REVIEW ARTICLE

Therapeutic methods used in patients with Eisenmenger syndrome

Olga Trojnarska, Karolina Plaskota

1st Cardiology Department, University of Medical Sciences, Poznań, Poland

Abstract

Patients with Eisenmenger syndrome form a small percentage of congenital heart disease patients. The rarity of this syndrome, combined with its complex pathophysiology, account for the insufficient understanding of the principles underlying its proper treatment. The main clinical symptoms are: cyanosis due to secondary erythrocytosis, resulting in increased blood viscosity, iron deficiency anemia (enhanced by unnecessary phlebotomies), blood clotting disturbances, heart failure and serious supraventricular and ventricular arrhythmias. Recent decades have seen developments in pulmonary hypertension pathophysiology which have led to the introduction of new groups of drugs: prostacycline analogs (Epoprostenol, Treprostinil, Beraprost, Illoprost), phosphodiesterase inhibitors (Sildenafil, Tadalafil), endothelin receptor antagonists (Bosentan, Sitaxantan, Ambrisentan) and nitric oxide. These drugs should be administered to patients in III–IV NYHA class. Despite successful early results, the therapeutic effect on patients with Eisenmenger syndrome has not been conclusively established. Our therapeutic efforts should be directed mainly towards preventing complications. As a rule, we should avoid agents with no established therapeutic efficacy and try to alleviate symptoms without any additional risk, so as not to disrupt the existing clinical balance. (Cardiol J 2009; 16, 6: 500–506)

Key words: treatment, Eisenmenger syndrome

Introduction

In 1897 an Austrian doctor, Viktor Eisenmenger, described a patient with ventricular septal defect (VSD) and cyanosis. Sixty years later, based on pathophysiological analysis, Paul Wood described this clinical situation as a secondary pulmonary hypertension with pulmonary vessel resistance exceeding 800 dyn/s/cm^{-5} and the presence of inversed or bidirectional flow between heart chambers or great vessels. He also claimed that the site of communication does not have any pathognomic significance [1]. Current data points to secondary pulmonary hypertension developing earlier in VSD and patent ductus arteriosus (PDA) than in atrial septal defect (ASD) [2]. Modern diagnosis of secondary pulmonary hypertension, also known as Eisenmenger syndrome (ES), can be made if mean pressure in the pulmonary trunk (hemodynamic measurement) exceeds 25 mm Hg at rest and 30 mm Hg during exercise [3]. Pulmonary hypertension results from vasoconstriction, pulmonary artery remodelling and aggravating thrombotic processes. Increased pulmonary blood flow leads to endothelial dysfunction of small arteries which triggers secretion of agents stimulating myocyte hypertrophy and proliferation, enhancing adherence and activation of platelets and leukocytes favoring

immune inflammation as well as activation of coagulation pathways. Endothelial damage disrupts the balance between vasoconstrictors, such as endothelin 1 and tromboxane A2, and vasodilators, including nitric oxide, vasoactive intestinal peptide or prostaglandin A1, favoring vasoconstriction. At an early stage of the disease, changes in the pulmonary arteries are functional and reversible, because a systolic component prevails. With time, plexiform lesions become irreversible. Histologic studies allowed for the staging of hypertension when Heath-Edward grading was created in 1958, or 20 years later with the introduction of the Rabinovith classification [4, 5].

Eisenmenger syndrome is observed in 5–10% of patients with congenital heart disease [6, 7]. It is caused by the following clinical conditions:
— isolated lesions without pulmonary outflow tract obstructions: ASD, VSD, PDA, anomalous pulmonary venous connection;
— complex lesions without pulmonary outflow tract obstruction:
  • common atrio-ventricular canal (CAVC),
  • ventriculoarterial discordance (dextro-transposition of the great arteries) or atrioventricular and ventriculoarterial discordance (levo-transposition of the great arteries) with a non-restrictive ventricular septal defect,
  • various forms of truncus arteriosus;
— large aortopulmonary connection:
  • aortopulmonary window,
  • aortopulmonary collaterals in patients with pulmonary atresia,
  • surgically created aortopulmonary connections (e.g. Potts and Waterson anastomoses) [8].

