REVIEW

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

Alecsandra HERNIC[1,2], Roxana ENACHE[2,3], Daniela-Noela RADU[2,3], Ioan M. COMAN[2,3], Carmen GINGHINĂ[2,3]

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 noțiunea 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 lifetimes[1], although improved awareness and early surgical/percutaneous interventions are most likely leading to a decline in its incidence in Western countries[2].

Eisenmenger Syndrome (ES) lies at the extreme end of the PAH-CHD spectrum[3,4] 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 cyanosis[5]. Chronic hypoxemia inevitably affects all the other organs, the result being a truly multi-system disease, as ES has traditionally been described[4].

[1] Clinicco Hospital, Brasov, Romania
[2] „Carol Davila" Universisty of Medicine and Pharmacy, Bucharest, Romania
[3] „Prof. Dr. C. C. Iliescu" Emergency Institute of Cardiovascular Diseases, Bucharest, Romania

Contact address:
Roxana ENACHE, Department of Cardiology, „Prof. Dr. C. C. Iliescu" Emergency Institute of Cardiovascular Diseases, 258 Street, Bucharest, Romania.
E-mail: roxenache@gmail.com

In most cases, ES occurs secondary to defects located distally to the tricuspid valve (so-called post-tricuspid defects), such as ventricular septal defects (VSDs), patent ductus arteriosus (PDA), aortopulmonary widow. It has also been described in complex forms of CHD without significant pulmonary outflow tract obstruction and non-restrictive extracardiac aorto-pulmonary connections, including palliative systemic-to-pulmonary shunts such as the Waterston and Potts shunts[3,4,6].

Pre-tricuspid defects include all forms of atrial septal defects and represent a particular group in the Eisenmenger population. These patients develop PAH later in life, have similarities to idiopathic PAH (iPAH) and generally carry poorer outcomes[3,4,6].

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

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[7,8] in these patients, although further studies concerning more specific outcomes and survival benefit are still warranted[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[9], patients with ES seem to have better outcomes than other PAH categories, especially when compared with

Table 1. Diagnostic work-up in Eisenmenger Syndrome (adapted from [4])

Clinical evaluation	Symptoms Shortness of breath at rest/on exertion Limited exercise capacity Palpitations Haemoptysis Angina Headache Dizziness Syncope/presyncope	Physical examination Weight Resting SpO2% Blood pressure Cyanosis Digital clubbing Heart rate, arrhythmia Systemic congestion: oedema, jugular vein distension, hepatomegaly
ECG	Presence of sinus rhythm Heart rate Supraventricular/ventricular arrhythmias Conduction abnormalities (right bundle branch block/atrioventricular block) RV/biventricular hypertrophy	Holter monitoring may be considered in case of syncope, palpitations, baseline ECG abnormalities
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 Dilation 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)

Non-invasive imaging	CT (specific indications)	Pulmonary artery diameters/calcification Pulmonary artery in situ thrombosis Compression of left main stem in case of pulmonary artery aneurysm Source of haemoptysis
Exercise testing	6MWD	Systematic at baseline and follow-up visits
	Cardiopulmonary exercise testing	Exercice capacity VO2 max %
Cardiac catheterization	Confirmation of diagnosis and haemodynamic assessment– right atrial pressure, sPAP, mPAP, dPAP, capillary wedge pressure, pulmonary vascular resistances cardiac output, SVO2 %, pulmonary-to-systemic flow ratio	Differential diagnosis: ES, PAH with left-to-right shunt, iPAH, segmental PH
Biomarkers	Full blood count Renal function Hepatic tests Coagulation panel NT-proBNP Uric acid CRP Serum iron, ferritin, total iron binding capacity, transferrin saturation coefficient Folic acid, vitamin B12	

CMR, cardiac magnetic resonance; CRP, C-reactive protein; CT, computed tomography; dPAP, diastolic pulmonary artery pressure; ECG, electrocardiogram; ES, Eisenmenger syndrome; iPAH, idiopathic pulmonary arterial hypertension; LGE, late gadolinium enhancement; LV, left ventricle; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; RA, right atrium; RV, right ventricle; RVEDP, right ventricle end-diastolic pressure; RVEF, right ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; SVO2%, mixed venous oxygen saturation; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography; VO2 max%, maximal oxygen consumption; 6MWD, 6-minute walking distance.

iPAH and PAH associated with connective tissue disease[2,9,10-15].

