Imaging risk in pulmonary arterial hypertension

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Risk assessment is essential in PAH to optimise treatment decisions aiming to slow disease progression. Imaging of the RV matters in the assessment of these patients, and needs to be seriously considered in the elaboration of more performant tools. https://bit.ly/3ibbo9F

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Pulmonary arterial hypertension (PAH) is a Janus-faced entity with, on one side, the pulmonary circulation and, on the other side, the right ventricle (RV) [1]. While the disease process is turned on at the site of the pulmonary resistive vessels, the patient symptomatology and prognosis are largely determined by RV structure and function adaptation to increased afterload [2, 3]. Yet, this important cardiac aspect of PAH pathophysiology remains insufficiently recognised. The study by Ghio *et al.* [4], in the present issue of the *European Respiratory Journal*, is therefore a welcome step forward.

Ghio *et al.* [4] report on the prediction of outcome in PAH by combined echocardiographic measurements of tricuspid annular plane systolic excursion (TAPSE), tricuspid regurgitation (TR) and inferior vena cava diameter (IVC) dimension. The study was based on pooled individual clinical assessments and comprehensive echocardiographic examinations from 517 PAH patients previously included in seven studies from five European and US academic centres. This is a commendable international collaborative effort, as always when investigating rare diseases. The rationale for the reported measurements was strong, as TAPSE corrected for the severity of TR would assess RV contractility adaptation to increased loading, and increased IVC reflect failure of this mechanism resulting in increased filling pressures and dimensions [5]. Combined measurements of TAPSE, TR and IVC outperformed other echocardiographic measurements previously shown to be predictors of outcome in PAH, such as right atrial (RA) surface area and pericardial effusion which are part of current guidelines recommendations for risk assessment [6].

PAH is a progressive disease with high mortality. Advances have been brought about with the introduction of therapies targeting the pulmonary circulation during the past two decades, but clinicians are facing now difficult choices among available drugs and their possible combinations depending on severity of the disease, accessibility and assessment of cost-effectiveness. Indeed, combination treatment strategies and the option of probably most effective parenteral prostacyclin therapies would be prescribed to patients with the highest risk of deterioration and shorter survival [6, 7]. Risk assessment is thus essential to optimise treatment decisions aimed at slowing progression of the disease [7].

European guidelines elaborated after the 5th World Symposium on Pulmonary Hypertension held in Nice in 2013 proposed a risk stratification for patients with PAH based on clinical assessment, biomarker levels,

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imaging, exercise testing and right heart catheterisation[6]. 14 parameters were used to categorise patients into a low risk green zone (<5% 1-year mortality), an intermediate risk yellow zone (5–10% 1-year mortality) and a high risk red zone (>10% 1-year mortality). The inherent assumption of the approach was that treatments should be titrated or combined to move patients into lower risk zones and thereby improve survival.

The European guidelines' risk assessment strategy was '*a posteriori*' validated by three retrospective studies [8–10] but with decreased numbers of relevant variables, depending on their availability, from eight [8] and six [9], down to only four [10]: functional class, 6-min walk distance, right atrial pressure (RAP) and cardiac index (CI), which could even be reduced to 3 with the addition of brain natriuretic peptide (BNP) or NT-proBNP levels, making RAP and CI irrelevant [10]. In the meantime, the United States Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) registry has allowed for a prospective validation of a score based on at least seven variables, including non-modifiable but important risk factors, characterised by a strong prognostic capability both at baseline and follow-up [11–14]. Both European and REVEAL risk scores are now proposed to direct PAH therapy with upfront or sequential combinations of drugs aiming at getting patients into low-risk states of best prognosis [7].

However, the majority of PAH patients remain in intermediate risk status or with overlapping risk assessments under a double combination of oral drugs, and there is little data offering support to the difficult decision of initial or sequential addition of parenteral prostacyclins. Two small uncontrolled studies in young patients with severe PAH have shown that upfront triple combination of drugs (two oral and one intravenous or subcutaneous prostacyclin) may be associated with marked clinical improvement along with previously unseen decreases in pulmonary vascular resistance (PVR) [15, 16] and reversal of RV dilatation ('reverse remodelling') [16] similar to initially observed inhaled nitric oxide-responder patients [17]. However, one does not know how these results may be translated to patients with still unsatisfactory responses to a double combination of oral drugs.

