Physiological Research Pre-Press Article

Title

Sildenafil is more selective pulmonary vasodilator than prostaglandin E_1 in patients with pulmonary hypertension due to heart failure

Authors

Hikmet Al-Hiti, MD, Vojtech Melenovsky, MD, PhD, Petr Syrovatka, MD, Jiri Kettner, MD, PhD, Ivan Malek, MD, PhD and Josef Kautzner, MD, PhD

Affiliation

Department of Cardiology, Institute for Clinical and Experimental Medicine – IKEM, Prague, Czech Republic

Corresponding author

Hikmet Al-Hiti, MD
Department of Cardiology, Institute for Clinical and Experimental Medicine - IKEM
Videnska 1958/9, Prague 4, 140 21, Czech Republic
hial@ikem.cz, phone: 420-261-365-100

Summary

In some patients, heart failure (HF) is associated with increased pulmonary vascular resistance (PVR). The magnitude and the reversibility of PVR elevation affect the HF management. Sildenafil has been recently recognized as potent PVR-lowering drug in HF. The aim of the study was to compare hemodynamic effects and pulmonary selectivity of sildenafil to prostaglandin E$_1$ (PGE$_1$). Right-heart catheterization was performed in 13 euvolemic advanced HF patients with elevated PVR (6.3±2 Wood´s units). Hemodynamic parameters were measured at the baseline, during i.v. infusion of PGE$_1$ (alprostadil 200 ng·kg^{-1}·min^{-1}) and after 40 mg oral dose of sildenafil. Both drugs similarly reduced systemic vascular resistance (SVR), but sildenafil had higher effect on PVR (-28% vs. -49%, p=0.05) and transpulmonary pressure gradient than PGE$_1$. The PVR/SVR ratio – an index of pulmonary selectivity, did not change after PGE$_1$ (p=0.7) but it decreased by -32% (p=0.004) after sildenafil. Both drugs similarly reduced pulmonary artery mean and wedge pressures and increased cardiac index (+27% and +28%). Sildenafil led more often to transplant-acceptable PVR while causing smaller drop of mean systemic pressure than PGE$_1$. In conclusion, vasodilatatory effects of sildenafil in patients with heart failure are more pronounced in pulmonary than in systemic circulation.

Introduction

Some patients with advanced heart failure (HF) develop pre-capillary pulmonary hypertension (PH) that adversely affects right ventricular function (Ghio et al. 2001), exercise capacity (Lewis et al. 2007) and prognosis (Di Salvo et al. 1995). The increase of PVR may occur due to structural remodeling of pulmonary vasculature, leading to "fixed", irreversible component of PVR. More frequently, elevated PVR results from vasomotor imbalance in pulmonary vascular territory that is partly reversible by hemodynamic unloading or by administration of vasodilators, such as nitrates or prostacyclin analogues. The magnitude of PVR increase and its reversibility with a vasodilator provide crucial information for management of patients with advanced HF (Costard-Jackle et al. 1992; Murali et al. 1992). Increased PVR, particularly if not reversible with vasodilator challenge, predicts poor heart transplant outcome, mainly due to high risk of postoperative failure of the graft right ventricle that is suddenly exposed to vascular bed with elevated resistance (Murali et al. 1993).

Attenuated sensitivity to endogenous cGMP-dependent vasodilatators is increasingly recognized as one of the key mechanisms of PVR elevation (Melenovsky et al. 2009). Intracellular cGMP is catabolized by cGMP-selective phosphodiesterase 5A (PDE5A), an enzyme that is highly abundant in the lung tissue (Kass et al. 2007). Inhibitors of PDE5A, like sildenafil, induce marked pulmonary vasodilatory response in pulmonary arterial hypertension. In patients and experimental animals with HF, pulmonary tissue-PDE5A activity is further upregulated (Forfia et al. 2007) and therefore pulmonary circulation may be even more susceptible to PDE5 inhibition than systemic circulation. The goal of the study was to compare the effects of sildenafil to a standard vasodilator, routinely used in patients with HF and increased PVR for hemodynamic testing. We hypothesized that acute inhibition of PDE5A with sildenafil is expected to provide more selective pulmonary vasodilatation, than administration of high-dose of prostaglandin E$_1$ (PGE$_1$).

