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SHORT COMMUNICATION

Phosphodiesterase-5 inhibitors for left ventricular assist device implantation complicated by right ventricular failure

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Abstract

Aims Phosphodiesterase-5 inhibitors (PDE5I) are frequently implemented after left ventricular assist device (LVAD) implantation to improve haemodynamics in patients with early postoperative right ventricular (RV) failure. It is unknown if long-term PED5I therapy beyond the early post-operative period provides any clinical benefit in stable outpatients, who have recovered from post-operative RV failure under univentricular device support. This study aimed to investigate the impact of PDE5I discontinuation on RV function and cardiopulmonary exercise capacity in patients on durable LVAD support.

Methods and results We enrolled 31 clinically stable LVAD recipients on long-term oral PDE5I therapy. The mean age was 53 years, and 90% were male. Patients discontinued PDE5I and underwent cardiopulmonary exercise testing, echocardiography, LVAD interrogation, and biomarker analysis at baseline and 4 weeks after PDE5I withdrawal. At 4 weeks, no significant changes were observed in echocardiographic indices of RV morphology and function but an increase in peak tricuspid regurgitation velocity (2.1 vs. 2.4 m/s, $P = 0.01$). Peak oxygen consumption (11.4 vs. 11.8 mL/min/kg, $P = 0.52$), minute ventilation/carbon dioxide production slope (33 vs. 35, $P = 0.56$), N-terminal pro-brain natriuretic peptide (1455 vs. 1399 pg/mL, $P = 0.55$), flow and power readings of the device, and quality of life (Kansas City Cardiomyopathy Questionnaire score 78.3% vs. 77.5%, $P = 0.62$) exhibited no significant changes. We observed an increase in 6-min walking distance (346 vs. 364 m, $P = 0.03$). Two patients were hospitalized for non-cardiac reasons (subtherapeutic INR, driveline infection). No patient was hospitalized for cardiac decompensation.

Conclusions In LVAD patients with a history of early post-operative RV failure, discontinuation of long-term PDE5I therapy was not associated with deterioration of RV function, exercise capacity, and quality of life. PDE5I should be critically evaluated until more evidence regarding the net clinical benefit of this pharmacologic intervention becomes available.

Keywords Mechanical circulatory support; Right ventricle; Pulmonary hypertension; Phosphodiesterase-5 inhibitors

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Background

Phosphodiesterase-5 inhibitors (PDE5I) after left ventricular assist device (LVAD) implantation are recommended by current guidelines for persistent pulmonary hypertension (PH) despite ventricular unloading (class IIb, level of evidence C). This is based on retrospective studies that demonstrated reduction of pulmonary artery (PA) pressure and pulmonary vascular resistance (PVR) in LVAD recipients receiving sildenafil.[1] Despite lack of robust evidence, long-term PDE5I therapy beyond the post-operative period is reported in up to 69% of LVAD recipients[2–4] and mainly aims at treating or

preventing right ventricular (RV) failure.[5] Lately, controversial data regarding PDE5I were published, causing both enthusiasm and caution, because their use was associated with improved survival and lower rates of LVAD thrombosis but also with increased bleeding risk.[6–8] Considering the incremental costs and the unclear net clinical benefit, there is an urgent need to investigate the utility of PDE5I in this clinical context.

