JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article
DOI: https://doi.org/10.23950/jcmk/9660

Surgical treatment of congenital heart disease with Eisenmenger syndrome

Ulugbek Mazhidov, Rakhima Mekenbayeva, Yerbol Aldabergenov

Pediatric Cardiac Surgery Department, National Scientific Medical Center, Nur-Sultan city, Republic of Kazakhstan

Received: 2021-01-15.
Accepted: 2021-01-16

J Clin Med Kaz 2021; 18(1):14-18

Corresponding author:
Rakhima Mekenbayeva.
E-mail: mrt.14@mail.ru

Abstract

Article provides review of the available world literature on performing surgical correction of the atrioventricular septal defect in patients with Eisenmenger syndrome such as: basic pathophysiological principles, technique, indications, clinical and hemodynamic results. Currently, according to the literature, there is no clarity in the choice of a method for correcting severe congenital heart defects in combination with Eisenmenger syndrome (one - or two-step approach). The article presents the results of studies of both one-and two-stage approaches to correction of the atrioventricular septal defect in this category of patients with their advantages and disadvantages.

Key words: atrioventricular septal defect, pulmonary hypertension, Eisenmenger syndrome, Down syndrome

Introduction

Pulmonary hypertension is a pathological condition that combines a group of diseases characterized by progressive increase in pressure in the pulmonary artery, pulmonary vascular resistance and, as a result, progressive right ventricular failure [1-3]. The concept of "pulmonary hypertension" (PH) was proposed in 1951 by Dresdaleetal. The main cause of PH in children is congenital heart defect (CHD) with systemic pulmonary shunts. The pathogenesis of pulmonary arterial hypertension (PAH) is based on three main processes that lead to pulmonary artery remodeling:

1 - Narrowing of vessels occurs as a result of an imbalance between vasodilators and vasoconstrictors in the pulmonary bloodstream;

2 - Proliferation of muscle wall and endothelial cells leads to narrowing of vascular lumen;

3 - Coagulation disorders lead to in situ microthrombosis and contributes to increase pulmonary vascular resistance.

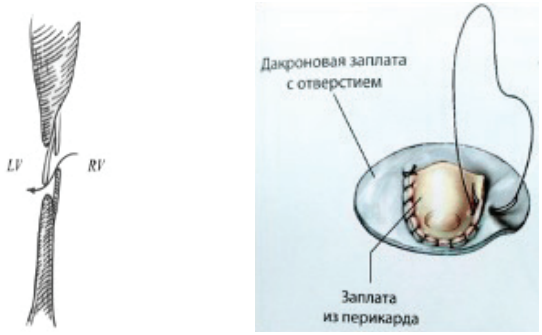
The remodeling mechanisms are currently not fully understood, but most likely include vascular narrowing, inflammation, thrombosis, cell proliferation and fibrosis. The most severe form of pulmonary arterial hypertension is Eisenmenger's syndrome [4,5]. It was first described in 1897 by Victor Eisenmenger as a complex of clinical manifestations associated with the remodeling of the vessels of the pulmonary circulation (PC), leading to the development of pulmonary hypertension and reversible shunt of the blood in any CHD that was untimely diagnosed with an intracardiac defect. This symptom complex is the final stage of the hemodynamic manifestation of most CHD in their natural course.

In 1958, Paul Wood introduced the concept of Eisenmenger syndrome - “high pulmonary hypertension with increased pulmonary vascular resistance and reverse or bidirectional blood flow through an intracardiac defect” [6,7]. The frequency of pulmonary hypertension followed by the development of Eisenmenger syndrome in the absence of timely surgical treatment depends on the type of malformation and age of the child. In approximately 50% of cases, in children with ventricular septal defect (VSD) or patent ductus arteriosus (PDA) pulmonary hypertension develops in early childhood, and among patients with atrioventricular septal defect (AVSD) and common arterial trunk (CAT) with unlimited pulmonary blood flow, severe PAH develops by the end of the second year of life [8]. The development of Eisenmenger syndrome is accompanied by a sharp increase in mortality. The lifespan of patients with Eisenmenger's syndrome is 20-50 years. Currently, the frequency of Eisenmenger’s syndrome is steadily decreasing due to the fact that

the diagnosis and surgical correction of CHD is performed in infancy or in early childhood. Applying adequate therapy can improve clinical symptoms and prognosis [9-10].

