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Eisenmenger's syndrome: a treatment update

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CONTENTS

Abstract

This article presents a brief overview of Eisenmenger's syndrome, a congenital or acquired condition that results in severe and potentially fatal pulmonary hypertension resulting from a systemic-to-pulmonary circulation connection. Traditional medical management of Eisenmenger's syndrome has provided limited success and heart-lung transplantation is the only definitive treatment. However, new advances in drug therapy have provided hope for patients suffering from this complex disorder. Here we will focus on new experimental therapies that have been or are currently being tested in clinical trials.

Introduction

Eisenmenger's syndrome was named after the Austrian physician Victor Eisenmenger, who first characterized this condition in 1897 (1). The presence of congenital heart disease leading to chronic pulmonary hypertension is the main feature of Eisenmenger's syndrome. From 1-2% of patients with congenital heart disease may develop Eisenmenger's syndrome. Clinical symptoms are associated with pulmonary hypertension and poor systemic output, including cyanosis, dyspnea, fatigue or syncope. The prognosis of patients with Eisenmenger's syndrome is actually better than those presenting other forms of pulmonary hypertension, such as primary pulmonary hypertension, although long-term survival depends on the age of onset and on other concomitant conditions, such as Down's syndrome. The management of Eisenmenger's syndrome was until recently limited to palliative measures involving fluid balance, oxygen therapy or phlebotomies, with critically ill patients requiring combined heart-lung transplantation (2). The lack of selective pulmonary vasodilators —with the exception of nitric oxide (NO)— initially compromised the use of vasodilator therapy, which was restricted to calcium channel antagonists (nifedipine, amlodipine) or nitroglycerin. Epoprostenol was the first drug specifically approved for pulmonary arterial hypertension that also showed benefit in Eisenmenger's syndrome. Fortunately, the availability of new pulmonary vasodilator therapies has dramatically improved the outcome of this condition. Other approaches include anticoagulants or diuretics, although their use is not recommended since they may worsen the pre-existing condition.

Pathophysiology of Eisenmenger's syndrome

Patients with Eisenmenger's syndrome usually present with congenital heart defects that cause pulmonary arterial hypertension resulting from a systemic-to-pulmonary circulation connection, usually a ventricular septal defect, although other cardiac anomalies have also been described (1). As a result of this defect, blood flows from the high-pressure systemic to the pulmonary circulation, where the resistance is lower (Fig. 1). Since the pressure is usually higher in the left ventricle, a left-to-right shunting of blood occurs. Blood is pumped from the left ventricle into the right ventricle and the pulmonary circulation. Increased blood flow may damage lung blood vessels, which become thicker, thus increasing pulmonary vascular resistance and causing pressure in the pulmonary arteries to rise. Over time, pulmonary pressure will equal or exceed systemic values, initially generating bidirectional communication, and subsequently a right-to-left or reverse blood shunting. In consequence, poorly oxygenated blood from peripheral tissues will empty into the left ventricle and reach the arterial circulation, leading to hypoxemia and cyanosis, a main feature of Eisenmenger's syndrome. Patients may also develop secondary erythrocytosis as a response to low oxygen blood levels in an attempt to increase tissue oxygenation (2). Hemodynamics in Eisenmenger's syndrome patients tend to be stable, although a trend towards a progressive increase in pulmonary and systemic vascular resistance over time has been observed in untreated patients (3).