Pathophysiology and clinical presentation of secondary pulmonary hypertension

The dynamics of the progression of secondary pulmonary hypertension depend on the size of the leak and its location. Pretricuspid shunt, responsible mainly for volume overload (ASD, anomalous pulmonary venous connection), is less frequently a cause of ES than 'post-tricuspid' shunts (VSD, PDA) generating volume and pressure overload. Long-term prognosis does not differ between these two groups of patients [7]. Patients with Down syndrome show a particular predilection for pulmonary hypertension [9]. Dynamic developments in the field of pediatric cardiac surgery have led to a reduction in the incidence of this syndrome in patients with simple shunt defects, but there are more cases observed in patients with complex defects whose lives have been substantially prolonged [10].

Clinical presentation of ES affects multiple organs and results from cardiac anatomic anomalies and post-operative complications, and to the greatest extent from size and direction of shunt and resultant blood changes: secondary erythrocytosis and eventual cyanosis. Increased haemoglobin production is an adaptive mechanism allowing for adequate tissue oxygenation. Increased hematocrit leads to higher blood viscosity followed by specific clinical symptoms, such as headaches, vertigo, paresthesias and myalgias. An additional cause of some of these symptoms is iron deficiency, observed mainly in patients who have undergone phlebotomy. Due to lowered count and dysfunction of platelets and disruption of intrinsic pathway (reduction of activation of II, VII, IX, X, V and von Willebrand factors), cyanotic patients often exhibit bleeding and thromboembolic complications, such as stroke, pulmonary bleeding and large pulmonary vessel thrombosis. Increased heme breakdown facilitates hyperuricemia and eventually joint and kidney changes related to gout. Gallstones containing calcium bilirubinate may lead to cholecystitis. Kidney dysfunction is often observed as a result of secondary glomerulopathy. These patients are at risk of developing infective endocarditis, cerebral abscess and pneumonia. Finally, frequent causes of death in this population are dangerous ventricular and supraventricular arrhythmias and progressive heart failure [9, 11, 12]. Obviously, survival rates in this group of patients are worse than the average population (55% reach 50 years of age) [13], but they are still significantly better than in patients with idiopathic pulmonary hypertension (75% die within three years of the diagnosis being made) [14].

Complex non-pharmacological care

The traditional, though still valid, approach to ES focuses on close monitoring of sufferers in highly specialized reference centers, cohorting adults with congenital heart disease (CHD) and lifestyle modifications in addition to adjunct therapies aimed at maintaining the existing balance of pressures in pulmonary and systemic circulations, as well as balance between bleeding and hemostasis.

General recommendations include instructing patients to abstain from physical exertion that could lower systemic pressure and enhance right to left shunt prior to decreased saturation. Besides, high pulmonary resistance eliminates additional left atrial and ventricular inflow, which precede a drop in ejection fraction.

Eisenmenger syndrome patients should avoid dehydration (i.e. diarrhea, vomiting, heat, fever)

facilitating an increase in blood viscosity and finally thrombotic complications. With adequate hydration, an air filter must be used to avoid air embolism if an intravenous line is in place [2, 11].

Non-cardiac necessary interventions should be performed in centers providing adequate anesthesia. Non-cardiac surgery is one of the commonest causes of death in this population. Most anesthetics lead to systemic drop in blood pressure and resultant aggravation of right to left shunt and desaturation. On the other hand, a sudden rise in resistance may lead to right ventricular failure. Intraoperative arrhythmias, significant blood loss and bleeding complications are typical of cyanosis. For that reason, local anethesia is preferred. However, epidural anesthesia is related with greater hypotensive effect and the risk of bleeding and is not superior than general anesthesia. It is important to carry out intraoperative monitoring of volemia and pressure changes as well as pulse oximetry to assess oxygen saturation [4, 8].

General practice is to apply phlebotomy which is allowed only in coexistent symptoms of excessive viscosity observed with hematocrit exceeding 65%. A serious side effect of these procedures is iron deficiency anemia resulting in microcytosis aggravating thrombotic complications. It is frequently missed, as the hemoglobin may be less then 15 g/dL, but should be greater then 18 g/dL [11]. Contrary to previous beliefs, increased hematocrit does not lead to dangerous strokes and its risk factors are low levels of iron, hypertension and atrial fibrillation [15]. Phlebotomy may be also applied before the planned surgical intervention to improve hemostasis. One phlebotomy cannot exceed 250–500 mL, at the same time replenishing with 750–1000 mL of IV saline. No more then four phlebotomies should be performed during one year. If this does not bring about clinical improvement, iron deficiency anemia must be suspected, and oral low dose of ferrous sultate (325 mg/d.) administered.