Methods

The study group consisted of HF patients considered for heart transplantation, but with severe pre-capillary pulmonary hypertension indicated to testing of PVR reversibility (transpulmonary pressure gradient >15 mmHg or PVR>3 w.u. in euvolemic state). Written informed consent was obtained from all subjects and the protocol was approved by the ethics committee of IKEM. Catheterization was performed via right internal jugular vein with 7F balloon-tipped pulmonary artery (PA) catheter (Corodyn, Braun AG, Germany) and bedside hemodynamic monitor (Solar 8000, GE, USA). All patients were in fasted state (>6 hours); breathed room air during the procedure and none was hypoxemic (O$_2$ saturation <90% by pulse oxymetry). Catheter position was optimized under fluoroscopic guidance. Cardiac output was measured by thermodilution and at least three measurements were averaged. Systemic blood pressure was measured with oscillometric cuff on the left arm. Hemodynamic parameters were measured after 20 minutes of rest (baseline) and after 5 minutes of continuous infusion of PGE$_1$ (alprostadil-Alprostan, Leciva, Czech Republic, infusion rate 200 ng·kg^{-1}·min^{-1}) into the central vein. After a 30minute washout period, an oral dose of sildenafil (Revatio, Pfizer, USA, dose 40 mg) was administered and measurements were repeated 1 hour later. Pulmonary vascular resistance (PVR) was calculated as transpulmonary pressure gradient (mean PA pressure − mean PA wedge pressure) divided by cardiac output and expressed as Wood´s units (w.u.). Pulmonary selectivity was quantified as the ratio of pulmonary to systemic vascular resistance (PVR/SVR). Transplantation-acceptable values were defined as transpulmonary pressure gradient $\leq$ 15 mmHg and PVR $\leq$ 3 w.u. All values are expressed as mean±SD. Drug-induced changes from baseline were compared with paired t-tests. A p-value of < 0.05 was considered as significant.

Results

The protocol included 13 subjects with symptomatic advanced HF, predominantly due to coronary artery disease. Clinical characteristics are summarized in the table 1. In medical history, 46% of subjects had diabetes, 23% had previous cardiac surgery and 54% received implantable defibrillator device. One subject had permanent atrial fibrillation. Diuretics and beta-blocking agents were administered in 100% of patients, angiotensin-converting enzyme or angiotensin-receptor inhibitors in 84%, aldosterone receptor antagonists in 77%, statins in 46%, digoxin in 23% and low-dose dobutamine in 31%. Hemodynamic parameters at baseline and after administration of both drugs are summarized in the table 2. All subjects had significant pre-capillary hypertension and were euvolemic. Baseline PVR positively correlated with systemic vascular resistance (r=0.86) and negatively with cardiac output (r=-0.67).

Administration of prostaglandin E_1 led to a significant reduction of PVR (-28%) and systemic vascular resistance (-30%), mean PA pressure, PA wedged pressure, with a simultaneous increase in cardiac index and stroke volume. There was only a trend in the reduction of transpulmonary gradient (-10%, p=0.08). The ratio of pulmonary to systemic vascular resistance (PVR/SVR ratio) did not change with PGE_1 infusion (from 0.27±0.06 to 0.28±0.08, p=0.6), indicating that PVR decreased proportionally to SVR reduction. After infusion of PGE_1, 31% of patients had transplantation-acceptable values of transpulmonary gradient and PVR. All subjects tolerated full PGE_1 dose.

Administration of 40 mg of sildenafil reduced PVR (-49%), transpulmonary pressure gradient (-36%), mean PA pressure, PA wedged pressure, systemic vascular resistance (-26%), increased cardiac index and stroke volume. PVR/SVR ratio decreased by 32% (from 0.27±0.06 to 0.19±0.08 p=0.0008, figure 2), indicating that sildenafil-induced PVR reduction was disproportionally larger than the reduction of SVR. Transplantation-acceptable values of transpulmonary gradient and PVR were attained in 69 % of patients.