The initial risk scores in PAH were based on expert clinician experience-derived multi-modality approach, from which cardiopulmonary exercise testing (CPET) assessment disappeared as it was insufficiently available in most centres, and echocardiographic assessment became downsized to measurements of RA surface area and pericardial effusion [8], or pericardial effusion alone [14]. The report by Ghio *et al.* [4] strongly suggests that the echocardiographic assessment of PAH needs to be revived, and that may lead to improved risk assessment and better therapeutic decisions.

The echocardiographic examination of PAH patients generates many measurements which have been shown to be of prognostic relevance by rigorous univariate and multivariable analysis, though most of the time in limited size mono-centric studies [18]. This abundance of information not accompanied by large cohort studies, where a close collaboration between centres becomes a reality, left many non-expert pulmonary hypertension (PH) clinicians perplexed. The originality of the study by Ghio *et al.* [4] is in the selection of easy to measure variables such as TAPSE, TR or IVC and demonstration that their physiologically meaningful combination is of prognostic relevance. TAPSE is indeed a robust though load-dependent measure of contractility and IVC diameter a reflection of increased RV and RA pressure and dimensions. The RV adapts in severe PH by increased contractility to preserve its coupling to the pulmonary circulation and it is only after this basic homeometric mechanism is exhausted that Starling's heterometric adaptation comes into play to preserve flow output, but at the price of increased dimensions and systemic congestion [2, 3, 5]. Thus, the TAPSE (corrected for TR) reflects contractility adaptation and increased IVC dimension its failure. The importance of both assessments of contractility and dimensions has been previously underscored by magnetic resonance imaging studies showing increased dimensions and decreased ejection fraction of the RV, heralding fatal deterioration in PAH in spite of preserved 6-min walk distance and decreased PVR [19].

Indeed, as always with good studies, the report by Ghio *et al.* [4] leaves still an open question: one does not know if the echocardiographic TAPSE-TR-IVC retains its independent prognostic capability when pooled with all clinical, biological, other imaging, CPET and right heart catheterisation measurements which would be ideally assessed in a prospective multi-centric protocol involving a large number of patients. Such collaborative effort would enable realistic estimates of weighted hazard ratios, reflecting the effect of interrelated variables important to the pathophysiology of PAH, and other inferential statistics of interest able to validate cut-off points across different subgroups of patients [20]. Large prospective data would also facilitate the use of nonlinear modelling techniques, which are more appropriate for complex dynamic interactions between pathophysiological variables, and increase the opportunity to evaluate a combination of markers leading to more accurate prognostic assessment [21].

Other echocardiographic parameters might emerge in a multidimensional approach, such as for example the TAPSE/systolic pulmonary artery pressure ratio which might be even more tightly linked to RV-arterial

coupling [22] and has been shown to be a strong independent predictor of outcome in heart failure [23, 24], PH related to chronic lung diseases [25], and PAH [26]. Echocardiography also allows for measurement of other load-dependent indices of pump failure, such as RV fractional area change [27], and more load-independent measures of RV contractility, such as the maximum velocity of isovolumic contraction [28] or longitudinal strain [29–31], and offers exploration of regional inhomogeneity of RV contraction which, alone [32] or in combination with CPET [33], may also be prognostically pertinent. Furthermore, echocardiographic dimension measurements such as RV and RA areas or left ventricular eccentricity index are crucial to the assessment of RV reverse remodelling, as an emerging marker of targeted therapies efficacy [16, 17, 34, 35].

As illustrated in figure 1, current PAH guidelines use only the tip of a huge echocardiographic iceberg.

As the clinical science of PAH is evolving, the report by Ghio *et al.* [4] is a refreshing reminder that imaging of the RV matters in the assessment of these patients, and needs seriously to be considered in the elaboration of more performant risk scores needed for further therapeutic progress.

