Diagnostic strategy and long-term treatment outcomes in Idiopathic Pulmonary Arterial Hypertension

W. Jacobs

Diagnostic strategy and long-term treatment outcomes in Idiopathic Pulmonary Arterial Hypertension treated in the Netherlands

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Chapter 1

General introduction

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In 1865 The German physician Klob reported autopsy findings of a patient who had developed progressive ankle oedema , dyspnoea and cyanosis prior to his death at 59. In stead of the cardiac pathology he expected, Klob found an impressive narrowing of the finer branches of the pulmonary artery with localised arteriosclerosis.[1] In 1891 Romberg described a similar clinical course in a 24-year old patient.[2] Other than the abnormalities in the pulmonary vessels he also noted a massive right ventricular hypertrophy.

This disease now known as Pulmonary Arterial Hypertension (PAH) is a rare disease with an estimated incidence of 1-2/million inhabitants per year for the idiopathic form.[3-5] Reported prevalence of PAH in patients with connective tissue disease varies from 2-50%[6-16] and it can be detected in 0,5% of HIV patients.[17-18] By consensus pulmonary hypertension is defined by a mean pulmonary artery pressure greater than 25mmHg. Pulmonary hypertension may arise due to various underlying alternative conditions and the clinician must have an understanding of the context in which PH occurs as different treatment strategies may be necessary in different situations. The clinical substrates of PH have been catalogued based on their pathological characteristics, clinical presentations, hemodynamic profiles and therapeutic outcomes into 5 different groups. The current classification of PH was provided by consensus at a world symposium of PH specialists held in Venice 2003 and is shown in table 1.[19] PAH is defined as pulmonary hypertension classified in group 1 according to the Venice classification and is either idiopathic or from the associated etiologies mentioned.

When examining PAH histopathology characteristics of PH with atheromatous changes, dilation of large pulmonary arteries and medial hypertrophy and remodelling of muscular arteries are found. If pulmonary hypertension persists right ventricular hypertrophy, dilation and ultimately failure are common sequelae. Besides these histopathologic features common to all causes of Pulmonary Hypertension, each of the forms of Pulmonary Arterial Hypertension are associated with characteristic lesions involving both the pre-acinar and intra-acinar arteries. These include constrictive lesions at the vessel intima, remodelling of the media or adventitia, as well as complex (plexiform) lesions involving changes of the entire vessel wall. In addition to constrictive and complex lesions, thrombosis of small vessels is noted frequently in the absence of evidence to suggest an embolic source. [20]

A diagnosis of PAH portends a dismal prognosis and before the advent of PAH specific therapies median survival of IPAH patients was estimated at 2.8 years.[21] The discovery of prostacyclin I2, in 1976 by Moncada and Vane[22] was the first step in the development of PAH specific therapies and currently there are three different classes of PAH specific drug therapies which are well established. They are the prostanoids, the endothelin receptor antagonists and the phosphodiesterase type 5 inhibitors and target three different pathways involved in abnormal contraction and proliferation of smooth muscle cells.[23] The development of these PAH specific therapies has improved survival.[24,25] However long-term survival in the modern management era remains poor[26] and knowledge on combining these drug therapies is limited. Currently the prostacyclin I2 analogue epoprostenol is widely perceived as the most potent PAH

Table 1 The Venice classification of pulmonary hypertension[19]

1. Pulmonary Arterial Hypertension (PAH)
- 1.1 Idiopathic (IPAH)
- 1.2 Familial (FPAH)
- 1.3 Associated with (APAH):
  - 1.3.1 Collagen vascular disease
  - 1.3.2 Congenital systemic-to-pulmonary shunts
  - 1.3.3 Portal hypertension
  - 1.3.4 HIV infection
  - 1.3.5 Drugs and toxins related
  - 1.3.6 Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic teleangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
- 1.4 Associated with significant venous or capillary involvement
  - 1.4.1 Pulmonary veno-occlusive disease (PVOD)
  - 1.4.2 Pulmonary capillary hemangiomatosis (PCH)
- 1.5 Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension with left heart disease
- 2.1 Left sided atrial or ventricular heart disease
- 2.2 Left sided valvular heart disease

3. Pulmonary hypertension associated with lung diseases and/or hypoxaemia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Sleep-disordered breathing
- 3.4 Alveolar hypoventilation disorders
- 3.5 Chronic exposure to high altitude
- 3.6 Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
- 4.1 Thromboembolic obstruction of proximal pulmonary arteries
- 4.2 Thromboembolic obstruction of distal pulmonary arteries
- 4.3 Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)

5. Miscelaneous

Sarcoidosis, Histiocytosis X, Lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

specific drug therapy available[27] and data corroborating this are reviewed in Chapter 2. However prostanoid adminstration, either intravenous, subcutaneous or by inhalation, can be bothersome, and the possibility of oral therapy with either an endothelin receptor antagonist or a phosphodiesterase-type 5 inhibitor is an attractive alternative. Aim of this thesis is to describe long-term treatment results in idiopathic PAH patients treated at the VU University Medical Centre, a referral centre for PAH patients in the Netherlands. Different treatment strategies were used in different time periods. Untill 2002 the only PAH specific therapy available in the Netherlands was i.v. epoprostenol. In Chapter 3 we describe treatment results with our current treatment strategy which

involves first-line oral therapy with the endothelin receptor antagonist bosentan and subsequently addition of alternative PAH specific therapies as needed. Treatment results in these patients are compared with our historical cohort of patients treated with first-line i.v. epoprostenol. Subsequently in Chapter 4 we describe efficacy of prostanoids added to oral therapy after treatment failure on first line therapy. In Chapter 5 we sought to determine causes of differential treatment effects between sexes using invasive haemodynamic and cardiac MRI follow-up measurements. In recent years PAH awareness has improved amongst physicians in the community and this has lead to increasing patient referrals. In Chapter 6 we consider a predictive model capable of identifying left diastolic heart failure as a differential cause of pulmonary hypertension in these patients; obviating the need for right heart catheterisation. To conclude we summarize current understanding of PAH specific drug treatments and discuss future prospects in chapter 7.

References

1. Klob J. Endarteriitis pulmonalis deformans. Wien Wochenbl 1865;31:45.
2. Romberg E. Über sklerose der lungen arterie. *Dtsch Arch Klin Med* 1891;48:197-206.
3. Abenhaim L, Moride Y, Brenot F, et al. Appetite suppressant drugs and the risk of primary pulmonary hypertension. International primary pulmonary hypertension study group. *N Engl J Med* 1996;335:609-616.
4. Group IPPHS: The international primary pulmonary hypertension study. *Chest* 1994;105:37S-41S.
5. Appelbaum L, Yigla M, Bendayan D, et al. Primary pulmonary hypertension in Israel: A national survey. *Chest* 2001;119:1801-1806.
6. MacGregor AJ, Canavan R, Knight C, Denton CP, Davar J, Coghlan J, et al. Pulmonary hypertension in systemic sclerosis: risk factors for progression and consequences for survival. *Rheumatology* (Oxford) 2001;40:453-9.
7. Morelli S, Barbieri C, Sgreccia A, Ferrante L, Pittoni V, Conti F, et al. Relationship between cutaneous and pulmonary involvement in systemic sclerosis. *J Rheumatol* 1997;24:81-5.
8. Murata I, Takenaka K, Yoshinoya S, Kikuchi K, Kiuchi T, Tanigawa T, et al. Clinical evaluation of pulmonary hypertension in systemic sclerosis and related disorders. A Doppler echocardiographic study of 135 Japanese patients. *Chest* 1997;111:36-43.
9. Koh ET, Lee P, Gladman DD, Abu-Shakra M. Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. *Br J Rheumatol* 1996;35:989-93.
10. Ungerer RG, Tashkin DP, Furst D, Clements PJ, Gong H, Jr., Bein M, et al. Prevalence and clinical correlates of pulmonary arterial hypertension in progressive systemic sclerosis. *Am J Med* 1983;75:65-74.
11. Yamane K, Ihn H, Asano Y, Yazawa N, Kubo M, Kikuchi K, et al. Clinical and laboratory features of scleroderma patients with pulmonary hypertension. *Rheumatology* (Oxford) 2000;39:1269-71.
12. Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of end stage lung disease in a cohort of patients with scleroderma. *Ann Rheum Dis* 2003;62:146-50.
13. Pan TL, Thumboo J, Boey ML. Primary and secondary pulmonary hypertension in systemic lupus erythematosus. *Lupus* 2000;9:338-42.
14. Asherson RA, Higenbottam TW, Dinh Xuan AT, Khamashta MA, Hughes GR. Pulmonary hypertension in a lupus clinic: experience with twenty-four patients. *J Rheumatol* 1990;17:1292-8.
15. Alpert MA, Goldberg SH, Singsen BH, Durham JB, Sharp GC, Ahmad M, et al. Cardiovascular manifestations of mixed connective tissue disease in adults. *Circulation* 1983;68:1182.

16. Hosoda Y, Suzuki Y, Takano M, Tojo T, Homma M. Mixed connective tissue disease with pulmonary hypertension: a clinical and pathological study. *J Rheumatol* 1987;14:826-30.
17. Nunes H, Humbert M, Sitbon O, Morse JH, Deng Z, Knowles JA, et al. Prognostic Factors for survival in human immunodeficiency virus-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2003;167:1433.
18. Humbert M, Nunes H, Sitbon O, Parent F, Herve P, Simonneau G. Risk factors for pulmonary arterial hypertension. *Clin.Chest Med* 2001;22:459-75.
19. Simmoneau G, Galiè N, Rubin L. et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;43, supplement 1(12):S5-S12.
20. Tiachman DB, Snow JL, Pietra GG. Histopathology of Pulmonary Arterial Hypertension. In: Taichman DB, Mandel J, editors: Pulmonary vascular disease, Philadelphia, 2006, Elsevrie Inc, pp 20-32.
21. D'alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;115:343-349.
22. Moncada S, Gryglewski R, Bunting S, et al. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* 1976;263,663-665.
23. Humbert M, Sitbon O and Simmonneau G. Treatment of pulmonary arterial hypertension. *N Eng J Med* 2004;351:1425-1436.
24. McLaughlin VV, Shillington and Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circ* 2002;106:1477-1482.
25. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005;25:244-249.
26. Survival in patients with idiopathic, familial and anorexigen associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010;122:156-163.
27. Badesch DB, Abman SH, Simmonneau G, et al. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest* 2007;131:1917-1928.

Chapter 2

Epoprostenol in pulmonary arterial hypertension

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Abstract

Background

Pulmonary arterial hypertension (PAH) is a devastating disease leading to right heart failure and death in a relatively young patient population. In recent years novel PAH specific therapies have become available.

Objective

To determine the place of epoprostenol in current PAH treatment strategies.

Methods: An extensive medline search was performed to evaluate the use of epoprostenol in PAH. Data from both human and animal studies were reviewed.

Results/conclusion

Epoprostenol is an effective and potent treatment in pulmonary arterial hypertension and has greatly improved survival, exercise capacity, PAH symptoms, pulmonary haemodynamics and disease progression. A major disadvantage is that it can only be delivered through a continuous intravenous pump infusion.

Introduction

Pulmonary arterial hypertension (PAH) is a rare disease with a poor prognosis. It was first described in the late 19th century as a clinical-pathological syndrome characterised by obstruction of the small pulmonary arteries and right ventricular hypertrophy in patients presenting with severe dyspnea and cyanosis.[1-2] Idiopathic pulmonary arterial hypertension (IPAH) has an estimated incidence of 1-2/million inhabitants/year in industrialized countries[3-5]. Reported prevalence of PAH in patients with connective tissue disease varies from 2-50%.[6-16] Furthermore PAH can be detected in 0,5% of HIV patients.[17,18]

In the past 15 years 3 groups of PAH specific drug therapies have become available. They are the endothelin-receptor antagonists, phosphodiesterase type 5 inhibitors and prostanoids. These medications have a vasodilatory effect on the pulmonary vasculature and target 3 major pathways involved in abnormal contraction and proliferation of pulmonary artery smooth muscle cells in PAH.[19] The first to be developed was the prostacyclin analogue epoprostenol.[20] Current treatment guidelines recommend epoprostenol as preferred first line therapy in the most severe PAH patients, i.e. those in New York Heart Association (NYHA) functional class 4 and state that epoprostenol can be considered in more severe NYHA class 3 patients. [21] Introduction of epoprostenol has significantly improved long-term survival in idiopathic PAH with a 3-year survival of 62.8% compared with 35.4% based on historical data.[22,23] However the high cost and the complex mode of delivery by continuous intravenous infusion and consequent risk of catheter related infections[24] are a major burden. Several alternative prostacyclin derivatives have recently been developed or are investigated.[25]

Chemistry and pharmacodynamics

Epoprostenol is a chemical analogue of prostacyclin (prostaglandin I2). Prostacyclin was discovered in 1976 by Moncada and Vane, while investigating how blood vessel walls make unstable prostanoids.[26] It is the main product of arachidonic acid in all vascular tissues and is formed through the cyclooxygenase pathway.[27] The ability of the vessel wall to synthesize prostacyclin is greatest at the intimal surface and progressively decreases towards the adventitia.[28] Prostacyclin relaxes isolated vascular strips. It has a hypotensive effect through vasodilation of all vascular beds studied, including the pulmonary and cerebral circulations.[29] In addition it is a potent inhibitor of platelet aggregation. For example prostacyclin inhibits thrombus formation in a constricted dog artery and an electrically damaged rabbit artery.[30,31] Also the substance disperses existing thrombocyte aggregates in vitro[26,30] and in vivo.[32] This anti-thrombotic effect is short-lasting in vivo, disappearing within 30 minutes of cessation of administration. In addition to its vasodilator and anti-aggregating effect prostacyclin also exhibits a cytoprotective effect.[33-37] For instance, in models of myocardial infarction prostacyclin reduces infarct size [38-40], arrhythmias[41], oxygen demand[40], and enzyme release from the infarcted areas.[42] Further investigations have demonstrated antiproliferative actions and the reduction of matrix secretion in smooth muscle cells, endothelial cells and fibroblasts, as well as an anti-inflammatory profile in leucocytes.[43] In vitro inhibition

of vascular smooth muscle cell growth by prostacyclin analogues has been shown.[44] Endothelial cells are the major source of endogenous prostacyclin. Its action is directed at both the local vascular wall and blood cells. In particular those blood cells that adhere to the endothelium. The main target of prostanoids is the IP receptor, which is abundantly expressed in blood vessels, leucocytes and thrombocytes and is rapidly activated by prostanoids. The IP receptor is coupled with Gs proteins and activates adenylate cyclase, leading to increased cyclic adenosine monophosphate levels in target cells, which explains most of the biological effects.[45] However, prostacyclin is not highly specific to the IP receptor. It also activates prostaglandin E (EP) receptors[46], which are located on the cell surface as well as in the nucleus[47,48], and peroxisome proliferator activated receptor (PPAR)δ, which is located in the nucleus.[49] Both PPARα and PPARδ may also be activated via IP receptor-dependent protein kinase (PK)A activation, but the intracellular prostaglandin (PG)I_2 from the endogenous PGI synthase seems to specifically activate the apoptosis pathway by activation of PPARδ.[50-53]

PAH is associated with vasoconstriction, thrombosis and proliferation, and this may be partly due to a lack of endogenous prostacyclin[43, 54, 55], secondary to prostacyclin synthase downregulation.[56] Vice versa overexpression of prostacyclin synthase protects against development of pulmonary hypertension in transgenic mice and rats.[57,58] After intravenous infusion of prostacyclin there are beneficial haemodynamic effects in the vast majority of patients, with a significant decrease in pulmonary vascular resistance and a minor decrease in systemic pressure. However if the dose is rapidly increased, systemic vasodilation may cause intolerable symptoms and a systemic pressure drop. In chronic prostacyclin therapy excessive prostacyclin dosage can lead to a high cardiac output state. In this circumstance by reducing the dose, cardiac output normalizes without worsening the clinical state.[59] If prostanoids are infused at a constant dose there may be IP receptor desensitisation with a complete loss of vasodilatory effect.[60] In clinical practice there is no loss of pharmacological effect during constant infusion in the short-term, but epoprostenol doses have to be gradually increased to keep the same level of pulmonary vasodilation and systemic side effects (from 4 $ng \cdot kg^{-1} \cdot min^{-1}$ as an average tolerated dose to ~20-60 $ng \cdot kg^{-1} \cdot min^{-1}$ after 1 year).

In PAH there is increased [^{18}F] fluorodeoxyglucose accumulation in the right ventricle indicating increased glucose metabolism.This accumulation increases with PAH disease severity and treatment induced decreases after epoprostenol administration were shown.[61] Chronic intravenous prostacyclin has been shown to reduce right ventricular (RV) size, septal displacement and tricuspid insufficiency, in pulmonary hypertension indicating an improvement in RV function due to decreased RV afterload.[62,63] It has been hypothesized that prostacyclin therapy would also benefit PAH patients through positive inotropic effects.[64] However in an animal model of acutely induced right heart failure and in an animal model of chronic PAH no positive inotropic effects of epoprostenol administration were found.[63,65] In a pulmonary angiography study epoprostenol treatment led to so-called cotton grass-like regional stains of the capillary imaging phase. These angiographic changes were attributed to vasodilation and it was suggested that alternatively they may be induced by neovascularistion.[66]

Prostacyclin analogues have induced neovascularisation in a mouse model[67] and in rats they enhanced neovascularisation in ischaemic myocardium by mobilizing bone marrow cells.[68]

Pharmacokinetics

In biological fluids at physiologic pH values there is a rapid enzymatic degradation and spontaneous hydrolysis of epoprostenol. Plasma half-life is 2-3 minutes. All metabolites are inactive or less active.[69] Metabolites are mostly excreted by urine.[70] Because of the rapid biotransformation epoprostenol can only be used as continuous infusion through a central venous catheter. Delivery through peripheral veins leads to painful vein irritation after a short time.

Epoprostenol is provided by the manufacturer as a stable freeze-dried preparation. It is supplied with an alkaline buffer, which allows it to remain stable in a dissolved form. After mixing the drug powder with the solvent, the solution can be used up to 12 hrs at room temperature. When cooled it can be used up to 48 hrs after reconstitution (SPC Flolan®).

Clinical efficacy

The first patient treated by epoprostenol was a 27 year old woman, who suffered from progressive dyspnea for over 6 years. A diagnosis of primary pulmonary hypertension was made. She was cyanotic, bed bound due to severe dyspnea and suffered from an intractable unproductive cough. Mild exertion such as standing and walking resulted in syncope. Peripheral oedema had occurred due to right-sided heart failure. After treatment with epoprostenol pulmonary vascular resistance decreased and exercise capacity improved. No further syncopal attacks occurred and peripheral oedema was eliminated. The patient learnt how to prepare and store the epoprostenol solution and was discharged home. She was treated with epoprostenol for more than a year at time of publication.[71] In 1987 Jones et al. reported 10 IPAH patients with subjective and clinical improvements and improved exercise capacity after 1-25 months of epoprostenol treatment.[72] Rubin et al. reported improved hemodynamics after epoprostenol treatment in several reports[73,74,75] Improved cardiac output and decreased pulmonary vascular resistance at 12 months and sustained improvement in exercise capacity at follow-up up till 18 months after initiation of prostanoids were shown in an open-label uncontrolled trial.[76] Subsequently a pivotal trial involving 81 IPAH was performed, after which the FDA and European health authorites approved epoprostenol for IPAH treatment. Patients were randomised to epoprostenol in addition to conventional therapy or conventional therapy alone. Conventional therapy consisted of warfarin, digoxin, oxygen and oral vasodilators.[77] Patients were followed for 12 weeks. Subjects on active therapy had a mean 32m improvement in 6-min walk distance compared with a 15m decrease in the conventional group ($p<0.01$). Pulmonary artery pressure decreased by 8% in the epoprostenol group, as opposed to a 9% increase in the conventional group ($p<0.001$). Cardiac index increased by 0.3 l/min/m^2 in the epoprostenol group versus a 0.2 l/min/m^2 decrease. All deaths ($n=8$) were in the placebo group ($p<0.01$). Since then observational cohort

studies demonstrated long-term beneficial effects of epoprostenol. McLaughlin reported clinical and haemodynamic improvements in 162 NYHA III and IV IPAH patients.[22] Patients had improved survival in comparison with expected survival based on historical data. The 1,2 and 3 year survival rates of 87.8, 76.3 and 62.8% were significantly better than the expected survival rates of 58.9, 46.3 and 35.4%. Sitbon et al. evaluated a cohort of 178 IPAH and reported similar results.[78] Compared with a historical cohort survival rates improved from 58,43,33 and 28% to respectively 85,70,63 and 55% at 1,2,3 and 5 years. Use of epoprostenol can delay or avoid lung transplantation in PAH.[79,80]

Additional evidence has emerged supporting epoprostenol use in PAH from associated causes. In a randomized 12-week trial scleroderma patients treated with epoprostenol experienced a 46m improvement in 6-minute walk distance compared to a 48m decrease in the conventional arm. The median difference in distance walked at 12 weeks between both groups was 108m ($p<0.001$).[81] A number of uncontrolled studies also suggest improvements in patients with connective tissue disease associated PAH[82,83,84], congenital left-to-right cardiac shunts[85] and HIV related PAH.[17,86] Results are ambiguous in portopulmonary hypertension [87]

Safety and tolerability

Treatment with epoprostenol has limitations based on its pharmacology. It requires initiation by experienced physicians in designated centres. Long-term epoprostenol infusion is costly and requires a permanent central venous catheter and a portable infusion pump. Medication needs to be prepared every other day when kept cold or twice daily when used at room temperature. Patients need education in sterile technique, operation of the pump and care of the catheter. Serious complications include infection and thrombosis of the catheter and temporary interruption of the infusion due to pump malfunction or line disconnection. Because of the short half-life of epoprostenol, interruption of infusion can be life-threatening. In a multicenter study the incidence of catheter related infections was 0.43/1000 intravenous infusion days for epoprostenol versus 1.11/1000 infusion days for i.v. treprostinil.[24]

Epoprostenol side effects are predominantly related to its vasodilatory effects. Side-effects are usually well tolerated, may be dose-related and vary in intensity between individuals. The most common side-effects include flushing (42%), headache (83%), nausea (67%), loose stool (37%), jaw discomfort (54%) and musculoskeletal pain (35%). Hyperthyroidism has rarely been reported (<1%).[22,77,78]

Alternative prostacyclin therapies

Several alternative prostacyclin analogues have recently been developed for intravenous (treprostinil, iloprost), subcutaneous (treprostinil) and inhaled (iloprost) administration and others are investigated for inhaled (treprostinil) or oral (beraprost, treprostinil) routes [25] These therapies have similar pharmacodynamic, but different pharmacokinetic properties. On a nanomolar basis drug efficacy amongst these different compounds is not equal. Practical advantage of these medications are that they do not need cooling. Also the longer half-lives of these drugs make patients less

prone to cardiovascular collapse in case of interrupted administration.
Oral beraprost improved exercise capacity after 3 and 6 months. However improvements were non-sustained at 9 and 12 months follow-up. Beraprost is currently not approved in Europe and the USA. But it is an approved therapy in Japan.[88]
Treprostinil has the advantage of less invasive subcutaneous administration. Treprostinil half-life is about 80 minutes when administerd subcutaneously and risks associated with treatment interruption are reduced. In a multicenter randomized placebo controlled trial involving 470 patients a 16m significant increase in 6-,minute walk distance occurred in the treprostinil group.[89] Sustained improvement in exercise capacity was reported in an open label study with a mean 26 months follow-up.[90] In a long-term observational study of 860 patients (811 PAH of which 412 IPAH, and 49 thromboembolic pulmonary hypertension) the effects of subcutaneous treprostinil, followed by addition of other PAH therapies if needed, were followed for up to 4 years. During follow-up 196/860(23%) discontinued the drug due to trepostinil infusion site pain and 3 due to other adverse event. During follow-up 136(16%) died, 117 (14%) discontinued owing to deterioration, 29(3%) withdrew consent and 11(1%) underwent lung transplantation. In total 97 patients (11%) switched to an alternative prostacyclin analogue, bosentan was added in 105 patients (12%) and sildenafil in 25(3%). Survival rates for the whole cohort were 87% at 1 year and 68% at 4 years. Survival in the IPAH subgroup was 72% at 4 years compared to 38% from historical data.[91] Alternatively treprostinil can be administered intravenously or orally. A randomized placebo-controlled trial is ongoing to determine efficacy of oral treprostinil.
Inhalation of prostanoids is possible for iloprost or treprostinil.[92-94] Inhaled iloprost needs administration by nebulizer 6-9 timed daily. Iloprost as well as treprostinil have also been used as i.v. infusion.[95-97] It is difficult to directly compare the clinical effects and side-effects of different prostanoids and different administration routes. This is due to differences in enrolled patient populations, the mode of application and dosing and trial design in the different randomised controlled trials that have been performed.[89, 92-98] No trials have compared efficacy of different prostanoids head on.

Combination therapy

Epoprostenol therapy is neither curative nor does it normalise pulmonary artery pressure in the majority of cases. Investigators have examined the effects of targeting multiple pathways and combined prostanoids with endothelin antagonists and phosphidiesterase type 5 inhibitors. In the Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-2 study 33 PAH patients were started on epoprostenol and randomised in a 2:1 ratio for addition of bosentan or placebo for a total duration of 16 weeks. In this small study no significant benefit in clinical or haemodynamic measurements could be observed from the addition of bosentan.[99] A study by Simmoneau et al. reported the results of a 16-week multinational, double-blind, placebo-controlled trial assessing safety and efficacy of sildenafil added to epoprostenol.[100] Patients had improvements in exercise capacity with a 26 m increase in 6-minute walk distance ($p<0.001$), improved pulmonary haemodynamics (mean

pulmonary artery pressure −3,8mm Hg; p<0.0001) and improved time to clinical worsening (p=0.012). This benefit was maintained at 1 year in the subsequent long-term open-label extension study.[101]

Costs and regulatory affairs

The cost of epoprostenol is approximately $100,000 per year in the U.S.A., but may be higher depending on patient dose. Most USA based insurance companies, as well as Medicaid and Medicare, will pay for epoprostenol. (Medicaid is the United States health program for selected low income groups and Medicare the federal health insurance plan for senior citizens > 65 years). Cost varies considerably between countries. For instance treatment cost is currently around $ 115.000 per year in the Netherlands, whilst treatment cost can rise in excess of $ 300.000 in other countries if list prices are not discounted.

