Review Article
Echocardiographic evaluation of right ventricular-arterial coupling in pulmonary hypertension

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Abstract: Pulmonary hypertension (PH) is a hemodynamic condition characterized by chronically elevated mean pulmonary artery pressure (m-PAP ≥ 25 mmHg) measured at rest by right heart catheterization (RHC). It includes a pre-capillary and a post-capillary form. Pulmonary artery hypertension (PAH) is a pre-capillary form of PH potentially generated by several heterogeneous systemic disorders, whose main hemodynamic change is represented by severely increased pulmonary vascular resistance (PVR). In order to preserve an efficient right ventricular-arterial (RV-PA) coupling, the right ventricle (RV) adapts to this chronic increase of its afterload, with a compensatory hypertrophy, until RV dilatation and dysfunction occur. Right ventricular (RV) function and especially RV-PA coupling assessment showed to be very important prognostic markers in this subset of patients, especially for those with pre-capillary PH. The aim of this review is to provide a pathophysiological insight into the spectrum of RV adaptive changes occurring in response to chronic increase of RV afterload and to present the role of echocardiographic parameters as possible tools for early non-invasive evaluation of RV-PA coupling, before overt heart failure ensues.

Keywords: Pulmonary hypertension, right ventricular-arterial coupling, echocardiography

Introduction

The normal adult pulmonary vascular bed is a low-pressure, low-resistance, and high compliance system, capable of accommodating large increases in blood flow with minimal elevations of mean pulmonary artery pressure (mPAP); the normal right ventricle (RV) is coupled to this low-pressure and high-compliance pulmonary circulation to ensure transfer of blood to the pulmonary arteries in an energy efficient fashion [1].

In physiological conditions, the right heart is "coupled" to the pulmonary circulation as a single cardiopulmonary unit, keeping a relative matching between contractility and afterload and a favourable right ventricular to pulmonary artery coupling (RV-PA coupling) [2].

As pulmonary hypertension (PH) develops, the vascular bed becomes a high-pressure, high-resistance, and low compliance system resembling the hemodynamic properties of the systemic arterial system. All these hemodynamic changes lead to an additional load on the contracting ventricle and altered RV-PA coupling.

Especially in pulmonary artery hypertension (PAH), RV-PA uncoupling detection is crucial for early identification of patients with poor prognosis [3].

Trans-thoracic echocardiography (TTE) implemented with two-dimensional speckle tracking (2DSTE) and three-dimensional (3D) technologies, due to its wide availability and ease of use at bedside, gained a pivotal role for diagnosis and prognostic stratification of patients affected by PH. The aim of this review is to summarize the available methods for RV-PA coupling evaluation with special focus on the role of echocardiography and to provide the clinical cardiologists with a practical and comprehensive overview of echocardiographic parameters that

Table 1. Hemodynamic definition and clinical classification of PH, adapted from 2015 European Guidelines on PH[1]

Definition	Parameters	Clinical classification
PH	mPAP ≥ 25 mmHg	All
Pre-capillary	mPAP ≥ 25 mmHg PAWP ≤15 mmHg PVR >3 WU	1. PAH 3. PH due to lung diseases 4. CTEPH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary	mPAP ≥ 25 mmHg PAWP >15 mmHg PVR ≤3 WU	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Combined	mPAP ≥ 25 mmHg PAWP >15 mmHg dTPG ≥ 7 mmHg and/or PVR >3 WU	

PH-pulmonary hypertension, mPAP-mean pulmonary artery pressure; PAWP-pulmonary artery wedge pressure; PVR-pulmonary vascular resistance; dTPG-diastolic trans-pulmonary gradient; PAH-pulmonary artery hypertension; CTEPH-chronic thromboembolic PH.

should never lack in the evaluation of these patients.

Definition and classification of PH

Pulmonary hypertension is not a disease but a pathophysiological and hemodynamic condition characterized by elevated m-PAP (m-PAP ≥ 25 mmHg) measured at rest by right heart catheterization (RHC) [4].

The hemodynamic classification of PH includes a pre-capillary and a post-capillary form [5]. Available data have shown that normal m-PAP at rest is 14+3 mmHg with an upper limit of normal of approximately 20 mmHg, for this reason a new definition based on lower threshold (m-PAP >20 mmHg) has been recently proposed [6]. However, the adoption of this new definition in future guidelines remains to be confirmed.

According to the clinical classification presented in the latest European guidelines [4], PH can be found in more than fifty clinical conditions classified in 5 groups which include pulmonary arterial hypertension (PAH) (Group 1), PH due to heart diseases (Group 2), lung diseases (Group 3), pulmonary thromboembolic disease (Group 4), and unclear and/or multifactorial mechanisms (Group 5) **Table 1**.

