Right cardiac involvement in lung diseases: a multimodality approach from diagnosis to prognostication

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Multimodality evaluation of the right heart in lung diseases

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Abstract

Lung diseases are among the main healthcare issues in the general population, having a high burden of morbidity and mortality. The cardiovascular system has a key role in patients affected by respiratory disorders. More specifically, the right ventricle (RV) enables the impaired lung function to be overcome in an initial stage of disease process, reducing the severity of dyspnea. In addition, two of the main causes of death in this setting are RV failure and sudden cardiac death (SCD).

Echocardiography is regarded as a useful and easily available tool in assessing RV function. Several non-invasive echocardiographic parameters of elevated pulmonary pressures and RV function have been proposed. The combination of different parameters and imaging methods is paramount and researches regarding RV impairment using these indices has been specifically addressed in relation to the chronic obstructive and restrictive lung disease in order to guide the clinicians in the management of these patients. Cardiac involvement in lung diseases is often observed, and RV changes are reported also in early stages of pulmonary diseases. The role of right ventricle in chronic respiratory disease patients has to be evaluated in detail to describe the response to therapy and the degree of disease progression through multimodality and advanced imaging techniques. The aim of this review is to describe the different pathophysiological

mechanisms of cardiac impairment in primary lung disease (such as chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and sarcoidosis) and to summarize the role of cardiac multimodality imaging in the diagnosis and the prognosis of these diseases.

Keywords: echocardiography, lung disease, chronic obstructive pulmonary disease, diagnosis, right heart.

Introduction

Despite improvements in therapeutic options, lung diseases are still one of the main healthcare issues, with high rates of morbidity and mortality [1]. It is known that the main physio-pathological mechanism responsible for the involvement of the right heart is hypoxia and related vasoconstriction of pulmonary vessels, leading to pulmonary hypertension (PH) [2]. This mechanism induces an increase of pulmonary vascular resistance (PVR) and, in the long run, chronic right heart failure. However, the right heart involvement occurring in patients affected by lung diseases is related to complex pathogenetic mechanism [2].

This review describes the right ventricular (RV) physiology and altered function occurring in patients with common chronic lung diseases, describing the role of multimodality imaging (MMI) in diagnosis and prognostication (**Graphical abstract**).

Right ventricular anatomy and its role in lung diseases

The right ventricle is characterized by a complex geometry, therefore, its imaging assessment by echocardiography is challenging. It is divided in three main parts: the inflow tract, the apical portion, and the outflow tract [2][3]. The physiology of RV contraction is quite elaborated too. It occurs through three different mechanisms: (1) inward movement of the free wall; (2) contraction of the longitudinal fibers; (3) traction on the free wall to the left ventricle (LV).

The key role of preload and afterload in conditioning RV cardiac output is another relevant topic. As regard to chronic lung diseases, the afterload is influenced by the degree of hyperinflation or

increased alveolar pressures, but also by the vasomotor tone resulting from the vasoactive mediators released in response to alveolar hypoxia or local inflammatory processes [4] [5][6][7].

In addition, the development of secondary polycythemia, consequent to chronic hypoxemia, may increase thrombi formation in the pulmonary circulation unit, leading to a further impairment of the RV function [8]. The deposition of fibrotic tissue with consequent alveolar disruption and parenchymal distortion, including lung vessels, is another process through which PVR could increase [9].Moreover, in systemic diseases with pulmonary involvement such as sarcoidosis and scleroderma, right heart function could be impaired secondary to a myocardial tissue infiltration rather than an increase in PVR[10-12]. In this case, the main factor causing the cardiac involvement is a process of deposition of inflammatory cells or an excessive deposition of fibrotic tissue that leads to right heart stiffness and finally to RV failure.

The pathophysiology of chronic RV pressure overload has been reported in medical literature. The first phase of homeometric adaptation was described as an increase in hypertrophy and RV contractility to overcome the increased afterload. When dilatation occurs, the RV begins the heterometric phase in which it is necessary to increase the end diastolic volume of the right ventricle in order to ensure an adequate stroke volume. In this second phase, RV function is gradually more influenced by preload. In addition, the lack of synchronization during the ventricular contraction post systolic shortening determines an inefficiency of the RV-pulmonary circulation unit leading to the development of right heart failure and "maladaptive" remodeling, which leads to RV failure and poor prognosis [13][14][15]." (Figure 1).