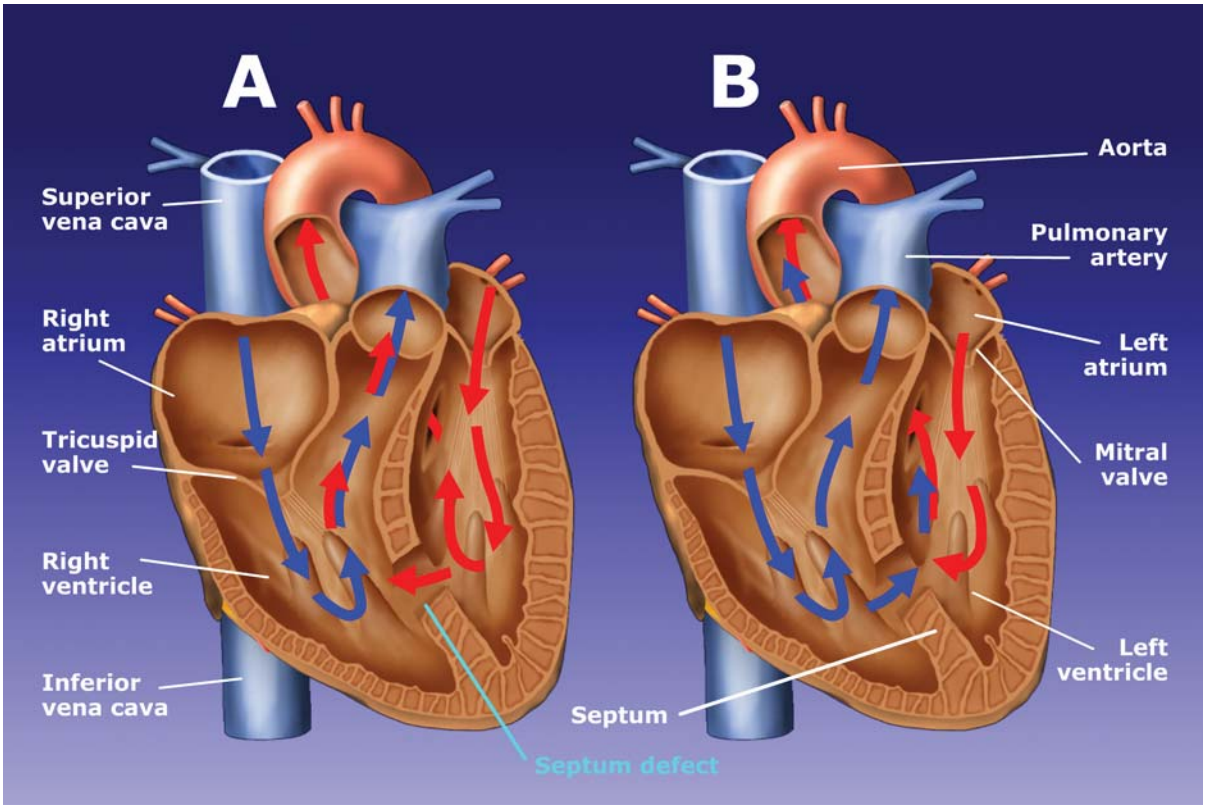

Fig. 1. **A**. Left-to-right shunt. Due to a ventricular septal defect, shunting of blood from the high-pressure left ventricle to the right ventricle and the pulmonary artery occurs. Increased pulmonary blood flow increases vascular resistance, leading to pulmonary arterial hypertension.**B**. Right-to-left shunt. Sustained pulmonary hypertension produces a reversal of the cardiac shunt with oxygen-poor blood flowing from the right to the left ventricle and into the aorta to reach the systemic circulation. Low blood oxygen levels result in cyanosis.

Under physiological conditions, endothelial cells produce a balanced secretion of vasoconstrictor (endothelin-1, or ET-1) and vasodilator (NO, prostacyclin) substances that regulate the vascular tone. However, chronically increased pulmonary arterial pressure causes endothelial cell damage and the release of vasoactive mediators, leading to vasoconstriction and vascular smooth muscle and endothelial cell proliferation. ET-1 is a potent vasoconstrictor and stimulates the proliferation of vascular smooth muscle cells through stimulation of ET_A and ET_B receptors, and it has been described to stimulate proliferation of smooth muscle in pulmonary arteries, which may be of importance in the pathogenesis of pulmonary arterial hypertension (4). Moreover, increased ET-1 plasma levels have been correlated with disease pathogenesis in different forms of pulmonary arterial hypertension, including Eisenmenger's syndrome (3). ET receptor gene expression has also been seen to be upregulated in severe forms of pulmonary hypertension (5). Altogether, these findings suggest a potential pathogenic role for ET-1 in Eisenmenger's syndrome, a hypothesis supported by observations of positive effects for selective ET_A receptor antagonists in patients with pulmonary hypertension associated with congenital heart disease (6). This led to further clinical investigations on the use of ET-1 antagonists for the treatment of Eisenmenger's syndrome, as discussed below.

