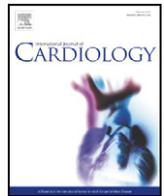




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The effects of phosphodiesterase 5 inhibition on hemodynamics, functional status and survival in advanced heart failure and pulmonary hypertension: A case–control study[☆]

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ABSTRACT

Background: The goal was to examine the hemodynamic and clinical effects of long-term therapy with PDE5 inhibitor sildenafil (SILD) in patients with advanced, pre-transplant heart failure (HF) and severe pulmonary hypertension (PH), in comparison to a similar control group (CON).

Methods: In this non-randomized, retrospective case–control study, 32 middle-aged patients (81% males) with advanced systolic HF (80% ≥ NYHA III, 56% ischemic) and severe pre-capillary PH (transpulmonary pressure gradient > 15 mm Hg) were studied before and after initiation of SILD (dose 73 ± 25 mg/day) and were compared to 15 CON patients, matched for key clinical characteristics (including PH severity, age and co-morbidities), not exposed to SILD. Changes at 3 months and the long-term outcome were compared between groups.

Results: SILD significantly reduced pulmonary vascular resistance (–32% vs. baseline), transpulmonary gradient (–25%) and increased cardiac output (+15%) compared to controls, without affecting systemic or ventricular filling pressures. SILD-treated subjects experienced an improvement in NYHA class and had a steady body weight which contrasted with significant weight loss in the CON group (by –4.8%, absolutely by 4.3 ± 6 kg). During follow-up (median 349 days from baseline), 60% of patients underwent heart transplantation. Two patients in CON group had severe post-transplant failure of the right ventricle, none in SILD group. Overall pre- and peritransplant survival (censored 30 days after transplantation) was significantly better in SILD than CON group (93.7 vs 60%, $p=0.0048$).

Conclusions: In patients with advanced HF and severe PH, SILD therapy has beneficial effects on hemodynamics, clinical status, cardiac cachexia, and contributes to improved peri-transplant survival.

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1. Introduction

Pulmonary hypertension (PH) develops in 60% of patients with moderate-to-severe heart failure (HF) [1,2] and is predominantly a consequence of elevated left atrial pressure transmitted backward into pulmonary circulation. However, structural remodelling [3] and endothelial dysfunction [4,5] in the pulmonary vascular tree result in an increase of pulmonary vascular resistance in some HF patients, leading to severe PH that is “out-of proportion” to left atrial pressure. By overloading the right ventricle, PH causes right ventricular dysfunction

and promotes the transition of left heart disease into biventricular failure which has high mortality [2]. Increased pulmonary vascular resistance, particularly if not reversible with a vasodilator challenge, is a crucial predictor of poor results of heart transplantation [6]. The underlying cause of such an adverse outcome is mainly acute post-transplant failure of the right ventricle of the graft suddenly exposed to vascular bed with elevated resistance [6]. Management of PH in the heart transplant candidates is therefore an issue of a critical importance.

Experimental animal studies have demonstrated that phosphodiesterase 5 (PDE5) is upregulated in the pulmonary vasculature in the HF state [7]. The inhibition of PDE5 enhances attenuated cGMP signalling and causes pulmonary vasodilatation in patients with HF and PH [5]. In several small clinical studies, long-term therapy with PDE5 inhibitor sildenafil was shown to decrease pulmonary vascular resistance, increase right ventricular function and improve exercise tolerance in patients with moderate heart failure without having serious adverse effects [8,9]. Based on these positive preliminary findings, many heart transplant centers adopted off-label use of sildenafil in

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selected heart transplant candidates with severe PH as a salvage approach to achieve transplantability [10–14], despite the fact that long-term, randomized outcome studies are not available. In this study, we report on the hemodynamics and clinical course of the largest ever-published cohort of sildenafil-treated advanced HF patients and severe PH who are compared to similar control patients without PDE5 inhibitor therapy.

