Respiratory Medicine Case Reports 21 (2017) 16–20

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Impact of advanced medical therapy for the outcome of an adult patient with Eisenmenger syndrome

Eglė Ereminienė [a], Marija Kinderytė [b, *], Skaidrius Miliauskas [c]

[a] Department of Cardiology, Lithuanian University of Health Sciences, Lithuania
[b] Faculty of Medicine, Lithuanian University of Health Sciences, Lithuania
[c] Department of Pulmonology and Immunology, Lithuanian University of Health Sciences, Eivenių 2, LT-50009, Kaunas, Lithuania

ARTICLE INFO

Article history:
Received 18 November 2016
Received in revised form
27 February 2017
Accepted 3 March 2017

Keywords:
Eisenmenger syndrome
Pulmonary arterial hypertension
Patent ductus arteriosus
Phosphodiesterase type-5 inhibitor
Endothelin receptor antagonist
Heart and lung transplantation

ABSTRACT

Eisenmenger syndrome (ES) is the most severe form of pulmonary arterial hypertension (PAH) associated with congenital heart disease. It is an extremely devastating condition with a serious impact on patients' life. Classical therapy of ES remains directed to avoid complications, such as erythrocytosis, treatment of congestive heart failure, prevention of infection, and secondary haematological abnormalities such as iron deficiency and coagulation disorders. However, the only effective treatment is heart–lung transplantation; still, morbidity and mortality after transplantation remain substantially high. Furthermore, waiting lists for heart–lung transplantation are long. Recent studies examining the use of advanced medical treatment in patients with ES have shown that it may have beneficial effects in patients with ES; however, additional studies need to be done to confirm its efficacy and appropriate clinical use. A 41-year-old female admitted to the Hospital of Lithuanian University of Health Sciences due to progressive dyspnea on minimal effort, heart failure symptoms leading to NYHA functional class III-IV. After clinical and instrumental investigations, ES secondary to unrepaired patent ductus arteriosus with severe PAH was diagnosed. Treatment with sildenafil was initiated together with the standard pharmacological therapy, and the patient was added to the waiting list for the heart and lung transplantation. After 24 months of stable condition, her clinical status deteriorated, and combination therapy (sildenafil and ambrisentan) was initiated. Clinical symptoms and exercise capacity improved, and she has been stable for 4 years thereafter. Our experience of the management of an adult patient with ES showed the benefits of treatment with advanced therapy with pulmonary vasodilators that improved the patient's quality of life and delayed the need for heart and lung transplantation.

1. Introduction

Eisenmenger syndrome (ES) is a clinical condition with the most advanced form of pulmonary arterial hypertension (PAH) associated with congenital heart defects (CHD) [1]. Clinically, ES presents with multiple organ involvement, with a progressive deterioration of function over time. In most cases, patients survive until their third or fourth decades of life. However, the signs and symptoms of ES in the advanced stages include central cyanosis, dyspnea, fatigue, dizziness, haemoptysis, syncope, and reduced quality and expectancy of life.

Clinical treatment of patients with ES traditionally has focused on palliative and supportive treatment. Medical treatment for ES often includes the use of diuretics, digoxin and antiarrhythmics. However, none of these approaches has proved to significantly modify the quality of life and survival rate in patients with ES. Heart and lung transplantation is the only effective treatment, although waiting lists for heart-lung transplantation are long, and it was performed on a restricted number of patients. Furthermore, morbidity and mortality after transplantation remain substantially high [2].

Currently, an increased understanding of the pathophysiology of ES and the success of disease-specific treatment for PAH has offered new hope for patients with ES. The advanced therapy (AT) for PAH has been shown to improve patients' functional capacity, quality of life, and long-term survival [3,4]. The medical treatment strategy for patients with PAH associated with congenital heart disease, and especially for subjects with Eisenmenger syndrome, is mainly

* Corresponding author.
E-mail address: kinderytem@gmail.com (M. Kinderytė).

http://dx.doi.org/10.1016/j.rmcr.2017.03.002

based on the clinical experience of experts rather being formally evidence-based [5]. There are only few studies to guide the use of pulmonary vasodilators in this population, and important questions such as indications for initiation, parameters demonstrating the effectiveness of treatment, and treatment goals remain unanswered. Accordingly, we herein present a case report of a patient with severe ES treated with PAH drugs.

