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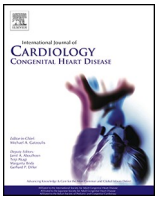

Update on Eisenmenger syndrome – Review of pathophysiology and recent progress in risk assessment and management

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ABSTRACT

Longstanding left-to-right shunting associated with congenital heart disease (CHD) can ultimately lead to pulmonary vascular remodeling, pulmonary arterial hypertension, and shunt reversal, the hallmark feature of Eisenmenger Syndrome (ES). ES is a multisystem disease, with hematologic, cardiovascular, renal, neurologic, immune, and other manifestations, each of which inform its management. Many of the most distinct and clinically important consequences relate to chronic hypoxemia. The incidence of ES in in countries with access to pediatric cardiology and cardiac surgery services has declined in recent decades, due to earlier diagnosis and intervention for CHD. Moreover, in the era of disease targeting therapies (DTT), ES appears to be associated with better quality of life and less limiting symptoms. In addition, observational studies suggest that these therapies, alone and in combination, may be associated with improved survival. Despite these developments, ES mortality remains high, with heart failure being the most common cause of death. In this review, we discuss the pathophysiology of ES, the evolving understanding of risk stratification, as well as recent progress in pharmacologic and surgical management. Ultimately, despite strides in understanding and management of this complex disease, significant knowledge gaps remain.

1. Introduction

Eisenmenger syndrome (ES) is defined as pulmonary hypertension due to a high pulmonary vascular resistance with reversed or bidirectional shunt [1]. It develops in the presence of a non-restrictive communication at the aortopulmonary, ventricular, or atrial level. The biological mechanisms are not fully understood, but a leading hypothesis is that increased shear stress on the pulmonary endothelium triggers pulmonary vascular remodeling, eventually resulting in irreversible pulmonary vascular disease (Fig. 1) [2].

With earlier diagnosis and treatment for congenital heart disease, the incidence of ES in high resource environments has decreased markedly, from 17.5 % as first described by Dr. Paul Wood in 1958 [1], to between 1 and 5.7 % in more contemporary registries [3,4]. However, a similar trend may not be seen in patients from regions with less robust access to medical resources [5]. Comprehensive reviews of ES have been published within the past several years [2,6]. In this update, we review the latest progress in understanding the pathophysiology, natural history, and management of ES.

2. Pathophysiology and clinical manifestations

2.1. Hypoxemia

Chronic hypoxemia is a cardinal manifestation of ES, a consequence of right-to-left or bidirectional shunt as well as impaired pulmonary diffusion in the context of pulmonary vascular remodeling. Physiologic sequelae and comorbidities of ES related to the consequences of hypoxemia are summarized in Fig. 2.

2.2. Secondary erythrocytosis, iron deficiency, and hyperviscosity syndrome

In response to chronic hypoxemia, there is increased erythropoietin release in the kidneys, which stimulates red blood cell production in the bone marrow and increases circulating red blood cell mass and hemoglobin [7]. This physiologic response is proportional to the degree of hypoxia in iron-replete patients [8], such that more severe hypoxemia results in higher circulating hemoglobin in an effort to maintain

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adequate oxygen delivery to peripheral tissues. In iron deficient patients however, this response is blunted due to decreased hemoglobin production, and hemoglobin level is inappropriately low although it may still be in the 'normal' range for an acyanotic patient. As such, monitoring and adequate repletion of iron stores is an important aspect of management in ES patients, as iron deficiency is a risk factor for poor prognosis [9]. IV iron repletion is safe in cyanotic patients with appropriate safety measures to avoid air emboli [10].

Markedly increased red blood cell mass has historically raised concern for hyper-viscosity syndrome, a phenomenon which can be manifested by neurological symptoms, mucosal bleeding, and myocardial ischemia [11,12]. While this does occur in the context of cyanosis and secondary erythrocytosis, there is a tenuous correlation between hematocrit and viscosity, iron deficiency, or a patient's severity or frequency of symptoms [12]. The symptoms are non-specific and are often due to other causes, and clinicians should maintain a high index of suspicion for clinical mimics. This is particularly true since the main treatments for hyper-viscosity syndrome, phlebotomy, or apheresis, may be harmful. Iron deficiency, dehydration, thyroid dysfunction, pheochromocytoma or paraganglioma, and cerebral abscesses are all more common with ES than in the general population and all can mimic the symptoms of hyper-viscosity [7]. Therapeutic phlebotomy (drawn in small volumes with equal volume fluid replacement to avoid hemodynamic embarrassment) or red cell apheresis should only be reserved for patients with hemoglobin >22 g/dL (or hematocrit >65 %), definitive hyper-viscosity symptoms, who have been adequately volume resuscitated and no other reversible causes have been found [6,12].

