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REVIEW

Imaging in pulmonary hypertension: Focus on the role of echocardiography



Imagerie dans l'hypertension pulmonaire : le rôle de l'échocardiographie

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KEYWORDS

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Summary Patients with pulmonary hypertension must be evaluated using a multimodality approach to ensure a correct diagnosis and basal evaluation as well as a prognostic assessment. Beyond the assessment of pulmonary pressures, the echocardiographical examination allows the evaluation of right ventricular adaptation to elevated afterload. Numbers of variables are commonly used in the assessment of the pulmonary hypertension patient in order to detect changes in right heart geometry, right-to-left interaction and right ventricular dysfunction. Whereas an isolated change in one echocardiographical variable is not meaningful, multiple echocardiographical variable modifications together provide accurate information. In this review, we will link pulmonary hypertension pathophysiological changes with echocardiographical indices and describe the clinical implications of echocardiographical findings.

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Abbreviations: 2D, Two-dimensional; 3D, Three-dimensional; dPAP, Diastolic pulmonary artery pressure; IVA, Isovolumic acceleration; IVCc, Isovolumic contraction velocity; LV, Left ventricle/ventricular; LVOT, Left ventricular outflow tract; mPAP, Mean pulmonary artery pressure; MPI, Myocardial performance index; PA, Pulmonary artery; PAH, Pulmonary arterial hypertension; PAP, Pulmonary artery pressure; PR, Pulmonary regurgitation; RA, Right atrium/atrial; RAP, Right arterial pressure; RV, Right ventricle/ventricular; sPAP, Systolic pulmonary artery pressure; TAPSE, Tricuspid annular plane systolic excursion; TR, Tricuspid regurgitation; VTI, Velocity-time integral.

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MOTS CLÉS

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Résumé L'imagerie cardiaque multi-modalité est indispensable à l'évaluation diagnostique et pronostique des patients atteints d'hypertension pulmonaire. Bien plus que la mesure des pressions pulmonaires, l'échocardiographie permet l'évaluation de la fonction ventriculaire droite traduisant l'adaptation du cœur droit à l'élévation des résistances pulmonaires. Alors que la modification isolée d'une variable échographique n'est que peu informative, celle de plusieurs paramètres échographiques est plus souvent pertinente. Dans cette revue, nous décrivons les modifications physiopathologiques du cœur droit et du couple VD-AP dans l'hypertension pulmonaire par l'approche échographique et soulignons l'intérêt clinique de ces différents paramètres échocardiographiques.

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Background

Pulmonary hypertension is a progressive and severe pulmonary, vascular and cardiac disorder. Pulmonary hypertension is defined by an increase in mean pulmonary artery pressure (mPAP) to ≥ 25 mmHg at rest as determined by right heart catheterization, the 'gold standard' [1]. Usually, patients are screened with echocardiography (Table 1), and right heart catheterization allows measurement of cardiac output and differentiation between pre- and postcapillary pulmonary hypertension. Pulmonary hypertension can be divided into subsets sharing similar underlying pathophysiology, detailed in Fig. 1 [2].

Although the degree of pulmonary hypertension characterizes this condition, it does not correlate with symptoms or survival. Right ventricular (RV) physiology (RV mass and function) is closely related to functional class, exercise capacity and survival [3,4]. Advanced therapies, which aim to decrease pulmonary vascular resistance, usually significantly improve RV function, but the observed decrease in mPAP is only moderate.

Table 1 Echocardiographical screening for patients at risk of pulmonary hypertension.

TR V_{\max}	
≤ 2.8 m/s + echocardiographical risk factors	PH possible
2.9–3.4 m/s	PH possible
> 3.4 m/s	PH likely

Echocardiographical risk factors suggesting pulmonary hypertension

- Dilated right ventricle/right atrium
- Increased PR velocity
- Pulmonary acceleration time < 105 ms
- TAPSE < 20 mm
- 'D-shaped' interventricular septum

PH: pulmonary hypertension; PR: pulmonary regurgitation; TAPSE: tricuspid annular plane systolic excursion; TE: tricuspid regurgitation.

In clinical practice, ultrasound is by far the most common RV imaging modality, especially in the setting of pulmonary arterial hypertension (PAH). Transthoracic echocardiography provides a number of variables for evaluating right heart haemodynamics (Table 2). It is critical to recognize early signs of PAH with echocardiography in order to reduce the delay between first symptoms and time of diagnosis. Echocardiography is particularly suitable in pulmonary hypertension studies as it is non-invasive, cost-effective and widely available.

Thus, the aim of this paper is to describe the cardiac alterations related to pulmonary hypertension, and to review and discuss the extent to which echocardiography plays a key role in early diagnosis and prognosis in pulmonary hypertension.

Right ventricular anatomy and pathophysiology

The right ventricle (RV) is the most anterior chamber of the heart and can be divided into three chambers: the inlet, the apex and the infundibulum. In comparison with the left ventricle (LV), the RV is characterized by prominent trabeculations that limit the accuracy of contour tracing to delineate the endocardial border. A complex shape, opposite to the ellipsoidal shape of the LV, also characterizes the RV [5]. When viewed in cross section, the RV is crescent shaped, whereas it appears triangular when viewed longitudinally or from the side. However, the RV shape is influenced by RV-LV interactions, depending on the position of the interventricular septum. In normal conditions, the RV volume is larger than the left ventricular (LV) volume, whereas the RV mass represents approximately only one fifth of the LV mass [6]. The myofibre arrangement is also particular, in that almost only two muscle layers compose the RV wall: the superficial layer (circumferential) and the deep layer (longitudinally arranged), thus explaining in normal RVs the predominance of longitudinal contraction, with no intermediate circumferential layer.

Regarding RV contraction physiology, three individual components lead to normal contraction: the inward motion of the free wall; longitudinal shortening; and the traction of the free wall, secondary to LV contraction [7]. In consequence, RV contraction relies mostly on LV-RV interaction and longitudinal deformation.