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[12], the right ventricle (RV) of Eisenmenger patients demonstrates significant resilience and resistance to failure[9] 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[16,17]. In contrast, the RV of Eisenmenger patients can withstand elevated afterload for decades, while reacting with significant hypertrophy but no failure[18].

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[15,19].

It has been postulated that the explanation partly lies in the preservation of a fetal phenotype of the RV[9], 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[20,21]. In the fetus, PAP and RV pressures are equal to the systemic ones across the cardiac cycle[22], 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[9], therefore preventing an evolution towards early right heart failure[2]. This would also explain the worse prognosis of patients who develop ES because of pre-tricuspid shunts, event which occurs in adulthood, after decades of the RV being "deconditioned" due to the decrease in pulmonary vascular impedance[9,23].

However, the exact role of this described mechanism is still to be completely deciphered, as it does

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 ventricle (LV) restricted filling, as seen in other forms of PAH[2,21]. Moreover, a linear correlation between both mass and systolic function of left and right ventricles has consistently been described in ES[9,21,24-26].

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 hypertrophy[23,28], 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 dysfunction[21], 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 capacity[29-31] 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 PAH[33], 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 dilation 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[23]. 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-

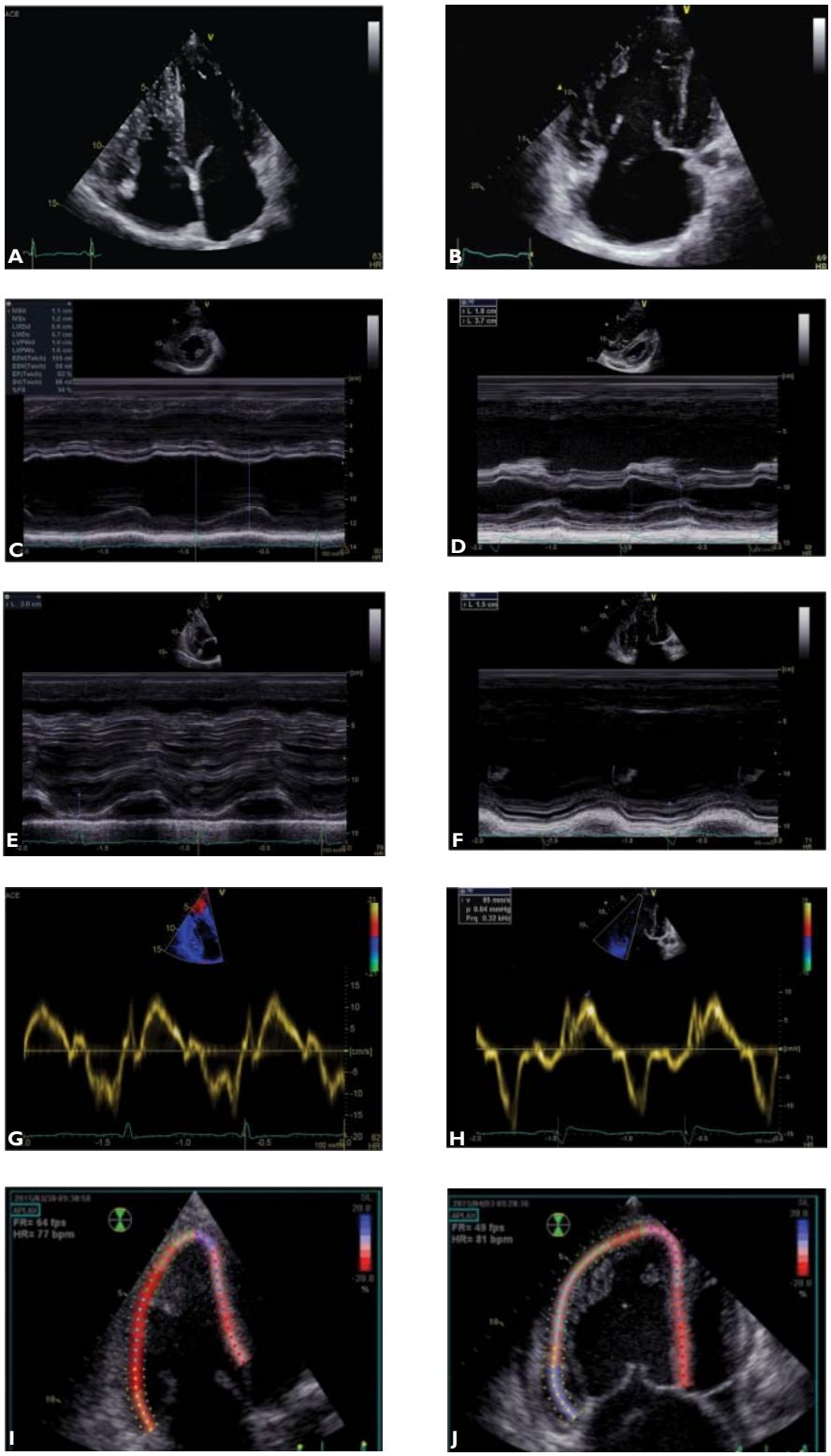

Figure 1. Comparison of echocardiographic characteristics in Eisenmenger syndrome secondary to a non-restrictive ventricular septal defect (left column) versus idiopathic pulmonary arterial hypertension (right column) RV, right ventricle. 1A. Transthoracic echocardiography, apical 4-chamber view, 2D 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: RV longitudinal dysfunction (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 EV 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[23], 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[47]. 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 cancer[10,18].

Alongside age, presence of sinus rhythm, oxygen saturation at rest[47], RA pressure[11] and BNP levels[35], multiple echocardiographic parameters have demonstrated prognostic significance in ES[35,38]. 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 outcome[35].

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 patients[35].

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 death[35].

LV eccentricity index has not shown prognostic value[35], 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 unclear[35,48].

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 shunts[2,9]. 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 RV[9]. Moreover, due to the intact interventricular septum, the less detrimental type of ventricular interdependency is also lost[2]. 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 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 output[15].

There is still speculation concerning the mechanism by which PAH develops in patients with isolated pre-tricuspid defects[2]; 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 predisposition[49].

Greater degrees of RV dilatation and systolic dysfunction[49] 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 strain[26], RVFAC[23] and higher BNP[49] 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 RV[49].

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 PDA[49].