2.3. Renal disease

Chronic kidney disease is prevalent in ES. Individuals with chronic hypoxemia and secondary erythrocytosis are at risk for lower glomerular filtration rate (GFR) and proteinuria [13]. One study reported proteinuria in upwards of 30 % of cyanotic patients, serum creatinine is elevated compared to acyanotic peers [14]. A larger cohort study found that patients with cyanotic congenital heart disease had a significantly lower GFR than patients with non-cyanotic congenital heart disease, which was associated with a poorer outcome [15]. Of note, estimated GFR calculated from cystatin C better predicts all-cause mortality and non-elective cardiovascular hospitalization in adults with congenital heart disease, compared to creatinine-based GFR estimation [16]. Albuminuria is also highly prevalent with ES and other cyanotic CHD, with a prevalence upwards of 60 % [13]. The clinical implications and management of chronic albuminuria in this context remain undefined, though in the absence of contraindications, it seems reasonable to consider standard therapies such as angiotensin-converting enzyme inhibitors.

2.4. Coagulopathy

Cyanotic heart disease causes derangements in platelet function and coagulation pathways, predisposing to both bleeding and thrombosis [17]. A recent retrospective cohort study of 1546 patients examining cause-specific mortality in ES found that thromboembolism accounted for 8.3 % (4th most common), and hemorrhage accounted for 7.3 % (5th most common) of known deaths [18]. Pulmonary artery thrombus may be found in up to 20 % of patients, and is associated with right or left ventricular dysfunction and larger caliber pulmonary arteries with lower velocity blood flow [19]. Cerebral thrombosis is also of concern; one study found a 47 % incidence of MRI-detected evidence of prior cerebral infarctions in patients with cyanotic congenital heart disease (70 % of whom had ES), though only 21 % had a history of a clinically diagnosed stroke. In this same study, 38 % of patients had imaging evidence of pulmonary thrombus, though 75 % of these patients had no prior known medical history of such [20]. This suggests that a significant portion of cerebral and pulmonary thrombosis in ES may be subclinical, though as patients with ES have the lowest baseline functional capacity across a large spectrum of congenital heart disease [21], incremental clinical changes brought on by thrombotic disease may be difficult to identify. Interestingly, despite the platelet and coagulation pathway derangements associated with cyanotic disease described earlier, in the two studies above, the incidence of pulmonary or cerebral thrombosis was not associated with differences in coagulation factors, platelet function, or degree of erythrocytosis [19,20].

The routine use of anticoagulation (i.e. in the absence of known thrombus or strong risk factor for thromboembolism such as atrial arrhythmias) is not recommended given competing thrombotic and hemorrhagic risks [22], and there does not appear to be an impact of anticoagulation on long-term survival [23,24]. The role of routine screening for and treatment of subclinical thrombosis in ES remains unclear.

2.5. Premature mortality

Historically, patients with ES have been found to have 70–80 % survival at 10 years, and 42 % at 25 years [25,26]. However, natural history studies in this population are affected by selection bias, including immortal time and referral bias [27], as well as confounding by inclusion of non-ES pulmonary arterial hypertension (PAH) patients in the cohort studies [26]. Once these biases were accounted for, 10-year survival for contemporary patients with ES was 57 % in the overall cohort and 34 % in patients naïve to disease targeting therapy (DTT) [24]. Overall, median survival is reduced by ~20 years in Eisenmenger patients compared to healthy controls, with worse outcomes in lesions of higher complexity [8]. As such, though the use of DTTs has improved outcomes, mortality in ES remains high.

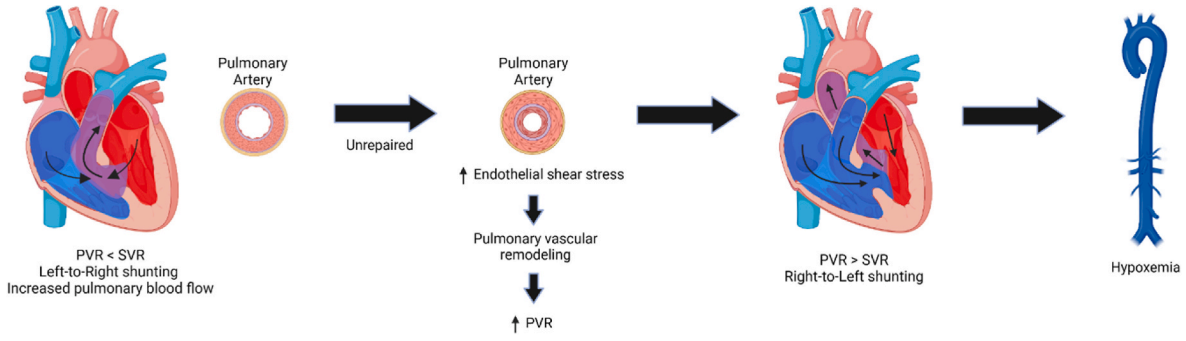

Fig. 1. Developmental pathophysiology of Eisenmenger Syndrome. Long-standing unrepaired left-to-right shunt (represented by ventricular septal defect in this figure) increases pulmonary blood flow and causes shear stress on the pulmonary vascular endothelium. Over time, this leads to an irreversible elevation in pulmonary vascular resistance resulting in a right-to-left or bidirectional shunt and systemic hypoxemia. PVR - pulmonary vascular resistance. SVR - systemic vascular resistance. Created with BioRender.com.