2. Case presentation

A 41-year-old female teacher with ES induced by untreated congenital heart defect - patent ductus arteriosus (PDA) which caused severe PAH - visited our hospital in 2010. Cardiac catheterization records (performed in 2003) confirmed the diagnosis of PDA; however, at that time, the repair could not be performed due to severe PAH. Recently, the patient has been unable to work because of the progressed symptoms, especially dyspnea on exertion. She had heart failure symptoms of New York Heart Association (NYHA) functional class III-IV. Peripheral Pulse oximetry (SpO2) reading at room air was 87%. On investigation, the haemoglobin level was 199 g/l, hematocrit – 46%, erythrocyte count – 6.85 × 1012/l, and NT-proBNP level – 105 pg/ml. The ECG revealed signs of right ventricular hypertrophy with right ventricular pressure overload (Fig. 1). The diagnosis of unrepaired (the parents refused operation) congenital heart defect – PDA – has been known from childhood. Transthoracic echocardiography showed existing PDA, but blood flow through the PDA was not recorded. Other findings were an enlarged right ventricle (RV) with hypertrophy of the free wall (11.7 mm) and paradoxical bulging of the septum into the left ventricle during systole, impairment of systolic RV function – TAPSE 12.7 mm (Table 1), good systolic left ventricular function with ejection fraction 50%, dilated pulmonary artery, and moderate tricuspid regurgitation.

Cardiac magnetic resonance imaging (MRI) revealed PDA connecting the aortic isthmus to the main pulmonary artery, reduced RV ejection fraction to 51% and the RV stroke volume of 26.28 ml/m^2 (Fig. 2). Hemodynamic monitoring by cardiac catheterization confirmed severe pulmonary hypertension with pulmonary artery pressure (PAP) 200/106 mmHg, mean pulmonary artery pressure (MPAP) 145 mmHg, right atrium pressure 11 mmHg, cardiac index (CI) 2.5 l/min/m^2 and pulmonary vascular resistance (PVR) of 2947.4 dyn s cm^{-5} (normal values – 120–250)/36.8 Wood units (WU). A PDA had bidirectional blood flow and defect size was 11 mm.

She was conservatively managed for several months, but her clinical status did not improve. Subsequently, AT for PAH with sildenafil 20 mg three times daily was initiated and the patient was added to a waiting list for heart and lung transplantation.

The initiation of sildenafil treatment improved her clinical status and exercise tolerance, NT-pro BNP levels decreased (Fig. 3A and B). Invasive haemodynamic data were without any significant change (Table 1).

After 24 months of sildenafil treatment, her symptoms started to worsen – exercise tolerance and heart failure symptoms began to deteriorate, and the patient had syncope. The level of NT-pro BNP elevated to 1003 pg/ml (Fig. 3A). Transthoracic echocardiography demonstrated existing PDA with right-to-left shunt. Also, it was obtained still elevated pressures in pulmonary artery (100 mmHg) and increased PVR of 1188 (14.85 WU). The dosage of sildenafil could not be increased because of the systemic hypotension of 100/60 mmHg with no symptoms and antihypertensive drugs. A decision was made to add endothelin receptor antagonist –