2. Materials and methods

This single-center, retrospective, non-randomised case–control analysis enrolled patients with advanced HF due to LV systolic dysfunction (EF<40%) who were referred for pre-transplant evaluation to the Institute for Clinical and Experimental Medicine in Prague (IKEM). At IKEM, 40–50 heart transplantations are performed annually with a total of >847 transplanted hearts since 1984. Patients in euvoletic hemodynamic state (right atrial pressure <10 mm Hg) with severe pre-capillary component of pulmonary hypertension (transpulmonary pressure gradient >15 mm Hg), regardless its acute reversibility, were offered sildenafil (SILD) therapy (sildenafil citrate p.o. 20–60 mg 3× daily, Revatio tbl., Pfizer) as an adjunct to optimized medical therapy to enable the patient's enrollment on waiting list and to maintain transplantability. From 36 subjects initiated on SILD (since 11/2007 till 7/2011), three patients underwent heart transplant before follow-up catheterization, one patient discontinued SILD due intolerance (leg swelling) and the remaining 32 patients were enrolled in the present analysis (SILD group).

Control group (CON) consisted of similar but earlier HF patients not exposed to SILD due to drug unavailability (since 12/2000 till 10/2010) who were selected to match baseline characteristics of the SILD group (gender, age, body composition, HF aetiology, cardiac output, volume status, pulmonary vascular resistance, medication) by a researcher unaware of follow-up data. The patients signed informed consents and the examination was approved by local ethics committee. The authors of this manuscript have certified that they comply with ethical guidelines of the 1975 Declaration of Helsinki and the Principles of Ethical Publishing in the International Journal of Cardiology [15].

At baseline, all patients underwent clinical, biochemical (BNP, Abbott-Architect CMIA), echocardiographic (Vivid 7, GE, USA) examinations and right heart catheterization using a Swan-Ganz catheter (Corodyn TDI, B Braun, Germany) via right internal jugular vein and 7 F sheath. Cardiac output was measured in triplicate by thermodilution and systemic BP was measured by non-invasive oscillometric method. All patients were re-examined after 3 months. In between, subjects were followed by cardiologists at IKEM and the diuretic dose was adjusted to clinical needs. After re-assessment at 3 months, patients were maintained on SILD till heart transplantation, including those who also received ventricular assist device (VAD). Sildenafil was usually tapered off the medication within a month after successful heart transplantation. To assess the impact on sildenafil survival, mortality was ascertained in all subjects by querying medical records and the survival was examined by Kaplan-Meier plots and Log-Rank test. Because mortality due to PH-related right-heart failure of the graft is not immediate, peri-transplant survival was censored 30 days after heart transplantation. All continuous variables are presented as mean ± SD in the tables and as mean ± SE in the figures. Unpaired t-test was used to test between-group difference in a change of the variable (Δ 3 months – baseline). Due to skewed distribution, BNP values were log-transformed before statistical testing. To demonstrate similar baseline risk in both groups, Seattle HF model was used to estimate probability of survival at 1 and 5 years [16]. Pearson's r was calculated for testing of correlations. Two sided p-value of <0.05 was considered as significant.

3. Results

Baseline characteristics are summarized in the Table 1. Due to the study design, both SILD and CON groups had an identical clinical and hemodynamic profile.

3.1. Effects on hemodynamics, body weight and clinical status after 3 months

Patients were re-evaluated after 101 ± 34 days. SILD was well tolerated and there were no serious adverse effects. Daily dose of SILD at re-evaluation was 73 ± 25 mg, with dosing 20 mg 3× daily in 72% and 40 mg 3× daily in 28% of patients. Changes in the hemodynamics from the resting state are summarized in Fig. 1. After 3 months, there was no significant change in right atrial pressure (Δ SILD: -0.03 ± 4.5 vs Δ CON: -0.93 ± 4.3 mm Hg, $p=0.52$), pulmonary capillary wedge pressure or heart rate (Δ SILD: -3.8 ± 12.4 , Δ CON: 1.6 ± 17 min⁻¹, $p=0.22$). In the SILD group, patients experienced significant 32 % reduction of pulmonary vascular resistance against baseline, 25% reduction of transpulmonary pressure gradient, 15% increase in cardiac output and a trend to lower of mean PA pressure compared to CON. The increase in cardiac output in SILD was driven by significant increase

Table 1

Baseline characteristics of sildenafil-treated and matched control group of patients with advanced heart failure and severe pulmonary hypertension.