The current era of ES has the benefit of numerous DTTs. Despite this, in contemporary series, the most common cause of mortality remains right heart failure, unchanged from the pre-DTT era [18,26]. Notably, hemoptysis and iatrogenic causes were more common causes of mortality in the pre-DTT era. Since that time, hemoptysis has decreased significantly as the cause of death, from 3rd most common to 5th most common [18].

Although long-term prognosis in ES continues to be sub-optimal, adult patients with ES appear to have better survival than adults with idiopathic pulmonary arterial hypertension, as well as more favorable hemodynamics [28]. Their improved survival and hemodynamics may be attributed to persistent right-to-left shunting that allows relief of pressure overload on the right ventricle, which helps preserve systemic perfusion at the expense of systemic desaturation. It is important to note that survivorship bias may impact the apparent better survival in ES as well, as a registry analysis that included patients diagnosed as children suggests that survival between ES and non-ES PAH populations are similar [29]. Furthermore, the comparison that showed better survival in ES compared to non-ES PAH was based on an earlier era of pulmonary hypertension management, before upfront combination therapy for newly diagnosed patients and care consolidation at PAH treatment centers was more commonplace. Upfront triple therapy including parenteral prostacyclin may improve mortality in non-ES PAH patients [30,31], and reduces time to clinical worsening [32,33] though whether or not this has led to a definite survival benefit in the modern era is unclear, as results from various registry studies are conflicting in this regard [32,34,35]. Regardless, as there have been significant advancements in management of both ES and non-ES PAH, a comparison study of these two populations in the modern era is needed.

3. Risk assessment

Risk stratification in this population is not straightforward, as tools derived for use in non-ES PAH are not well suited to ES, given distinct risks, comorbidities, and sequelae (e.g., those related to hypoxemia). Numerous clinical, laboratory, and imaging variables have been independently examined in observational studies as predictors of outcomes in ES. The derivation and, in some cases, validation of specific risk models are described below, but with this uncommon disease we are intrinsically limited in our ability to compare the independent value of specific variables by sample size and inconsistency of data collection across centers. Further, there is often substantial overlap in the pathophysiology underlying these biomarkers, without reason to think that one set of markers is likely to predict outcomes substantially better than all others. Finally, thoughtful consideration should be given in each case to potentially dominant patient-specific factors that may not play into population-level risk estimates (e.g., advanced chronic kidney disease, dementia).

Clinically, the development of right heart failure and higher NYHA functional class is correlated with poor outcomes in ES patients [8,9], corroborated by a similar association seen with higher BNP [36] and NTproBNP [26] concentrations. As is the case in other populations, heart failure hospitalization appears to be a strong predictor of mortality for adults with congenital heart disease and pulmonary hypertension, an association that remains significant even after adjusting for age and NYHA class [37]. A deterioration of exercise capacity to 6MWD <300 meters, and a decrease in resting SpO_2 are incrementally related to adverse outcomes, independent of baseline variables including use of DTTs [9]. 1 min sit-to-stand test correlated well with 6MWD and WHO functional class in a single-center study of 40 patients with PAH-CHD, most of which had ES [38]. Another study found that breathing reserve <30 % predicted on cardiopulmonary exercise test (CPET) was associated with higher mortality in ES; of note, this study also included patients with non-ES, idiopathic PAH, for whom breathing reserve was not a prognostic marker [39].

Similar correlations are seen between imaging markers cardiac function and prognosis; echocardiographic measurements of right ventricular function and intracardiac filling pressures, including tricuspid annular plane systolic excursion <15 mm, ratio of right ventricular systolic to diastolic duration, RA area, and RA:LA ratios are all associated with mortality in ES patients [40]. Diffuse myocardial fibrosis as assessed by cardiac MRI measured extracellular volume (ECV) is also higher in ES patients compared to healthy controls, and greater fibrosis corresponds to maladaptive RV remodeling, increased RV afterload, and