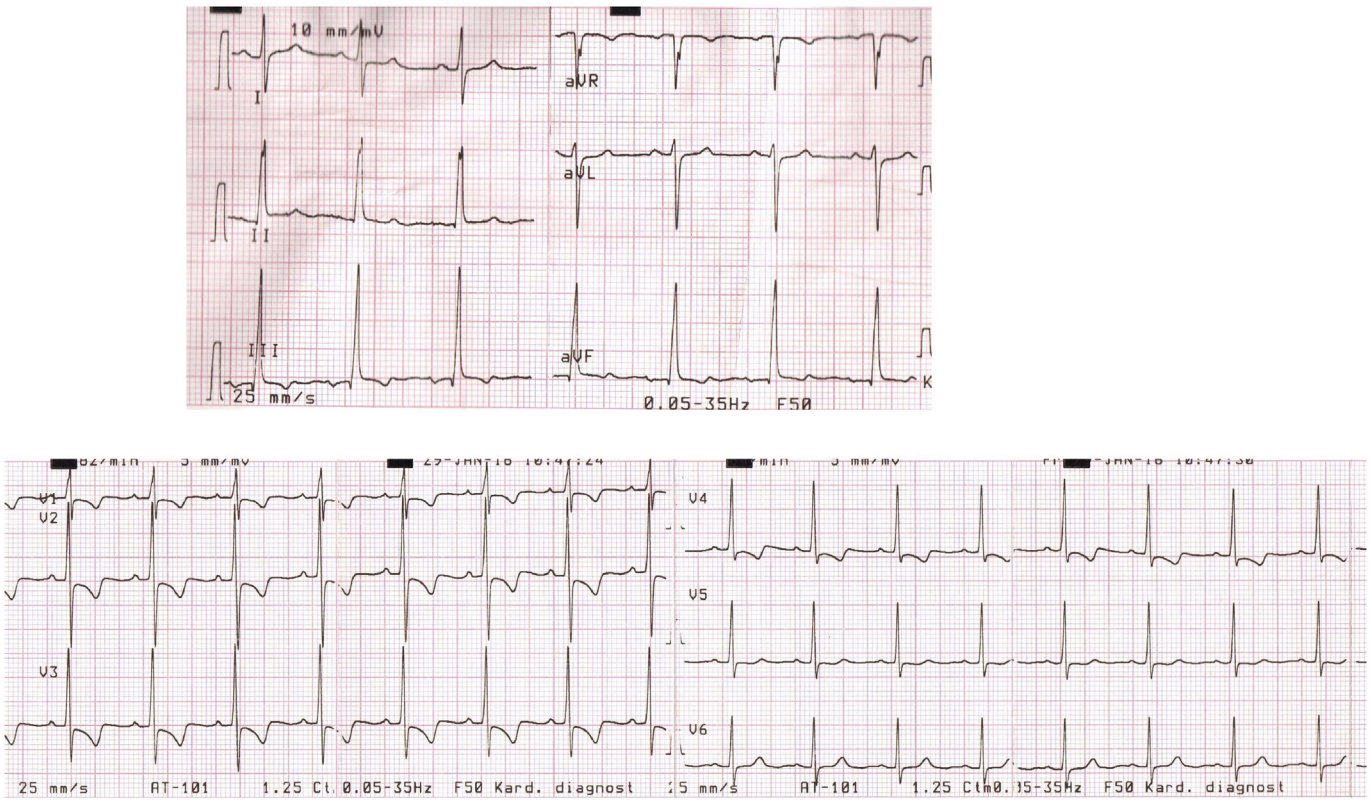

Fig. 1. Sinus rhythm, right axis deviation, dominant R wave in the V1, deep S wave in the leads V5-6, and T wave inversions in V1-4 leads, suggesting right ventricular hypertrophy with right ventricular pressure overload.

Table 1
Presentation of hemodynamic changes (mean pulmonary artery pressure, cardiac index, pulmonary capillary wedge pressure), systolic function of right ventricular, exercise capacity evaluation based on spiroergometry parameters, and blood oxygen saturation in a patient with ES receiving disease-specific treatment for PAH from 2010 to 2016.