	SILD-group n=32	CON-group n=15	p
Clinical characteristics			
Age, years	50.4 ± 10.2	55.5 ± 5.5	0.1
Gender – males/females, %	81 / 19	100 / 0	0.1
HF aetiology – ischemic/non-ischemic, %	56 / 44	60 / 40	0.7
NYHA class	3.1 ± 0.6	3.0 ± 0.4	0.4
NYHA II/III/IV, %	9 / 72 / 19	7 / 87 / 7	0.4
ICD, %	62 %	53 %	0.6
Body mass index, kg.m ⁻²	27 ± 4.1	28.4 ± 4.4	0.4
Diabetes mellitus, %	19	27	0.9
Serum creatinine, μmol/l	101 ± 27	114 ± 29	0.1
B-type natriuretic peptide, ng/l	1116 ± 807	986 ± 461	0.6
Haemoglobin, g.l ⁻¹	140 ± 21	142 ± 14	0.8
Seattle HF model			
Estimated 1-year survival, %	88 ± 8.5	88 ± 8.2	0.8
Estimated 5-year survival, %	59 ± 20	56 ± 20	0.7
Echocardiography			
LV ejection fraction, %	22 ± 3.6	22 ± 2.5	0.8
LV end-diastolic diameter, mm	75 ± 5.6	72 ± 8.7	0.3
RV end-diastolic diameter, mm	40.8 ± 8.5	36.9 ± 6.3	0.2
RV dysfunction grade, (0–5)	2.9 ± 0.9	3.3 ± 0.6	0.2
HF pharmacotherapy			
Furosemide, mg/day	110 ± 78	105 ± 87	0.8
ACE or AR inhibitor use, %	81	93	0.2
Beta-blocker use, %	97	94	0.9
Hemodynamic data			
Systolic systemic pressure, mm Hg	108 ± 12	106 ± 13	0.7
Diastolic systemic pressure, mm Hg	76 ± 9	71 ± 12	0.2
Heart rate, min ⁻¹	84 ± 12	78 ± 13	0.2
Right atrial pressure, mm Hg	8.3 ± 3.1	7.4 ± 2.9	0.3
PA mean pressure, mm Hg	47 ± 6.7	43 ± 6	0.8
PA pulse pressure, mm Hg	41 ± 11.9	43.9 ± 7.8	0.1
PA capillary wedge pressure, mm Hg	27.8 ± 6	27 ± 4.2	0.4
Transpulmonary gradient, mm Hg	19.2 ± 5.7	16.1 ± 5.3	0.1
Cardiac output, l.min ⁻¹	3.6 ± 0.8	3.9 ± 0.8	0.2
Pulmonary vascular resistance-PVR, WU	5.5 ± 1.9	4.4 ± 2.2	0.1
Systemic vascular resistance-SVR, WU	22.7 ± 5.3	19.9 ± 4.9	0.1
PVR/SVR ratio	0.25 ± 0.07	0.22 ± 0.09	0.3

NYHA: New York Heart Association functional class, HF: heart failure, PA: pulmonary artery, WU: Wood's Units; ICD: implantable cardioverter–defibrillator, ACE: angiotensin converting enzyme, AR: angiotensin-II receptor. Values are means ± SD, T-test or chi-square test used for comparisons. Seattle Heart Failure score was calculated according to Levy et al. (Ref. [16]). LV: left ventricular, RV: right ventricular.

