ECRONICON OPEN ACCESS

EC PAEDIATRICS
Review Article

Eisenmenger Syndrome in Children: A Review on Current Perspectives and Advanced Therapies

Mariam Mahmoud Hassan El Makkawy[1]*, Safwat Hassan Gad[2], Wan Ariffin bin Abdullah[3] and Jamaluddin Bin Haji Mohamad[4]

[1]Member of Royal College of Paediatrics and Child Health, London, UK and Senior Lecturer, Faculty of Medicine, Department of Paediatrics, Malaysian Allied Health Science Academy (MAHSA University), Malaysia

[2]Senior Associate Professor, Faculty of Medicine, Department of Paediatrics, AIMST University, Malaysia

[3]Senior Professor, Faculty of Medicine, Department of Paediatrics, Malaysian Allied Health Science Academy (MAHSA University), Malaysia

[4]Professor, Faculty of Medicine, Department of Paediatrics, Malaysian Allied Health Science Academy (MAHSA University), Malaysia

***Corresponding Author:** Mariam Mahmoud Hassan El Makkawy, Member of Royal College of Paediatrics and Child health, London, UK and Senior Lecturer, Faculty of Medicine, Department of Paediatrics, Malaysian Allied Health Science Academy (MAHSA University), Malaysia.

Received: May 20, 2024; **Published:** May 31, 2024

Abstract

Eisenmenger syndrome (ES) is the most advanced form of pulmonary arterial hypertension associated with congenital heart disease, it is first described by Victor Eisenmenger, was defined by Paul Wood in pathophysiologic terms as pulmonary hypertension at systemic level, caused by a high pulmonary vascular resistance, with reversed or bidirectional shunt at aorto-pulmonary, ventricular, or atrial level. Despite major breakthroughs in pediatric cardiology and cardiac surgery that have dramatically improved the course of congenital heart diseases over the past half century, ES is still encountered in between 1% and 5.6% of large tertiary congenital heart diseases cohorts, posing challenges to patients' quality of life and longevity and to health care. Although patients with ES can survive into the fourth and fifth decades of life, their condition is associated with high morbidity, reduced functional status, and frequent hospitalizations.

Keywords: *Eisenmenger Syndrome; Pulmonary Arterial Hypertension; Pulmonary Vascular Resistance; Congenital Heart Diseases;*

Abbreviations

ASD: Atrial Septal Defect; BMPR2: Bone Morphogenetic Protein Receptor II Gene; CHD: Congenital Heart Disease; ERA: Endothelin Receptor Antagonist; ES: Eisenmenger Syndrome; Hb: Hemoglobin; HF: Heart Failure; HLT: Heart and Lung Transplantation; LT: Lung Transplantation; NO: Nitric Oxide; PA: Pulmonary Artery; PDE-5: Phosphodiesterase Type 5; PVD: Peripheral Vascular Disease; PVR: Pulmonary Vascular Resistance; PVRi: Pulmonary Vascular Resistance Index; Qp/Qs: Pulmonary Cardiac Output to the Systemic Cardiac Output; RCT: Randomized Controlled Trial; RV: Right Ventricle; SOX-17: SRY-Box Transcription Factor 17 Gene; SUPER-1: Sildenafil Use in Pulmonary Arterial Hypertension Research; TBX4: T-Box Transcription Factor Gene; VSD: Ventricular Septal Defect; WU: Wood Unit

Overview and Pathophysiology

Eisenmenger syndrome (ES) is the most advanced form of pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD), it is first described by Victor Eisenmenger, was defined by Paul Wood in pathophysiologic terms as pulmonary hypertension at systemic level, caused by a high pulmonary vascular resistance (PVR), with reversed or bidirectional shunt at aorto-pulmonary, ventricular, or atrial level [1]. Long-term exposure of the pulmonary bed to increased pulmonary flow and pressure from a post-tricuspid (e.g. ventricular septal defect [VSD]) left-right shunt results in vascular remodeling and dysfunction. This, in turn, leads to a rise in PVR, which, if severe enough, results in reversal of the shunt and the clinical cyanosis characteristic of ES. Once ES is established, the defect is no longer surgically correctable, as it is felt to act as a relief valve for the right ventricle (RV) [2].

