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Therapy with sildenafil in a patient with pulmonary hypertension associated with end-stage left ventricular failure (RCD code: II-1B.1)

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Abstract

In the last decade the great progress was made in the therapy of pulmonary arterial hypertension (PAH). Unfortunately, there is still lack of evidence-based data how to manage with pulmonary hypertension due to left heart diseases (PH-LHD). Approximately 60% of patients with heart failure with reduced ejection fraction (HFREF) develop PH-LHD and this condition is associated with a very poor prognosis. We report the case of 51-year-old man with a history of myocardial infarction, with HFREF who was previously disqualified from heart transplantation (HTX) due to PH. We added sildenafil (20 mg t.i.d.) to the standard therapy of HFREF in this patient. After 3 months of treatment with sildenafil we observed improvement in hemodynamic parameters, right and left ventricle performance as well as exercise capacity. Although we demonstrated the benefit of treatment with sildenafil in so called "no option" patients, further randomized trials are needed to confirm the advantage of sildenafil therapy in patients with PH due to HFREF. JRCD 2014; 1 (8): 32–37

Key words: phosphodiesterase type 5, reduced ejection fraction, pulmonary wedge pressure

Background

In the last decade, a substantial progress in the therapy of pulmonary arterial hypertension (PAH) was made. According to the European Society of Cardiology (ESC) guidelines issued in 2009, there are several types of agents targeted on specific pathophysiological mechanisms of PAH, such as calcium channel blockers, prostanoids, endothelin receptor antagonists, and phosphodiesterase type 5 (PDE5) inhibitors. The treatment of PAH with 1 or more of the above types of agents is well established on the basis of evidence from numerous clinical trials. Unfortunately, there is still a lack of evidence from randomized clinical trials on the so called non-PAH forms of pulmonary hypertension (PH) [1].

PH due to left heart disease (PH-LHD), also called postcapillary PH or "venous" PH, is the most common type of PH. It is defined as a mean pulmonary artery pressure (mPAP) of 25 mm Hg or higher and pulmonary artery wedge pressure (PAWP) exceeding 15 mm Hg with normal or reduced cardiac output. PH-LHD is further classified into passive, if a transpulmonary gradient (TPG = mPAP – PAWP) is 12 mm Hg or less, or reactive (out of proportion), if TPG is higher than 12 mm Hg. PH-LHD is a consequence of various pathologies including left ventricular (LV) systolic dysfunction, LV diastolic dysfunction, or valvular disease [2]. Approximately 60% of the patients with severe left heart failure and low ventricular ejection fraction develop PH-LHD, and this condition is associated with a particularly poor prognosis for these patients [3].

Case presentation

We describe a case of a 51-year-old Caucasian man with a history of ischemic heart disease after anterolateral myocardial infarction in 2007, with chronic heart failure (CHF) and a markedly reduced LV ejection fraction (LVEF), after implantable cardioverter-defibrillator implantation in 2008. Coronary angiography performed in 2008 showed the proximal occlusion of the left anterior descending artery, with no significant changes in other coronary arteries. The LVEF was estimated at 20% by ventriculography. In 2009, right heart catheterization (RHC) was performed and PH-LHD with high pulmonary vascular resistance (PVR) was

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Table 1. Right heart catheterization at baseline and after 3 months of therapy with sildenafil in a patient with pulmonary hypertension associated with left ventricular systolic dysfunction

Hemodynamic measurements at baseline				Hemodynamic measurements after 3 months of therapy with sildenafil	
parameter	**baseline**	**after NO**	**after sildenafil**	**baseline**	**after NO**
mPAP (mm Hg)	40	44	39	35	39
PVR (dyne × s × cm^{-5})	309	397	305	209	344
TPG (mm HG)	10	12	8	8	11
CI (L/min/m^2)	1.4	1.3	1.7	1.6	1.5
PAWP (mm Hg)	30	32	27	27	27
PA_{Sat} (%)	49.8	50.2	53.1	56.6	52.4

NO – nitric oxide, mPAP – mean pulmonary artery pressure, PVR – pulmonary vascular resistance, TPG – transpulmonary gradient, CI – cardiac index, PAWP – pulmonary artery wedge pressure, PA_{Sat} – blood oxygen saturation in the pulmonary artery

diagnosed. An acute vasodilator test with nitroglycerin showed no significant decrease of mPAP or PVR. Accordingly, the patient was no longer considered for heart transplantation.