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

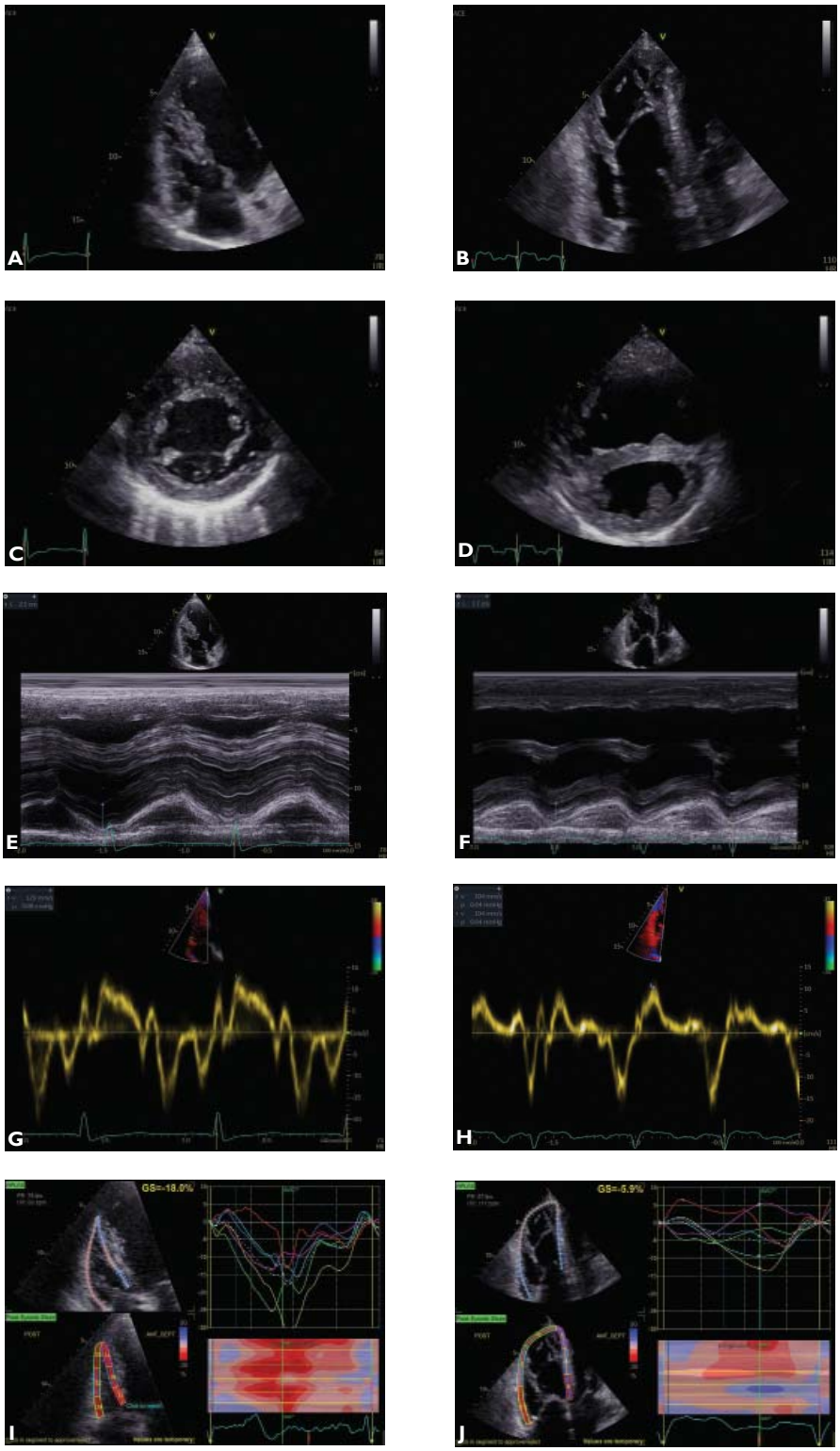

Figure 2. Comparison of echocardiographic characteristics in Eisenmenger syndrome secondary to a non-restrictive ventricular septal defect (left column) vs. non-restrictive atrial septal defect (right column) RV, right ventricle. 1A. Transthoracic echocardiography, apical RV-focused view, 2D examination: adaptive RV hypertrophy with no dilation. 1B. Transthoracic echocardiography, apical RV-focused 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 21mm). 1F. Transthoracic echocardiography, apical RV-focused view, M-mode examination: mild RV longitudinal dysfunction (TAPSE 17mm). 1G. Transthoracic echocardiography, apical RV-focused view, TDI: normal RV longitudinal function (S'VD 12.6 cm/s). 1H. Transthoracic echocardiography, apical RV-focused view, TDI: mild RV longitudinal dysfunction (S'VD 10.4 cm/s). 1I. Transthoracic 2D speckle-tracking echocardiography, apical RV-focused view: mildly reduced RV systolic function (6-segments longitudinal strain -18%). 1J. 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.