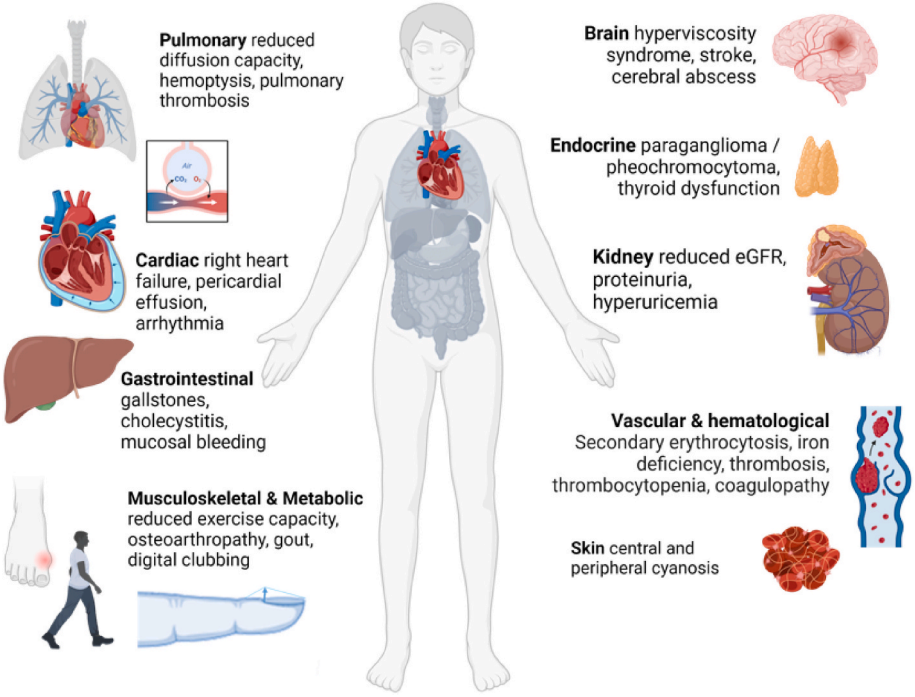

Fig. 2. Multisystem complications of Eisenmenger syndrome. While the primary pathophysiology relates to pulmonary vascular remodeling consequent to chronic left-to-right shunting, most clinical sequelae relate to chronic hypoxemia, which is caused largely by right-to-left shunting. Created with BioRender.com.

RV systolic dysfunction in ES, as well as with increased serum NT-proBNP levels [41]. In this study, an ECV threshold of 29 % performed well in identifying ES patients at > 10 % risk of mortality within the following year.

It has been challenging to definitively determine whether the location of the defect, pre-tricuspid (ASD) versus post-tricuspid (VSD/PDA), is associated with outcomes among adults with ES. A study of MRI characteristics of 54 patients with ES found that patients with pre-tricuspid shunts had significantly lower RV function and higher markers of adverse ventricular remodeling [42]. Pre-tricuspid defects that cause ES are associated with a poorer prognosis, despite having a shorter time since ES diagnosis compared to post-tricuspid defects [43]. This may be due to poor RV adaptation to increased pulmonary artery pressures later in life in the pre-tricuspid defect group, as opposed to RV remodeling earlier in life in patients with post-tricuspid defects. It is important to note, however, that survivorship bias likely plays a role in these findings, as pre-tricuspid shunts may remain silent and asymptomatic in childhood, whereas post-tricuspid shunts are more likely to