- 1 Pulmonary arterial hypertension**
- 1.1 Idiopathic
 - 1.2 Heritable (BMP2; ALK1, ENG and others)
 - 1.3 Drug and toxin induced
 - 1.4 Associated pulmonary arterial hypertension
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease (CHD-PAH)
 - 1.4.5 Schistosomiasis
 - 1.4.6 Chronic haemolytic anaemia
 - 1' Pulmonary veno-occlusive disease and/or capillary haemangiomatosis
 - 1'' Persistent pulmonary hypertension of the newborn
- 2 Pulmonary hypertension due to left heart disease**
- 3 Pulmonary hypertension due to lung diseases and/or hypoxia**
- 4 Chronic thromboembolic pulmonary hypertension**
- 5 Pulmonary hypertension with unclear multifactorial mechanisms**

Figure 1. Fifth World Symposium on pulmonary hypertension (Nice, 2013) updated classification of pulmonary hypertension.

Right ventricle/pulmonary artery coupling

Under normal circumstances, the pulmonary circulation unit has lower vascular resistance and greater distensibility than the systemic circulation. There is a complex relationship between RV systolic function, preload and afterload. The RV has a heightened sensitivity to afterload elevation [8,9] (i.e. mainly increased pulmonary vascular resistance). Preservation of RV-pulmonary artery (PA) coupling is critical for the maintenance of RV function: PAs facilitate the transition from an RV pulsed flow to an almost continuous flow at the capillary levels. Under pathological conditions, increased PA stiffness leads to higher pulsatile RV work and promotes RV dysfunction. Resistances in the small vessels mainly represent pulmonary vascular resistance. With regard to this definition, pulmonary vascular capacitance is a measure of global workload of the RV, accounting for large vessels and pulsatile elements. A high-capacitance allows the forward pulmonary blood to be 'stored' in the capacitant vessels and decreases the RV load. The RV evolution from compensated to decompensated follows changes in the pulmonary vascular bed: from a normal high-capacitance state to

arterial vasoconstriction and proliferative obstructive vascular remodelling.

The RV adapts better to volume overload than to pressure overload. Different types of overload result in different types of RV adaptation. For example, experimental PA banding (pressure overload) leads to RV hypertrophy, mild RV dilatation and reduced exercise capacity with calcineurin activation, whereas volume loading (shunt) leads to hypertrophy and severe RV dilatation with preserved exercise capacity [10]. Echocardiography is helpful for distinguishing volume overload with increased pulmonary pressures but normal pulmonary vascular resistances from normal (or reduced) flow elevated PA pressures and pulmonary vascular resistances (PAH). It is crucial to differentiate between these presentations, especially in atrial septal defect patients, in order to determine the need for defect closure or pulmonary vasodilators.

RV adaptation to increased pressure overload in pulmonary hypertension depends on the overload severity and the rapid onset of the disease; this suggests that RV remodelling has an important role in protecting against pulmonary hypertension (as in congenital PAH). RV myocardial hypertrophy is the first adaptive remodelling response. Changes

Table 2 Most validated and useful variables in the routine evaluation of pulmonary hypertension patients.

Clinical situation	Echocardiographical variables	Clinical relevance	
Diagnosis	TR V_{\max}	RV-RA gradient—estimation of sPAP ($4 \times V_{\max}^2 + \text{RAP}$)	$V_{\max} > 2.8 \text{ m/s}$ sPAP $> 35 \text{ mmHg}$
	PR V_{\max}	mPAP = $4 \times V_{\max}^2 + \text{RAP}$	mPAP $\geq 25 \text{ mmHg}$
	Telediastolic PR velocity	dPAP = $4 \times \text{velocity}^2 + \text{RAP}$	sPAP = 3 mPAP–2 dPAP
	Pulmonary acceleration time		$< 93 \text{ ms}$
	TAPSE	Systolic dysfunction	$< 18 \text{ mm}$
	S'	Predictor of sPAP $> 40 \text{ mmHg}$	$< 12 \text{ cm/s}$
	RV diameter (D1)		$> 40\text{--}42 \text{ mm}$
	3D RV end-diastolic volume		$> 89 \text{ mL/m}^2$
	RV wall thickness	RA pressure	$> 5 \text{ mm}$
	RA area		$> 18 \text{ cm}^2$
IVC diameter and compliance		$> 21 \text{ mm}$	
Aetiological approach	Intra- or extracardiac shunt	Contrast TTE sometimes useful (TOE if necessary)	Congenital PAH
	TR V_{\max} /pulmonary VTI	Increased pulmonary vascular resistance	> 0.2
	E/E'm	LV filling pressures	> 10 (group 2 patients)
	PA thrombosis		Group 4 patients? (or pulmonary hypertension complicated by PA thrombosis)
Prognosis	TAPSE		$< 16 \text{ mm}$
	S'		$< 10 \text{ cm/s}$
	RV fractional area change		$< 35\%$
	Peak longitudinal RV strain		$\geq 19\%$
	IVCv		$< 9 \text{ cm/s}$
	Tei index (PW)		> 0.4
	Main PA diameter		$> 29 \text{ mm}$
	LV eccentricity index		> 1.4
Pericardial effusion		Presence	
Follow-up	RV diameter	Improves with advanced therapy	
	RV fractional area change		
	Tei index		
	Mitral E/A and E/E'		

IVC: inferior vena cava; IVCv: isovolumetric contraction velocity; LV: left ventricle; mPAP: mean pulmonary artery pressure; PA: pulmonary artery; PAH: pulmonary arterial hypertension; PAP: pulmonary artery pressure; PR: pulmonary regurgitation; PW: pulsed-wave; RA: right atrial; RAP: right atrial pressure; RV: right ventricle; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography; TR: tricuspid regurgitation.

in sarcomeric protein expression and renin-angiotensin system activation promote RV myocardial ischaemia, whereas dilatation occurs subsequently. The increased preload initially compensates for the reduced contractility, to maintain the stroke volume. The RV becomes more spherical due to the increased RV volume, compressing the LV and causing diastolic dysfunction. With chronic pressure overload, right atrial (RA) contractility and distensibility increase [11] until RA pressure increases. Progressively, as the RV dilates, the filling pressures increase, leading ultimately to RV failure. The intensity of the neurohormonal activation contributes to RV adverse remodelling and failure. The presence of

functional tricuspid regurgitation (TR), caused by RV/RA dilatation, also contributes to the reduced cardiac output.

