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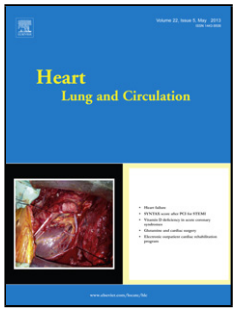

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Non-Invasive Assessment of Pulmonary Vascular Resistance in Pulmonary Hypertension: Current Knowledge and Future Direction

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Abstract

Pulmonary Hypertension (PHT) is relatively common, dangerous and under-recognised. Pulmonary hypertension is not a diagnosis in itself; it is caused by a number of differing diseases each with different treatments and prognoses. Therefore, timely and accurate recognition of the underlying cause for PHT is essential for appropriate management. This is especially true for patients with Pulmonary Arterial Hypertension (PAH) in the current era of disease-specific drug therapy.

Measurement of Pulmonary Vascular Resistance (PVR) helps separate pre-capillary from post-capillary PHT, and is measured with right heart catheterisation (RHC). Echocardiography has been used to derive a number of non-invasive surrogates for PVR, with varying accuracy. Ultimately, the goal of non-invasive assessment of PVR is to separate PHT due to left heart disease from PHT due to increased PVR, to help streamline investigation and subsequent treatment.

In this review, we summarise the physiology and pathophysiology of pulmonary blood flow, the various causes of pulmonary hypertension, and non-invasive surrogates for PVR.

Keywords: Pulmonary hypertension (PHT); Doppler echocardiography; Pulmonary arterial hypertension; Pulmonary vascular resistance (PVR); Heart failure with preserved ejection fraction (HFpEF)

Introduction

Pulmonary Hypertension (PHT), defined by a mean pulmonary artery pressure at or above 25 mmHg, can be broadly differentiated physiologically into pulmonary arterial hypertension (PAH) due to increased pulmonary vascular resistance (PVR), PHT due to increased pulmonary venous pressure but with a normal PVR (usually due to left heart disease), or a combination of both abnormalities. This differentiation is a crucial step in the investigation of patients with PHT, since the treatment of PHT due to left heart disease is fundamentally different from PHT due to abnormally increased pulmonary vascular resistance. Simply identifying the presence of PHT is necessary but not sufficient to manage such patients, and measurement of PVR is a key step. However, assessment of PVR usually requires right heart catheterisation (RHC), which is invasive, has potential complications, and therefore not universally performed in the investigation of PHT.

Pulmonary hypertension is relatively common and associated with a high risk of death(1), yet often goes unrecognised for extended periods. Regardless of aetiology, the common consequence of all forms of untreated PHT is symptomatic breathlessness, progressive right ventricular failure and ultimately death. With the development of effective advanced therapy for PAH, there is a need for simple non-invasive tools that can estimate PVR and help identify patients who would benefit from more comprehensive investigation, including right heart catheterisation. In this review, we will review and summarise the biochemical compounds and mechanical variables that affect blood flow through the pulmonary vasculature. We will also summarise techniques that have been used to non-invasively estimate PVR.

Physiology of Pulmonary Blood Flow and Pulmonary Vascular Resistance

Normal pulmonary circulation is low-pressure, low-resistance and highly dynamic, which allows major increases in pulmonary blood flow in response to exercise with only small increases in pressure. Pulmonary arterial blood flow regulation is maintained by pulmonary vascular resistance and recruitment of additional pulmonary capillaries, without the option of diversion through different vascular beds. This differs markedly from the systemic circulation, in which exercise results in hyperaemia in skeletal muscles, flow-mediated dilatation of conduit arteries, and dynamic changes in peripheral vascular resistance for each relevant vascular bed.

The degree of pulmonary arterial tone, via smooth muscle contraction, is governed by a series of vasoactive compounds released by the pulmonary vascular endothelium. Patients with PAH have increased levels of compounds that are responsible for vasoconstriction, thrombosis and smooth muscle cell hyperplasia (2-4). Each of the compounds exerts different effects on vascular smooth muscle, endothelial cell, surrounding blood cell responses. These responses are summarised in Table 1.