Pulmonary artery hypertension (PAH) (Type 1 according to clinical classification), is a relatively rare form of pre-capillary PH, whose diagno-sis is based upon the following hemodynamic parameters: m-PAP ≥ 25 mmHg, pulmonary artery wedge pressure (PAWP) ≤15 mmHg and PVR >3 Wood Units (WU). In contrast, post-capillary PH due to left heart disease (Type 2) is characterized by increased PAWP (>15 mmHg) at RHC; however mixed forms of pre capillary and post-capillary hypertension can be encountered in clinical practice, causing challenging diagnostic dilemmas and management issues.

RV adaptation to afterload

In PAH which can be diagnosed in several and heterogeneous systemic diseases, such as connective tissue disorders, HIV infection, portal hypertension, drug-induced PH, the increase of PVR is followed by an irreversible anatomical remodelling of pulmonary vasculature with narrowing of pulmonary vessels and a chronic pressure overload on the RV [7].

The difference of RV failure in PH in comparison to left ventricular (LV) failure is that the RV fails after a long-time adaptation to increased afterload [8] and especially in PAH, RV dysfunction appears the tip of the iceberg after a continuum of hemodynamic alterations (**Figure 1**).

Initially a "homeometric" adaptation occurs, characterized by RV hypertrophy and increased wall thickness. When compensatory mechanisms fail to maintain a favourable RV-PA coupling, RV enlargement ensues ("heterometric
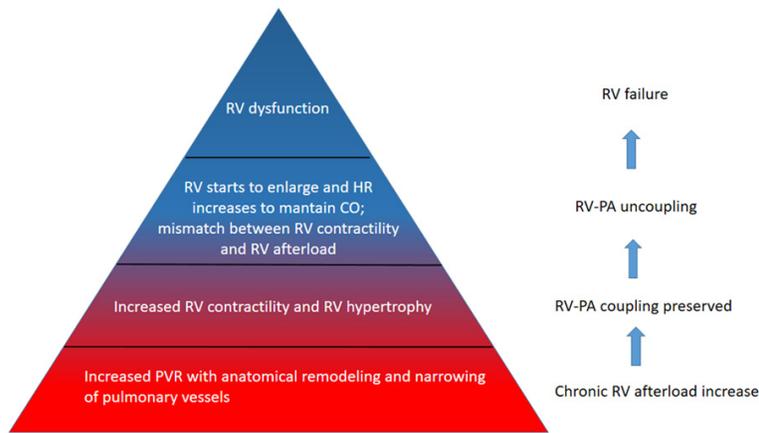
Figure 1. Pulmonary artery hypertension iceberg. Schematic representation of pathophysiological and hemodynamic alterations of PAH. In the first stage of the disease, in response to a chronic increase of RV afterload, RV "homeometric" adaptation occurs with preservation of RV-PA coupling; in the second stage of the disease RV "heterometric" adaptation follows with RV-PA uncoupling, leading to RV failure at end-stage. PAH-pulmonary artery hypertension; RV-right ventricle; HR-heart rate; CO-cardiac output; PVR-pulmonary vascular resistance.
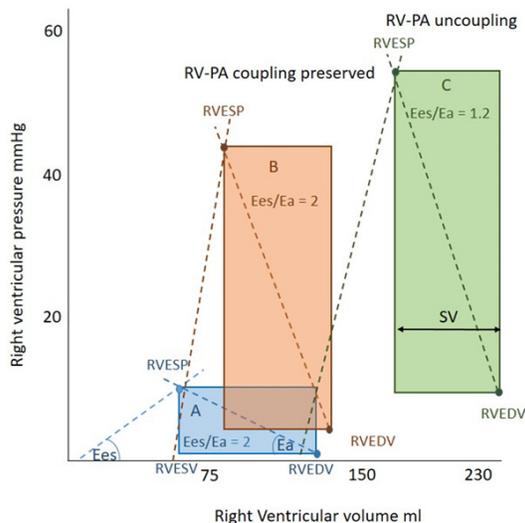

Figure 2. Right ventricular pressure-volume (P-V) loop relationship. Ees is the slope of the end-systolic pressure volume relation as measure of RV contractility, and Ea is a measure of the arterial load. A. RV P/V Loops in a normal subject, Ees/Ea is within normal range. B. RV P/V Loops in a patient with early stage PH, RV contractility enhances in order to cope with a chronically increased afterload and RV-PA coupling is still preserved. C. RV P/V Loops in a patient with PH and RV-PA uncoupling, RV enlarges and HR increases in order to maintain SV, Ees/Ea ratio decreases. Ees, End-systolic elastance; Ea, arterial elastance; ESP, end-systolic pressure; ESV, end-systolic volume; SV, stroke volume.

adaptation"), in order to maintain an effective stroke volume (SV) [9].