Abid et al. calculated the cost needed to prevent 1 death per year in different diseases and with different therapies. In the treatment of PAH epoprostenol cost was estimated at $968,000 per life saved per year. This compared to $406,000 per life saved for bosentan, $873,000 per life saved for inhaled iloprost and $1,715,000 per life saved for subcutaneous treprostinil. This compared to $315,000 per life saved for an automatic cardiac defibrillator, $654,968 per life saved for a left ventricular assist devices, $1,080,000 per life saved for the treatment of follicular non-Hodgkin's lymphoma with Cyclophosphamide, Adriamycin, Vincristine, Prednisone and Rituximab, $1,795,846 per life saved for pacemakers for atrial fibrillation, and $16,065,000 per life saved for treatment of lupus nephritis with Mycophenolate mofetil. It was concluded that the costs of epoprostenol and other PAH treatments are at an acceptable cost effectiveness range compared to other pharmacotherapeutic and biotechnological interventions in other diseases.[102] In a cost-minimization analysis two theoretical U.S.A. cohorts of 270 patients were treated with subcutaneous treprostinil and intravenous epoprostenol, and were evaluated over 3 years. Probabilistic sensitivity analyses resulted in average 3-year cost-savings of 41,051 US dollars per patient in favour of treprostinil. The greatest savings came from reduced or minimal hospitalizations attributed to the dose titration and treatment of adverse events, such as sepsis, associated with epoprostenol and its delivery system.[103] This was confirmed by a canadian cost-minimization analysis evaluating two cohorts of 60 patients, treated with treprostinil or epoprostenol. The Canadian evaluation included both the provincial ministries of health and societal perspectives: on a per-patient level, treatment with treprostinil resulted in an average annual savings of 14,504 US dollars and 15,452 US dollars, respectively.[104]

The financial aspect of chronic epoprostenol treatment for PAH and comparing costs are a complicated issue. Due to tachyphylaxia epoprostenol doses can increase from an initial 500-1000 micrograms per day to more than 6000 micrograms per day over a period of several years. In some countries epoprostenol is provided by hospital pharmacies only. In other countries epoprostenol is delivered by community pharmacists when the patient is at home. Reimbursement systems differ between countries, with or without separated financial systems for hospital use and use in

the community-setting. The costs per saved life year, whether or not adjusted for the quality of life, are under debate. Controlling epoprostenol treatment cost is of some concern. As an alternative, treatment may be offered for a fixed price, irrespective of the dose. Discussions between providers and payers should contribute to mutual agreement on acceptable cost for life saving treatments like epoprostenol in a rare disease such as PAH. The recent approval of 2 generic forms of epoprostenol in the U.S.A. will likely contribute to cost reduction.

Conclusion and expert opnion

Epoprostenol was the first PAH specific therapy developed and leads to improved exercise capacity, improved haemodynamic parameters, decreased PAH symptoms and decreased mortality. Improvements persist at long-term follow-up. Many clinicians view epoprostenol as the gold standard treatment to which other treatments should be compared. Its introduction has lead to great improvements in outcome in mostly young patients suffering from a devastating disease with a poor prognosis. For some patients PAH specific therapies have turned their disease chronic. The introduction of oral treatment alternatives from different drug classes and the development of inhaled and subcutaneously administered prostanoids have limited the use of epoprostenol. However, considering its potency epoprostenol remains first choice therapy for severe patients in NYHA class IV. In NYHA II and III patients the orally administered endothelin receptor antagonists and phosphodiesterase type 5 inhibitors are preferred first-line therapy. Combining oral therapies is effective and can delay clinical deterioration and the need for additional epoprostenol [105,106]. Clinical efficacy of epoprostenol remains excellent when used as second line therapy. Whether upon deterioration on oral therapy epoprostenol should substitute oral therapy or be used as add on therapy is unknown. No data are available comparing the different prostanoid compounds. In NYHA III patients not improving on oral therapy the choice of prostanoid is currently determined by clinical experience, patient preference, drug availability and costs. It is unknown whether patients started on first-line i.v. epoprostenol have improved long-term outcomes compared to patients started on less invasive therapies. Epoprostenol treatment is expensive and invasive. PAH symptoms may remain despite epoprostenol treatment. Long-term survival remains unsatisfactory. Further research is warranted.

References

1. Klob J. Endarteriitis pulmonalis deformans. Wien Wochenbl 1865;31:45.
2. Romberg E. Über sklerose der lungen arterie. Dtsch Arch Klin Med 1891;48:197–206.
3. Abenhaim L, Moride Y, Brenot F, et al. Appetite suppressant drugs and the risk of primary pulmonary hypertension. International primary pulmonary hypertension study group. N Engl J Med 1996;335:609-616.
4. Group IPPHS: The international primary pulmonary hypertension study. Chest 1994;105:37S-41S.
5. Appelbaum L, Yigla M, Bendayan D, et al. Primary pulmonary hypertension in Israel: A national survey. Chest 2001;119:1801-1806.
6. MacGregor AJ, Canavan R, Knight C, Denton CP, Davar J, Coghlan J, et al. Pulmonary hypertension in systemic sclerosis: risk factors for progression and consequences for survival. Rheumatology (Oxford) 2001;40:453-9.
7. Morelli S, Barbieri C, Sgreccia A, Ferrante L, Pittoni V, Conti F, et al. Relationship between cutaneous and pulmonary involvement in systemic sclerosis. J Rheumatol 1997;24:81-5.
8. Murata I, Takenaka K, Yoshinoya S, Kikuchi K, Kiuchi T, Tanigawa T, et al. Clinical evaluation of pulmonary hypertension in systemic sclerosis and related disorders. A Doppler echocardiographic study of 135 Japanese patients. Chest 1997;111:36-43.
9. Koh ET, Lee P, Gladman DD, Abu-Shakra M. Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. Br J Rheumatol 1996;35:989-93.
10. Ungerer RG, Tashkin DP, Furst D, Clements PJ, Gong H, Jr., Bein M, et al. Prevalence and clinical correlates of pulmonary arterial hypertension in progressive systemic sclerosis. Am J Med 1983;75:65-74.
11. Yamane K, Ihn H, Asano Y, Yazawa N, Kubo M, Kikuchi K, et al. Clinical and laboratory features of scleroderma patients with pulmonary hypertension. Rheumatology (Oxford) 2000;39:1269-71.
12. Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of end stage lung disease in a cohort of patients with scleroderma. Ann Rheum Dis 2003;62:146-50.
13. Pan TL, Thumboo J, Boey ML. Primary and secondary pulmonary hypertension in systemic lupus erythematosus. Lupus 2000;9:338-42.
14. Asherson RA, Higenbottam TW, Dinh Xuan AT, Khamashta MA, Hughes GR. Pulmonary hypertension in a lupus clinic: experience with twenty-four patients. J Rheumatol 1990;17:1292-8.
15. Alpert MA, Goldberg SH, Singsen BH, Durham JB, Sharp GC, Ahmad M, et al. Cardiovascular manifestations of mixed connective tissue disease in adults. Circulation 1983;68:1182.
16. Hosoda Y, Suzuki Y, Takano M, Tojo T, Homma M. Mixed connective tissue disease with pulmonary hypertension: a clinical and pathological study. J Rheumatol 1987;14:826-30.
17. Nunes H, Humbert M, Sitbon O, Morse JH, Deng Z, Knowles JA, et al. Prognostic Factors for survival in human immunodeficiency virus-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2003;167:1433.
18. Humbert M, Nunes H, Sitbon O, Parent F, Herve P, Simonneau G. Risk factors for pulmonary arterial hypertension. Clin.Chest Med 2001;22:459-75.
19. Humbert M, Sitbon O, Simmoneau G. Treatment of pulmonary arterial hypertension. N Eng J Med 2004;351:1425-36.
20. Gryglewski RJ. Prostaglandins, platelets, and atherosclerosis. *CRC Crit Rev Biochem* 1980;7:291–338.
21. Badesch DB, Abman SH, Simmonneau G, et al. Medical therapy for pulmonary arterial hypertension. Updated ACCP evidence-based clinical practice guidelines. *Chest*. 2007; 131:1917-1928).
22. McLaughlin, VV, Shillington, A, Rich, S Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106,1477-1482.

23. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. J Am Coll Cardiol 2002;40:780-788.
24. Barst R, Berman-Rosenzweig E, Horn E, et al. Bloodstream infections among patients treated with intravenous epoprostenol or intravenous treprostinil for pulmonary arterial hypertension-seven sites, United States, 2003-2006. Morb Mortal Wkly Rep 2007; 56(8): 170-2.
25. Gomberg-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. Eur Respir J 2008;31:891-901.
26. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* 1976;263:663–665.
27. Bunting S, Gryglewski R, Moncada S, et al. Arterial walls generate from prostaglandin endoperoxides a substance (prostaglandin X) which relaxes strips of mesenteric and celiac arteries and inhibits platelet aggregation. *Prostaglandins* 1976;12:897-913.
28. Moncada S, Herman AG, Higgs EA, et al. Differential formation of prostacyclin (PGX or PGI2) by layers of the arterial wall. An explanation for the antithrombotic properties of vascular endothelium. *Thromb Res* 1977;11:323-344.
29. Moncada S, Vane JR. Pharmacology and endogenous roles of prostaglandinendoperoxides, thromboxane A2 and prostacyclin. *Pharmacol Rev* 1979;30:293-331.
30. Utaba FB, Moncada S, Vane JR. The effect of prostacyclin (PGI2) on platelet behaviour, thrombus formation in vivo and bleeding time. *Thromb Haemost* 1979;41:425-435.
31. Aiken JW, Gorman RR, Shebuski RJ. Prevention of blockage of partially obstructed coronary arteries with prostacyclin correlates with inhibition of platelet aggregation. *Prostaglandins* 1979;17:483-494.
32. Szczeklik A, Gryglewski RJ, Nizankowski R, et al. Circulatory and anti-platelet effects of intravenous prostacyclin in healthy men. *Pharmacol Res Commun* 1978;10:545-556.
33. Whittle BJR. Role of prostaglandins in the defense of the gastric mucosa. *Brain Res Bull* 1980;5 (suppl 1): 7-14.
34. Moncada S, Vane JR. The prostacyclin/thromboxane balance and cardiovascular disease. In: Isselbacher KJ. Symposium celebrating the Harvard Medical School bicentennial. New York: *John Wiley & sons*, 1982:83-113.
35. Vane JR. Clinical potential of prostacyclin. Adv Prostaglandins Thromboxane, *Leukot Res* 1983;11:449-456.
36. Demling RH, Smith M, Gunther R, et al. The effect of prostacyclin infusions on endotoxin-induced lung injury. *Surgery* 1981;89:257-263.
37. Araki H, Lefer AM. Cytoprotective actions of prostacyclin during hypoxia in isolated perfused cat liver. *Am J Physiol* 1980;238(suppl):H176-H181.
38. Jugdutt BF, Hutchins GM, Bulkley BH, et al. Infarct size reduction by prostacyclin after coronary artery occlusion in conscious dogs. *Clin Res* 1979;27:177A.
39. Ogletree ML, Lefer AM, Smith JB, et al. Studies on the cytoprotective effect of prostacyclin in acute myocardial ischaemia. *Eur J Pharmacol* 1979;56:95-103.
40. Ribeiro LGT, Brandon TA, Hopkins DG, et al. Prostacyclin in experimental myocardial ischaemia: effects on hemodynamics, regional myocardial blood flow, infarct size and mortality. *Am J Cardiol* 1981;47:835-840.
41. Starnes VA, Primm RK, Woosley RL, et al. Administration of prostacyclin prevents ventricular fibrillation following coronary occlusion in conscious dogs. *J Cardiovasc Pharmacol* 1982;4:765-769.
42. Ohlendorf R, Perzborn E, Schrör K. Prevention of infarction-induced decrease in circulating platelet count by prostacyclin. *Thromb Res* 1980;19:447-453.
43. Olschewski H, Olschewski A, Rose F, et al. Physiologic basis for the treatment of pulmonary hypertension. *J Lab Clin Med* 2001;138:287–297.

44. Clapp LH, Finney P, Turcato S, et al. Differential effects of stable prostacyclin analogs on smooth muscle cell proliferation and cyclic AMP generation in human pulmonary artery. *Am J Respir Cell Mol Biol* 26;194-201.
45. Chow KB, Jones RL, Wise H. Protein kinase A-dependent coupling of mouse prostacyclin receptors to Gi is cell-type dependent. *Eur J Pharmacol* 2003;474:7–13.
46. Abramovitz M, Adam M, Boie Y, et al. The utilization of recombinant prostanoid receptors to determine the affinities and selectivities of prostaglandins and related analogs. *Biochim Biophys Acta* 2000;1483:285–293.
47. Bhattacharya M, Peri K, Ribeiro-da-Silva A, et al. Localization of functional prostaglandin E2 receptors EP3 and EP4 in the nuclear envelope. *J Biol Chem* 1999;274:15719–15724.
48. Bhattacharya M, Peri KG, Almazan G, et al. Nuclear localization of prostaglandin E2 receptors. *Proc Natl Acad Sci USA* 1998;95:15792–15797.
49. Gupta RA, Tan J, Krause WF, et al. Prostacyclin-mediated activation of peroxisome proliferator-activated receptor delta in colorectal cancer. *Proc Natl Acad Sci USA* 2000;97:13275–13280.
50. Hatae T, Wada M, Yokoyama C, Shimonishi M, Tanabe T. Prostacyclin-dependent apoptosis mediated by PPAR delta. *J Biol Chem* 2001;276:46260–46267.
51. Kliewer SA, Sundseth SS, Jones SA, et al. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. *Proc Natl Acad Sci USA* 1997;94:4318–4323.
52. Lazennec G, Canaple L, Saugy D, Wahli W. Activation of peroxisome proliferator-activated receptors (PPARs) by their ligands and protein kinase A activators. *Mol Endocrinol* 2000;14:1962–1975.
53. Gray JP, Burns KA, Leas TL, Perdew GH, Vanden Heuvel JP. Regulation of peroxisome proliferator-activated receptor alpha by protein kinase C. *Biochemistry* 2005;44:10313–10321.
54. Christman BW. Lipid mediator dysregulation in primary pulmonary hypertension. *Chest* 1998;114: Suppl. 3 205S–207S.
55. Christman BW, McPherson CD, Newman JH, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 1992;327:70-75.
56. Tuder RM, Cool CD, Geraci MW, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med* 1999;159:1925–1932.
57. Geraci MW, Gao B, Sheperd DC, et al. Pulmonary prostacyclin synthase overexpression in transgenic mice protects against development of hypoxic pulmonary hypertension. *J Clin Invest* 103;1509-1515.
58. Tahara N, Kai H, Niiyama H et al. Repeated gene transfer of naked prostacyclin synthase plasmid into skeletal muscles attenuates monocrotaline-induced pulmonary hypertension and prolongs survival in rats. *Hum Gene Ther* 2004;15:1270-1278.
59. Rich S, McLaughlin V. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. *J Am Coll Cardiol* 1999;34:1184-1187.
60. Schermuly RT, Pullamsetti SS, Breitenbach SC, et al. Iloprost-induced desensitization of the prostacyclin receptor in isolated rabbit lungs. *Respir Res* 2007;8:4.
61. Oikawa M, Kagaya Y, Otani H, et al. Increased [^{18}F]fluorodeoxyglucose accumulation in right ventricular free wall in patients with pulmonary hypertension and the effect of epoprostenol. *J Am Coll Cardiol* 2005;45:1849-1855.
62. Hinderliter AL, Willis PW, Barst RJ, et al. Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension. *Circulation* 1997;95:1479-1486.
63. Kerbaul F, Brimioulle S, Rondelet B, et al. How prostacyclin improves cardiac output in right heart failure in conjunction with pulmonary hypertension. *Am J Respir Crit Care Med* 2007;175:846-850.
64. Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. *J Am Coll Cardiol* 1999;34:1184-1187.
65. Wauthy P, Abdel Kafi S, Mooi WJ, et al. Inhaled nitric oxide versus prostacyclin in chronic shunt-induced pulmonary hypertension. *J Thorac Cardiovasc Surg* 2003;126:1434-1441.
66. Sakuma M, Demachi J, Nawata J, et al. Epoprostenol infusion therapy changes angiographic findings of pulmonary arteries in patients with idiopathic pulmonary arterial hypertension. *Circ J* 2008;72:1147-1151.

67. Pola R, Gaetani E, Flex A, et al. Comparative analysis of in vivo angiogenic properties of stable prostacyclin analogues: A possible role for peroxisome proliferator –activated receptors. *J Mol Cell Cardiol* 2004;36:363-370.
68. Miyahara Y, Ohnishi S, Obata H, et al. Beraprost sodium enhances neovascularisation in ischaemic myocardium by mobilizing bone marrow cells in rats. *Biochem Biophys Res Commun* 2006;349:1242-1249.
69. Herner SJ, Mauro LS. Epoprostenol in primary pulmonary hypertension. *Ann Pharmacother* 1999;33:340-347.
70. Brash AR, Jackson EK, Saggese CA, et al. Metabolic dispostion of prostacyclin in humans. *J Pharmacol Exp Ther* 1983;226:78-87.
71. Higenbottam T, Wheeldon D, Wells F, Wallwork J. Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). *Lancet* 1984;1:1046–1047.
72. Jones DK, Higenbottam TW, Wallwork J. Treatment of primary pulmonary hypertension intravenous epoprostenol (prostacyclin). *Br Heart J* 1987;57:270-278.
73. Rubin LJ, Mendoza J, Hood M, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomised trial. *Ann Intern Med*;1990:112:485-491.
74. Weir EK, Rubin LJ, Ayres SM, et al. The acute administration of vasodilators in primary pulmonary hypertension. Experience from the National Institutes of Health registry on primary pulmonary hypertension. *Am Rev Respir Dis* 1989;140:1623–1630.
75. Rubin LJ, Groves BM, Reeves JT, Frosolono M, Handel F, Cato AE. Prostacyclin-induced acute pulmonary vasodilation in primary pulmonary hypertension. *Circulation* 1982;66:334–338.
76. Barst RJ, Rubin LJ, McGoon MD., et al. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med* 1994;121:409-415.
77. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;334:296–302.
78. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002;40:780–788.
79. Robbins IM, Christman BW, Newman JH, Matlock R, Loyd JE. A survey of diagnostic practices and the use of epoprostenol in patients with primary pulmonary hypertension. *Chest* 1998;114:1269–1275.
80. Conte JV, Gaine SP, Orens JB, et al. The influence of continuous intravenous prostacyclin therapy for primary pulmonary hypertension on the timing and outcome of transplantation. *J Heart Lung Transplant* 1998;17:679-685.
81. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000;132:425–434.
82. Humbert M, Sanchez O, Fartoukh M, et al. Short-term and long-term epoprostenol (prostacyclin) therapy in pulmonary hypertension secondary to connective tissue diseases: results of a pilot study. *Eur Respir J* 1999;13:1351-1356.
83. Klings ES, Hill NS, Ieong MH, et al. Systemic sclerosis associated pulmonary hypertension: short- and long-term effects of epoprostenol (prostacyclin). *Arthritis Rheum* 1999;42:2638-2645.
84. McLaughlin VV, Genther DE, Panella MM, et al. Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. *Ann Intern Med* 1999;130:740-743.
85. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. *Circulation* 1999;99:1858–1865.
86. Aguilar RV, Farber HW. Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. *Am J Respir Crit Care Med* 2000;162:1846–1850.
87. Krowka MJ, Swanson KL. How should we treat portopulmonary hypertension? *Eur Respir J* 2006;28:466–467.
88. Barst RJ, McGoon M, McLaughlin V, et al. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;41:2119-2125.

89. Simonneau G, Barst RJ, Galiè N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165:800–804.

90. Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. Chest 2006;129:1636-1643.

91. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J;28:1195-1203.

92. Olschewski H, Simonneau G, Galiè N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;347:322–329.

93. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006;174:1257–1263

94. Voswinckel R, Enke B, Reichenberger F, et al. Favourable effects of inhaled treprostinil in severe pulmonary hypertension. J Am Coll Cardiol 2006;48:1672-1681.

95. Higenbottam TW, Butt AY, Dinh-Xuan AT, et al. Treatment of pulmonary hypertension with the continuous infusion of a prostacyclin analogue, iloprost. Heart 1998;79:175-179.

96. Ewert R, Opitz CF, Wensel R, et al. Continuous intravenous iloprost to revert treatment failure of first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. *Clin Res Cardiol* 2007;96:211-217.

97. Tapson VF, Gomberg-Maitland M, Mc Laughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective multicentre open label 12 week trial. *Chest* 2006;129:683-688.

98. Galiè N, Humbert M, Vachiéry JL, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002;39:1496–1502.

99. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004;24:353–359.

100. Simonneau G, Burgess G, Collings L, et al. Safety and efficacy of combination therapy with sildenafil and epoprostenol in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006;3:A58.

101. Simonneau G, Rubin LJ, Galiè N, et al. Safety and efficacy of sildenafil-epoprostenol combination therapy in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2007; 175: A300.

102. Abid F, Delgado O, Rahaghi FF. A cost analysis of the treatment of pulmonary arterial hypertension. *Chest* 2007 132: 632S.

103. Narine L, Hague LK, Walker JH, et al. Cost-minimization analysis of treprostinil vs. epoprostenol as an alternate to oral therapy non-responders for the treatment of pulmonary arterial hypertension, *Curr Med Res Opin* 2005;21(12):2007-16.

104. Einarson TR, Granton JT, Vincente C, et al. Cost-effectiveness of treprostinil versus epoprostenol in patients with pulmonary arterial hypertension: a Canadian analysis. *Can Respir J* 2005 Nov-Dec;12(8):419-25.

105. Hoeper MM, Faulenbach C, Golpon H, et al. Combination therapy with bosentan and sildenafil in idipathic pulmonary arterial hypertension. *Eur Respir J* 2004;24:1007-1010.

106. Mathai SC, Girgis RE, Fisher MR, et al. Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. *Eur Respir J* 2007;29:469-475.

Chapter 3

Long-term outcomes in pulmonary arterial hypertension in the first-line epoprostenol or first-line bosentan era

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Abstract

Background

The aim of this study was to describe the long-term outcomes in idiopathic pulmonary arterial hypertension (IPAH) treated with first-line bosentan or intravenous (I.V.) epoprostenol, and additional therapy as needed.

Methods

In a single-center, retrospective longitudinal cohort, data on right heart catheterization, 6-minute walk distance (6MWD), disease progression and mortality were collected. Outcomes were assessed in first-line bosentan and first-line epoprostenol patients. In order to reduce selection bias due to differences between the groups, 2 independent analyses were performed. First a comparison was made of WHO functional class (FC) III patients. Second, to control for disease severity, a matched pairs analysis was performed, with matching according to baseline cardiac output and exercise capacity and irrespective of NYHA class at baseline.

Results

Thirty seven IPAH patients initiated first-line bosentan treatment and 37 first-line I.V. epoprostenol. Twenty-nine of the bosentan patients and 16 I.V. epoprostenol were in WHO FC III; demographic profiles were similar, although hemodynamic measurements and 6MWD suggested more severe disease in the I.V. epoprostenol group at treatment initiation. At 1 and 3 years, median change in 6MWD for patients initiating bosentan was +54 m (95% CI: -3; 76) and +71 m (-123; 116), respectively, and +92 (17; 128) and +142 m (-6; 242) for I.V. epoprostenol. Absence of disease progression in WHO FC III at 1 and 3 years, respectively, was 72% and 45% in bosentan and 75% and 44% in I.V. epoprostenol. Survival at 1 and 3 years was 93% and 89% in bosentan and 94% and 75% in I.V. epoprostenol. Results were confirmed in matched pairs analysis of 16 bosentan and 16 I.V. epoprostenol patients with similar disease severity.

Conclusions

Greater 6MWD improvements occur in first-line epoprostenol treated patients. Survival and time to disease progression is similar in both first-line treatment groups.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature, leading to high morbidity, right heart failure and death. Idiopathic pulmonary arterial hypertension (IPAH) has an estimated incidence of 1–2 per million inhabitants per year.(1–4) During recent years several disease specific drug therapies were approved for PAH.(5) Before the availability of these therapies, a median survival in IPAH of 2.8 years was reported in a U.S. registry.(6) McLaughlin et al. described improved long-term survival in IPAH with intravenous (I.V.) epoprostenol therapy when compared with these historical data (7) and later demonstrated long-term survival improvements in first-line bosentan treated patients.(8) Sitbon et al. compared survival in different treatment strategies, notably bosentan as first-line therapy followed by other therapy as needed, versus historical data on initiation of therapy with epoprostenol. When corrected for baseline haemodynamics, survival estimates for bosentan and epoprostenol were nearly identical. However, no data on exercise capacity were reported in this study. (9) Provencher et al. describe the long-term outcomes of a consecutive sample of IPAH treated with first-line bosentan in a single centre. Mean duration of follow-up in this study was 24±15 months and, during this period, prostanoid therapy was added in 44% of patients. (10) No studies have yet investigated changes in exercise capacity and time to disease progression in first-line epoprostenol compared with first-line bosentan treated patients. The aim of this study was to describe the long-term outcomes of exercise capacity, time to disease progression and survival in IPAH patients who initiated I.V. epoprostenol first-line treatment or bosentan first-line treatment and additional therapy as needed.

Methods

Study design and patients

We performed a retrospective, longitudinal cohort study of IPAH treated at the VU University Medical Centre (VUMC) who initiated first-line therapy with I.V. epoprostenol or oral bosentan between January 1998 and December 2006. Patients were included if ≥18 years of age. Patients were excluded if PAH-specific treatments were started before an initial visit to the VUMC, or prior to 1998.