Table 1: Vasoactive compounds affecting pulmonary vascular resistance and drugs for PHT targeting those compounds

Compounds	Effects	Therapeutic agents modulating these compounds
Thromboxane A_2 (TxA_2)	Vasoconstrictor, stimulator of platelet aggregation and proliferation	None
Prostacyclin	Vasodilator, inhibitor of platelet aggregation and has antiproliferative property (counteracts thromboxane A_2)	Epoprostenol, Iloprost
Endothelin-1 (ET-1)	Potent vasoconstrictor and stimulator of pulmonary artery smooth muscle cells proliferation	Endothelin receptor antagonists (e.g. bosentan, macitentan)
Nitric Oxide (NO)	Vasodilator and inhibitor of platelet activation and vascular smooth-muscle cell proliferation, counteracts endothelin-1's actions	Inhaled NO Phosphodiesterase inhibitors (e.g. sildenafil) reduced the inactivation of cyclic guanosine monophosphate through which NO mediates its effects

Serotonin	Vasoconstrictor	No therapeutic agent available currently

Pulmonary blood flow is further regulated via capillary recruitment. In states of resting cardiac output, a number of capillary beds are in a collapsed state having neither blood perfusion nor ventilation. As the CO increases, there is an increase in the capillary blood volume resulting in recruitment of these distensible capillary beds without an increase in PVR.

Despite the responsive nature of this system, many additional factors affect pressure through the pulmonary vasculature. The Hagen-Poiseuille equation below describes the relationship between pressure, flow, viscosity and radius in a hollow, straight, non-distensible tube (5).

$$\Delta P = \frac{8\mu LQ}{\pi r^4}$$

ΔP **= pressure change**
L **= length of pipe**
μ **= dynamic viscosity**
Q **= volumetric flow rate**
r **= radius**

The change in pressure across the pulmonary artery is inversely proportional to the fourth power of the radius. If the radius of the pulmonary artery decreases (e.g. due to smooth muscle hypertrophy, hypoxic vasoconstriction or pulmonary thromboembolic disease), there is an accompanying disproportionate increase in the pressure across the pulmonary artery,

and a higher up-stream pressure will be required in order to maintain normal down-stream pressures.

There are additional effects on pulmonary pressures from blood viscosity (e.g. hyperviscosity syndromes increase pulmonary pressures whereas anaemia decreases pulmonary pressures or increased blood flow rates (high cardiac output or valvular disease).

Finally, the dynamics of blood flow in the left heart affect pulmonary blood flow. In a normal heart, left ventricular relaxation during diastole is an active (ATP dependent) process, causing a rapid fall in ventricular pressure and a "suction" effect on left atrial blood. This results in relative emptying of the pulmonary vein blood into the left atrium, and a fall in pulmonary capillary pressure. Further, during ventricular systole, the downward motion of the mitral valve toward the ventricular apex elongates the left atrium creating a systolic "suction" effect on pulmonary vein blood. Simultaneous right ventricular systolic contraction ensures a constant supply of blood into this low pressure circuit with rapid pulmonary capillary transit. These events cause efficient systolic and diastolic pulmonary capillary blood transit. Conditions that decrease left ventricular and left atrial compliance such as chronic atrial fibrillation, the stiff left atrial syndrome(6, 7), left ventricular hypertrophy and restrictive cardiomyopathy(8), disrupt the finely balanced transit through the pulmonary circulation and increase pulmonary capillary pressures.

Measurement of Pulmonary Vascular Resistance

In humans *in vivo*, pulmonary haemodynamics are most accurately measured invasively using right heart catheterisation. The mean pulmonary artery pressure (mPAP) can be measured by averaging the pressure inside the pulmonary artery throughout the cardiac cycle. To measure the pulmonary capillary wedge pressure (PCWP), the catheter is advanced into a branch pulmonary artery, and a small balloon attached near the tip of the catheter is inflated until the

pulmonary artery is occluded. The mean pressure measured at the tip of the catheter is taken to be the back-pressure from the left heart, and approximates the left atrial pressure in the absence of pulmonary vein stenosis. A mean PCWP <15 mmHg is generally accepted to indicate normal left atrial mean pressure, and is required to diagnose PAH, excluding PHT due to left heart disease(9).

The PVR is the resistance generated by the pulmonary vasculature against which the blood must travel from right to left side of the heart and is influenced by the transpulmonary gradient and the cardiac output:

$$PVR = TPG/CO$$

$$TPG = mPAP\text{-}PCWP$$

TPG – Transpulmonary gradient

mPAP – mean Pulmonary Artery Pressure in mmHg

PCWP – Pulmonary Capillary Wedge Pressure in mmHg

CO – Cardiac Output in L/min

In general, the higher the TPG and/or the lower the CO, the higher the PVR. Pulmonary vascular resistance is preferred to TPG, since it takes blood flow into account (10). The equivalent measure in the systemic circulation, the systemic vascular resistance (SVR), is generated by a number of different systemic arterial vascular beds and is approximately 10-fold higher than the PVR. A normal PVR is 1–3 mmHg.min/L, and decreases further with exercise and increased CO. For convenience, the mmHg.min/L units are often dropped and presented as Wood Units (WU), in honour of Earl Wood, an early pioneer in the field.