Despite major breakthroughs in pediatric cardiology and cardiac surgery that have dramatically improved the course of CHD over the past half century, ES is still encountered in between 1% and 5.6% of large tertiary CHD cohorts, posing challenges to patients' quality of life and longevity and to health care [3].

Observational studies have shown that there may be differences in the natural course and ventricular adaptation to long-standing pulmonary vascular disease, depending on the location of the defect in ES patients and the presence of a uni- or biventricular heart. In an echocardiographic study of 191 patients with ES and noncomplex CHD, the location of the defect was associated with different physiological adaptation of the RV to the PH and, possibly, a different prognosis: pre-tricuspid shunts were older, had larger RVs, and a trend toward worse prognosis when compared to post-tricuspid lesions [4,5].

Prevalence in childhood

Unlike adult ES, the prevalence of ES among children remains unclear. European pediatric PAH registries report 30%-40% of PAH-CHD cases to be attributed to ES [6]. Although ES usually manifests itself in adulthood, complex underlying CHD accelerates its clinical phenotype, particularly among children with genetic abnormalities such as Down syndrome, with hypoxemia ensuing in childhood [7]. Pediatric PAH-CHD occurs in a heterogeneous group of patients with various presentations and phenotypes, with overall worse survival among children with ES when compared with adults [3].

Complications

Although patients with ES can survive into the fourth and fifth decades of life, their condition is associated with high morbidity, reduced functional status, and frequent hospitalizations. ES is characterized by chronic hypoxemia and multiorgan involvement, including secondary erythrocytosis (often with iron deficiency) and increased thrombotic and bleeding diathesis, high arrhythmic burden, risk of infections, and progressive heart failure (HF). In addition, patients with ES have the worst exercise tolerance among patients with CHD and the highest prevalence of renal dysfunction [8,9].

Secondary erythrocytosis, iron deficiency, and venesection

The effect of chronic hypoxemia causes a compensatory secondary erythrocytosis aimed at increasing the blood's oxygen-binding capacity. This process requires substantial iron stores for the production of hemoglobin (Hb) and is likely the main cause of the iron deficiency commonly found in cyanotic patients [10]. Prophylactic or routine venesection to maintain a hematocrit level within an arbitrary predetermined level (hematocrit < 65%) is not indicated [11]. This is one of the major misconceptions in the management of patients with cyanotic CHD and routine venesection can be harmful to these patients, as they can result in iron deficiency, reduced exercise tolerance, impaired oxygen transport capacity due to "relative anemia", and may increase the risk of cerebrovascular events [12].

Genetic modulators

The role of genetic factors in modulating the onset and disease severity of idiopathic PAH is nowadays established, with mutations in the bone morphogenetic protein receptor II gene (*BMPR2*) being the most common [13]. More recently, a role for pathogenetic polymorphisms in PAH-CHD has been suggested: *BMPR2* mutations were identified in 6% of adults and children with PAH-CHD (mainly Eisenmenger syndrome or post-repair), although the role of *BMPR2* in PAH-CHD remains unclear [14]. An increased prevalence of mutations in the SRY-Box Transcription Factor 17 gene (*SOX-17*) and T-box transcription factor gene (*TBX4*) has been identified in patients who developed PAH after ventricular septal defect repair and patients with pre-tricuspid shunts and Eisenmenger physiology [15]. Other genes (*ABCC8* and *SMAD1*) have been described in patients with PAH associated with a small/coincidental defect [15]. Genetic factors may explain the variability in the development of peripheral vascular disease (PVD) in patients with pre-tricuspid shunts, in whom the increased pulmonary blood flow alone is deemed insufficient for the development of PVD [16].

Investigations

Complete blood cell count, biochemical profiles, and iron investigations, as well as blood gas assessments, are all employed in the diagnosis of Eisenmenger syndrome. Electrocardiography can also reveal symptoms of right ventricular hypertrophy and an underlying heart abnormality. Imaging investigations can detect structural problems in the heart and pulmonary changes, including permanent changes in the lungs. The stage of pulmonary vascular pathology can be determined using histologic findings [17].