The progression from homeometric to heterometric adaptation depends upon several factors, including the time of onset and the aetiology of PH, genetic and neuro-hormonal factors, regulating cell hypertrophy, and fibrosis [10].

For example, it was shown that RV adaptation in idiopathic PAH is characterized not only by increased RV hypertrophy but also by local inflammation, ischemia and excessive fibrosis, responsible for a less effective RV contractility and less preserved RV-PA coupling [11, 12]. On the contrary, RV adaptation in patients with congenital heart disease and Eisenmenger syndrome is more beneficial due to the lower amount of RV fibrosis and RV diastolic stiffness [13]. The prognostic role of RV-PA coupling has been demonstrated in several disease states: even in the setting of heart failure with both reduced and preserved ejection fraction (EF), or in patients with advanced heart failure potentially candidates for cardiac transplant, RV-PA coupling demonstrated to be an important predictor of outcome [14-16].

Invasive assessment of RV-PA coupling

Right ventricular-pulmonary artery coupling can be defined as the relationship between RV contractility and RV afterload. RV contractility or ventricular elastance (Ees) is a load independent parameter of intrinsic myocardial function; RV afterload is the opposition to ventricular ejection and includes a pulsatile component or arterial elastance (Ea) and a steady component, represented by mPAP and PVR [7]. Ventricular-arterial coupling can be invasively derived from the ratio between ventricular elastance and arterial elastance (Ees/Ea). In physiologic conditions Ees/Ea ratio is between 1,5 and 2, allowing the RV flow output a minimal energy cost and optimal RV-PA coupling [17].

Right heart catheterization is the gold standard technique for RV-PA coupling evaluation, allowing direct estimation of RV pressures and volumes.

Table 2. Echocardiographic probability of PH in symptomatic patients with a clinical suspicion of PH, adapted from 2015 European Guidelines on PH[1]

Peak TR velocity	≥ 2 echocardiographic signs of PH	Probability of PH
< 2,8 m/sec	NO	Low
< 2,8 m/sec	YES	Intermediate
>2,8 m/sec; < 3,4 m/sec	NO	Intermediate
>2,8 m/sec; < 3,4 m/sec	YES	High
>3,4 m/sec	Not required	High

TR-tricuspid regurgitation; PH-pulmonary hypertension.

Arterial elastance can be invasively derived by the creation of multiple pressure-volume (P-V) loops obtained by reducing ventricular diastolic filling, through partial vena cava occlusion, or otherwise by the Valsalva maneuver [2]. The slope of this line is the RV end-systolic elastance and the linear regression line connecting these P-V points is used to determine the end-systolic P-V relationship (**Figure 2**). This method remains difficult and time consuming; therefore, it is predominantly used as a research tool.

According to the more commonly used "single-beat method", Ees is derived from the ratio between end-systolic pressure (ESP) to end-systolic volume (ESV) (ESP/ESV) and Ea is obtained from the ratio between ESP to SV (ESP/SV) invasively assessed from P-V loops [18]. Since the Ees/Ea ratio can be simplified by omitting ESP as common terms, Ees/Ea is also estimated by the ratio of SV/ESV, (also defined as the "volume method") [19].

When RV contractility cannot rise anymore to match RV afterload, RV-PA uncoupling occurs and the ratio Ea/Ees decreases. A value of 0,8 has been identified as marker of RV-PA uncoupling [20]. However, this invasive approach is technically demanding, expensive, and not feasible at the bedside, for this reason, non-invasive surrogates of Ees/Ea therefore, have been investigated.

Non-invasive assessment of RV-PA coupling: from catheter to probe

Although RHC is the gold standard for diagnosis and periodic monitoring of patients affected by PAH, due to its invasive nature, it should be performed with caution and only when clinically indicated. Echocardiography plays a role of paramount importance for both diagnosis and

prognostic stratification of patients affected by PAH and according to the latest Guidelines on PH [4], it should be performed in all patients that, according to symptoms and history, are with suspected PH. In this setting, echocardiography can provide precious hemodynamic information, useful for diagnosis, prognosis and therapeutic guidance.

