REVIEW

The Heroic Chamber – an Outlook on the Right Ventricle in Eisenmenger Syndrome

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ABSTRACT
Despite being at the extreme spectrum of congenital heart disease-associated pulmonary hypertension, patients with Eisenmenger syndrome have better outcomes compared to other types of pulmonary arterial hypertension, especially in the case of post-tricuspid shunts. This survival advantage seems to be at least partly due to significant resilience of the right ventricle and a relative resistance to failure. This paper aims to review the concept of right ventricular adaptive remodeling in Eisenmenger syndrome, its impact on prognosis and the role of multimodality imaging in the right ventricle’s assessment in this setting.

Keywords: Eisenmenger syndrome, right ventricle, multimodality imaging.

REZUMAT
Deși se situează în punctul extrem al spectrului hipertensiunii pulmonare asociate bolilor cardiace congenitale, pacienții cu sindrom Eisenmenger evoluează favorabil comparativ cu alte tipuri de hipertensiune arterială pulmonară, mai ales în cazul șunturilor post-tricuspidiene. Acest avantaj prognostic pare a fi datorat, cel puțin parțial, unei rezistențe semnificative a ventriculului drept împotriva disfuncției și insuficienței de pompă. Lucrarea de față își propune să revizuiască noţiunea de remodelare adaptativă a ventriculului drept în sindromul Eisenmenger, impactul său prognostic și rolul evaluării multi-modale în evaluarea ventriculului drept în acest context.

Cuvinte cheie: sindrom Eisenmenger, ventricul drept, imagistică multi-modală.

GENERAL CONSIDERATIONS

According to published data, up to 10% of all congenital heart disease (CHD) patients develop pulmonary arterial hypertension (PAH) of any severity during their lifetimes1, although improved awareness and early surgical/percutaneous interventions are most likely leading to a decline in its incidence in Western countries2.

Eisenmenger Syndrome (ES) lies at the extreme end of the PAH-CHD spectrum3,4 and is a consequence of unrepaired non-restrictive defects at the atrial, ventricular or aorto-pulmonary level permitting significant left-to-right shunting which leads to an increased blood flow to the pulmonary circulation. The latter increases shear stress at the level of the pulmonary endothelium and triggers endothelial dysfunction and vascular remodeling of the pulmonary arteries. When shunting remains unaddressed, the morphological alterations of the arterial wall become permanent, leading to advanced PAH and elevated pulmonary vascular resistances (PVR). In time, elevation of pulmonary arterial pressures (PAP) above those of the systemic circulation will lead to bidirectional shunting and shunt reversal, expressed clinically as central cyanosis5. Chronic hypoxemia inevitably affects all the other organs, the result being a truly multi-system disease, as ES has traditionally been described6.

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Management in ES is complex and challenging. Shunt reversal precludes subsequent defect closure and treatment options become limited. If palliation and careful fluid balance to prevent hemodynamic destabilization had been the mainstay for many decades, modern pulmonary vasodilator therapy and lung/heart-lung transplantation seem to improve hemodynamics, exercise tolerance and overall quality of life and even survival\textsuperscript{7,8} in these patients, although further studies concerning more specific outcomes and survival benefit are still warranted\textsuperscript{2,4}.

Despite its multi-system involvement and oftentimes more elevated mean pulmonary artery pressures (mPAP), as well as the burden of an uncorrected cardiac defect, chronic hypoxemia and erythrocytosis\textsuperscript{9}, patients with ES seem to have better outcomes than other PAH categories, especially when compared with

Table 1 briefly displays the main clinical features and diagnostic tools in Eisenmenger syndrome.