The complex interrelation of all these different mechanisms, in concert with the preload, the afterload and the intrinsic contractility, determines RV function. Clinicians should consider all these points to properly assess cardiac involvement in lung diseases in order to provide the appropriate management of these patients. For example, the management of PH related to chronic lung diseases could be challenging since no randomized control trial has shown benefits with vasodilators. Moreover, some Authors described a potential harmful effect of vasodilators in COPD and IPF patients, due to an imbalance between ventilation/perfusion, leading to worse prognosis [16][17]. For these reasons, a multimodality approach is warranted not only to assess any contributing causes of PH such as left heart disease, thromboembolic disease, and sleep-disordered breathing, but also to obtain an early diagnosis of right heart involvement before overt PH appears. To reach this goal, echocardiography was described as a useful and easily available

tool in assessing RV function providing useful prognostic information. Several non-invasive echocardiographic parameters of elevated systolic pulmonary artery pressure (sPAP) (Figure 2) and RV function (Figure 3) could be useful for this purpose. As listed in **Table 1**, in the field of in lung diseases, different cut-off values for the non-invasive assessment of RV impairment have been proposed in medical literature. However, the combination of different parameters and imaging techniques is often required. In the following paragraphs, the evidence regarding RV impairment will be specifically addressed in relation to the different pulmonary diseases.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is the most frequent pulmonary disease in the general population. The clinical manifestations and the degree of severity could be very heterogeneous [18]. Echocardiography is a useful and available tool to assess RV involvement and his progression over time in COPD, by the application of several parameters [19] [20].

In particular, as reported in the current guidelines by the European Society of Cardiology and European Respiratory Society (ESC/ERS), echocardiographic evaluation is indicated in all patients with symptoms of greater severity than the underlying pulmonary disease may suppose. PH secondary to lung disease or chronic hypoxemia corresponds to group 3 of PH classification [21].

However, the RV evaluation in patients with COPD should not be limited to sPAP evaluation. In fact, increased sPAP values at rest are a sign of advanced pulmonary circulation impairment [22].

The gold-standard method for diagnosis of PH remains right heart catheterization (RHC). Potential indications for RHC in advanced lung disease are (i) proper diagnosis or exclusion of PH in candidates for surgical treatments (transplantation, surgical or endoscopic lung volume reduction), (ii) to exclude alternative etiologies for PH such as pulmonary arterial hypertension (PAH) group 1; chronic thromboembolic pulmonary hypertension (CTEPH) or group 2 pulmonary hypertension, (iii) episodes of RV failure and (iv) inconclusive echocardiographic findings in cases with a high level of suspicion and potential therapeutic implications [23].The drawbacks of this technique are the requirement of specific expertise and that its usefulness in patients is justified only if it leads to a change of therapeutic strategy, so this method cannot be applied routinely [21].

However, RV remodeling already occurs in early stages of disease and even before PH development, so a deeper evaluation of RV function is warranted since the very beginning of the disease [22]. More specifically, the mid-end diastolic diameter of the right ventricle (RVEDd) was increased in COPD patients compared to a control group (28 ± 4,8 mm vs 24,4 ± 4,3 mm)[24]. In addition, Mynkland et al. reported a higher value of the RV wall thickness (1,5 ±0,2 mm vs. 2,0±5 mm, p <0,01) [24]. This last point was confirmed even in COPD patients with mild hypoxemia [25]. Another interesting feature is the observation of RV outflow tract (RVOT) remodeling[26]. RVOT is the portion of the right ventricle mainly affected in the early stages of chronic pressure overload. This occurs because RVOT is the last segment that takes part in the right ventricle contraction and therefore the one exposed to a greater after-load [24][26]. Supporting this hypothesis, it was described how RV wall thickness at the RVOT level was increased compared to the control cases in the early stages of COPD [24][26]. Although these interesting physio-pathological considerations, no cut-offs for RVOT thickness are available to assess initial remodeling process.

Regarding the RV diastolic function evaluated by tissue Doppler imaging (TDI), it has been described that RV index of myocardial performance (RIMP), with a cut off of 0.43, is able to accurately discriminate the remodeling of the right ventricle in subjects with COPD without PH [23]. In addition, TDI appeared as useful in assessing the response to therapy during COPD exacerbations [28]. In this setting, speckle tracking echocardiography (STE) is able to better define RV function [28]. Particularly, free wall RV longitudinal strain (fwRVLS) of the basal portion with a cut off < -23% was associated with an early impairment of RV function [24]. When considering the tricuspid pulse wave (PW) Doppler pattern, patients with PH had higher peak A velocity, lower E velocity and longer isovolumetric relaxation time, than COPD patients without PH [29]. In addition, echocardiography is able to detect severely increased sPAP values with good accuracy compared to the invasive assessment [30] [31]. The non-invasive measurement of sPAP is calculated by adding the systolic atrioventricular gradient between right ventricle and right atrium (RA) (evaluated by the modified Bernoulli equation applied to the TR jet) to the right atrial pressures evaluated by echocardiography [19]. For practical reasons, we will refer to the above-mentioned method by writing sPAP. However, the pulmonary hemodynamics assessment could be challenging. According to some 32] [33], in case of increased pulmonary pressure the non–invasive measurement of sPAP is less accurate than the gold standard method. Nevertheless, Jiang et al. reported that a multiparametric echocardiographic approach has a good diagnostic accuracy