The VUMC is a tertiary referral centre for PAH in The Netherlands. Diagnosis is confirmed by right heart catheterisation (RHC) and treatment is standardized. (11) PAH is defined by an elevated mean pulmonary artery pressure (mPAP) >25mmHg at rest, combined with a normal pulmonary arterial wedge pressure ≤ 15 mmHg and by exclusion of pulmonary embolism, parenchymal lung disease and hypoxaemia as underlying cause. To make a diagnosis of idiopathic PAH thereafter the possibility of PAH from associated causes has to be excluded.(12) At the VUMC, prior to commercial availability of bosentan (Tracleer®; Actelion Pharmaceuticals), WHO FC III and IV IPAH patients initiated I.V. epoprostenol as first-line therapy. In 2003, after bosentan

became available, the standardized regimen in WHO FC III IPAH patients changed to bosentan first-line therapy: 62.5mg b.i.d., increased to 125mg b.i.d. after one month. Additional PAH-specific treatments are commenced in case of a deterioration of WHO FC class or a greater than 10% decrease in 6-minute walk distance (6MWD) since last visit, measured on two occasions, in combination with increasing PAH symptoms, such as shortness of breath, syncope or signs of right heart failure.(11)
Today, a stepwise treatment approach is implemented in WHO FC III patients. Patients initiate bosentan therapy first-line with the addition of sildenafil (Revatio®; Pfizer), and then I.V. epoprostenol (Flolan®; GlaxoSmithKline) or subcutaneous (S.C.) treprostinil (Remodulin®; United Therapeutics), as required. At the VUMC, sildenafil has been available since 2004 and treprostinil since 2005. In WHO FC IV patients, epoprostenol or treprostinil are the first-line therapy options. Initially patient follow-up is at least every 4 months, and usually once a year thereafter or more frequently if needed.
Disease severity is assessed by patient symptoms, 6MWD and WHO FC designation. Disease progression was defined as the first occurrence following first-line treatment initiation of any of the following events: deterioration in WHO FC, atrial balloon septostomy, listing for lung transplantation, death or a 10% or more decrease in 6MWD since last assessment or a 20% decrease in 6MWD since baseline. Other PAH-specific medications added during follow-up, catheter infusion site related infections and liver enzyme abnormalities were recorded. Requirements of the hospital research and ethical review boards were met, including patient informed consent.

Data analysis

Disease outcomes were assessed in patients treated with first-line bosentan and first-line epoprostenol. Two independent analyses were performed. The first analysis was confined to WHO FC III idiopathic PAH to reduce selection bias due to differences between the treatments. According to STROBE guidelines (13,14) continuous variables were summarized by mean, median, standard deviation, standard error, 25th percentile, 75th percentile, minimum, maximum and number of values and 95% Confidence Interval (CI). Categorical data were summarized by frequencies and proportions and time-to-event endpoints using Kaplan-Meier methods, and including 95% two-sided CIs of the event rate. In a second analysis to control the influence of disease severity at baseline, a matched pairs analysis was performed matching patients in both treatment groups based on cardiac output (CO) and 6MWD. In this analysis the allowed maximal difference in CO between matched patients was 0.5 L/min and the maximal difference in 6MWD 50 m. In this second analysis patients could be included independent of WHO FC at baseline. The analyses were performed using SPSS.

Results

Patient characteristics

104 IPAH patients started first-line therapy at the VUMC: 37 started bosentan and 37 epoprostenol. Other first-line treatments were: sildenafil (n=7), treprostinil (n=4), calcium channel blockers (n=7), sitaxentan (n=11) and ambrisentan (n=1). Reasons for starting PAH first-line therapy other than bosentan or I.V. epoprostenol were trial participation (n=15), positive vasoreactivity testing for the choice of calcium channel blockers (n=7), patient personal preference for treprostinil (n=4) and doctor preference (n=4). The mean (±SD)/median (min; max) exposure to first-line therapy in the bosentan group was 27.9 (±18.2) /25.0 (1.6; 68.9) months and in the epoprostenol group 43.4 (±29.2)/49.1 (0.07; 104.5) months. Four of the 37 patients were started on bosentan before it was commercially launched in Feb 2003 and 7 of 37 patients initiated I.V. epoprostenol first-line after bosentan was commercially available.

Twenty-nine of the 37 patients starting bosentan and 16 of the 37 starting epoprostenol were in WHO FC III at the start of treatment. The demographic characteristics appear somewhat similar in these patients (Table 1). Hemodynamics at start of first-line therapy in WHO FC III patients are displayed in Table 2 and may be more severely impaired in the epoprostenol group, as indicated by a higher pulmonary vascular resistance and right atrial pressure and lower stroke volume index.

PAH-specific therapy regimen in WHO FC III patients

Figure 1 depicts the number of WHO FC III patients starting first-line bosentan or epoprostenol according to year of initiation. The mean (±SD)/median (min; max) exposure to first-line therapy was 27.4 (±17.9)/25.0 (1.6; 60.2) months, and 51.4 (±26.2)/57.8 (0.6; 97.1) months in first-line bosentan and I.V. epoprostenol patients, respectively.

Of the patients with bosentan first-line therapy, 11 (37.9%) received one additional PAH-specific medication and 8 (27.6%) received two. In 1 patient, a PAH-specific therapy was added and subsequently a switch from bosentan to another PAH-specific therapy was made. Four patients (13.8%) switched to another PAH-specific medication and 5 (17.2%) stayed on bosentan monotherapy throughout the observation period. Twenty (69.0%) of the first-line bosentan therapy patients received sildenafil, 3 (10.3%) I.V. epoprostenol, 4 (13.8%) S.C. treprostinil and 2 (6.9%) oral treprostinil as part of a combination regimen.

Of the 16 first-line I.V. epoprostenol patients, 9 (56.3%) received one additional PAH-specific medication and 2 (12.5%) received two additional medications. Two patients (12.5%) switched to another PAH-specific therapy and 3 (18.8%) remained on epoprostenol monotherapy. Eight patients (50.0%) in the first-line epoprostenol group received sildenafil, 4 patients (25.0%) bosentan, and 1 patient (6.3%) sitaxentan as part of a combination regimen.

Kaplan-Meier estimates of the proportion of patients who had another PAH-specific medication initiated respectively, were 47%, 76%, and 84% at 12, 24 and 36

Table 1. Patient characteristics at first-line treatment initiation

	Bosentan All N=37	I.V epoprostenol All N=37	Bosentan WHO III N=29	I.V. epoprostenol WHO III N=16
Gender, n (%): female : male	29 (78) : 8 (22)	28 (76) : 9 (24)	23 (79) : 6 (21)	13 (81) : 3 (19)
Race, n (%): Caucasian Asian Other	33 (89) 2 (5) 2 (5)	35 (95) 1 (3) 1 (3)	27 (93) 0 2 (7)	16 (100) 0 0
Age, years: Mean ± SD Median (min, max)	48.0 ± 17.6 44.6 (16.9, 81.8)	45.9 ± 12.4 44.8 (26.4, 74.7)	49.6 ± 17.0 52.3 (20.6, 75.4)	44.5 ± 8.8 45.3 (30.3, 62.4)
Height, cm: Mean ± SD Median (min, max)	169 ± 7 169 (154, 187)	167 ± 8 167 (150, 183)	169 ± 7 169 (154, 187)	166 ± 8 167 (150, 176)
Proportion of patients diagnosed <1998, n (%)	7 (19)	7 (19)	5 (17)	3 (19)
Time since diagnosis, (months): Mean ± SD Median (min; max)	33 ± 62 3 (0, 290)	17 ± 28 5 (0, 111)	32 ± 66 3 (0, 290)	23 ± 35 8 (0, 111)
WHO FC, n (%): II : III : IV	5 (14) : 29 (78) : 3 (8)	0 (0) : 16 (43) : 21 (57)	n.a.	n.a.
6 MWD, (m): n Mean ± SD Median (min, max)	35 374 ± 142 379 (9, 600)	36 213 ± 159 238 (0, 498)	27 362 ± 133 379 (9, 600)	16 332 ± 107 347 (90, 498)

months in first-line bosentan patients and respectively 0%, 28%, and 50% in first-line I.V. epoprostenol. These data also reflect the differing availabilities of other PAH-specific medications between the first-line I.V. epoprostenol and first-line bosentan treatment eras.

Exercise capacity in WHO FC III patients

In patients with values at initiation of therapy and after 4 months, median (25^{th}; 75^{th} percentiles) 6MWD at initiation of first-line therapy was 370 m (256; 447) in the bosentan group (n=24) and 365 m (265; 414) in the I.V. epoprostenol group (n=15). The respective median (95% CI) 6MWD improvement at 4 months was +40 m (-5; 77) in the bosentan group and +96 m (68; 182) in the I.V. epoprostenol group.

In patients with values at initiation of therapy and after 2 years, median (25^{th}; 75^{th} percentiles) 6MWD at initiation of first-line therapy was 397 m (264; 456) in the bosentan group (n=17) and 369 m (275; 414) in the I.V. epoprostenol group

Table 2. Hemodynamic characteristics at start of treatment

	RHC			CMR		
	Bosentan WHO III N=29	**I.V. epoprostenol WHO III N=16**	**p-value***	**Bosentan WHO III N=29**	**I.V. epoprostenol WHO III N=16**	**p-value***
Mixed venous O_2 saturation, %: n Mean ± SD Median (min, max)	23 63 ± 8 64 (50, 78)	14 57 ± 14 60 (19, 76)	0.34	RVEF, %: n Mean±SD Median (min, max)	18 30 ± 14 27 (10, 64)	10 24 ± 9 23 (11, 41)	0.21
mPAP, mmHg: n Mean ± SD Median (min, max)	28 55 ± 14 56 (32, 89)	16 61 ± 10 62 (47, 81)	0.11	LVEF, %: n Mean ± SD Median (min, max)	18 61 ± 21 57 (21, 100)	10 55 ± 15 59 (30, 73)	0.46
mRAP, mmHg: n Mean ± SD Median (min, max)	28 8 ± 4 6 (2, 16)	16 12 ± 6 11 (3, 23)	<0.01	RVEDV, mL: n Mean ± SD Median (min, max)	19 167 ± 45 168 (90, 261)	10 165 ± 37 166 (112, 215)	0.93
PVR, dyn*s*cm-5: n Mean ± SD Median (min, max)	26 1059 ± 452 945 (266, 2129)	16 1345 ± 496 1387 (602, 2526)	0.07	LVEDV, mL: n Mean ± SD Median (min, max)	19 80 ± 23 80 (41, 138)	10 65 ± 25 64 (21, 92)	0.20
Cardiac output, L/min: n Mean±SD Median (min, max)	26 4.3 ± 1.1 4.3 (2.8, 7.3)	15 3.6 ± 1.0 3.3 (1.9, 5.5)	0.07	Cardiac output, L/min: n Mean ± SD Median (min, max)	19 4.0 ± 1.8 3.8 (1.3, 9.1)	10 2.9 ± 1.0 3.2 (1.5, 4.6)	0.07
SVI, mL/m2: n Mean ± SD Median (min, max)	26 30 ± 11 28 (11, 62)	14 24 ± 10 23 (3, 39)	0.16	SVI, mLl/m2: n Mean ± SD Median (min, max)	19 26 ± 12 23 (9, 55)	10 19 ± 7 19.3 (8, 29)	0.06
				Right ventricular mass, g: n Mean ± SD Median (min, max)	10 100 ± 37 93 (52, 182)	10 103 ± 25 106 (57, 142)	0.57

RHC = right heart catheterization; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PVR = pulmonary vascular resistance; SVI = stroke volume index; CMR = cardiac magnetic resonance imaging; RVEF = right ventricular ejection fraction; LVEF = left ventricular ejection fraction, RVEDV=right ventricular end-diastolic volume, LVEDV=left ventricular end-diastolic volume, SVI = stroke volume index, *Mann-Whitney U test

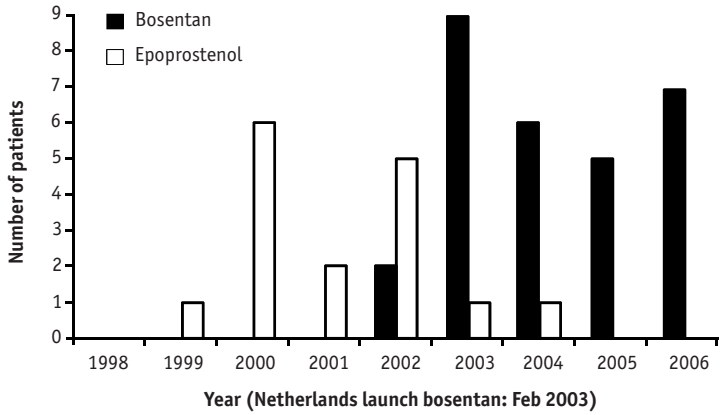


Figure 1. Number of WHO FC III idiopathic pulmonary arterial hypertension patients (n=45) starting first-line epoprostenol or bosentan in the period 1998-2006.

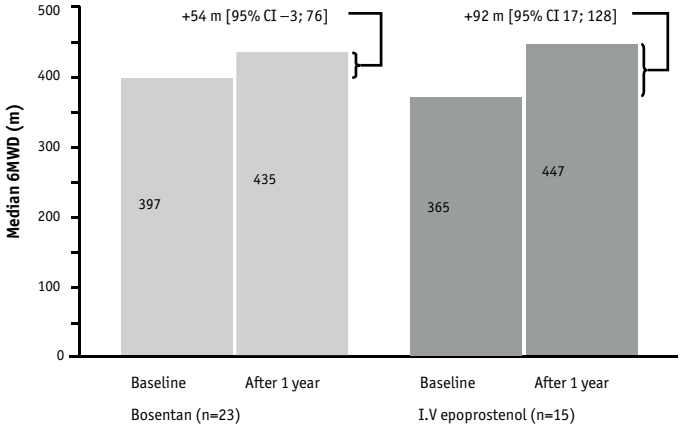


Figure 2A. Box plots showing change in 6MWD: median (95% CI) 6MWD at baseline and after 1 year is depicted for WHO FC III idiopathic pulmonary arterial hypertension patients treated with first-line bosentan or first-line epoprostenol.

(n=13). The respective median (95% CI) 6MWD improvement at 2 years was +68 m (45; 79) in the bosentan group and +136 m (1; 215) in the I.V. epoprostenol group. Improvements in 6MWD after 1 and 3 years are depicted in Figure 2A and Figure 2B.

Time to disease progression and survival in WHO FC III

Kaplan-Meier estimates of the proportion of patients without disease progression in the bosentan group were 72% (95% CI: 48%; 97%) at 1 year, 57% (95% CI:

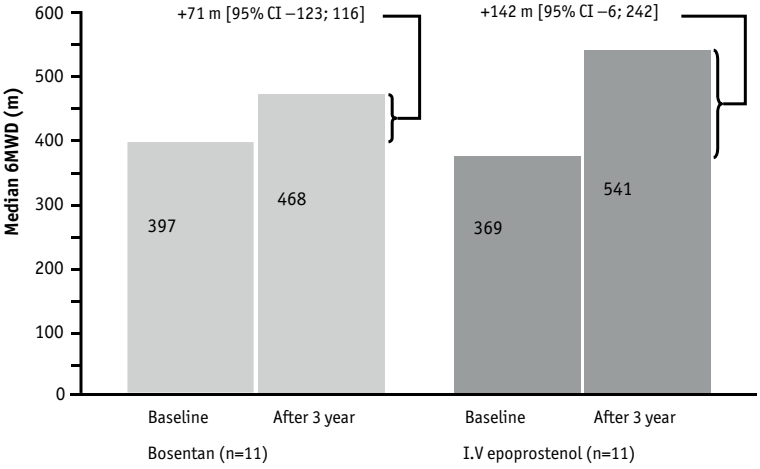


Figure 2B. Box plots showing change in 6MWD: median (95% CI) 6MWD at baseline and after 3 years is depicted for WHO FC III idiopathic pulmonary arterial hypertension patients treated with first-line bosentan or first-line epoprostenol.

31%; 82%) at 2 years and 45% (95% CI: 17%; 74%) at 3 years. In the epoprostenol group, these were 75% (95% CI: 42%; 100%), 50% (95% CI: 17%; 83%), and 44% (95% CI: 11%; 76%), respectively. There were no differences in time to disease progression between both groups (Figure 3). During follow-up disease progression occurred in 16 bosentan and 12 epoprostenol. Reasons for disease progression in the bosentan group were worsening WHO FC (n=3), death (n=1) and a decrease in 6MWD distance of 10% or more since last assessment or 20% since baseline (n=13). Reasons for disease progression in epoprostenol were atrial septostomy (n=1), lung transplant listing (n=1), worsening WHO FC (n=3), death (n=1) and a decrease in 6MWD of 10% or more since last assessment or 20% since baseline (n=8). Multiple reasons for disease progression were possible.

Kaplan-Meier estimates of survival in patients starting bosentan were 93% (95% CI: 68%; 100%), 89% (95% CI: 64%; 100%), and 89% (95% CI: 64%; 100%) at 1, 2, and 3 years, respectively. In the epoprostenol group these were 94% (95% CI: 61%; 100%), 88% (95% CI: 55%; 100%), and 75% (95% CI: 42%; 100%), respectively. Survival was also similar in both groups (Figure 4).

Matched patient analysis (entire population)

Matched pairs of patients were selected according to baseline cardiac output and exercise capacity in order to control for disease severity. The selected analysis set contained 2 cohorts of 16 patients (43 % of bosentan patients and 43% of epoprostenol patients). These cohorts were well matched for haemodynamic and exercise variables (Table 3 and Table 4).

Median (95% CI) 6MWD improvements were +64 m (27; 80), +66 m (-9; 109),

Table 3. Demographic data and baseline characteristics in matched cohort idiopathic PAH patients

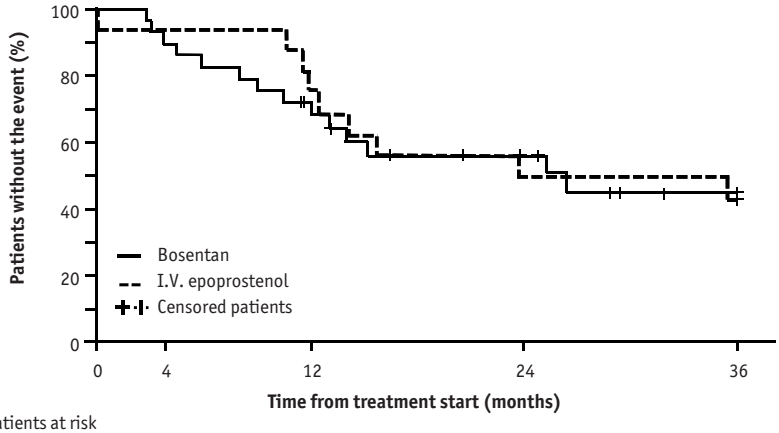
	Bosentan matched cohort N=16	**Epoprostenol matched cohort N=16**
Gender, n (%): female : male	14 (88) : 2 (13)	14 (88) : 2 (13)
Race, n (%):		
Caucasian	15 (94)	16 (100)
Asian	1 (6)	0 (0)
Age, years:		
Mean ± SD	45.4 ± 16.7	44.0 ± 8.6
Median (min, max)	46.7 (20.6, 75.2)	45.3 (29.8, 55.3)
Height, cm:		
Mean ± SD	169 ± 7	164 ± 7
Median (min, max)	168 (159, 187)	165 (150, 176)
Proportion of patients diagnosed <1998, n (%)	3 (19)	3 (19)
Time since diagnosis, (months):		
Mean ± SD	18.8 ± 34.6	19.4 ± 30.3
Median (min; max)	1.5 (0.7 ; 97.3)	5.7 (0.6 ; 85.3)
6 MWD, (m):		
n	16	16
Mean ± SD	334 ± 120	326 ± 119

+78 m (-37; 161) and + 98 m (-123; 182) in first-line bosentan after respectively 4 months, 1, 2 and 3 years. This compared to greater improvements of respectively +113 m (76; 193), +110 m (12; 265), +180 m (63; 327) and +142 (116; 242) in first-line epoprostenol.

Kaplan-Meier estimates of the proportion of patients without disease progression in the matched pairs analysis were similar for both treatment groups with respectively 75%, 60% and 43% without disease progression after respectively 1, 2 and 3 years in the bosentan group and respectively 81%, 63% and 50% without disease progression in the epoprostenol group (Figure 5). Kaplan-Meier estimates of survival in the matched pairs analysis after 1,2 and 3 years respectively were 100%, 92% and 92% in the bosentan group and respectively 100%, 88% and 88% in the epoprostenol group (Figure 6).

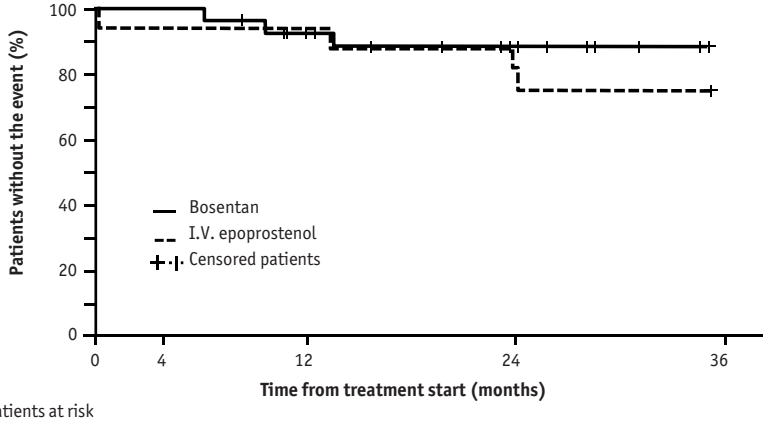
Line infections and liver enzyme abnormalities (entire population)

Adverse events were reported in 8 out of 37 patients in the bosentan group (21.6 %) and in 17 out of 37 patients in the epoprostenol group (46.0 %). The most common



Patients at risk				
Bosentan	26	19	11	4
I.V. epoprostenol	15	12	8	7

Figure 3. Kaplan-Meier estimates showing time to disease progression in WHO FC III IPAH treated with first-line bosentan or first-line epoprostenol.



Patients at risk				
Bosentan	29	24	18	11
I.V. epoprostenol	15	15	14	12

Figure 4. Kaplan-Meier estimates showing survival in WHO FC III IPAH treated with first-line bosentan or first-line epoprostenol.

adverse event was catheter site infection in I.V. eproprostenol-treated patients. This event occurred in 17 patients (46.0 %) in the first-line epoprostenol group and in 5 first-line bosentan (13.5 %). In first-line bosentan elevated serum ASAT (aspertate aminotransferase) levels >3-5 x upper limit of normal (ULN) occurred in 1 patient (2.7 %) during follow-up. Elevation >5-8 x ULN in 1 (2.7%) and >8 x ULN in 1 (2.7%). Elevated serum ALAT (alanine aminotransferase) levels >3-5 x ULN occurred

Table 4. RHC Hemodynamic baseline characteristics in matched cohorts idiopathic PAH starting first-line bosentan or epoprostenol.

	Bosentan N=16	**I.V. epoprostenol N=16**
Mixed venous O_2 saturation, %:		
n	14	14
Mean ± SD	60 ± 8	59 ± 9
mPAP, mmHg:		
n	16	16
Mean ± SD	59 ± 11	63 ± 11
mRAP, mmHg:		
n	16	15
Mean ± SD	8 ± 4	10 ± 4
PVR, dyn*s*cm^{-5}:		
n	16	16
Mean ± SD	1126 ± 428	1201 ± 459
Cardiac output, L/min:		
n	16	16
Mean±SD	4.1 ± 1.2	4.1 ± 1.2
SVI, mL/m^2:		
n	16	16
Mean ± SD	27 ± 9	26 ± 10

RHC = right heart catheterization; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PVR = pulmonary vascular resistance; SVI = stroke volume index

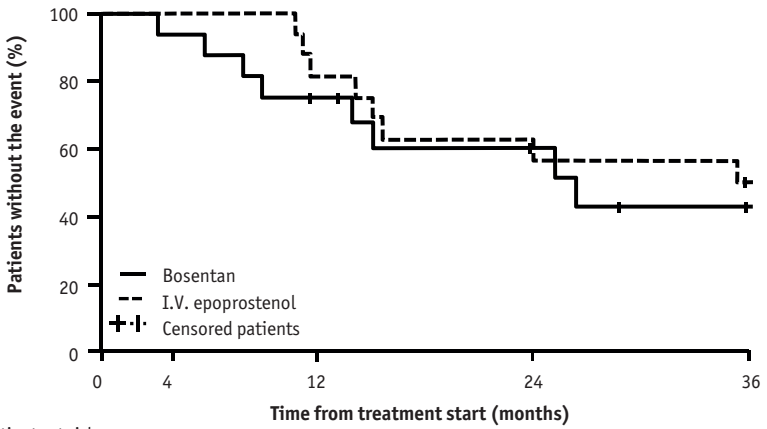


Figure 5. Kaplan-Meier estimates of time to disease progression in the idiopathic PAH patients included in matched cohorts of first-line bosentan or first-line epoprostenol treatment.

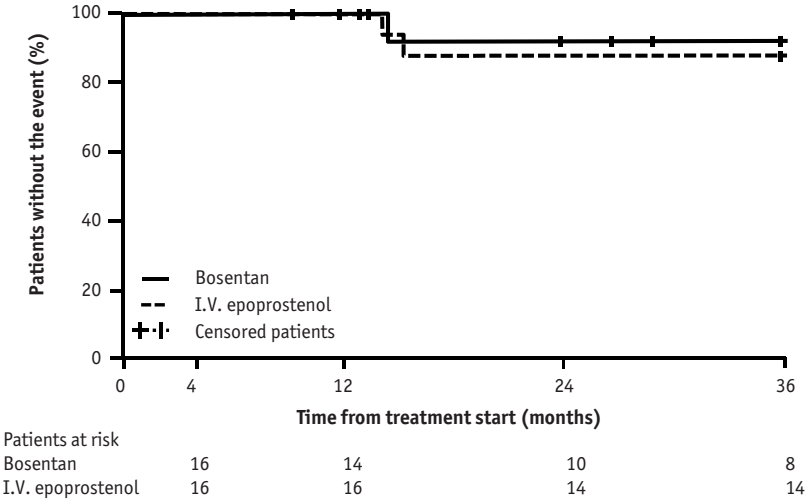


Figure 6. Kaplan-Meier estimates of survival in the idiopathic PAH patients included in matched cohorts of first-line bosentan or first-line epoprostenol treatment.

in 1 (2.7%) and >8 x ULN in 2 (5.41%). In first-line epoprostenol ASAT elevations >3-5 x ULN were reported in 1 (2.7%) and no ALAT elevations > 3 x ULN were reported.