A number of congenital heart defects are combined with chromosomal abnormalities, including Down syndrome [11-13]. The frequency of CHD with trisomy on the 21st chromosome in European countries is 11.2 cases per 10,000 newborns [14-19]. The most common congenital heart defects that are associated with Down syndrome are AVSD (43%), VSD (32%), atrial septal defect (ASD) (10%), tetralogy of Fallot (TOF) (6%), and PDA (4%) [20-23]. According to some sources, about 70% of all patients with AVSD have a signs of Down syndrome. Congenital heart disease is a main cause of morbidity and early mortality in patients with Down syndrome. A number of authors [16,21-23] showed in patients with Down syndrome a high activity of the type 1 superoxide dismutase enzyme, which gene is located in chromosome 21, that lead to increase of hydrogen peroxide level in the blood. This leads to oxidative processes, on the one hand, and the absence of an antioxidant system response to enhance the oxidative process on the other, which plays an important role in the pathogenesis of PH. It is believed that patients with Down syndrome have a higher risk of pulmonary arterial hypertension development than patients without it [24]. This is due to a decrease in the number of alveoli, thinning of the media of pulmonary arterioles and impaired endothelial function in these patients. The reason for this is gene translocation [25]. According to the European Recommendations (2015), to diagnose pulmonary hypertension, including Eisenmenger syndrome, it is necessary to catheterize the pulmonary artery with a test for vasoreactivity. For children under 1 year of age, pulmonary catheterization is performed with caution due to the high risk of complications. The diagnostic algorithm for patients [26] with pulmonary hypertension is presented in Figure 1.

Figure 1 - Valve patch in the ventricular septal defect with the possibility of shunting to one side (arrow). A - a side view; B - left ventricle side view.



Surgical correction of the atrioventricular septal defect with Eisenmenger's syndrome

The long-term existence of arterio-venous shunt leads in a distant period to the development of heart failure, caused by both malformation and developing pulmonary hypertension with irreversible changes in pulmonary vessels. Surgical intervention has a high risk of complications, particularly acute cardiovascular failure. Previously, treatment strategies suggested that the correction of the heart defect should be postponed until the moment when the child will gain weight (age 6-9 months). Currently, the prevailing opinion is that early surgical intervention (during the first 6 months of life) prevents the development of serious complications. In patients with AVSD (without correction) a pronounced irreversible increase in total pulmonary vascular resistance (TPVR) may lead to the appearance of right-left shunt, accompanied by the development of cyanosis and arterial hypoxia (i.e. Eisenmenger's syndrome).

Until recently, patients with Eisenmenger's syndrome were considered inoperable, and therapy was symptomatic, without taking into account the causes and mechanisms of the syndrome. As a therapy used cardiac glycosides, diuretics and anticoagulants. The pathogenesis of pulmonary hypertension is based on the imbalance between vasoconstrictors and vasodilators in the pulmonary bloodstream. Currently, pathogenetic PAH-specific therapy has appeared which corrects this imbalance. The medicines of choice are: antagonists of endothelin receptors (Bozentan); phosphodiesterase-5 inhibitors (sildenafil, tadalafil); prostacyclins (Epoprostenol, Treprostinil, Iloprost) [25,27]. The therapy significantly increases the life expectancy of patients. Previously, in patients with Eisenmenger's syndrome, the closure of septal defects was contraindicated, as it eliminated the natural "safety" valve for further disease progression. There was also a fear that the unjustified elimination of right-left shunt, moves patients with Eisenmenger syndrome into the category of patients with idiopathic pulmonary hypertension, which significantly impairs their prognosis and quality of life. In addition, there was no convincing data on the quality of life of these patients in the long-term period.