The question of antithrombotic therapy remains unanswered. Due to both thrombotic and bleeding risk in these patients, treatment with coumarin derivatives is accepted only in atrial fibrillation, intracardiac mechanical prostheses and conduits with advanced heart failure. An indication for such treatment are episodes of massive pulmonary thrombosis, seen in about 30% of patients with ES, although a great expert on the topic, Josef Perloff, is against the administration of coumarin derivatives even in such circumstances. He maintains that antithrombotic agents may lead to usually intractable pulmonary hemorrhage [16, 17]. Hemoptysis is a frequent clinical complication which can be life-threatening and may require an adequate therapeutic approach including hospitalization, restricting physical activity and cough reflex elimination. Bronchoscopy is contraindicated as a potential source of pulmonary hemorrhage. If no clinical improvement ensues, platelet mass, fresh frozen plasma, factor VIII, vitamin K or cryoprecipitate should be administered [11].

A high risk of serious pulmonary infections necessitates flu and anti-pneumococci vaccination [9].

Oxygen administration does not usually lead to increased saturation, but can bring about dry airways [18].

There are no evidence-based recommendations for arrhythmias and heart failure in patients with secondary pulmonary hypertension. Serious supraventricular arrhythmias require emergency cardioversion to restore sinus rhythm. Due to the high risk of clinical deterioration in patients with ES, no preliminary prolonged antithrombotic therapy is required [19]. Chronic pharmacotherapy of arrhythmias should exclude negative inotropic agents. Heart failure treatment in this population is also based on theoretical pathophysiological assumptions. Diuretic use must be moderate, so as not to cause increased hematocrit or a drop in cardiac output. Vasodilator administration is limited due to the danger of decreased systemic pressure and enhanced right to left shunt followed by desaturation [20]. A small retrospective study focusing on angiotensin-converting enzyme (ACE) inhibitors used by ten cyanotic patients showed improvements in physical endurance in those patients with no adverse effects on blood pressure or oxygen saturation, despite the afterload reducing agent. It was postulated that improvement of cardiac output on ACE inhibitors offsets the potential for worsening of right to left shunting in those patients [21].

Pregnancy is strongly contraindicated in these patients because of very high mortality among pregnant women [22]. Gravidas with pulmonary hypertension, high pulmonary resistance compounded with increased volemia may lead to right ventricular failure. At the same time, diminished 'return' to the left ventricle leads to decreased cardiac output. Extreme cases may feature syncope or even death resulting from coronary or central neural system ischemia. Pregnancy-related drop in systemic pressure enhances right to left shunt, augmenting cyanosis and causing often life-threatening hypoxemia [9]. An additional factor contributing to a higher risk of life-threatening complications in cyanosis is susceptibility to thromboembolic complications, bleeding and the risk of pulmonary artery rupture [23].

Most sudden deaths and irreversible hypoxia related deaths are seen within the first ten days of delivery [24]. The risk of death in idiopathic hypertension is 30%, and reaches 50% in secondary pulmonary hypertension. This gloomy statistic, despite the substantial medical progress made, has not changed over the last few decades [25]. Secondary pulmonary hypertension poses significant risk for the fetus, even if pulmonary pressure does not exceed half of the systemic values [22]. Patients with this diagnosis should be strongly discouraged from becoming pregnant. Due to substantial risk to the mother's health, pulmonary hypertension is an indication for early termination of pregnancy. If a woman decides to continue pregnancy, bed rest is necessary as well as treatment of right ventricular failure. Antithrombotic therapy, oxygen, prostacyclins and nitric oxide can all be implemented, even though there is no evidence supporting this approach [26]. Contraception is recommended, taking into account estrogen-related risk of thrombotic complications and progesterone-related increase in volemia [27].

The ultimate therapy in this group of patients is lung or heart-lung transplantation. The decision to transplant should be made after deep consideration. The procedure should be offered to patients in the advanced stages of the disease because of the long term good clinical status of ES patients compared to patients with pulmonary hypertension related to other conditions. The analysis of survival rate of 605 heart-lung or lung transplants of end stage ES patients shows that recipients are not a homogeneous group. Patients with ventricular septal defect have a better prognosis than those with ASD or persistent ductus arteriosus [28]. Lung transplant should be accompanied by anatomical correction of the defect. It should be remembered that patients with pulmonary hypertension due to cardiac defect associated with shunt have the highest perioperative mortality amongst all subjects of heart-lung transplants [29].