The first echocardiographic measurement to be performed in these patients is the peak of tricuspid regurgitation (TR) jet velocity; the probability of PH at echocardiography is defined as "low", "intermediate" or "high" according to peak TR jet velocity and the presence of other echocardiographic signs of PH (**Table 2**; **Figure 3**).

The opportunity of performing further investigation, especially RHC, is defined by the probability of PH according to echocardiographic parameters [4].

A standard RHC provides useful tools for RV-PA coupling evaluation through the relationship between basic hemodynamic measurements: mPAP, PVR, cardiac output (CO) and right atrial pressure (RAP) (**Table 3**, invasive method) [17]. However, in the recent years several parameters obtained with TTE and cardiac magnetic resonance (CMR), have been investigated, with the aim to validate hybrid or completely non-invasive surrogates of invasively derived RV-PA coupling [21]. For this purpose, a simple echocardiographic index of RV function is 'matched' to an index of RV afterload. Tricuspid annular plane systolic excursion (TAPSE) is the most important parameter of RV longitudinal function and its abnormality threshold is < 17 mm; other methods of RV function assessment include the peak systolic tissue Doppler velocity (denoted S'; abnormal < 12 cm/sec) and the right ventricular area change (RVFAC) [22, 23].

A hybrid approach that offers promising insight into RV-PA coupling, matches TAPSE to invasively measured PVR (TAPSE/PVR) or RVFAC to mPAP (RVFAC/mPAP), obtained from RHC [24, 25].

Van de Veerdonk et al. [20] provided an example of this hybrid approach in patients with PAH, investigating the relationship between cardiac
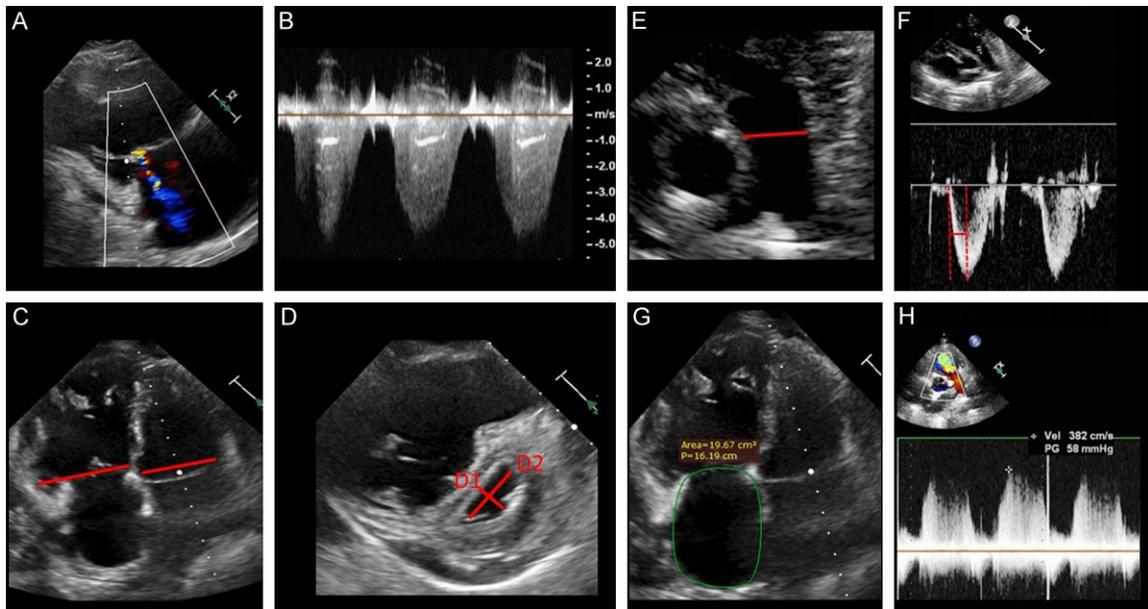
Figure 3. Echocardiographic signs of PH. A. Tricuspid regurgitation (TR) jet obtained with colour-Doppler across tricuspid valve, from parasternal right ventricular (RV) inflow view. B. Peak TR Velocity, measured by Continuous Wave Doppler across tricuspid valve in apical four chamber view (A4C) or parasternal short axis (PSAX) view for RV inflow, peak TR velocity >2,8 m/sec is considered abnormal. C. The ratio between the basal diameter of right and left ventricle (RV/LV ratio) is measured at end-diastole from the standard A4C view without foreshortening; the ratio RV/LV >1 suggests RV dilatation. D. Eccentricity Index is measured from PSAX axis view at mid LV level; the ratio D2/D1 ≥ 1.1 is considered abnormal. E. Pulmonary artery diameter is measured in PSAX in end diastole; a diameter of >25 mm is considered abnormal. F. RV outflow tract acceleration time is measured in PSAX, with sample volume of pulsed wave Doppler positioned in the RV outflow tract; acceleration time of < 100 ms is considered a marker of PH. G. Right atrial area is measured in A4C view at end ventricular systole just prior to tricuspid valve opening; a right atrial area >18 cm^2 is considered abnormal. H. Early diastolic pulmonary regurgitation (PR) jet velocity is measured in PSAX or parasternal RV outflow view; an early PR velocity >2.2 m/s is considered a marker of PH.