stroke volume (Δ SILD: 8.9 ± 12 , Δ CON: -2.6 ± 17 ml, $p=0.01$). Systemic vascular resistance was also significantly reduced but to lesser extent (-12.2%) than pulmonary vascular resistance. No significant changes to systemic blood pressure (systolic BP, Δ SILD: 1.1 ± 13 , Δ CON: 1.7 ± 12 mm Hg, $p=0.89$; diastolic BP, Δ SILD: -1.9 ± 13 , Δ CON: 3.3 ± 12 mm Hg, $p=0.08$) were observed. The ratio of pulmonary to systemic vascular resistance (PVR/SVR ratio) decreased in SILD-treated patients, while there was no change in the CON group (Δ SILD: -0.06 ± 0.09 , Δ CON 0.00 ± 0.07 , $p=0.04$). There were no significant differences in hemodynamic response to SILD between patients with ischemic and non-ischemic aetiology of HF.

Interestingly, SILD-treated patients maintained a steady body weight (BW) as compared with CON group in which body weight decreased (by -4.8% , absolutely by 4.3 ± 6 kg, Fig. 2A). Significant body weight loss (weight loss >6%) [17] was observed in 40% of CON and only 6 % of SILD group. Body weight change in the entire cohort did not correlate with the change of furosemide daily dose; however, it inversely correlated with the change of mean PA pressure ($r=-0.32$, $p=0.02$), PA wedge pressure ($r=-0.37$, $p=0.01$) and mean right atrial pressure ($r=-0.29$, $p=0.05$; Fig. 2C). No significant difference