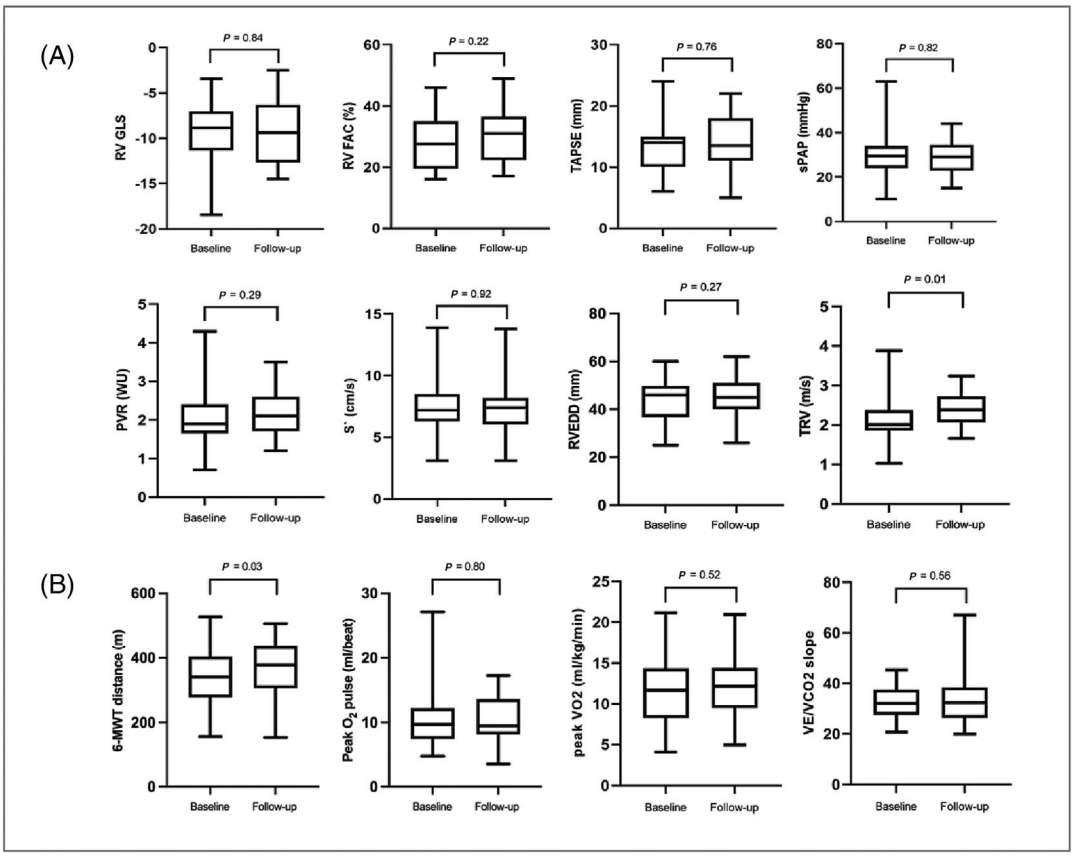
Aims

The PDE5I after LVAD implantation complicated by post-operative RV failure (PIVAD) study is a prospective, single-arm, interventional study aiming to evaluate RV function, exercise capacity, and quality of life (QoL) before and after discontinuation of PDE5I in LVAD patients who have recovered from post-operative RV failure.

Methods

The study included LVAD recipients on long-term PDE5I therapy that had been initiated due to early post-operative RV failure and was continued uninterrupted thereafter. Early RV failure was defined according to the 2014 INTERMACS definition (*Table S2*).[9] Patients were included if they were clinically stable without evidence of complications or other acute systemic illness. Exclusion criteria included persistent PH with an indication for oral PDE5I, immobility, insufficient image quality, and incompliance. All patients provided written consent. The institutional ethics committee approved the study (Registration No.: 177923BO), which conforms with the principles outlined in the Declaration of Helsinki. Patients discontinued PDE5I and underwent multiparametric assessment at baseline and 4 weeks after drug discontinuation. Study procedures included 6-min walking test, cardiopulmonary exercise testing, transthoracic echocardiography, LVAD interrogation,

Figure 1 Comparative assessment of (A) echocardiographic parameters of right ventricular function and (B) exercise testing at baseline and 4 weeks after phosphodiesterase-5 inhibitor discontinuation. 6-MWT, 6-min walking test; peak O_2 pulse, peak oxygen uptake/heart beat; peak VO_2 = peak oxygen uptake at the end of maximal exercise; PVR, pulmonary vascular resistance; RV FAC, right ventricular fractional area change; RV GLS, right ventricular global longitudinal strain; RVEDD, right ventricular end-diastolic diameter; s', tissue Doppler peak systolic velocity at the lateral tricuspid annulus; sPAP, estimated systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TRV, maximal tricuspid regurgitation velocity; VE/VCO_2, minute ventilation/carbon dioxide production.



laboratory testing, evaluation of QoL with the Kansas City Cardiomyopathy Questionnaire and sexual male function assessment with the International Index of Erectile Function (IIEF) at baseline and follow-up. Exam protocols and statistical methods are provided in the *Supporting Information*. The primary outcome was change in echocardiographic parameters of RV function. Secondary analysis was performed for NYHA class, 6-min distance, peak VO_2, N-terminal pro B-type natriuretic peptide (NT-proBNP), QoL, IIEF and LVAD readings (ClinicalTrials.gov number: NCT04117659).