Table 3. Methods for right ventricular-arterial coupling evaluation

Method	RV afterload	RV function	RV-PA coupling
Invasive (standard RHC)	mPAP = 50 mmHg, PVR = 7 WU	CO = 5,7 ml RAP = 5 mmHg	preserved
		CO = 2,5 ml RAP = 20 mmHg	not preserved
Non-invasive	PASP = 60 mmHg RVOT notched pattern RVOT AT < 100 msec pPTT 130 msec	TAPSE = 24 mm TAPSE/PASP = 0,4 S' = 14 cm/sec FAC = 55% RVFWS = -28%	preserved
		TAPSE = 16 mm TAPSE/PASP = 0,26 S' = 9 cm/sec FAC = 35-40 % RVFWS = -17%	not preserved

RHC-right heart catheterization; mPAP-mean pulmonary artery pressure; PVR-pulmonary vascular resistance; RVOT-right ventricular outflow tract; AT-acceleration time; pPTT-pulmonary pulse transit time; TAPSE-tricuspid annular plane systolic excursion; CO-cardiac output; RAP-right atrial pressure; FAC-fractional area change; RVFWS-Right ventricular free wall strain; PASP-pulmonary artery systolic pressure; SV-stroke volume; ESV-end-systolic volume.

MRI derived right ventricular ejection fraction (RVEF) with invasive PVR assessment.

Completely non-invasive ratios have been proposed as bedside surrogate of RV-PA coupling,
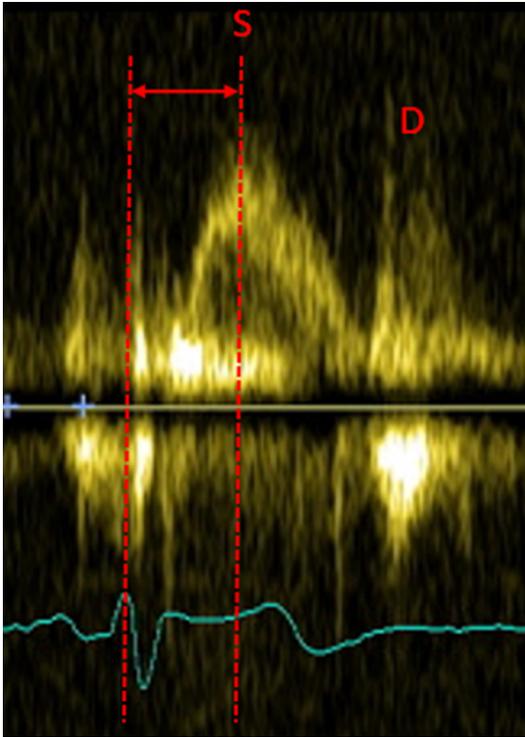
Figure 4. Echocardiographic evaluation of pulmonary pulse transit time (pPTT). Transthoracic echocardiography, pPTT is obtained with Pulsed wave-Doppler in the pulmonary veins measuring the interval between R wave in the electrocardiogram trace and the corresponding peak late systolic pulmonary vein flow velocity (S).

such as the ratio of RVFAC to RV end-systolic area [26], or the ratio of TAPSE to pulmonary artery acceleration time (AT) [27] and the ratio of S' to RV end-systolic area index [28]. However not all of these echocardiographic parameters have been directly compared with invasive P-V loop measures of RV contractility and afterload; therefore, their incremental prognostic value has to be confirmed.

Among non-invasive surrogates of RV-PA coupling, only TAPSE/PASP emerged as an independent predictor of invasively measured RV-PA coupling and associated with significantly improved prognostic prediction of outcome, when compared with either variable separately (**Table 3**, non-invasive method) [29].

In the setting of PH secondary to left heart disease, such as in heart failure with preserved and reduced EF, Guazzi et al. [15] combined functional capacity assessed by cardiopulmo-

nary exercise testing and RV-PA coupling, as evaluated by TAPSE/PASP. The group with RV-PA uncoupling as expressed by a TAPSE/PASP ratio < 0, 36 mm/mmHg had worse functional capacity and the poorest outcome in terms of cardiac events.