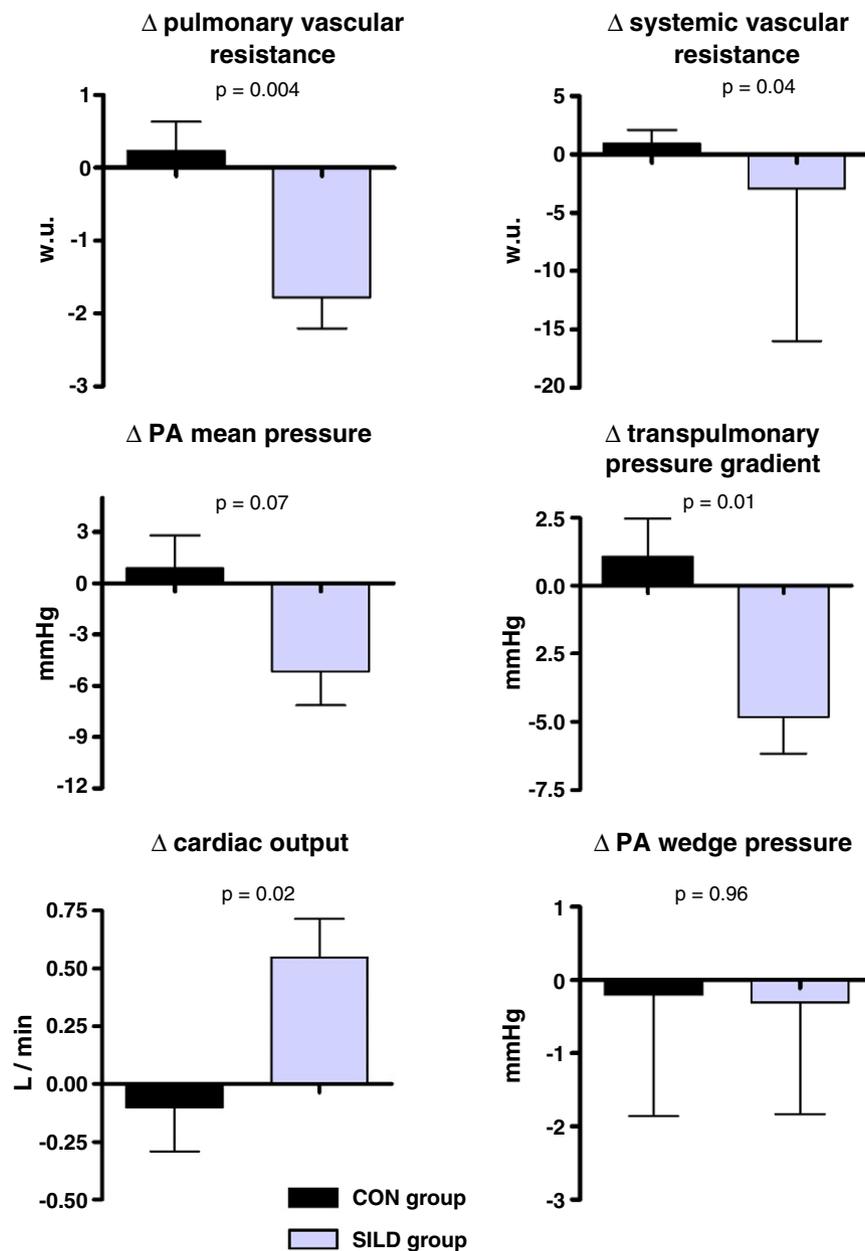


Fig. 1. Hemodynamic changes (Δ) after three months from baseline examination in SILD-treated patients (grey) and CON-patients (black) with advanced heart failure and severe pulmonary hypertension. Between-group differences of changes within groups are compared with unpaired t-test. WU: Wood's Units. PA: pulmonary artery.

was observed in changes in right ventricular (RV) size ($p=0.07$) and systolic dysfunction ($p=0.6$), tricuspid regurgitation grade ($p=0.69$), haemoglobin concentration ($p=0.17$) and serum creatinine concentration ($p=0.72$). Furosemide daily dose showed a trend toward an increase in the CON group (Fig. 2B).

In the SILD group, 31% of patients presented with an improvement, 66% had no change and only 3% had worsening of NYHA class. In the CON group, only 7% of patients had an improvement, 80% had no change and 13% had worsening of NYHA class (Fig. 3). The average change in NYHA class differed significantly between both groups (Δ SILD -0.3 ± 0.5 vs. Δ CON $+0.1 \pm 0.5$, $p<0.01$). SILD-treated patients had also a decrease in plasma BNP levels compared to CON (Fig. 2B).

3.2. Effects on long-term outcome

Median follow-up time since baseline examination reached 349 days (IQR: 226–625) in the SILD group and 408 days (IQR: 229–857) in the

CON group ($p=0.95$, Mann-Whitney U test). Overall pre-transplant and peri-transplant survival (censored 30 days after the transplantation) was significantly better in the SILD group than in the CON group (93.8% vs. 60%, $p=0.0048$, Fig. 4). In the SILD group, two patients died before transplantation. Nineteen patients (59%) underwent successful heart transplantation and all of them lived at 30 days after the procedure. Three of them (9.4%) had pre-transplant ventricular assist device (VAD) implanted as bridge-to-transplant (left-VAD in all cases) and continued on sildenafil. Remaining eleven subjects of SILD group were either delisted or still on transplant waiting list (2 of them on left-VAD). No patient needed post-transplant VAD for right ventricular failure.

In the CON group, four patients died before transplantation. None of the CON patients obtained pre-transplant VAD bridging. Nine patients (60%) underwent transplantation and two died within 30 days after the procedure. Two transplanted patients needed right-VAD for post-transplant failure of the right ventricle.

