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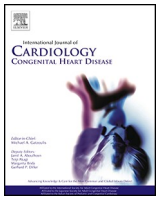

Right heart reverse remodeling: *"facta non verba"*

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ABSTRACT

Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling and arterial narrowing, leading to a progressive rise in right ventricular (RV) afterload and poor survival outcomes. PAH prognosis largely depends on RV remodeling and function: when the increased afterload exceeds the RV's adaptive capacity, ventricular-arterial uncoupling occurs, ultimately causing right heart failure and death. In this clinical setting the primary treatment goal is to achieve low mortality risk and right heart reverse remodeling (RHRR). Unfortunately, the definition of RHRR vary across studies and imaging modalities (echocardiography or Cardiac Magnetic Resonance). The likelihood of RHRR increases with a significant reduction in pulmonary vascular resistance (PVR) from baseline, ideally by at least 50 %. Evidence supports initial triple therapy, including parenteral prostanoids, as the most effective approach to reduce PVR enough to facilitate RHRR and thus achieve the low-risk status.

1. Introduction

Pulmonary arterial hypertension (PAH) is a rare and progressive disease, characterized by proliferation of endothelial cells and pulmonary artery smooth muscle cells and plexiform lesions, leading to increase in pulmonary vascular resistance (PVR) and right ventricular (RV) pathological remodeling. Right heart failure occurs in the late stages of the disease, when the RV loss its ability to face the excessive afterload [1].

A multiparametric risk stratification is pivotal to predict outcomes and guide the therapeutic approach, with the goal of achieving and maintaining a low risk profile [3]. Treatment aims to break down PVR, the static component of the RV afterload, and to increase pulmonary arterial compliance, the pulsatile component [2,11], with the final goal of maintaining or achieving a low risk profile.

2. Adaptative mechanisms of the right ventricle to increased afterload

The right ventricle, traditionally considered the low-pressure and preload suitable counterpart of the left ventricle, has been neglected for years due to its minor involvement in the most frequent cardiovascular diseases. Retracing the RV evolution over-time from embryology may help clinicians deepen the knowledge of such a complex chamber [4].

Ancestrally, the cardiocirculatory system was divided into two directly connected sections: the low-resistance pulmonary vascular bed, aimed to promote the O2 uptake by the alveoli, and the high-resistance systemic vascular bed allowing local regulation of O2 delivery. This division resulted in a binary structure of the heart. Indeed, despite the common origin from blast precursors, the right ventricle undergoes a region-specific evolution prompted both by different loading conditions (after-birth decrease in PVR), and by a highly conserved genetic and epigenetic background [5].

Functionally, the RV tolerates volume overload better than pressure overload. Bartelds et al. evaluated the different patterns of functional and molecular adaptation to volume and pressure overload in mice. Despite similar degree of RV hypertrophy, the pressure-loaded mice had moderately increased RV volumes and reduced exercise capacity, mainly due to calcineurin-activation and increased ratio of beta/alpha-Myosin Heavy Chain (MHC) [6–10,15]. Conversely, volume-loaded mice had higher RV volumes and normal exercise capacity, with only moderately increased beta/alpha-MHC ratio and no increase in Modulatory-Calcineurin-Interacting-Protein 1 expression [12,13].

Beyond functional and molecular changes, chronic pressure load of the RV also induces:

- Changes in gene expression, with the re-expression of genes for fetal sarcomeric proteins and the consequent return to a fetal-like pattern of energy substrate metabolism, switching from fatty acid to glucose oxidation;
- Increased collagen deposition (mainly collagen I type), activation and expansion of fibroblast secreting large amount of extracellular matrix and significant expansion of macrophages in the RV wall, resulting in the increase in RV stiffness [16]. Given the key role of oxidative stress with the generation of reactive oxygen species (ROS) in these pathological changes, therapies targeting oxidative stress may be promising options for PAH [17].

Although interesting from a physio-pathological and educational point of view, the distinction between RV pressure and volume overload

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is rather artificial, since in clinical practice the two processes frequently coexist, as demonstrated by the clinical course of PAH: in the early stages of the disease, the RV responds to increased afterload with wall thickness associated with no significant changes in volumes (concentric RV hypertrophy). The resulting increased mass-to-volume ratio reduces the wall tension and maintains RV-PA coupling and cardiac output. When homeometric adaptation gets exhausted, uncoupling occurs, wall stress increases and the RV shifts towards a maladaptive remodeling, characterized by eccentric hypertrophy, progressive dilation and systolic dysfunction [14,18,32] (Fig. 1). Consequentially, tricuspid anulus dilatation leads to functional tricuspid regurgitation, with superimposed volume-overload further worsening patient's prognosis. Indeed, due to ventricular interdependence, the final stage of the disease shows impairment of both ventricles, including reduced LV filling pressure and performance.