Despite its importance in PHT diagnosis and management, RHC has a number of drawbacks. It is invasive with potentially serious risks such as ventricular arrhythmias, thromboembolism, myocardial or valvular injury, pulmonary infarction and rupture of a

pulmonary artery. Right heart catheterisation requires significant skills and standardisation of the procedure, and is not universally available. Although RHC accurately measures the PCWP, it may not reflect the true left ventricular filling pressure (11, 12), particularly if mitral stenosis (13), pulmonary vein stenosis or a noncompliant left atrium (6) is present.

Clinical Classification and Epidemiology of Pulmonary Hypertension

Pulmonary hypertension is defined as an increased resting mPAP at or above 25 mmHg, measured with RHC (9). Pulmonary hypertension is not a disease in itself, but simply a marker of a pathophysiological abnormality that requires explanation. A clinical classification of PHT has been provided by the World Health Organisation (WHO) with several more recent updates (14). The Latest Classification (NICE 2013) classified PHT into five groups, summarised in Table 2.

Table 2: NICE classification of pulmonary hypertension, with abridged examples for each group.

Pulmonary Hypertension Group	Examples
Group 1 **Pulmonary Arterial Hypertension**	Idiopathic PAH PAH associated with other diseases: Scleroderma Congenital heart disease
Group 2 **PHT due to Left Heart Disease**	Myocardial disorders: Valvular heart disease Congenital LV inflow or outflow obstruction
Group 3 **PHT due to Lung Disease**	COPD and Interstitial lung disease Sleep disorders Chronic hypoxia
Group 4	Multiple chronic pulmonary emboli

Chronic Pulmonary Thromboembolic Disease (CTEPH)	
Group 5	Haematologic disorders
PHT with multifactorial cause	Chronic renal failure

The data from recent studies suggest the true prevalence of PHT in the general population is higher than previously reported (15-17). We have previously reported a minimum 'indicative' prevalence for all forms of PHT at 326 cases/100,000 inhabitants of Armadale and its surrounding area in Western Australia. Left heart disease-associated PHT was the commonest cause (250 cases/100,000) and had the worst prognosis. Patients with PAH who were treated with disease specific therapy had the best prognosis (18). Moreover, there is significant delay between symptom onset and the time of diagnosis leading to poor prognoses (19, 20).

Previously, patients with group 1 PHT (PAH) had worse survival than other groups. The era of advanced therapy has improved the overall prognosis of PAH patients (21) with some trials suggesting one-year survival rates of 84% (22). Advanced therapy includes specific pulmonary vasodilator drugs, such as Prostacyclin, endothelin receptor antagonists (ERAs) and phosophodiesterase type-5 (PDE-5) inhibitors. These decrease the rate of progression and complications as well as improve symptoms associated with PAH, with the greatest benefits derived from early commencement of therapy.

A Proposed Pathophysiological Classification of PHT based on PVR

The latest clinical classification for pulmonary hypertension only partially reflects the underlying pathophysiology of each disease. For this reason, there is an overlap in treatment between groups. An alternative method of classification is to describe the pathophysiology

underpinning the PHT. Using this method, the causes of PHT can be subdivided into two major groups: pre-capillary or post-capillary based on whether the pulmonary vascular resistance is normal or increased. Pre-capillary PHT is defined by a high transpulmonary gradient of at least 12 mmHg, a high pulmonary vascular resistance of >3 WU and pulmonary capillary wedge pressures of <15 mmHg (normal left heart filling pressure). These "high PVR" pulmonary hypertension patients may respond to pulmonary vasodilator therapy, and would include individuals with Group 1 or Group 3 PHT. Some patients from groups 4 or 5 may also be included, depending on their PVR.

Post-capillary pulmonary hypertension, or "normal PVR" pulmonary hypertension, is characterised by an increased PCWP of >15 mmHg but normal or low PVR(9, 10). These patients are predominantly Group 2 (left heart disease).

Some patients have a mixed picture, with PCWP due to elevated LV filling pressures, but with coexisting increased PVR. These individuals have a disproportionate rise in their pulmonary artery pressure beyond that expected from the degree of left heart disease alone. Such patients may respond only partially to diuretic therapy and treatment of their left heart disease, however the use of pulmonary vasodilator therapy in this situation is controversial(23-26).

