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

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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.

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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 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
based on the clinical experience of experts rather than 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/m² (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 atrial pressure 11 mmHg, cardiac index (CI) 2.5 l/min/m² 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.](image-url)
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/m² to 36 ml/m². 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 unrepaird. A large unrepaird 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

| Date | Mean pulmonary artery pressure (mmHg) | Cardiac index (l/min/m²) | 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*| 76                                    | 3.2                      | 5                               | 21                              | 17.4                          | 92                                           |
| 2016 | 70                                    | 3.2                      | 5                               | 19                              | 15.2                          | 94                                           |

* Results after 6 months of combination therapy (sildenafil + ambrisentan).

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).
showing that tadala.

Mukhopadhyay et al. reported data from 16 Eisenmenger patients and mean PAP) as well as in symptoms, peripheral oxygen satura-

tions, improvements in pulmonary hemodynamics (including 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 combina-

tion 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.

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