Date	Mean pulmonary artery pressure (mmHg)	Cardiac index (l/min/m^2)	Pulmonary wedge pressure (mmHg)	RV systolic function (TAPSE) (mm)	Spiroergometry VO2 (ml/kg/min)	Peripheral capillary oxygen saturation, SpO2 (%)
2010	145	2.5	6	12,7	9.5	87
2011	133	3	14	16	13.8	88
2012[a]	76	3.2	5	21	17.4	92
2016	70	3.2	5	19	15.2	94

[a] Results after 6 months of combination therapy (sildenafil + ambrisentan).

ambrisentan 5 mg once daily, because of deterioration of the patient's clinical condition, physical capacity and of registered persistent increased pressures in pulmonary artery, PVR and occurred syncope.

The combination therapy (sildenafil and ambrisentan) seemed to be well tolerated, and the patient's symptoms improved. Cardiac MRI revealed an improvement in the RV ejection fraction from 51% to 59%, and RV stroke volume - from 26.28 ml/m^2 to 36 ml/m^2. The changes of haemodynamic and functional data are presented in Table 1. The patient's functional class has improved from IV to II-III, and exercise capacity has increased from 150 to 430 m. Her general condition has been stable for a period of 4 years, and she continues to do well with marked improvements in her quality of life.

3. Discussion

Despite advances in diagnosis and treatment, approximately 10% of patients with congenital heart disease (for example large atrial septal defect) will develop PAH later in life whereas up to 50% of the large patent ductus arteriosus will develop PAH in childhood if left unrepaired. A large unrepaired left-to-right intracardiac or extracardiac shunt leads to progressive PAH with reversal of the direction of the shunt and development of cyanosis, the so-called ES. Several congenital heart defects cause ES. The lesions most common to ES typically include ventricular septal defect, atrial septal defect, and less commonly - patent ductus arteriosus. The morbidity and mortality rates in patients with ES are significantly affected by PAH. ES has been associated with reduced life expectancy, even if many patients live to their third or fourth decade [6]. However, previously published studies suggest that patients with PAH associated with CHD (such as patients with ES) have a better prognosis and survival rates compared with those with PAH associated with a structurally normal heart [7].

Although the exact prevalence of ES is unknown, but it is believed to account for approximately 4% of adult patients who have been seen at large tertiary centres for congenital heart disease [8]. The achievements in surgery and paediatric cardiology have reduced the prevalence of ES in the Western world by approximately 50% during the last 50 years [9]. The medical treatment strategy for patients with PAH associated with CHD, and especially for subjects with ES, is mainly based on the clinical experience of experts rather than being evidence-based [5].

Until recently, management options for patients with ES have been limited to palliative measures or heart-lung transplantation [10]. Classical therapy of the ES remains directed towards avoiding

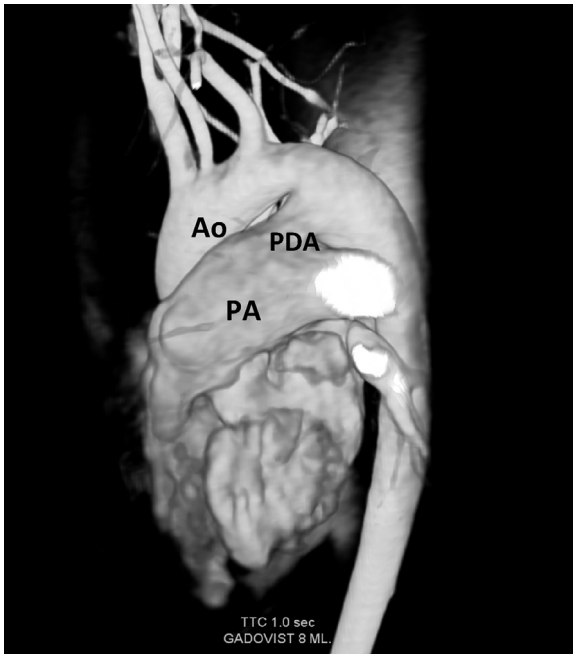

Fig. 2. Cardiac magnetic resonance angiography 3D rendered image, lateral projection. Ao: aorta; PDA: patent ductus arteriosus; PA: pulmonary artery.