3. Prognostic significance of right ventricle remodeling in PAH

The compensatory mechanisms adopted by the RV to face the increased afterload aim to maintain an adequate right ventricular-pulmonary arterial (RV-PA) coupling, defined as the ratio of RV end-systolic elastance (E_{es}), a measure of ventricular contractility, to pulmonary arterial elastance (E_a), representing the RV afterload [18–20]. Nevertheless, these compensatory mechanisms, at first protective, become prognostically unfavorable in the long term. The switch from a well-adapted RV to a maladapted RV is reflected in the reduction of the RV mass/volume ratio, derived from cardiac magnetic resonance (CMR): PAH patients with lower values of M/V ratio, indicative of eccentric hypertrophy, have worse clinical parameters (e.g. WHO functional class and 6MWD), hemodynamics and lower RV to pulmonary arterial coupling compared to patients with higher M/V ratio, suggestive of concentric hypertrophy [18–21]. The identification of the RV adaptation pattern, through the assessment of RV mass and volume parameters, has prognostic implication: patients with a low-right ventricular mass/volume (M/V) ratio are at significantly higher risk of clinical worsening than patients with a high RV M/V ratio [22]. Similarly, PAH patients with maladaptive remodeling, expressed by high RV volume associated with low mass, resulted to have worse survival and higher risk of treatment failure than the others [23]. However, despite the undisputed prognostic value for right heart evaluation, CMR is less widely available in clinical practice and requires repetitive breath-holds for imaging acquisition, long scanning times and specific skills for image interpretation.

Conversely, echocardiography is readily available, thus supporting clinicians in the regular assessment of RV structure and function. Due to the complex anatomy, the echocardiographic evaluation of the RV requires the acquisition of different views and the integration of qualitative and quantitative methods. The visual assessment of RV function ("eyeballing") is widely used in clinical practice due to its simplicity and speed; however, compared to advanced imaging techniques such as MRI, it has some pitfalls as the lack of accuracy in grading dysfunction, with >40 % discordance even among experts [45]. Therefore, current guidelines recommend combining eyeballing with other echocardiographic parameters such as a) the tricuspid annular plane systolic excursion related to systolic pulmonary artery pressure (TAPSE/PASP ratio), a straightforward non-invasive measure of RV-arterial coupling; RV end-diastolic area to left ventricular end-diastolic area ratio (RVEDA/LVEDA) and c) tricuspid regurgitation severity.

Phenotyping of PAH patients by combining degrees of RV remodeling and RV PA-coupling may provide additional prognostic information to current risk stratification tools [24,25]. New evidence focused on the role of Speckle tracking echocardiography in PAH patients, allowing a reproducible and clinically meaningful RV strain-derived patterns definition with high clinical worsening prediction power [43]. Moreover, the integrated ultrasound measurement of Stroke Work (SW) derived from the pressure and strain loops resulted to correlate with the assessment based on invasively measured pressure-volume (PV) loops; also wasted work has shown to correlate with invasive measurements of load-independent RV function [44].

4. Role of right heart reverse remodeling in PAH

Experiences coming from pulmonary endarterectomy (PEA) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) [27] and bilateral lung transplantation in advanced PAH have shown the remarkable ability of the right ventricle to reverse remodel and regain its physiologic morphology and function with significant unloading [28].