In 2011, the patient was admitted to the Center for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow, Poland, for clinical and hemodynamic assessment.

On admission, he was in New York Heart Association (NYHA) class III and a physical examination showed no signs of heart failure decompensation (normal breath sounds on lung auscultation; regular heart rhythm of 80/min with no heart murmurs on heart auscultation; no peripheral edema, liver enlargement, ascites, or cyanosis). He was on a stable treatment with an angiotensin – converting enzyme inhibitor, β-blocker, furosemide, spironol, digoxin, and acetylsalicylic acid. An electrocardiogram showed sinus rhythm with a heart rate of 80/min, left axis deviation, QRS duration of 110 ms, PQ interval of 200 ms, abnormal Q-wave in I and aVL, low progression of R-wave in V3–V6, and sustained ST-elevation in V2-V6.

To evaluate exercise capacity, the cardiopulmonary exercise test (CPET) and 6-minute walking test (6MWT) were performed. Oxygen consumption (peak VO_2) in CPET was 4 mL/kg/min, and ventilation efficiency (VE/VCO_2) was 34.3. The distance in 6MWT was 195 m, with the Borg scale of 7 (range, 0–10). No significant desaturation during exercise was observed. Echocardiography revealed the following abnormalities: enlargement of all heart chambers, markedly reduced LVEF (15%), vast dyskinesis of the apex and adjacent segments, moderate tricuspid valve and pulmonary valve regurgitation, mild mitral valve regurgitation, tricuspid annular plane systolic excursion of 11 mm, and estimated right ventricular systolic pressure of 60 mm Hg.

For the hemodynamic assessment of the patient, RHC with the acute vasodilator test was performed. Hemodynamic measurements were noted at baseline, 5 minutes after administration of inhaled nitric oxide (NO) (at a dose of 20 ppm), and 10 minutes after cessation of NO. Next, the patient received 50 mg of sildenafil p.o. and hemodynamic measurements were repeated 30 minutes after sildenafil administration. As shown in table 1, after NO inhalation, an increase of mPAP, PVR, TPG, and PAWP was observed. Unlike NO, sildenafil decreased mPAP, PVR, PAWP, and LV end-diastolic pressure. Moreover, the vasodilator effects of sildenafil were associated with an increase in cardiac output, cardiac index, and pulmonary artery blood saturation (PA_{Sat}).

All the results were presented to a team of specialists including a cardiologist, interventional cardiologist, and cardiac surgeon. Considering high mPAP and PVR with an insufficient decrease after the use of vasodilators, the team decided against heart transplantation in the patient and recommended a long-term therapy with sildenafil. After obtaining written informed consent from the patient, a treatment with oral sildenafil (20 mg 3 times/day) was started in an open-label clinical study approved by the local ethics committee. Sildenafil was well-tolerated and the patient did not report any side effects of treatment. After 3 months, the clinical and hemodynamic status of the patient was evaluated again. He was still in NYHA class III but he reported subjective improvement in exercise capacity. Compared with baseline, the peak VO_2 measured in CPET increased (from 4 to 7.3 mL/kg/min) and VE/VCO_2 decreased (from 34.3 to 29.6). There was also a significant improvement in the results of the 6MWT (from 195 to 246 m). In RHC performed after 3 months of sildenafil therapy, a decrease of mPAP, PVR, PAPW, and TPG and an increase in cardiac output, cardiac index, and PA_{Sat} were observed. The hemodynamic measurements are presented in table 1.

According to the study protocol, due to clinical and hemodynamic improvement, the continuation of therapy with sildenafil and a clinical follow-up assessment every 6 months were recommended.

Discussion

Pathophysiology of PH-LHD

Increased afterload of the LV and high LV end-diastolic pressure are the principal features of CHF with low LVEF. Elevated

Table 2. European Society of Cardiology Guidelines on the management of patients with pulmonary hypertension associated with left heart disease*

Statement	Class[a]	Level[b]
The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease	I	C
Patients with "out-of-proportion" PH due to left heart disease should be enrolled in RCTs targeting PH-specific drugs	IIa	C
Increased left-sided filling pressures may be estimated by Doppler echocardiography	IIb	C
Invasive measurements of PAWP or LV end-diastolic pressure may be required to confirm the diagnosis of PH due to left heart disease	IIb	C
RHC may be considered in patients with echocardiographic signs suggesting severe PH in patients with left heart disease	IIb	C
The use of PAH-specific drug therapy is not recommended in patients with PH due to left heart disease	III	C