There are few publications in the literature on successful surgical treatment of patients with Eisenmenger syndrome [25, 27-31]. Recent researches show the possibility of remodeling lung vessels when taking PAH-specific therapy, in particular endothelin antagonists [32-34]. Unfortunately, there is no single tactic for managing such patients. There is no doubt that all patients in the preoperative period should undergo PAH-specific therapy, which can have a positive effect in the postoperative period. In addition, there is no consensus on whether intracardiac communication should be completely eliminated, or whether fenestration should be left on the patch, acting as a shunt [35]. Maintaining fenestration on the patch, which subsequently acts as a valve, was proposed by Charles P. Bailey. In 1959, he demonstrated a series of successful operations in patients with septal heart defects and high pulmonary hypertension who were left fenestration on the patch. The operation was successful in some patients, in the distance there was a gradual decrease in pressure in the pulmonary artery, which allowed in the long term correction of the defect [36].

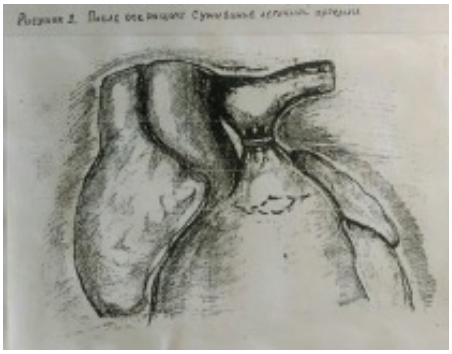
However, despite the positive results, this operation has not been widely used. Nowadays, Novick with co-authors, began to study the possibility of using the valve-containing patch technique in patients with high pulmonary hypertension. The plastic of septal defects is made with Dacron, in which they create a fenestratation. The size of the patch is determined by the diameter of the septal defect, and the diameter of the fenestration is determined by the area of the body surface and the saturation of arterial blood with oxygen in the preoperative period (Table 1).

Table 1 Fenestration diameter on patch depending on oxygen saturation of arterial blood and body surface area

Body surface area	pre-operative SatO2	Fenestration diameter
< 1 m^2	> 91%	4 mm
< 1 m^2	< 91%	6 mm
> 1 m^2	> 91%	6 mm
> 1 m^2	< 91%	8 mm

The technique of the operation is that patients with high pulmonary hypertension can use a Dacron patch with an eccentrically made hole 5 mm in diameter, covered by a valve, on the left ventricle, which provides blood shunt from right to left. This technique unloads the right ventricle in high pulmonary hypertension (Figure 2).

Figure 2 - Pulmonary artery narrowing surgery by Mueller. The picture is drawn by the author of the article Mazhidov U.A.



The key point in the treatment of patients with Eisenmenger syndrome is the concept of reversibility of changes in the vascular wall. Previously, oxygen was supposed to be an inhaled vasodilator. It was suggested that an increase in arterial blood oxygen saturation during the test by 5% or more is a criterion for the patient's operability [37]. In a study conducted Huang J .B. with colleagues [38], increased blood saturation with oxygen was shown against the background of PAH-specific therapy in patients with Eisenmenger syndrome. In addition, there was a decrease and normalization of pulmonary pressure after surgery. It was also noted that in 59.2% of cases in the postoperative period the pressure in the pulmonary artery was high. Thus, the strategy of "diagnosis-treatment-surgery-treatment" when in preoperative stage after diagnosis of Eisenmenger syndrome appointed PAH-specific therapy, which allows more rationally selection of patients for surgical correction, which shows good results in prospective. The PAH-specific therapy seems to lead to the remodeling of the lung vessels, which has a favorable effect on the results of surgical correction of the defect.

Despite the possibility of using PAH-specific therapy, the issue of correction of complex heart defects, combined with Eisenmenger syndrome, which complicated by the development of pulmonary hypertension, remains debatable. In the patient's management tactics, a one-stage correction of congenital heart defects complicated by high pulmonary hypertension can lead to death, even though nitrogen oxide and oxygen are used in high concentration. There are publications in the literature about the possibility of this approach in correcting complex CHDs combined with Down syndrome and complicated by the development of Eisenmenger syndrome [39].

