Interdisciplinary CardioVascular and Thoracic Surgery 2023, 36(1), ivac289
https://doi.org/10.1093/icvts/ivac289

ORIGINAL ARTICLE

Cite this article as: Sugimura Y, Kalampokas N, Arikan M, Rellecke P, Dalyanoglu H, Tudorache I *et al*. Preoperative Levosimendan therapy reduces postoperative right ventricular failure in patients undergoing left ventricular assist device implantation. Interdiscip CardioVasc Thorac Surg 2023; doi:10.1093/icvts/ivac289.

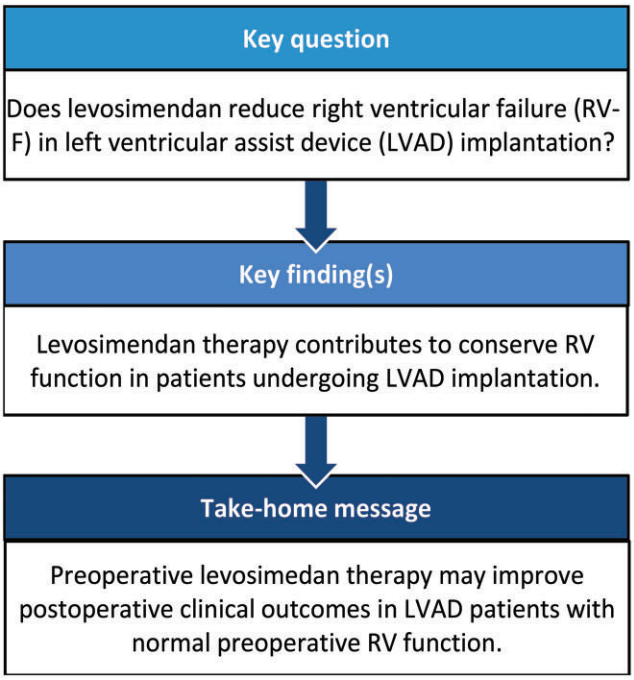
Preoperative Levosimendan therapy reduces postoperative right ventricular failure in patients undergoing left ventricular assist device implantation

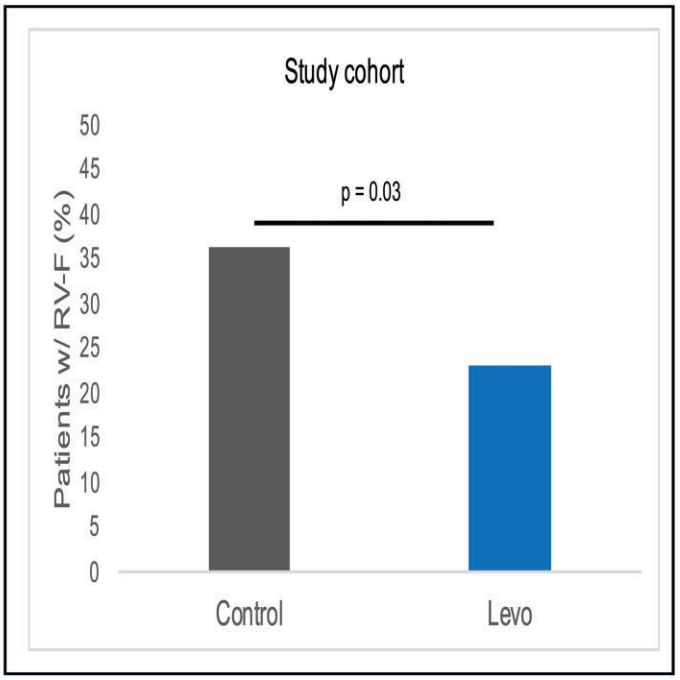
Yukiharu Sugimura [a,b,†], Nikolaos Kalampokas[a,†], Metin Arikan[a], Phillip Rellecke[a], Hannan Dalyanoglu[a], Igor Tudorache [a], Ralf Westenfeld [c], Udo Boeken [a], Artur Lichtenberg [a], Payam Akhyari [a,b,*] and Hug Aubin [a]