Endothelial cells also produce the endogenous vasodilator NO, which plays a key role in the regulation of vascular tone. Via activation of soluble guanylate cyclase, NO stimulates the production of cyclic guanosine monophosphate (cGMP), which mediates relaxation by decreasing the intracellular calcium concentration ($[Ca]_i$). In vascular smooth muscle, contraction is primarily regulated by $[Ca]_i$ signaling. Therefore, a reduction in $[Ca]_i$, achieved by a cGMP-dependent mechanism, culminates in decreased phosphorylation of the myosin light chain and subsequent blood vessel relaxation (7). In pulmonary arterial hypertension, targeting the NO/cGMP signaling pathway either by directly administering NO or by increasing cGMP levels via phosphodiesterase inhibition has improved treatment outcome in patients suffering from this condition. Eisenmenger's syndrome therapy may also benefit from these approaches.

Treatments under clinical investigation for Eisenmenger's syndrome

The medical treatment of Eisenmenger's syndrome is directed toward improvement of symptoms, with special

emphasis on not destabilizing the fragile equilibrium, which could lead to heart failure. An ideal drug to treat Eisenmenger's syndrome would improve pulmonary arterial hypertension by reducing pulmonary vascular resistance and increasing pulmonary blood flow, without adverse effects on the systemic circulation. For instance, a reduction in systemic vascular resistance would increase the right-to-left shunting of blood, thereby worsening systemic hypoxemia and cyanosis. The following section will discuss investigational drugs that have been studied for Eisenmenger's syndrome. A summary of relevant clinical studies is given in Table I.

Endothelin receptor antagonists: bosentan

As mentioned earlier, ET-1 signaling appears to be involved in the pathophysiology of Eisenmenger's syndrome. Previous observations of positive effects of selective ET_A receptor antagonism with BQ-123 in patients with pulmonary hypertension associated with congenital heart disease (6) prompted further studies with Actelion's orally active dual ET_A and ET_B receptor antagonist bosentan (Tracleer®). The first study to investigate the effect of bosentan in patients with chronic pulmonary hypertension related to congenital heart disease, the majority of whom presented with Eisenmenger's syndrome, reported improved exercise and hemodynamic parameters after 16 weeks of bosentan treatment. At week 16, 13 patients improved World Health Organization (WHO) functional class by 1, while the rest remained stable. Exercise evaluation (*i.e.,* 6-min walk test) demonstrated increased oxygen consumption, exercise capacity and duration compared to baseline. General improvement of all hemodynamic parameters was observed, including decreased pulmonary arterial and aortic pressure, decreased pulmonary vascular resistance and enhanced pulmonary blood flow. Systemic oxygen delivery and systemic vascular resistance were not affected by bosentan therapy, suggesting selectivity for the pulmonary vasculature (8).

This research team further investigated the long-term safety and tolerability of bosentan treatment in an extension of the first study in the remaining 19 patients (2 patients who had improved on bosentan therapy subsequently died due to arrhythmic events) (9). Bosentan treatment appeared to be safe and well tolerated, and patients remained clinically stable without changes in WHO classification over 2 years. Unexpectedly, exercise parameters returned to baseline values despite sustained clinical improvement.

However, exercise capacity was seen to improve, together with functional status, in another long-term open study evaluating bosentan therapy over 1 year in 33 patients with pulmonary arterial hypertension due to congenital heart disease, 70% of whom presented with Eisenmenger's syndrome (10). Similar results were obtained in another open clinical study in 23 patients with Eisenmenger's syndrome due to different congenital heart anomalies. In these subjects, bosentan therapy over a mean period of 10 months resulted in significantly improved WHO functional class and oxygen saturation (11). Another small study reported comparable results after a 6-month treatment period (12).

BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5) was the first placebo-

Table I: Clinical studies of experimental therapies for Eisenmenger's syndrome (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Bosentan	Open	Bosentan, 31.25 mg o.d. [10-20 kg], 31.25 mg b.i.d. [20-40 kg] or 62.5 mg b.i.d. [> 40 kg] p.o. x 16 wks	21	Bosentan improved the clinical status in the short- and mid-term and also improved hemodynamics in patients with pulmonary hypertension related to congenital heart disease, including 13 patients with Eisenmenger's syndrome	8
	Open	Bosentan, 31.25 mg p.o b.i.d. [20-40 kg] or 62.5 mg p.o. b.i.d. [> 40 kg] x 4 wks → 62.5 mg p.o. b.i.d. [20-40 kg] or 125 mg p.o. b.i.d. [> 40 kg] up to 2 y	19	Long-term use of bosentan over 2 years in patients with pulmonary arterial hypertersion, including Eisenmenger's syndrome, was safe and induced clinical stability; however, exercise parameters at 2 years slowly returned to baseline levels	9
	Open Multicenter	Bosentan, 125 mg p.o. b.i.d. [titrated from 62.5 mg b.i.d. over 4 wks] x ≥1 y	33	Bosentan was well tolerated and effectively improved clinical status and exercise capacity in adults with pulmonary arterial hypertension associated with congenital heart disease (23 patients presented with Eisenmenger's syndrome)	10
	Open	Bosentan, 199 [mean] mg/d x 10 [mean] mo	23	Bosentan was associated with potential clinical benefit after 3-6 months of treatment in patients with Eisenmenger's syndrome	11

Continuation

Table I (Cont.): Clinical studies of experimental therapies for Eisenmenger's syndrome (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Bosentan	Open	Bosentan, 62.5 mg p.o. b.i.d. x 1 mo → 125 mg p.o. b.i.d. x 5 mo	12	Bosentan was safe, well tolerated and effective in patients with pulmonary hypertension associated with Eisenmenger's syndrome	12
	Multicenter Randomized Double-blind	Bosentan, 62.5 mg p.o. b.i.d. x 4 wks → 125 mg p.o. b.i.d. x 12 wks Placebo	54	Bosentan was well tolerated and associated with significant improvements in hemodynamics and exercise capacity without worsening oxygen saturation in patients with Eisenmenger's syndrome	13
	Open	Bosentan, 62.5 mg [titrated from 31.25 mg] p.o. b.i.d. x 4 wks → 125 mg p.o. b.i.d. x 8 wks	10	Bosentan was safe and well tolerated and improved clinical status and pulmonary hemodynamics in adult patients with Eisenmenger's syndrome	14
	Open	Bosentan, p.o. x 24 wks	60	A clinical study was initiated to assess the effects of medium-term oral bosentan therapy in patients with Eisenmenger's syndrome and pulmonary hypertension	15
Sildenafil	Open	Sildenafil, 6.25 mg p.o. t.i.d. [escalated up to 300 mg/d]	8	Sildenafil was safe and effectively decreased pulmonary arterial pressure and pulmonary vascular resistance in patients with Eisenmenger's syndrome	16
	Randomized Double-blind Crossover	Sildenafil, 3.125 [children < 30 kg], 6.25 [children > 30 kg] or 25 [adults] mg p.o. on d 1 → [if no response] 25 [children < 30 kg], 50 [children > 30 kg] or 100 [adult] mg p.o. t.i.d. x 6 wks Placebo	20	Sildenafil was associated with a significant reduction in pulmonary arterial pressure, improvements in exercise tolerance and NYHA functional class in patients with idiopathic pulmonary arterial hypertension (n=10) and Eisenmenger's syndrome (n=10)	17
	Multicenter Randomized Double-blind	Sildenafil, p.o. x 16 wks Placebo	204	A phase II/III study will evaluate the efficacy, safety and pharmacokinetics of sildenafil in children with pulmonary hypertension, either primary or associated with collagen vascular disease or congenital heart lesions	18
Tadalafil	Open	Tadalafil, 1 mg/kg p.o o.d. 40 [max.] mg x 12 wks	16	Tadalafil was well tolerated, improved symptoms and decreased pulmonary vascular resistance in most patients with Eisenmenger's syndrome	19
	Multicenter Randomized Double-blind	Tadalafil x 16 wks Placebo	400	This trial will evaluate the effects of tadalafil on the 6-min walk distance, dyspnea, cardiopulmonary hemodynamics, quality of life and function in patients with pulmonary arterial hypertension	20
Bosentan + Sildenafil	Open	Bosentan, 0.75 mg/kg p.o. b.i.d. x 4 wks → Bosentan, 125 mg p.o. b.i.d. + Sildenafil, 0.5 mg/kg p.o. t.i.d or q.i.d	11	Combination of oral bosentan and sildenafil improved clinical status, exercise capacity and hemodynamics in patients with pulmonary arterial hypertension of different origin (idiopathic, n=4; secondary to congenital heart disease, n=5; other, n=2)	22
	Randomized Double-blind Placebo-controlled	Bosentan x 3 mo → Id. + Sildenafil, 50 mg p.o. t.i.d. x 3 mo Bosentan x 3 mo → Id. + Placebo x 3 mo	20	A phase III study was initiated to evaluate the effect of bosentan plus sildenafil for the treatment of Eisenmenger's syndrome	23