in predicting severely augmented sPAP in patients with COPD and PH [34]. PH grading according to invasive and noninvasive measures of pulmonary artery pressures is shown in **Table 2** [34][35]. In fact, increased sPAP values can be indirectly estimated by other RV parameters. In particular, RV end diastolic transverse diameter >38 mm, pulmonary artery diameter > 27 mm; and a tricuspid annular plane systolic excursion (TAPSE)< 16,5 mm have shown to predict increased sPAP values with good accuracy [35].

Cardiac magnetic resonance imaging (CMR) is considered as the gold standard technique for non-invasive assessment of RV volume and function, since no geometric assumptions are necessary [36]. In COPD, CMR provides information of pulmonary artery stiffness through the pulse wave velocity (PWV). PWV was described as a non-invasive marker of PH (sensitivity (93.5%), specificity (92.8%)) and a good predictor of major adverse cardiac events (MACEs) in COPD patients (HR = 4.75, 95% CI 1.00 to 22.59, p = 0.03) [37]. The non-invasive assessment of the pulmonary artery elastance has been evaluated by Computed tomography (CT) too. However, this method is not yet standardized and currently its routine clinical use is still not advisable [38]. In addition, a ratio of pulmonary artery to aorta >1 assessed by CT was described as a good predictor of increased sPAP values in patients with a history of frequent COPD exacerbations [39].

Exercise stress imaging was also applied to COPD patients. Even if it is not considerable as a routine imaging method, patients with exercise mean pulmonary atrial pressure (mPAP) values >30 mmHg were more likely to develop PH over time [40].

Several indices of RV function have been associated with the prognosis in COPD. With regard to sPAP values, it has been seen that the development of severe PH is associated with increased mortality. Moreover, PH has been associated with higher probability of acute exacerbation of COPD [40].

RV MPI evaluated by echocardiography was associated with quality of life and the BODE index (Body mass index, airflow obstruction, Dyspnea and Exercise), a multiparametric score used to predict long term outcomes in COPD [41].

In addition, RV diastolic function parameters by TDI were associated to an improvement of the symptoms after response to therapy in the setting of an acute exacerbation of COPD [27].

Furthermore, speckle tracking echocardiography (STE) allows to assess the degree of improvement of RV function (fw RVLS: 18.1 ± 3.4% vs. 22.9 ± 3.7%, p < 0.001) and the improvement of the 6MWT distance (6MWTD Δ) (r = 0.41, p = 0.04) after a pulmonary rehabilitation program [42].

Idiopathic pulmonary fibrosis (IPF)

Idiopathic interstitial pneumonias (IIP) are a subgroup of diffuse pulmonary interstitial diseases in which the correct diagnosis could be tricky [43]. This review focuses on the cardiac involvement in idiopathic pulmonary fibrosis (IPF), the most frequent and better described among IIPs.

The main mechanism of RV damage is considered the increase of PVR secondary to the progressive rearrangement and fibrotic distortion of alveolar parenchyma, leading to honeycombing lesions [6].The impact of lung parenchymal destruction in the risk of PH onset is supported by the observation that patients with combined pulmonary fibrosis and emphysema (CPFE) show an increased risk of developing PH, which is associated with a poor prognosis [44].

The assessment of right heart function could be useful in the multi-parametric approach of these patients to evaluate prognosis and tailor available therapy. As recently confirmed by American Thoracic Society Document for diagnosis, IPF is considered a progressive disease but its clinical course is still unpredictable at the moment of diagnosis, ranging from a slow relentless decline of lung volumes to a more aggressive deterioration, sometimes punctuated by episodes of acute worsening of hypoxemia, called “acute exacerbation” of disease [43]. PH is considered among the most negative prognostic factor for IPF patients and, therefore, an early detection of this complication could be very useful in the clinical management of these patients (e.g. for a timely referral to a lung transplant evaluation). Also, in IPF patients, the evidence demonstrates that assessing the RV involvement only by sPAP incompletely describes right heart involvement. In addition, sPAP is impaired only in the terminal phase of the disease and other parameters could be useful in earlier stages to asses RV function such as fwRVLS and RV global longitudinal strain (RVGLS) [45].