Discussion

These data show long-term treatment results in first-line epoprostenol and first-line bosentan treated idiopathic IPAH patients. For a prolonged period I.V. epoprostenol was the only available PAH-specific medication. However, since the dual endothelin receptor antagonist bosentan became commercially available in The Netherlands in 2003 WHO FC III patients are started on oral bosentan therapy, and additional PAH specific therapies are added as needed. In this study, since the WHO FC III patients represent the largest group with similar disease severity for analysis, and because labelling and reimbursement access is similar for bosentan and I.V. epoprostenol in WHO FC III, focus is given to patients who were in WHO FC III at the start of treatment. In WHO FC III patients, exercise capacity improved at 1, 2 and 3 years in first-line bosentan and first-line I.V. epoprostenol patients. A greater improvement was observed in the I.V. epoprostenol patients at all time points. Time to disease progression and survival were similar in both treatment groups. In an independent analysis of our population, irrespective of WHO FC at baseline, and controlling for disease severity

by matched patient analysis according to CO and 6MWD at baseline, these findings were confirmed. In earlier studies of epoprostenol treatment in IPAH, improvements in exercise capacity correlated with increased stroke volume, cardiac output and pulmonary flow with the most significant effects occurring within the first 4 months. (15-17) Sitbon found that reaching a threshold 380 m 6MWD 3 months after starting PAH specific therapy, but not the magnitude of 6MWD improvement, is prognostic of survival.(18) This is in accordance with our study findings showing no survival differences despite greater exercise improvements in first-line epoprostenol.

Only one earlier study by Sitbon et al. compared first-line epoprostenol with first-line bosentan therapy and additional medication as needed.(9) The epoprostenol group in this study was a WHO FC III retrospective clinical needs-based treatment cohort and was compared with the long-term treatment results of WHO FC III patients treated with first-line bosentan as part of randomized clinical trials. In this study 75% of patients remained on bosentan monotherapy after 2 years; in our patient group this was 17% after a median 25 months in a setting where stringent criteria for adding therapy are upheld. Compared with our patients, survival in the Sitbon study was very similar with Kaplan-Meier estimates of 97%, 91% and 87% at 1, 2 and 3 years, respectively in bosentan first-line patients, and 91%, 84% and 75% in epoprostenol first-line patients.

There are several limitations to our study. The retrospective nature and reliance on the medical chart introduces the possibility of misclassification bias. Furthermore, measurements of exercise capacity and disease progression may not necessarily occur on a regular and consistent basis. The relationship between first-line therapy and additional therapies is confounded, as the choice of other PAH-specific therapies was greater post-commercial availability of bosentan relative to the I.V. epoprostenol era pre-February 2003. The small sample size limits our ability to detect differences in outcomes such as disease progression or survival. (9)

Our study does provide important real-life data on different treatment strategies in a rare disease setting. Diagnostic strategy, treatment and follow-up of IPAH at our hospital is standardized to a great extent and follow-up is at regular intervals. The alteration of treatment protocol after the introduction of bosentan permits a description of consecutive treatment strategies in different time periods.

To conclude, first-line epoprostenol-treated patients experienced great improvements in 6MWD whilst first-line bosentan-treated patients demonstrated less substantial improvements. Survival and time to disease progression is similar in both first-line treatment groups.

References

1. Simonneau G, Robbins IM, Beghetti M, et al Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009; 54:S43-S54.
2. Abenhaim L, Moride Y, Brenot F, et al. Appetite suppressant drugs and the risk of primary pulmonary hypertension. International primary pulmonary hypertension study group. N Engl J Med 1996; 335:609-616.
3. Group IPPHS: The international primary pulmonary hypertension study. Chest 1994; 105:37S-41S.
4. Appelbaum L, Yigla M, Bendayan D, et al. Primary pulmonary hypertension in Israel: A national survey. Chest 2001; 119:1801-1806.
5. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest 2007; 131:1917-1928.
6. D'alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991; 115:343-349.
7. McLaughlin V, Shillington RN, Rich S. Survival in primary pulmonary hypertension. The impact of epoprostenol therapy. Circulation 2002; 106:1477-1482.
8. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005; 25:244-249.
9. Sitbon O, McLaughlin VV, Badesch RJ, et al. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. Thorax 2005; 60:1025-1030.
10. rovencher S, Sitbon O, Humbert M, Cabrol S, Jaïs X, Simonneau G. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. Eur Heart J 2006; 27:589-595.
11. Jacobs W, Boonstra A, Marcus JT, Postmus PE, Vonk-Noordegraaf A. Addition of prostanoids in pulmonary hypertension deteriorating on oral therapy. J Heart Lung Transplant 2008; 28:280-284.
12. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 Expert consensus document on pulmonary hypertension. J Am Coll Cardiol 2009; 53:1573-1619.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370:1453-1457.
14. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Ann Intern Med 2007; 147:W163-194.
15. Kerbaul F, Brimioulle S, Rondelet B, Dewachter C, Hubloue I, Naeije R. How prostacyclin improves cardiac output in right heart failure in conjunction with pulmonary hypertension. Am J Respir Crit Care Med 2007; 175:846-850.
16. Roeleveld RJ, Vonk-Noordegraaf A, Marcus TJ, et al. Effects of epoprostenol on right ventricular hypertrophy and dilation in pulmonary hypertension. Chest 2004; 125:572-579.
17. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996; 334:296-302.
18. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780-788.

Chapter 4

Addition of prostanoids in pulmonary hypertension deteriorating on oral therapy

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Abstract

Background

The World Health Organisation recommends adding prostacyclin derivatives to oral therapy in deteriorating pulmonary arterial hypertension (PAH) patients. However there are no data defining the usefulness of intravenous or subcutaneous prostanoids in this setting.The aim of our study was to describe the efficacy of addition of intravenous or subcutaneous prostanoids in idiopathic pulmonary arterial hypertension (PAH) patients deteriorating on bosentan or on bosentan-sildenafil.

Methods

Treatment at our hospital is according to a predefined protocol. First line therapy is bosentan. Upon clinical worsening, defined by a 10% decrease in 6 minute walk distance (6MWD) in combination with increasing PAH symptoms or deterioration of NYHA functional class, prostanoids are initiated. Response is assessed by change in 6MWD, NYHA class and after 2004 also by cardiac MRI and Nterminal-proBNP (BNP).

Results

63 idiopathic PAH (iPAH) started oral therapy. In 16 iPAH prostanoids were added after 20.6 ± 18.1 (± SD) months. Mean 6-minute walk distance improvement after 4 months prostanoids was +86m ($p<0.01$) in the bosentan group versus +41m ($p<0.05$) in the bosentan-sildenafil group and improvements persisted at long-term follow-up. NYHA class improved, BNP decreased and cardiac MRI functional parameters improved.

Conclusions

From these results we conclude that addition of subcutaneous or intravenous prostanoids can be efficacious in PAH deteriorating on oral therapy.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature, leading to right heart failure and death. Novel therapies target three different pathways of abnormal pulmonary artery smooth-muscle cell proliferation and contraction: the prostacyclin, nitric oxide and endothelin pathways.[1-4] Data on combining these therapies are limited. Sildenafil added to bosentan improves exercise capacity.[5-7] Bosentan added to beraprost or iloprost improves exercise capacity and hemodynamics.[8, 9] However, bosentan-epoprostenol up-front showed no benefit versus epoprostenol in limited patient numbers. However, this study was underpowered and therefore inconclusive.[10] For inhaled iloprost added to bosentan studies are contradictory. McLaughlin showed improved exercise capacity. A study by Hoeper et al. failed to show a positive effect.[11-13]
Currently first-line oral therapy is preferred.[14-16] However 56% need additional treatment within 2 years.[17] The WHO recommends adding a prostacyclin derivative in PAH worsening on oral therapy.[18] No studies describe efficacy of combination therapy with subcutaneous or intravemous prostanoids added to existing oral therapy. The aim of this study was to describe short and long-term efficacy of intravenous epoprostenol or subcutaneous treprostinil in PAH deteriorating on oral therapy.

Methods

Study design and patients

We performed an observational study of idiopathic PAH attending our hospital and starting first line bosentan from January 2002-September 2007. Our hospital is a referral centre for PAH in the Netherlands. Treatment is standardized. Diagnosis is confirmed by right heart catheterisation. In New York Heart Association (NYHA) class III patients first-line therapy is bosentan (Tracleer®; ActelionPharmaceuticals): 62.5mg b.i.d., increased to 125mg b.i.d. after one month. Assessment is at least every 4 months by symptoms, 6-minute walk distance (6MWD) and NYHA class. In our centre clinical worsening is defined by a deterioration of NYHA class or a greater than 10% decrease in 6MWD, measured on 2 occasions, in combination with increasing PAH symptoms, such as shortness of breath, collapse or signs of right heart failure. Upon clinical worsening sildenafil is added and upon further clinical worsening intravenous or subcutaneous prostanoids. Adding sildenafil is possible since 2004. Patients treated with bosentan versus bosentan-sildenafil were compared for prostanoid efficacy.

Addition of prostanoids

Prostanoid choice is a personal decision taking side effects and mode of delivery into consideration. Treprostinil (Remodulin®; UnitedTherapeutics, Silverspring, U.S.A.) dose is gradually increased to 10ng/kg/min after 1 week and 20ng/kg/min

after 6 weeks. Epoprostenol (Flolan®;GlaxoSmithKline, London, United Kingdom) is titrated to the maximal tolerated dose, usually 6.0-8.0ng/kg/min after 1week. Further dose adjustments are according to patient need. Prostanoids are not started in patients unable to deal with continuous pump infusion and if declined.

Magnetic resonance imaging and N-terminal Pro-B-type natriuretic peptide

Since 2004 cardiac MRI is performed during change of therapy as part of an ongoing study evaluating clinical value of MRI in PAH. A Siemens-1.5T-Sonata scanner is used to acquire short-axis cine images from apex to base. Endocardial contours are delineated manually by a blinded observer and processed using MASS software (Department of radiology, Leiden University Medical Centre) to obtain right- and left-ventricular end-diastolic volume (RVEDV and LVEDV) and left-ventricular end-systolic volume (LVESV). Strokevolume (SV) is calculated: LVEDV-LVESV=SV. Parameters are indexed for body surface area. NT-proBNP is measured by electrochemoluminescence immunoassay (ECLIA,Roche).

Requirements of hospital research and ethical review boards were met. Informed consent was obtained.

Statistical analysis

6MWD was analysed by ANOVA, MRI parameters and NT-proBNP by two-tailed t-test, NYHA class by Wilcoxon. Results are presented as mean±SE. Pearson correlation compared MRI parameter and 6MWD changes. GraphPad Prism® version 4 software was used.

Results

Patient characteristics

In the study period 63 idiopathic PAH started oral therapy. Follow-up was 32.8±18.1 months. At end of the observation period 19 of these patients remained stable on bosentan, 18 were stable on bosentan-sildenafil and in 16 prostanoids were added. In 10 clinical worsening and death occurred without prostanoid initiation. Reasons for not starting prostanoids despite clinical worsening and death were inability to deal with pump infusion (n=5), death from non-PAH cause (n=2; 1 pneumonia and 1 trauma), out of hospital death before initiation of prostanoids (n=2) and patient declination (n=1).

The characteristics of the 16 patients in whom prostanoids were added are depicted in table 1. In 6 patients prostanoids were added to bosentan and in 10 to bosentan-sildenafil. Mean time between start oral therapy and addition of prostacyclin was 20.6 ± 5.0 months. This was shorter for patients treated with bosentan compared to those treated with bosentan-sildenafil: 8.7 ± 1.8 versus 27.8 ± 7.0 months (p=0.06).

Table 1. Patient characteristics*.

Subjects n	16
Men	3
Women	13
Age yrs ± SD	37.0 ± 10.9
Prostanoid added:	
Epoprostenol	6
Treprostinil	10
Right heart catheterisation at baseline	
MPAP, mmHg	56 ± 4
RAP, mmHg	7.1 ± 1.2
SvO2, %	66 ± 2
CI, l/min/m2	2,6 ± 0,15

* Data are represented as mean ± SE where appropriate; m = months; yrs = years; PAP = pulmonary artery pressure; RAP = right atrial pressure; Sv02 = mixed venous 02 saturation; CI = cardiac index.

NYHA functional class , 6MWD and outcomes

After prostanoid addition NYHA class improved by 1 class or more in 10 and remained unchanged in 6 ($p = 0.002$). In the 16 patients in whom prostanoids were added mean 6MWD was 400 ± 32m at baseline, 425 ± 27m after 4 months oral therapy, 363 ± 27m at start prostanoids and 427 ± 24m 4 months thereafter. A 61 ± 17m 6MWD decrease led to prostanoid addition. 4 months thereafter 6MWD improved 64 ± 18m ($p<0.001$; 95%CI 22.4 to 105.6; Fig 1). Treprostinil and epoprostenol efficacy were not significantly different (Table2). After 4 months prostanoids all patients had stabilized or improved.

At end of observation after 18.4 ± 3.9 months prostacyclin 6MWD was 436 ± 22 m, showing a persisting 73 ± 22m improvement compared to 6MWD at start prostanoids ($p=0.005$; 95% CI 25.6 to 119.7). 6MWD was still better than at start oral therapy 37.0 ± 4.4 months earlier. 1/16(6%) death had occurred. This was in the bosentan-prostanoid group after 15 months prostanoids. Post-mortem revealed pulmonary veno-occlusive disease. The 15 remaining showed persisting clinical improvement.

Prostanoid efficacy: bosentan versus bosentan-sildenafil

6MWD in the bosentan group was 323±53m at addition of prostanoids, 409±48m four months thereafter and 447 ± 48m at end of observation. 6MWD in the bosentan-sildenafil group respectively were 387 ± 30m, 428 ± 23m and 429 ± 23m. Improvements at 4 months prostanoids were +86m ($p<0.01$) in bosentan and + 41m ($p<0.05$) in bosentan-sildenafil (Fig.2). The 6MWD improvement in the bosentan group was not significantly different from the improvement in the bosentan-sildenafil group ($p=0.10$). Time on prostanoids was 27.0 ± 7.7 months in bosentan and 13.2 ± 3.5 months in bosentan-sildenafil.

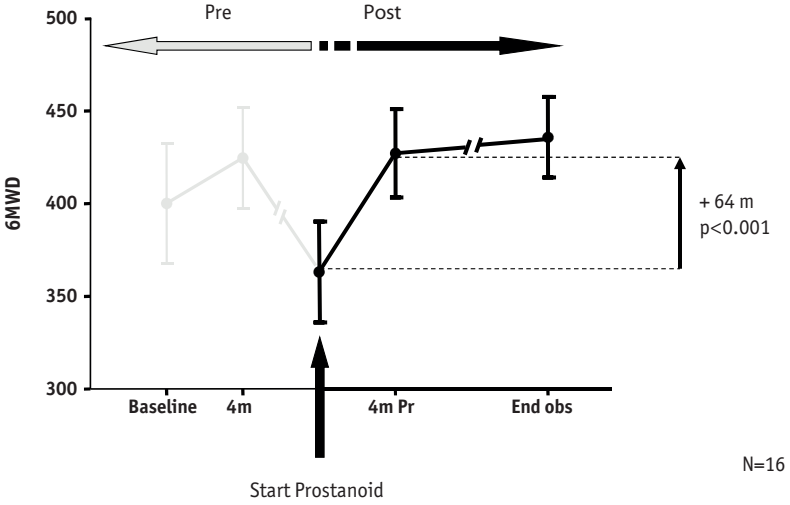

Figure 1. Mean 6-minute walk distance (6MWD) in meters ± SE in 16 idiopathic pulmonary arterial hypertension patients treated with first-line oral therapy and addition of prostanoids on clinical worsening. 6MWD is depicted at baseline, after 4 months oral therapy (4m), at addition prostanoid, after 4 months prostanoid (4m Pr) and at end of observation (End obs). Significant improvements occur after prostanoid addition ($p<0.001$). Prostanoid addition is after 20.6 ± 5.0 months oral therapy. End observation is after 18.4 ± 3.9 months prostanoid treatment.

Table 2. Change in 6-minute walk distance (6MWD) in metres in treprostinil and epoprostenol subgroup after 4 months of prostanoid therapy.

	6MWD at start prostanoid	Change in 6MWD	95% CI
Epoprostenol	263 ± 48	+ 83	+ 14 to + 152
Treprostinil	421 ± 93	+ 57	+ 8 to + 107

Table 3. Cardiac MRI parameters before and 6 months after addition of prostanoid therapy (n=10)*.

	Before	After	Mean change	95% CI	p-value
SVI (ml/m2)	27.1 ± 3.0	36.1 ± 2.7	+ 9.0	+ 5.4 to + 12.5	< 0.001
LVEDVI (ml/m2)	42.1 ± 3.4	53.2 ± 4.6	+ 11.1	+ 6.2 to + 16.0	< 0.001
RVEDVI (ml/m2)	84.0 ± 7.8	76.5 ± 7.0	- 7.5	- 0.9 to – 14.1	< 0.05
CO (L/min)	4.0 ± 0.3	4.7 ± 0.4	+ 0.7	0.0 to + 1.5	P=0.06
RVEF (%)	33 ± 5	44 ± 6	+ 12	+ 4 to + 19	P<0.01
LVEF (%)	66 ± 5	70 ± 3	+ 6	- 3 to + 14	P=0.19

* Values are given as mean ± SE. SVI = stroke volume index; LVEDVI = left-ventricular end-diastolic volume index; RVEDVI = right-ventricular end-diastolic volume index; CO = cardiac output; RVEF = right ventricular ejection fraction; LVEF = left ventricular ejection fraction.

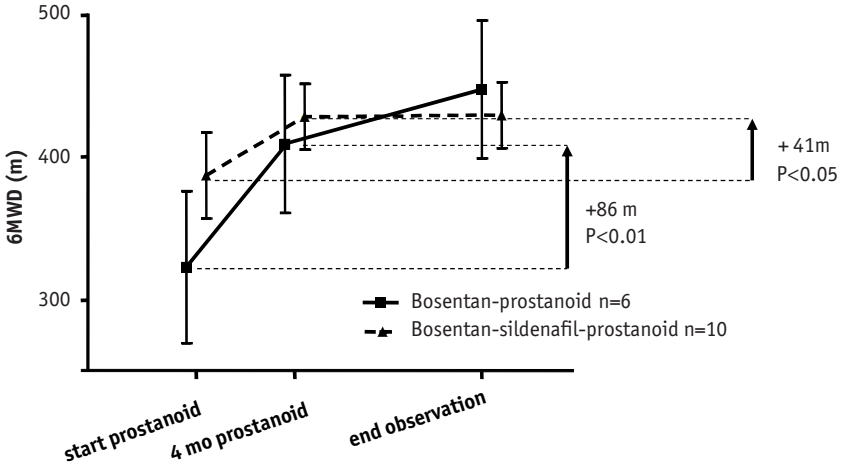

Figure 2. Change in 6-minute walk distance (6MWD) after addition of prostacyclin in idiopathic pulmonary arterial hypertension patients treated with bosentan-prostacyclin before 2004 (n=6) and with bosentan-sildenafil-prostacyclin after 2004 (n=10). 6MWD is in meters ± SE and is depicted before addition of prostanoids, 4 months thereafter (4 mo prostanoid) and at end observation and shows significant improvements in both treatment groups (respectively p<0.01 and p<0.05).

Cardiac MRI and N-terminal-proBNP serum levels

MRI was performed in 10 patients before and 6 months after prostanoid addition. Results in table 3 show improved RVEF, stroke volume and improved RV and LV end-diastolic volumes after prostanoid addition. MRI parameter and 6MWD improvements pearson r correlation values were 0.94 (p<0.001) for LVEDVI; r = -0.49 (p=0.18) for RVEDVI; r=0.64 (p=0.06) for SVI and r=0.57 (p=0.11) for CI.

NT-proBNP was measured in 11 patients. After prostanoids NT-proBNP decreased from 2830 ± 818nanog/L to 1574±447nanog/L. Mean decrease was 1256 ± 430nanog/L (95%CI 298 to 2215; p<0.05). BNP decrease was 987 ± 1224nanog/L in bosentan and 1316 ± 489 nanog/L in bosentan-sildenafil and not significantly different between both groups (p=0.78).

Prostanoid dose and adverse effects

At end observation treprostinil dose was 38.4 ± 5.7 ng/kg/min and epoprostenol dose 16.0±2.8ng/kg/min. Maximal doses were reached after respectively 16.2 ± 5.9 and 7.3 ± 2.8 months. No treatment related deaths occurred.

4/10 treprostinil had needle insertion site irritation. Usually symptoms subsided. One was switched to epoprostenol. 2 treprostinil patients reported headaches and 1 nausea. Symptoms subsided spontaneously. 1 diarrhoea was treated with loperamide. 4/6 epoprostenol had intravenous portacath catheter infections, for which it was replaced. In 2 infections recurred and these were switched to subcutaneous treprostinil. Rate of infusion related infections was 0.7/1000 prostanoid infusion days.

Discussion

These data are the first describing efficacy and long-term follow-up of intravenous or subcutaneous prostanoids added in PAH deteriorating on oral therapy. 6MWD and NYHA class improve. This improvement persists at long-term follow-up. Our data are further supported by an improvement in cardiac function measured by MRI and decreased NT-proBNP serum levels. NYHA class, 6MWD, NT-proBNP, stroke volume and right- and left-ventricular end-diastolic volume are all known to correlate with disease severity and outcome in PAH.[19-22]

The 64m increase in 6MWD after prostanoid addition compares favourably to the 30m increase reported for inhaled iloprost added to bosentan.[11] The improvement could be a sole effect of prostacyclin.[2] However the BREATHE-2 study showed a tendency towards improved hemodynamics with first-line bosentan-epoprostenol compared to epoprostenol alone.[10] Since oral therapy was continued a synergistic effect cannot be excluded.

This study did not aim to investigate effects of sildenafil added to bosentan. Earlier studies[5-7] showed this strategy leads to improved exercise capacity. In our study time till addition of prostacyclin increased from 8.7±1.8 to 27.8±7.0 months after the introduction of sildenafil. It remains unclear whether prostacyclin addition is beneficial in non-deteriorating PAH. Furthermore we cannot exclude a differential treatment effect between epoprostenol and treprostinil. Mortality in our patients is similar to rates recently reported.[17] Initial improvement with oral therapy is in line with earlier study results.

Adverse effects of prostanoid addition were few and mainly related to infectious and inflammatory complications at the prostanoid infusion site. The rate of this complication was similar to earlier reported figures.[23] Post-mortem in the only PAH death after addition of prostanoids revealed pulmonary veno-occlusive disease thus explaining her bad outcome.

Study limitations include lack of a control group and limited patient numbers. Performing an adequately sized randomized placebo controlled trial addressing the issue of adding subcutaneous or intravenous prostanoids in patients worsening on oral therapy deprives deteriorating patients of the chance of improvement on prostanoids. Considering limited life expectancy of these patients this would not be ethically sound practice. Data on safety and long-term efficacy of combination therapy in PAH are sparse. Due to the rarity of the disorder it is practically impossible to obtain answers to all questions regarding efficacy, adverse effects and long-term outcome with combination therapy from randomised controlled trials. Some of the most relevant data currently available have not been derived from formal trials but from large pulmonary hypertension centres presenting long-term experiences with their therapeutic concepts.[24] To support the findings of this uncontrolled study, we used NT-proBNP and MRI measurements. These data show that addition of prostacyclin improves pulmonary hemodynamics and right ventricular function. For all above reasons we believe this observational study has high clinical value.

Conclusion

The results of this study show that adding subcutaneous or intravenous prostanoids in patients deterioration on oral therapy is an effective treatment approach in idiopathic PAH.

References

1. Humbert M, Sitbon O, Simmoneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004; 351: 1425-1436.
2. Barst RJ, Rubin LJ, Long WA, *et al*. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The primary pulmonary hypertension study group. *N Engl J Med* 1996; 334: 296-302.
3. Galiè N, Ghofrani HA, Torbicki A, *et al*. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; 353: 2148-2157.
4. Rubin LJ, Badesch BB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002 ; 346 : 896-903.
5. Hoeper MM, Faulenbach C, Golpon H, *et al*. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004; 24: 1007-1010.
6. Mathai SC, Girgis RE, Fisher MR, *et al*. Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. *Eur Respir J* 2007; 29: 469-475.
7. van Wolferen SA, Boonstra A, Marcus JT, *et al*. Right ventricular reverse remodelling after sildenafil in pulmonary arterial hypertension. *Heart* 2006; 92: 1860-1861.
8. Hoeper, MM, Taha N, Bekjarova A, *et al*. Bosentan treatment in patients with primary pulmonary hypertension receiving nonparenteral prostanoids. *Eur Respir J* 2003; 22: 330-334.
9. Seyfarth HJ, Pankau H, Hammerschmidt S, *et al*. Bosentan improves exercise tolerance and tei index in patients with pulmonary hypertension and prostanoid therapy. Chest 2005; 128: 709-713.
10. Humbert M, Barst RJ , Robbins IM, *et al*. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; 24: 353-359.
11. McLaughlin VV, Oudiz RJ, Frost A, *et al*. Randomized study of adding iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006; 174: 1257-1263.
12. Hoeper MM, Leuchte H, Halank, *et al*. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2006; 28: 691-694.
13. Tsangaris H, Armaganidis A, Argentos S, *et al*. Pre-operative long-term optimisation with prostanoids in initially inoperable severe chronic thromboembolic pulmonary hypertension (CTEPH): a step forward ? *J Heart Lung Transplant* 2007; 26: 1079-1083.
14. McLaughlin VV. Survival in patients with pulmonary hypertension treated with first-line bosentan. *Eur J Clin Invest* 2006; 36s: 10-15.
15. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension *Eur Respir J* 2005; 26: 858-863.
16. Sitbon O, McLaughlin VV, Badesch DB, *et al*. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. *Thorax* 2005; 60: 1025-1030.