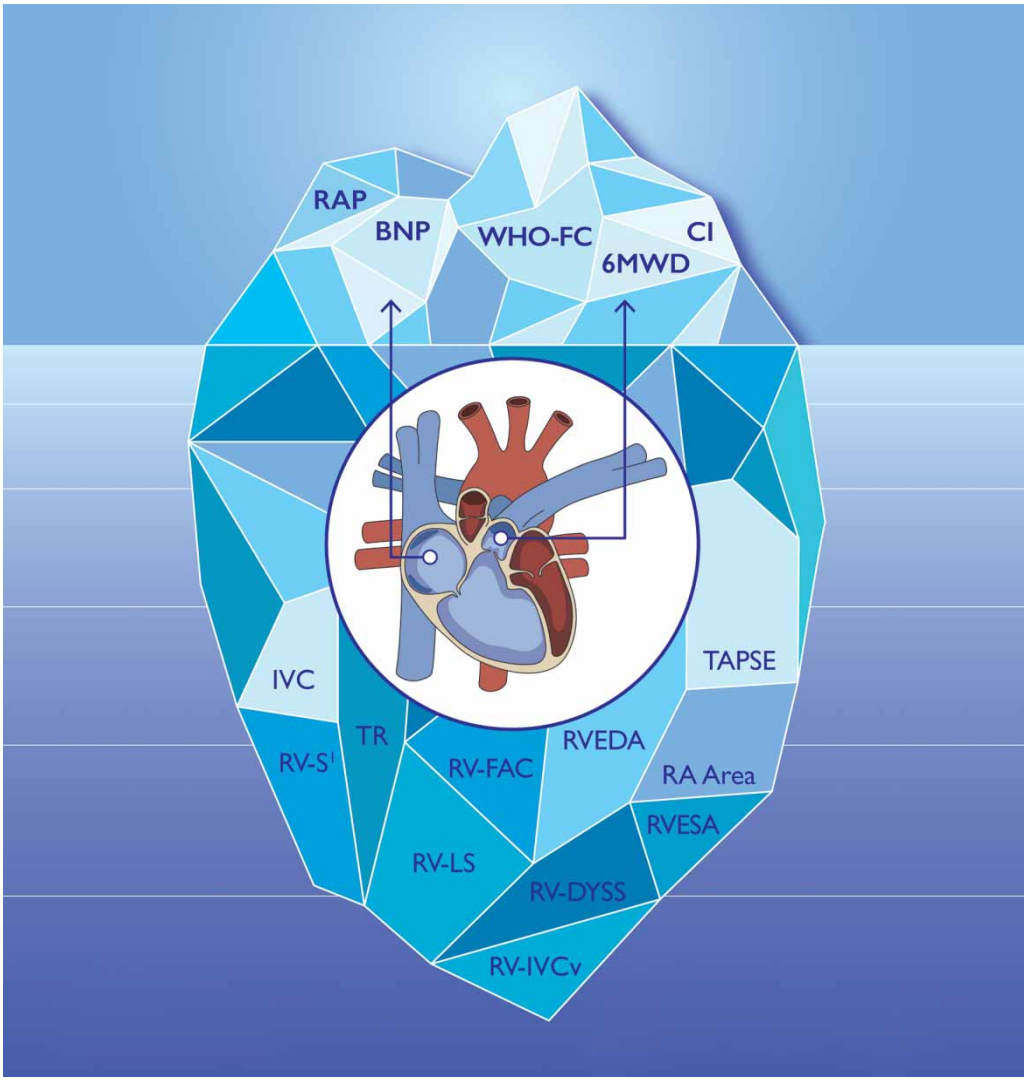

FIGURE 1 Imaging the tip of the iceberg in the pulmonary arterial hypertension clinical setting. World Health Organization functional class (WHO-FC), brain natriuretic peptide (BNP), 6-min walk distance (6MWD), right atrial pressure (RAP) and cardiac index (CI) are all indirect clinical signs of right ventricular (RV) function representing the tip of a huge iceberg. Below the clinical evidence echocardiographic-derived indices directly reflect RV function. IVC: inferior vena cava; RV-S': right ventricular systolic velocity by tissue doppler imaging; TR: tricuspid regurgitation; RV-LS: right ventricular longitudinal strain; RV-FAC: right ventricular fractional area change; RVEDA: right ventricular end diastolic area; RV-DYSS: right ventricular dyssynchrony; RV-IVCv: right ventricular isovolumic contraction velocity; TAPSE: tricuspid annular plane systolic excursion; RA: right atrial; RVESA: right ventricular end systolic area.

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