| Table 1. Diagnostic work-up in Eisenmenger Syndrome (adapted from [4]) |
|---|---|
| **Clinical evaluation** | **Physical examination** |
| Symptoms | Weight |
| Shortness of breath at rest/on exertion | Resting SpO2% |
| Limited exercise capacity | Blood pressure |
| Palpitations | Cyanosis |
| Haemoptysis | Digital clubbing |
| Angina | Systemic congestion: oedema, jugular vein distension, hepatomegaly |
| Headache | |
| Dizziness | |
| Syncope/presyncope | |
| **ECG** | Holter monitoring may be considered in case of syncope, palpitations, baseline ECG abnormalities |
| Presence of sinus rhythm | |
| Heart rate | |
| Supraventricular/ventricular arrhythmias | |
| Conduction abnormalities (right bundle branch block/atrioventricular block) | |
| RV/biventricular hypertrophy | |
| **Non-invasive imaging** | |
| Chest X-ray | Position of cardiac apex (RV hypertrophy) |
| | Cardiothoracic ratio |
| | Position of aortic arch (left/right) |
| | Pulmonary outflow tract dilation/calcification |
| | Dilatation of pulmonary arteries |
| | Pruning of peripheral pulmonary vessels |
| | Pleural/pericardial effusion |
| **TTE** | |
| Systematic analysis of cardiac morphology and ventriculo-arterial connections | |
| Description of the shunt (location, direction, haemodynamic significance) | |
| RV and LV dimensions, systolic and diastolic function | |
| LV eccentricity index | |
| RA dimensions and area | |
| Presence of pericardial effusion | |
| Estimation of PAP and RVEDP | |
| **TEE (unanswered questions on TTE)** | |
| Shunt description | |
| Ventricular function | |
| Co-existing valve disease | |
| Co-existing morphologic anomalies (i.e. anomalous pulmonary venous drainage) | |
| Suspicion of complications (intracardiac thrombosis/ endocarditis) | |
| **CMR (complex lesions/inadequate patient echogenicity)** | |
| Detailed description of cardiac morphology | |
| Shunt description and quantification | |
| Quantification of RV volumes and RVEF | |
| RV fibrosis (LGE) | |
It has been postulated that the explanation partly lies in the preservation of a fetal phenotype of the RV, due to the fact that it has been exposed to increase afterload since birth, thus being “primed” to withstand significant chronic volume and pressure overload.

In the fetus, PAP and RV pressures are equal to the systemic ones across the cardiac cycle, due to the large and non-restrictive ductus arteriosus. The subpulmonary wall thickness and contractile force are similar to the systemic ones, and the interventricular septum remains flat, in a central position, for the entire duration of the cardiac cycle. In contrast to structurally normal hearts, non-restrictive post-tricuspid defects lead to persistently equalized systemic and pulmonary pressures after birth. Subsequently, in Eisenmenger patients, it appears that the RV wall thickness and contractility never regress as a consequence of never being exposed to a decline in afterload, therefore preventing an evolution towards early right heart failure.

However, the exact role of this described mechanism is still to be completely deciphered, as it does not explain the better prognosis of patients with iPAH and PAH associated with connective tissue disease.

The better prognosis of these patients could be explained by the fact that despite similar morphologic lesions in the pulmonary arteries and severely elevated PVR, the right ventricle (RV) of Eisenmenger patients demonstrates significant resilience and resistance to failure when compared to patients with similar pulmonary hemodynamics but no shunt.

**WHY IS THE RIGHT VENTRICLE IN EISENMENGER SYNDROME DIFFERENT?**

Patients with ES demonstrate certain hemodynamic particularities when compared with other forms of PAH. Severe iPAH and other forms of secondary PAH evolve towards significant RV dilation and dysfunction, which in turn leads to right heart failure. In contrast, the RV of Eisenmenger patients can withstand elevated afterload for decades, while reacting with significant hypertrophy but no failure.

In addition, while cardiac output is generally decreased in patients presenting with iPAH, both it and right atrial (RA) pressures remain relatively preserved in patients with ES for similar levels of systolic PAP, until very late during the course of the disease.
not appear to be the sole explanation for the superior outcomes in this group, since, for example, patients who develop ES after shunt closure fare far worse than those with unresolved defects.21

One other definite contributing factor is the defect itself, which acts as a „decompression” valve for the right heart, at the cost of chronic hypoxemia, this positive effect having been speculated in certain cases of iPAH when an atrial septostomy is performed.18

Another important point is the particular interaction between the right and left ventricles, especially in the case of large interventricular defects, when the equalization of left and right pressures leads to two ventricles functioning as a single unit and exhibiting a less harmful type of interdependence; thus, preservation of the cardiac output may be further explained by the absence of paradoxical septal motion and left ventricular (LV) restricted filling, as seen in other forms of PAH.22-21. Moreover, a linear correlation between both mass and systolic function of left and right ventricles has consistently been described in ES9,21,24-26.