More specifically, D’Andrea et al. described that in patients with IPF without PH, fwRVLS was lower compared to control (basal fwRVLS: -19.4±5.7 vs -14.7+ 6.7; midwall fwRVLS: -16.5±6.5 vs -13.5±9.5)[46]. In addition, a RVGLS ≥-18% was able to differentiate controls and IPF (area under the curve (AUC) :0.89; sensitivity 81.4% and specificity 90.2%) [46].

In addition, a lower contractile reserve of the RV, evaluated by stress echocardiography, was found in the early stages of the disease. More specifically, fwRVLS and RVGLS increase (ΔfwRVLS and ΔRVGLS respectively) during exercise was lower in patients with IPF (2.1± 0.9 and 1.2 ± 0.6) vs control patients (5.3 ± 2.2 and 5.9 ± 2.4) [46].

Sarcoidosis

Sarcoidosis is a systemic granulomatous idiopathic disease that affects the lungs in the majority of cases (90%), while a clinical manifest cardiac involvement occurs in around 5% of patients [10]. However, some Authors reported that cardiac sarcoidosis (CS) carries a strong prognostic burden, being responsible for as much as 85% of deaths in these patients [47]. The cardiac involvement is characterized by different grades of severity, from asymptomatic forms to SCD. The underlying mechanism is peculiar, consisting in an infiltration of cells in cardiac tissue. This means that the grade of severity is strongly influenced by the extension but also by the location of the pathologic process. The common clinical manifestation of CS is conduction abnormalities and/or ventricular arrhythmias leading to SCD [10].

Assessment of cardiac involvement in CS

According to the 2014 European *Heart* Rhythm Association (*EHRA)* guidelines, the gold standard for diagnosis of CS is cardiac biopsy proving non caseating granuloma on histological examination of myocardial tissue [48]. However, given the focal characteristics of this disease, this method is often inconclusive. For this reason, non-invasive techniques are warranted to make a provisional diagnosis in presence of biopsy-proven extracardiac sarcoidosis [48]. In the symptomatic forms of cardiac sarcoidosis, ECG and standard echocardiogram can provide useful information [49]. Echocardiography can detect cardiac structural abnormalities such as regional wall motion abnormalities, increased myocardial wall thickness or enhanced ventricular wall echogenicity. As regard to second-level echocardiographic imaging techniques, it was described that RVGLS, with a cut off value of -19% could be useful in the early assessment of the RV impaired function and to estimate prognosis [50][51]. However, in patients with non-cardiac sarcoidosis, ECG abnormalities prevalence is highly variable, ranging from 4 to 55%, with frequently non-specific findings for inflammation and not sensitive for detecting early changes in CS [49]. For these reasons, the diagnosis of CS could be challenging, and a multimodality imaging approach could be helpful. The recent American Thoracic Society (ATS) guidelines on diagnosis and detection of sarcoidosis did not recommend routinely echocardiographic assessment in sarcoidosis patients with no suspicion of cardiac disease. On the contrary, in patients with suspected sarcoid cardiac involvement, a conditional recommendation for CMR as first-line imaging technique was made [52].

As regard to CMR, T2 weighted images could be used to detect myocardial inflammation and edema in CS whereas late gadolinium enhancement (LGE) imaging to delineate myocardial tissue with expanded extracellular space as occurs in infiltration, scarring or fibrosis.

Another second level imaging technology is the radionuclide imaging with ^{67}Gallium-citrate SPECT and FDG-PET. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) which provides the advantages of whole heart evaluation and has the ability to identify granulomas with active inflammation, with a moderate-to-good accuracy. Therefore, FDG-PET was endorsed by ATS guidelines as a potential alternative to CMR for detection of cardiac localizations of diseases [52].^{67}Gallium-citrate is specific for inflammation, however it has relatively low sensitivity and poor spatial resolution compared with FDG-PET [49].

Right atrium: a not-to-be-forgotten chamber

The RA is an often forgotten and poorly studied heart chamber, however, it has the role of collecting blood during systole and favoring RV filling during diastole. In addition, an alteration in the RA volume can lead to tricuspid regurgitation [53]. The prognostic role of this cardiac chamber has not been evaluated in the context of pulmonary disease. However, in other clinical scenarios, such as chronic systolic heart failure, right atrial dilatation has shown an unfavorable prognostic value [54]. Therefore, it is mandatory to include the assessment of RA size (by area and volume) and function (by STE) in the echocardiographic report when evaluating a pulmonary patient.