Assessment of pulmonary artery pressures

Standard Doppler echocardiography provides a reliable estimation of PAP: in the absence of pulmonary flow obstruction, TR peak velocity and pulmonary valve acceleration time are correlated with systolic PAP (sPAP) and mPAP, respectively, as assessed by right heart catheterization. sPAP is considered equal to RV systolic pressure in the absence of pulmonary

valve stenosis or outflow tract obstruction. RV systolic pressure can be determined by the addition of RA pressure (RAP) to the pressure gradient between the right chambers, calculated using the modified Bernoulli equation: $\Delta P = 4 \times TR V_{max}^2$. European guidelines [12] consider the echocardiographical diagnosis of pulmonary hypertension 'likely' when $TR V_{max}$ is >3.4 m/s and 'possible' when $TR V_{max}$ is between 2.9 and 3.4 m/s or when $TR V_{max}$ is ≤ 2.8 m/s with additional variables suggestive of pulmonary hypertension (RV dilatation, hypertrophy or increased pulmonary regurgitant velocity). To improve the accuracy of echocardiography and limit the angle dependency, the TR jet should be appreciated from multiple RV views. However, in severe TR with laminar flow, the peak velocity does not reflect the RV-RA pressure gradient because of early equalization of RV and RA pressures. In the latter, peak early diastolic and end-diastolic velocities obtained from pulmonary regurgitation (PR) flow can provide an estimation of mPAP and diastolic PAP (dPAP).

When present, PR is characterized by a rapid rise in flow velocity after the valve closure and a gradual deceleration until the next opening. Peak PR velocity can estimate the mPAP using the equation $mPAP = 4 \times PR V_{max}^2 + RAP$, whereas end-diastolic PR enables the calculation of dPAP using the equation $dPAP = 4 \times \text{end-diastolic PR velocity}^2 + RAP$.

Exercise-induced pulmonary hypertension is an early phase of the disease [13]. However, as age is an important confounding factor for the elevation of PAP with exercise, stress echocardiography is not recommended, even in high-risk patients. On the other hand, in patients with established elevated sPAP, elevation of PAP with exercise can be used as a surrogate for RV contractile reserve; a recent study has demonstrated the prognostic value of this variable in PAH patients [14].

Imaging the right ventricle

Right ventricular linear dimensions

Measurement of the dimensions of the RV is an important part of echocardiography, as they describe RV remodelling. RV free wall thickness reflects the degree of RV hypertrophy; it should be measured at the end of diastole in subcostal or parasternal long-axis view, preferably at the level of the tip of the anterior tricuspid leaflet. The normal cut-off for RV wall thickness, excluding trabeculations and papillary muscle, is 5 mm. As there may be beneficial and detrimental RV hypertrophy regarding different metabolic pathways [15], RV wall thickening is not independently associated with survival in pulmonary hypertension.

As the RV dilates in response to RV failure and increased pressure overload, RV enlargement is a predictor of mortality in patients with pulmonary disease and pulmonary hypertension [16,17]. RV dimensions should be measured at the basal mid-cavity level as well as longitudinally using the four-chamber view. The basal diameter (RV D1, upper limit 42 mm; Fig. 2A) should also be compared with LV dimensions, to help to distinguish enlarged RV from global heart dilatation. One major limitation of this two-dimensional (2D) technique is that it is highly dependent on the probe and patient position. Beyond RV dilatation, PA dilatation is

important to detect because of its prognostic importance [18].

Right ventricular three-dimensional assessment

Complex anatomy is usually best assessed using a three-dimensional (3D) technique. Three-dimensional echocardiography can be used to assess RV volumes and ejection fraction; it leads to less underestimation of volumes and improved variability compared with 2D-echocardiography and provides an accurate and reproducible RV ejection fraction that could help with serial measurements. The lower cut-off for 3D RV ejection fraction is 44% and 3D echocardiography correlates well with cardiac magnetic resonance in children [19] and adults [20,21]. The upper reference limits for 3D-indexed RV end-diastolic and end-systolic volumes are 89 mL/m² and 45 mL/m², respectively.

Tricuspid regurgitation

In PAH, TR occurs as the result of the effect of increased RV afterload on RV dilatation and function. TR is usually caused by tricuspid annular dilatation, altered RV geometry and apical displacement of tricuspid leaflets, failing to adapt. Moderate or greater degrees of TR are commonly seen in advanced pulmonary hypertension [22], the severity of TR being correlated with functional capacity. TR also contributes to reduced cardiac output.

Right ventricular fractional area change

RV fractional area change, defined as (end-diastolic area – end-systolic area)/end-diastolic area $\times 100$ (Fig. 2A), is a simple 2D way to assess RV systolic function using the apical four-chamber view. Despite the limitations inherent to the method (difficult contour tracing, foreshortened apical view because of RV dilatation), it has been correlated with cardiac magnetic resonance data [23] and is considered as the gold standard in RV assessment. A RV fractional area change of $<35\%$ indicates RV systolic dysfunction and changes in time correlate with clinical deterioration [24]. However, the significant variability, when measured by echocardiography and compared with cardiac magnetic resonance, explains why it requires multiple measurements.

Longitudinal right ventricular function

Longitudinal systolic RV function can be estimated using tricuspid annular plane systolic excursion (TAPSE) and S' (also called tricuspid valve Sm). TAPSE (Fig. 2B) is one of the simplest measurements, an M-mode measure obtained from the apical view, which is of critical importance. Beyond reflecting longitudinal function, TAPSE also correlates with global indices of RV global function [25–27]. RV dysfunction is considered for TAPSE <16 mm. TAPSE has significant prognostic importance in PAH [28], especially in patients with idiopathic PAH, systemic sclerosis-associated PAH [29] and Eisenmenger's syndrome [30]. However, TAPSE is angle and operator dependent and varies according to heart motion (the reference point being located outside the heart) and the severity of TR and RV-LV interactions [31]. Tissue Doppler

