arteriovenous malformations) were an important contributor to hypoxaemia. If bubbles appear in the left heart more than 3–5 beats after appearing in the right, the shunt is usually intrapulmonary.

Agitated saline contrast may also be helpful to improve the spectral Doppler trace for more accurate measurement of tricuspid and pulmonary valve velocities.

Exercise and Dobutamine Stress Echocardiography

The role for exercise echocardiography for the diagnosis of pulmonary hypertension is controversial. In 2009, ''exercise-induced'' pulmonary hypertension was removed from the international pulmonary hypertension definition. The controversy exists predominantly because age-specific normative values are not well-established and the pressure rises recorded during exercise are difficult to interpret in the absence of some measure of cardiac output in order to understand whether the rise simply reflects a physiological increase in flow or a true disorder of pulmonary vascular resistance. An increase in pulmonary artery pressure with exercise may occur when the cardiac output markedly increases, even when pulmonary vascular resistance is normal [32,33].

It is recognised, however, that there is a subset of patients who have an abnormal increase in pulmonary artery pressure with exercise that is probably a precursor to pulmonary hypertension [34] and it seems likely that detecting pulmonary hypertension during stress may enable earlier detection of disease which has important prognostic implications in Group 1 pulmonary hypertension as earlier therapy may improve outcomes [1].

Because pulmonary artery pressure falls rapidly when exercise ceases, studying patients during exercise is ideal. Exercise may be performed on a semi-supine ergometer with a side tilt, although, even in patients with good resting TTE windows it is often difficult to obtain data once the subject is hyperventilating. Dobutamine may used as an alternative to avoid the technical issues if exercise TTE is not feasible [35]. Ideally doses $\leq$20 μg/kg/min should be used to minimise vasomotor effects on the pulmonary circulation. Measurements should be performed at least at rest and at peak stress. The left ventricular outflow tract can be measured at rest and incorporated with left ventricular outflow tract velocity time interval (LVOT VTI) and heart rate recordings at rest and during exercise to calculate the cardiac output. Pulmonary artery systolic pressure is estimated from the tricuspid regurgitation peak velocity, using the baseline right atrial pressure estimation. TAPSE should also be measured at rest and peak to characterise right ventricular contractile reserve [36]. Left ventricular measurements, in addition to the LVOT VTI should include E/E' for diastolic function assessment.

Current evidence suggests that an absolute cut-point for the diagnosis of exercise-induced pulmonary hypertension is inadequate. The rate of increase in pulmonary pressure

relative to the cardiac output is probably a more meaningful diagnostic tool [37]. This requires data collection at numerous time-points during a maximal exercise test, ideally more than four. Mounting evidence from invasive and non-invasive studies suggests that the slope of the estimated mean pulmonary artery pressure (using the formula described above for the peak tricuspid regurgitation velocity or early pulmonary regurgitation velocity) versus cardiac output plot ranges from 0.5 to 3.0 mmHg/L/min [38,39]. A mean pulmonary artery pressure/cardiac output slope >3 mmHg/L/min is probably abnormal unless cardiac output exceeds 10 L/min and may form the basis for updated definitions of exercise-induced pulmonary hypertension in the future [37]. Identifying an abnormally high slope does not differentiate between patients with normal or high left atrial pressure (Group 2 Pulmonary Hypertension).

Diagnostic Approach

The diagnostic approach for a patient in whom pulmonary hypertension is suspected from an echocardiographic perspective is shown in Figure 4.

Because approximately 10% of patients with scleroderma and a significant proportion of those with mixed connective tissue disease will develop pulmonary hypertension, annual screening is recommended for these groups [40].

Serial Monitoring

Regular monitoring is required for most patients with pulmonary hypertension to assess for deterioration or improvement on disease-specific therapy. With repeated measures, there is likely to be variability over time due to the inherent limitation of any echocardiographic measurement. Steps should be taken to minimise potential confounding factors in order to optimise the data such as regular education of sonographers to ensure optimal data collection, side-by-side comparison and ideally use of the same equipment and with the same personnel. Hydration status can also make significant differences to pulmonary pressures and TTE appearances.

In the setting of Group 1 Pulmonary Arterial Hypertension in particular, accurate serial measures are important to help clinicians to understand treatment responses.