THE CONCEPT OF “ADAPTIVE HYPERTROPHY”

The process of ventricular remodeling in PAH is governed by complex interactions between the degree of increase in afterload, timing of pulmonary hypertension onset, causative agent, neurohormonal signaling, myocardial perfusion and metabolism, as well as genetic and epigenetic elements.27

It appears that despite greater degrees of RV hypertrophy23,28, patients with ES develop a more adaptive type of remodeling: more concentric (higher mass to volume ratio), with longstanding preservation of systolic and diastolic functions, in contrast to the eccentric remodeling observed in iPAH or PAH associated with connective tissue disease for example, which tends to rapidly devolve towards dilation, systolic and diastolic dysfunction.27

Published data has described less fibrosis in the RV of patients with ES compared with iPAH, which would imply a lesser degree of diastolic dysfunction21, a finding sustained by with the fact that RA pressures also tend to remain normal in ES.28

Knowledge concerning the extent of the impact of myocardial ischemia on RV function in PAH is limited. Animal models have suggested more angiogenesis in the hypertrophied RV secondary to increased afterload, although with more capillary rarefaction and diminished maximal coronary vasodilator capacity29-31 and reduced myocardial perfusion reserve has been described on cardiac magnetic resonance (CMR) in PAH patients;32 however, myocardial perfusion imaging with single photon emission-CT (SPECT) has shown less perfusion defects in patients with ES than previously reported in PAH33, which might imply better myocardial perfusion in the RV of ES patients.

IMAGING THE RIGHT VENTRICLE IN EISENMENGER SYNDROME

Despite the numerous advances in the field of multimodality imaging in the last decade, transthoracic echocardiography (TTE) remains the cornerstone in the non-invasive evaluation of RV function and hemodynamics in patients with ES.34

A comprehensive TTE examination should permit assessment of RV dimensions and mass, by means of standard diameters, RV free wall thickness and 3D-acquired volumes if the acoustic window permits adequate acquisitions; parameters of systolic function, such as tricuspid annular plane systolic excursion (TAPSE), tissue Doppler systolic velocity (S’), RV fractional area change (RVFAC), myocardial performance index (MPI), myocardial deformation imaging-derived parameters (RV free-wall strain) and 3D-RV ejection fraction (RVEF), depending on acoustics; the degree of valvular regurgitation and pulmonary hemodynamics.

Despite similar measured pulmonary pressures and vascular resistances, patients with ES tend to have more pronounced RV hypertrophy than those with iPAH and chronic thromboembolic PH, as evaluated by RV free-wall thickness.23

In the Eisenmenger population, RV dilatation tends to be milder (Figure 1), with no impact on survival; contrarily, RA dilation, as a measure of right pressure overload and possibly RV diastolic dysfunction, has demonstrated prognostic significance independently of the location of the shunt.35

While one large longitudinal cohort found mostly mild degrees of RV longitudinal dysfunction in ES patients, with a TAPSE <15 mm in only 23% of patients and an S’ <8 cm/s in 18% of patients,35 another echocardiographic comparative study showed no difference in longitudinal function between ES and other types of PH.36 Nevertheless, both TAPSE and S’ have demonstrated prognostic significance in this context.35,36