Japanese surgeon N. Ohashi with co-authors [39], it has been suggested that two-stage correction of complex heart defects with pulmonary hypertension is preferable in patients with Down's syndrome. Their main argument is that two-stage correction prevents further damage of the lung vessels.In their work, they showed the effectiveness of a two-stage approach in patients with various congenital heart defects (ASD, VSD, PDA) based on the ongoing lung biopsy at each stage of treatment, and also making non-invasive examination methods (X-rays to determine cardiothoracic index (CTI); Echo to determine the ratio between pulmonary and systemic blood flow (Qp/Qs) and the ratio between pulmonary and systemic blood pressure (Pp/Ps). In patients with Down syndrome, the risk of pulmonary hypertension depends largely on factors such as alveolar hypoplasia and thickening of the middle shell, which can lead to pulmonary hypertension in an early age. It has been proven, in an experimental way that the narrowing of the pulmonary artery, in patients with a number of congenital heart defects, such as VSD, PDA and ASD, should be performed as early as possible (Figure 2). Irreversible pulmonary hypertension can develop within a few months after birth.

Conclusion

The natural course of a number of congenital heart defects with pulmonary hypertension ultimately leads to the development of Eisenmenger syndrome. Irreversible changes in the pulmonary-arterial bloodstream lead to right-left shunt, which is manifested by diffuse cyanosis, arterial hypoxemia. Previously, patients with Eisenmenger syndrome were anoperable, however recent studies demonstrated the possibility of correcting the condition itself and the causes of it. The PAH-specific therapy allowed surgical correction of the defect in a number of cases, having a positive effect in the postoperative period. Thus, it can be said that the treatment of Eisenmenger syndrome has a consistent step-by-step nature: diagnostic-therapeutic treatment-operative treatment-therapeutic treatment. The administration of PAH-specific therapy allows more rational selection of patients for surgical correction, which shows acceptable results. Despite the possibility of using PAH-specific therapy, the issue of correction of complex heart defects, combined with Eisenmenger syndrome, which complicated by the development of pulmonary hypertension, remains debatable. In the prevention of the development of pulmonary hypertension and the treatment of patients with Eisenmenger syndrome, pulmonary artery narrowing is the first stage of treatment. At the same time narrowing should be performed as early as possible to prevent development of irreversible changes in pulmonary artery. Before correction of the defect, it is necessary to ensure that changes in the lung vessels are reversible.

Available publications in the literature do not make it clear that a one-or two-step approach should be used in patients with severe congenital heart defects in combination with Eisenmenger syndrome. It is necessary to conduct a comparative analysis of the results of two groups of patients, on the basis of which conclusions will be made and practical recommendations for the treatment of this category of patients will be given.

Disclosures: There is no conflict of interest for all authors.