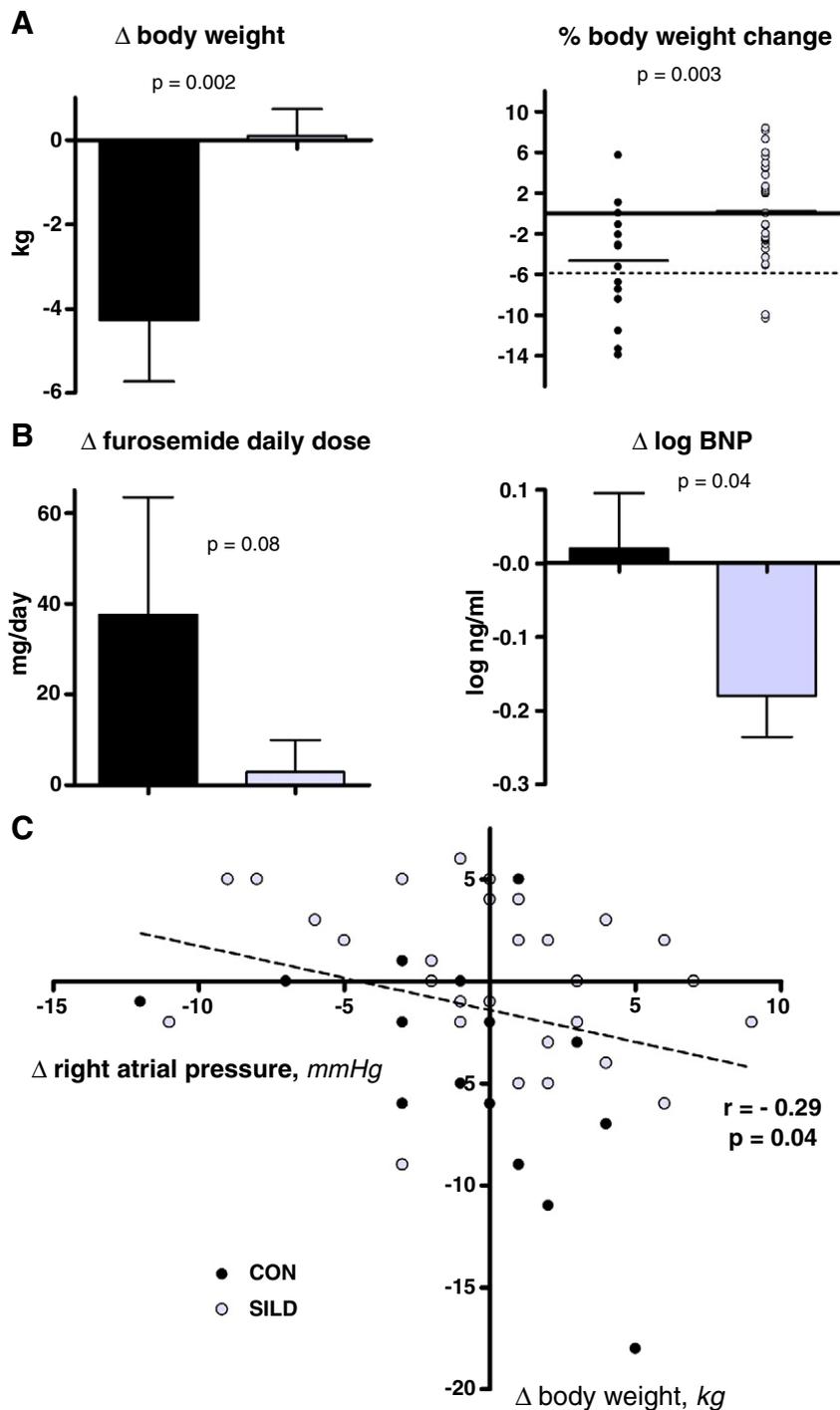


Fig. 2. A–B) Clinical characteristics after three months from baseline examination in SILD-treated patients (grey) and CON-patients (black) with advanced heart failure and severe pulmonary hypertension. Dotted line (A right) denotes prognostically relevant weight loss in HF [17]. C) Correlation between changes (Δ) of body weight and right atrial pressure during right heart catheterization.