Individual responses of PVR and transpulmonary pressure gradient after both interventions are summarized in figure 1 (left). The response to sildenafil was more homogenous than to PGE_1. The only person with no reduction of PVR after sildenafil had also minimal response to PGE_1. The person was treated with biventricular mechanical support to lower PVR, but unfortunately died from bleeding and postoperative right heart failure soon after heart transplantation. The reduction of PVR or transpulmonary pressure gradient after sildenafil reasonably correlated with PGE_1-induced changes, i.e. poor responders to PGE_1 also poorly responded to sildenafil (figure 1 — right panels). Sildenafil-induced change of PVR, transpulmonary pressure gradient and mean systemic blood pressure were on average significantly larger than PGE_1-induced effects. Both drugs also significantly differed in change of the PVR/SVR ratio ($p=0.001$), demonstrating a higher vasodilatatory selectivity of sildenafil in pulmonary circulation (figure 2).

Discussion

The principal finding of the study is that sildenafil produces larger dilatation in pulmonary than in systemic vascular territory, while the effects of PGE$_1$ are proportional in both vascular beds. Although the mechanisms underlying enhanced responsiveness of pulmonary vessels to sildenafil are not yet precisely delineated in patients with HF, they might be linked to higher PDE5A expression in the pulmonary than in systemic resistance arterioles. High PDE5A activity leads to desensitization of vascular wall to endogenous cGMP-dependent vasodilators, namely nitric oxide and natriuretic peptides (Forfia P et al. 2007). It has been recently shown that HF patients with high PVR have attenuated transpulmonary cGMP release that can be restored by sildenafil administration (Melenovsky et al. 2009). By acting more downstream, PDE5A inhibition induces larger pulmonary vasodilatation than provision of nitric oxide itself. Therefore, nitroglycerine or nitroprusside that have only minimal effect ($< 10\%$) on PVR/SVR ratio (Murali et al. 1991). Higher reduction of PVR than of SVR with sildenafil in HF patients has been noticed before (Allaeddini et al. 2004, Al-Hesayen et al. 2006), but our study is the first to compare sildenafil with other vasodilator.

Conversely, PGE$_1$ leads to less selective vasodilatation with only minimal change of PVR/SVR ratio and is associated with larger tendency to induce systemic hypotension. Alprostadil (PGE1) and other prostacyclin analogues are largely degraded during first passage through pulmonary circulation, but some degradation products (PGE0) also have vasodilatatory properties. If administered in high dose, prostacyclin analogues and active metabolites spill over into systemic circulation and often produce systemic hypotension (Radovancevic et al. 2005, von Scheidt et al. 2006) with unwanted sympathetic activation (Montalescot et al. 1998).

The study has several relevant clinical implications for pathophysiology and therapy of HF. If PVR elevation in chronic HF patients is not reversible by a vasodilator, the risk of acute right heart failure of transplanted graft is very high (Costard-Jackle et al. 1992). On the other hand,

patients with reversible PVR elevation have similar post-transplant outcomes as low PVR patients (Klotz et al. 2003). In our study, sildenafil showed superior ability than PGE$_1$ to unmask the reversible component of PH. Almost ¾ (73%) of patients reached a satisfactory reduction of the transpulmonary gradient, in contrast to only 31% after PGE$_1$. Therefore, hemodynamic testing of heart transplantation candidates using sildenafil seems to be a promising alternative to testing with PGE$_1$, particularly with an intravenous formulation (Al Hasayen et al. 2006). The responders could be then treated orally for the long-term, as the benefits of sildenafil on pulmonary hemodynamics seem to persist, without drug tolerance development (Lewis et al. 2007, Guazzi et al. 2007).