Continuation

Table I (Cont.): Clinical studies of experimental therapies for Eisenmenger's syndrome (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Nitric oxide/ Iloprost	Open	Nitric oxide, 20 ppm inhal. over 10 min → Iloprost, 25 ng/kg/min inhal. over 10 min → Nitric oxide + Iloprost over 10 min	15	Inhaled iloprost was as effective as nitric oxide in lowering pulmonary vascular resistance by increasing cAMP and cGMP in children with pulmonary hypertension and congenital heart disease. The combination of both vasodilators, however, was not more potent than either substance alone	24

Abbreviations: NYHA: New York Heart Association; cAMP: cyclic adenosine 5'-monophosphate; cGMP: cyclic guanosine 5'-monophosphate

controlled trial to investigate the effects of bosentan in patients with Eisenmenger's syndrome (13). In this study, 54 patients were randomized 2:1 to receive bosentan or placebo for 16 weeks. Bosentan therapy did not induce any change in systemic arterial blood oxygen saturation, which if reduced indicates worsening of the right-to-left shunt. Moreover, hemodynamic changes in treated patients included a reduction in pulmonary vascular resistance and mean pulmonary arterial pressure compared to placebo. Mean systemic arterial pressure also decreased, but this was well tolerated, with only 1 patient experiencing a vasovagal effect. Exercise and functional capacity markedly improved with bosentan therapy. The overall safety profile was comparable to that demonstrated by bosentan in other forms of pulmonary arterial hypertension. Although the incidence of adverse events was higher in the bosentan group, these were reversible after dose reduction or discontinuation (*i.e.*, increased liver enzymes).

Further evidence of bosentan's safety and tolerability was reported in a small open-label study in patients with Eisenmenger's syndrome following up to 3 months of oral therapy. Clinical symptoms also showed a positive trend towards improvement (14). An ongoing open study will also examine the efficacy of medium-term bosentan therapy in patients with clinically relevant pulmonary hypertension due to Eisenmenger's syndrome (15).

Phosphodiesterase type 5 (PDE5) inhibitors

PDE5 inhibitors prevent cGMP degradation, thus favoring its accumulation and relaxing vascular smooth muscle cells, a therapeutic strategy that has proven successful in the treatment of erectile dysfunction and forms of pulmonary hypertension. Selective pulmonary vasodilatation with little systemic hypotension is achieved, since PDE5 localizes preferentially in pulmonary vasculature. Evidence that sildenafil produced a reduction in pulmonary arterial pressure and pulmonary vascular resistance, together with improvement in functional class, was reported in a small open clinical study (16). Sildenafil doses were escalated up to 300 mg daily without major adverse events and patients were followed for a mean of 9 months.

