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Commentary on: Echocardiography in Pulmonary Arterial Hypertension: Is It Time to Reconsider Its Prognostic Utility?

Dimitrios Tsiapras MD PhD FESC*, Eftychia Demerouti MD FESC

Non Invasive Cardiology Department, Onassis Cardiac Surgery Center, Athens, Greece

*Correspondence should be addressed to Dimitrios Tsiapras, dtsiapras@hotmail.com

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Introduction

Pulmonary Arterial Hypertension (PAH) represents a rare but devastating disease due to small pulmonary arterial vessels remodelling and increased pulmonary vascular resistance leading to right ventricular dysfunction, right heart failure and death. According to Guidelines [1], the therapeutic management is based on risk stratification at the time of diagnosis and during patients' follow-up every 3-6 months. In recent years, despite the therapeutic advances in the field of PAH, survival remains poor. This raises the question if the RV afterload reduction and the near-normal or normal RV function should be the goal of treatment. Right ventricle plays predominant role in survival in PAH as patients' clinical status and prognosis is based on right ventricular adaptation in increased afterload. Imaging (based on echocardiography or magnetic resonance) plays a significant role in non-invasive right ventricular function study [2] although in recent risk stratification scheme the parameters used do not directly assess it. Echocardiography is increasingly incorporated into daily clinical practice and seems to be the missing piece in PAH risk stratification.

PAH Risk Stratification

PAH prognosis assessment has considered to be of great importance since the publication of the first US National Institutes of Health idiopathic PAH (IPAH) registry three decades ago [3]. Over the years, many different clinical, functional, imaging, biochemical and invasive parameters have been utilised in formulas or calculators to predict outcome in PAH as the French Pulmonary Hypertension Network (FPHN) registry risk equation[4], the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk equation [5] and risk score [6,7], but also many others [8-10]. The 2015 ESC/ERS PH guidelines [1] recommend PAH risk stratification in low, intermediate and high risk based on expected one-year mortality. This multivariate approach necessitates clinical, biochemical, exercise, functional and haemodynamic parameters [1-11].

Many registry studies have also been published using various risk stratification strategies as Swedish PAH Registry (SPAHR) [12], COMPERA [13] and FPHN registry [14], with a unique confirmation: Low risk patients at baseline and in the first follow up have the best prognosis when treated according to recommended therapeutic strategies, mainly based on aggressive therapeutic approach. Specifically, initial oral combination therapy is recommended for low and intermediate risk patient and upfront combination therapy including prostanoids for high risk patients. However, in our daily clinical practice, majority of patients are stratified as intermediate risk with heterogeneity between different patients' profile, so many of them need a more aggressive approach than others. Moreover, Reveal Lite-2 risk score [15] interestingly revealed the increase in the 1-year death rate between intermediate-risk and high-risk groups from 7.1% to 25.1%. This observation highlights the growing evidence to identify more risk groups or to use continuous variables strongly associated with survival rather than risk category. Variables closely related to RV adaptation to increased afterload determine prognosis in PAH and echocardiography relies on the opportunity to assess RV function easily and non-invasively. Echo-derived parameters are used to assess a normal or near-normal RV function, the ideal goal of treatment in PAH.

Right Ventricular function improvement as a treatment goal in PAH

Right ventricular function and progressive dysfunction is the basic determinant of morbidity and mortality in patients

with PAH [16]. The underlying mechanisms of RV adaptation and remodelling seem to be hypertrophy, dilatation, fibrosis of ventricular walls together with metabolic and hormonic processes as response to an increase in PVR. Adaptive RV remodelling is based on preserved myocardial microcirculation while on the other hand maladaptive remodelling with eccentric hypertrophy, dilatation and myocardial fibrosis take place.

The 6th World Symposium on Pulmonary Hypertension [17] recommended early achievement of a low-risk patient as treatment goal in PAH patients, requiring risk assessment at each visit in intervals of 3-6 months. Low and intermediate risk patients should be treated with oral combination therapy and high-risk patients with triple therapy including parenteral prostacyclin. Right Heart Catheterization represents an accurate monitoring strategy and Cardiac Index is the first parameter associated to survival, reflecting indirectly RV function, already used in risk stratification assessment according to Guidelines. Interestingly, RV afterload reduction is not recommended to be the treatment goal, even though numerous studies suggest that greater RV afterload reduction leads to a profound reverse RV remodelling improving RV function and prognosis [18]. However, reaching threshold levels for pulmonary arterial pressure or vascular resistance seems to play pivotal role in interrupting the self-perpetuating injury of pulmonary vascular disease. Initial oral combination therapy especially using parenteral prostacyclin early after PAH diagnosis provides greater hemodynamic improvement with more robust reductions in mPAP and PVR, parameters proved to be related to adverse pulmonary arterial and right heart remodelling [18].