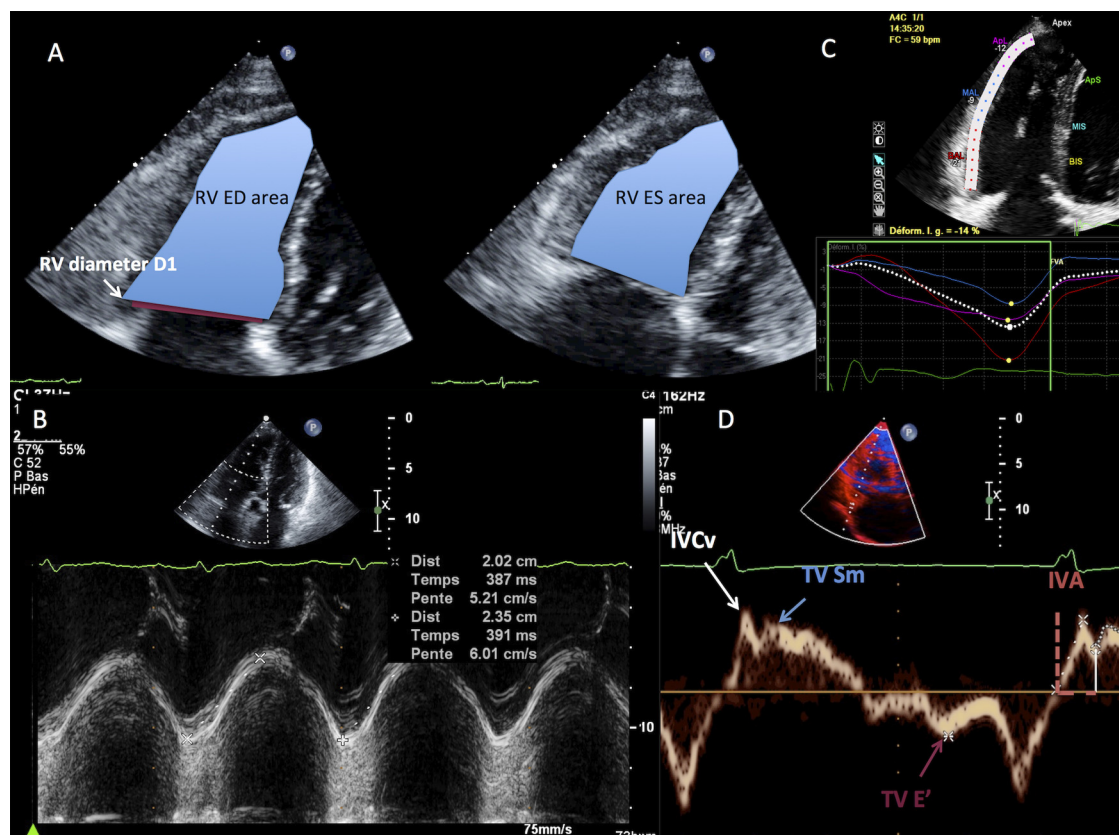


Figure 2. Assessment of right ventricular function. (A) Apical view focused on the right ventricle (RV) with RV inlet end-diastolic measurement (D1) and end-diastolic area (RV ED area) and end-systolic area (RV ES area) tracing, allowing calculation of RV fractional area change $(RV\ ED\ area - RV\ ES\ area) / RV\ ED\ area$. (B) Measurement of TAPSE using the four-chamber view. (C) Example of RV free wall speckle-tracking study showing a decreased longitudinal strain. (D) Tissue Doppler imaging with pulsed Doppler at the tricuspid lateral annulus; the example shows the measurement of S' (tricuspid valve [TV] Sm), the isovolumic contraction peak velocity (IVCv) and acceleration during isovolumic contraction (IVA). [BRAD: french abbreviations used in figure e.g. ITV rather than VTI].

imaging can also determine the peak systolic velocity of the lateral tricuspid annulus (by pulsed tissue Doppler and/or colour-coded tissue Doppler) (Fig. 2D). S' is well correlated with TAPSE and the lower reference limit in normal control patients has been established as 10 cm/s [32,33]. However, these variables remain limited, given that, as shown by a 3D study [34], under pathological conditions the RV has differential regional function, with distinct features for each compartment, thus having a different effect on the overall systolic function.

Another tissue Doppler variable derived from the basal free RV wall that is useful in clinical practice is myocardial acceleration during isovolumic acceleration (IVA) (Fig. 2D) [35]. IVA is defined by the peak isovolumic myocardial velocity (IVCv) divided by time to peak velocity, the zero crossing line defining the onset of myocardial acceleration. IVA is less load-dependent than other indices [36], but is frequency dependent, explaining why it should be indexed to the heart rate (divided by \sqrt{RR} [ms]). The lower reference limit by pulsed-wave tissue Doppler imaging is 2.2 m/s². Despite being a reliable indicator of RV function [37], IVA has not yet been related to prognosis in patients with PAH; however, IVCv (peak velocity) has been identified recently as an independent predictor of clinical outcomes in group 1 pulmonary hypertension patients [38].

Right ventricular adaptation

The RV myocardial performance index (MPI) or Tei index [39] (Fig. 3A), defined by the ratio of isovolumic time divided by ejection time, reflects the global RV performance and adaptation. It can be obtained either by pulsed Doppler on RV outflow and the tricuspid valve (using similar RR intervals) or by tissue Doppler imaging. Reference values differ between these two methods [40] (upper reference limits 0.40 [pulsed Doppler] and 0.55 [tissue Doppler]). This index is related to prognosis in PAH and is associated with clinical improvement following advanced therapies [41]. In chronic thromboembolic pulmonary hypertension, RV MPI is correlated with disease severity and associated with outcomes [42]. RV MPI has also been validated in paediatric pulmonary hypertension, MPI being correlated with mPAP and response to therapy [43]. The measure of total isovolumic time provides with the same indications than MPI; it has been related to outcomes in Eisenmenger's syndrome [30] and is related overall to the disease severity and degree of pulmonary hypertension [44,45]. Calculation of the systolic to diastolic duration ratio (S/D ratio) is another means of assessing RV adaptation. Durations of systole and diastole are measured from the apical view (Fig. 3B) to obtain the clearest Doppler signal of TR. Systolic duration is measured as the