Results

The study included 32 patients with continuous-flow LVADs. One patient died due to ischaemic stroke before completing

Table 1 Comparison of clinical, laboratory, and echocardiographic characteristics at baseline and follow-up

Variables	Baseline	Follow-up	Delta	*P* value
Symptoms and signs, *n* (%)				
NYHA functional class				
I	4 (13)	4 (13)	0	1.00
II	15 (48)	15 (48)	0	
III	12 (39)	12 (39)	0	
IV	0	0	0	
Bendopnoea	4 (7)	3 (5)	−2	1.00
Fatigue	10 (16)	8 (12)	−4	0.58
Palpitations	2 (3)	2 (3)	0	1.00
Peripheral oedema	3 (5)	2 (3)	−2	1.00
Jugular vein distention	1 (2)	1 (2)	0	1.00
Hepatomegaly	1 (2)	1 (2)	0	1.00
Transthoracic echocardiography				
TAPSE (mm)	13.6 ± 4.5	13.9 ± 4.6	0.3 ± 4.9	0.76
s' wave velocity (cm/s)	7.34 ± 2.4	7.4 ± 2.5	0.03 ± 1.4	0.92
Systolic PAP (mmHg)	29 ± 13	29 ± 8	0.5 ± 9.0	0.82
RVEDD basal (mm)	44.2 ± 8.9	45.3 ± 8.7	1.1 ± 4.7	0.27
RV ejection time (ms)	281.1 ± 55.1	288.9 ± 38.1	7.8 ± 70.4	0.58
RV fractional area change (%)	30 ± 9	31 ± 9	1.7 ± 1.4	0.22
Pulmonary vascular resistance (Wood units)	2 ± 0.8	2.2 ± 0.6	0.2 ± 0.7	0.29
Tricuspid regurgitation maximal velocity (m/s)	2.1 ± 0.6	2.4 ± 0.4	0.3 ± 0.5	0.01
Right atrial pressure (mmHg)	7.8 ± 5.1	8 ± 5	0.2 ± 4.2	0.79
RV outflow tract velocity time integral (cm)	12.5 ± 4.5	12.8 ± 4.1	0.3 ± 4.3	0.69
Pulmonary artery acceleration time (ms)	115 ± 36	104 ± 28	−10.4 ± 37.9	0.18
RV free wall longitudinal strain				
Basal	−9.59 ± 4.15	−10.04 ± 4.99	0.45 ± 5.3	0.67
Midventricular	−9.31 ± 3.65	−8.90 ± 3.80	−0.41 ± 4.4	0.64
Apical	−8.71 ± 4.77	−9.17 ± 4.74	0.46 ± 5.6	0.68
Global	−9.20 ± 3.42	−9.37 ± 3.62	0.16 ± 4.02	0.84
LVAD interrogation results[a]				
Flow (L/min)	4.4 ± 0.6	4.5 ± 0.6	0.03 ± 0.4	0.69
Power (W)	3.8 ± 0.4	3.8 ± 0.5	0.02 ± 0.1	0.21
Pulsatility index	4.1 ± 1.2	4.4 ± 1.4	0.3 ± 1.1	0.13
Low-flow alarm, *n*	0.1 ± 0.3	0.2 ± 0.6	0.1 ± 0.5	0.26
Pulsatility index event, *n*	60.5 ± 50	49.9 ± 54	−10.6 ± 30.0	0.07
Power fault	0	0	0	1.00
Laboratory tests				
NT-proBNP (pg/mL)[b]	1455 (919–4371)	1399 (787–4700)	−164 ± 1502	0.55
Creatinine (mg/dL)	1.4 ± 0.6	1.3 ± 0.5	−0.1 ± 0.3	0.14
eGFR (mL/min/1.73 m^2)	52 ± 13	56 ± 11	4 ± 13	0.10
Sodium (mmol/L)	138.3 ± 3.0	138.2 ± 2.8	0.13 ± 0.55	0.82
AST (U/L)	23 ± 9	25 ± 9	2 ± 6	0.29
ALT (U/L)	25 ± 14	29 ± 13	4 ± 9	0.05
Total bilirubin (mg/dL)	0.7 ± 0.4	0.8 ± 0.6	0.1 ± 0.6	0.30
GGT (U/L)[b]	38 (26–75)	39 (28–58)	−7.0 ± 22.0	0.09
Haemoglobin (g/dL)	12.5 ± 2	13 ± 2.3	0.5 ± 1.1	0.04
KCCQ score (%)	78.3 ± 13	77.5 ± 14.8	−0.8 ± 7.9	0.62
IIEF score	15.7 ± 7.8	14.6 ± 8.4	−1.1 ± 4.4	0.35

ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; IIEF, International Index of Erectile Function, IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVAD, left ventricular assist device; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAP, pulmonary artery pressure; RV, right ventricular; RVEDD, right ventricular end-diastolic diameter; s', tissue Doppler peak systolic velocity at the lateral tricuspid annulus; TAPSE, tricuspid annular plane systolic excursion.

[a]Alarms refer to the prior 4 weeks both for baseline and follow-up interrogation.

[b]Values refer to median (IQR).

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Table 2 Comparison of 6-min walking test and cardiopulmonary exercise test results at baseline and follow-up. Right heart catheterization data of a subgroup of patients

Variables	Baseline	Follow-up	Delta	*P* value
6-min walking test				
6-min walking distance, m	346 ± 97.7	364.5 ± 100.8	18.5 ± 44.5	0.03
Pre-exertion Borg scale symptom severity	1.4 ± 2.8	1.1 ± 2.8	−0.3 ± 3.3	0.78
Post-exertion Borg scale symptom severity	3.56 ± 5.6	3.4 ± 4.9	−0.1 ± 5.1	0.89
Cardiopulmonary exercise test				
Anaerobic threshold reached, *n* (%)	21 (91.3)	20 (87)	−4.3	0.15
Maximal work load (watts)	72.7 ± 22.9	80.4 ± 21.3	7.7 ± 22.0	0.09
Respiratory exchange ratio	1.2 ± 0.1	1.18 ± 0.2	−0.03 ± 0.2	0.55
Peak oxygen uptake (mL/min/kg)	11.4 ± 3.6	11.8 ± 4	0.5 ± 3.1	0.52
VE/VCO_2 slope	33.2 ± 6.6	35 ± 12.6	1.8 ± 13.1	0.56
Peak O_2 pulse (mL/beat)	10.2 ± 4.9	9.9 ± 3.5	−0.3 ± 4.9	0.80
Peak O_2 pulse (% target)	56.7 ± 24	56 ± 17.4	−0.8 ± 24.4	0.89
Maximal heart rate (beats/min)	98.8 ± 24.4	103 ± 20.3	4.2 ± 15.3	0.22
% target heart rate	58.7 ± 14	65.4 ± 18	6.7 ± 19.0	0.12
Right heart catheterization[a]				
mPAP (mmHg)	14.9 ± 6.8	16.8 ± 5.8	−1.9 ± 3.7	0.63
PAWP (mmHg)	7.4 ± 6.1	11.1 ± 4.7	−3.8 ± 2.7	0.20
PVR (WU)	1.5 ± 0.8	1.1 ± 0.6	0.4 ± 0.4	0.37

6-MWT, 6-minute walking test; DBP, diastolic blood pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; SO_2, peripheral oxygen saturation (by pulse oximetry); VE/VCO_2, minute ventilation per unit carbon dioxide production.
[a]Subgroup of eight patients with available right heart catheterization data.