The range of abnormalities are summarised in Figure 1 below.

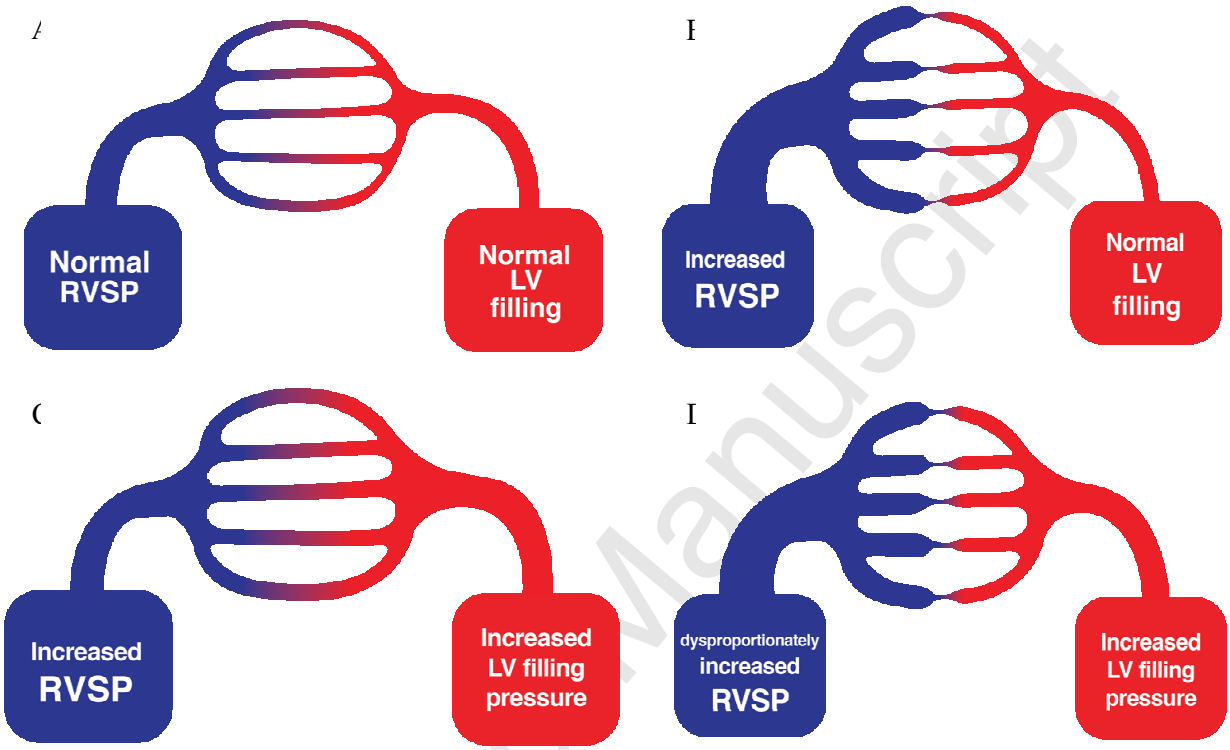
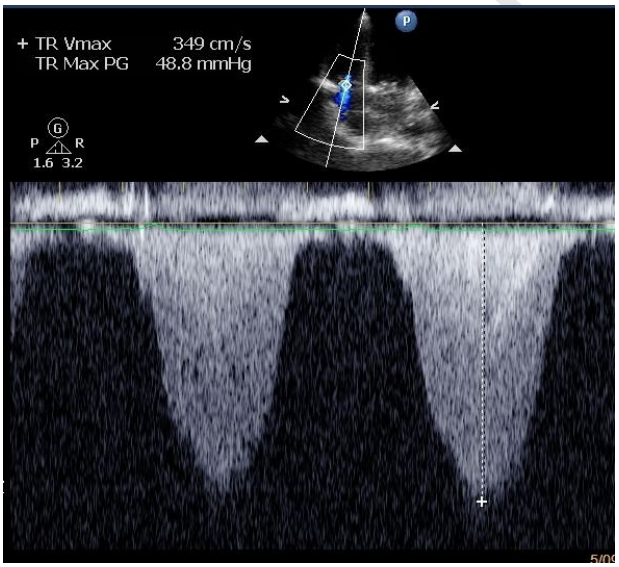


Figure 1: The range of abnormalities in PHT. Panel A shows a normal scenario with normal PVR and normal LV filling pressures. Panel B shows normal LV filling pressures but increased PVR resulting in PAH. Panel C demonstrates increased LV filling pressures with normal PVR, resulting in pulmonary hypertension due to left heart disease. Panel D shows a mixed picture, with increased LV filling pressure but a disproportionate increase in pulmonary artery pressure caused by increased PVR. PVR = Pulmonary Vascular Resistance; RVSP= right ventricular systolic pressure; LV= left ventricle.