Currently, the concept of right heart reverse remodeling (RHRR) is

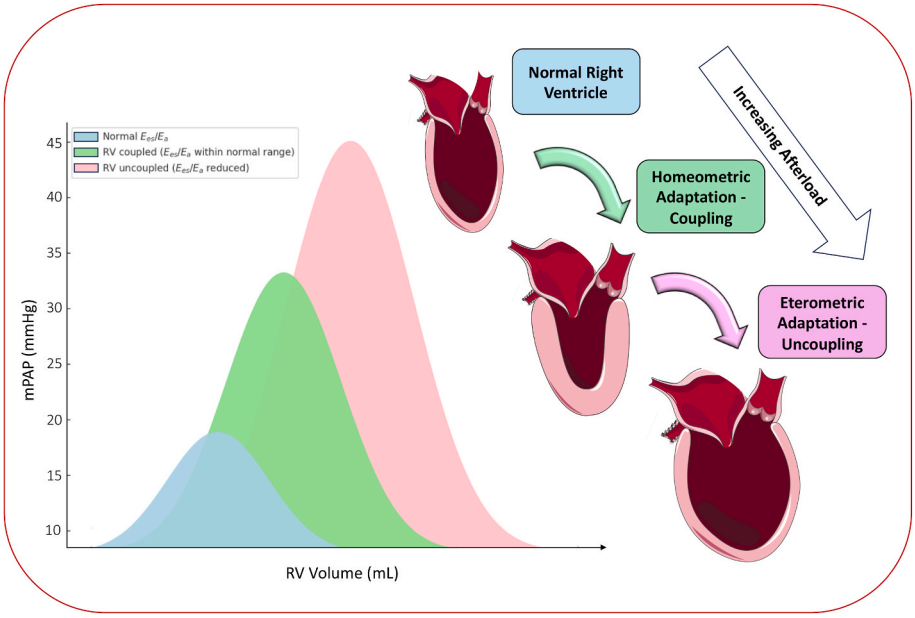

Fig. 1. The clinical course of PAH: in the early stages, the right ventricle (RV) faces the afterload-mismatch increasing both wall thickness, with concentric hypertrophy (Homeometric adaptation) and mass-volume ratio to reduce wall tension and maintaine RV-PA coupling and cardiac output. When homeometric adaptation gets exhausted, uncoupling occurs, wall stress increases and the RV shifts to an eccentric hypertrophy, with enlargement and dysfunction of the RV.

not standardized. Badagliacca and collegues proposed the combination of the following simple echocardiographic parameters predictors of outcome for its definition: decrease in RV end-diastolic area (RVEDA), right atrial area (RA) and LV eccentricity index (LV-EIs): RHRR at 1-year of follow up was associated with a better outcome in PAH treatment-naïve patients and improved the prognostic power of models exclusively based on traditional clinical and hemodynamic variables [26]. Of note, the likelihood of RHRR resulted to be related to the amount of afterload reduction: a mild decrease in PVR, typical of less aggressive treatment strategies, is insufficient to ensure adequate RV reverse remodeling; a large reduction in PVR (>50 %) is required to recover RV size and function by a significative hemodynamic improvement [29–34,47]. Impressive results in terms of afterload reduction (PVR decrease of 70–90 %) and improvements in RVEDA and RVFAC have been achieved with initial triple combination treatment including a parenteral prostanoid [35–39,48]. However, the optimal therapeutic strategy to reverse RV remodeling in severe PAH remains to be defined. New interesting findings in this regard may come from new drugs, as the inhibitor of activin signaling sotatercept. Further studies are needed to reach such conclusions [40–42].

5. Conclusions

Assessment of RV adaptation to the increased afterload is a crucial step in the routine evaluation of PAH patients: right ventricular mass and volumes assessed through cardiac magnetic resonance and parameters derived from echocardiography are extremely useful in clinical practice to differentiate patients with adaptive and maladaptive remodeling (concentric vs eccentric hypertrophy respectively). Phenotyping of PAH patients through the combination of simple and user-friendly echocardiographic measurements representing different degrees of RV dilatation and RV-PA coupling (e.g. TAPSE/PASP and RVEDA/LVEDA ratios) may help non-invasive prediction of prognosis in PAH patients, providing additional information to current risk stratification tools [46].

In accordance with the pathophysiological model of afterload mismatch, a significant decrease in PVR (>50 %) is required to significantly reduce RV dimensions and restore its systolic function, with the final aim of achieving a low-risk status. Currently, a universal definition of right heart reverse remodeling is lacking. Future studies are welcome to further define RHRR, improving gap in evidence in PAH.

CRediT authorship contribution statement

Tommaso Recchioni: Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **Giovanna Manzi:** Writing – review & editing, Writing – original draft. **Alexandra Mihai:** Writing – review & editing. **Francesca Ileana Adamo:** Writing – review & editing. **Annalisa Caputo:** Writing – review & editing. **Domenico Filomena:** Writing – review & editing. **Giorgia Serino:** Writing – review & editing. **Silvia Papa:** Supervision. **Nadia Cedrone:** Writing – review & editing. **Carmine Dario Vizza:** Writing – review & editing, Writing – original draft, Supervision. **Roberto Badagliacca:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

R. Badagliacca reports personal fees from UT, Dompè, Ferrer, Bayer, MSD and AOP Orphan Pharmaceuticals, outside the submitted work. D. Vizza reports personal fees from GSK, UT, Dompè, Bayer and MSD, outside the submitted work.

Other authors have nothing to disclose.

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