17. Provencher S, Sitbon O, Humbert M, *et al*. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2006 ; 27: 89-595.

18. Galiè N, Seeger W, Naeije R, Simonneau G, Rubin LJ. Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; 43: 81-88.

19. Miyamoto S, Nagaya N, Satoh T, *et al*. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension: comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000; 161: 487-492.

20. Souza R, Jardim C, Julio Cesar Fernandez C, *et al*. NT-proBNP as a tool to stratify disease severity in pulmonary arterial hypertension. *Respir Med* 2007; 101: 69-75.

21. van Wolferen SA, Marcus JT, Boonstra A, *et al*. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2007 ; 28 : 1250-1257.

22. Sitbon O, Humbert M, Nunes H, *et al*. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 20: 780-788.

23. Barst R, Berman-Rosenzweig E, Horn E, *et al*. Bloodstream infections among patients treated with intravenous epoprostenol or intravenous treprostinil for pulmonary arterial hypertension--seven sites, United States, 2003-2006. *Morb Mortal Wkly Rep* 2007; 56: 170-2.

24. Hoeper MM. Observational trials in pulmonary arterial hypertension: low scientific evidence but high clinical value. *Eur Respir J* 2007; 29: 432-434.

Chapter 5

The right ventricle explains sex differences in survival in idiopathic pulmonary arterial hypertension

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Abstract

Background

Male sex is an independent predictor of worse survival in pulmonary arterial hypertension (PAH). This finding might be explained by more severe pulmonary vascular disease, worse right ventricular function or different response to therapy. The aim of this study was to investigate the underlying cause of sex differences in survival in treated PAH patients.

Methods

This was a retrospective cohort study of 101 patients with PAH (82 idiopathic, 15 heritable, 4 anorexigen associated) who were diagnosed at our institute between February 1999 and January 2011 and underwent right heart catheterisation (RHC) and cardiac magnetic resonance imaging (CMR) to assess right ventricular function. Change in pulmonary vascular resistance was taken as a measure of treatment response on the pulmonary vasculature, whereas change in right ventricular ejection fraction was used to assess right ventricular response to therapy.

Results

Pulmonary vascular resistance and right ventricular ejection fraction were comparable between men and women at baseline, however male patients had a worse transplant-free survival compared to female patients ($p=0.002$). While male and female patients showed a similar reduction in PVR after one year, RVEF improved in female patients whereas it deteriorated in male patients. In a mediator analysis, after correcting for confounders, 39.0 % of the difference in transplant-free survival between men and women was mediated through changes in RVEF after initiating PAH medical therapies.

Conclusions

This study suggests that differences in RVEF response with initiation of medical therapy in IPAH explain a significant portion of the worse survival seen in males.

Introduction

Pulmonary arterial hypertension (PAH) is a rare disease characterized by obstructive lesions of the small pulmonary vessels, leading to increased pulmonary artery pressure (PAP), right-sided heart failure and death within several years.[1-2] Despite the advent of improved therapies outcome remains poor.[3,4] Prognosis correlates with severity of right ventricular (RV) structure and function.[2,5] More recently, male sex was identified as an independent predictor of mortality.[6-10] Men treated with endothelin receptor antagonists had less six minute walk improvement.[11] The cause of these sex differences is unknown, however a distinct vascular and/or right ventricular response to medical therapies is one possibility. Considering the need for improved treatments and "personalized therapy", a better understanding of these sex differences would be important. The aim of our study was to investigate the role of the pulmonary vasculature and the right ventricle in explaining sex differences in survival of treated IPAH.

Methods

Study design and patients

All idiopathic (IPAH), anorexigen associated (APAH) and heritable PAH (HPAH) treated at the VU University Medical Center (VUMC) between February1999 and January 2011 were eligible. Diagnosis was according to the guidelines and included right heart catheterisation (RHC). Medical treatment comprised prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase type-5 inhibitors either alone or in various combinations. Patients with a positive vasodilator challenge were treated with calcium antagonists.[1] This was a retrospective cohort study of patients enrolled in an ongoing prospective study to assess the clinical value of cardiac magnetic resonance imaging (CMR) in PAH. All patients who had RHC and CMR performed prior to initiation of medical therapy (N = 101 out of N= 186 patients evaluated during this period) were included.

Right Heart Catheterisation

Hemodynamic assessment was performed with a 7-F balloon tipped flow directed Swan-Ganz catheter (131HF7, Baxter Healthcare Corp. , Irvine, California). Baseline and follow-up RHC measurements of pulmonary artery pressure (PAP), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) were obtained. Pulmonary vascular resistance (PVR) was calculated as (80·(meanPAP-PCWP)/CO). Vasoreactivity testing was with inhaled nitric oxide (20 ppm). Acute vasoreactivity defined as a mean PAP reduction ≥ 10 mmHg to reach an absolute value ≤ 40 mmHg with increased or unchanged cardiac output.

Cardiac Magnetic Resonance Imaging

CMR was performed on a Siemens Avanto 1.5 T and 1.5 T Sonata scanner (Siemens Medical Solutions, Erlangen, Germany), equipped with a 6-element phased-array coil. ECG-gated cine imaging was performed using a balanced steady, free precession pulse sequence, during repeated breath-holds. Short-axis slices were obtained with, slice thickness 5 mm and interslice gap 5 mm, fully covering both ventricles from base to apex. Temporal slice resolution between 35 and 45 ms, voxel size 1.8 x 1.3 x 5.0 mm^3, flip angle 60°, receiver bandwidth 930 Hz/pixel, TR/TE 3.2/1.6 ms, matrix 256 x 156.

End-diastolic and end-systolic endocardial and epicardial contours were delineated manually by an observer blinded to other clinical information and processed using MASS software (Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands) to obtain right ventricular end-diastolic and end-systolic volumes (RVEDV and RVESV respectively) and RV mass. Papillary muscles and trabeculae were excluded from the cavity, and included in RV mass. Right ventricular stroke volume (RVSV) and ejection fraction (RVEF) were calculated: RVSV = RVEDV − RVESV and RVEF = RVSV/RVEDV.[12] RV mass / RVEDV was used as a measure of relative RV wall thickness.[13,14]

Data analysis

Measurements are reported as mean ± standard deviation and median (interquartile range) where appropriate. Continuous variables were compared using student t-tests or Mann-Whitney U, where not normally distributed. Categorical variables compared using Pearson Chi-square tests and Fisher's exact tests, as needed.

Follow-up was until September 2011. Transplant-free sex survival differences were confirmed using Kaplan Meier curves and logrank test. Confounders accounted for by Cox regression. Variables leading to a ≥10% change in the coefficient for sex were included in the final survival prediction model. Variables screened for confounding included: age, height, weight, WHO functional class, number of comorbidities (1, 2 and ≥3), RVEF, RV wall thickness, glomerular filtration rate (GFR, Cockroft), PVR and type of medical therapy used (prostacyclin yes/no, endothelin receptor antagonist yes/no and phosphodiesterase type 5 inhibitor yes/no).

Sex differences in secondary treatment outcomes (Nt-proBNP, 6-minute walk distance and renal function), RHC hemodynamics and CMR were confirmed using linear regression with the follow-up measurement as the dependent variable and the baseline measurement and sex as independent variables. WHO class change differences were confirmed by ordinal regression. Multiple imputation was used for missing follow-up MRI variables. We multiply imputed 100 datasets. Linear regression models were estimated in each dataset and regression coefficients and standard errors pooled and the p-value of each coefficient in the model determined. To correct for confounders a similar approach was used as discussed above for the survival analysis.

An exploratory mediator analysis was done to confirm that transplant-free sex survival differences were mediated through differences in RVEF change. Analysis was done according to Baron and Kenny[15] and consists of 3 steps. In step 1, sex was confirmed

as an independent predictor of transplant-free survival by Cox regression. Step 2 was to confirm that sex was an independent predictor of the proposed mediator by linear regression. Step 3 employs a Cox regression model for transplant-free survival including sex and the potential mediator as independent variables and its purpose is to confirm the proposed mediator is a significant predictor of survival, while controlling for sex. RVEF and PVR changes were both examined as potential mediators. This was done by adding follow-up measurements of respectively RVEF and PVR to a Cox regression equation containing gender and the baseline value. A greater than 10% change in the coefficient of sex after adding the follow-up value of the proposed mediator was accepted as evidence of significant mediation. The magnitude of the indirect (mediated) effect was calculated according to the following formula:

Indirect effect = 1 – (c' / c)

In the formula, c is the coefficient for sex in the Cox regression formula predicting survival, corrected for baseline RVEF; c' is the coefficient for sex in the Cox regression formula predicting survival corrected for RVEF baseline value and RVEF change by adding the follow-up RVEF value to the equation. In addition a mediator analysis corrected for all potential confounders mentioned earlier was performed.[16]
Analysis were performed using IBM SPSS statistics 19.0 software. This study was approved by the VUMC Research and Ethics Review boards (METC), and informed consent obtained. (approval number 2012288)

Results

Patient characteristics and treatments

One-hundred-eighty-six patients (155 IPAH, 25 HPAH and 6 APAH) were treated at the VUMC between February1999 and January 2011. Eight-five patients were excluded. Reasons for exclusion were: no MRI due to logistical reasons (n=44), first-line treatment elsewhere (n=25), contraindications for MRI (n=11) and no PAH medication initiated (n=5). Apart from age table 1 indicates similar characteristics compared to those included for further analysis (n=101). The six-minute walk tended to be greater in those included, however the % predicted distance was similar. The remaining 101 patients all had CMR and RHC at baseline before starting PAH specific medical therapies (table 2). In these patients men had larger RVEDV and RVESV, but had similar invasively measured hemodynamics and similar RVSV and RVEF compared to women. Median (IQR) time between baseline CMR and RHC was 0.2 (0.0-1.95) months. Table 3 depicts prescribed medications between baseline and follow-up assessment. Follow-up CMR and RHC were performed after respectively 1.1 (0.9-1.7) and 1.1 (0.9-2.2) years. Time on PAH specific medication was 5.4 (2.1-7.7) years. Time to addition of other PAH specific therapy was 5.0 (2.3-6.0) months for those patients who had PAH specific drugs added before follow-up measurements.

Table 1. Patient characteristics and Right Heart Catheterisation (RHC) measurements in Pulmonary Arterial Hypertension included in study (n=101) compared to those excluded (n=85)

	n=101	n=85
Age, years	48 ± 16	57 ± 18
Gender, m/f	26/75	28/57
BMI, kg/m^2	26 ± 5	28 ± 6
WHO FC, n		
Class I	3	1
Class II	14	19
Class III	41	53
Class IV	27	28
Comorbidities, n		
0	34	30
1	32	22
2	20	19
≥ 3	15	14
6MWD, m	362 ± 162	307 ± 126
6MWD, % predicted	61 ± 24	58 ± 21
Creatinine, mmol/L	98 ± 21	100 ± 23
GFR, ml/min	78 ± 24	76 ± 31
NT-proBNP, ng/L*	1765 ± 1865	1824 ± 2486
RHC		
RAP, mmHg	9 ± 5	9 ± 6
mPAP, mmHg	56 ± 14	49 ± 12
PCWP, mmHg	8 ± 5	10 ± 7
CO, L/min	4.60 ± 1.63	4.65 ± 1.75
CI, L/min/m^2	2.50 ± 0.93	2.51 ± 0.96
PVR, dyn·s·cm^{-5}	957 ± 493	802 ± 462
PVRI, dyn·s·cm^{-5}·m^2	1760 ± 919	1505 ± 835

Data are presented as mean ± SD. BMI = body mass index; WHO FC = world health organization functional class; 6MWD = six-minute walk distance; GFR = glomerular filtration rate (Cochroft); RAP = right atrial pressure; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; CI = cardiac index; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; BSA = body surface area. * NT-proBNP was measured in a subgroup of respectively n=72 and n=40.

Table 2. Baseline patient characteristics and Right Heart Catheterisation (RHC) and Cardiac Magnetic Resonance Imaging (CMR) measurements in male (n=26) and female (n=75) Pulmonary Arterial Hypertension

	Male n=26	Female n=75	p-value
Age, years	50 ± 19	47 ± 15	0.31
Idiopathic, n (%)	23 (88)	59 (79)	0.55
Heritable, n (%)	3 (12)	12 (16)	0.75
Anorexigen, n (%)	0 (0)	4 (5)	0.57
BMI, kg/m^2	27 ± 3	26 ± 6	0.34
WHO FC, n (%)			0.09
Class I	1 (4)	0 (0)	
Class II	7 (27)	12 (16)	
Class III	13 (50)	40 (53)	
Class IV	5 (19)	23 (31)	
Comorbidities, n (%)			0.82
0	9 (35)	25 (33)	
1	6 (23)	26 (35)	
2	8 (31)	12 (16)	
≥ 3	3 (12)	12 (16)	
6MWD, m	388 ± 189	353 ± 150	0.40
6MWD, % predicted	62 ± 27	61 ± 23	0.82
Creatinine, mmol/L	110 ± 27	94 ± 17	0.001
GFR, ml/min	88 ± 31	75 ± 19	0.01
NT-proBNP, ng/L*	1414 ± 1668	1887 ± 1913	0.34
RHC			
RAP, mmHg	10 ± 6	9 ± 5	0.11
mPAP, mmHg	53 ± 15	57 ± 13	0.29
PCWP, mmHg	8 ± 4	8 ± 5	0.65
CO, L/min	4.73 ± 1.63	4.55 ± 1.63	0.61
PVR, dyn⋖⋖cm^{-5}	903 ± 545	963 ± 473	0.61
Acute vasoreactivity #	3/23 (13%)	7/66 (11%)	0.71
CMR			
RVEDV, ml	177 ± 68	137 ± 41	0.001
RVEDVI, ml/m^2	89 ± 36	76 ± 21	0.03
RVESV, ml	124 ± 54	93 ± 35	0.001
RVESVI, ml/m^2	62 ± 28	52 ± 19	0.04
RVEF, %	31 ± 13	33 ± 11	0.44
RVSV, ml	53 ± 30	44 ± 19	0.38
RVSVI, ml/m^2	27 ± 17	25 ± 10	0.38
RV mass, g	104 ± 41	81 ± 28	0.009
RV mass / RVEDV, g/ml	0.64 ± 0.31	0.62 ± 0.23	0.75

Data are presented as mean ± SD. BMI = body mass index; WHO FC = world health organization functional class; 6MWD = six-minute walk distance; GFR = glomerular filtration rate; RAP = right atrial pressure; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; PVR = pulmonary vascular resistance; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume; RVEF = right ventricular ejection fraction; RVSV = right ventricular stroke volume. CMR volumes are also provided indexed for body surface area. * NT-proBNP was measured in a subgroup of n=20 males and n=52 females. # Acute vasoreactivity was measured in a subgroup of n=66 females and n=23 males. RV mass / RVEDV is a measure of relative RV wall thickness.

Table 3. Pulmonary arterial hypertension medical treatment regimens in respectively men and women.

	Male (n=26)	Female (n=75)	p-value
First-line therapy:			
Prostacyclin	4 (15%)	23 (31%)	0.20
ERA	13 (50%)	30 (40%)	0.74
PDIE5	4 (15%)	9 (12%)	0.74
ERA + PDIE5	2 (8%)	3 (4%)	0.60
ERA + Prostacyclin	0 (0%)	3 (4%)	0.57
Ca^{2+} blocker	3 (12%)	7 (9%)	0.71
Add-on therapy:			
ERA + PDIE5 add-on	4 (15%)	17 (23%)	0.58
ERA + Prostacyclin add-on	1 (4%)	1 (1%)	0.45
Prostacyclin + PDIE5 add-on	0 (0%)	2 (3%)	1.00
PDIE5 + Prostacyclin add-on	1 (4%)	0 (0%)	0.26
Ca^{2+} blocker + PDIE5 add-on	0 (0%)	1 (1%)	1.00
Ca^{2+} blocker +Prostacyclin add-on	0 (0%)	2 (3%)	1.00
Switch:			
From ERA to PDIE5	1 (4%)	3 (4%)	1.00
From Ca^{2+} blocker to Prostacyclin	0 (0%)	2 (3%)	1.00

ERA = endothelin receptor antagonist. PDIE5 = phosphodiesterase type 5 inhibitor. Data are presented as number of patients n (% within sex).

Survival and secondary treatment outcomes

In the 101 patients included median (IQR) follow-up time was 5.7 (2.5 to 8.1) years, and there were 26 deaths and 5 lung transplants. In males, cumulative transplant-free survival was 84% at 1 year and 57% at 5 years. In females, survival was 100% at 1 year and 85% at 5 years (logrank p=0.002; HR 3.04; 95% CI 1.45-6.41; figure 1). The association between sex and survival after adjustment for confounders in multivariate analysis remained (HR 7.21; 95% CI 4.18-12.43; p<0.001). The confounders retained in the final model were height, GFR and WHO functional class.

Male patients had higher NTproBNP, lower 6MWD and more severe functional class at follow-up in basic (table 4) and covariate-adjusted (table 5) models.

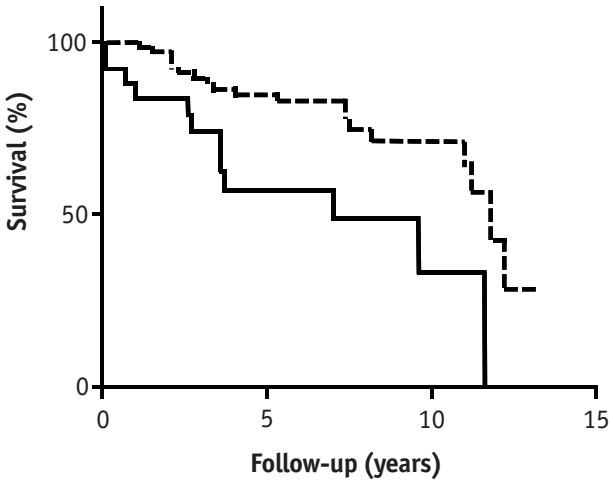

Figure 1. Transplant-free survival in male (solid line) and female (dashed line) patients with pulmonary arterial hypertension starting first-line pulmonary arterial hypertension specific therapies.

RHC hemodynamics and CMR

RHC showed no significant differences in treatment response associated with sex (table 4 and 5). Median PVR changes (IQR) were -78 (-523 to +10) dyn·s·cm^{-5} in males and -165 (-436 to +92) dyn·s·cm^{-5} in females.

Eighty patients had baseline and follow-up CMR performed. Reasons for not performing follow-up measurements in males were: patient deceased n=3, patient follow-up < 1 year n=3, patient too disabled to undergo CMR n=3, unknown n=1. In females these were patient refusal n=4, patient follow-up < 1 year n=3, patient too disabled n=2, psychiatric disorder n=1 and technical CMR problem n=1. Corrections for missing follow-up measurements were made by multiple imputation.

After the baseline assessment, RVEF decreased in males (median, IQR) -1.0 (-11.9 to +6.9) % and increased in females +3.6 (-3.0 to +13.0) %. Table 4 and 5 depict results of univariate and multivariate analysis of sex difference in CMR changes. Calculated RVEF change corrected for confounders was -1.8 ± 6.5 % in males and +5.3 ± 5.4 % in females ($p<0.001$).

Mediator analysis

Step 1 and step 2 of the mediator analysis were reported above. In step 1 sex was confirmed as an independent predictor of survival. In step 2 sex was confirmed as an independent predictor of RVEF change. Results of step 3 are reported in table 6, which shows the results of cox regression for transplant-free survival with sex

Table 4. Results of linear regression of sex differences in right heart catheterisation (RHC), MRI and other secondary treatment outcome parameters corrected for the baseline value.

parameter	Difference for men vs. women in follow-up measure after adjustment for baseline	95% CI	p-value
NT-proBNP, ng/L	+1385	+482 to +2288	<0.01
6MWD, m	-71	-123 to -19	<0.01
Creatinine, mmol/L	+17	+6 to +29	<0.01
GFR, ml/min	-5	-11 to +1	0.12
WHO FC	+1.4	+0.4 to +2.3	<0.01
Heart rate, beat/min	+3	-7 to +13	0.56
RAP, mmHg	+2	-1 to +6	0.17
mean PAP, mmHg	+1	-7 to +9	0.81
Cardiac output, Lmin	+0.2	-1 to +1	0.78
Stroke volume, ml	-4	-19 to +11	0.59
PVR, dyn·s·cm^{-5}	-60	-301 to +182	0.63
RVEF, %	-8.1	-14 to -2	<0.01
RVEDV, ml	+11.9	-5 to +29	0.18
RVESV, ml	+13.8	-2 to +30	0.09
RVSV, ml	-5.5	-14 to +3	0.19
RV mass, g	+2.9	-12 to +18	0.70
RV mass / RVEDV, g/ml	+0.04	-0.09 to +0.16	0.57

b = coëfficient for sex (male = 1; female = 0). 6MWD = 6-minute walk distance; GFR = glomerular filtration rate; RAP = right atrial pressure; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; RVEF = right ventricular ejection fraction; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume; RVSV = right ventricular stroke volume.

and the baseline value of the potential mediator. The B coefficient of sex changed substantially after RVEF follow-up measurements were added to the equation and significance of sex as predictor of transplant-free survival was lost, thus showing evidence that the impact of sex on survival was mediated through RVEF at follow-up. There is no evidence for mediation through PVR changes as the B coefficient for sex remains similar in the cox regression formula with sex and baseline PVR compared to the formula with sex, baseline PVR and follow-up PVR. The amount of change in B for sex after adding follow-up values of RVEF or PVR to the Cox regression equation gives a sense of how much of the variance in outcome associated with sex is explained by changes of each hemodynamic parameter. In the basic model, 42.8 % of the effect of sex on survival was mediated through RVEF. After adjustment for confounders this was 39.0 %.

Table 5. Results of multivariate analysis* of sex specific right heart catheterisation (RHC), MRI and other treatment outcome parameter changes compared to baseline.

parameter	Difference for men vs. women in follow-up measure after adjustment for baseline and confounders	95% CI	p-value
NT-proBNP, ng/L	+1385	+482 to +2288	<0.01
6MWD, m	-70	-127 to -12	0.02
Creatinin, mmol/L	+14	+3 to +25	0.01
GFR, ml/min	-6	-13 to 0	0.05
WHO FC	+1.9	+0.9 to +3.0	<0.001
Heart rate, beat/min	+5	-7 to +17	0.42
RAP, mmHg	+2	-1 to +6	0.25
mean PAP, mmHg	+2	-8 to +11	0.73
Cardiac output, L/min	+0.0	-1 to +1	0.99
Stroke volume, ml	-7	-24 to +11	0.45
PVR, dyn·s·cm^{-5}	-35	-337 to +267	0.82
RVEF, %	-7.2	-13 to -1	0.02
RVEDV, ml	-0.4	-19 to +18	0.97
RVESV, ml	+5.2	-13 to +23	0.58
RVSV, ml	-9.5	-19 to 0	0.04
RV mass, g	+3.8	-13 to +21	0.67
RV mass / RVEDV, g/ml	+0.09	-0.05 to +0.24	0.22

*Multivariate analysis results showing the coëfficient b for sex (male = 1; female = 0) corrected for potential confounding by age, weight, height, number of comorbidities, baseline RVEF, GFR, PVR, WHO functional class and type of PAH specific medical therapy initiated.
6MWD = 6-minute walk distance; GFR = glomerular filtration rate; RAP = right atrial pressure; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; RVEF = right ventricular ejection fraction; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume; RVSV = right ventricular stroke volume.

Table 6. Results from cox-regression for transplant-free survival with respectively sex and the baseline measurement and subsequently sex, the baseline measurement and the follow-up measurement for respectively RVEF and PVR. Crude analysis (A) and analysis including corrections for confounders (B) is reported.*

	B	Exp (B)	95% CI of Exp (B)	p-value
A				
Gender (male vs female)	**1.029**	2.80	1.33 - 5.91	**0.007**
Baseline RVEF	-0.05	0.95	0.92 - 0.99	0.007
Gender	**0.589**	1.80	0.81 - 4.01	**0.15**
Baseline RVEF	-0.01	0.99	0.95 - 1.04	0.81
Follow-up RVEF	-0.07	0.94	0.89 - 0.98	**0.006**
B				
Gender	**1.397**	4.04	2.50– 6.54	**0.004**
Baseline RVEF	-0.05	0.95	0.93 - 0.97	0.009
Gender	**0.852**	2.34	0.93 – 5.92	**0.07**
Baseline RVEF	-0.01	0.99	0.95 - 1.04	0.76
Follow-up RVEF	-0.07	0.94	0.89 – 0.98	**0.006**
A				
Gender	**1.11**	3.04	2.08 – 4.45	**0.003**
Baseline PVR	0.00	1.00	1.00 - 1.00	0.95
Gender	**1.20**	3.31	1.53 – 7.16	**0.002**
Baseline PVR	0.00	1.00	1.00 - 1.00	0.53
Follow-up PVR	0.00	1.00	1.00 - 1.00	0.12
B				
Gender	**1.51**	4.52	1.83 – 11.18	**0.001**
Baseline PVR	0.00	1.00	1.00 - 1.00	0.84
Gender	**1.476**	4.38	1.77 – 10.84	**0.001**
Baseline PVR	0.00	1.00	1.00 - 1.00	0.48
Follow-up PVR	0.00	1.00	1.00 - 1.00	0.19

* RVEF = right ventricular ejection fraction; PVR = pulmonary vascular resistance.