Limited data exist in the literature addressing the effect of PAH-specific drug therapy on afterload reduction and RV function. An inverse correlation was found to exist between PVR changes and MRI-derived RV ejection fraction (RVEF) after one-year of drug monotherapy in 110 patients [19]. More studies on double oral PAH drug therapy led to a modest improvement in PVR, usually <50%, associated with a weak improvement of RV function [20]. Van de Veerdonk et al. [21] demonstrated a mild improvement in MRI-derived RVEF, not associated with significant changes in RV end-diastolic volume with oral drug therapy. A multicentre prospective study by Badagliacca et al. [20] showed a PVR reduction of more than 50% to be associated with a great likelihood of RH reverse remodelling defined as a decrease in RV end diastolic area, left ventricular systolic eccentricity index and right atrium area. In this study, RH reverse remodelling (RHRR) was found to be an independent predictor of patients' risk stratification using the REVEAL risk score [20]. A study by Weatherald et al. [22] demonstrated that after initial therapy in intermediate-risk patients, about 25% had progressive RV dilatation, whereas approximatively 40% experienced reductions in mPAP and RV end diastolic area (RVEDA), highlighting the different phenotypes of intermediate-risk patients, a group poorly characterized by risk stratification alone. In this study, stroke volume index was a useful independent predictor of morbidity and mortality.

The appropriate therapeutic management to achieve RV reverse remodelling in PAH remains unclear, however significant data offers a recent retrospective study by Badagliacca et al. [20] suggesting the important role of early and aggressive combination therapy including prostanoids in intermediate-risk patients. The largest reduction in mPAP and PVR was achieved when patients were treated with initial parenteral prostanoid and single oral drug therapy for 6 months. A close relationship between PVR and both RVEDA and RV fractional area change (RVFAC) was found in case of a reduction of PVR more than 40%. In Sitbon et al.'s study [23], triple upfront therapy including prostacyclins has been found to reduce PVR by 67%, accompanying by a great functional improvement in 6minutes walk distance and WHO Functional Class. Similar hemodynamic improvement has been demonstrated in the study of D'Alto et al. [24], where the combination of oral therapy and subcutaneous treprostinil resulted in a significant improvement of RV dimensions and function [25]. Initial combination therapy, including parenteral prostacyclins, is associated with a greater RHRR than with other treatment strategies and specifically, more than 50% of RHRR was obtained with >50% reduction in PVR [26]. All data verify that robust hemodynamic improvements can reverse pathologic remodeling of the right ventricle and restore RV function to normal in PAH [18], so if normal RV function were the goal of treatment during patients' follow-up, the prognosis could be better.

Echocardiography and Prognostic Implications

Many echocardiographic parameters of RV function have been described in the literature, however only the presence of pericardial effusion and the RA area are quoted for risk stratification in the current guidelines [1]. Pericardial effusion in PAH is driven by increased right atrial pressure and reflects RV diastolic dysfunction [27,28] but presents late in course of PAH disease, identifying high-risk patients. RA size is proved to be relevant to PAH prognosis, increasing the risk of all-cause mortality by 50% for every 5-unit increase in RA area in a recent meta-analysis [29]. Echocardiographic indices assessing RV function have also been prognostically evaluated but only by small, single-centre studies, and there has not been any systemic evaluation of the RV function along with the other parameters of clinical scores.

Estimation of RV dimensions and systolic function by echocardiography is a challenging task due to its unique anatomy [30]. Accurate calculation of RV volumes and RVEF by echocardiography is a difficult task although use of contrast agent infusion and 3D echocardiography improve the accuracy compared to MRI which is the preferred imaging technique in clinical practise [31]. RV end diastolic area (RVEDA), end systolic area (RVESA) and fractional area change (RVFAC) has been widely used in clinical practise as a surrogate