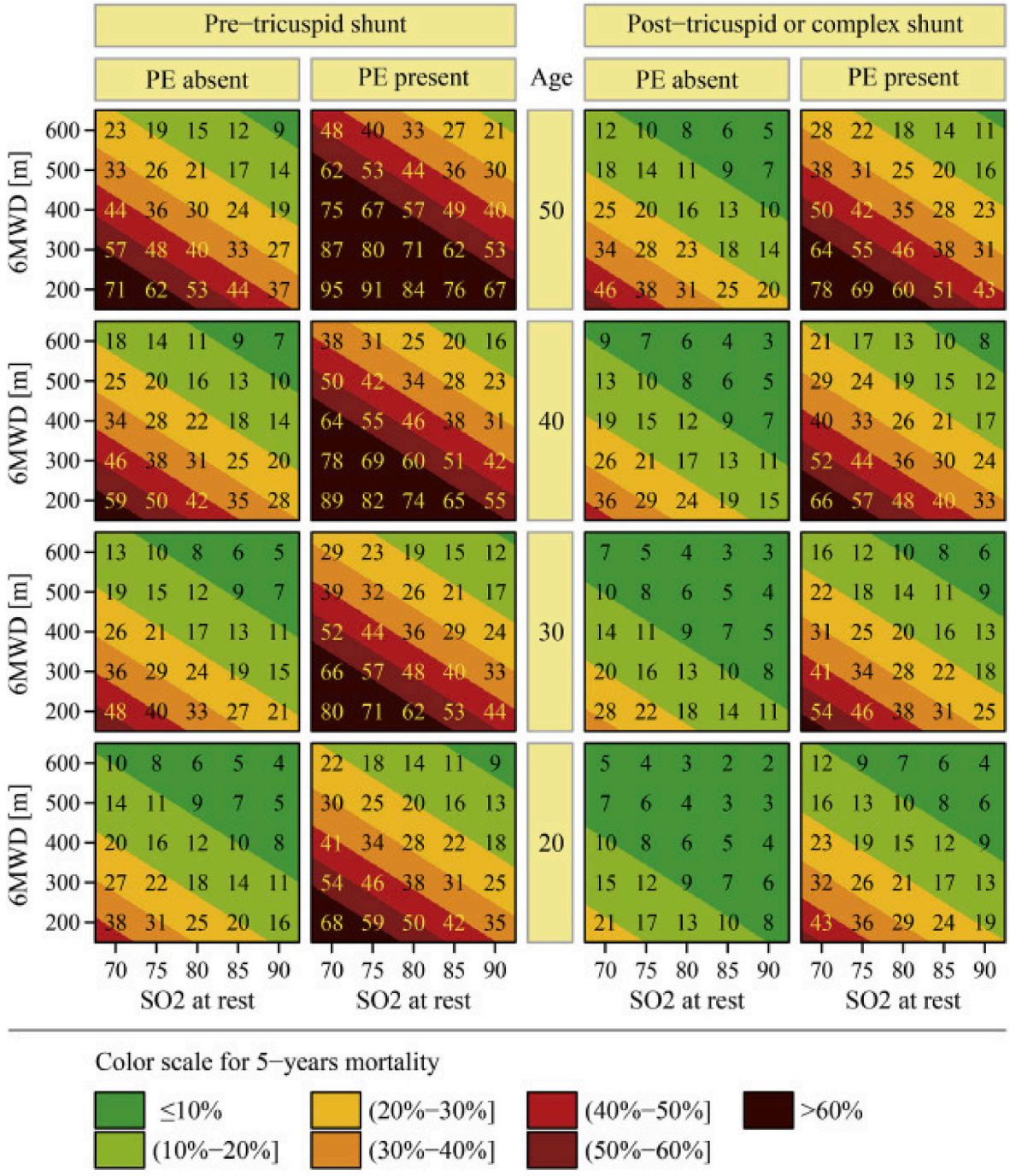

Fig. 3. Estimated 5-year mortality for individuals with Eisenmenger Syndrome, based on multivariable Cox regression model using age (in years), underlying shunt type, presence of pericardial effusion(PE), 6-min walk test distance (6MWD) and arterial oxygen saturation(SO_2) at rest, in air. This figure presents the central estimate for mortality.

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cause a murmur and symptoms and therefore be detected earlier in life before ES develops.

Proposing to develop a simple, broadly applicable risk assessment approach, a large multicenter study of 1098 ES patients used multivariate analysis to identify the following risk factors for mortality: 1) older age, 2) presence of a pre-tricuspid shunt 3) lower resting arterial oxygen saturation 4) absence of sinus rhythm, and 5) presence of pericardial effusion [44]. The addition of 6-min-walk-distance (6MWD), data for which was available only in a subset, to the multivariate analysis suggested that this may be an additional independent predictor of death, and enabled the construction of a table presenting estimated absolute 5-year mortality for patients with ES (Fig. 3) [45].

4. Pharmacologic management

A summary of pharmacologic and surgical management strategies in ES are provided in Table 1, and are discussed in detail below.

4.1. Heart failure medications

A registry analysis of German ES patients showed that many patients were on chronic heart failure medications, despite the absence of evidence of their effectiveness in the ES population. This analysis found no mortality benefit with the use of Digoxin, chronic angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blockers (ARB). Interestingly, the benefit of beta-blocker use in this population approached significance [24]. Small studies examining the role of beta blockers in WHO Group I PAH have shown mixed results [46–48].

The role in ES of other heart failure medications, including sodium-glucose co-transporter inhibitors (SGLTi), angiotensin-neprilysin inhibitors (ARNi), and mineralocorticoid receptor antagonists (MRA) is unclear. As the most common cause of mortality in the ES population remains right heart failure, there is a theoretical benefit of neurohormonal blockade and protection against adverse remodeling that these medications provide. However, it should be noted that while studies suggest hemodynamic and functional benefit to the right ventricle in patients with left ventricular dysfunction [49–52], no such data exists to suggest benefit in patients with primarily pre-capillary pulmonary hypertension, aside from animal studies [53]. Nevertheless, the pleiotropic effects of these medications continue to be better understood, and may yet show benefit for right ventricular dysfunction due to pre-capillary pulmonary hypertension, and by extension in ES patients, in the future.

4.2. Pulmonary vasodilators

Elevated pulmonary vascular resistance is the hallmark pathophysiology of ES. The use of pulmonary vasodilators for PAH in general has been an active area of research in recent years, and positive results in that sphere have resulted in increasing use in ES patients specifically [24]. Overall, pulmonary vasodilator medications appear to improve functional capacity. Although randomized controlled trials evaluating the impact of pulmonary vasodilators in ES have not been powered for mortality, observational studies suggest that their use may be associated with a survival benefit, either alone or in combination [24,26,43,54,55].