Tello et al. [29] validated TAPSE/PASP as a reliable method for RV-PA coupling assessment in patients with severe idiopathic and thrombo-embolic PH: a cut-off value of TAPSE/PASP < 0.31 mm/mm Hg was able to predict RV-arterial uncoupling, defined as Ees/Ea < 0.805, with a sensitivity of 87.5% and specificity of 75.9%.

In conclusion, TAPSE/PASP is an easily executable ratio that could be used for early bedside identification of RV-PA uncoupling in patients with PAH, encouraging the implementation of PH therapy for RV unloading, before heart failure ensues. However, further studies are needed to evaluate the possible benefit of this ratio in current risk assessment strategies for severe PH.

Pulmonary wave transmission

Pulmonary pulse transit time (pPTT), defined as the time for the systolic pressure pulse wave to travel from the pulmonary valve to the pulmonary veins, revealed to be a promising non-invasive surrogate of RV-PA coupling [30].

This interval can be easily obtained at bedside with TTE measuring the interval between R wave in the electrocardiogram trace and the corresponding peak late systolic pulmonary vein flow velocity, measured by pulsed wave-Doppler in the pulmonary veins (**Figure 4**).

Recently, Wibmer et al. [31] showed that mean pPTT, was significantly shorter in 12 consecutive patients with PH (6 patients with group 1 PH and 6 patients with group 3 PH) compared with 12 subjects without any cardiovascular or respiratory disease (138.0±16.78 msec vs 383.5±23.84 msec). Interestingly, within the PH group, the subgroup of patients with pulmonary fibrosis showed significantly shorter pPTT than the subgroup of patients with PH without pulmonary fibrosis. These data are consistent with those reported by K.W. Prins et al. [30] and M. Dogan et al. [32] who confirmed the reduction of pPTT in patients with PAH and systemic

sclerosis respectively, compared with controls. Importantly pPTT was most strongly associated with markers of RV-PA coupling as defined by RVFAC/mPAP (r = 0.72, P < 0.0001) and by TAPSE/mPAP (r = 0.74, P < 0.0001) [30]. All these findings encourage the use of pPTT as surrogate marker of pulmonary hemodynamic and vascular alterations in PH, especially with pulmonary fibrosis.

From a pathophysiological perspective, a reduction of pPTT could be associated with the progressive alterations that occur on pulmonary vasculature of patients affected by PH [33]. It is demonstrated that in PH, decreased pulmonary arterial compliance and arterial stiffening compromise wave transmission between the proximal and distal vasculature, leading to increased pulse wave velocity, reduction of pPTT and premature reflection of waves from the distal pulmonary vasculature [33].

Although the significance of arterial waves in PH is not well understood, the correlation between invasively measured RV-PA coupling and pPTT, reinforce the use of this parameter as a surrogate marker of intrinsic pulmonary vascular disease, thereby allowing its use for monitoring of disease progression and regression [34].

In addition, the shape of the pulsed wave Doppler profile in the RV outflow tract (RVOT) can provide interesting hemodynamic insights into pulmonary vascular status: the presence of a notched Doppler signal, either a late systolic or mid-systolic notching, are highly specific for an increased PVR and loss of pulmonary vascular compliance [35].

The time to peak velocity of this pulsed wave Doppler pattern in the RVOT, referred to as the AT provides similar information with respect to RV afterload. An AT < 70 ms denotes a marked increase in RV afterload, 70-100 ms mild to moderately increased RV afterload, and >100 ms relatively normal RV afterload (**Figure 3**) [36].

Both loss of pulmonary arterial compliance and impaired RV-PA coupling are clinically important, because they are associated with increased mortality in patients with PH.

Right ventricular strain

Echocardiography is the most widely available technique to evaluate RV performance. However, conventional echocardiographic measurements of RV function are not always reliable due to the complex geometry of the right heart chamber and varying loading conditions [23]. Longitudinal deformation analysis through 2DSTE does not rely on geometrical assumptions and therefore, provides angle-independent assessment of regional myocardial deformation [37]. This echocardiographic technique demonstrated to be a promising tool not only for the evaluation of RV systolic function but also for risk stratification of patients with PH [38]. Compared with the left ventricle, RV global longitudinal strain (RVGLS) is obtained only from the apical-four chamber view, with special focus on the RV chamber. The speckles for RV longitudinal function analysis are manually located in the endocardial border of RV free wall (RVFW) to obtain RVFW strain. As for LV longitudinal function, RV longitudinal strain is expressed with negative values.