In chronic HF, an increased PVR due to precapillary pulmonary vasoconstriction is partly an adaptive mechanism preventing pulmonary congestion. In volume-overloaded HF patients, extensive and selective pulmonary vasodilatation (for example with inhaled nitric oxide) can increase pulmonary capillary pressure and trigger pulmonary edema (Loh E et al. 1994). Interestingly, this was not observed in our study – the average PA wedge pressure dropped after sildenafil, despite substantial pulmonary vasodilatation. This may be explained by simultaneous increase of diastolic left ventricular compliance, by an increase of stroke volume from LV afterload reduction or by attenuated interventricular diastolic interaction from unloading of the right ventricle (Morris-Thurgood et al. 2000). Increased cardiac contractility could also theoretically contribute to stroke volume augmentation, but only neutral (Lepore et al. 2005) or negative (Borlaug et al. 2005) effects on left ventricular inotropy are previously reported for sildenafil. In several short-term studies, sildenafil improved hemodynamics, quality of life and exercise tolerance (Guazzi et al. 2007) in HF patients, but the long-term safety of PDE5A inhibition in general HF population still needs to be carefully tested.

The study has several limitations. The number of studied subjects is relatively small. Due to long plasma half-life of sildenafil (3-5 hours) compared to alprostadil (5-10 minutes), the administration of drugs was not in a random order. However, both administrations were separated

by 90 minutes, which provided enough time for washout. Third, the infusion of PGE$_1$ was not titrated to maximally-tolerated dose and this may affect the rate of PVR reversibility compared to other reports (von Scheidt et al. 2006).

In conclusion, the study demonstrated that the vasodilatatory effects of sildenafil are more pronounced in pulmonary than in systemic circulation and that sildenafil had a superior ability than PGE$_1$ to unmask reversible pre-capillary component of pulmonary hypertension due to advanced heart failure.

Acknowledgements:

Reference List

ALAEDDINI J, UBER PA, PARK MH , VENTURAHO, MEHRA MR: Efficacy and safety of sildenafil in the evaluation of pulmonary hypertension in severe heart failure. *Am J Cardiol* **94**:1475-1477, 2004.

AL HESAYEN A, FLORAS JS, PARKER JD. The effects of intravenous sildenafil on hemodynamics and cardiac sympathetic activity in chronic human heart failure. *Eur J Heart Fail* **8**:864-868, 2006

BORLAUG BA, MELENOVSKY V, MARHIN T, FITZGERALD P, KASS DA: Sildenafil inhibits beta-adrenergic-stimulated cardiac contractility in humans. *Circulation* **112**:2642-2649, 2005

COSTARD-JACKLE A, FOWLER MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. *J Am Coll Cardiol* **19**:48-54, 1992

DI SALVO TG, MATHIER M, SEMIGRAN MJ, DEC GW: Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. *J Am Coll Cardiol* **25**:1143-1153, 1995.

FORFIA PR, LEE M, TUNIN RS, MAHMUD M, CHAMPION HC, KASS DA:. Acute phosphodiesterase 5 inhibition mimics hemodynamic effects of B-type natriuretic peptide and potentiates B-type natriuretic peptide effects in failing but not normal canine heart. *J Am Coll Cardiol* **49**:1079-1088, 2007

GHIO S, GAVAZZI A, CAMPANA C, INSERRA C, KLERSY C, SEBASTIANI R, ARBUSTINI E, RECUSANI F, TAVAZZI L: Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol* **37**:183-188, 2001

GOLDSMITH SR. Type 5 phosphodiesterase inhibition in heart failure: the next step. *J Am Coll Cardiol* **50**:2145-2147, 2007

GUAZZI M, SAMAJA M, ARENA R, VICENZI M, GUAZZI MD: Long-term use of sildenafil in the therapeutic management of heart failure. *J Am Coll Cardiol* **50**:2136-2144, 2007

KASS DA, CHAMPION HC, BEAVO JA. Phosphodiesterase type 5: expanding roles in cardiovascular regulation. *Circ Res* **101**:1084-1095, 2007