[a] Class of recommendation
[b] Level of evidence
LV – left ventricular, PAWP – pulmonary artery wedge pressure, PH – pulmonary hypertension, RCT – randomized controlled trial, RHC – right heart catheterization
* Based on the European Society of Cardiology Guidelines for the diagnosis and treatment of pulmonary hypertension [2]

LV end-diastolic pressure is transmitted passively "backward" to the left atrium and pulmonary vasculature; it leads to pulmonary vascular damage and reactive increase in PVR and pulmonary artery pressure. The right ventricle (RV) is a low-pressure, high-volume pump that allows the blood to flow into a highly compliant pulmonary circulation. The RV can accommodate large changes in volume with minimal pressure changes but if the pulmonary pressure rises, the RV dilates, which leads to maladaptive RV hypertrophy and fibrosis. As a consequence, RV failure develops, with the clinical manifestation of hepatic congestion, peripheral edemas, cachexia, and, ultimately, death.

A number of studies provided evidence that RV performance is an important determinant of exercise capacity [4,5] and, also, an independent predictor of survival in patients with LV heart failure, especially in the presence of PH-LHD [6,7]. Several studies have also proved that exercise capacity, measured by peak VO_2, is more closely associated with RVEF than with LVEF in patients with CHF [6].

The process of pulmonary vascular damage and remodeling in PH-LHD is similar, to some extent, to that observed in PAH, with the characteristic features including smooth muscle cell dysfunction, vasoconstriction, endothelial dysfunction and cell proliferation, inflammatory cell activation, and thrombosis.

Management strategy in PH-LHD

Diagnosis

According to the ESC guidelines, the diagnostic approach to PH-LHD is similar to that to PAH [2].

Doppler echocardiography remains the best diagnostic tool used for screening; abnormal LV systolic and diastolic dysfunction as well as valvular diseases are easily detectable by echocardiography [2]. Data on tissue Doppler echocardiography show that the ratio of early mitral flow velocity (E) and early tissue Doppler velocity (E') closely correlates with LV filling pressures: when the E/E' ratio exceeds 15, LV filling pressure is elevated, and when the ratio is lower than 8, LV filling pressure is within the normal range; if the ratio is between 8 and 15, additional noninvasive testing is required. Although increased left-sided filling pressure can be estimated by Doppler echocardiography, invasive measurements of PAWP or LV end-diastolic pressure in RHC are necessary to confirm the diagnosis of PH-LHD [8].

The measurement of plasma brain natriuretic peptide (BNP) levels for the diagnosis of left heart disease in the presence of PH is not very useful because elevated BNP levels are observed in both pathophysiological conditions [2].

An elevated TPG on RHC (>12 mm Hg) suggests fixed changes in the pulmonary circulation. The acute vasodilator test performed during RHC is recommended in heart transplant candidates to identify patients with unresponsive (fixed) pulmonary hypertension who are at a high risk of acute postoperative RV failure. In heart transplant candidates, a persistent increase in PVR above 2.5 Wood units or of TPG above 15 mm Hg or both is associated with up to a 3-fold increase in the risk of RV failure and early post-transplant mortality [9]. Because there is no standardized protocol for the acute vasodilator test, various agents are used to test the responsiveness of pulmonary hypertension, including inotropic agents, prostanoids, NO, and PDE5 inhibitors [2,10]. Our data have shown that a standard protocol for pulmonary artery reactivity with NO used in patients with idiopathic PAH is not useful for detecting this reactivity in heart transplant candidates with severe PH due to LV systolic dysfunction. Compared with NO, sildenafil is superior in detecting pulmonary artery reactivity; however, further head-to-head studies are needed to indicate the vasodilator of choice for testing pulmonary artery reactivity in this group of patients [11].