4.2.1. Endothelin receptor antagonists (ERAs)

The largest randomized controlled trials in ES have been done with ERAs. The BREATHE-5 trial was a multicenter, randomized, double-blind, placebo-controlled study that evaluated the effect of 16 weeks of bosentan in ES patients who were WHO FC III. Bosentan was well tolerated and significantly improved both hemodynamics and exercise capacity (by PVRi and 6MWD, respectively), compared to placebo [56]. This benefit was sustained on 40 week follow up during the open label extension of this trial [57]. In the larger more recent randomized placebo-controlled MAESTRO trial, the ERA macitentan was not associated with benefit. While it is possible this represents a distinction between different ERAs, it may have instead reflected the less sick population sampled (WHO functional class II and III) as well as inclusion of a more heterogenous population with some on PDE5 inhibitors [58].

Table 1
Management options and current evidence on their impact on outcomes in Eisenmenger Syndrome.

Treatment Options	Effect in Eisenmenger Syndrome	Comment
Heart Failure Medications		
Digoxin	No demonstrated mortality benefit	Possible trend toward increased mortality.
ACEi or ARB	No mortality benefit	Lower blood pressure may preclude adding DTT.
Beta blockers	No demonstrated mortality benefit	Trend towards benefit.
SGLT2i	Not yet studied in ES	
ARNi	Not yet studied in ES	
Pulmonary vasodilators		
ERA	Bosentan improves hemodynamics and exercise capacity	Similar benefit not seen with macitentan (but studied in patients with less advanced symptoms)
PDE-5i	Sildenafil and tadalafil improve exercise capacity, functional class, hemodynamics	
Prostanoids	Inhaled iloprost improves exercise capacity, QOL, RV function	Effect may be attenuated with combined DTT.
	Intravenous epoprostenol improves exercise capacity, hemodynamics, and oxygen saturation	IV therapy associated with embolic risk, though small retrospective studies suggest safe; subcutaneous prostanoids often preferred.
Selexipag	Improves hemodynamics and exercise capacity	
Riociguat	Not studied in ES	
Other medications		
Anticoagulation	No mortality benefit	May prevent in situ thrombosis while also increasing risk of hemoptysis. Not routinely recommended in ES.
Surgical Management		
Treat and Repair	Acceptable short- and medium-term outcomes in carefully selected case series population	Often improves acute symptomatology. No long-term outcomes data. Increasing evidence that this approach provides benefit in a select subset of patients.
Transplant	VSD – better survival with combined heart-lung transplant	Consider transplant evaluation with escalation in therapy
	ASD – better survival with bilateral lung transplant	Limited data to guide transplant timing and strategy.
Other Therapies		
Exercise Training	Improved exercise capacity in ES subgroup of larger PAH-CHD population	Better studied in PAH-CHD population as a whole. Appears safe and well tolerated.

Abbreviations: ES – Eisenmenger Syndrome. ACEi – angiotensin converting enzyme inhibitor. ARB – angiotensin receptor blocker. ARNi – angiotensin receptor-neprilysin inhibitor. SGLT2i – sodium-glucose transport protein 2 inhibitor ERA – Endothelin receptor antagonist. PDE-5i – Phosphodiesterase type 5 inhibitor. DTT – Disease targeting therapy. PAH-CHD – pulmonary arterial hypertension due to congenital heart disease. RV – right ventricular. QOL – Quality of Life.

4.2.2. PDE-5 inhibitors

The PDE5 inhibitors sildenafil and tadalafil have both been found to be associated with improvements in exercise capacity, functional class, and hemodynamics in patients with ES in small randomized controlled trials [59,60].

4.2.3. Prostanoids

Inhaled iloprost increases 6MWD, and subjective quality of life measures, and RV function [61], though this effect may be attenuated when added to background maximal oral therapy [62]. Continuous intravenous epoprostenol has been proven to be effective in WHO Group I PAH, with symptomatic, hemodynamic, and mortality benefit [63]. Its use in patients with PAH-CHD and ES has been hampered by concerns for an indwelling central line in the presence of a right-to-left shunt, which may pre-dispose the patient to embolic strokes from line-related thrombi or infection. The small retrospective studies that have examined its use in ES have found improved pulmonary hemodynamics, oxygen saturation, and exercise capacity with few adverse effects over the short term [64,65]. Subcutaneous treprostinil as an add on therapy to maximally tolerated oral therapy in ES has shown similar results [65, 66].

Selexipag, an oral selective prostacyclin receptor agonist with benefit in PAH [67], has been shown to have hemodynamic and functional benefit in a small case series of ES patients [68], though the magnitude of benefit and tolerability is lower in these patients than in patients with PAH after defect correction [69].