Recently, a 6-week, randomized, double-blind, placebo-controlled, crossover clinical study showed significant improvement in exercise capacity (*i.e.*, 6-min walk test) in sildenafil-treated patients compared to controls. A significant reduction in pulmonary arterial pressure and improvement in New York Heart Association (NYHA) functional class after 6 weeks of treatment with sildenafil were also observed in patients with both idiopathic pulmonary arterial hypertension and Eisenmenger's syndrome. Concerning the safety profile, sildenafil was well tolerated, with no headache and no significant change in systolic and diastolic blood pressure reported (17). Evaluation of sildenafil in children with pulmonary arterial hypertension associated with congenital heart disease or collagen vascular disease is currently ongoing at Pfizer (18).

Tadalafil is another selective PDE5 inhibitor developed by Lilly Icos for the treatment of erectile dysfunction. Its potential benefit in Eisenmenger's syndrome was investigated in a 3-month open clinical study that recruited 16 patients with Eisenmenger's syndrome. Pulmonary vascular resistance and mean pulmonary arterial pressure were significantly lower compared to baseline after tadalafil treatment, and systemic oxygen saturation was improved. Functional class improvements were also observed (19). Tadalafil is currently being investigated at Lilly Icos in a larger randomized, controlled phase III clinical trial (PHIRST-1) (20). Four hundred patients with pulmonary arterial hypertension associated with different conditions, including congenital heart disease, are expected to be recruited. The PHIRST-1 trial will provide new data on the efficacy of tadalafil on exercise tolerance, dyspnea, cardiopulmonary hemodynamics, quality of life and function in these patients.

The effects of vardenafil, a more potent and selective PDE5 inhibitor, have also been examined in a small group of patients suffering from pulmonary arterial hypertension, 2 of whom presented with Eisenmenger's syndrome (21). Acute administration of vardenafil (5 mg) decreased both pulmonary and systemic vascular resistance and increased cardiac output. Prolonged vardenafil treatment (3 months) decreased pulmonary arterial pressure and vascular resistance, without affecting systemic arterial pressure or cardiac output. Only minor adverse events were reported in this pilot study.

Combined therapy: sildenafil and bosentan

Experience gathered with the ET-1 receptor antagonist bosentan and PDE5 inhibitor monotherapy suggested a potential benefit for combining both approaches in Eisenmenger's syndrome. Therefore, oral combined

treatment with bosentan and sildenafil was tested in patients suffering from different forms of pulmonary arterial hypertension. This open-label observational study showed that combination therapy was safe and improved exercise capacity and clinical status according to NYHA class, which correlated with increased oxygen saturation. Mean pulmonary arterial pressure significantly decreased relative to baseline (22). The efficacy of combined bosentan and sildenafil treatment in patients with Eisenmenger's syndrome will be further investigated in a randomized, placebo-controlled phase III clinical study that is expected to enroll 20 patients (23).

Nitric oxide

As mentioned earlier, endogenous NO participates in the regulation of vascular tone. It is a potent vasodilator that exerts its effects on vascular smooth muscle by increasing the production of cGMP. Inhaled NO has been suggested to improve symptoms of pulmonary arterial hypertension. In fact, a small open-label study in 15 pediatric patients with pulmonary arterial hypertension associated with congenital heart disease evaluated the effects of inhaled NO (iNO) compared to aerosolized iloprost, a prostacyclin analogue approved for the treatment of pulmonary arterial hypertension (24). iNO and iloprost demonstrated comparable efficacy in reducing pulmonary vascular resistance through a decrease in the cyclic nucleotides cGMP and cAMP, respectively. No changes in systemic vascular resistance and arterial pressure were reported with either of the study drugs. However, synergy was not observed with combined therapy.

Besides its potential therapeutic effect, the response to iNO has also been suggested to be useful for identifying severe cases of Eisenmenger's syndrome and for optimizing subsequent therapy. In this open-label study, reduced pulmonary vascular resistance in response to NO was found to depend on baseline pulmonary hemodynamics (25). Further investigation revealed that the responsiveness to iNO may predict mid-term survival in patients with pulmonary arterial hypertension associated with congenital heart disease (26).

Online links

Subscribers to Integrity can access the online animations: Eisenmenger's syndrome and Phosphodiesterase type 5 Inhibitors in Pulmonary Hypertension: Mechanism of Action.

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