RV global longitudinal strain measured with 2DSTE is reduced in patients with PH, if compared to controls (-12.6 vs -16%), and a cutoff value of -13.7% is able to predict reduced long-term survival [39].

In another study, patients with PH regardless the aetiology, have shown more impaired values of RVFW strain compared with normal controls, with a cut-off of -19% associated with worse functional class and outcome [40] (**Figure 5**). Moreover, RVFW strain presented a good correlation with brain natriuretic peptides, hemodynamic measurements, such as mPAP, PVR and with 6-minute walking test and showed a significant improvement after specific PH therapy, allowing follow up of patients during treatment [41].

In addition to reduced RV strain, RV dyssynchrony measured with tissue Doppler imaging [42] and with 2DSTE was detected in patients with mPAP between 20 mmHg and 25 mmHg, indicating that RV deformation is impaired even in mild/borderline PH [43]. Furthermore, when RV dyssynchrony was added to a multivariate model including conventional parameters, it was able to improve the prediction of functional capacity in this setting of patients [44].
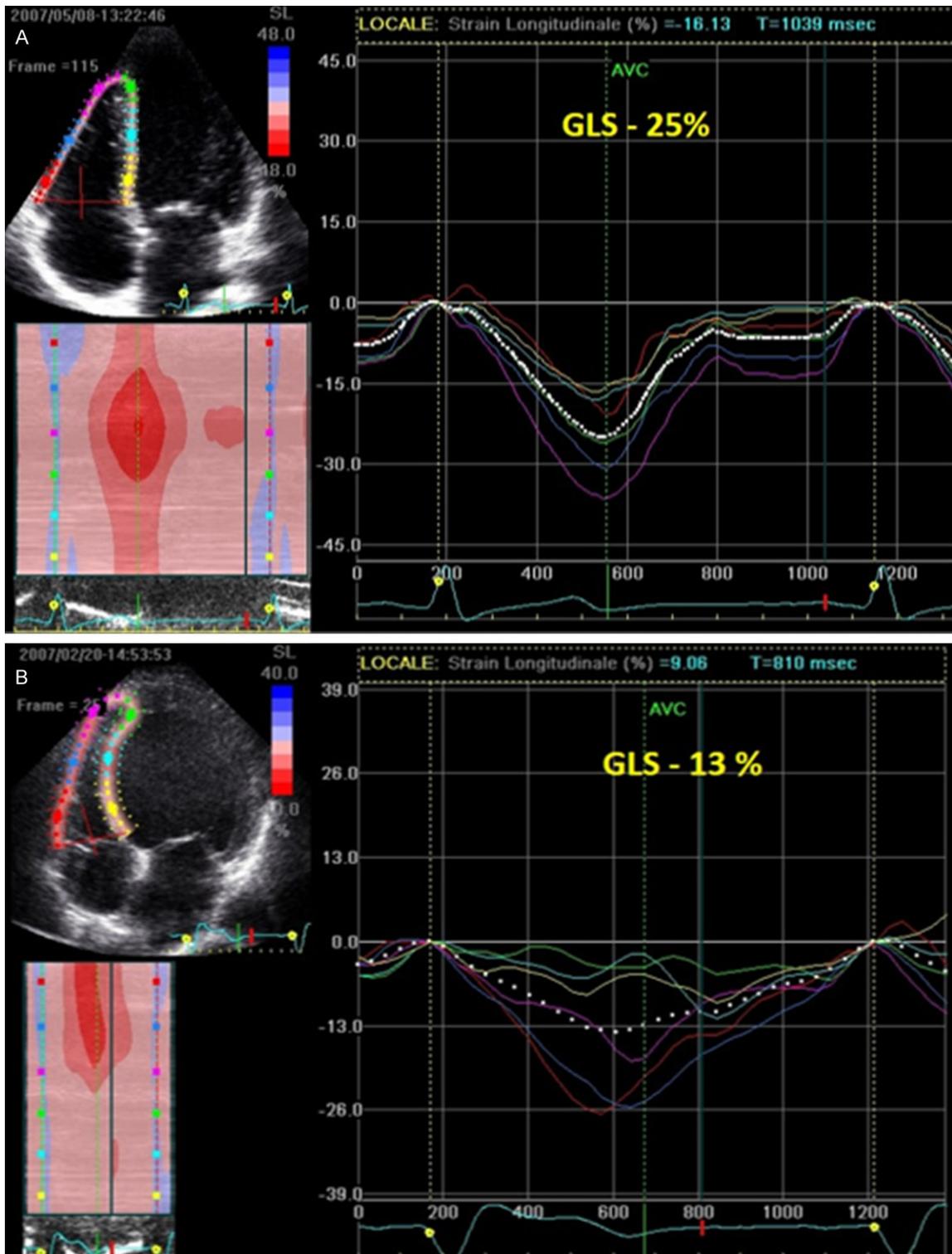
Figure 5. Right ventricular longitudinal peak systolic strain with two-dimensional speckle-tracking echocardiography in apical 4-chamber view. (A) normal longitudinal RV function (-25%) and (B) reduced longitudinal performance (-13%) in a patient with idiopathic pulmonary artery hypertension (B).