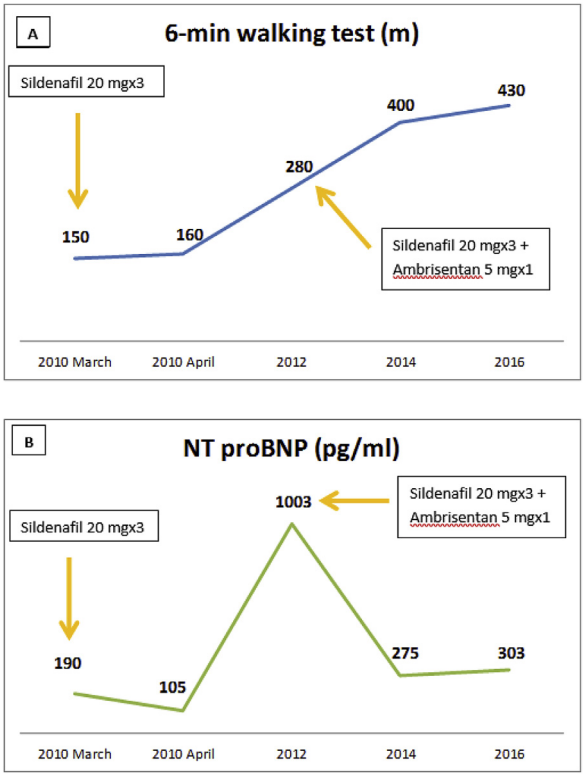

Fig. 3. Presentation of clinical and laboratory changes in a patient with ES receiving disease-specific treatment for PAH from 2010 to 2016. **A:** An improvement in the heart failure marker (NT-proBNP). **B:** An improvement in exercise capacity (a 6-min walking test).

complications, such as congestive heart failure, and prevention of infection, erythrocytosis, and coagulation abnormalities. Bonello and colleagues in their study found that at 30, 40, 50, and 60 years of age, the survival of ES patients was, respectively, 96%, 87%, 67%, and 49% [11]. Conventional empirically used pharmacological treatment, including diuretics, antiarrhythmics, anticoagulants, iron supplementation, and oxygen therapy does not seem to alter the survival rate [12]. There is no specific treatment for ES, apart from both heart and lung transplantation, particularly for those with a poor prognosis and failure to respond to pharmacological treatment. Transplant surgery is, however, associated with high perioperative mortality, and previous surgical procedures seem to have a negative impact on survival after transplantation [13]. Survival rates after transplantation for ES patients are similar to those reported in non-ES recipients [9]. Concerning the long-term outcomes of heart and lung transplantation, 1-, 5-, and 10-year survival rates for ES patients were 72.6%, 51.3%, and 27.6%, respectively, compared with 74.1%, 48.1%, and 26.0%, respectively, in non-ES patients, and there was no difference in overall survival [14].

A recent retrospective study showed that patients who received novel, advanced, and targeted therapies, including endothelin receptor antagonists, phosphodiesterase type-5 inhibitors (PDE-5i) and prostacyclin analogues, have benefited from significantly longer mean times to death or listing for transplant, compared to patients receiving standard care [15]. Patients on AT for PAH were, in fact, at significantly lower risk of death (comparing 7-year mortality of 30.8% without AT versus 5.7% with AT) [6]. The double-blind, placebo-controlled trial BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5) is the only randomized controlled trial in patients with ES, which demonstrated that bosentan significantly reduced PVR and improved exercise capacity versus placebo – the change from baseline of 6-min walking distance in the placebo group decreased by 9.7 m, but increased by 43.4 m in the group of patients treated with bosentan for 16 weeks. According to the guidelines for diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology and the European Respiratory Society, bosentan is currently approved in Europe for ES patients in NYHA class 3 (Class IB recommendation) [5]. One other type of AT medications is PDE-5i. During a prospective, open-label trial on sildenafil, significant improvements in functional class, oxygen saturation, and cardiopulmonary hemodynamics were observed after 6 months. However, the 6-min walking distance showed no significant change [9]. However, the study of Zhang ZN, Jiang X, Zhang R et al. showed in 84 ES patients treated with open-label sildenafil for 1 year significant improvements in pulmonary hemodynamics (including PVR and mean PAP) as well as in symptoms, peripheral oxygen saturation and 6-min walking distance (+56 m) [16]. In addition, Mukhopadhyay et al. reported data from 16 Eisenmenger patients showing that tadalafil (PDE-5i) reduces PVR, MPAP and increased peripheral oxygen saturation after 12 weeks of therapy [17]. A retrospective review of 8 patients with ES showed that 3 months of prostacyclin analog – epoprostenol administration resulted in improved WHO functional class, increased oxygen saturation, decreased PVR and increased 6-min walking distance [18,19]. However, epoprostenol therapy has problems related to long-term catheter use. The improvement of the pharmacological management of PAH over the last two decades has been associated with a decreased number of patients requiring transplantation for PAH.