Discussion

Our data confirmed previous findings of worse outcome in males.[6] This survival difference was not associated with either baseline characteristics or differences in responsiveness of the pulmonary vascular bed to therapy, but rather differences in RVEF after starting medical therapies. BNP changes are correlated with RV strain and RVEF measured by CMR and the BNP differences found in our study further support our CMR findings.[17-19] In an earlier study RVEF change difference between survivors and non-survivors in PAH was 8%, further illustrating that the difference found in our study is clinically meaningful.[20]

Sex differences have been well documented in diseases of the left ventricle. In the Framingham study, worse survival was observed in male heart failure patients.[21] Systolic heart failure is predominantly found in men whereas women rather present with heart failure with preserved ejection fraction.[22] In analogy female pressure loaded hearts showed more preserved ejection fractions in aortic stenosis.[23] In a recent study of hypertensive patients left ventricular mass variance explained by arterial blood pressure was much higher in females. This could be interpreted as further evidence of better cardiac adaptation in females.[24]

Little is known about sex differences in disease of the right ventricle. Healthy women have lower RV mass, smaller RV volumes, and higher RVEF than men.[25] Ventetuolo et al. showed an association between higher estradiol levels and improved RVEF in women and an association between increased androgen levels and increased right ventricular mass and right ventricular volumes.[26] In a rodent model testosterone and oestradiol both caused pulmonary vasodilation.[27] In male mice testosterone affected RV hypertrophic stress response after pulmonary artery banding through increased myocyte size and increased fibrosis. Testosterone deprivation through castration improved survival in these mice.[28] In addition estrogen and estrogen receptor agonist therapy restored RV structure and function in a rodent model of monocrotaline induced PH.[29]

Our study found no differences in pulmonary vascular responses to PAH specific medications. Hitherto no other studies in humans reported on sex differences in pulmonary vascular response. We found no sex differences in cardiac output, and this further points out the problems with only looking at resting cardiac output, rather than at RV structure and RV systolic function (RVEF). During disease progression resting cardiac output can be maintained through an increased heart rate. In addition stroke volume can be relatively preserved through the Starling mechanism. However, in progressive RV dilation RVEF will decrease and RVEF may be a more sensitive parameter for disease progression.[2] It can not be ruled out that CO differences do occur upon exercise.

Our study has some limitations. Not all patients evaluated at our center were included. While those included appeared similar to those excluded, selection bias could still be possible. We attempted to account for a variety of confounders, however we cannot exclude residual or unmeasured confounding. There were some missing data; we used multiple imputation to allow inclusion of all subjects in the study sample in all

analyses. Finally, this is an observational study, preventing us from confirming causality, however the use of sex as our exposure and prospective reassessments of RV function support causal inferences. We only studied the idiopathic, heritable and anorexigen associated form of PAH, so these findings may not be generalizable to other forms of PAH. However sex differences in survival are also reported in connective tissue disease associated PAH[30], although in associated PAH the survival difference was limited to elderly patients.[9] Since RVEF could explain 40 % of the observed survival difference, other factors must contribute. However, these factors cannot be identified through our study, as the small patient number prohibits further exploratory analysis.

In conclusion our study suggests a sex difference in cardiac adaptation to treatment with long-term improvements in RVEF in women, but not in men. Mediator analysis suggests this different cardiac adaptation may cause decreased survival in males. To further improve treatments the pathophysiology of sex differences in cardiac response to medical therapies should further be elucidated. Evidence for differences in cardiac responses in associated forms of PAH should be studied. Furthermore, the role of sex hormones, and the potential of substances targeting sex-specific pathways, such as estrogen receptor agonists should be further evaluated.[29]

References

1. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2009;30: 2493-2537.
2. van Wolferen SA, Marcus JT, Boonstra A, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J 2007;28:1250-1257.
3. Thenappan T, Shah SJ, Rich S, et al. A USA-based registry for pulmonary arterial hypertension: 1982-2006. Eur Respir J 2007;30:1103-1110.
4. Gomberg-Maitland M, Dufton C, Oudiz RJ, et al. Compelling evidence of long-term outcome in pulmonary arterial hypertension ? A clinical perspective. J Am Coll Cardiol 2011;57:1053-1061.
5. Kawut SM, Horn EM, Berekashvili KK, et al. New predictors in outcome in idiopathic pulmonary arterial hypertension. Am J Cardiol 2005;95:199-203.
6. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010;122:156-153.
7. Humbert M, Sitbon O, Yaïci A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J 2010;36:549-555.
8. Kane GC, Maradit-Kremers H, Slusser JP, et al. Integration of clinical and hemodynamic parameters in the prediction of long-term survival in patients with pulmonary arterial hypertension. Chest 2011;139:1285-1293.
9. Shapiro S, Traiger GL, Turner M, et al. Sex differences in the diagnosis, treatment, and outcome of patients with pulmonary arterial hypertension enrolled in the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Chest 2012;141:363-373.
10. Thenappan T, Glassner C, Gomberg-Maitland M. Validation of the pulmonary hypertension connection equation for survival prediction in pulmonary arterial hypertension. Chest 2012;141:642-650.

11. Gabler NB, French B, Strom BL, et al. Race and sex differences in response to endothelin receptor antagonists for pulmonary arterial hypertension. Chest 2012;141:20-26.
12. Vonk Noordegraaf A, Galiè N. The role of the right ventricle in pulmonary arterial hypertension. Eur Respir Rev 2011;20:243-253.
13. Gaash WH, Zile MR. Left ventricular structural remodelling in health and disease. J Am Coll Cardiol 2011;58:1733-1740.
14. Lorenz CH, Walker ES, Graham TP, et al. Right ventricular performance and mass by use of cine MRI late after atrial repair of transposition of the great arteries. Circulation 1995;92:233-239.
15. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic and statistical considerations. J Pers Soc Psychol 1986;51:1173-1182.
16. Kenny DA, Kashy DA, Bolger N. 1998. Data analysis in social psychology. In D Gilbert, S Fiske, G lLindzey (Eds.), The handbook of social psychology (Vol. 1; pp. 115-139), New York.
17. Oyama-Manabe N, Sato T, Tsujino I, et al. The strain encoded (SENC) MR imaging for detection of global right ventricular dysfunctionin pulmonary hypertension. Int J Cardiovasc Imaging 2013;29:371-378.
18. Blyth KG, Groening BA, Mark PB, et al. NT-proBNP can be used to detect right ventricular systolic dysfunction in pulmonary hypertension. Eur Respir J 2007;29:737-744.
19. Vonk Noordegraaf A, Westerhof N. Right ventricular ejection fraction and NT-proBNP are both indicators of wall stress in pulmonary hypertension. Eur Respir J 2007;29:622-623.
20. van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011;58:2511-2519.
21. Ho KKL, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in the Framingham heart study subjects. Circulation 1993;88:107-115.
22. Cleland JGF, Swedberg K, Follath F, et al. The euroheart failure survey programme – a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003;24:442-463.
23. Carroll JD, Carroll EP, Feldman T, et al. Sex-associated differences in left ventricular function in aortic stenosis of the elderly. Circulation 1992;86:1099-1107.
24. Cipolline F, Arcangeli E, Greco E, et al. Gender difference in the relation blood pressure-left ventricular mass and geometry in newly diagnosed arterial hypertension. Blood Press 2012;21:255-264.
25. Kawut SM, Lima JA, Barr RG, et al. Sex and race differences in right ventricular structure and function: the Multi-ethnic study of atherosclerosis-right ventricle study. Circulation 2011;123:2542-2551.
26. Ventetuolo CE, Ouyang P, Bluemke DA, et al. Sex hormones are associated with right ventricular structure and function. The MESA-Right ventricle study. Am J Respir Crit Care Med 2011;183:659-667.
27. English KN, Jones RD, Jones TH, et al. Gender differences in the vasomotor effects of different steroid hormones in rat pulmonary and coronary arteries. Horm Metab Res 2001;33:645-652.
28. Hemnes AR, Maynard KN, Champion HC, et al. Testosterone negatively regulates right ventricular load stress responses in mice. Pulm Circ 2012;2:352-358.
29. Umar S, Lorga A, Matori H, et al. Estrogen rescues preexisting severe pulmonary hypertension in rats. Am J Respir Crit Care Med 2011;184:715-723.
30. Condliffe R, Kiely DG, Peacock AJ, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med 2009;179:151-157.

Chapter 6

A clinical prediction rule to non-invasively identify left-sided heart failure in a population suspected of pulmonary arterial hypertension

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Abstract

Background

Exclusion of pulmonary hypertension secondary to left-sided heart disease (LHF) is pivotal in the diagnosis of Pulmonary Arterial Hypertension (PAH). In case of doubt, invasive measurements are recommended. Aim was to investigate whether it is possible to diagnose LHF as cause of pulmonary hypertension using non-invasive parameters in a population suspected of PAH.

Methods

All patients suspected of PAH and referred to our PH unit and in whom a diagnosis of PAH or LHF was made were included. The retrospective patient cohort attended our clinic between April 1998 and July 2010, and was used to build the predictive model (300 PAH and 80 LHF). The patient cohort attending our clinic from August 2010 to December 2012 was used to prospectively validate our model (79 PAH and 55 LHF).

Results

In multivariable analysis a medical history of left heart disease, SV1 + RV6 in mm on ECG and left atrial dilation or left valvular heart disease > mild on echocardiography were independent predictors of LHF. After corrections for optimism the derived risk score system showed good predictive characteristics: R^2 0.66. and AUC 0.93. In patients with a risk score ≥ 72, there is 100% certainty that the cause of PH is LHF. Using this risk score system the number of right heart catheterisations in LHF may be reduced with 20%.

Conclusions

In a population referred under suspicion of PAH a predictive model incorporating medical history, ECG and echocardiography data can diagnose LHF non-invasively in a substantial percentage of cases.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature, leading to high morbidity, right heart failure and death within 2-3 years if left untreated.[1-2] While PAH is rare, pulmonary hypertension secondary to left heart-failure (LHF) is more common.[3] Right heart catheterisation (RHC) is recommended for final diagnosis when PAH is suspected clinically.[4] An invasively measured pulmonary capillary wedge pressure (PCWP) of 15 mmHg and/or increased left ventricular end-diastolic pressure (LVEDP) are used to discriminate between LHF and pulmonary hypertension (PH) from other causes. LHF is caused by chronic heart failure attributed to left ventricular systolic or diastolic dysfunction, or by valvular diseases.[5] PH with normal wedge pressure fits a diagnosis of PAH, provided other causes of PH with normal wedge, including lung disease and chronic thromboembolic PH are excluded.[6] Increased PH awareness, in combination with high LHF prevalence, and in particular difficulties in diagnosing heart failure with preserved ejection fraction non-invasively, have increased referrals to PAH centres and number of RHC performed.[7] A model to predict in advance the likelihood of LHF can decrease burden to the patient and economical cost associated with these referrals. Although rare, complications of RHC such as ventricular tachyarrhythmia, vascular or ventricular perforation, bleeding, pneumothorax and even death may occur.[8]
Aim of this study was to develop a non-invasive predictive model of left-heart failure as cause of pulmonary hypertension in a patient population referred to a tertiary PH center, suspected of PAH clinically. Predictors of heart failure in patient medical history, electrocardiography and echocardiography were used in order to identify referred patients in whom a firm diagnosis of LHF could be made non-invasively.[9-13]

Methods

Study design and patients

The VU University Medical Centre is a tertiary referral center for diagnosis and treatment of PH in The Netherlands. All patients suspected of PAH and referred to our PH unit and in whom a diagnosis of PAH (PH group 1) or PH secondary to LHF (PH group 2) was made were included. The retrospective patient cohort attended our clinic between April 1998 and July 2010, and was used to build the predictive model. The patient cohort attending our clinic from August 2010 to December 2012 was used to prospectively validate our model.
All patients underwent RHC, since echocardiography was not considered conclusive for the diagnosis of pulmonary hypertension secondary to left heart disease in this patient cohort. In all patients PH was present based on a mean pulmonary artery pressure above 25 mmHg. We used the following decision rule to discriminate between precapillary PH and pulmonary hypertension secondary to LHF. If wedge pressure was 15 mmHg or less the diagnosis precapillary PH was made.[14] If wedge

pressure was more than 15 mmHg at rest or increased above 15 mmHg after 500 ml of saline infusion, the diagnosis PH secondary to left heart failure was made.[15] In case no reliable wedge was obtained LVEDP was measured. In precapillary PH Chronic thromboembolic pulmonary hypertension (PH group 4) was ruled out by the combination of ventilation-perfusion scintigraphy and CT-angiography. PH due to parenchymal lung disease (PH group 3) was excluded by lung function testing and high resolution CT, in addition polysomnography was performed to exclude sleep disordered breathing.

Potential LHF predictors known from the literature were recorded from medical history, electrocardiographic and echocardiographic parameters. Predictors recorded were age, body mass index and sex, a medical history of respectively hypertension, diabetes, dyslipidaemia, left heart disease (either coronary artery disease or left valvular heart disease > mild) and smoking history > 1 packyear. From electrocardiography the S deflection in V1 (SV1; mm), the R deflection in V6 (RV6; mm) and electrocardiographic evidence of left atrial dilation (yes/no) and from the echocardiographic parameters the echocardiographic presence of left atrial dilation (yes/no) or left valvular heart disease > mild (yes/no) were included in the analysis. Echocardiographic left atrial dilation was defined according to recommendations for chamber quantification from the American Society of Echocardiography .[16] Severity of valvular heart disease assessed according to European Association of Echocardiography guidelines.[17-19] Echocardiographic parameters were scored by a cardiologist blinded to the diagnosis; electrocardiographic data measured by an observer blinded to the definite diagnosis.

Data analysis

Patient characteristics in both groups were described. Continuous variables reported as mean and standard deviation, (SD), and categorical data as frequencies or proportions.

Model building

The effect of the predictor variables was evaluated by univariate logistic regression. Potential nonlinear behaviour of continuous factors was examined using restricted cubic spline functions and spline plots. We used multiple imputation to fill in variables with missing values by using the Multivariate Imputation by Chained Equation (MICE) procedure. This method estimates several plausible values to fill in the missing values in the variables. We imputed 10 data sets. Multivariable logistic regression with backward elimination determined the final model. Variable selection was done by taking into account the imputed data sets. This means that logistic regression models were estimated in each imputed data set, that regression coefficients and standard errors were pooled and the p-value of each coefficient in the multivariable model determined.[20] This step was repeated until variables with a p-value < 0.10 were retained in the final model. Regression coefficients and standard errors were converted to odds ratio's (OR) and corresponding 95% confidence intervals.

Performance of the prediction model

The performance of the prediction model was studied in terms of discrimination, explained variance and calibration. Discrimination expresses how well the prognostic model distinguishes between patients with LHF and PAH, and was obtained by the area under the Receiver Operating Characteristic (ROC) curve (AUC). The explained variance calculated as Nagelkerke's R^2, gives an indication of how much of the variance in the outcome can be explained by the predictors. To reflect how well predicted and observed probabilities agreed and to obtain insight into the model's calibration, the calibration slope was calculated. The calibration slope can be used as a shrinkage factor to shrink the regression coefficients. This is done because prognostic models usually perform better in subjects used to build the model than in new subjects due to optimism in regression coefficients and performance measures.[21] For internal validation bootstrapping was used. The AUC, explained variation and slope were calculated on each imputed data set and averaged over the 10 imputed data sets.

Derivation and prospective validation of the clinical risk score

The coefficients in the model were transformed in easy to use risk scores by dividing all regression coefficients by the lowest coefficient value. The clinical performance of the risk scores was also evaluated. For this evaluation we considered the test characteristics of the clinical risk score in terms of sensitivity, specificity, positive and negative predictive values, at different categories of risk scores. The Hosmer-Lemeshow test was used to test the goodness of fit of the risk score model.

In the prospective patient cohort the developed clinical risk score was calculated for each patient and sensitivity, specificity, positive and negative predictive value were calculated at different risk score values, which were suggested as cut off values in the developmental set. Discrimination (AUC) and explained variance (Nagelkerke's R^2) were determined in the prospective cohort.

Analysis was done using SPSS 18 and R software.[22] We used adapted versions of the MICE and Design libraries. Requirements of the hospital research and ethical review board (METC) were met, including patient informed consent.

Results

Patient characteristics

Between April 1998 and July 2010, 300 PAH and 80 LHF were diagnosed. Patient characteristic and hemodynamics at diagnosis in LHF and PAH patients are defined in table 1.

Logistic regression, model and LHF risk score

Univariate logistic regression was used descriptively and results are depicted in table 2. Using backward regression, a medical history of left heart disease (LHD; yes=1/

Table 1. Patient characteristics and haemodynamics of patients diagnosed as pulmonary arterial hypertension (PAH) or Left-heart failure (LHF).

	PAH n=300	LHF n=80	p-value
Age (years)	51.1 ± 16.6	64.2 ± 13.8	<0.001
Gender (male; %)	27 (22-32)	36 (27-47)	0.09
BMI (kg/m^2)	25.5 ± 5.5	28.1 ± 5.8	<0.001
Medical history:			
Diabetes (%)	10 (7-14)	30 (21-41)	<0.001
Hypertension (%)	19 (15-24)	41 (31-52)	<0.001
Dyslipidaemia (%)	10 (7-14)	33 (23-43)	<0.001
Smoking > 1 packyear (%)	47 (41-53)	59 (48-69)	0.08
Left valvular disease > mild (%)	2 (1-4)	43 (32-53)	<0.001
Coronary artery disease (%)	7 (4-10)	31 (22-42)	<0.001
Left Heart disease (%)	8 (6-12)	58 (47-68)	<0.001
Electrocardiography:			
Left atrial dilation (%)	9 (7-13)	5 (2-13)	0.27
SV1 + RV6 (mm)	10.8 ± 5.5	17.3 ± 9.0	<0.001
Echocardiography:			
Left atrial dilation (%)	24 (20-29)	86 (77-92)	<0.001
Left valvular disease > mild (%)	9 (7-13)	65 (54-75)	<0.001
Right Heart Catheterisation:			
Right atrial pressure, mmHg	9± 9	12 ± 7	0.08
PAP, mmHg	48 ± 15	42 ± 12	0.02
Cardiac Output, L/min	5.09 ± 2.09	5.37 ± 2.18	0.45
Heart rate, beat/min	81 ± 14	80 ± 17	0.74
PVR, dyn·s/cm^5	792 ± 545	435 ± 323	<0.01
Wedge pressure, mmHg	9 ± 5	21 ± 6	<0.001
TPG, mmHg	40 ± 16	21 ± 12	<0.001
Mixed venous O2 saturation, %	65 ± 11	64 ± 10	0.65

Continuous variables are depicted as mean ± SD; nominal data are presented as percentage of the total number of patients within respectively the PAH and LHF group (95% CI). PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; TPG = transpulmonary gradient.

Table 2. Odds ratio (OR) for LHF derived from univariate logistic regression.

	Odds ratio	95% CI	p-value
Male sex	1.56	0.92-2.64	0.09
Age (per 5 years)	1.32	1.20-1.45	<0.001
Body mass index (per 5 units)	1.45	1.17-1.80	<0.01
History of:			
Hypertension	2.88	1.69-4.90	<0.001
Diabetes	3.99	2.16-7.36	<0.001
Smoking	1.57	0.94-2.63	0.08
Dyslipidaemie	4.32	2.37-7.88	<0.001
Coronary artery disease	6.26	3.25-12.06	<0.001
Left valve disease>mild	34.55	13.76-86.72	<0.001
Left Heart Disease	14.88	8.14-27.21	<0.001
ECG:			
Left atrial dilation	0.55	0.18-1.63	0.28
SV1 + RV6 (per 5 mm)	1.96	1.59-2.42	<0.001
Echo:			
Left atrial dilation	19.92	7.20-55.11	<0.001
Left valve disease>mild	18.55	7.87-43.72	<0.001

no=0), the sum of SV1 and RV6 on electrocardiography (ECG; mm), the presence of left atrial dilation on echocardiography (LAD; yes=1/no=0) and the presence of left valvular heart disease > mild on echocardiography (LVD; yes=1/no=0) were identified as predictors of LHF (table 3). After correction for optimism (after boot strapping) the following model could be constructed:

$$-5.22 + (2.26*\text{LHD}) + (0.10*\text{ECG}) + (2.08*\text{LAD}) + (2.28*\text{LVD})$$

The model had high predictive value with a R^2 of 0.67 and an AUC of 0.93. After correction for optimism these values respectively were 0.65 and 0.93 (Fig. 1). From the model a LHF risk scoring system was derived (table 3). The LHF risk scores resulted in similar predictive characteristics: R^2 0.66, AUC 0.93. Goodness of fit of the risk score model was confirmed by the Hosmer-Lemeshow test (p=0.99). Table 4 shows the performance of the risk score model in terms of sensitivity, specificity and positive and negative predictive values at different risk score categories. In Figure 2

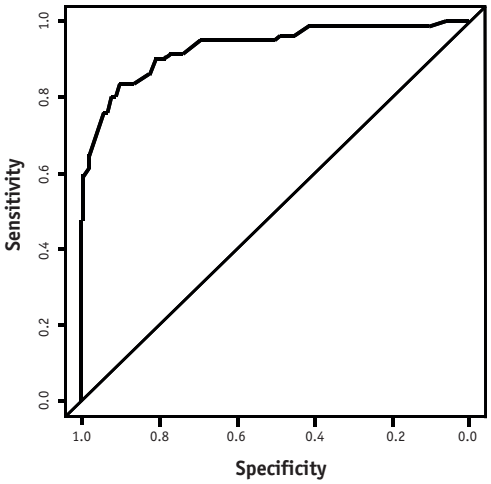

Figure 1. Receiver operator curve characteristics of the risk score for prediction of Left-Heart Failure in a population referred to a tertiary center on suspicion of Pulmonary Arterial Hypertension.

Table 3. Results from backward binary logistic regression, identifying independent predictors of LHF and the subsequently derived Left-Heart Failure risk scoring system.

	Odds ratio	95% CI	p-value	Risk scores[a]
History of:				
Left Heart Disease	10.0	4.0-25.2	<0.001	22
ECG:				
SV1+RV6 (per mm)	1.12	1.06-1.20	<0.001	1*(SV1+RV6)
Echo:				
Left atrial dilation	12.2	4.1-36.1	<0.001	20
Left valve disease > mild	7.5	2.5-22.2	<0.001	22

[a] **The total risk score is calculated as follows:** For presence of a medical history of left heart disease the patient is attributed 22 points. If echocardiographic left atrial dilation is present an additional 20 points are scored and if echocardiographic left valvular disease > mild is present an additional 22 points are scored. The sum of the S deflection in V1 and the R deflection in V6 on electrocardiography in mm is the risk score attributed for the electrocardiography in each patient. The total score in each patient constitutes the left heart failure risk score for that individual.

Table 4. Sensitivity, specificity, positive and negative predictive value at various cut-off points using the risk score system, derived from the model.

Risk score	Sens (%)	Spec (%)	PPV (%)	NPV (%)
≥ 0	100	0	21	n.a.
≥ 8	99	25	26	99
≥ 16	95	55	36	98
≥ 24	95	64	41	98
≥ 32	91	77	51	97
≥ 40	84	89	67	95
≥ 48	78	93	74	94
≥ 56	64	98	90	91
≥ 64	51	100	98	89
≥ 72	44	100	100	87
≥ 80	24	100	100	83
≥ 88	5	100	100	80
≥ 96	0	100	100	79

the number of true and false positives and true and false negatives in the same risk score categories are presented. Using a risk score cut off value of ≥ 72, LHF could be diagnosed non-invasively in 44 % (95% CI 33-55) of patients, with a positive predictive value (PPV) of 100 % (95% CI 88-100) and 100 % specificity (95% CI 98-100). Alternatively, using a cut off value of ≥ 64, LHF was diagnosed non-invasively in 53 % (95% CI 42-63), with a PPV of 98 % (95% CI 87-100) and 100 % specificity (95% CI 98-100). Using the risk score with a ≥ 72 cut off no PAH patients were falsely classified as LHF, whilst using a ≥ 64 cut off 1/300 (0.3 %, 95% CI 0-2) of PAH patients were falsely classified as LHF.

Risk scores and wedge pressures

Patients were divided in the following categories according to wedge pressure at diagnosis: < 10, 10-15, 16-20 and > 20 mmHg. Risk scores were calculated for patients in these groups. Mean (median) risk scores ± SD respectively were 19 (12) ± 15, 23 (16) ± 18, 54 (56) ± 30 and 57 (61) ± 21 (Fig. 3).

Prospective validation

In the prospective validation cohort 134 patients (79 PAH and 55 LHF) attended our clinic between August 2010 and December 2012. Mean (median) risk scores respectively were 23 (21) ± 16 and 46 (40) ± 24. Using the proposed risk score cut off ≥ 72 positive predictive value remained 100 % (95% CI 70-100), specificity was 100 % (95% CI 94-100), sensitivity 20 % (95% CI 11-33) and negative predictive value 64 % (95% CI 55-72). At this cut off LHF was diagnosed non invasively in 20%,

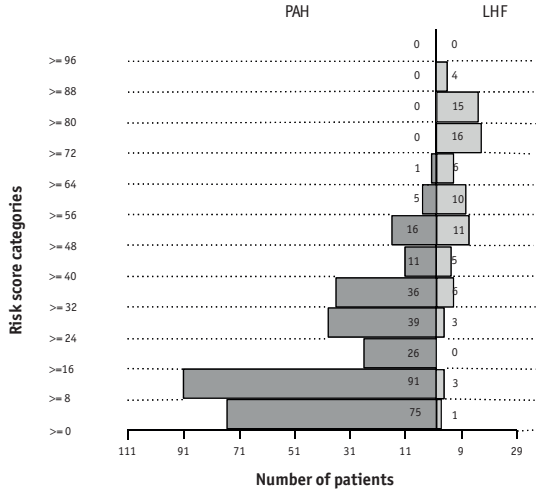

Figure 2. Pyramid graph of patients (n) with Left-Heart Failure (LHF) and Pulmonary Arterial Hypertension (PAH), divided according to the total risk score outcomes of individual patients.