KLOTZ S, DENG MC, HANAFY D, SCHMID C, STYPMANN J, SCHMIDT C, HAMMEL D, SCHELD HH: Reversible pulmonary hypertension in heart transplant candidates—pretransplant evaluation and outcome after orthotopic heart transplantation. *Eur J Heart Fail* **5**:645-653, 2003

LEPORE JJ, MAROO A, BIGATELLO LM, DEC GW, ZAPOL WM, BLOCH KD, SEMIGRAN MJ: Hemodynamic effects of sildenafil in patients with congestive heart failure and pulmonary hypertension: combined administration with inhaled nitric oxide. *Chest* **127**:1647-1653, 2005

LEWIS GD, SHAH R, SHAHZAD K, CAMUSO JM, PAPPAGIANOPOULOS PP, HUNG J, TAWAKOL A, GERSZTEN RE, SYSTROM DM, BLOCH KD, SEMIGRAN MJ: Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation* **116**:1555-1562, 2007

LOH E, STAMLER JS, HARE JM, LOSCALZO J, COLUCCI WS. Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. *Circulation* **90**:2780-2785, 1994

MELENOVSKY V, AL-HITI H, KAZDOVA L, JABOR A, SYROVATKA P, MALEK I, KETTNER J, KAUTZNER J. Transpulmonary B-type natriuretic peptide uptake and cyclic guanosine monophosphate release in heart failure and pulmonary hypertension: the effects of sildenafil. *J Am Coll Cardiol*. **54:** 595-600, 2009

MONTALESCOT G, DROBINSKI G, MEURIN P, MACLOUF J, SOTIROV I, PHILIPPE F, CHOUSSAT R, MORIN E, THOMAS D: Effects of prostacyclin on the pulmonary vascular tone and cardiac contractility of patients with pulmonary hypertension secondary to end-stage heart failure. *Am J Cardiol* **82**:749-755, 1998

MORRIS-THURGOOD JA, FRENNEAUX MP. Diastolic ventricular interaction and ventricular diastolic filling. *Heart Fail Rev* **5**:307-323, 2000

MURALI S, KORMOS RL, URETSKY BF, SCHECHTER D, REDDY PS, DENYS BG, ARMITAGE JM, HARDESTY RL, GRIFFITH BP: Preoperative pulmonary hemodynamics and early mortality after orthotopic cardiac transplantation: the Pittsburgh experience. *Am Heart J* **126**:896-904, 1993

MURALI S, URETSKY BF, ARMITAGE JM, TOKARCZYK TR, BETCHART AR, KORMOS RL, STEIN KL, REDDY PS, HARDESTY RL, GRIFFITH BP: Utility of prostaglandin E1 in the pretransplantation evaluation of heart failure patients with significant pulmonary hypertension. *J Heart Lung Transplant* **11**:716-723, 1992

MURALI S, URETSKY BF, REDDY PS, TOKARCZYK TR, BETSCHART AR: Reversibility of pulmonary hypertension in congestive heart failure patients evaluated for cardiac transplantation: comparative effects of various pharmacologic agents. *Am Heart J* **122**:1375-1381, 1991

RADOVANCEVIC B, VRTOVEC B, THOMAS CDCROITORU M, MYERS TJ, RADOVANCEVIC R, KHAN T, MASSIN EK, FRAZIER OH: Nitric oxide versus prostaglandin E1 for reduction of pulmonary hypertension in heart transplant candidates. *J Heart Lung Transplant* **24**:690-695, 2005