[a] Department of Cardiac Surgery, Medical Faculty and University Hospital, Heinrich-Heine-University Medical School, Duesseldorf, Germany
[b] Department of Cardiac Surgery, Medical Faculty and RWTH University Hospital Aachen, RWTH Aachen University, Aachen, Germany
[c] Division of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Duesseldorf, Germany

* Corresponding author. Department of Cardiac Surgery, Medical Faculty and RWTH University Hospital Aachen, RWTH Aachen University, Aachen, Germany. Tel: +49-241-8012345; fax: +49-241-80-33-12345; e-mail: pakhyari@ukaachen.de (P. Akhyari).

Received 9 September 2022; received in revised form 12 November 2022; accepted 20 December 2022





Abstract

OBJECTIVES: Perioperative mortality and complications still remain high after left ventricular assist device (LVAD) implantation, especially in highly compromised patient cohorts. Here, we evaluate the effects of preoperative Levosimendan therapy on peri- and postoperative outcomes after LVAD implantation.

[†]The first authors contributed equally to this work.

METHODS: We retrospectively analysed 224 consecutive patients with LVAD implantation for end-stage heart failure between November 2010 and December 2019 in our centre with regard to short- and longer-term mortality as well as incidence of postoperative right ventricular failure (RV-F). Out of these, 117 (52.2%) received preoperative i.v. Levosimendan therapy within 7 days before LVAD implantation (Levo group).

RESULTS: In-hospital, 30-day and 5-year mortality was comparable (in-hospital mortality: 18.8% vs 23.4%, $P = 0.40$; 30-day mortality: 12.0% vs 14.0%, $P = 0.65$; Levo vs control group). However, in the multivariate analysis, preoperative Levosimendan therapy significantly reduced postoperative RV-F but increased postoperative vasoactive inotropic score ([RV-F: odds ratio 2.153, confidence interval 1.146–4.047, $P = 0.017$; vasoactive inotropic score 24 h post-surgery: odds ratio 1.023, confidence interval 1.008–1.038, $P = 0.002$). These results were further confirmed by 1:1 propensity score matching of 74 patients in each group. Especially in the subgroup of patients with normal preoperative RV function, the prevalence of postoperative RV-F was significantly lower in the Levo- group as compared to the control group (17.6% vs 31.1%, $P = 0.03$; respectively).

CONCLUSIONS: Preoperative Levosimendan therapy reduces the risk of postoperative RV-F, especially in patients with normal preoperative RV function without effects on mortality up to 5 years after LVAD implantation.

Keywords: Levosimendan • Left ventricular assist device • Right heart failure • Mechanical circulatory support • End-stage heart failure

ABBREVIATIONS

ASD	Atrial septum defect
AVR	Aortic valve replacement
CI	Confidence interval
HF	Heart failure
HM	Heartmate
ICM	Ischaemic cardiomyopathy
INTERMACS	Interagency registry for mechanically assisted circulatory support
LAA	Left atrial appendage
LIS	Less invasive
LVAD	Left ventricular assist devices
OR	Odds ratio
PSM	Propensity score matching
RV-F	Right ventricular failure
TVR	Tricuspid valve repair
VIS	Vasoactive inotropic score

INTRODUCTION

The introduction of the newest generation of left ventricular assist devices (LVAD) has further increased survival in patients with end-stage heart failure (HF) requiring long-term mechanical circulatory support either as bridge-to-transplant or destination therapy [1]. Improved hemocompatibility of the devices and growing experiences in patient management have significantly reduced therapy-inherent complications such as pump-thrombosis and thromboembolic events. However, outcome after LVAD implantation is still predominantly conditioned by the preoperative patient status and perioperative complications. In already highly compromised patient cohorts, perioperative mortality and morbidity remain high, with especially right ventricular failure (RV-F) being an often unforeseeable and major mortgage on patient outcome. Hence, further improvement of perioperative treatment strategies is strongly warranted [2].