Although longitudinal function evaluated by deformation imaging appears to be similarly reduced in both ES and iPAH patients, the short-axis contractile function is preserved in comparison to other PAH eti-
Figure 1. Comparison of echocardiographic characteristics in Eisenmenger syndrome secondary to a non-restrictive ventricular septal defect (left column) versus idiopathic pulmonary arterial hypertension (right column) RV, right ventricle. 1A. Transthoracic echocardiography, apical 4-chamber view, 2D examination: adaptive RV hypertrophy with no dilation. 1B. Transthoracic echocardiography, apical 4-chamber view, 2D examination: maladaptive RV hypertrophy and significant dilation. 1C. Transthoracic echocardiography, short-axis view, M-mode examination: adaptive RV hypertrophy with no dilation. 1D. Transthoracic echocardiography, short-axis view, M-mode examination: maladaptive RV hypertrophy and significant dilation. 1E. Transthoracic echocardiography, apical RV-focused view, M-mode examination: normal RV longitudinal function (TAPSE 20mm). 1F. Transthoracic echocardiography, apical RV-focused view, M-mode examination: normal RV longitudinal function (TAPSE 15mm). 1G. Transthoracic echocardiography, apical RV-focused view, TDI: normal RV longitudinal function (S’VD 13 cm/s). 1H. Transthoracic echocardiography, apical RV-focused view, TDI: RV longitudinal dysfunction (S’VD 9.5 cm/s). 1I. Transthoracic 2D speckle-tracking echocardiography, apical RV-focused view: mildly reduced RV systolic function (6-segments longitudinal strain -18.7%). 1J. Transthoracic 2D speckle-tracking echocardiography, apical RV-focused view: severe RV systolic dysfunction (6-segments longitudinal strain -8.2%).
ologies\(^{37}\). This could be explained by the already described preservation of the “fetal” phenotype of the RV. Morphologic analysis has described the presence of a third, middle layer of cardiomyocytes in the RV of tetralogy of Fallot patients, with a circumferential orientation\(^{38}\). Therefore, in addition to reduction in radial wall stress secondary to hypertrophy, a supplementary circumferential myocardial layer might contribute to the preservation of short-axis function in the RV of ES patients\(^{37}\). Contrarily, significant reduction in both long-axis and short-axis systolic function has been described in PAH patients in an earlier CMR study\(^{39}\).

In accordance with the hypothesis of “adaptive remodelling”, when compared to other types of PH, the RV of patients with ES demonstrates better performance as assessed by RV fractional area change (RVFAC)\(^{23}\) and myocardial performance index (MPI)\(^{37}\), both of which classically represent more global measures of LV systolic function and combine longitudinal and transverse function evaluation, but also better RV free-wall strain\(^{23}\) (Figure 1). What is more, RV strain seems to be reduced globally in the Eisenmenger group, whereas PAH patients present relatively preserved strain at the level of the interventricular septum (IVS) in comparison to the RV free wall\(^{37}\). This observation might be interpreted in light of the particular type of right ventricular remodeling in ES, which begins early enough after birth so that the IVS becomes assimilated as an integral part of the RV\(^9\).

It has become obvious in recent years that hemodynamic evaluation in PH should analyze not only RV function, pulmonary pressures and vascular resistances, but the cardiopulmonary system as a unit, and that an essential concept in this respect being ventriculo-arterial coupling\(^{34}\). The better performance of the RV in ES is due to its ability to uphold satisfactory coupling in the presence of increased afterload for longer periods of time compared to other PAH etiologies\(^{40}\).

ES patients have not only better RV function but also less impaired pulmonary artery (PA) stiffness than patients with other types of PH and similar PVR\(^{41}\). Moreover, it has been shown that pulmonary artery compliance, a measure of the elastic properties of the pulmonary vasculature, is inversely related to PVR in CHD-associated PAH and is able to predict mortality in these patients\(^{42}\).

Accurate assessment of the RV through TTE is often problematic, given its tridimensional anatomy, retrosternal position, preload dependency and complex contraction mechanics\(^{43}\). The obvious advantages of CMR in this setting have helped elevate the investigation to „gold-standard” technique in the evaluation of the RV volumes, systolic function, tissue properties in CHD, given its high reproducibility and lack of anatomical assumptions\(^{34}\).