VON SCHEIDT W, COSTARD-JAECKLE A, STEMPFLE HU, DENG MC, SCHWAAB B, HAAFF B, NAEGELE H, MOHACSI P, TRAUTNITZ M: Prostaglandin E1 testing in heart failure-associated pulmonary hypertension enables transplantation: the PROPHET study. *J Heart Lung Transplant* **25**:1070-1076, 2006
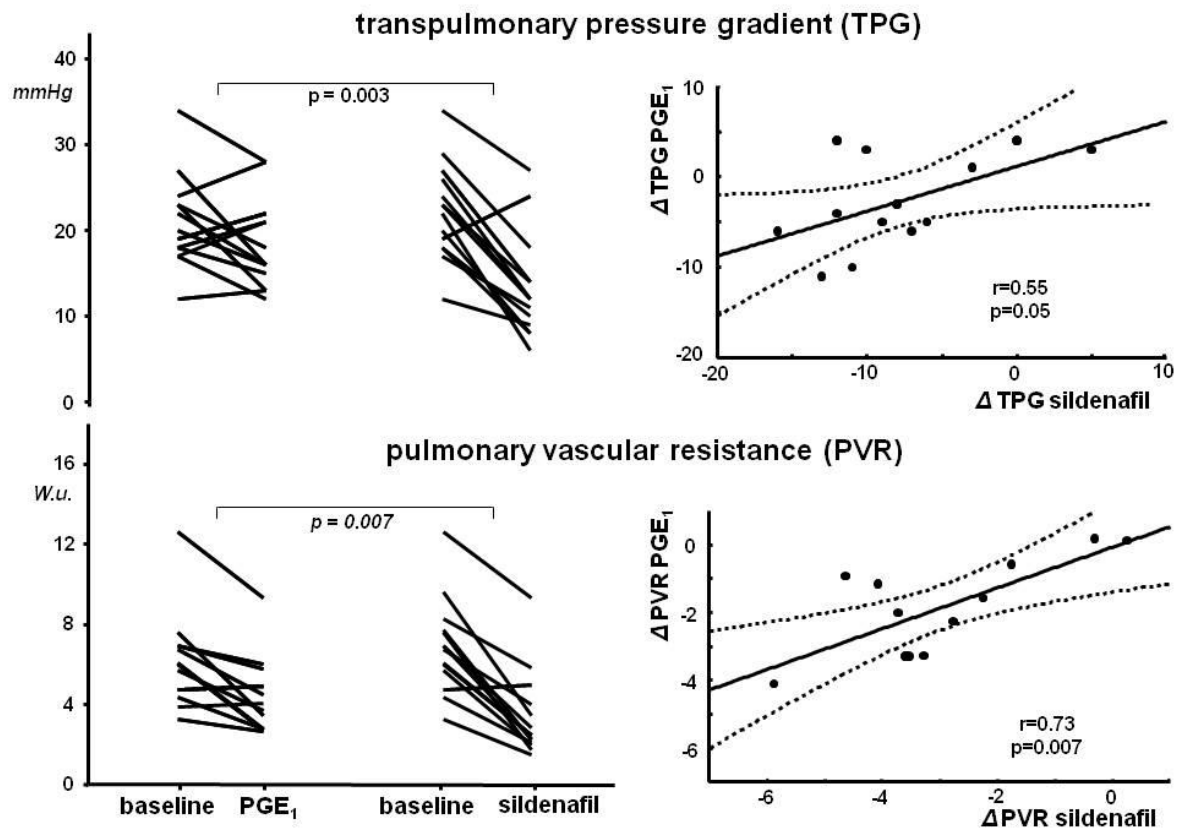
Figures

Figure 1. Left: Individual responses of transpulmonary pressure gradient and pulmonary vascular resistance (PVR) to administration of prostaglandin E$_1$ (at rate 200 ng·kg^{-1}·min^{-1} i.v.) or sildenafil (40 mg orally) in patients with heart failure and pulmonary hypertension.