Levosimendan, a calcium sensitizer and adenosine triphosphate potassium channel opener, is increasingly used in cardiovascular medicine due to its inotropic, vasodilative and cardioprotective effects [3–9]. In contrast to other inotropes, it enhances cardiac function by improving myocardial contractility and reducing cardiac pre- and afterload, without increasing myocardial oxygen consumption nor affecting intracellular calcium concentration [9, 10]. Levosimendan therapy has also been postulated to restore RV vascular coupling leading to improved RV function [10, 11]. Due to its mode of action and reported beneficial effects on decompensated HF patients [10], Levosimendan is increasingly used in cardiac surgery [12–14]. Although recent studies have shown promising results, the positive effects of Levosimendan on patient outcomes remain controversial in many cases [4–6, 12–15]. Hence, here, we evaluate the impact of preoperative i.v. Levosimendan therapy on clinical outcome after LVAD implantation.

MATERIALS AND METHODS

Ethical approval

This study was approved by the local ethics committee (2020-1058) and complied with the principles outlined in the Declaration of Helsinki.

Study design

In this retrospective cohort study, we analysed the clinical outcome of 224 consecutive patients who underwent LVAD implantation for end-stage HF between 10 November and 19 December in our centre. Patients were divided into 2 groups, depending on whether they had preoperative i.v. Levosimendan therapy within 7 days before LVAD implantation (Levo group, $n = 117$) or whether they were operated on without prior Levosimendan treatment (control group, $n = 107$). Clinical outcome was analysed with regard to 30-day in-hospital and 5-year mortality. Furthermore, regarding in-hospital adverse events, peri- and postoperative complications [including RV-F (defined as the need for perioperative mechanical RV support), kidney failure (requiring renal replacement therapy), stroke (neurological symptoms with pathologic neuroimaging), sepsis (systemic involvement by infection requiring anti-microbial treatment), acute respiratory distress syndrome (hypoxemia with pathologic lung imaging), pump malfunction (confirmed device thrombus), prolonged respiratory weaning (requiring tracheostomy), postoperative inotrope score (IS) defined as dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (mcg/kg/min), postoperative vasoactive inotropic score (VIS) defined as vasoactive-inotropic score (VIS) = IS + 10 × milrinone dose (μg/

kg/min) + 10,000 × vasopressin dose (units/kg/min) + 100 × norepinephrine dose (μg/kg/min)] [16], and the duration of ICU/hospital stay was also evaluated. The perioperative mechanical RV support was initiated if post-implant RV-F defined by the interagency registry for mechanically assisted circulatory support (INTERMACS) occurred [17]. For subgroup analyses, patients were stratified according to their preoperative echocardiographic RV function and divided into 2 groups: normal RV function and impaired RV function (defined as ≥ moderate impairment by visual contractility and tricuspid annular plane systolic excursion <17 mm on the preoperative echocardiographic exam; $n = 82$ and $n = 142$, respectively). In the setting of preoperative temporary mechanical circulatory support, support was temporarily gradually reduced to allow echocardiographic estimation of RV function. In both subgroups, patients with (Levo group) or without preoperative i.v. Levosimendan therapy (control group) were analysed and compared with regard to above end points.

Data management

All data were collected by retrospective review of the patients' medical records, including standardized documentation on diagnostic exams, complication management and follow-up therapy; all data were recorded according to the recommendation of the 'Association for Clinical Data Management' and institutional quality assurance standards.

Clinical management

LVAD implantation as well as postoperative and follow-up management were performed following institutional standards. For preoperative Levosimendan therapy, patients received Levosimendan (Simdax®, Orion Pharma, Hamburg, Germany) with a dose of 0.1 μg/kg body weight/min without loading dose as a continuous venous infusion for 24 h within 7 days before LVAD implantation. The decision for preoperative Levosimendan therapy was at the discretion of the surgical team. Criteria for Levosimendan administration included perceived RV dysfunction and the absence of potential contraindications such as persistent hypotension or frequent malign rhythm episodes. With growing experience usage became more liberal and increased over time, including also patients with normal RV function and absence of potential contraindications. According to the recent ESC recommendation, all general pharmacological therapies for HF were preoperatively administered in patients undergoing LVAD implantation. Furthermore, we administrated inhalation of nitric oxide routinely if intraoperative RV function was impaired before weaning from heart-lung-machine. The analysis was performed by means of transoesophageal echocardiography and Swan-Ganz catheter by the present team with the board-certified anaesthesiologists, cardiologists and cardiac surgeons.