Treatment

Although PH-LHD is the most common type of PH, there is currently no specific treatment for this condition. Therefore, according to the ESC guidelines, the management of PH-LHD should be aimed at the optimal treatment of the underlying disease [1]. No heart failure drugs are contraindicated in PH [12]. A sustained reduction of PH is expected in a few weeks to months in most

Table 3. Major clinical trials on the use of pulmonary vasodilators in patients with chronic heart failure

Study name/Reference	Agent	Number of patients randomized	Main clinical outcomes
FIRST [14]	epoprostenol	471	terminated early; hemodynamic and clinical improvement but decrease in survival in the epoprostenol group
REACH-1 [15]	bosentan	377	terminated early; no apparent benefit in the bosentan group
ENABLE [16]	bosentan	1613	early risk of worsening of CHF and the need of hospitalization in the bosentan group
Lewis GD et al. [17]	sildenafil	34	increase of peak VO_2 in CPET; improvement in the 6MWT and QoL in the sildenafil group
Guazzi M et al. [18]	sildenafil	45	decrease in sPAP and E/E' ratio; increase in LVEF and E'; improvement of VO_2, VE/VCO_2, and QoL in the sildenafil group

FIRST – The Flolan International Randomized Survival Trial; a randomized controlled trial of epoprostenol therapy for severe congestive heart failure, REACH – Multicentre, double-blind, placebo-controlled study of long-term endothelin blockade with bosentan in chronic heart failure, ENABLE – Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure, CPET – cardiopulmonary exercise test, LVEF – left ventricular ejection fraction, QoL – quality of life, 6MWT – six-minute walking test, sPAP – systolic pulmonary artery pressure

patients successfully operated for mitral valve disease, even if PH represents a risk factor for surgery [13].

Only a few studies have examined the role of drugs currently recommended in PAH in PH-LHD. Randomized clinical trials (RCTs) evaluating the effects of chronic use of epoprostenol and bosentan in advanced heart failure have been terminated early due to an increased rate of events in the group receiving drug treatment compared with that on conventional treatment. A number of studies suggested that sildenafil (PDE5 inhibitor) may improve exercise capacity and quality of life in patients with PH-LHD. Thus, the use of PAH-specific drugs is not recommended until robust data from long-term studies are available [1,2].

ESC recommendations for PH-LHD are summarized in the table 2.

Clinical trials and small studies on the treatment of PH-LHD due to LV dysfunction

There was a remarkable development in the therapy of PAH over the last decade. The positive results of PAH treatment have led to attempts to treat PH-LHD secondary to CHF with the same groups of vasodilators as used for PAH therapy (Table 3).

Prostanoids

In a large-scale randomized controlled trial – Flolan International Randomized Survival Trial (FIRST) [14] – 471 patients with severe left heart failure (NYHA classes III–IV) were randomized to epoprostenol infusion or standard CHF treatment. The primary endpoint was survival and secondary endpoints were clinical events, congestive heart failure symptoms, distance walked in 6 minutes, and quality of life (QoL). Epoprostenol administration resulted in a significant increase in the cardiac index (from 1.81 to 2.61 L/min/m^2), decrease in pulmonary capillary wedge pressure (from 24.5 to 20.0 mm Hg), and decrease in systemic vascular resistance (from 20.76 to 12.33 Wood units). However, the trial was terminated early because of a strong trend toward decreased survival in patients treated with epoprostenol. Chronic intravenous epoprostenol therapy did not improve the results of the 6MWT or the QoL. Considering the above results, there is a limited role of epoprostenol or other prostacyclin agonists in the therapy of patients with PH-LHD [14].

Endothelin receptor antagonists

In a large pilot study, Research on Endothelin Antagonism in Chronic Heart Failure (REACH-1), 377 patients with CHF (NYHA classes III–IV) were randomized to receive bosentan (goal doses of 500 mg twice daily) or placebo for 26 weeks. Safety concerns led to an early termination of the trial (increased risk of heart failure in the first month of treatment) when only 174 patients had an opportunity to complete 26 weeks of therapy. Bosentan delivered no apparent benefit when all patients were analyzed, but in the subgroup of patients who were treated for at least 26 weeks, a significant beneficial effect of bosentan was observed [15]. A large randomized trial, Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE), [16] evaluated the effects of bosentan in patients with CHF (NYHA classes III–IV). A total of 1613 patients were randomized to receive either bosentan (125 mg twice daily) or placebo. The primary endpoint of all-cause mortality or hospitalization for heart failure was reached in 321 of 808 patients on placebo and 312 of 805 patients receiving bosentan. Treatment with bosentan demonstrated an early risk of worsening heart failure and the need of hospitalization due to fluid retention. The results from the ENABLE study have shown a doubtful potential benefit of nonspecific endothelin receptor blockade in heart failure.