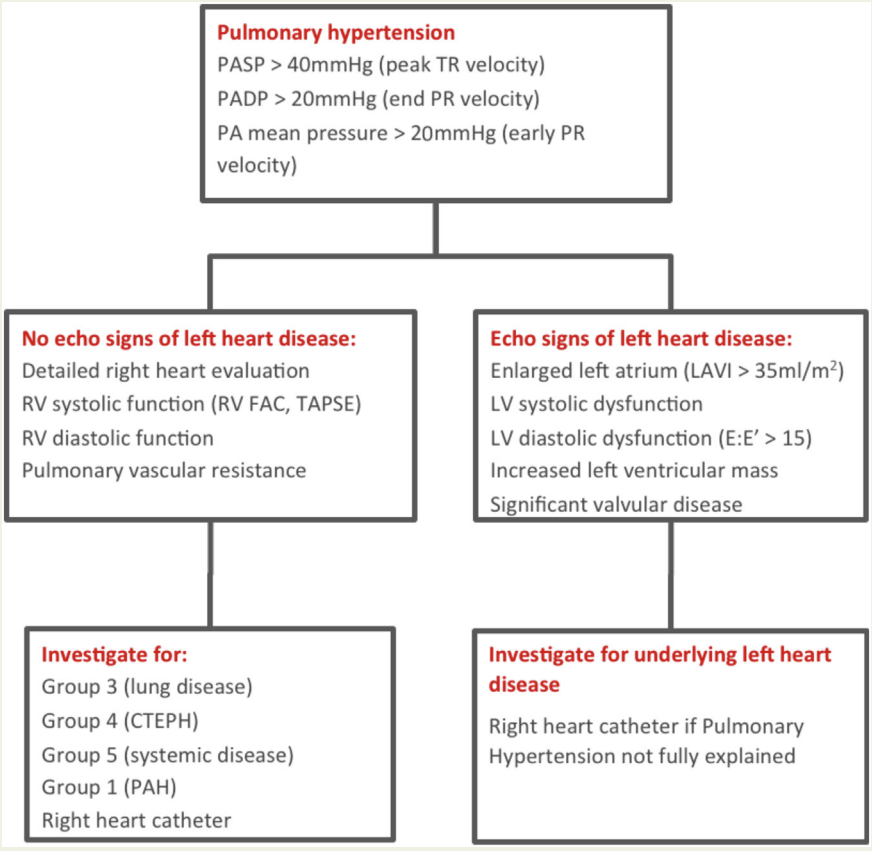

Figure 4 A diagnostic approach to a patient with clinical suspicion of pulmonary hypertension.
Reproduced from Celermajer and Playford [49]. Abbreviations: PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; PA, pulmonary artery; RV, right ventricular; FAC, fractional area change; TAPSE, tricuspid

Prognostic Utility of Echocardiography in Pulmonary Hypertension

Almost all of the echocardiographic indices discussed have been shown to have prognostic utility. The presence of a pericardial effusion has consistently been shown to be associated with poor prognosis in the setting of pulmonary arterial hypertension [24,41,42], except in the setting of Eisenmenger's syndrome [9,22].

Higher Tei index [43], greater right atrial area [24], larger inferior vena cava (IVC) diameter [44], lower TAPSE [44,45], higher estimated mean and diastolic pulmonary artery pressure [44], the degree of interventricular septal shift [44], right ventricular diameters [46], biventricular index [11] and right ventricular end-systolic remodelling ratio [26] have all been reported to be associated with adverse clinical outcomes in the setting of pulmonary hypertension. Right ventricular systolic to diastolic duration ratio is associated with poor outcome in paediatric pulmonary hypertension [21] and Eisenmenger's syndrome [22] but has not been studied in broader pulmonary hypertension settings. Additional predictors in the setting of Eisenmenger's syndrome reported by Moceri et al. [22] include reduced TAPSE, right atrial area and greater ratio of right atrial to left atrial area.

Newer echocardiographic techniques have also been shown to predict poor outcome in pulmonary hypertension including reduced right ventricular longitudinal strain [15–19], poor global right ventricular area strain [20] and reduced three-dimensional right ventricular ejection fraction or greater end-systolic indexed volumes [14,20,47,48].

Conclusions

Echocardiography has an essential role as a screening tool for pulmonary hypertension. Aside from providing direct and indirect evidence for raised pulmonary pressure, potential causes may also be identified. Echocardiographic data has prognostic utility and may assist in assessing response to therapy and the need for treatment escalation. Although traditional echocardiographic techniques are inadequate for accurate assessment of right ventricular volumes, ejection fraction and global contractility, newer echocardiographic techniques such as three-dimensional echocardiography allow accurate assessment of these indices and are being increasingly utilised in clinical practice as the technology, experience and evidence base develops.

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