Identifying increased PVR and/or abnormal left heart filling pressure helps guide therapy, particularly in the era of advanced therapies which target the pulmonary vasculature (27-32). Heart failure with preserved ejection fraction (HFpEF) causing PHT due to increased filling pressures should not be misclassified as PAH (33), particularly since some pulmonary vasodilator therapy in this group of patients may be harmful.

Echocardiography in Pulmonary Hypertension

Echocardiography (echo) is the most commonly used noninvasive tool for identifying PHT, and is particularly useful when screening for PHT (34). Using the velocity of tricuspid regurgitation (TRV), pulmonary artery systolic pressure (PASP) can be estimated (35-37) (Figure 2). There is a strong association between the pulmonary artery pressure (PAP) measured by right heart catheterisation and that obtained by echo (18, 38).



$PASP = RAP + 4(TRV)^2$

Figure 2. From Apical 4-chamber view, the tricuspid regurgitation velocity (TRV) is measured by using continuous wave Doppler. The PASP is estimated using the modified Bernoulli equation ($\Delta P=4V^2$). P=change in pressure, V=velocity of flow(36).

Pulmonary Vascular Resistance Estimation with Echocardiography

A number of echocardiographic markers have been proposed for the noninvasive estimation of PVR(39-42). However, many of these markers cannot reliably separate PHT due to left heart disease from PHT due to increased PVR. Currently, there is no single reliable method of estimating PVR non-invasively that has been tested and proven in a large-scale study.

As early as 1975, researchers have described methods to estimate PVR non-invasively. In a study by Hirschfeld et al. (39), 64 patients with congenital heart disease underwent RHCs and echo examinations. Fifty-seven patients had both examinations on the same day and four patients had them within one month; however, three patients' echoes were done three to five years after RHC. The ratio of right ventricular ejection time (RVET) to right ventricular pre-ejection period (RPEP) was found to correlate well with invasive measurements of pulmonary artery diastolic pressure (PADP), PVR and mPAP. The correlation coefficient of the proposed index with PVR was 0.69. The study was limited to patients with congenital heart diseases and extrapolation to PHT patients due to other aetiologies may not be appropriate. Dabestani et al. examined the pulmonary artery flow velocities by pulsed Doppler echocardiography in 39 patients and found a negative linear correlation between pulmonary artery acceleration time and total pulmonary resistance(43).

Scapellato, and colleagues simultaneously performed Doppler echocardiographic and RHC measurements in 63 patients with sinus rhythm and severe heart failure(40). Doppler measurements from pulmonary flow and TRV curve were correlated with invasive PVR. Among the investigated variables, the acceleration time of pulmonary systolic flow was found to have best correlation with the invasive PVR (r=-0.68). The correlation coefficient improved to 0.96 by using the equation:

PVR= -0.156+1.154*[(PEP/AcT) /TT]

PEP = Pre-ejection period

AcT=Pulmonary acceleration time

TT= Total systolic time

The principal advantages of this study were simultaneous measurement of both echo and RHC, and the relative simplicity and accuracy of their equation up to 9 WU. However, the study was small and excluded patients with atrial fibrillation and those without heart failure.

The formula described by Abbas et al. in 2003 is commonly used in echo laboratories as a noninvasive PVR assessment. They performed simultaneous echo and RHC in 44 patients (41). They found a close association (r=0.93, CI 0.87–0.96) between the invasively measured PVR and the ratio of the TRV to the velocity time integral of the flow through the right ventricular outflow tract ($TVI_{RVOT,}$). Their equation approximated to the following:

$$PVR_{ECHO} = 0.16 + 10 \times TRV/TVI_{RVOT}$$

This method is easy to calculate from standard echo measurements, but the study was relatively small, did not include patients with PVR over 6 WU, and did not account for left atrial pressure, an essential component of the invasively measured PVR. In subsequent analyses, the original Abbas equation was shown to underestimate invasive PVR assessment in those with PVR over 6 WU(44), which could be partly corrected by incorporating assessment of LV filling pressures into the equation (using E:E' ratios). The E:E' ratio is calculated as the ratio of the early diastolic flow through the mitral valve (measured using pulsed wave Doppler echo) to the early diastolic descent velocity of the medial mitral annulus (measured using pulsed wave tissue Doppler velocities). The E:E' ratio is commonly used as a surrogate for left ventricular filling pressure (45-47) and predicts mortality in left heart disease(48-50). Using data from five separate studies, Abbas et al. demonstrated a more robust association between PVR and TRV^2/TVI_{RVOT} (42), including patients with a PVR > 6 WU. The ratio has been further validated by a similar study in post-cardiac surgery patients in an intensive care setting (51).