Surgical indication and procedure

Indications for LVAD implantation were determined based on the European Association for Cardio-Thoracic Surgery guidelines. In this study, 3 therapy concepts were categorized: 'bridge to transplant', 'bridge to candidacy' and 'destination therapy'. In 68 patients (30.4%), the LVAD was implanted via less-invasive (LIS) approach. We implanted 3 different devices: HeartWare HVAD (Medtronic, Minneapolis, MN), Heartmate (HM) 2 (Abbott, Inc., Chicago, IL, USA) and HM 3. Combined operations were performed in 25 patients: aortic valve replacement (AVR, $n = 6$); atrial septum defect (ASD) closure ($n = 5$); left atrial appendage (LAA) closure ($n = 6$); AVR + LAA closure ($n = 1$); AVR + tricuspid valve repair (TVR, $n = 1$); ASD closure + LAA closure ($n = 1$); ASD closure + TVR ($n = 1$); TVR + mitral valve repair ($n = 1$); TVR + mitral valve replacement ($n = 1$); left ventricular thrombectomy ($n = 1$); and coronary artery bypass grafting ($n = 1$).

Statistics

Statistics were analysed by SPSS Statistics 26 (IBM Corporation, Armonk, NY). Survival was estimated using the Kaplan–Meier method. Student's *t*-test or Mann–Whitney *U*-test (for numerical variables) and Chi-square or Fisher's exact test (for categorical variables) were used for statistical comparisons as appropriate. To reduce the bias due to potential confounders, propensity score matching (PSM) was performed using demographic and clinical characteristics [age, gender, baseline disease, therapy concept (bridge to transplant), profile of INTERMACS, preoperative mechanical support, impaired RV function, preoperative dialysis, operative approaches, device choices] between groups. The calliper value of PSM was regulated at 0.03 [18].

Furthermore, we performed multiple logistic regression analysis with several variables for which a significant difference has been shown in previous univariate analysis. All tests were two-tailed, and *P*-values <0.05 were considered statistically significant. All results are presented in the corresponding tables as mean values with the standard deviation or percentages, respectively.

RESULTS

Baseline characteristics

Patient and procedural characteristics of the study population are outlined in Table 1. Briefly, the mean age at LVAD implantation was 57.3 ± 11.5 years, 86.6% ($n = 194$) of the patients were male, and ischaemic cardiomyopathy (ICM) was the predominant aetiology of terminal HF in 59.8% of the patients. The majority of patients (57.1%) presented either with INTERMACS stadium I (37.9%) or stadium II (19.2%). In all ICM patients ($n = 134$), INTERMACS stadium I ($n = 52$, 38.8%) and II ($n = 26$, 19.4%) were regarded to patients with acute ICM, whereas INTERMACS stadium III ($n = 21$, 15.7%) and IV ($n = 35$, 26.1%) were regarded to patients with chronic ICM.

Ninety-one patients (40.6%) had preoperative mechanical support with 74 patients (33.0%) on venoaterial extracorporeal membrane oxygenation either with (16 patients, 7.1%; IABP, $n = 9$, microaxial pump, $n = 7$) or without (58 patients, 25.9%) additional mechanical assist devices, such as surgical microaxial pumps. Concerning operative approaches, LIS LVAD implantation technique (LIS-LVAD), with partial upper ('J' shaped) sternotomy and left-sided mini-thoracotomy, was performed in 68 patients (38.4%). There were no significant differences between the Levo and control groups regarding baseline characteristics other than the operative approach and the choice of device (LIS-LVAD: 37.6% vs 22.4%, $P = 0.01$; sternotomy: 62.4% vs 77.6%, $P = 0.01$; HM 3: 36.8% vs 19.6%, $P = 0.005$; HVAD: 59.8% vs 74.8%, $P = 0.02$, Levo vs control group, respectively).