References

1. Eisenmenger V. Die angeborenen Defecte der Kammer scheidewand des Herzens. *Z Klin Med.* 1897; 32:1-28.
2. Simonneau G, Galiè N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2004; 43(12):5-12. https://doi.org/10.1016/j.jacc.2004.02.037
3. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. *I. BrMedJ.* 1958; 2:701-709 https://doi.org/10.1136/bmj.2.5098.701
4. Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. *Circulation*. 2007; 115(8):1039-1050 https://doi.org/10.1161/CIRCULATIONAHA.105.592386
5. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J. Am. Coll. Cardiol.* 2009; 54(1):43-54. https: // doi.org/10.1016/j.jacc.2009.04.012
6. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. *BMJ*. 1958; 2(5098):701-709 https://doi.org/10.1136/bmj.2.5098.701
7. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. *Br Med J.* 1958; 2(5099):755-62 https://doi.org/10.1136/bmj.2.5099.755
8. Kidd L, Driscoll DJ, Gersony WM, Hayes CJ, Keane JF, O'Fallon WM, et al. Second natural history study of congenital heart defects. Results of treatment of patients with ventricular septal defects. *Circulation*. 1993; 87(2):I38-I51.
9. Berman EB, Barst RJ. Eisenmenger's syndrome: current management. *ProgCardiovascDi.s*. 2002; 45(2):129-138. https://doi.org/10.1053/pcad.2002.127492
10. Vongpatanasin W, Brickner ME, Hillis LD, Lange RA. The Eisenmenger syndrome in adults. *Ann Intern Med.* 1998; 128(9):745-755 https://doi.org/10.7326/0003-4819-128-9-199805010-00008
11. Humbert M, Morrell N.W., Archer S.L., Stenmark K.R., MacLean M.R., Lang I.M. et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J.Am.Coll.Cardiol*. 2004; 43(S):13-24
12. Maurice Beghetti, NazzarenoGaliè. Eisenmenger Syndrome. A Clinical Perspective in a New Therapeutic Era of Pulmonary Arterial Hypertension, *J. Am. Coll. Cardiol*. 2009; 53(9):733-740.
13. Hartway S. A parent's guide to the genetics of Down syndrome. *Adv Neonatal Care.* 2009; 9(1):27-30 https://doi.org/10.1097/01.ANC.0000346092.50981.c0
14. Ranweiler R. Assessment and care of the newborn with Down syndrome. *Adv Neonatal Care*. 2009; 9(1):17-24; Quiz 25-6. https://doi.org/10.1097/01.ANC.0000346090.05240.ab
15. Lamb N.E., Feingold E., Savage A., Avramopoulos D., Freeman S. Characterization of susceptible chaisma configuration that increases the risk for maternal non-disjunction of chromosome 21. *Human Molecular Genetics.* 1997; 6:1391-1399. https://doi.org/10.1093/hmg/6.9.1391
16. Holland A.J., Cleveland D.W. (June 2012). «Losing balance: the origin and impact of aneuploidy in cancer». *EMBO Rep*. 13(6):501-14. DOI:10.1038/embor.2012.55. PMID 22565320. https://doi.org/10.1038/embor.2012.55
17. Lawinger P. et al. The neuronal repressor REST/NRSF is an essential regulator in medulloblastoma cells. *Nature Med*. 2000; 6:826-831 https://doi.org/10.1038/77565
18. Fuller G. N. et al. Many human medulloblastoma tumors over express repressor element-1 silencing transcription (REST)/neuron-restrictive silencer factor, which can be functionally countered by REST-VP16. Mol. *Cancer Ther.* 2005; 4:343-349
19. Su X. et al. Abnormal expression of REST/NRSF and Myc in neural stem/progenitor cells causes cerebellar tumors by blocking neuronal differentiation. Mol. Cell. Biol. 2006; 26:1666-1678. https://doi.org/10.1128/MCB.26.5.1666-1678.2006
20. Majumder S. REST in good times and bad: roles in tumor suppressor and oncogenic activities. *CellCycle*. 2006; 5:1929-1935. https://doi.org/10.4161/cc.5.17.2982
21. Mik G., Gholve P.A., Scher D.M., Widmann R.F., Green D.W. Down syndrome: orthopedicissues. *Curr Opin Pediatr*. 2008; 20(1):30-6. https://doi.org/10.1097/MOP.0b013e3282f35f19
22. Loane M., Morris J.K., Addor M.C. et al. (January 2013). «Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening». *Eur. J. Hum. Genet.* 21(1):27-33. https://doi.org/10.1038/ejhg.2012.94
23. Frost A.E., Quinones M.A., Zoghbi W.A., Noon G.P. Reversal of pulmonary hypertension and subsequent repair of atrial septal defect after treatment with continuous intravenous epoprostenol. J. Heart. *Lung Transplan*t. 2005; 24(4):501-503. https://doi.org/10.1016/j.healun.2004.02.004
24. Vida V.L., Barnoya J., Larrazabal L.A., Gaitan G., de Maria Garcia F., Castaneda A.R. Congenital cardiac disease in children with Down's syndrome in Guatemala. *Cardiol Young*. 2005; 15:286-90 https://doi.org/10.1017/S1047951105000582
25. Galie N., Humbert M., Vachiery J.L., Gibbs S., Lang I. et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal*. 2015; 1-58
26. Schwerzmann M., Zafar M., McLaughlin P.R., Chamberlain D.W., Webb G., Granton J. Atrial septal defect closure in a patient with 'irreversible' pulmonary hypertensive arteriopathy. *Int. J. Cardiol.* 2006; 110(1):104-107.20. https://doi.org/10.1016/j.ijcard.2005.05.062
27. Balling G, Gildein HP, Genz T, Kaemmerer H, Hess J. Transcatheter closure of a non-restrictive patent ductusarteriosuswith an Amplatzer muscular ventricular septal defect occluder. *Int.JCardiol.* 2007; 117(1):e40-e42.
28. Dimopoulos K., Peset A., Gatzouulis M.A. Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy. *Int.J.Cardiol.* 2008; https://doi.org/10.21693/1933-088X-6.3.126
29. Yamauchi H., Yamaki S., Fujii M., Iwaki H., Tanaka S. Reduction in recalcitrant pulmonary hypertension after operation for atrial septal defect. *Ann Thorac. Surg*. 2001; 72(3):905-906 https://doi.org/10.1016/S0003-4975(00)02537-6
30. Huang J.B., Liu Y.L., Yu C.T., Lv X.D., Du M., Wang Q. et al. Lung iopsy findings in previously inoperable patients with severe pulmonary hypertension associated with congenital heart disease. *Int. J. Cardiol.* 2011; 151(1):76-83. https://doi.org/10.1016/j.ijcard.2010.04.094
31. Galie N., Beghetti M., Gatzoulis M.A., Granton J., Berger R.M., Lauer A. et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006; 114(1):48-54. https://doi.org/10.1161/CIRCULATION AHA.106.630715