Finally, the importance of professional psychological help to ES patients must be underscored. Living with activity-limiting chronic illness and visible cyanosis may be a great hurdle for some young people [30].

Pharmacological approach

The last decades have seen much progress in the study of pathophysiology of pulmonary hypertension,n which has resulted in the introduction of new groups of agents for the treatment of this condition: prostacycline derivatives, phosphodi-

esterase inhibitors, endothelin receptor antagonists or nitric oxide. These drugs should be administered to patients in New York Heart Association (NYHA) functional class III and IV [9]. Their therapeutic effect in ES patients has not been fully documented. Due to intracardiac shunt, agents effective in pulmonary hypertension related to other causes can produce varying results. Pulmonary pressure lowering drug can usually decrease systemic pressure. This situation may lead to an increased right to left shunt, followed by decreased blood saturation and decreased cardiac output. It is necessary to evaluate clinical efficacy of the drug in the separate group of patients. Such evaluation is unfortunately very difficult due to the small number of patients and relatively low mortality in this group. Therefore, the primary end points of the studies are characteristics related to patients' clinical status, such as six-minute walk test, ventricular function or natriuretic hormones. There are only a few randomized trials in the therapy of pulmonary hypertension which involved patients with CHD and they did not form a separate group eligible for adequate analysis [31–36].

The best studied group of drugs lowering pulmonary pressure are prostacyclin derivatives. Their vasodilator effect, resulting from adenyl cyclase activation leading to increased intracellular adenosine monophosphate, is accompanied by antiproliferative and antiplatelet effects which are responsible for the agent's efficacy in spite of impaired vasodilation [37]. Epoprostenol is administered IV due to its short half-time (3–5 min). It has the strongest effect of all known agents. It has a documented positive impact in CHD patients improving effort tolerance and saturation [38, 39]. Venous cannulation poses a threat of infection and thromboembolism but these complications are not more frequent in ES than idiopathic hypertension [40, 41]. Therapeutic effects of Epoprostenol, recognized as improved cardiac function, are also comparable [35, 36, 38]. Search for new improved ways of administration led to the introduction of Treprostinil administered subcutaneously just like insulin preparations with microinjection pump (half-time of 30–80 min). Simmoneau et al. [31] have proved its efficacy in a randomized, multi-center trial including 469 patients with different etiologies of pulmonary hypertension. One hundred and nine patients represented Eisenmenger syndrome, six-minute walking test improvements did not differ significantly from the ones achieved in other pulmonary hypertension patients and was inversely related to baseline cardiac function parameters. Oral Beraprostem led to clinical improvements only in patients with

idiopathic hypertension in a three-month observation period, with no beneficial effect after one year [42]. This agent is not currently used in Europe. Available literature does not include a thorough analysis of volatile prostanoid Illoprost use in the analyzed group of patients.

It has been demonstrated that about 30% of patients with pulmonary hypertension associated with CHD react with decreased pulmonary resistance after nitric oxide therapy [43]. In spite of constant technological progress, the administration of this substance is still difficult; there are reports of effective therapy in women in childbirth who are at particular risk [44].

Sildenafil, oral inhibitor of 5 phosphodiesterase enhances vasodilation of nitric oxide by increasing cGMP concentration and has antiproliferative properties towards smooth muscles of the vessels [45]. Besides, this drug increases contractility of the hypertrophic right ventricle [46]. One large randomized trial SUPER-1 (Sildenafil Use in Pulmonary arterial hypertension) [47] and two smaller trials [36, 48] established the safety profile of the agent and short-term efficacy manifested as improved effort tolerance in patients with all sorts of pulmonary hypertension. These studies included patients with Eisenmenger syndrome but their data was not analyzed separately. Improved cardiac function after Sildenafil was observed in a few other studies which analyzed three, seven and 20 cases of secondary pulmonary hypertension respectively [49––51]. Sastry et al. [52] proved that efficacy of four months of Sildenafil in the group including 90% of ES patients is comparable to the one observed in the SUPER-1 study. Short-term analysis proved the efficacy of another phosphodiesterase inhibitor: Tadalafil in 16 patients with ES [53]. Available studies show good safety profile of both preparations.