4. Discussion

Although several recent case-series have reported the effectiveness of PDE5 inhibition in the management of patients with advanced HF and severe PH [10–12], this is the first study that compares the clinical outcome of SILD-treated patients with control patients of similar clinical profile. This is an important point, since the “clinical stabilization effect” of chronic PDE5 inhibition may become apparent only when contrasted to a sliding clinical status of the control group. Three months of sildenafil treatment led to a substantial hemodynamic effect characterized by the reduction of pulmonary vascular resistance and the increase of

cardiac output, without altering pulmonary artery wedge pressure or systemic blood pressure. These favourable hemodynamic changes were associated with an improvement in NYHA class and a preservation of body weight in the SILD-treated patients. In contrast, the CON population presented with body weight loss and more frequent clinical worsening. Finally, the pre and peritransplant survival was significantly better in the SILD group than in the CON patients with advanced HF and PH of similar severity.

The beneficial effects of SILD on hemodynamics were reported recently in several small placebo-controlled studies in patients with moderate systolic [8,9] or diastolic heart failure [18]. In this study, SILD

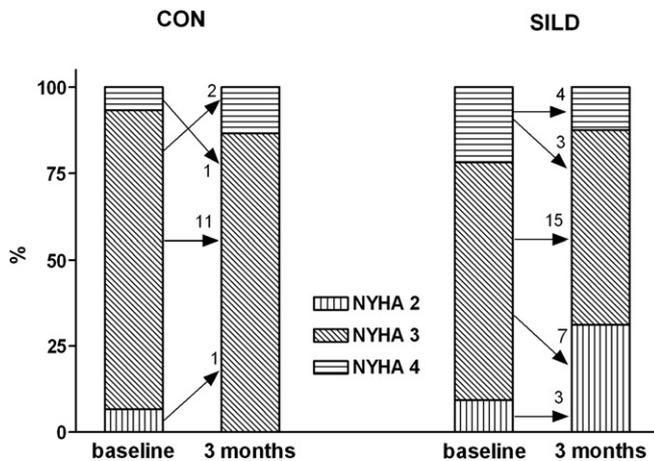


Fig. 3. New York Heart association (NYHA) functional categories in SILD-treated patients (right) and CON patients at baseline and after 3 months.

reduced pulmonary vascular resistance by 32% and transpulmonary pressure gradient by 25%. Due to the increase of cardiac output, the net effect of SILD on mean pulmonary artery pressure was only marginal, as reported elsewhere [9]. The effects of SILD on pulmonary vasculature are mediated by improving endothelial function and cGMP-dependent signalling [5], but also by alleviation of structural remodelling of pulmonary vessels due to presence of HF [3,19].

Similarly to other clinical reports [5,8,9,20], sildenafil therapy in HF was not associated with an increase in left ventricular filling pressure. In contrast to highly-selective pulmonary vasodilators like high-dosed inhaled nitric oxide [21], SILD-induced reduction of pulmonary vascular resistance is not associated with overloading of the left heart, likely due to simultaneous augmentation of stroke volume and cardiac output, observed also in other studies [5,9]. The increase in stroke volume can be explained by an improvement of left ventricular filling from SILD-enhanced diastolic ventricular compliance [22], by diminished inter-ventricular interaction from unloading of the right ventricle [23] or by reduced afterload imposed on the left ventricle [24]. The possibility of increased contractility after PDE5 inhibition, particularly in the hypertrophied right ventricle has been proposed [25], but so far has not supported by in-vivo clinical investigations [26,27]. We were not able to demonstrate any effects on right ventricular size and function, but we may have missed the effects due to a type II error and higher variability of measurements.