4.2.4. Riociguat

Riociguat is a soluble guanylate cyclase (sGC) stimulator with vasodilation and antiproliferative effects. It is approved to treat chronic thromboembolic pulmonary hypertension (CTEPH) as well as pulmonary arterial hypertension. Though data on Riociguat use in ES is currently lacking, subgroup analysis of the trials that showed benefit in PAH showed that in patients with persistent or recurrent PAH after CHD correction (PAH-CHD), Riociguat use was associated with sustained improvement in functional and hemodynamic parameters (6MWD, PVR, NTproBNP, and WHO functional class) at 2 years [70]. The majority of these patients were not on other DTT therapies at baseline, and thus the incremental benefit of Riociguat on background DTT therapy in PAH-CHD is unclear.

4.2.5. Role of combination therapy

As has been established in other forms of PAH, combination DTT may be more effective than monotherapy, with incremental improvement in hemodynamics and functional capacity [71]. A recent registry study of PAH-CHD and ES patients showed that patients on dual therapy (the majority of which were PDE5i + ERA) had a significantly improved survival than patients on monotherapy [26]. The benefit of dual-over mono-therapy in ES patients has been seen in other studies as well [43,72]. In the absence of reproducible definitive clinical trials, however, it is challenging to be certain that initial dual therapy (or triple therapy) provides benefit given the confounding by indication intrinsic to such observational research. Patients on triple therapy including prostanoids, for example, have worse survival than those on monotherapy, dual therapy, or no therapy [43], presumably due to the reason for triple therapy: more severe disease.

Prior ESC/ERS guidelines recommended starting ERA monotherapy in patients with a 6MWD <450 m, and then adding a second agent if there is no improvement [22]. This recommendation, presumably, would have been intended to be interpreted in the larger clinical context since 6MWD is impacted by musculoskeletal and neurocognitive factors; for example, one study reported an average a 6MWD of only 280 m for individuals with trisomy 21 *without* cardiac disease [73]. The recent 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension have specified bosentan as the initial therapy for ES in symptomatic patients, without mention of the 6MWD criteria, which aligns with most recent 2018 AHA/ACC guidelines for congenital heart disease [12]. Other reasonable approaches to starting and escalating therapies in symptomatic patients have been proposed previously [5,6]. At the moment no strong data support starting or escalating therapy in the asymptomatic patient, though given the presence of essentially universal functional impairment, some have proposed that individuals with ES are almost never truly asymptomatic. This is largely a semantic distinction of whether 'symptoms' should be considered as classically defined ('Symptoms can only be reported by the person experiencing them,') [74] or more broadly considered to include the presence of meaningful functional limitation in the absence of subjective distress. The upshot is that both the patient's personal experience of disease and measured clinical data must be considered holistically when deciding whether and which therapies to prescribe for individuals with ES.

5. Surgery

5.1. Treat and Repair"

ES has historically been a contraindication for defect closure, given the high perioperative risk and poor long-term outcomes in the setting of irreversible obstructive pulmonary vascular disease [75]. DTTs improve hemodynamic parameters and may lead to reverse remodeling of the pulmonary vasculature, raising the possibility that a 'treat and repair' approach, with aggressive DTTs followed by repair, may be feasible. There are case reports and series of this strategy in ES that show good short-term and medium-term outcomes [76–78], though long-term outcomes remain unclear. In many cases, this approach may be associated with the resolution of hypoxemia, symptomatic relief, and improved functional status. However, treat-and-repair should not be viewed as a cure, even if there are promising reports of improved functional capacity and relief of hypoxemia. After repair, patients with high PVR generally continue to be maintained on DTTs. Moreover, the prognosis with ES is often relatively favorable, and it is challenging to identify patients with PAH-CHD who are most likely to have an improved outcome, despite work suggesting specific hemodynamic parameters to guide this decision [54,79]. Given the lack of long-term safety and outcomes data for ES, a 'treat-and-repair' approach cannot be systematically recommended at this time.

5.2. Transplant

In the setting of deterioration despite maximal medical therapy, heart-lung transplant or bilateral lung transplant with defect correction should be considered, though some groups advocate for starting transplant evaluation when the patient is escalated to triple therapy [6]. Data to guide transplant strategy in ES is scarce. The type of heart defect appears to play a role; ES in the context of a VSD was associated with better survival after heart-lung transplant, while ES with ASDs had better survival with bilateral lung transplant and defect correction in one study of 442 patients with ES. In this study, the most common cause of death in patients with VSDs undergoing lung transplant and defect repair was ventricular failure, perhaps due to unmasked left ventricular dysfunction as resolution of pulmonary vascular disease increased left ventricular preload following lung transplant. Such left ventricular dysfunction would be less common in the context of an isolated ASD [80]. One advantage of bilateral lung transplant with defect repair over heart-lung transplant, though, may be shorter wait times. Another study found that short-term outcomes for heart-lung transplant were worse in ES patients than in patients with pulmonary arterial hypertension, driven by immediate post-operative risk (within 30 days of transplant) [81].