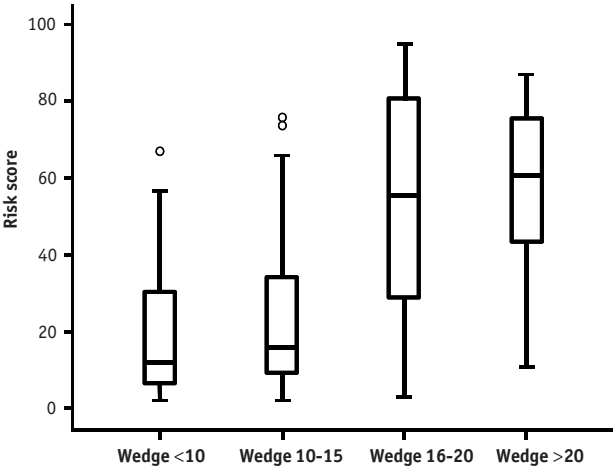

Figure 3. Box and whisker plots of the risk scores in patient groups with different wedge pressures at right heart catheterisation. Borders of boxes are the 25th and 75th percentile. All measurements are between the whiskers, except for outliers (o), which are more than 1.5x the hight of the box above the 75th percentile. Median values are depicted as well.

without misclassifying any PAH. Using a cut off score ≥ 64 positive predictive value was 92 % (95% CI 65-100), specificity 99 % (95% CI 93-100) and sensitivity and negative predictive value respectively 22 % (95% CI 13-35) and 64 % (95% CI 56-72). AUC in the prospective cohort was 0,80 (95% CI 0.72-0.87) and Nagelkerke's R^2 0,36.

Discussion

Risk factors for heart failure are well known from the literature[9,10]. Current LHF guidelines recommend diagnosing LHF using patient history, physical examination, laboratory, electrocardiographic and echocardiographic measures.[7,12] Whether these algorithms apply in the setting of PH is unknown. In PH signs of left heart failure might be mimicked on echocardiography due to underfilling of the left ventricle. This is especially the case for diastolic left heart failure.[23] Therefore, a substantial proportion of patients referred to a PAH center has LHF as underlying cause. Signs that can unmask the presence of an underlying LHF are left atrial enlargement and left ventricular hypertrophy on echocardiography[6]. However, the predictive value of these parameters as a single measurement or in combination with medical history data is insufficient[24], in a setting where other signs of left heart failure are absent. For this reason wedge pressure or LVEDP measurement are demanded to confirm the diagnosis of LHF as a cause of pulmonary hypertension invasively (WHO group 2). Any effort made to improve referral patterns to PAH centers should not lead to missed PAH diagnosis in any patient, since early detection and treatment of PAH improves exercise capacity and pulmonary hemodynamics[25] and delayed start of PAH specific medications decreases survival even with a short-term interval.[26] Incidence rates of LHF are high, whereas PAH remains a rare disease, which further challenges the chances of a correct PAH diagnosis by non-invasive means.[27,28] Our results show that in a group of patients referred with a diagnosis of PAH by means of a set of easy to use parameters from medical history, echocardiography and electrocardiography, LHF can be diagnosed non-invasively in a substantial number of patients. Our results showed that patients with a clinical risk score ≥ 72, have a 100% certainty that the cause op PH is LHF. In those patients a right heart catheterization may not be required. And the number of right heart catheterisations in LHF may be reduced by 20%.

From our data coronary artery disease and left valvular heart disease were independent LHF predictors. This is not surprising since both were important predictors in the Framingham and NHANES I study.[9,10] Coronary artery disease is currently the most common cause of left-heart failure.[12] Left heart disease leads to heart-failure and subsequent pulmonary hypertension only through increased left ventricular filling pressures, causing subsequent mitral valvular insufficiency, increased left atrial filling pressures, and left atrial dilation and subsequent pulmonary venous hypertension.[11] Electrocardiographic evidence of left ventricular hypertrophy (LVH) had well predictive characteristics. LVH is a feature of left heart disease, whereas in PAH left ventricular atrophy can be present.[29] Left atrial dilation on MRI has high predictive value when comparing PAH and left heart failure.[30] However, echocardiography underestimates CMR derived left atrial volume,[31] explaining why echocardiographic left atrial dilation, though more frequently present in pulmonary venous hypertension has insufficient discriminatory power as a single parameter.[24,32] In addition electrocardiographic evidence of left atrial dilation was not significantly correlated with LHF. This may be due to suboptimal correlation with echocardiographic left atrial dilation,[33,34] further affected by non-specific P-wave changes due to severe right

sided atrial strain. It should be stressed, that for accurate non-invasive predictions data from medical history, and electro- and echocardiography need to be combined. Although our study is limited by its single center design, we internally validated our model by boot strapping and in addition performed a prospective validation study, which validated our results for external use. The echocardiography parameters were measured according to current guidelines and are widely used. Therefore it is unlikely that these observations were operator dependent. The proportion of LHF in our study is substantial, but still relatively low compared to non-tertiary secondary referral centers or primary care settings.[28] Since predictive values are strongly dependent on disease prevalence in the patient cohort studied, higher PPV for LHF is to be expected at lower patient risk scores, in settings with a smaller PAH prevalence. Our model was developed in a tertiary referral setting and since populations differ, validation in community hospitals is warranted, before its use is recommended outside PAH centers. Since the prevalence of LHF compared to PAH is much higher in these hospitals, we may expect a larger reduction in number of RHC in these populations. Bonderman et al. developed a decision tree to exclude PAH. Relying on the CHAID procedure (Chi-Squared Automatic Interaction Detection), two out of 28 clinical, echocardiographic or ECG parameters were automatically identified (right ventricular strain on ECG, defined as ST-segment deviation and T-wave inversion in leads V1-V3, and NT-proBNP with a cut off of 80 pg/ml) Bonderman et al. showed that in the case of absence of right ventricular strain and subsequently an NT-proBNP level ≤ 80 pg/ml, PAH can be excluded.[35] Our model differs compared to the Bonderman study, as we specifically aimed to identify LHF as alternative cause of PH, whereas the Bonderman model aimed to exclude PAH, and also included patients with normal pulmonary pressures. Considering this, and also since logistic regression models have better predictive characteristics compared to regression trees, the Bonderman model and our own model may have additional value in reducing the need for RHC.[36]

The advantage of the approach used in our study is that it does not require sophisticated measures. The aim was to develop an easy to use prediction model using simple parameters, which are easy to obtain on short notice in clinical practice. More complex echo parameters such as E/E' were not included not only to provide for simplicity of the model, but also because LA dilation measured by echo had better receiver-operator characteristics for determining the presence or absence of diastolic dysfunction in an earlier study.[37]

To conclude, our data show that LVH on ECG, left atrial dilation and left valvular heart disease on echo and medical history data on coronary artery disease and past valvular heart disease measured in combination can be used in a non-invasive prediction model of LHF, when echocardiography is inconclusive in excluding LHF as cause of PH. Using simple clinical parameters LHF can be diagnosed with a high level of certainty. In addition, although RHC remains necessary in case of doubt, the number of RHC can be reduced. Finally, although our data require validation in a non-referral setting, they might be of help for the referring specialist to select patients.

References

1. Simonneau G, Galiè N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004; 43:1S-12S
2. D'alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991; 115:343-349
3. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary arterial hypertension: The task force on diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493-2537.
4. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55-66.
5. Oudiz RJ. Pulmonary hypertension associated with left-sided heart disease. Clin Chest Med 2007;28:233-241.
6. Hoeper MM, Barbera JA, Channick RN, et al. Diagnosis, assessment and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009;54:S85-96.
7. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539-2550.
8. Hoeper MM, Lee SH, Voswinckel R, et al. Complications of right heart catheterisation procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol 2006;48:2546-2552.
9. Kannel WB, D'Agustino RB, Silbershatz H, et al. Profile for estimating risk of heart failure. Arch Intern Med 1999;159:1197-1204.
10. He J, Ogden LG, Bazzamo LA, et al. Risk factors for congestive heart failure in US men and women. NHANES I epidemiologic follow-up study. Arch intern med 2001;161:996-1002.
11. Leung DY, Boyd A, Ng AA, et al. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. Am Heart J 2008;156:1056-1064.
12. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. The task force for the diagnosis and treatment of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388-2442.
13. Fox KF, Cowie MR, Wood DA, et al. Coronary artery disease as the cause of incident heart failure in the population. Eur Heart J 2001;22:228-236.
14. McLaughlin VV, Badesch DB, Barst RJ, et al. ACCF/AHA 2009 Expert consensus document on pulmonary hypertension: a report of the american college of cardiology foundation task force on expert consensus documents and the american heart association. J Am Coll Cardiol 2009;53:1573-619.
15. Robbins IM, Hemnes AR, Pugh ME, et al. High prevalence of pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension.Circ Heart Fail 2014;7:116-122.
16. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79-108.
17. Lancellotti P, Moura L, Pierard LA, et al. European association of echocardiography recommendations for the assessment of valvular regurgitation Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr 2010;11:307-332.
18. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr 2009;10:1-25.

19. Lancellotti P, Tribouilloy C, Hagendorff A, et al. European association of echocardiography recommendations for the assessment of valvular regurgitation Part 1: aortic and pulmonary regurgitation (native valve disease). Eur J Echocardiogr 2010;11:223-244.
20. Wood AM, White IR, Royston P. How should variable selection be performed with multiple imputed data ? Stat Med 2008;27:3227-3246.
21. Harrel FE, Regression modeling strategies. Berlin: Springer: 2001.
22. R Development Core Team 2010. R: A language and environment for statistical computing. R Foundation for statistical computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.
23. Shapiro BP, Nishimura RA, McGoon MD, et al. Diagnostic dilemmas: diastolic heart failure causing pulmonary hypertension and pulmonary hypertension causing diastolic dysfunction. Advances in Pulmonary Hypertension 2006;5:13-20.
24. Thenappan, T, Shah S, Gomberg-Maitland M, et al. Clinical characteristic of pulmonary hypertension in patients with heart failure and preserved ejection fraction. Circ Heart Fail 2011;4:257-265.
25. Galiè N, Rubin LJ, Hoeper MM, et al. Treatment of patients with mildly progressive pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet 2008;371:2093-2100.
26. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;334:296-302
27. Bleumink GS, Knetsch AM, Sturkenboom MCJM, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure. The Rotterdam study. Eur Heart J 2004;25:1614-1619.
28. Gabbay E, Yeow W, Playford, et al. Pulmonary arterial hypertension (PAH) is an uncommon cause of pulmonary hypertension (PH) in an unselected population: the Armadale echocardiography study. Am J Resp Crit care Med 2007;175:A713.
29. Hardziyenka M, Campian ME, Reesink HJ, et al. Right ventricular failure following chronic pressure overload is associated with reduction in left ventricular mass: evidence for atrophic remodeling. J Am Coll Cardiol 2011;57:921-928.
30. Crawley SF, Johnson MK, Dargie HJ, et al. LA volume by MRI distinguishes idiopathic from pulmonary hypertension due to HFpEF. JACC Cardiovasc Imaging 2013;6:1120-1121.
31. Whitlock M, Garg A, Gelow J, et al. Comparison of left and right atrial volume by echocardiography versus cardiac magnetic resonance imaging using the area-length method. Am J Cardiol 2010;106:1345-1350.
32. Brittain EL, Pugh ME, Wang L, et al. Predictors of diastolic-to-wedge gradient in patients evaluated for pulmonary hypertension. PLoS One. 2013;8:e76461.
33. Waggoner AD, Adyanthaya AV, Quinones MA, et al. Left atrial enlargement. Echocardiographic assessment of electrocardiographic criteria. Circulation 1976;54:553-557.
34. Lee KS, Appleton CP, Lester SJ, et al. Relation of electrocardiographic criteria for left atrial enlargement to two-dimensional echocardiographic left atrial volume measurements. Am J Cardiol 2007;99:113-118.
35. Bonderman D, Wexberg P, Martischnig AM, et al. A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. EurRespir J 2011;37:1096-1103.
36. Austin PC. A comparison of regression trees, logistic regression, generalized additive models, amd multivariate adaptive regression splines for predicting AMI mortality. Statist Med 2007;26:2937-2957.
37. Tsang TSM, Barnes ME, Gersh BJ, et al. Left atrial volume as a morphophysiologic expression of left ventricular dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002;90:1284-1289.

Chapter 7

Pulmonary vascular versus right ventricular function changes during targeted therapies of pulmonary hypertension: an argument for upfront combination therapy ?

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Abstract

Pulmonary arterial hypertension is untreated a progressive disease of the pulmonary vasculature, ultimately leading to right heart failure and death. Current treatment is aimed to target three different pathways : the prostacyclin, endothelin and nitric oxide pathways. These therapies improve functional class, increase exercise capacity and improve hemodynamics. In addition, data from a metaanalysis provide compelling evidence for improved survival. Despite these treatments, outcome is still grim and the cause of death is inevitable right ventricular failure. One explanation for this paradox of hemodynamic benefit and still worse outcome is that the right ventricle does not benefit from a modest reduction in pulmonary vascular resistance. This review describes the physiological concepts, which might underly this paradox. Based on these concepts we argue that not only a significant reduction in PVR but also a significant reduction in pulmonary artery pressure is required to save the right ventricle. Hemodynamical data from clinical trials hold the promise that these hemodynamical requirements might be met if upfront combination therapy is used.

Pulmonary Arterial Hypertension (PAH) is a progressive disease of the pulmonary vasculature leading to right heart failure and death.[1] Recent therapeutic advances include drugs targeting three seperate signalling pathways[2] involved in the pathogenesis of PAH. First the prostacyclin pathway evolves around prostaglandin I2 (prostacyclin)[3], the main product of arachidonic acid in the vascular endothelium, which induces vascular relaxation by stimulating the production of cyclic AMP and inhibits smooth muscle cell growth[4]. Several drugs were developed targeting the prostacyclin pathway: epoprostenol[5] delivered by continuous intravenous infusion, inhaled or intravenous iloprost and either inhaled, subcutaneous or intravenous treprostinil. The second pathogenic pathway is the endothelin pathway: this involves endothelin-1, which has vasoconstrictor effects and proliferative effects on the smooth muscle cell. The effects of endothelin-1 are mediated through the $endothelin_A$ and $endothelin_B$ receptors. Bosentan[6] and ambrisentan[7] have been developed as endothelin receptor blocking agents. The third pathway targeted by PAH specific medications is the NO pathway: Nitric oxide (NO) is a potent endogenous, endothelium derived, vasodilator, that directly relaxes vascular smooth muscle through stimulation of soluble guanylate cyclase and increased production of intracellular cyclic guanosine monophosphate (cGMP).[8] However, long-term inhaled nitric oxygen therapy is very cumbersome to use and in addition an interruption of administration can cause hemodynamic deterioration.[9] An alternative approved strategy of increasing activity of endogenous NO is to enhance nitric-oxide dependent cGMP-mediated pulmonary vasodilation through inhibition of phosphodiësterase type 5. Phosphodiësterase type 5 inhibitors such as oral sildenafil[10] and tadalafil[11] have been developed to achieve vasodilation in this manner. All drugs briefly discussed above, were shown to improve exercise capacity and pulmonary hemodynamics. with vasodilatory and antiproliferative effects on the pulmonary vasculature.[2] Meta-analysis of randomized controlled trials

show that treatment with such targeted therapies also improves survival in PAH patients.[12,13] Observational studies support this, with improved survival in patients treated in the modern management era compared to historical cohorts.[14-16] However, despite the advent of these therapies PAH remains a progressive, fatal disease, with considerable room for improvement, especially for certain subgroups of patients, characterized by more severe outcomes. A number of factors have been associated with mortality in PAH. These include type of PAH (such as scleroderma associated and portopulmonary hypertension), presence of comorbidities, functional status, exercise capacity at baseline, hemodynamic parameters such as PVR, mean right atrial pressure and cardiac output, but also male sex, renal function and brain natriuretic peptide levels.[17] of these parameters functional status, expressed as New York Heart Association (NYHA) functional class is one of the strongest predictors of outcome, not only at baseline, but also after medical treatments have been initiated.[15] In addition to NYHA IV PAH, NYHA III patients with rapid progression of symptoms or severely compromised hemodynamics, such as right atrial pressure > 15 mmHg or cardiac index < 2.0 $L \cdot min^{-1} \cdot m^{-2}$ should be considered as severe disease[18] Currently despite increasing PAH awareness in the community a large number of patients are diagnosed with more advanced disease.[19] Untreated median survival in NYHA III PAH is 32 months and for NYHA IV patients this is further reduced to a mere 6 months.[20] Given their poor prognosis and high rates of mortality optimal treatment should be initiated without further delay. For patients who persist in NYHA III and IV despite first-line monotherapy, survival is particularly poor and in these patients additional therapies are needed.[15]

The paradox between: hemodynamic benefit and clinical deterioration

Right heart failure in pulmonary hypertension is primarily caused by increased afterload. In addition, right ventricular load is proportional to pulmonary vascular resistance if cardiac output is kept constant.[21] From this it follows that normalisation of load thus will lead to restoration of the right ventricle as can be observed in patients with chronic thromboembolic pulmonary hypertension who received pulmonary endarterectomy[22] Based on this observation one might expect that also a modest reduction in PVR as observed in PAH patients who receive PAH specific treatment will automatically be followed by an improvement of right ventricular function[23].Based on the published clinical trials it is fair to expect that a large proportion of patients do have an initial reduction in PVR and that this effect sustains over time[24] However, survival is still grim with a 55% survival reported at 3 years in treated incident PAH. Also many patients continue to have marked limitations of normal daily activities.[14] The question is: if we can achieve a reduction in PVR in the majority of patients, why is survival still worse ? To study this further we investigated the relation between changes in right ventricular function and PVR In a large cohort of PAH patients. Results show a poor correlation between changes in right ventricular function, described as right ventricular ejection fraction, and PVR.[25] In this study changes in right ventricular ejection fraction were associated with survival, but changes in PVR were not, with similar changes in PVR in survivors versus non-survivors. So

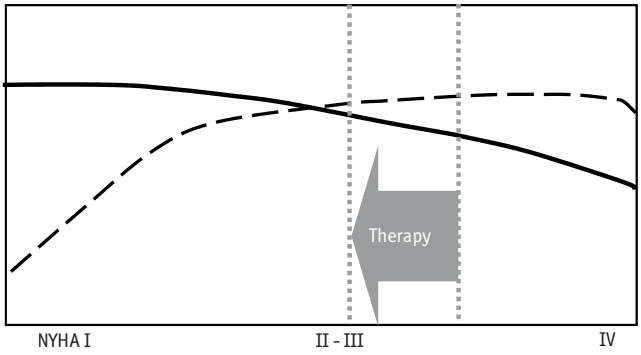

Figure 1. Mean pulmonary artery pressure (– – –) and stroke volume (——) in pulmonary arterial hypertension at different stages of disease severity, classified by NYHA class. Although PVR decreases with therapy this does not mean that right ventricular work decreases: power/beat = stroke volume x pulmonary artery pressure. Starting point arrow = point of diagnosis in most patients.

why can the right ventricle deteriorate even if PVR is lowered ? Sniderman asked himself this question already in the nineties and suggested that the hemodynamical response of the right ventricle to a modest PVR reduction, which is an increase in cardiac output with almost no change in pulmonary artery pressure (Figure 1), might explain this paradox. As a consequence of the unaltered pulmonary artery pressure, pathological wall tension on the right ventricle, defined as: pressure x radius/(2 x wall thickness), will persist. Echocardiographic and MRI studies in PAH showed that treatment has little impact on right ventricular diameter or volume during single agent treatment.[24,26,27] In case of a failing right ventricle at baseline, pathological wall tension will remain unaltered and the right ventricle might continue to fail. Indeed, hemodynamical data from the RCT's show that single agent has little impact on a reduction of pulmonary artery pressure. Figure 1 illustrates this further, describing the theoretical hemodynamic improvement that a patient will experience if diagnosed in advanced stage. The yardstick to improve right ventricular function according to Sniderman is thus to reduce pulmonary artery pressure.[28] Another possible explanation is right ventricular power. Power per beat is defined by stroke volume x mean pulmonary artery pressure. In case a reduction in PVR leads to an increase in stroke volume without a decrease in pulmonary artery pressure, right ventricular power might even increase in case the load is reduced. (Figure 1) In fact from the pulmonary artery pressure and stroke volume improvements reported in trials of PAH specific medications it follows that these medications mostly increase power output of the right ventricle.[23] For these two reason a modest reduction in right ventricular load in advanced disease will not automatically lead to improvement of right ventricular function and thus improved survival.

In early disease, the situation might be different. A reduction in PVR will in that case lead to a significant reduction in pulmonary artery pressure.[29] However, since most patients are diagnosed in an advanced stage, the only solution to reduce right

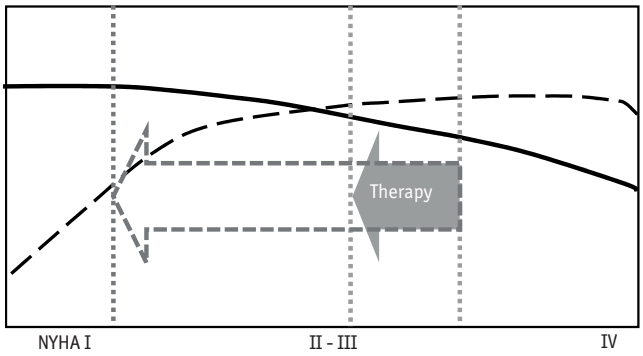

Figure 2. A greater reduction in PVR (dashed arrow), may reduce pulmonary artery pressure and is required to reduce right ventricular power. Such a PVR reduction may potentially be achievable by upfront combination therapy. (– – – = pulmonary artery pressure; ——— = stroke volume)

ventricular power and wall tension is to reduce PVR more. (Figure 2) The question remains whether this can be achieved by using current medications.

Can we achieve a reduction in pulmonary artery pressure by means of current medication?
Current guidelines recommend first-line monotherapy with agents targeting the prostacyclin, endothelin or NO pathway.[1,2] Sequential combination therapy is currently recommended when clinical improvement fails to occur on monotherapy or further disease progression occurs.[30] Epoprostenol is currently recommended as the treatment of choice for those patients with advanced disease.[1,5] However long-term survival in PAH treated with epoprostenol remains dismal, with 63% survival at 3 years in a mixed cohort of incident and prevalent PAH patients.[15] Though numerous clinical studies of combination therapy have hitherto been reported, most have examined the effect of sequential addition of treatment, and not upfront combination therapies. Only 1 trial studied upfront combination epoprostenol and bosentan versus epoprostenol and placebo : the Bosentan Randomized trial of Endothelin Antagonist Therapy for PAH (BREATHE-2) study. Improvements in PVR and mean PAP were greater in the upfront bosentan-epoprostenol treatment group, compared to epoprostenol-placebo treated patients: respectively -35% versus -26% for PVR change and -9% versus -2% for mean PAP change. However, the difference did not reach statistical significance in this study, probably also due to the small sample size.[31] In a larger but retrospective study patients matched for age, NYHA functional class and PVR at diagnosis and treated with either first-line epoprostenol or first-line bosentan-epoprostenol were compared. Patient groups were compared for NYHA functional class and 6-minute walk distance changes and pulmonary hemodynamic improvements assessed by right heart catheterisation at follow-up. In this study PVR improvement from treatment initiation to first follow-up was significantly greater in those who received epoprostenol-bosentan combination therapy, compared to

those receiving epoprostenol monotherapy : -48% ± 17% (±SD) versus -29% ± 17% respectively (p=0.0001). A trend towards improved survival was described (p=0.07), emphasizing the possible benefit of upfront combination therapy. Changes in exercise capacity and functional class were similar between combination and monotherapy patients in this study.[32] From the same French study group a small series of 10 patients starting upfront triple combination therapy was reported: 4 NYHA class III and 6 NYHA class IV patients, with severely compromised hemodynamics (mean cardiac index 1.6 ± 0.4 $L \cdot min^{-1} \cdot sec^{-1}$ and mean PVR 1798 $dyn \cdot s \cdot^{cm-5}$).[31] For the 7 patients with available data after 4 months of combination therapy, there was an impressive improvement in exercise capacity (from 290 ± 146 m at baseline to 454 ± 67 m during follow) and a 71% reduction in PVR and normalisation of cardiac index. Mean PAP improved from 68 ± 17 mmHg at baseline to 45 ± 13 mmHg at 4 months (n=7; p<0.01) and 48 ± 10 mmHg at last visit (n=5; p<0.01). After a median 18.5 months follow-up (range 1-36 months) all patients were alive and in NYHA functional class I or II. In patients who were reassessed (n=5) at 12-28 months the positive findings established at 4 months were maintained.[33] No further studies evaluating first-line combination therapy have been reported to date. Other studies have assessed the effect of combination therapy with prostanoids only in a sequential approach. The Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil (PACES) study described the effects of the addition of oral sildenafil or placebo in patients stable on epoprostenol treatment. Those in the combination arm not only showed improvements in 6-minute walk distance and health related quality of life scores, but also had longer times to clinical worsening and less need for epoprostenol dose increases.[34] In this study hemodynamic changes were different with a -2.8 mmHg mean PAP decrease in combination therapy, compared to a + 1.1 mmHg mean PAP increase with epoprostenol plus placebo (treatment difference -3.8 mmHg (95% CI -5.6 to -2.1)). PVR change was -151 $dyne \cdot sec^{-5} \cdot cm^{-5}$ in combination therapy compared to +39 $dyne \cdot sec^{-5} \cdot cm^{-5}$ in continued epoprostenol plus placebo. Relative increase in cardiac output was +0.9 L/min in patients with epoprostenol-sildenafil therapy (95% CI 0.5 to 1.2 L/min). The Iloprost Inhalation Solution Safety and pilot Efficacy Trial in combination with Bosentan for evaluation in Pulmonary Arterial Hypertension (STEP) evaluated the addition of inhaled iloprost or placebo to ongoing bosentan therapy. In this trial patients randomized to iloprost demonstrated improvements in 6-minute walk distance, functional status, time to clinical worsening and decreased PVR.[35] Further small non randomized studies describe that oral sildenafil added to patients stable on bosentan leads to improved exercise capacity measured by 6-minute walk distance and increased VO2max[36], sildenafil added to subcutaneous treprostinil improves tread mill times and dyspnea fatigue scores[37], bosentan added to subcutaneous treprostinil leads to significant additional improvements in 6-minute walk distance, Borg dyspnea score and also decreases mean PAP further from 56 ± 16 mmHg before bosentan start to 47 ± 12 mmHg (p<0.001), compared to 60 ± 15 mmHg at baseline, before treprostinil initiation.[38] In another small descriptive study subcutaneous treprostinil or intravenous epoprostenol added to oral bosentan or oral bosentan-sildenafil improved 6-minute walks, NYHA functional class and

also improved right ventricular ejection fraction and decreased right ventricular end-diastolic volumes measured by MRI.[39] Currently it is unclear which of the possible combinations of PAH specific therapies confer the greatest clinical gain. PAH specific medical therapies are costly and cost effectiveness of combining these therapies is uncertain. Furthermore, the possibility of adverse events due to drug interactions is increased in the setting of combination therapy. However, the results of the studies are encouraging since they all show a larger decrease in PVR, and an indication exists that an even larger reduction in PVR can be achieved through upfront combination therapy. However, compelling evidence is lacking that upfront combination therapy is more advantageous compared to a sequential add-on strategy. Of interest in this respect is a large multicenter study comparing upfront ambrisentan in combination with tadalafil to ambrisentan monotherapy, using clinical worsening as an endpoint.[40] Another study comparing upfront tadalafil and treprostinil versus treprostinil monotherapy was cancelled due to poor recruitment.[41]

In conclusion current treatments do lower PVR in the majority of patients and these effects are likely to sustain over time. However, this reduction in PVR might fail to halt the progression of right ventricular failure, since single agent therapy does not reduce right ventricular power, nor right ventricular wall tension. Recent data from combination therapy offers the promise that a more pronounced effect on PVR and PAP can be reached. Whether this approach also can lead to a better improvement of right ventricular function and survival is still an open question.