Although echocardiographic diagnosis has been described, cardiac catheterization is still considered the gold standard method of diagnosis Echocardiography is the mainstay of non-invasive diagnostic tools during the early screening that depicts intracardiac and extracardiac malformations, hemodynamic changes, right heart overload, PAH [18]. In recent years, cardiac CT has emerged as the standard of reference for identification and characterization of PAH-CHD. Cardiac CT allows a non-invasive display of pulmonary artery development, depicting a three-dimensional assessment of the anatomic relations between the pulmonary artery and adjacent structures [19].

Medical PH therapy

The introduction of advanced PH therapies for symptomatic patients with ES may substantially improve clinical outcomes [20]. Bosentan, a dual endothelin receptor antagonist (ERA), was the first drug to be studied in ES, with a small randomized controlled trial (RCT) showing improvement in hemodynamics (decreased mean pulmonary artery pressure and PVR index) and exercise capacity without compromising SaO_2 [21] and was recommended as a first-class drug in symptomatic patients with ES.

There are scarce data on the safety and efficacy of advanced PAH therapies in children with ES, based mainly on adult RCTs including children > 12 years of age [22].

Inhalation nitric oxide (NO) is a potent and selective pulmonary vasodilator. In ES, relaxation of the endothelium-dependent pulmonary blood vessels is disturbed. Patients with ES who in-hale NO can directly reduce pulmonary hyper-tension and increase oxygenation due to the optimization of the ventilation-perfusion relationship. Inhalation nitric oxide also has an antithrombotic effect and is also used in preparation for a pulmonary heart transplant [23].

Phosphodiesterase type 5 inhibitors. Oral PDE-5 inhibitors have several benefits, namely increasing vasodilatation of Nitric Oxide (NO) by increasing cGMP concentrations, having anti-proliferative effects of vascular smooth muscle cells, and increasing contractility of right ventricular hypertrophy. SUPER-1 research (Sildenafil use in pulmonary arterial hypertension) shows that Sildenafil can improve exercise capacity in pulmonary arterial hypertension. Also, it has a short-term safety and efficacy profile. Sastry., *et al.* prove that the administration of sildenafil for four months is comparable to that observed in the SUPER-1 study [24,25].

The use of calcium channel blockers in patients with Eisenmenger syndrome is not recommended because it can reduce systemic arterial pressure and increase right to left shunting, which causes syncope and sudden death [25]. The use of anticoagulation in ES remains a controversial issue and should be carefully considered on a case-by-case basis. Current guidelines state that anticoagulation in ES should be offered for atrial arrhythmias and in the presence of PA thrombus or embolism in patients at low bleeding risk [18].

Corrective interventions

Closure of the septal heart defect, either by percutaneous or surgical procedures, is generally contraindicated in adult patients with PAH associated with systemic to pulmonary shunts because of high mortality and poor outcome. In addition, closure of the defect may take away the "safety valve" in patients with further progression of pulmonary vascular disease and reversal of the pressure gradient between the systemic and pulmonary circulations. The indications for patients to be considered for correction are not uniformly defined and may include pulmonary artery vasoreactivity and/or the presence of a pulmonary to systemic flow ratio of at least 1.5 to 1.0 [26].

Children diagnosed later in life, who have developed pulmonary vascular disease (resistance exceeding 6 Wood units "WU"/m^2) and have poor vasodilator response, are at high risk of sustained pulmonary hypertension, right heart failure, and hypertensive crises immediately after surgery [27].

Cardiac catheterization is required prior to and after establishing PAH therapies to document the decrease in PVR to levels that would allow partial (or complete) closure of the defect, thus abolishing ventricular overload and reducing the risk of progression of PVD. Current European society of cardiology adult CHD guidelines make clear recommendations on a treat-and-repair strategy for patients with an atrial septal defect and baseline PVR ≥ 5 WU [28]. They recommend fenestrated closure of the defect after PAH therapy if the PVR drops to < 5 WU and there is evidence of RV volume overload with a Qp/Qs > 1.5. It is worth noting that this cut-off is reasonably conservative; in the past, atrial septal defects were closed with a PVR of 6-8 WU [29].