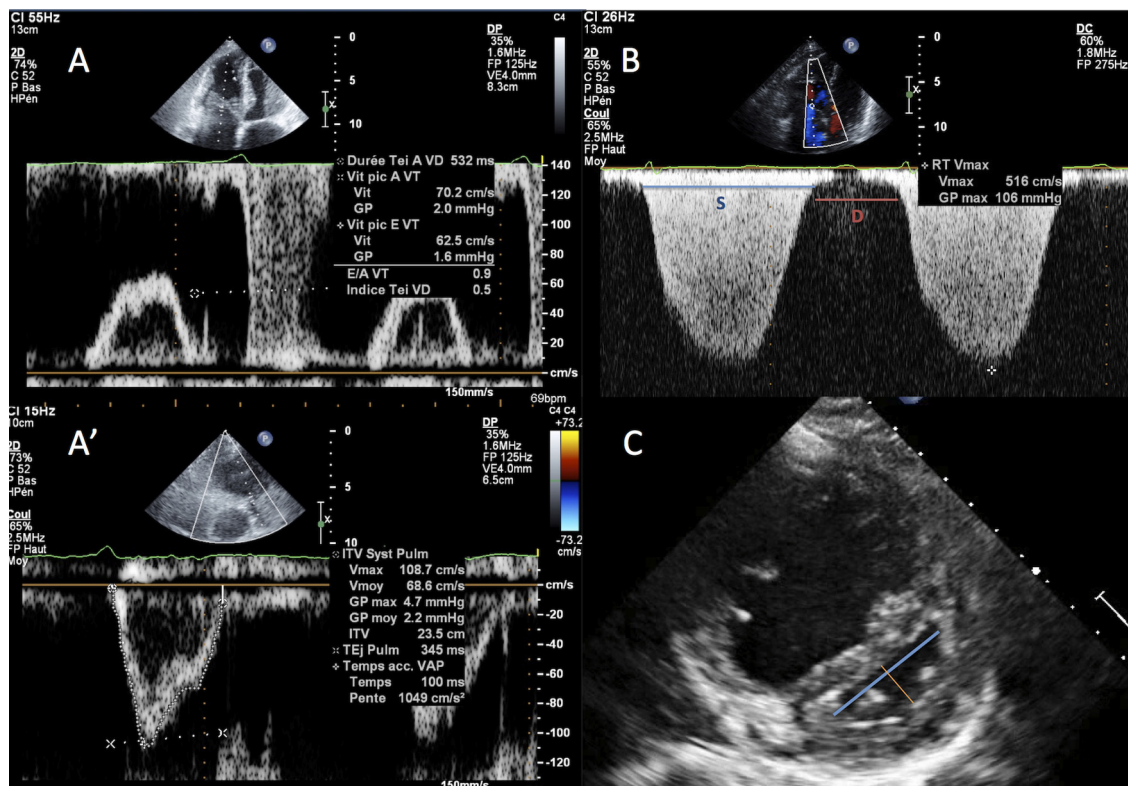


Figure 3. Assessment of right ventricular adaptation and right ventricle/left ventricle interaction. (A) Transtricuspid flow recorded with pulsed Doppler, with measurement of tricuspid valve E (TV E) and 'Tei a' (the interval between two transtricuspid flows). (A') Pulmonary flow with tracing of velocity-time integral (VTI) and measurement of pulmonary ejection time 'Tei b'; Tei index (or right ventricular [RV] myocardial performance index) can be calculated using the formula $(a-b)/b$. (B) Tricuspid regurgitation (TR) flow in pulmonary hypertension, with peak velocity 5.2 m/s and an example of the S/D ratio calculation (S = duration of tricuspid regurgitation; D = interval between S and the next TR flow). (C) Short-axis view with determination of left ventricular eccentricity index (>1.4).

duration of the TR flow, whereas diastolic duration is considered from termination to onset of TR. An increase in the S/D ratio reflects a certain degree of RV dysfunction, with longer systole and abnormal cardiac performance; it is one of the strongest independent predictors of death in a population with Eisenmenger's syndrome and independently predicts lung transplantation and death in paediatric PAH (cut-off 1.4) [46].

Speckle-tracking imaging

Speckle-tracking imaging can help to identify the early signs of RV dysfunction and to follow patients under therapy. RV systolic longitudinal strain is reduced in PAH (Fig. 2C) and probably accounts for the RV global dysfunction, given the fibre arrangement; it also improves in conjunction with the 6-minute walked distance in responders to advanced therapy [47]. An RV longitudinal strain $<19\%$ has been described as an independent predictor of all-cause mortality [48].

One question of critical importance in RV evaluation is whether or not the 'RV dysfunction' will normalize after a lung transplant; in other words, if normalizing RV afterload allows the full recovery of RV function. Most of our indices are load-dependent and thus will change in response to different RV afterloads. However, in routine practice, it can indeed be useful to monitor the variations in load-dependent

indices as it gives us valuable information about the RV consequence of modified loading conditions.

Right atrial function

Three main functions of the right atrium (RA) have been described: the reservoir function for the systemic venous return; the passive conduit role in early diastole; and the active conduit with atrial contraction in late diastole [49]. Subcostal and four-chamber incidences are the main acoustic windows for the RA assessment.

RA surface, as estimated by planimetry in four-chamber view [50], is a marker of RV diastolic dysfunction. The upper limit for RA dilatation is 18 cm^2 [33]. When the acoustic window is not adequate, linear dimensions can be used; however, they correlate less well with 3D RA volume. The intensity of RA dilatation correlates with the degree of PAH [51] and is also predictive of survival in idiopathic PAH [52] and in Eisenmenger's syndrome [30]. The prognostic role of the RA area/LA area ratio has also been demonstrated in these patients. 2D RA volume assessment is not routinely recommended. In a recent study, RA remodelling, as assessed by 3D echocardiography, was the most independent predictive factor of adverse outcomes [53], using RA dilatation and RA sphericity index.

RAP can be estimated by echocardiography and reflects elevated RV filling pressures. RAP is most commonly estimated by IVC diameter and collapsibility during a sniff test. The assessment is quite easy in patients with low or elevated RA pressure. When IVC diameter is <2.1 cm with inspiratory collapse >50%, it suggests a normal RA pressure of 3 mmHg, whereas when the IVC diameter is >2.1 cm with an inspiratory collapse <50%, it suggests an elevated RA pressure of 15 mmHg. In intermediate cases, a value of 8 mmHg may be determined, but the use of other indices is preferable. Indices of elevated RA pressure are: restrictive tricuspid filling pattern; tricuspid E/E' ratio >6 [54]; and hepatic vein systolic filling fraction <55%.