Interestingly, we observed body weight reduction in CON subjects, but this weight loss was prevented in SILD-treated patients. Despite the trend towards an increase of furosemide daily dosage in the CON group over the course of study, the observed body weight loss

cannot be explained by more intense diuresis as both groups patients stayed compensated (mean right atrial pressure <10 mm Hg) at the time of both hemodynamic examinations. Moreover, we observed an inverse relation between change of right atrial pressure and change of body weight, i.e. patients with the largest weight loss had actually an increase in volume load. Observed body weight loss thus most likely reflects cardiac cachexia that is frequent in advanced HF and is associated with dismal prognosis. In the SOLVD trial, body weight loss $\geq 6\%$ was the strongest predictor of death (adjusted hazard ratio of 2.1) [17], highlighting the relevance of our observation. Weight stabilization effects of SILD could be explained by mitigating right heart failure that is closely linked to cachexia [28], by an alleviation of neurohumoral activation or by direct anti-cachectic effects of PDE5 inhibitors. In experimental animals, both acute [29] and chronic [30] PDE5 inhibition potentiates vascular and metabolic action of insulin in skeletal muscle, suggesting that HF-induced insulin resistance and hypercatabolism may be affected by sildenafil. The potential anti-catabolic effects of SIL therapy in advanced HF deserves further investigations.

In agreement with studies showing improvement of exercise capacity after extended SILD therapy in moderate HF [8,31,32], we also observed improvement in NYHA functional class in our patients in a more advanced stage of the disease. We were not able to identify any hemodynamic change that would significantly correlate with NYHA change, suggesting that the improvement of clinical status after PDE5 inhibition in HF is due to complex action on pulmonary circulation, kidney and myocardium [7], rather than influencing a single target.

Despite the beneficial effects of SILD on hemodynamic and clinical surrogates, the overall impact on mortality in HF has been uncertain due to possibility of unwanted inotropic stimulation of failing myocardium by PDE5 inhibitors [25]. In this study, we were able to demonstrate lower long-term mortality in SILD-treated patients with advanced HF and PH, with lower incidence of severe post-transplant right heart failure, although more frequent VAD use can also contribute to better survival.

The limitations of this study are its retrospective character and the absence of randomization. Therefore, observations could be influenced by selection bias. We tried to minimize it by careful matching of baseline variables of both groups, blinded of future outcomes. In addition, we were not able to analyze hemodynamic measurements beyond a three month period due to highly variable trajectories of individual patients. Survival benefit in the SILD group cannot be ascribed solely to PDE5 inhibitors, but also to more aggressive PH management in that group that included more often LVAD implantation to bridge patients to transplantation. We were not able to separate these effects in our analysis.

In conclusion, our study indicates that therapy with PDE5 inhibitors in patients with advanced HF and severe PH has beneficial effect on hemodynamics, clinical status and body weight loss due to cardiac cachexia. Aggressive management of PH with sildenafil and left heart unloading with LVAD seems to favourably affect mortality in these patients. However, this needs to be confirmed in a randomized, outcome-based clinical study.

Conflict of interest

Dr. Kautzner is a member of Advisory Board for GE Healthcare. Otherwise, there are no relationships with industry posing a conflict of interest in this paper.

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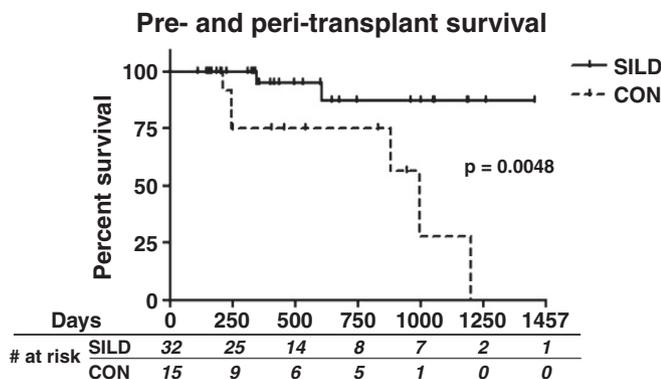


Fig. 4. Kaplan-Meier plots of pre- and peri-transplant survival (censored at 30 days after transplantation) since baseline examination in SILD-treated and control (CON) groups. Log-rank test used for comparison.

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