Similarly, to iPAH, RV ejection fraction, as a measure of global systolic function, has been shown to predict mortality in ES. Interestingly, the same study demonstrated prognostic significance of biventricular function\(^{44}\), a finding unique to this group of patients and highlighting the importance of ventricular interdependency in the course of the disease. In addition, late gadolinium enhancement (LGE) imaging detected fibrosis in both the RV and the LV of Eisenmenger patients, though it did not correlate to clinical outcome\(^{45}\).

A comparative study found significant differences between ES subsets of patients according to the location of the defect: compared to patients with post-tricuspid defects, those with pre-tricuspid shunts had higher RV and RA volumes, lower RVEF and worse ventriculo-arterial coupling (lower SV/ESV)\(^{46}\), which correlates with the overall agreement that the prognosis in this group is comparatively worse.

However, higher costs, lack of validation of protocols concerning evaluation of PAP and still limited worldwide availability reinforce the importance of echocardiographic parameters\(^2\).

Cardiac catheterization remains mandatory for the definite diagnosis of PAH. In addition to accurate hemodynamic assessment and shunt quantification, it allows for an indirect evaluation of preload by means of right atrial pressure, while PAP and PVR reflect afterload, and SV reflects contractility\(^{34}\). In the setting of CHD, the Fick method is standard to measure cardiac output (CO) because of the potential inaccuracies of thermodilution. RHC in ES patients demonstrated better CO than iPAH or CTEPH, despite similar levels of PAP\(^{43}\), while PVRi, aortic oxygen saturation, RAP, PA oxygen saturation, and SVC oxygen saturation predicted adverse outcomes\(^{47}\).

**PREDICTORS OF OUTCOME**

Despite modern era treatment strategies, mortality remains high in patients with ES when compared to the general population\(^{77}\). A large multicentre study published in 2017 reported a shift in why these patients die over the last 40 years: possibly due to better referral to tertiary centers and therefore prevention of high-risk situations (elective surgery, pregnancy) and effective management of complications, such as bron-
chial vessel embolization, the incidence of death by hemoptysis, thromboembolism and peri-procedural complications has significantly decreased; therefore, Eisenmenger patients tend to live long enough to die from heart failure or cancer10,18.

Alongside age, presence of sinus rhythm, oxygen saturation at rest16, RA pressure11 and BNP levels35, multiple echocardiographic parameters have demonstrated prognostic significance in ES35,38. Despite better overall RV longitudinal function in Eisenmenger patients, even mildly impaired TAPSE had an impact on prognosis. Duration of tricuspid regurgitation, a surrogate measure of reduced adaptation to pressure overload and compromised RV function, has also demonstrated an impact on outcome35.

As discussed above, RA area has shown prognostic value and also reflects a predisposition towards arrhythmia, a known predictor of hemodynamic imbalance and sudden cardiac death in these patients35.

A composite score comprising TAPSE, RA area, ratio of RA to left atrium (LA) area and ratio of RV effective systolic to diastolic duration has been proposed as a predictor of mortality in ES, suggesting a threefold increase in all-cause risk of death35.

LV eccentricity index has not shown prognostic value35, in correlation with the assumption that the ventricular interdependency in ES secondary to post-tricuspid shunts is less harmful than in PAH. Pericardial effusion has been consistently associated with worse prognosis, although the reason for its incidence and high prognostic significance are unclear35,48.

In the absence of standardized evaluation protocols in ES, more studies are needed with respect to prognostic significance of imaging parameters, so they may be integrated in the routine evaluation of these patients.

**DOES LOCATION OF THE DEFECT MATTER?**

An important aspect worth noting is that most of the concepts described above apply to patients who develop ES secondary to post-tricuspid shunts25. Those born with defects proximal to the tricuspid valve (i.e. ostium secundum and ostium primum atrial septal defects, sinus venosus defects) do go through the phase of decreased pulmonary pressures and vascular impedance, therefore losing the advantage of „priming” in the RV9. Moreover, due to the intact interventricular septum, the less detrimental type of ventricular interdependency is also lost2. When they do develop pulmonary hypertension, it occurs in adult age and generally leads to more rapid dilation and deterioration of the RV function (Figure 2) and worse outcomes than in the case of post-tricuspid defects. Nonetheless, their survival appears to be somewhat better than in patients with iPAH, possibly due to the presence of the open interatrial communication which permits the decompression of the pulmonary circulation and preservation of LV filling and thus cardiac output15.