There is one study that demonstrated the use of AT for PAH as a bridge to transplantation. Adriaenssens and colleagues presented a follow-up of more than 9 years, in which the mean survival time for patients on AT was significantly longer than for patients on standard care (6.7 + 0.7 vs. 2.7 + 0.5 years, respectively). In addition, in the standard care group, the mean time until death or effective heart–lung transplantation was shorter (3.5 + 0.9 years) when compared to that in the AT group (7.8 + 1.0 years) [5].

Our case illustrates the clinical manifestation of ES with congenital heart defect and severe PAH and the effectiveness of AT combination in this patient, resulting in reduced heart failure symptoms, improved functional test results (exercise capacity) and readings of RV function measurements obtained during transthoracic echocardiography and cardiac MRI, and a reduced invasive diagnostic parameter – PVR and CI. The patient recovered impressively well (the functional class improved from IV to II-III), and she returned to full-time work. Her general condition has been stable for a period of 4 years, and she continues to do well with marked improvements in her quality of life. In addition, the patient had a possibility to undergo heart-lung transplantation twice, but refused because of good physical condition. The combination of AT for the patient with ES demonstrates favourable clinical outcome, an improvement in the patient's quality of life, and a delay in the need for heart-lung transplantation.

Disclosure

The authors have no conflict of interest that should be declared.

References

[1] B.J.M. Mulder, Changing demographics of pulmonary arterial hypertension in congenital heart disease, Eur. Respir. Rev. 19 (118) (2010) 308–313. http://err.ersjournals.com/content/19/118/308.

[2] J.D. Hosenpud, L.E. Bennett, B.M. Keck, B. Fiol, M.M. Boucek, R.J. Novick, The registry of the international society for heart and lung transplantation: sixteenth official report – 1999, J. Heart Lung Transplant. 18 (7) (1999) 611–626, http://dx.doi.org/10.1016/S1053-2498(99)00114-X.

[3] V.V. McLaughlin, O. Sitbon, D.B. Badesch, R.J. Barst, et al., Survival with first-line bosentan in patients with primary pulmonary hypertension, Eur. Respir. J. 25 (2) (2015) 244–249, http://dx.doi.org/10.1183/09031936.05.00054804.

[4] V.V. McLaughlin, A. Shillington, S. Rich, Survival in primary pulmonary hypertension: the impact of epoprostenol therapy, Circulation 106 (12) (2002) 1477–1482, http://dx.doi.org/10.1161/01.CIR.0000029100.82385.58.

[5] N. Galie, M. Humbert, J.L. Vachiery, S. Gibbs, I. Lang, et al., 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, Eur. Heart J. 27 (2016) 67–119, http://dx.doi.org/10.1093/eurheartj/ehv317.

[6] K. Dimopoulus, R. Inuzuka, S. Golleto, G. Giannakoulas, et al., Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension, Circulation 121 (1) (2010) 20–25, http://dx.doi.org/10.1161/CIRCULATIONAHA.109.883876.