follow-up, and 31 patients comprised the analytic cohort. Details regarding the derivation of the study cohort are provided in *Figure S1*. Mean age was 53 years and 90% were male. Enrolment took place 57–1433 days post-implantation. The mean duration on LVAD support at the time of study enrolment was 267 days. Twenty-six patients were on tadalafil, and five patients received sildenafil. Baseline characteristics are summarized in *Table S1*. Heart failure (HF) symptoms remained unchanged at 4 weeks with most patients in NYHA ≤II after PDE5I withdrawal. No changes were observed in anatomical and haemodynamic parameters of RV function but an increase in maximal tricuspid regurgitation velocity (TRVmax) (2.1 vs. 2.4 m/s, $P = 0.01$) without change of the estimated systolic PA pressure. RV global longitudinal strain did not change significantly after PDE5I discontinuation (*Figure 1*). No relevant changes of NT-proBNP, liver, and kidney function were observed and no changes in average LVAD flow, power, and pulsatility index. We recorded no power deviations beyond the predefined windows at both assessments. There were no differences in low-flow alarms and pulsatility index events. KCCQ and IIEF in the subset of 28 male patients remained unchanged after PDE5I discontinuation. Clinical, echocardiographic, and laboratory findings are summarized in *Table 1*. Mild increase of walking distance was observed in 6-MWT (346 vs. 365 m, $P = 0.03$). Peak oxygen consumption and VE/VCO_2 slope remained unchanged (see *Table 2* and *Figure 1*). The study protocol did not include an invasive haemodynamic evaluation; however, as right heart catheterization was performed routinely in bridge-to-transplant LVAD patients, these data were available in a subgroup of patients. As demonstrated in *Table 2*, we did not observe any significant changes of pulmonary pressures after PDE5I discontinuation. Two patients were hospitalized for reasons not pertinent to haemodynamic status (subtherapeutic INR, infection). We did not observe HF hospitalizations or change in medications such as escalation of diuresis or new drug initiation.

Conclusions

These findings highlight the potential futility of this pharmacologic intervention in patients under LVAD support. Despite a significant increase in TRVmax, RV function did not change, suggesting that RV was able to accommodate any changes in afterload induced by PDE5I withdrawal. Both at baseline and follow-up, mean TRVmax ≤2.8 m/s was observed, which is associated with a low probability of PH. The finding of stable RV function is supported by NT-proBNP, end-organ function, and exercise test results that did not exhibit any changes compatible with apparent or imminent RV failure. The mild increase in walking distance may indicate the ongoing gain of functional status and uncomplicated recovery as most patients were enrolled after the first year post-implantation and were on optimal medical HF therapy, as seen in *Table S1*.

Despite the absence of randomized data and haemodynamic correlation studies, a high utilization rate of off-label PDE5I has been observed, which exceeds by far the rates of persistent PH after LVAD in the modern era. Beyond incremental costs, there is growing evidence that PDE5I are associated with bleeding risk, presumably due to their antiplatelet function. Regarding the latter, it has been shown that phosphodiesterase-5 is abundant in platelets and sildenafil

attenuates platelet aggregation via the cGMP-dependent protein kinase pathway.[10] However, recent data demonstrated the beneficial effect of PDE5I on mortality, pump thrombosis, and ischaemic stroke,[6,11] further promoting the scientific interest in this class of agents. Their potential role in preventing late-onset RV failure is largely unknown and a topic of great interest for future studies.

Predicting late RV failure after LVAD implantation remains challenging and an unmet need. Several parameters including the PA pulsatility index have been recently proposed,[12,13] while the impact of LVAD speed optimization as a means to prevent late RV failure is a promising approach[14] that should be further addressed in future studies.

Discontinuation of PDE5I in stable patients who have recovered from post-operative RV failure may be reasonable and safe unless persistent PH mandates ongoing pulmonary vasodilation. Their net clinical benefit still needs to be studied in large prospective trials with randomized study design and longer follow-up.

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Conflict of interest

The authors report no financial relationships with industry relevant to the submitted work.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics.
Table S2. Interagency Registry for Mechanically Assisted Circulatory Support definition of right ventricular failure after Left Ventricular Assist Device implantation
Figure S1. Derivation of the analytic cohort of the study. During the study period 41 LVAD recipients on long-term PDE5I were assessed for eligibility. Nine patients were excluded as PDE5I therapy was interrupted in 7 patients, 1 patient declined consent and 1 patient was clinically unstable due to systemic infection. One patient died before follow-up and 31 were included in the final analysis.
Figure S2. Anatomical, functional and hemodynamic assessment of the right ventricle. A1, A2. Estimation of right ventricular fractional area change, B. Peak systolic velocity of the lateral tricuspid annulus by tissue doppler imaging, C. Tricuspid annular plane systolic excursion, D. Tricuspid regurgitation maximal velocity, E. Longitudinal strain of the basal, midventricular and apical segments of the free right ventricular wall. (Intraventricular septum not included in global longitudinal strain calculation).

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