Left ventricular assessment

Differentiating pre- from postcapillary pulmonary hypertension

As described in multiple studies, echocardiography can be used to detect elevated LV filling pressures, distinguishing PAH from pulmonary venous hypertension. Typically, PAH patients present a mitral inflow typical of impaired relaxation [55] and E/E' <10, suggesting normal LV filling pressures, with a compressed and underfilled LV [56]. In contrast, group 2 pulmonary hypertension patients will usually present with an elevated E/E' ratio.

Right ventricle/left ventricle relationship

As the RV pressure overload progresses, the interventricular septum shifts to the left, compressing the LV. The normal short-axis view becomes distorted and the left ventricle becomes 'D-shaped' with a flattening ventricular septum, leading to diastolic dysfunction. This can be quantified by the eccentricity index (Fig. 3C) (ratio of the LV anteroposterior and septolateral dimensions), the value of which under normal conditions is 1. The timing of the septal shift can help to distinguish RV volume overload (end-diastolic shift only) from pressure overload (predominant end-systolic shift). This index is a strong predictor of outcomes in PAH [52] and improves with advanced therapies [57]. Speckle-tracking imaging could provide further insights into LV mechanics in PAH and recent studies have indicated that abnormal LV torsion and circumferential strain are present in PAH [58]. A significant relationship between decreased LV strain and clinical outcomes has also been observed [59].

Cardiac output is also of prognostic importance. The aortic output can be measured using this formula: $\pi \times \text{LV outflow tract (LVOT) diameter}^2 / 4 \times \text{LVOT velocity-time integral (VTI)} \times \text{heart rate}$. This estimation correlates with invasive cardiac output, but remains relatively inaccurate (heart rhythm variability, abnormal shape of LVOT). Pulmonary VTI < 12 cm, TAPSE < 18 mm and S' < 10 cm/s are simple but useful predictors of low cardiac output [28].

Pulmonary artery function

Pulmonary vascular resistance is a strong predictor of outcomes in pulmonary hypertension; it accounts for the

resistance in small vessels. Estimation with echocardiography remains controversial: dividing TR velocity peak (m/s) by pulmonary VTI (cm) allows differentiation between high PAP related to high pulmonary vascular resistance (ratio ≥ 0.2) or to increased pulmonary blood flow (<0.2) (e.g. in atrial septal defect patients) [60]. However, a reliable estimation of pulmonary vascular resistance using a formula that includes this ratio (pulmonary vascular resistance = $\text{TRV}_{\text{max}}/\text{VTI} \times 10 + 0.16$) is not valid in patients with pulmonary vascular resistance >8 Wood units.

Pulmonary vascular capacitance (accounting for medium and large vessels), as assessed by echocardiography (stroke volume divided by pulmonary pulse pressure: $[\text{LVOT diameter}^2 \times \pi/4 \times \text{subaortic VTI}] / [4 \times ((\text{peak TR})^2 - [\text{end-diastolic PR}]^2)]$), is an independent predictor of outcomes in a cohort of adults with PAH [61]. Estimation of PA compliance, to determine the pulsatile nature of the PA flow, can be obtained using colour M-mode tissue Doppler imaging on the right PA (to measure diameters) and peak TR gradient (compliance [dyne] = $[\text{PA systolic} - \text{diastolic diameter}] / [\text{diastolic diameter} \times \text{systolic pressure}] \times 10^4$) and correlates well with invasive measurement of compliance [62] in children, normal compliance being >40% change/100 mmHg.

The future of right ventricular echocardiography in pulmonary hypertension

Given its safety and technical progress, it is likely that the role of echocardiography in the management of PAH will increase in the future. However, in RV assessment, especially in PAH, one test should never be considered as a 'stand alone' test. The multivariable approach should be the rule, combining different echocardiographical variables to obtain an 'RV performance score' or even combining the results of different examinations (e.g. echocardiography and right heart catheterization). The multivariable approach has its place in diagnosis, an echocardiographical rule accurately defining pulmonary hypertension haemodynamics [63], as well as in prognosis, a score built on the strongest echocardiographical predictors of outcomes in Eisenmenger's syndrome allowing the identification of very high-risk patients. Current prognosis equations would benefit from the incorporation of echocardiographical variables; it would improve their predictive power and help to identify patients who would benefit from further specific therapies.

Screening patients for possible pulmonary hypertension is an important step towards early diagnosis and treatment of PAH. Research into early markers of diagnosis is of critical importance. In this setting, exercise echocardiography in conjunction with recent echocardiographical techniques might allow important progress.

In the near future, 3D and speckle-tracking imaging will be part of the routine assessment of PAH patients, with simple technology becoming more accessible; these techniques will allow us to gain insight into RV mechanics in pulmonary hypertension. 3D RV volumes can be obtained directly by 3D acquisition with a specific probe or, more recently, by 3D modelling adapted from 2D acquisition (knowledge-based

reconstruction) [64]. However, further larger studies are needed if this new technique is to be included as part of our daily clinical practice.

Efforts are being made in echocardiography laboratories to maintain the best quality of routine evaluation examinations as well as to homogenize PAH echocardiographical examinations according to American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines. This will allow regular and accurate follow-up of our patients and prognostic information will come, not just from one examination, but also from the evolution of echocardiographical variables. Several studies suggest that RV dimensions, fractional area change [25], MPI and LV filling [57] improve over the time with advanced therapy. In PAH, stable or improved RV ejection fraction on serial assessment is associated with low mortality in patients receiving advanced therapy [65]. As such, echocardiography is a method of choice for serial assessment of pulmonary hypertension patients. Furthermore, the load-dependency of our RV function indices becomes an asset, allowing us to monitor with serial examinations RV function evolution related to afterload changes.