PDE5 inhibitors

As the clinical trials with prostanoids and endothelin receptor antagonists in the treatment of patients with CHF have failed, much attention has been focused recently on PDE5 inhibitors and their potential utility in the treatment of patients with CHF and PH-LHD. The efficacy of PDE5 inhibition in the treatment of PAH is encouraging [17–22]. In CHF due to LV systolic dysfunction, there is an impaired endothelium-dependent NO–cyclic guanosine monophosphate (cGMP)-mediated vasodilatation in the pulmonary and skeletal muscle vasculature. Therefore, inhibition of PDE5, the principle enzyme responsible for cGMP catabolism, has been postulated as a potent mechanism to prevent pulmonary and

systemic vasoconstriction that contributes to increased RV and LV afterload in CHF [23]. Moreover, it has been suggested that PDE5 inhibition blunts β-adrenergic signaling [24] and prevents cardiac hypertrophy and remodeling [25]. Sildenafil is a specific PDE5 inhibitor that increases NO availability and NO-mediated vasodilatation [26]. It has been shown to improve endothelium-dependent, flow-mediated brachial artery dilation in patients with CHF [27].

In a small study performed by Lewis et al. [17], 34 patients with symptomatic CHF (NYHA classes II–IV; LVEF <40%) and PH were randomized to a 12-week treatment with sildenafil (25 to 75 mg orally 3 times/day) or placebo. Compared with placebo, a significant increase in peak VO_2 measured by the CPET was observed in the sildenafil group. Moreover, sildenafil reduced PVR and increased cardiac output with exercise without altering PAWP or mPAP, heart rate, or systemic vascular resistance. It was also associated with improvement in the results of the 6MWT and QoL.

In yet another randomized, placebo-controlled study with sildenafil [18], 45 patients (NYHA classes II–III; LVEF <40%) were assigned either to placebo or sildenafil (50 mg 3 times/day) for 1 year. Although baseline systolic pulmonary artery pressure (sPAP) measured by echocardiography was only slightly elevated in all patients, it was significantly decreased in the sildenafil group after 1 year of follow-up. Moreover, only in the sildenafil group, a significant increase in LVEF and early diastolic tissue Doppler velocity (E') and a decrease in the E/E' ratio were observed. These changes were accompanied by a decrease of the left atrial volume index and LV mass index. Furthermore, sildenafil improved exercise performance (peak VO_2), ventilation efficiency (VE/VCO_2), and QoL in patients with CHF and slightly elevated PH. The results have provided evidence that chronic PDE5 inhibition has a beneficial effect also on LV diastolic function and cardiac geometry.

The same group of investigators conducted another randomized study to assess the effects of sildenafil treatment in patients with CHF [19]. A total of 46 patients (NYHA classes II–III; LVEF ≤45%) were rando y assigned to placebo or sildenafil at a dose of 50 mg twice daily for 6 months. At baseline, sPAP in all patients was within the upper normal range, but it decreased significantly after 6 months in the sildenafil group. Moreover, in an active treatment group, there was a significant increase in brachial artery flow-mediated dilatation as well as reduction in the effect of ergoreflex on ventilation and VE/VCO2 measured by the CPET.

Left ventricular and biventricular assist devices

Elevated PVR unresponsive to pharmacological vasodilatation is a major contraindication for heart transplantation. The postoperative course of patients with CHF and PH-LHD is associated with an increased risk of life-threatening right heart failure [9,27]. Mechanical support using an implantable LV assist device (LVAD) is an efficient approach to treat severe PH in patients with end-stage heart failure before heart transplantation. Data from trials on patients with CHF and severe PH treated with an LVAD suggest that it is associated with a reduction in PH that was resistant to pharmacological treatment with vasodilators [28–30]. However, in a number of patients undergoing the placement of LVAD, acute RV failure occurs because of PH and high PVR, requiring the simultaneous placement of an RVAD [31]. According to the latest ESC guidelines for the diagnosis and treatment of acute and CHF [12], an LVAD or biventricular assist device (BiVAD) is recommended in selected patients with end-stage CHF despite optimal pharmacological and device treatment, and who are otherwise suitable for heart transplantation, to improve symptoms and to reduce the risk of hospitalization for worsening HF and to reduce the risk of death while awaiting transplantation (I, B). A BiVAD rather than LVAD support should be considered as a "bridge to transplantation" in patients with biventricular failure or in those at high risk of developing RV failure after LVAD implantation.

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