There is still speculation concerning the mechanism by which PAH develops in patients with isolated pre-tricuspid defects2; it has been argued that volume overload to the pulmonary circulation caused by the initial left-to-right shunt leads to the development of plexogenic pulmonary arterial disease as result of a genetic predisposition49.

Greater degrees of RV dilatation and systolic dysfunction49 have been described in pre-tricuspid shunts; higher RA pressures are indicative of worse diastolic function. In addition, the ventricular interdependency is more reminiscent of that seen in iPAH, a conclusion drawn based on a higher eccentricity index. Better RV transverse free-wall strain26, RVFAC23 and higher BNP49 have been described in patients with ES secondary to pre-tricuspid shunting in echocardiographic studies.

Concerning differences between different types of post-tricuspid shunts, it has been shown that RV function tends to be superior in patients with complete atrioventricular septal defects (AVSDs) in comparison to those with VSDs. An explanation for this might be that AVSD patients develop PAH earlier in infancy, and they also have an additional atrial defect that augments diastolic offloading of the RV49.

In the case of shunting at the aorto-pulmonary level, RVFAC was lower but longer pulmonary acceleration time at the level of the right ventricular outflow tract (RVOT), which might be indicative of lower elastance and better right ventriculo-arterial coupling in protosystole, as a result of the shunting from the pulmonary artery to the descending aorta through the PDA49.

**CONCLUSION**

Although still burdened with significant morbidity and mortality, patients with Eisenmenger Syndrome tend to fare better than those with other types of PAH, most notably iPAH and PAH associated with connective tissue disease. Especially in the case of post-tricuspid shunts, the RV seems to present remarkable
Figure 2. Comparison of echocardiographic characteristics in Eisenmenger syndrome secondary to a non-restrictive ventricular septal defect (left column) vs. non-restrictive atrial septal defect (right column) RV, right ventricle. A. Transthoracic echocardiography, apical RV-focused view, 2D examination: adaptive RV hypertrophy with no dilation. B. Transthoracic echocardiography, apical RV-focused view, 2D examination: maladaptive RV hypertrophy and significant dilation. C. Transthoracic echocardiography, short-axis view, M-mode examination: adaptive RV hypertrophy with no dilation. D. Transthoracic echocardiography, short-axis view, M-mode examination: maladaptive RV hypertrophy and significant dilation. E. Transthoracic echocardiography, apical RV-focused view, M-mode examination: normal RV longitudinal function (TAPSE 21mm). F. Transthoracic echocardiography, apical RV-focused view, M-mode examination: mild RV longitudinal dysfunction (TAPSE 17mm). G. Transthoracic echocardiography, apical RV-focused view, TDI: normal RV longitudinal function (S’VD 12.6 cm/s). H. Transthoracic echocardiography, apical RV-focused view, TDI: mild RV longitudinal dysfunction (S’VD 10.4 cm/s). I. Transthoracic 2D speckle-tracking echocardiography, apical RV-focused view: mildly reduced RV systolic function (6-segments longitudinal strain -18%). J. Transthoracic 2D speckle-tracking echocardiography, apical RV-focused view: severe RV systolic dysfunction (6-segments longitudinal strain -5.9%)
resilience against dysfunction and failure due to the preservation of a "fetal" phenotype, less detrimental ventricular interdependency and the presence of the defect itself acting as a decompression valve for the overloaded pulmonary circulation.

Future studies might address possible therapeutic strategies, such as the manipulation of molecular targets that induce the "priming" of the RV, possible use of angiogenesis stimulation agents to enhance microcirculation in a hypertrophied RV and whether agents that tackle RV fibrosis might mitigate the risk of right heart failure, all of them having as the definite goal an increased survival in ES patients.

Compliance with ethics requirements:
The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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