[7] C. Arnott, C. Boehm, E. Lau, D.S. Celermajer, Survival outcomes in severe congenital versus non-congenital pulmonary hypertension, Heart Asia 8 (1) (2016) 3–7, http://dx.doi.org/10.1136/heartasia-2015-010702.

[8] G.P. Diller, M.A. Gatzoulis, Pulmonary vascular disease in adults with congenital heart disease, Circulation 115 (2007) 1039–1050, http://dx.doi.org/10.1161/CIRCULATIONAHA.105.592386.

[9] M. Beghetti, N. Galie, Eisenmenger syndrome: a clinical perspective in a new therapeutic era of pulmonary arterial hypertension, J. Am. Coll. Cardiol. 53 (9) (2009) 733–740, http://dx.doi.org/10.1016/j.jacc.2008.11.025.

[10] G.P. Diller, K. Dimopoulos, D. Okonko, W. Li, S.V. Babu-Nrayan, et al., Exercise intolerance in adult congenital heart disease, Circulation 112 (6) (2005) 828–835, http://dx.doi.org/10.1161/CIRCULATIONAHA.104.529800.

[11] B. Bonello, S. Renard, J. Mancini, et al., Life span of patients with Eisenmenger syndrome is not superior to that of patients with other causes of pulmonary hypertension, Cardiovasc. Diagnosis Ther. 4 (5) (2014) 341–349, http://dx.doi.org/10.3978/j.issn.2223-3652.2014.10.03.

[12] L. Daliento, J. Somerville, P. Presbitero, L. Menti, S. Brach-Prever, G. Rizzoli, S. Stone, Eisenmenger syndrome: factors relating to deterioration and death, Eur. Heart J. 19 (12) (1998) 1845–1855, http://dx.doi.org/10.1053/euhj.1998.1046.

[13] H. Goerler, A. Simon, B. Gohrbandt, et al., Heart-lung and lung transplantation in grown-up congenital heart disease: long-term single center experience, Eur. J. Cardio Thoracic Surg. 32 (6) (2007) 926–931, http://dx.doi.org/10.1016/j.ejcts.2007.08.024.

[14] S.C. Stoica, K.D. McNeil, K. Perreas, L.D. Sharples, et al., Heart-lung transplantation for Eisenmenger syndrome: early and long-term results, Ann. Thorac. Surg. 72 (6) (2001) 1887–1891. https://www.ncbi.nlm.nih.gov/pubmed/11789765.

[15] T. Adriaenssens, M. Delcroix, K. Van Deyk, W. Budts, Advanced therapy may delay the need for transplantation in patients with the Eisenmenger syndrome, Eur. Heart J. 27 (12) (2006) 1472–1477, http://dx.doi.org/10.1093/eurheartj/ehl017.

[16] Z.N. Zhang, X. Jiang, R. Zhang, X.L. Li, B.X. Wu, Q.H. Zhao, Y. Wang, L.Z. Dai, L. Pan, M. Gomberg-Maitland, Z.C. Jing, Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicenter study, Heart 97 (2011) 1876–1881, http://dx.doi.org/10.1136/heartjnl-2011-300344.

[17] S. Mukhopadhyay, M. Sharma, S. Ramakrishnan, et al., Phosphodiesterase-5 inhibitor in Eisenmenger syndrome: a preliminary observational study, Circulation 114 (7) (2006) 1807–1810, http://dx.doi.org/10.1161/CIRCULATIONAHA.105.603001.

[18] S.M. Fernandes, J.W. Newburger, P. Lang, D.D. Pearson, J.A. Feinstein, et al., Usefulness of epoprostenol therapy in the severely ill adolescent/adult with Eisenmenger physiology, Am. J. Cardiol. 91 (5) (2003) 632–635, http://dx.doi.org/10.1016/S0002-9149(02)03328-3.

[19] H. Fukushima, Update on medical treatment of patients with Eisenmenger syndrome, Int. Heart J. 56 (2015) 3–7, http://dx.doi.org/10.1536/ihj.14-347.