Conclusion

Echocardiography is a widely available, cost-effective, safe and reliable examination, which provides us with major diagnostic and prognostic information. Comparison of serial assessments allows monitoring of the efficacy of advanced therapies. More recent ultrasound techniques, such as 3D echocardiography and speckle-tracking, are promising; they may provide additional data regarding RV and PA mechanics in pulmonary hypertension and may allow the preclinical detection of high-risk patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

- [1] Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D42–50.
- [2] Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D34–41.
- [3] Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010;122:164–72.
- [4] D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;115:343–9.
- [5] Ho SY, Nihoyannopoulos P. Anatomy, echocardiography, and normal right ventricular dimensions. *Heart* 2006;92(Suppl. 1):i2–13.
- [6] Lorenz CH, Walker ES, Morgan VL, et al. Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. *J Cardiovasc Magn Reson* 1999;1:7–21.
- [7] Jiang L. Principle and practice of echocardiography. In: Weyman AE, editor. Right ventricle. Baltimore: Lippincott Williams & Wilkins; 1994. p. 901–21.
- [8] Chin KM, Kim NH, Rubin LJ. The right ventricle in pulmonary hypertension. *Coron Artery Dis* 2005;16:13–8.
- [9] MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part one. *Am J Respir Crit Care Med* 1994;150:833–52.
- [10] Bartelds B, Borgdorff MA, Smit-van Oosten A, et al. Differential responses of the right ventricle to abnormal loading conditions in mice: pressure vs volume load. *Eur J Heart Fail* 2011;13:1275–82.
- [11] Gaynor SL, Maniar HS, Bloch JB, et al. Right atrial and ventricular adaptation to chronic right ventricular pressure overload. *Circulation* 2005;112:1212–1218.
- [12] Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493–537.
- [13] Alkotob ML, Soltani P, Sheatt MA, et al. Reduced exercise capacity and stress-induced pulmonary hypertension in patients with scleroderma. *Chest* 2006;130:176–81.
- [14] Grunig E, Tiede H, Enyimayew EO, et al. Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. *Circulation* 2013;128:2005–15.
- [15] Sutendra G, Dromparis P, Paulin R, et al. A metabolic remodeling in right ventricular hypertrophy is associated with decreased angiogenesis and a transition from a compensated to a decompensated state in pulmonary hypertension. *J Mol Med (Berl)* 2013;91:1315–27.
- [16] Burgess MI, Mogulkoc N, Bright-Thomas RJ, et al. Comparison of echocardiographic markers of right ventricular function in determining prognosis in chronic pulmonary disease. *J Am Soc Echocardiogr* 2002;15:633–9.
- [17] van Wolferen SA, Marcus JT, Boonstra A, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2007;28:1250–7.
- [18] Zylkowska J, Kurzyna M, Florczyk M, et al. Pulmonary artery dilatation correlates with the risk of unexpected death in chronic arterial or thromboembolic pulmonary hypertension. *Chest* 2012;142:1406–16.
- [19] Niemann PS, Pinho L, Balbach T, et al. Anatomically oriented right ventricular volume measurements with dynamic three-dimensional echocardiography validated by 3-Tesla magnetic resonance imaging. *J Am Coll Cardiol* 2007;50:1668–76.
- [20] Jenkins C, Chan J, Bricknell K, et al. Reproducibility of right ventricular volumes and ejection fraction using real-time three-dimensional echocardiography: comparison with cardiac MRI. *Chest* 2007;131:1844–51.
- [21] Leibundgut G, Rohner A, Grize L, et al. Dynamic assessment of right ventricular volumes and function by real-time three-dimensional echocardiography: a comparison study with magnetic resonance imaging in 100 adult patients. *J Am Soc Echocardiogr* 2010;23:116–26.
- [22] Hinderliter AL, Willis PWT, Long WA, et al. Frequency and severity of tricuspid regurgitation determined by Doppler echocardiography in primary pulmonary hypertension. *Am J Cardiol* 2003;91:1033–7 [A9].
- [23] Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;7:79–108.