The current European Society of Cardiology/European Respiratory Society guidelines describe a definitive treat-and-repair management approach for ASDs only [30]. Patients with ASD, VSD, or patent ductus arteriosus should undergo repair if their baseline PVR is < 3 WU. For a patient with an ASD and PVR > 5 WU that falls below 5 WU with therapy, surgery can be offered. However, the treat-and-repair approach for VSD is not definitively described in these guidelines. In the pediatric literature, patients with an unrepaired shunt and a pulmonary vascular resistance index (PVRi) > 8 WU/m^2 are likely inoperable. The guidelines recommend considering shunt closure for a PVRi of < 4 WU/m^2, with individualized decision-making for subjects in the 4 to 8 WU/m^2 range [31]. Regardless of patient age, a multidisciplinary and multiparameter approach to individualized patient decision-making is recommended [32]. Younger age is an important prognostic factor for operability and long-term outcome [33]. The United Kingdom pediatric experience followed patients with different types of pulmonary hypertension and showed that those who underwent complete repair of congenital heart disease with residual significant pulmonary hypertension had the poorest survival, highlighting the importance of proper patient selection [33].

Transplantation

The only definitive treatment for ES is lung transplantation (LT) with shunt closure or heart and lung transplantation (HLT). In a worldwide registry of 605 transplanted ES patients over a 10-year period, Waddell., *et al*. found that, in this heterogeneous group, post-transplantation survival related to the underlying cause of the ES, and HLT appeared to be better than LT with shunt correction: 30 days and 1-year survival rates were 80.7% and 70.1% compared with 68% and 55.2%, respectively [35]. In another study of 51 patients with ES transplanted in the UK, the 1-, 5-, and 10-year survival rates for ES were 72.6%, 51.3%, and 27.6%, respectively, compared to non-ES of 74%, 48.1%, and 26%, respectively with no difference in survival overall [36]. Even though it has been suggested that patients with ES may have a better post-transplantation prognosis than patients with PAHi or other types of congenital heart defects, the general lack of organs and suboptimal survival after LT or HLT underline the need for alternative therapeutic options [37].

Conclusion

Although patients with ES can survive into the fourth and fifth decades of life, their condition is associated with high morbidity, reduced functional status, and frequent hospitalizations.

Bibliography

1. Eisenmenger V. "Die angeborenen Defecte der Kammerscheidewand des Herzens". *Zeitschrift fur klinische Medizin* 32 (1897): 1-28.
2. Diller GP., *et al*. "Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study". *European Heart Journal* 27.14 (2006): 1737-1742.
3. Diller GP., *et al*. "Current therapy and outcome of Eisenmenger syndrome: Data of the German National Register for congenital heart defects". *European Heart Journal* 37.18 (2016): 1449-1455.
4. Moceri P., *et al*. "Physiological differences between various types of Eisenmenger syndrome and relation to outcome". *International Journal of Cardiology* 179 (2015): 455-460.
5. Alonso-Gonzalez R., *et al*. "Pulmonary hypertension and congenital heart disease: an insight from the REHAP National Registry". *International Journal of Cardiology* 184 (2015): 717-723.
6. Haworth SG and Hislop AA. "Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006". *Heart* 95.4 (2009): 312-317.
7. Van Loon RL., *et al*. "Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005". *Circulation* 124.16 (2011): 1755-1764.
8. Dimopoulos K., *et al*. "Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease". *Circulation* 117.18 (2008): 2320-2328.
9. Kempny A., *et al*. "Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life-single centre experience and review of published data". *European Heart Journal* 33.11 (2012): 1386-1396.
10. Rosove MH., *et al*. "Chronic hypoxaemia and decompensated erythrocytosis in cyanotic congenital heart disease". *Lancet* 2.8502 (1986): 313-315.
11. Silversides CK., *et al*. "Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: complex congenital cardiac lesions". *Canadian Journal of Cardiology* 26.3 (2010): e98-e117.
12. Broberg CS., *et al*. "Blood viscosity and its relationship to iron deficiency, symptoms, and exercise capacity in adults with cyanotic congenital heart disease". *Journal of the American College of Cardiology* 48.2 (2006): 356-365.
13. Machado RD., *et al*. "Pulmonary arterial hypertension: a current perspective on established and emerging molecular genetic defects". *Human Mutation* 36.12 (2015): 1113-1127.
14. Roberts KE., *et al*. "BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease". *European Respiratory Journal* 24.3 (2004): 371-374.
15. Cruz-Utrilla A., *et al*. "Clinical implications of the genetic background in pediatric pulmonary arterial hypertension: data from the Spanish REHIPED registry". *International Journal of Molecular Sciences* 23.18 (2022): 10433.