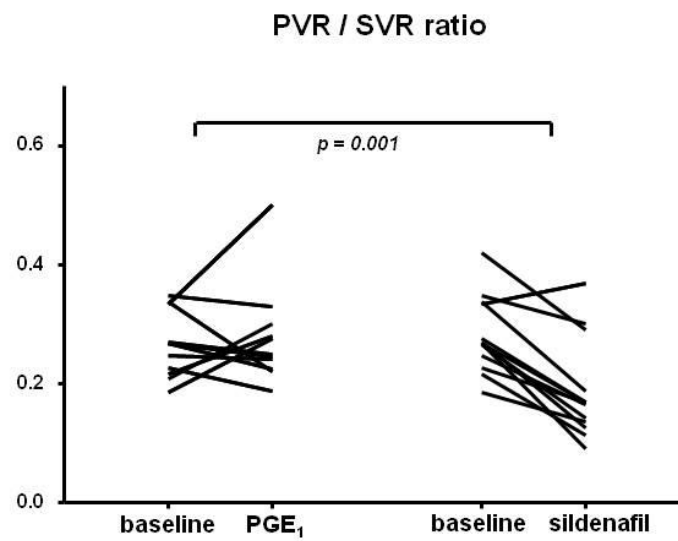Right: correlation between change (Δ) of transpulmonary pressure gradient or PVR induced by sildenafil or PGE$_1$.

Figure 2. Ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR) – an index of pulmonary selectivity of vasodilatation, before and after administration of sildenafil (40 mg orally, right panel) or prostaglandin E_1 (200 ng·kg^{-1}·min^{-1} i.v., left panel) in patients with advanced heart failure and pre-capillary pulmonary hypertension.

Table 1. Baseline characteristics (n=13)

Age, *years*	51 ± 12
Gender, m/f,*n*	10 / 3
Body mass index, *kg·m⁻²·*	27 ± 3.5
Etiology: CAD / DCM, *n*	10 / 3
NYHA functional class	2.7 ± 0.6
MLHFQ score	43 ± 22
Furosemide daily dose, *mg*	101 ± 60
Hemoglobin, *g ·l⁻¹*	133 ± 17
Serum creatinine, *μmol ·l⁻¹*	104 ± 21
Plasma BNP, *ng ·l⁻¹*	887 ± 686
LV ejection fraction, *%*	24 ± 4
LV end-diastolic diameter, *mm*	69 ± 6.2
Right atrial pressure, *mmHg*	8.2 ± 2.7
Systemic blood pressure – systolic/diastolic, *mmHg*	120 ± 15 / 70 ± 9

BNP: B-type natriuretic peptide, CAD: coronary artery disease, DCM: dilated cardiomyopathy, LV: left ventricle, MLHFQ: Minnesota Living with Heart Failure Questionnaire, NYHA: New York Heart Association.

Table 2. Hemodynamic parameters (n=13)

	rest	Δ PGE$_1$	Δ sildenafil	P ‡
Heart rate, *min^{-1}*	78 ± 13	1.8 ± 7	- 8.5 ± 9	*0.09*
PA mean pressure, *mmHg*	47 ± 6	- 8.5 ± 9 †	-11 ± 7 †	*0.4*
PA wedged pressure, *mmHg*	26 ± 4	- 5.8 ± 7 †	- 3.2 ± 5 *	*0.3*
Transpulmonary gradient, *mmHg*	21 ± 5	- 2.7 ± 5	- 8 ± 6 †	***0.02***
Cardiac index, *l·min^{-1}·m^{-2}*	1.7 ± 0.3	0.5 ± 0.3 †	0.5 ± 0.4 †	*0.9*
Stroke volume, *ml*	46 ± 12	8.1 ± 8 †	15 ± 9 †	*0.07*
Pulmonary vascular resistance, *w.u.*	6.3 ± 2	- 1.8 ± 1 †	- 3.2 ± 2 †	***0.05***
PVR / SVR	0.27 ± 0.05	0.01 ± 0.08	- 0.08 ± 0.06 †	***0.004***
Systemic vascular resistance, *w.u.*	24 ± 7	- 6.7 ± 3 †	- 6.5 ± 4.5 †	*0.8*
Mean systemic arterial pressure, *mmHg*	80 ± 9	- 12 ± 3.5 †	- 6.6 ± 8 *	***0.04***

All comparisons by paired t-tests: * p<0.05, † p<0.01 vs baseline. ‡ comparisons of changes (Δ). PA: pulmonary artery, w.u.: Wood´s units. PVR: pulmonary vascular resistance, SVR: systemic vascular resistance