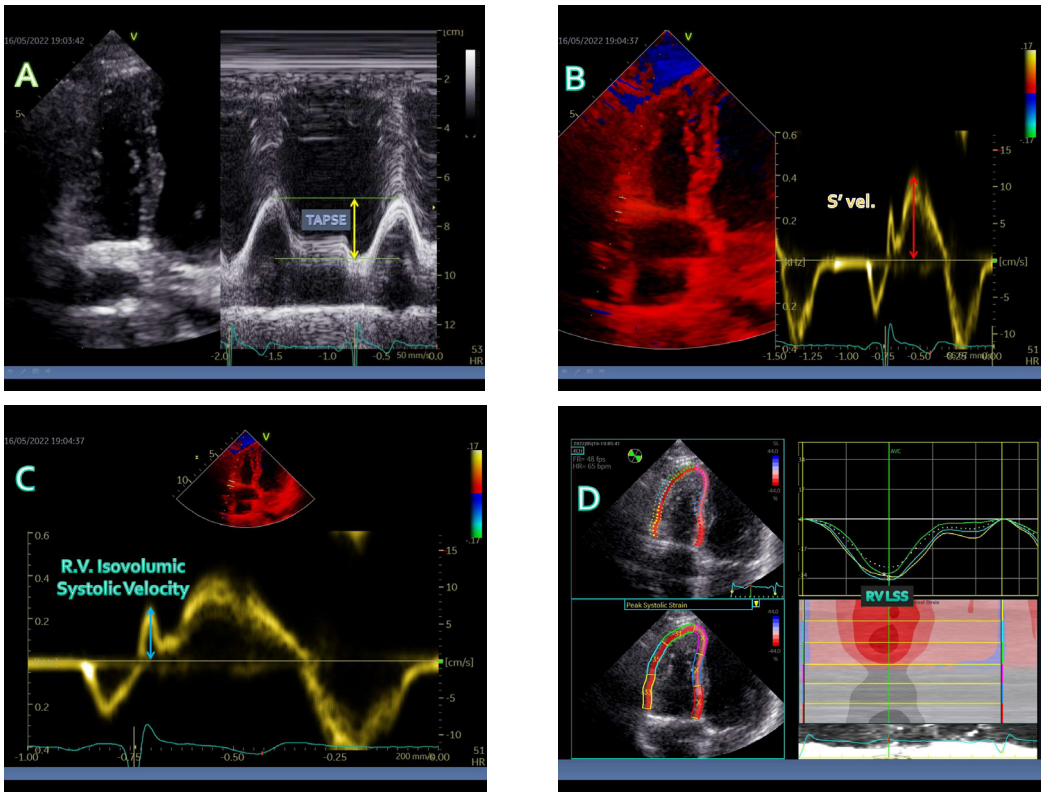

Figure 1: Echocardiographic parameters validated for the right ventricular function study based on longitudinal free right ventricular systolic motion: **a)** tricuspid annulus plane systolic excursion (TAPSE), **b)** tricuspid annulus systolic velocity (s') **c)** RV isovolumic peak velocity and **d)** speckle tracking derived RV free wall longitudinal systolic strain (RVLSS).

of volumes and ejection fraction. Furthermore, as longitudinal motion of RV walls during systole exceeds the circumferential component, many other echocardiographic indices studying this longitudinal myocardial contraction have been proved to correlate with RV EF, patient clinical status and prognosis. These parameters, widely used are a) tricuspid annulus plane systolic excursion (TAPSE), b) tricuspid annulus systolic velocity (s') c) RV isovolumic peak velocity and d) speckle tracking derived RV free wall longitudinal systolic strain (RVLSS) (**Figure 1**).

These echo-derived ejection phase and dimensional parameters have been proven to be of prognostic relevance in the clinical setting [29,32-35]. TAPSE is an easily measured parameter with prognostic significance but does not advertently reflect RV afterload [34,36-39]. Isovolumetric indexes of RV systolic function as dP/dt (max) and RV isovolumic peak velocity less affected by afterload [40,41], the ratio between early diastolic myocardial velocity at the tricuspid lateral annulus [E] and early diastolic tricuspid inflow [E'] are proved to be of prognostic relevance in PAH [42-44]. The new echocardiographic techniques as speckle tracking algorithms seem promising for RV function assessment and its prognostic impact is demonstrated in clinical studies. However, although regional and global 2D strain measurements are somewhat influenced by RV afterload, the prognostic value of 2D strain has been demonstrated in clinical studies [45-48]. According to RV dysfunction's pathophysiology in PAH, parameters like TAPSE/PASP and RHRR [49] also represent promising parameters to improve the validation of risk tools.

An important question is how best to incorporate the accumulating data on echocardiographic parameters for the prognostic significance of PAH into clinical practice. According to the published data, TAPSE, RA area, RVFAC, eccentricity index, and RVLSS are implicated in PAH prognosis. Dr Farmakis et al. [30] suggest clinicians to use in their daily clinical practice, evaluating RV function in PAH patients at baseline, and during their follow-up after specific drug therapy initiation. Right heart catheterization still represents the gold standard for diagnosis and stratification of PAH according to haemodynamic profile but it is not an easily and frequently applied technique. Non-invasive techniques, especially echocardiography, remain to be validated against RHC, although it does predict outcomes in PAH [50,51]. Notably, D'Alto et al. [24] did find significant correlation between RH dimensions and PVR changes, supporting the evidence of the added value of echocardiographic evaluation of RV in PAH risk assessment.

Perhaps the lack of strong correlation of echocardiographic parameters and patients' prognostic data is based on wide echocardiography application and the inherent subjectivity of

the technique. Unacceptable values of interobserver variability have been provided in common echo parameters used to study heart failure patients during cardiac resynchronization therapy [52] and stress echo studies [53]. Advanced echo techniques, such as contrast echo and 3D Echo, and continuous operators training is the key for reproducibility and accuracy. A special care is given from all cardiology scientific societies on appropriate training and accreditation on echocardiography of their members and there is also a continuous effort on standardization of the technique [54]. Undoubtedly echocardiography remains an undisputable useful tool for following up patients with PAH and may be valuable guidance for therapeutic decisions in experienced hands.

Conclusions

Echocardiography is undoubtedly the most widely used tool for assessing RV function in clinical practice, representing a rapid and low-cost examination. It may help in RV adaptation to increased afterload evaluation and non-invasive assessment of PAH patient's status during follow up [55,56], improving prognostication [57]. Moreover, it may play a pivotal role in risk assessment and the normal right ventricular function could be the appropriate treatment goal in PAH.

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