16. Forlemu AN., *et al*. "Atrial septal defect with Eisenmenger syndrome: a rare presentation". *Case Reports in Cardiology* (2020): 8681761.

17. Diller GP and Gatzoulis MA. "Pulmonary vascular disease in adults with congenital heart disease". *Circulation* 115.8 (2007): 1039-1050.

18. Baumgartner H., *et al*. "2020 ESC guidelines for the management of adult congenital heart disease". *European Heart Journal* 42.6 (2021): 563-645.

19. Galie N., *et al*. "2015 ESC/ ERS guidelines for the diagnosis and treatment of pulmonary hypertension". *Kardiologia Polska* 73 (2015): 1127-1206.

20. Dimopoulos K., *et al*. "Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension". *Circulation* 121.1 (2010): 20-25.

21. Broberg CS., *et al*. "Blood viscosity and its relationship to iron deficiency, symptoms, and exercise capacity in adults with cyanotic congenital heart disease". *Journal of the American College of Cardiology* 48.2 (2006): 356-365.

22. Stout KK., *et al*. "2018 AHA/ACC guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines". *Journal of the American College of Cardiology* 73.12 (2019): 1494-1563.

23. Triastuti N., *et al*. "Usage of inhaled nitric oxides in cases of Eisenmenger syndrome". *Indonesian Journal of Medical Sciences and Public Health* 1.1 (2020): 13-19.

24. Brennan K and Hatch DM. "Eisenmenger's Syndrome". In: Consults in Obstetric Anesthesiology. Switzerland: Springer Nature (2018): 185-187.

25. D'Alto M and Diller GP. "Pulmonary hypertension in adults with congenital heart disease and Eisenmenger syndrome: Current advanced management strategies". *Heart* 100.17 (2014): 1322-1328.

26. Therrien J., *et al*. "Canadian Cardiovascular Society Consensus Conference 2001 update: recommendations for the management of adults with congenital heart disease part III". *Canadian Journal of Cardiology* 17.11 (2001): 1135-1158.

27. Beghetti M. "Pulmonary arterial hypertension related to congenital heart disease". Munich: Elsevier (2006).

28. Baumgartner H., *et al*. "2020 ESC guidelines for the management of adult congenital heart disease". *European Heart Journal* 42.6 (2021): 563-645.

29. Akagi S., *et al*. "Treat-and-repair strategy is a feasible therapeutic choice in adult patients with severe pulmonary arterial hypertension associated with a ventricular septal defect: case series". *European Heart Journal - Case Reports* 2.2 (2018): yty033.

30. Humbert M., *et al*. "2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension". *European Respiratory Journal* 61.1 (2023): 2200879.

31. Abman SH., *et al*. "Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society". *Circulation* 132.21 (2015): 2037-2099.

32. Ivy DD and Frank BS. "Treat and repair for congenital heart disease and pulmonary hypertension: not a panacea". *JACC: Advances* 3.4 (2024): 100891.

33. Rabinovitch M., *et al*. "Vascular structure in lung tissue obtained at biopsy correlated with pulmonary hemodynamic findings after repair of congenital heart defects". *Circulation* 69.4 (1984): 655-667.

34. Haworth SG and Hislop AA. "Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006". *Heart* 95.4 (2009): 312-317.

35. Waddell TK., *et al*. "Heart-lung or lung transplantation for Eisenmenger syndrome". *Journal of Heart and Lung Transplantation* 21.7 (2002): 731-737.

36. Stoica SC., *et al*. "Heart-lung transplantation for Eisenmenger syndrome: early and long-term results". *Annals of Thoracic Surgery* 72.6 (2001): 1887-1891.

37. Christie JD., *et al*. "The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report - 2010". *Journal of Heart and Lung Transplantation* 29.10 (2010): 1104-1118.

Volume 13 Issue 6 June 2024