Limitations

The right heart imaging provides many useful information in the field of pulmonary diseases. However, there are several limitations that should be underlined. First of all, the poor acoustic window in most cases due to lung hyper-distention causes a worsening of image quality. More specifically, the low acoustic impedance derives from an increase of air inside the chest. This prevents optimal ultrasound transmission which results in lower image quality. Secondly, the proper assessment of RV parameters could be challenging and time-consuming. These limitations are quite valid, especially for advanced imaging techniques such as STE and three-dimensional (3D) echocardiography. Despite the limitations found in RV assessment, 3D echocardiography showed promising results in the assessment of RV volumes and ejection fraction in other clinical scenarios such as PH [55]. In fact, this method allows to better describe RV function, its specific

role in pulmonary diseases has not been investigated so far, but only in the context of RV pressure overload of the right ventricle in primary PH [56]. In the field of echocardiographic examination with a specific training and correct probe orientation the image quality limits could be overcome in many cases [57].

Conclusion

Cardiac involvement in lung diseases has been widely observed, RV changes are reported also in early stages of pulmonary diseases. Strengthening the role of right ventricle in a prospective manner and including it in a multidisciplinary clinical evaluation involving cardiologists, pulmonologist, radiologists in chronic respiratory patients is a relevant topic in the field of chronic lung disease. Future research is required in evaluating the response to therapy and the degree of disease progression through multimodality and advanced imaging technologies.

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Table 1: Non-invasive normal value of RV function in Primary lung diseases

	Cutoff	References
RVFWT	<5mm	[19]
RVEDD	<35 mm	[35]
Pulmonary artery diameter	<27mm	[35]
P/A ratio	<1	[40]
Rimp (MPI)	<0.43	[25]
mPAP[1]	<25mmHg	[19]
FwRVLS (basal portion)	<-23%	[24]
RVGLS	<-19%	[51]
ACT	> 105 ms	[19]
TRVmax/RVOT TVI	<0.15	[19]
ePVR((TRVmax/RVOT TVI) x 10 + 0.16	<3W U	[19]
EI[2]	<1	[57]

[1]mPAP could be estimated by modified Bernoulli equation: 4 x (early pulmonary regurgitation velocity)2 +RAP; Mahan's equation mPAP = 79-(0,45x PA act (ms); and when ACT <120ms: mPAP = 90-(0,62x acceleration time (ACT); [2]EI >1 in diastole is associated with volume over-load; if > 1 in both diastole and systole is associated with pressure overload. *ACT, acceleration time; EI, eccentrcity index; fwRVLS, free wall right ventricular longitudinal strain.; mPAP, mean pulmonary artery pressure ;PVR, pulmonary vascular resistance; P/A, Pulmonary artery /aorta ratio; RIMP right ventricular index of myocardial performance; RVOT TVI, right ventricular outflow tract time velocity integral; RVEDD right ventricular end diastolic diameter.*

Table 2: Grading of pulmonary hypertension (PH) according to noninvasive (sPAP) and invasive (mPAP) measures.

	sPAP[34]	mPAP [35]
Mild	20-39mmHg	>25mmHg
Moderate	40-59 mmHg	>25mmHg
Severe	>60mmHg	>35 or >25 and CO <2.5 L/min

CO, cardiac output; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure.