Endothelin receptor antagonists (ETA and ETB) have good efficacy records in pulmonary hypertension. Hormone levels have been elevated in Eisenmenger syndrome patients [54] and that provided the basis for the use of this group of drugs. Bosentan is an oral ETA and ETB receptor blocker which lowers the pressure and pulmonary vascular resistance, decreases fibrotic and inflammatory changes of the vessels, including long-term observation, which was confirmed during controlled clinical trials of patients with varied underlying pathophysiological causes [32, 55]. A few open-label uncontrolled studies showed efficacy of this agent in patients with ES confirming clinical improvements including effort tolerance and hemodynamic parameters of the pulmonary circulation [56, 57].

Long-term positive effects of Bosentan have also been reported [58, 59]. BREATH 5 (Bosentan Randomised Trial of Endothelin Antagonist Therapy) was the first large, randomized, multi-center trial designed and carried out according to the rules of evidence based medicine. It included 56 patients and lasted for 16 months. It confirmed decreased resistance and pulmonary pressure and an increase in cardiac output measured with six-minute walking test, with no changes in blood saturation [60]. What's more, there were no reported imbalances between pulmonary and systemic circulation, which make this drug one of the most promising agents in ES patients. Good response to the drug was reported in all participating patients with ES after 24 consecutive weeks of observation [61]. The long term efficacy has been questioned by van Loon et al. [62] for Bosentan in this group of patients. Two controlled, randomized trials (STRIDE 1 and STRIDE 2) dealt with selective endothelin receptor antagonist: Sitaxantan. Quite large study groups of 178 and 247 patients, among them ES patients who did not form a separate group undergoing distinct analysis, confirmed the efficacy and safety of the administered agent [34, 36, 47].

Good results with Bosentan and Epoprostenol prompted researchers to combine both therapies. But this did not produce any better therapeutic results [63–65]. Lack of data on this sort of treatment in patients with ES resulted in the lack of indications for it.

Recent years have seen the arrival of a new selective ETA receptor antagonist called Ambrisentan. It requires more clinical investigation and its efficacy is evaluated in the ARIES (Ambrisantan in Patients with Moderate to Severe Pulmonary Arterial Hypertension) study [66]. This new arrival into pharmaceutical market made Faber [67] thoroughly review currently available pharmacological strategies. Meta-analysis of 16 trials conducted in 2005 showed that the treatment improved physical endurance, yet did not improve mortality in patients with pulmonary hypertension [68]. The only exception turned out to be epoprostenol [40]. Another point is the fact that even though most clinical trials of drugs in pulmonary hypertension focus on comparing results of an imprecise six-minute walking test; the most significant improvements in the latter parameter were achieved after rational rehabilitation [69]. Although both the patient and physician aim at clinical improvement, only small changes are achieved despite varied therapies used. It seems that we are still at the beginning of the path. Constant research into the molecular basis of

the pathology of this condition is focusing on inflammatory and proliferative processes. This seems reasonable taking into account the past use of three paths of modulation of vessel wall resistance [70]. New light can be shed on the pathophysiology of pulmonary hypertension through analysis of right ventricular function, with the expansion of echocardiography and magnetic resonance and the implementation of specific biomarkers for the cardiac function evaluation. The objectivity of drug studies would be enhanced with a change of end points into a single one: patients' death, despite methodological problems (small groups, relatively low short-term mortality). Such planning requires multi-center co-operation and marked prolongation of studies [67]. Examples of contradictory conclusions were the results of the study on oral beraprost, which showed a significant improvement in a three-month randomized controlled trial, but failed to show sustained benefit in a subsequent long-term observation [42].

Summary

Studies of targeted pharmacological therapy for pulmonary hypertension, especially of patients with Eisenmenger syndrome, have been conducted for little more than a decade. Despite certain methodological inaccuracies, we may hope for their dynamic developments. While waiting for an effective therapeutic agent, we can provide patients with rational care. Our therapeutic efforts should concentrate on preventing complications. We should avoid drugs with no established therapeutic efficacy record, and try to alleviate symptoms without any additional risk, so as not to disrupt the existing clinical balance.

Acknowledgements

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