In conclusion, RV strain and RV dyssynchrony are both valuable tools for early RV dysfunction detection and for prognostic stratification of patients with early or advanced PH, before deterioration of conventional echocardiographic parameters [45].

Table 4. Echocardiographic follow-up of a patient with PAH. The identification of RV-PA uncoupling should encourage the implementation of specific therapy to avoid the development of overt RV failure

Echocardiographic Parameters	Normal heart	PH with preserved RV-PA coupling	PH with RV-PA uncoupling	RV failure
PAPs mmHg	15	70	70	50
TAPSE mm	25	30	18	12
TAPSE/PAPs	1,6	0,42	0,25	0,24
Septal S' cm/sec	13	12	9	6
RVFWS %	-28	-23	-18	-13
FAC %	50	45	40	30
RV Basal Diameter mm	35	40	43	50

PAPs, Pulmonary artery systolic pressure; TAPSE, Tricuspid annular plane systolic excursion; RVFWS, Right ventricular free wall strain; FAC, Fractional m.

Three-dimensional echocardiography

The use of volumes for non-invasive assessment of RV-PA coupling was first validated with CMR, which is currently considered the non-invasive gold standard for the estimation of RV volumes and EF [46]. Indeed the simplified formula SV/ESV obtained with CMR demonstrated to be feasible when compared with RHC and showed to be a reliable index of RV-PA coupling in adult and paediatric patients with PH [47]. Three-dimensional (3D) echocardiography has been validated for RV volume measurements, with good inter- and intra-observer reproducibility, since it allows a correct visualization of complex RV geometry and delineation of apical trabeculae and endocardial borders, overcoming the limitation of two-dimensional echocardiography [48].

Aubert et al. [49] used SV/ESV ratio obtained by means of 3D echocardiography to assess RV-PA coupling in a group of 91 patients with PH, showing a good correlation with the reference measurements of arterial and ventricular elastance obtained with RHC and CMR. Moreover, despite a systematic overestimation of volumes, RV-PA coupling was significantly impaired in patients with severe PH, suggesting failure of the RV to maintain coupling.

In addition, the efficacy of 3D derived volumes for RV-PA coupling evaluation was successfully tested in a paediatric population with PH. Patients with RV-PA uncoupling, presented a decreased SV/ESV ratio if compared with normal controls (0.88±0.18 versus 1.24±0.23) and interestingly, SV/ESV correlated with RVFW strain and disease severity, behaving as a strong predictor of adverse clinical events [50]. In this subset of patients, the use of 3D echocardiography reveals to be particularly favourable, in order to avoid sedation often required in children who undergo CMR.

Conclusions and future directions

Pulmonary hypertension is a chronic pathophysiological condition characterized by a high burden of morbidity and mortality, with majority of patients experiencing important limitations in daily activities and impairment of their quality of life. The extreme heterogeneity of possible underlying aetiologies, the long time between the onset of symptoms and diagnosis and the late initiation of a specific therapy, contribute to the poor outcome of these patients. Moreover, the low specificity of symptoms requires a high level of suspicion and a teamwork of several specialists for achievement of correct diagnosis.

Catheterization rightfully remains the gold standard for diagnosing PAH; however, due to the low prevalence of the disease and the cost and risk of invasive procedure, there is a need for non-invasive screening tools for diagnosis and follow-up of patients in order to reduce diagnostic delay and allow monitoring of therapy.

Echocardiography provides a great amount of important hemodynamic information and due to its ease of use and the possibility of being performed at bedside has proven particularly suitable for the periodical follow-up of these patients, allowing early detection of intrinsic pulmonary vascular disease and RV-PA uncoupling before RV failure (**Table 4**).

For this purpose, simplified methods to assess RV-arterial coupling, including conventional echocardiographic parameters as well as 2DSTE and 3D echocardiography, should be incorporated into routine clinical follow-up and future clinical trials.

Disclosure of conflict of interest

None.

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