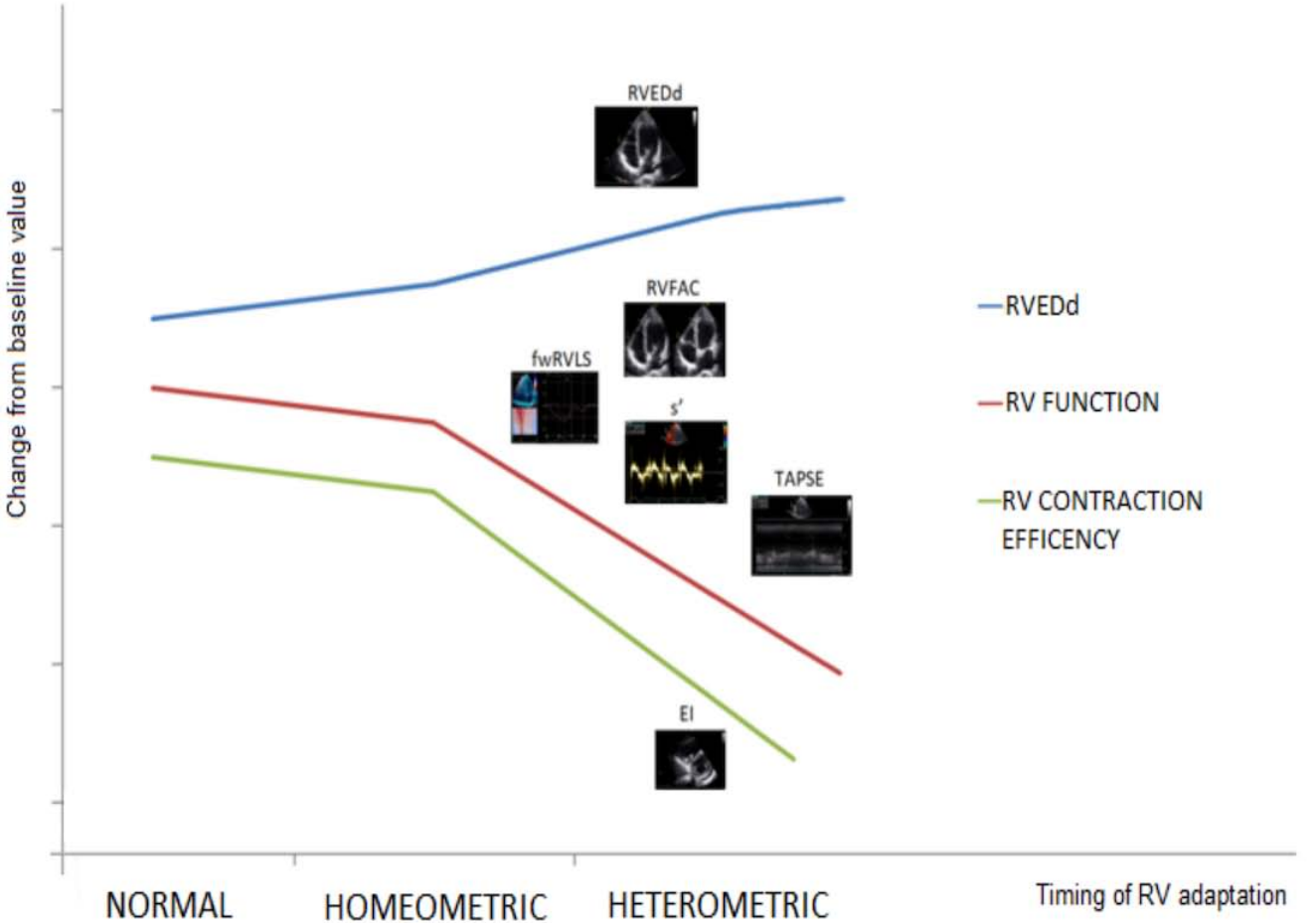
Figure legend

Graphical abstract. Multimodality evaluation of the right heart in lung diseases.

Figure 1. Right ventricular (RV) response to progressive chronic pressure overload. The evolving phases of RV adaptation to pressure overload could be non-invasively assessed by different echocardiographic parameters. In the early stage of homeometric RV adaptation, the use of advanced techniques could be useful to detect the subtle impairment of RV function, such as measuring free wall RV longitudinal strainby Speckle Tracking Echocardiography. Later during the homeometric RV adaptation phase, overt RV systolic dysfunction could be recognized by reduced RV fractional area change and s' wave by tissue doppler imaging. Finally, in the heterometric phase, RV structural changes and desynchronization occur, and these could be evaluated also by basic echocardiographic parameters, i.e. RV diameters, systolic pulmonary artery pressure (sPAP) and tricuspid annular plane systolic excursion.
EI, eccentricity index; fwRVLS, free wall right ventricular longitudinal strain; RVEDd, right ventricular end diastolic diameter; RV, right ventricle; RVFAC, right ventricular fractional area change; TAPSE, Tricuspid annular plane systolic excursion.