References

1. Duffels MGJ, Engelfriet PM, Berger RMF et al. Pulmonary arterial hypertension in congenital heart disease: An epidemiologic perspective from a Dutch registry. International Journal of Cardiology 2007;120:198–204.
2. Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. Circulation 2007;115:1039–1050.
3. Favoccia C, Constantine AH, Wort SJ et al. Eisenmenger syndrome and other types of pulmonary arterial hypertension related to adult congenital heart disease. Expert Review of Cardiovascular Therapy 2019;17:449–459.
4. Arvanitaki A, Giannakoulas G, Baumgartner H et al. Eisenmenger syndrome: diagnosis, prognosis and clinical management. Heart 2020;106:1638-1645.
5. Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease; a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation 1958;18:533-547.
6. Chaix MA, Gatzoulis MA, Diller GP et al. Eisenmenger Syndrome: A multisystem disorder Do not destabilize the balanced, but fragile physiology. Canadian Journal of Cardiology 2019;35:1664-1674.
7. Dimopoulos K, Inuzuka R, Goletto S et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 2010;121:20–5.
8. Arnott C, Strange G, Bullock A et al. Pulmonary vasodilator therapy is associated with greater survival in Eisenmenger syndrome. Heart 2017;0:1–7.
9. Hopkins WE. The remarkable right ventricle of patients with Eisenmenger syndrome. Coron Artery Dis 2005;16:19-25.
10. Hjortshøj CMS, Kempny A, Jensen AS et al. Past and current cause- specific mortality in Eisenmenger syndrome. Eur Heart J 2017;38:2060–7.
11. Barst RJ, Ivy DD, Foreman AJ et al. Four- and seven- year outcomes of patients with congenital heart disease- associated pulmonary arterial hypertension (from the REVEAL registry). Am J Cardiol 2014;113:147–55.
12. Arnott, C, Boehm C, Lau E et al. Survival outcomes in severe congenital versus non-congenital pulmonary hypertension. Heart Asia 2016;8:3–7.
13. Saha A, Balakrishnan KG, Jaiswal PK et al. Prognosis for patients with Eisenmenger syndrome of various aetiology. Int J Cardiol 1994; 45: 199–207.
14. Niwa K, Perloff JK, Kaplan S et al. Eisenmenger syndrome in adults: ventricular septal defect, truncus arteriosus, univentricular heart. J Am Coll Cardiol 1999;34:223–232.
15. Hopkins WE, Ochoa LL, Richardson GW et al. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. J Heart Lung Transplant 1996;15:100–105.
16. Hopkins WE. Heart disease caused by lung disease. Medical management of pulmonary diseases,1999; 581–593.
17. Rich S. Pulmonary hypertension. In: Braunwald Heart disease. A textbook of cardiovascular medicine (Sixth Edition) 2001;1908–1935.
18. Celermajer DS. Eisenmenger syndrome: a rare malady that continues to fascinate. Eur Heart J 2017;0:1–2
19. Benza RL, Miller DP, Gomberg-Maitland M et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164–172.
20. Kaemmerer H, Mebus S, Schulze-Neick I et al. The adult patient with Eisenmenger syndrome: a medical update after Dana Point part I: epidemiology, clinical aspects and diagnostic options. Curr Cardiol Rev 2010;6:343–355.
21. Gomez-Arroyo J, Santos-Martinez LE, Beltran M et al. Differences in Right Ventricular Remodeling Secondary to Pressure Overload in Patients with Pulmonary Hypertension. American Journal of Respiratory and Critical Care Medicine 2014;5:603-606.
22. Rudolph AM. The changes in the circulation after birth. Their importance in congenital heart disease. Circulation 1970;41:343–359.
23. Giusca S, Popa E, Amzulescu MS et al. Is Right Ventricular Remodeling in Pulmonary Hypertension Dependent on Etiology? An Echocardiographic Study. Echocardiography 2015;33:546–554.
24. Hopkins WE, Waggoner AAD. Right and left ventricular area and function determined by two-dimensional echocardiography in adults with the Eisenmenger syndrome from a variety of congenital anomalies. Am J Cardiol 1993;72:90–94.
25. Hopkins WE, Waggoner AD. Severe pulmonary hypertension without right ventricular failure: the unique hearts of patients with Eisenmenger syndrome. Am J Cardiol 2002;89:34–38.
26. Moceri P, Iriart X, Bouvier P. Speckle-tracking imaging in patients with Eisenmenger syndrome. Archives of Cardiovascular Disease 2016;109:104-112.
27. Vonk-Noordegraaf A, Haddad F, Chin KM. Right Heart Adaptation to Pulmonary Arterial Hypertension. JACC 2013;62:D22-33.
28. Van der Bruggen CEE, Tedford RJ, Handoko L et al. RV pressure overload: from hypertrophy to failure. Cardiovascular Research 2017; 113:1423-1432.
29. White FC, Nakatani Y, Nimmo L et al. Compensatory angiogenesis during progressive right ventricular hypertrophy. Am J Cardiovasc Pathol 1992;4:51–68.
30. Murray PA, Vatner SF. Reduction of maximal coronary vasodilator capacity in conscious dogs with severe right ventricular hypertrophy. Circ Res 1981;48:25–33.
31. Botham MJ, Lemmer JH, Gerren RA et al. Coronary vasodilator reserve in young dogs with moderate right ventricular hypertrophy. Ann Thorac Surg 1984;38:101–107.
32. Claussen JV, Skrok J, Shehata ML et al. Right and left ventricular mypcardial perfusion reserve correlate with right ventricular function and pulmonary hemodynamics in patients with pulmonary arterial hypertension. Radiology 2011;258:119–127.
33. Gupta A, Patel C, Gupta SK. Myocardial perfusion abnormalities in Eisenmenger syndrome. Nuclear Medicine Communications 2020; 41:206–211.
34. Vonk Noordegraaf A, Haddad F, Bogaard HJ et al. Noninvasive Imaging in the Assessment of the Cardiopulmonary Vascular Unit. Circulation 2015;131:899-913.