- [24] Mauritz GJ, Kind T, Marcus JT, et al. Progressive changes in right ventricular geometric shortening and long-term survival in pulmonary arterial hypertension. *Chest* 2012;141:935–43.
- [25] Brown SB, Raina A, Katz D, et al. Longitudinal shortening accounts for the majority of right ventricular contraction and improves after pulmonary vasodilator therapy in normal subjects and patients with pulmonary arterial hypertension. *Chest* 2011;140:27–33.
- [26] Sato T, Tsujino I, Ohira H, et al. Validation study on the accuracy of echocardiographic measurements of right ventricular systolic function in pulmonary hypertension. *J Am Soc Echocardiogr* 2012;25:280–6.
- [27] Ueti OM, Camargo EE, Ueti Ade A, et al. Assessment of right ventricular function with Doppler echocardiographic indices derived from tricuspid annular motion: comparison with radionuclide angiography. *Heart* 2002;88:244–8.
- [28] Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006;174:1034–41.
- [29] Mathai SC, Sibley CT, Forfia PR, et al. Tricuspid annular plane systolic excursion is a robust outcome measure in systemic sclerosis-associated pulmonary arterial hypertension. *J Rheumatol* 2011;38:2410–8.
- [30] Mocerì P, Dimopoulos K, Liodakis E, et al. Echocardiographic predictors of outcome in Eisenmenger syndrome. *Circulation* 2012;126:1461–8.
- [31] Lopez-Candales A, Rajagopalan N, Saxena N, et al. Right ventricular systolic function is not the sole determinant of tricuspid annular motion. *Am J Cardiol* 2006;98:973–7.
- [32] Meluzin J, Spinarova L, Bakala J, et al. Pulsed Doppler tissue imaging of the velocity of tricuspid annular systolic motion: a new, rapid, and non-invasive method of evaluating right ventricular systolic function. *Eur Heart J* 2001;22:340–8.
- [33] Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713 [quiz 86–8].
- [34] Calcutteea A, Chung R, Lindqvist P, et al. Differential right ventricular regional function and the effect of pulmonary hypertension: three-dimensional echo study. *Heart* 2011;97:1004–11.
- [35] Vogel M, Schmidt MR, Kristiansen SB, et al. Validation of myocardial acceleration during isovolumic contraction as a novel non-invasive index of right ventricular contractility: comparison with ventricular pressure-volume relations in an animal model. *Circulation* 2002;105:1693–9.
- [36] Kjaergaard J, Snyder EM, Hassager C, et al. Impact of preload and afterload on global and regional right ventricular function and pressure: a quantitative echocardiography study. *J Am Soc Echocardiogr* 2006;19:515–21.
- [37] Yang T, Liang Y, Zhang Y, et al. Echocardiographic parameters in patients with pulmonary arterial hypertension: correlations with right ventricular ejection fraction derived from cardiac magnetic resonance and hemodynamics. *PLoS One* 2013;8:e71276.
- [38] Ernande L, Cottin V, Leroux PY, et al. Right isovolumic contraction velocity predicts survival in pulmonary hypertension. *J Am Soc Echocardiogr* 2013;26:297–306.
- [39] Tei C, Dujardin KS, Hodge DO, et al. Doppler echocardiographic index for assessment of global right ventricular function. *J Am Soc Echocardiogr* 1996;9:838–47.
- [40] Rojo EC, Rodrigo JL, Perez de Isla L, et al. Disagreement between tissue Doppler imaging and conventional pulsed-wave Doppler in the measurement of myocardial performance index. *Eur J Echocardiogr* 2006;7:356–64.
- [41] Sebbag I, Rudski LG, Therrien J, et al. Effect of chronic infusion of epoprostenol on echocardiographic right ventricular myocardial performance index and its relation to clinical outcome in patients with primary pulmonary hypertension. *Am J Cardiol* 2001;88:1060–3.
- [42] Blanchard DG, Malouf PJ, Gurudevan SV, et al. Utility of right ventricular Tei index in the non-invasive evaluation of chronic thromboembolic pulmonary hypertension before and after pulmonary thromboendarterectomy. *JACC Cardiovasc Imaging* 2009;2:143–9.
- [43] Dyer KL, Pauliks LB, Das B, et al. Use of myocardial performance index in pediatric patients with idiopathic pulmonary arterial hypertension. *J Am Soc Echocardiogr* 2006;19:21–7.
- [44] Lindqvist P, Waldenstrom A, Wikstrom G, et al. Right ventricular myocardial isovolumic relaxation time and pulmonary pressure. *Clin Physiol Funct Imaging* 2006;26:1–8.
- [45] Mauritz GJ, Marcus JT, Westerhof N, et al. Prolonged right ventricular post-systolic isovolumic period in pulmonary arterial hypertension is not a reflection of diastolic dysfunction. *Heart* 2011;97:473–8.
- [46] Alkon J, Humpl T, Manlhiot C, et al. Usefulness of the right ventricular systolic to diastolic duration ratio to predict functional capacity and survival in children with pulmonary arterial hypertension. *Am J Cardiol* 2010;106:430–6.
- [47] Fukuda Y, Tanaka H, Sugiyama D, et al. Utility of right ventricular free wall speckle-tracking strain for evaluation of right ventricular performance in patients with pulmonary hypertension. *J Am Soc Echocardiogr* 2011;24:1101–8.
- [48] Haecck ML, Scherp tong RW, Marsan NA, et al. Prognostic value of right ventricular longitudinal peak systolic strain in patients with pulmonary hypertension. *Circ Cardiovasc Imaging* 2012;5:628–36.
- [49] Gaynor SL, Maniar HS, Prasad SM, et al. Reservoir and conduit function of right atrium: impact on right ventricular filling and cardiac output. *Am J Physiol Heart Circ Physiol* 2005;288:H2140–5.
- [50] Otto CM. The practice of clinical echocardiography. 4th ed. Philadelphia: Saunders; 2012.
- [51] Cioffi G, de Simone G, Mureddu G, et al. Right atrial size and function in patients with pulmonary hypertension associated with disorders of respiratory system or hypoxemia. *Eur J Echocardiogr* 2007;8:322–31.
- [52] Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol* 2002;39:1214–9.
- [53] Grapsa J, Gibbs JS, Cabrita IZ, et al. The association of clinical outcome with right atrial and ventricular remodeling in patients with pulmonary arterial hypertension: study with real-time three-dimensional echocardiography. *Eur Heart J Cardiovasc Imaging* 2012;13:666–72.
- [54] Nageh MF, Kopelen HA, Zoghbi WA, et al. Estimation of mean right atrial pressure using tissue Doppler imaging. *Am J Cardiol* 1999;84:1448–51 [A8].
- [55] Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107–33.
- [56] Gurudevan SV, Malouf PJ, Auger WR, et al. Abnormal left ventricular diastolic filling in chronic thromboembolic pulmonary hypertension: true diastolic dysfunction or left ventricular underfilling? *J Am Coll Cardiol* 2007;49:1334–9.
- [57] Galie N, Hinderliter AL, Torbicki A, et al. Effects of the oral endothelin-receptor antagonist bosentan on echocardiographic and doppler measures in patients with pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;41:1380–6.
- [58] Puwanant S, Park M, Popovic ZB, et al. Ventricular geometry, strain, and rotational mechanics in pulmonary hypertension. *Circulation* 2010;121:259–66.

- [59] Hardegee EL, Sachdev A, Fenstad ER, et al. Impaired left ventricular mechanics in pulmonary arterial hypertension: identification of a cohort at high risk. *Circ Heart Fail* 2013;6:748–55.
- [60] Abbas AE, Fortuin FD, Schiller NB, et al. A simple method for non-invasive estimation of pulmonary vascular resistance. *J Am Coll Cardiol* 2003;41:1021–7.
- [61] Mahapatra S, Nishimura RA, Oh JK, et al. The prognostic value of pulmonary vascular capacitance determined by Doppler echocardiography in patients with pulmonary arterial hypertension. *J Am Soc Echocardiogr* 2006;19:1045–50.
- [62] Dyer K, Lanning C, Das B, et al. Non-invasive Doppler tissue measurement of pulmonary artery compliance in children with pulmonary hypertension. *J Am Soc Echocardiogr* 2006;19:403–12.
- [63] Opatowsky AR, Ojeda J, Rogers F, et al. A simple echocardiographic prediction rule for hemodynamics in pulmonary hypertension. *Circ Cardiovasc Imaging* 2012;5:765–75.
- [64] Bhave NM, Patel AR, Weinert L, et al. Three-dimensional modeling of the right ventricle from two-dimensional transthoracic echocardiographic images: utility of knowledge-based reconstruction in pulmonary arterial hypertension. *J Am Soc Echocardiogr* 2013;26:860–7.
- [65] van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol* 2011;58:2511–9.