6. Other therapies

Several other supportive or ancillary interventions have been proposed for individuals with ES. There are still questions about efficacy and the balance of risk and benefit for many of these, including anticoagulation and supplemental oxygen (e.g., nocturnal). Exercise training, conversely, has become increasingly accepted as a generally safe and effective therapy for individuals with PAH related to CHD, including those with ES.

Table 2
Selected key evidence gaps in the assessment and management of Eisenmenger syndrome.

Topic	Selected Evidence Gaps
Kidney Disease	Clinical implications and effect of treatment of albuminuria
Natural History	Comparative outcomes in ES compared to non-ES PAH in the modern era, with focus on mechanisms of observed differences
Coagulopathy	RCTs on effect of routine anticoagulation with VKA, DOAC, or antiplatelet agents for primary thromboembolic prevention Approach to subclinical in situ pulmonary thrombosis (e.g., anticoagulation)
Pharmacologic Management	Role of heart failure therapies, particularly ARNi, SGLT2i, and MRA Effect of pharmacologic treatment on mortality and/or cardiac hospitalization Role of newer therapies, such as riociguat Indications to initiate DTT, beyond symptoms and functional status RCTs of upfront combination therapy Timing and strategy of sequential combination therapy based on RCTs
Surgical Management	Long term outcomes of 'Treat and Repair' approach Optimal timing of initiating transplant evaluation Optimal transplant strategy (bilateral lung transplant + defect correction vs heart-lung transplant)

ES – Eisenmenger syndrome. VKA – Vitamin K Antagonist. DOAC – direct oral anticoagulant. ARNi – angiotensin receptor neprilysin inhibitor. SGLT2i – sodium-glucose transport protein 2 inhibitor. DTT – disease targeting therapy. RCT – randomized controlled trial.

6.1. *Exercise*

Exercise training in patients with PAH-CHD on the background of medical therapy increased 6MWD, peak VO_2, and maximal workload, though did not affect oxygen saturation or functional class compared to baseline in a non-randomized prospective study [82]. In a subgroup analysis of PH patients, patients with ES who were randomized to a home-based exercise training program had improved 6MWD compared to those who were not [83]. Exercise programs appear to be safe in the PAH-CHD population; in a small prospective study of patients with PAH-CHD, an exercise program was well tolerated, and no adverse effects of participation were seen at 1 year. Moreover, patients in the exercise program improved 6MWD, minimum hemoglobin saturation with activity, and functional class at 1 year compared to those who were not [84].

6.2. *Unmet needs and future perspectives*

Many unmet needs in the field of Eisenmenger Syndrome parallel those in the field of congenital heart disease at large. In particular, the significant genotype-phenotype heterogeneity, small available sample size and low absolute event rates makes it difficult to perform internally valid, adequately powered randomized controlled trials. Indeed, most current practice recommendations in Eisenmenger syndrome are based on expert opinion, extrapolation from non-ES PAH-CHD and PAH populations, and non-randomized, retrospective cohort studies of relatively small populations. The BREATHE-5 and MAESTRO trials are important exceptions, though they are themselves limited by relatively short term follow up, small sample sizes, and phenotype heterogeneity. Table 2 highlights key evidence gaps in the assessment and management of ES.

Towards this end, precision medicine may be particualrly pertinent in interpreting the natural histories and impact of therapies in extreme and uncommon phenotypes, such as ES. This would be supported by a shift toward a lifespan approach to the disease that takes into account the interplay between a patient's genotype, its relationship to phenotype, as well as their specific environmental exposures and risk factors. While a large amount of data from an individual patient can be collected in each of these categories, their complex interactions would challenge attempts at holistic interpretation, suggesting a possible role for artificial intelligence in patient data interpretation, performing personalized risk assessment, and designing optimal treatment strategies [85].

7. Conclusions

Eisenmenger syndrome is a consequence of chronic left-to-right shunt in the setting of diverse congenital heart disease diagnoses. Pulmonary vascular remodeling and chronic hypoxemia are associated with multisystem effects which, in turn, determine the natural history of this disease. Despite progress in risk stratification and advances in medical and surgical management, ES is still associated with a substantially elevated risk of premature morbidity and mortality, and significant knowledge gaps remain. Adequately powered randomized clinical trials examining important clinical endpoints (e.g., mortality, hospitalizations) are largely lacking due to a low and decreasing prevalence of disease, as well as challenges studying a syndrome with such widespread and heterogeneous clinical effects. As with many aspects of adult congenital heart disease care, a 'one size fits all' approach is unlikely to best serve patients given the heterogeneity of underlying cardiac lesions and variable prominence of specific clinical consequences. An individualized approach to surveillance and management of ES is preferable, applying the best available data with careful extrapolation recognizing the limits of our evidence-base.

CRediT authorship contribution statement

Ranjan Banerjee: Writing – review & editing, Writing – original draft, Conceptualization. **Alexander R. Opotowsky:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or relevant relationships that could reasonably appear to influence the work reported in this paper, other than ARO being an Editorial Board Member.

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Appendix A. Supplementary data

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