A further study by Haddad et al. in 2009 demonstrated that invasively measured PVR correlated well with the index of PASP to the heart rate (HR) times the TVI_{RVOT} [PASP/(HR x TVI_{RVOT})] in 51 patients with established PAH (52). This method is also simple to use and the measurements required for the equation are routinely performed in most echocardiography laboratories. The small number of participants again limited this study. Additional sources of error include the need to estimate the right atrial pressure in their equation.

Table 3: Summary of echocardiographic methods for estimating PVR

Investigators and References	**Surrogate Indexes/Formulae**	**Number of patients**	**Correlation coefficient (r) of surrogate index with PVR**
Hirschfeld et al. (39)	RVET/ RPEP (RVET= right ventricular ejection time, RPEP =right pre-ejection period.)	64	0.69
Scapellato et al. (40)	PVR=0.156+1.154*[(PEP/AcT) /TT] (PEP=Pre-ejection period, AcT=Acceleration time, TT=total systolic time of pulmonary flow.)	63	0.96
Abbas et al. (original) (41)	TRV/TVI_{RVOT} (VTR= Tricuspid Regurgitation Velocity	44	0.929 (95% confidence interval 0.87 to 0.96)

	Velocity, TVI_{RVOT}=Time Velocity Integral of the flow through the right ventricular outflow tract)		
Abbas et al. (Analysis of raw data from 5 validation studies)(42)	TRV/TVI_{RVOT} (original) TRV^2/TVI_{RVOT} (modified)	150 patients on final analysis	0.76 0.79
Haddad et al. (50)	$PASP/(HR \times TVI_{RVOT})$	51	0.860 (95% confidence interval, 0.759-0.920)

Recently, a new echocardiographic method for estimating transpulmonary gradients has been proposed by Scalia et al. (53). The ePLAR, or echocardiographic pulmonary to left atrial ratio is the ratio of peak tricuspid regurgitation velocity (a marker of pulmonary artery systolic pressure) and E:E' ratio (a marker of left ventricular filling pressure).

$$\text{ePLAR} = \frac{\text{TRV}}{\text{E: E'}}$$

ePLAR = Echocardiographic Pulmonary to Left Atrial Ratio

TRV = Tricuspid Regurgitation Velocity

E: E' = The ratio of transmitral E-wave to septal mitral annular Doppler Tissue Imaging E'-wave

The marker is simple, non-invasive, and uses measurements performed as part of a standard echocardiogram. For 16,356 "normal" echocardiograms without PHT, the mean ePLAR was

0.30 +/- 0.09m/s. For 133 patients with PHT, the ePLAR helped separate those with elevated PVR from those with PHT due to left heart disease: In 35 patients with pre-capillary PHT confirmed using RHC (with elevated PVR, mean 6.5+/-3.6 WU), the mean ePLAR was 0.44 +/- 0.22 m/s. The ePLAR was significantly lower (0.18 +/- 0.18 m/s) in those with PHT due entirely to left heart disease (81 patients, mean PVR 3.1+/-2.7 WU). The major limitation of the study is non-simultaneous performance of echocardiograms and RHC. Although helpful to identify patients with elevated transpulmonary gradients, ePLAR does not take cardiac output into account.

Conclusions

Pulmonary hypertension is common and associated with significant mortality. A rigorous approach to its diagnosis is required by every echo laboratory, starting with estimation of pulmonary artery pressure. Pulmonary hypertension is not a diagnosis in itself, and identification of the underlying cause will determine approaches to treatment. Estimation of PVR is an important aspect of the diagnostic workup and a number of non-invasive methods for PVR measurement have been proposed. Like their invasive counterparts, most non-invasive methods rely on a combination of pulmonary artery pressure and flow assessment; however, most studies describing these methods suffer from small sample study size, limited reliability across a broad range of patients, and do not take left atrial pressure into account. New methods such as ePLAR show promise, but require further study in large cohorts with differing forms of pulmonary hypertension.

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