35. Moceri P, Dimopoulos K, Liodakis E et al. Echocardiographic predictors of outcome in Eisenmenger syndrome. Circulation 2012; 126: 1461–1468.
36. Van de Bruaene A, De Meester P, Voigt JU et al. Right Ventricular Function in Patients With Eisenmenger Syndrome. Am J Cardiol 2012;109:1206 –1211.
37. Kalogeropoulos AP, Border WL, Georgiopoulou VV et al. Right ventricular function in adult patients with Eisenmenger physiology: Insights from quantitative echocardiography. Echocardiography 2010; 27:937–945.
38. Sanchez-Quintana D, Anderson RH, Ho SY. Ventricular myoarchitecture in tetralogy of Fallot. Heart 1996;76:280–286.
39. Fayad ZA, Ferrari VA, Kraitchman DL et al. Right ventricular regional function using MR tagging: Normals versus chronic pulmonary hypertension, Magn Reson Med 1998;39:116–123.
40. D'Alto M, Scognamiglio G, Dimopoulos K et al. Right heart and pulmonary vessels structure and function. Echocardiography 2015;1:S3–S10.
41. Enache R, Popa E, Badea R, et al. Assessment of pulmonary artery elastic properties in patients with Eisenmenger syndrome - a comparison to other types of pulmonary hypertension. Eur Heart J Cardiovasc Imaging 2017;18 (suppl 3): iii287.
42. Cheng XL, Liu ZH, Gu Q et al. Prognostic Value of Pulmonary Artery Compliance in Patients with Pulmonary Arterial Hypertension Associated with Adult Congenital Heart Disease. Int Heart J 2017; 58:731-738.
43. Abouzeid CM, Shah T, Johri A et al. Multimodality Imaging of the Right Ventricle. Curr Treat Options Cardiovasc Med 2017;19:82.
44. Jensen AS, Broberg CS, Rydman R et al. Impaired right, left, or biventricular function and resting oxygen saturation are associated with mortality in Eisenmenger syndrome: A clinical and cardiovascular magnetic resonance study. Circ Cardiovasc Imaging 2015;8(12): e003596.
45. Broberg CS, Prasad SK, Carr C et al. Myocardial fibrosis in Eisenmenger syndrome: A descriptive cohort study exploring associations of late gadolinium enhancement with clinical status and survival. J Cardiovasc Magn Reson 2014; 16:32.
46. Gong C, He S, Chen X et al. Diverse Right Ventricular Remodeling Evaluated by MRI and Prognosis in Eisenmenger Syndrome With Different Shunt Locations. J Magn Reson Imaging. 2021;10:1002
47. Hascoët S, Baruteau AE, Humbert M et al. Long-term outcomes of pulmonary arterial hypertension under specific drug therapy in Eisenmenger syndrome. J Heart Lung Transplant. 2017;36(4):386-398.
48. Kempny A, Sørensen Hjortshøj C, Gu H et al. Predictors of Death in Contemporary Adult Patients With Eisenmenger Syndrome A Multicenter Study, Circulation. 2017;135:1432–1440.
49. Moceri P, Kempny A, Liodakis E et al. Physiological differences between various types of Eisenmenger syndrome and relation to outcome. Int J Cardiol 2015;179:455-460.