Figure 2. Non-invasive indices of pulmonary hypertension in lung diseases acquired by transthoracic echocardiography. A) Right Ventricular end diastolic diameter (RVEDd) ; B) Pulmonary artery PA artery dilation; C) Spectral continuous wave Doppler signal of tricuspid regurgitation corresponding to the right ventricular (RV) – right atrial (RA) pressure gradient; D) D-shape of the left ventricle due to RV pressure and/or volume overload**.** *LA, left atrium; left ventricle; PA pulmonary artery; sPAP, systolic pulmonary artery pressure; PH pulmonary hypertension; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; TAPSE, Tricuspid annular plane systolic excursion; fwRVLS, free wall right ventricular longitudinal strain.*

Figure 3. Transthoracic echocardiography parameters of right ventricular (RV) function useful to evaluate patients with pulmonary disease. A) S' wave of TDI of the right ventricle; B) tricuspid annular plane systolic excursion (TAPSE); C) Right ventricular fractional area change (RVFAC) measured as (EDA –ESA)*100 \ EDA; D) free-wall right ventricular longitudinal strain (FwRVLS). *EDA, end-diastolic area; ESA end-systolic area; fwRVLS, free wall right ventricular longitudinal strain.*


RVEDd
RVFAC
fwRVLS
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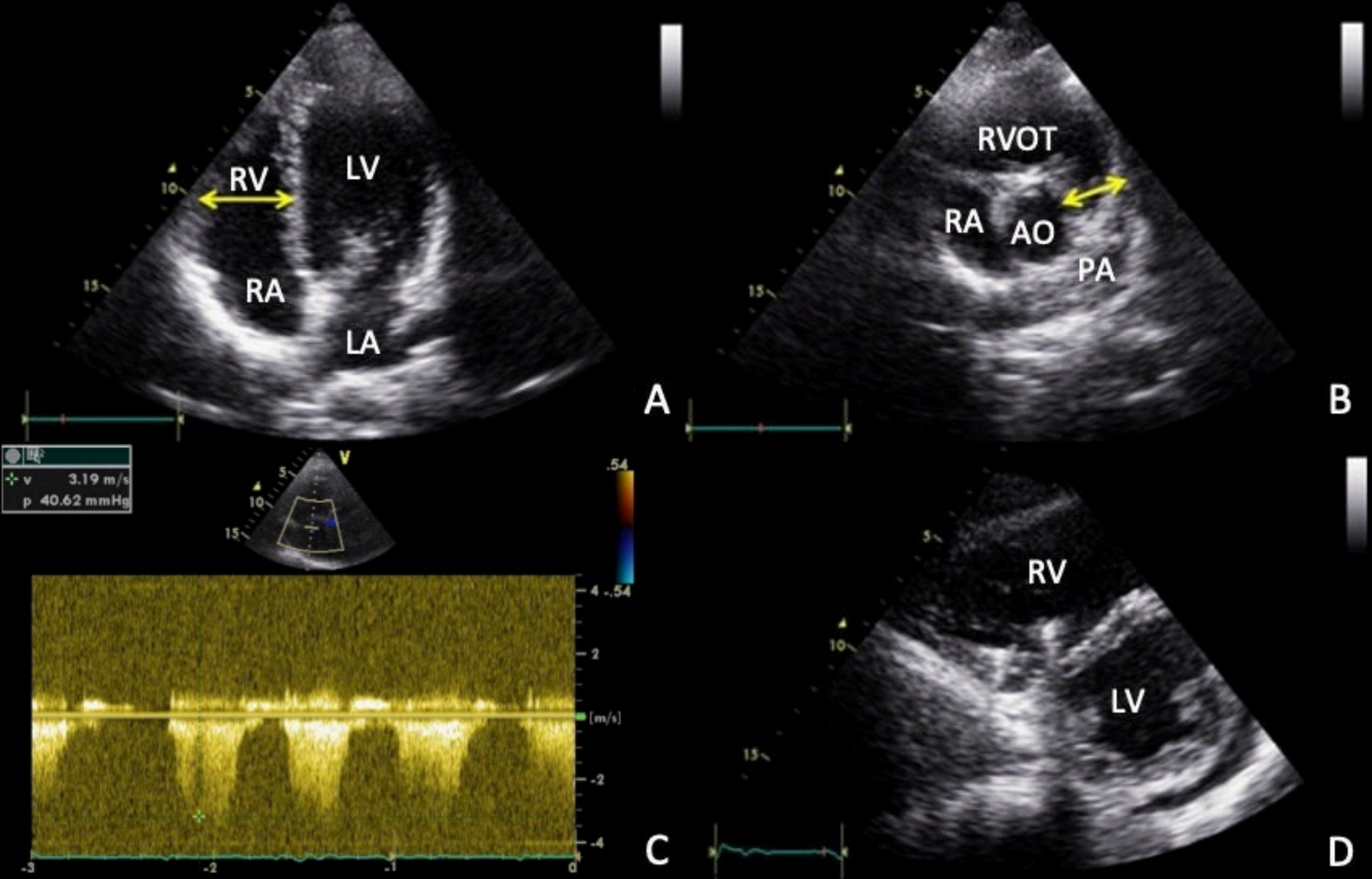
TAPSE
EI
Change from baseline value
RVEDd
RV FUNCTION
RV CONTRACTION EFFICENCY
NORMAL
HOMEOMETRIC
HETEROMETRIC
Timing of RV adaptation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RA
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v 3.19 m/s
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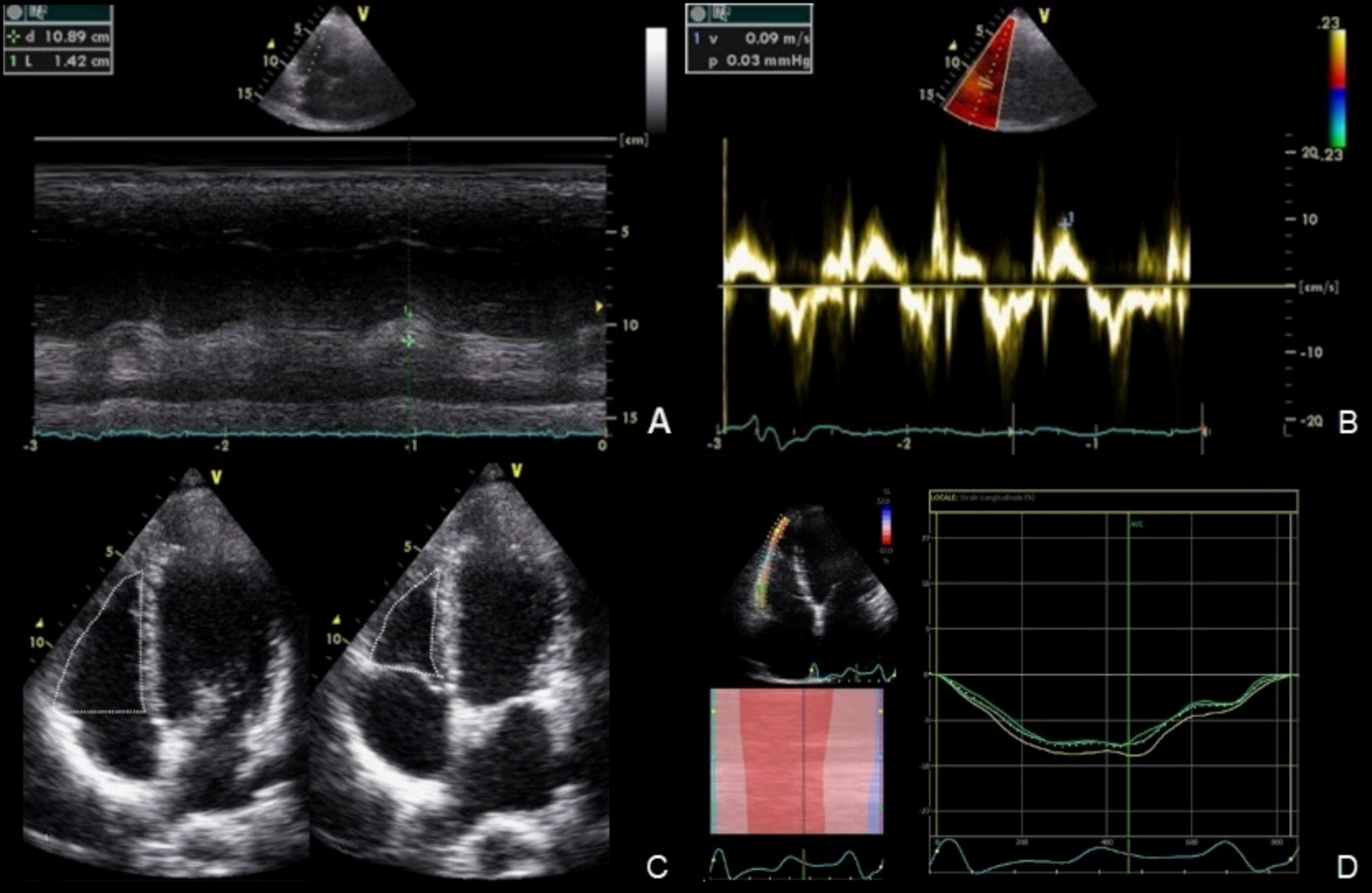
d 10.89 cm
1 L 1.42 cm
1 v 0.09 m/s
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