References

1. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2009;30:2493-2537.
2. Humbert M, Sitbon O, Simonneau G. Drug therapy: Treatment of pulmonary arterial hypertension. New Eng J Med 2004;351:1425-1436.
3. Moncada S, Gryglewsli R, Bunting S, et al. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature 1976;263:663-665.
4. Clapp LH, Finney P, Turcato S, et al. Differential effects of stable prostacyclin analogues on smooth muscle proliferation and cyclic AMP generation in human pulmonary artery. Am J Respir Cell Mol Biol 2002;26:194-201.
5. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Eng J Med 1996;334:296-302.
6. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Eng J Med 2002;346:896-903.
7. Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension. Results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117:3010-3019.
8. Pepke-Zaba J, Higenbotham TW, Dinh-Xuan AT, et al. Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. Lancet 1991;338:1173-1174.
9. Hasuda T, Satoh T, Shimuchi A, et al. Improvement in exercise capacity with nitric oxide inhalation in patients with precapillary pulmonary hypertension. Circulation 2000;101:2066-2070.

10. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Eng J Med 2005;353:2148-2157.
11. Galiè N, Brundage BH, Ghofrani HA, et al; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009;119(22):2894-2903.
12. Galiè N, Manes A, Negro L, et al. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 2009;30:394-403.
13. Macchia A, Marchioli R, Tognoni G, et al. Systematic review of trials using vasodilators in pulmonary arterial hypertension: Why a new approach is needed. Am Heart J 2010;159:245-257.
14. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010;122:156-163.
15. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780-788.
16. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with First-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005;25:244-249.
17. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation 2010;122:164-172.
18. Sitbon O, Simonneau G. Optimal management of severe pulmonary arterial hypertension. Eur Respir Rev 2011;20:254-261.
19. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the reveal registry. Chest 2010;137:376-387.
20. d'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med 1991;115:343-349.
21. Saouti N, Westerhof N, Helderman F, et al. Right ventricular oscillatory power is a constant fraction of total power irrespective of pulmonary artery pressure. Am J Respir Crit Care Med 2010;182:1315-1320.
22. Reesink HJ, Marcus JT, Tulevski II, et al. Reverse rig ht ventricular remodeling after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension: utility of magnetic resonance imaging to demonstrate restoration of the right ventricle. J Thorac Cardiovasc Surg 2007;133:58-64.
23. Handoko ML., de Man FS, Allaart CP, et al. Perspectives on novel therapeutic strategies for right heart failure in pulmonary arterial hypertension: lessons from the left heart. Eur Respir Rev. 2010;115:72-82.
24. van Wolferen SA, Boonstra A, Marcus JT, et al. Right ventricular reverse remodelling after sildenafil in pulmonary arterial hypertension. Heart 2006;12:1860-1861.
25. van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011;58:2511-2519.
26. Hinderliter AL, Willis PW, Barst RJ, et al. Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension. Primary Pulmonary Hypertension Study Group. Circulation 1997;95:1479-1486.
27. Galiè N, Hinderliter AL, Torbicki A, et al. Effects of the oral endothelin receptor antagonist bosentan on echocardiographic and doppler measures in patients with pulmonary arterial hypertension. J Am Coll Cardiol 2003;41:1380-1386.
28. Sniderman AD, Fitchett DH. Vasodilators and pulmonary arterial hypertension: the paradox of therapeutic success and clinical failure. Int J Cardiol 1988;20:173-181.
29. Galiè N, Rubin LJ, Hoeper MM, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial.
30. Hoeper MM, Markevych I, Spiekerkoetter E, et al. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. Eur Respir J 2005;26:858-863.

31. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. Eur Respir J 2004;24:353-359.
32. Kemp K, Savale L, O'Çallaghan DS, et al. Usefulness of first-line combination therapy with epoprostenol and bosentan in pulmonary arterial hypertension: An observational study. J Hart Lung Transplant 2012;31:150-158.
33. Sitbon O, Jais X, Savale L, et al. Upfront triple combination therapy of i.v. epoprostenol with oral bosentan and sildenafil in idiopathic and heritable pulmonary arterial hypertension. Am J respir Crit care Med 2011;183:A5910.
34. Simonneau G, Rubin LJ, Galiè N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension. A randomized trial. Ann Intern Med 2008;149:521-530.
35. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J resp Crit care Med 2006;174:1257-1263.
36. Hoeper MM, Faulenbach C, Golpon H, et al. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. Eur Respir J 2004;24:1007-1010.
37. Gomberg-Maitland M, McLaughlin V, Gulati M, et al. Efficacy and safety of sildenafil added to treporstinil in pulmonary hypertension. Am J Cardiol 2005;96:1334-1336.
38. Benza RL, Rayburn BK, Tallaj JA, et al. Treprostinil-based therapy in the treatment of moderate-to-severe pulmonary arterial hypertension: long-term efficacy and combination with bosentan. Chest 2008;134:139-145.
39. Jacobs W, Boonstra A, Marcus JT, et al. Addition of prostanoids in pulmonary hypertension deteriorating on oral therapy. J Heart Lung Transplant 2009;28:280-284.
40. A study of first-line ambrisentan and tadalafil combination therapy in subjects with pulmonary arterial hypertension (PAH) (AMBITION). http://clinicaltrials.gov/ct2/show/NCT01178073. Date last updated: Dec 8 2011. Date last accessed: May 30, 2012.
41. Treprostinil combined with tadalafil for pulmonary hypertension (T2). http://clinicaltrials.gov/ct2/show/NCT01302444. Date last updated: May 1,2012. Date last accessed: May 30, 2012.

Chapter 8

Summary and conclusion

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Idiopathic Pulmonary arterial hypertension (PAH) is characterised by progressive obstruction and narrowing of the small pulmonary arteries. This results in increased pulmonary vascular resistance, leading to progressive right ventricular pressure load, eventually resulting in right heart failure and death.[1] Effective PAH specific medical therapies have been provided to the patients at VU University Medical Centre (VUMC) from the late 1990's. Thus, despite PAH being a rare disease, a relatively large patient cohort has been established with long-term follow-up data available.

Different PAH specific medical therapies have become available in different time periods. Epoprostenol is widely perceived as the most potent therapy currently available and is reviewed in Chapter 2. However, treatment is bothersome with continuous infusion required. At VUMC Before 2003 medical therapy consisted of intravenous epoprostenol. Since oral bosentan became available in 2003 and subsequently oral sildenafil in 2004 an alternative strategy became possible starting first-line oral therapies and reserving first-line intravenous epoprostenol only for the most severe patients. From 2005 subcutaneous prostacyclin infusion (treprostinil) was added to the medical armamentarium at VUMC as an alternative somewhat less invasive method of prostacyclin treatment.

In chapter 3 we show that first-line epoprostenol treated patients from our historical cohort have greater exercise improvements measured by six-minute walk distance, compared to patients treated with first-line bosentan. This is further corroborated in a matched pairs analysis. However compared to current first-line bosentan treated patients time to disease progression was similar and no survival differences were found between first-line epoprostenol treated patients and patients treated with first-line oral therapy and prostacyclin as add-on medication upon clinical deterioration. The advent of oral therapies has delayed the time of onset of prostacyclin, thus delaying the need for bothersome continuous infusion therapies. Combination oral bosentan-sildenafil therapy further postponed the need for prostacyclin therapies. In chapter 4 we subsequently show that delayed initiation of prostacyclin as add-on therapy (either intravenous epoprostenol or subcutaneous treprostinil) still leads to excellent improvements in exercise capacity and WHO functional class, after deterioration on oral therapy. And this is further illustrated by subsequently observed NT-proBNP decreases and improvements in right ventricular ejection fraction and right and left ventricular end-diastolic volumes measured by MRI.

Since sex differences in treatment outcomes and survival are known from the literature[2-6] and worse outcomes in males are confirmed in our database, we sought to determine the cause of this sex survival difference. In our patient cohort follow-up is standardised and includes right heart catheterisation and cardiac MRI at baseline and at 1 year follow-up. In chapter 5 we show that sex differences in survival are mediated through differences in right ventricular ejection fraction (RVEF) improvements after initiation of medical therapies, with no improvements in males, versus substantial improvements in females.

Increased pulmonary hypertension awareness, in combination with high left heart-failure prevalence, have augmented referrals to PAH centres. In pulmonary hypertension signs of left heart failure may be mimicked on echocardiography due

to under filling of the left ventricle. This is especially the case for diastolic left heart failure.[7] Therefore, a substantial proportion of patients referred to a PAH centre might have left heart failure as the underlying cause. Efforts made to improve referral patterns to PAH centres should not lead to missed PAH diagnosis, since delayed start of PAH specific therapies decreases survival even with a short-term interval.[8] Unnecessary referral should however be reduced, representing burden to the patient, including right heart catheterisation, and economical cost. In chapter 6 we show that a simple clinical risk score including parameters from medical history, electrocardiography and echocardiography could obviate the need for right heart catheterisation in 20% of left heart failure patients referred, without misclassifying any PAH patient.
In chapter 7 we review current treatment options. Current PAH specific medical therapies lower pulmonary vascular resistance (PVR) and this effect is likely sustained over time. However, this reduction in PVR might fail to halt progression of right ventricular failure, since single agent therapy does not reduce right ventricular power and right ventricular wall tension. An argument is made for upfront combination therapies. As they offer the promise that a more pronounced beneficial effect on PVR and also pulmonary artery pressure can be reached, and thus indeed reduced right ventricular power and wall stress, which could prevent right heart failure in the end.

Conclusion and future perspectives

Based on the results of this thesis we conclude that:
- Addition of subcutaneous or intravenous prostanoids can be efficacious in PAH deteriorating on oral therapy, leading to improved exercise capacity and WHO functional class, decreased NT-proBNP levels and improved RVEF and right and left ventricular end-diastolic volumes.
- First-line epoprostenol treatment may lead to greater improvement in exercise capacity than first-line bosentan. However, these greater exercise improvements did not translate into longer time to disease progression or survival.
- In a population suspected of PAH left heart failure can be diagnosed with a high degree of certainty by non-invasive means in a substantial number of patients, using a clinical risk score including simple parameters from medical history, electrocardiography and echocardiography.
- Poor prognosis in male PAH patients can be explained by differences in adaptation of the right ventricle.

An unanswered question is whether upfront combination treatment is better than sequential. In addition it is unclear yet when prostacyclin treatment must be initiated. The possible benefit of upfront combination treatment can only be assessed in a prospective randomised controlled multicenter study. Such a study is currently underway (AMBITION trial) and results are expected this year. Based on the outcome of this study future treatment strategy studies can be designed.
The predictive model to identify left-heart failure non-invasively as an alternative

cause of PH in a population suspected of PAH, should be validated in non-referral centers. Currently the OPTIEK study is set up to validate our non-invasive risk score in this manner.
The observation that males have a poor right ventricular response to therapy compared to females, questions the role of sex hormones. Laboratory studies are required to further explore the role of sex hormones in the pressure overloaded right ventricle. The potential of substances targeting sex-specific pathways, such as estrogen receptor agonists should be further evaluated.

References

1. Galiè N, Hoeper MM, Humbert M, et al. Guidleines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2009;30:2493-2537.
2. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010;122:156-153.
3. Humbert M, Sitbon O, Yaïci A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010;36:549-555.
4. Kane GC, Maradit-Kremers H, Slusser JP, et al. Integration of clinical and hemodynamic parameters in the prediction of long-term survival in patients with pulmonary arterial hypertension. *Chest* 2011;139:1285-1293.
5. Shapiro S, Traiger GL, Turner M, et al. Sex differences in the diagnosis, treatment, and outcome of patients with pulmonary arterial hypertension enrolled in the registry to evaluate early and long-term pulmonary arterial hypertension disease management. *Chest* 2012;141:363-373.
6. Thenappan T, Glassner C, Gomberg-Maitland M. Validation of the pulmonary hypertension connection equation for survival prediction in pulmonary arterial hypertension. *Chest* 2012;141:642-650.
7. Shapiro BP, Nishimura RA, McGoon MD, et al. Diagnostic dilemmas: diastolic heart failure causing pulmonary hypertension and pulmonary hypertension causing diastolic dysfunction. *Advances in Pulmonary Hypertension* 2006;5:13-20.
8. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;334:296-302.
9. A study of first-line ambrisentan and tadalafil combination therapy in subjects with pulmonary arterial hypertension (PAH) (AMBITION). GlaxoSmithKline. Available: http://www.clinicaltrials.gov/ct2/show/study/NCT01178073 [2014, May 19].

Nederlandse samenvatting

Diagnostische strategie en lange termijn behandeluitkomsten in idiopatische pulmonale arteriële hypertensie

Idiopathische Pulmonale arteriële hypertensie (PAH) wordt gekarakteriseerd door progressieve obstructie en vernauwing van de kleine pulmonaal arteriën. Dit resulteert in een toegenomen pulmonale vaatweerstand en een progressieve rechterventrikelbelasting. Dit culmineert uiteindelijk in een rechtszijdig hartfalen en de dood van de patiënt.[1] Sedert eind jaren '90 worden effectieve PAH-specifieke medicamenteuze therapieën voorgeschreven in het VU Medisch Centrum (VUMC). Daarmee was het VU ziekenhuis het eerste centrum in Nederland waar dit gebeurde. Ondanks het feit dat het hier gaat om een zeldzame aandoening, is er inmiddels een relatief groot patiëntencohort met lange-termijn follow-up data ontstaan.
Epoprostenol wordt momenteel gezien als het meest potente middel dat beschikbaar is en wordt in review besproken in **hoofdstuk 2**. Behandeling met epoprostenol kan alleen door middel van continue intraveneuze toediening en is daardoor zeer belastend voor de patiënt. Sedert 2003 is oraal bosentan beschikbaar gekomen en sedert 2004 oraal sildenafil. Een alternatieve behandelstrategie is daardoor mogelijk geworden. Er kan nu gestart worden met eerstelijns orale therapie. Epoprostenol in eerstelijn blijft alleen gereserveerd voor de meest zieke patiënten. Vanaf 2005 is subcutaan toegediende prostacycline (treprostinil) toegevoegd aan het medicinaal armamentarium in het VUMC, als een alternatieve wat mindere belastende prostacycline infusiemethode.
In **hoofdstuk 3** tonen we aan dat patiënten behandeld in ons historisch patiënten cohort met eerstelijns epoprostenol een grotere toename in inspanningscapaciteit hadden. Dit in vergelijking met patiënten die behandeld werden met eerstelijns orale bosentan therapie in het huidige tijdsgewricht. Dit wordt verder onderbouwd in een matched pairs analyse. Deze grotere verbetering in inspanningscapaciteit vertaalde zich niet in een langere tijd tot ziekteprogressie. Er werd ook geen verschil in overleving vastgesteld wanneer de start van prostacycline werd uitgesteld ten faveure van orale therapie. Combinatie orale therapie met zowel bosentan als sildenafil kan de prostacyclinevrije periode nog verder verlengen.
In **hoofdstuk 4** tonen we vervolgens aan dat uitgestelde prostacycline therapie als add-on bij eerstelijns orale therapie in de vorm van hetzij i.v. epoprostenol, danwel s.c. treprostinil, nog steeds zeer effectief is. Na starten van i.v. epoprostenol en s.c. treprostinil als add on therapie verbetert de inspanningscapaciteit en WHO functionele klasse, na eerdere verslechtering onder orale therapie. Met cardiale MRI tonen we verbeteringen in rechterventrikelejectiefractie en rechter- en linkerventrikel eind-diastolische volumina. Daarnaast verbeteren de serum NT-proBNP waarden, als maat voor verminderde rechterventrikelwandspanning.
Geslachtsverschillen in behandeluitkomsten en -overleving zijn bekend uit de literatuur.[2-6] In **hoofdstuk 5** bevestigen we de slechtere behandeluitkomsten bij mannen in onze database. We hebben de oorzaak van dit verschil in overleving onderzocht. Follow-up in ons patiëntencohort is gestandaardiseerd. Rechterhartcatheterisatie en cardiale MRI worden vervaardigd op baseline bij diagnose en één jaar na de start van PAH-specifieke medicamenteuze therapie. We hebben rechterventrikelejectiefractie (RVEF) veranderingen met cardiale MRI vergeleken. Er treden geen RVEF verbeteringen op na het starten van medicamenteuze therapie bij mannen. Daartegenover staan

substantiële RVEF verbeteringen bij vrouwen. Door een mediatoranalyse wordt aangetoond dat dit een belangrijke verklaring is voor de betere overleving bij vrouwen.
In **hoofstuk 6** beschrijven we een predictie model dat linkszijdig hartfalen als alternatieve oorzaak voor pulmonale hypertensie kan aantonen in een populatie verdacht voor PAH. Het ontstaan van medicamenteuze behandelopties voor PAH heeft geleid tot toegenomen alertheid met betrekking tot het ziektebeeld pulmonale hypertensie. In combinatie met de hoge prevalentie van linkszijdig hartfalen als alternatieve oorzaak voor pulmonale hypertensie, heeft dit ervoor gezorgd dat het aantal verwijzingen naar tertiaire pulmonale hypertensie centra toeneemt. Bij pulmonale hypertensie kunnen tekenen van linkszijdig hartfalen aanwezig lijken op echocardiografie door onder vulling van de linkerventrikel. Dit geldt met name in het geval van diastolisch linkszijdig hartfalen.[7] Daarom kan het zo zijn dat een substantieel aantal van de patiënten, dat wordt doorverwezen naar een PAH-centrum uiteindelijk linkszijdig hartfalen blijkt te hebben. Pogingen de verwijspatronen naar PAH centra te verbeteren mogen niet leiden tot uitstel van de diagnose van PAH. Het uitstellen van de start van behandeling met PAH specifieke therapie heeft immers direct al een nadelig effect op de overleving. Dit treedt zelfs al op bij een kort interval.[8] Desalniettemin dient het aantal onnodige verwijzingen omlaag gebracht te worden. Op die manier worden de belasting voor de patiënt, met onder andere een rechtscatherisatie in de work-up en daarnaast de economische kosten verbonden aan een niet-noodzakelijke verwijzing verminderd. We tonen aan dat een eenvoudige klinische risicoscore bestaande uit parameters uit de anamnese, elektrocardiografie en echocardiografie, 20% van de patiënten met linkszijdig hartfalen aanvullend kan aanwijzen. Bij deze patienten is een rechtscatheterisatie niet noodzakelijk. Door gebruik van de risicoscore werden geen PAH-patiënten gemist.
In **hoofdstuk 7** overzien we de huidige behandelopties. Deze verlagen de pulmonale vaatweerstand en dit effect lijkt aan te houden over de tijd. Toch kan deze verlaging van de pulmonale vaatweerstand het progressieve rechterventrikelfalen niet duurzaam een halt toebrengen. We beargumenteren dat dit veroorzaakt wordt doordat monotherapie rechterventrikelarbeid en rechterventrikelwandspanning niet kan verlagen. Om dit te bereiken lijkt eerstelijnscombinatietherapie noodzakelijk waardoor grotere dalingen in pulmonale vaatweerstand en ook dalingen in pulmonale arteriële druk ontstaan. Uiteindelijk kan dan wel de gewenste vermindering in de rechterventrikelarbeid en –wandspanning bereikt worden.

Conclusie en toekomstperspectief

Op basis van de resultaten van dit proefschrift concluderen we dat:
- Toevoegen van subcutaan of intraveneus toegediende prostacycline is effectief in PAH, welke verslechtert onder orale PAH specifieke therapie. Inspanningscapaciteit, WHO functionele klasse, NT-proBNP, rechterventrikelejectiefractie en rechter- en linkerventrikel eind-diastolische volumina verbeteren.
- Eerstelijnsepoprostenolbehandeling geeft grotere verbetering in inspanningscapaciteit dan eerstelijnsbosentan. Dit verschil in inspanningscapaciteit vertaalt zich niet in verschillen in tijd tot ziekteprogressie of -overleving.
- In een populatie verdacht van PAH kan linkszijdig hartfalen met een hoge mate van zekerheid worden vastgesteld bij een substantieel aantal patienten. Dit door een klinische risicoscore te berekenen, welke gebruik maakt van relatief eenvoudige parameters uit de medische voorgeschiedenis, electrocardiografie en echocardiografie.
- De slechte prognose in mannen met PAH kan worden verklaard door een verschil in adaptatie van de rechterventrikel.

Onbeantwoord blijft de vraag of eerstelijnscombinatietherapie beter is dan sequentiële. Daarnaast is het onduidelijk wat het beste tijdstip is om prostacyclinetherapie te starten. Het mogelijke voordeel van eerstelijnscombinatietherapie kan alleen beoordeeld worden in een prospectieve gerandomiseerde multicenterstudie. Op dit moment is een dergelijke studie gestart (AMBITION studie) en de eerste resultaten worden nog dit jaar verwacht.[9] Op basis van de uitkomst van deze studie kunnen toekomstige behandelstrategieën worden opgesteld.
Het door ons ontwikkelde predictiemodel om linkszijdig hartfalen non-invasief vast te stellen als alternatieve oorzaak voor PH (in een populatie verdacht van PAH) moet worden gevalideerd in de non-tertiaire setting. Op dit moment wordt de OPTIEK-studie opgezet om onze non-invasieve risicoscore op deze wijze te valideren.
De observatie dat mannen een slechtere rechterventrikeladaptatie hebben na het starten van de medicamenteuze therapie, doet de vraag rijzen wat de pathofysiologische betekenis is van geslachtshormonen in dit kader. Laboratoriumstudies zijn nodig om de rol van geslachtshormonen in de druk overbelaste rechterventrikel verder te onderzoeken. Medicatie die aangrijpt op seks-specifieke pathways, zoals oestrogeen receptor agonisten, moet verder worden onderzocht.

Dankwoord

Curriculum Vitae

List of publications

Dankwoord

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Curriculum Vitae

Wouter Jacobs (1971) werd geboren in Amsterdam. Na het doorbrengen van de kindertijd in achtereenvolgens Lagos (Nigeria), Athene (Griekenland) en Bangkok (Thailand), werd de middelbare school doorlopen op het Fons Vitae Lyceum in Amsterdam. De studie geneeskunde werd gevolgd aan de Universiteit van Amsterdam. Hierna werd de opleiding tot arts voor longziekten en tuberculose gevolgd aan het VU Medisch Centrum. Hij werkt nu als longarts in het Martini ziekenhuis te Groningen. Hij woont samen met zijn vrouw Sharon van Wijk en hun vier kinderen: Lieve, Julius, Tessel en Leonoor.

Wouter Jacobs (1972) was born in Amsterdam. After spending his childhood overseas in respectively Lagos (Nigeria), Athens (Greece) and Bangkok (Thailand), he finished his secondary education (VWO) at the Fons Vitae Lyceum in Amsterdam. He then studied medicine at the University of Amsterdam and subsequently received his training as chest physician from the VU University Medical Center. Currently he works as chest physician at the Martini Hospital, Groningen, the Netherlands. He lives with his wife Sharon van Wijk and their four children: Lieve, Julius, Tessel and Leonoor.

List of publications

W. Jacobs and A. Vonk Noordegraaf. Epoprostenol in pulmonary arterial hypertension. Expert Opin Drug Metab Toxicol 2009;5:83-90.

W.Jacobs, A. Boonstra, J.T. Marcus, et al. Addition of prostanoids in pulmonary arterial hypertension deteriorating on oral therapy. J Heart Lung Transplant 2009;28:280-284.

W.Jacobs, M. Brand, DM Rosenberg, et al. Long-term outcomes in pulmonary arterial hypertension in the first-line epoprostenol or first-line bosentan era. J Heart Lung transplant 2010;29:1150-1158.

W. Jacobs, A. Vonk-Noordegraaf. Pulmonary vascular versus right ventricular function changes during targeted therapies of pulmonary hypertension – An argument for upfront combination therapy ? European cardiology 2012;8:209-212.

W. Jacobs, M.C. van der Veerdonk, P. Trip, et al. The right ventricle explains sex differences in survival in idiopathic pulmonary arterial hypertension. Chest 2014;145:1230-1236.

W. Jacobs, A. Vonk Noordegraaf, R. Golding, et al. Respiratory complications and Goldenhar syndrome. Breathe 2007;3:305-308.

W. Jacobs, A. Vonk Noordegraaf, T.G. Sutedja, et al. Twee zeldzame manifestaties van amyloïdose in het respiratoire systeem. Ned Tijdschr Geneeskd 2007;151:2055-2060.

S.A. Wolferen, M.C. van de Veerdonk, Mauritz GJ, W. Jacobs et al. Clinically significant change in stroke volume in pulmonary hypertension. Chest 2011;139:1003-1009.

H. Groepenhoff, N. Westerhof, W.Jacobs et al. Exercise stroke volume and heart rate response differ in right and left heart failure. Eur J Heart Fail 2010;12:716-720.