32. Budts W., Van Pelt N., Gillyns H., Gewillig M., Van de Werf F., Janssens S. Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome. *Heart.* 2001; 86(5):553-558.37. https://doi.org/10.1136/heart.86.5.553
33. Humbert M., Sitbon O., Simonneau G. Treatment of pulmonary arterial hypertension. *N. Engl. J. Med*. 2004; 351(14):1425-1436. https://doi.org/10.1056/NEJMra040291
34. Novick W.M., Sandoval N., Lazorhysynets V.V., Castillo V., Baskevitch A., Mo X. et al. Flap valve double patch closure of ventricular septal defects in children with increased pulmonary vascular resistance. *Ann.Thorac.Surg*. 2005; 79(1):21-28 https://doi.org/10.1016/j.athoracsur.2004.06.107
35. Larios R., Fitch E.A., Blanco G., Bailey C.P. The use of an artificial foraminal valve prosthesis in the closure of interatrial and interventricular septal defects. *Dis Chest*. 1959; 36:631-41. https://doi.org/10.1378/chest.36.6.631
36. Liu Y.L., Hu S.S., Shen X.D., Li S.J., Wang X., Yan J. et al. Midterm results of arterial switch operation in older patients with severe pulmonary hypertension. *Ann. Thorac.Surg*. 2010; 90(3):848-855.
37. Huang J.B., Liu Y.L., Yu C.T., Lv X.D., Du M., Wang Q. et al. Lung biopsy findings in previously inoperable patients with severe pulmonary hypertension associated with congenital heart disease. *Int. J. Cardiol.* 2011; 151(1):76-83. https://doi.org/10.1016/j.ijcard.2010.04.094
38. Epting C.L., Wolfe R.R., Abman S.H., Deutsch G.H., Ivy D. Reversal of Pulmonary Hypertension Associated with Plexiform Lesions in Congenital Heart Disease: A Case Report. Pediatr. *Cardiol*. 2002; 23(2):182-185. https://doi.org/10.1007/s00246-001-0044-9
39. Ohashi N., Matsushima M., Maeda M., YamakiS. Two-Stage Procedure for Pulmonary Vascular Obstructive Disease in Down Syndrome With Congenital Heart Disease. *Circ. J.* 2006; 70:1446-1450 https://doi.org/10.1253/circj.70.1446