Table 1: Clinical characteristics in consecutive 224 patients undergoing left ventricular assist device implantation

	All patients ($n = 224$)	Levo group ($n = 117$)	Control group ($n = 107$)	P-Value
Age (years)	57.3 ± 11.5	58.2 ± 12.0	56.4 ± 11.0	0.24
Male, *n* (%)	194 (86.6)	105 (89.7)	89 (83.2)	0.15
Bridge to transplant, *n* (%)	160 (71.4)	77 (65.8)	83 (77.6)	0.06
INTERMACS profile 1, *n* (%)	85 (37.9)	41 (35.0)	44 (41.1)	0.35
INTERMACS profile 2, *n* (%)	43 (19.2)	29 (24.8)	14 (13.1)	0.03
ICM, *n* (%)	134 (59.8)	65 (55.6)	69 (64.5)	0.17
DCM, *n* (%)	86 (38.4)	49 (41.9)	37 (34.6)	0.26
Myocarditis, *n* (%)	4 (1.8)	3 (2.6)	1 (0.9)	0.36
Pre. mech. support, *n* (%)	91 (40.6)	41 (35.0)	50 (46.7)	0.08
Impaired RV function, *n* (%)	82 (36.6)	44 (37.6)	38 (35.5)	0.75
Dialysis, *n* (%)	47 (21.0)	28 (23.9)	19 (17.8)	0.26
LIS, *n* (%)	68 (30.4)	44 (37.6)	24 (22.4)	0.01
Sternotomy, *n* (%)	156 (69.6)	73 (62.4)	83 (77.6)	0.01
Combined operation, *n* (%)	25 (11.2)	13 (11.1)	12 (11.2)	0.98
HVAD, *n* (%)	150 (67.0)	70 (59.8)	80 (74.8)	0.02
HM2, *n* (%)	10 (4.5)	4 (3.4)	6 (5.6)	0.43
HM3, *n* (%)	64 (28.6)	43 (36.8)	21 (19.6)	0.005

Data are documented as *n* (%) or mean ± standard deviation.

DCM: dilated cardiomyopathy; HM: Heartmate; HVAD: HeartWare HVAD; ICM: ischaemic cardiomyopathy; INTERMACS: interagency registry for mechanically assisted circulatory support; Levo: Levosimendan; LIS: less-invasive surgery; mech.: mechanical; pre.: preoperative; RV: right ventricle.

Clinical outcomes

Postoperative outcomes are presented in Table 2. Thirty-day mortality and in-hospital mortality showed no differences between the Levo and control groups [30-day mortality: 12.0% vs 14.0%, $P = 0.65$ (Fig. 1); in-hospital mortality: 18.8% vs 23.4%, $P = 0.40$; respectively]. Regarding peri- and postoperative complications, patients in the Levo group had significantly less prevalence of postoperative RV-F as compared to those in the control group (23.1% vs 36.4%, $P = 0.03$, respectively) (Fig. 2a), whereas they were in need of higher vasoactive [inotropic support during the first 48 h after LVAD implantation (VIS at 24 h post-implantation: 31.0 ± 20.9 vs 22.7 ± 20.3, $P = 0.004$; at 48 h post-implantation: 21.4 ± 17.8 vs 16.7 ± 15.9, $P < 0.05$; VS at 24 h post-implantation: 21.8 ± 16.9 vs 14.2 ± 16.0, $P < 0.001$; at 48 h post-implantation: 15.1 ± 14.1 vs 10.6 ± 11.5, $P = 0.01$, respectively)]. Other parameters did not statistically differ between groups.

On the other hand, preoperative Levosimendan therapy did not have a significant impact on postoperative RV-F in the subgroup of patients with preserved right ventricular function on ECMO before LVAD implantation ($n = 54$) ($P = 0.173$).

In multivariate analysis, preoperative Levosimendan therapy significantly reduced postoperative RV-F but led to increased VIS at 24 h post-implantation [RV-F: $P = 0.017$, odds ratio (OR) 2.153, confidence interval (CI) 1.146–4.047; VIS 24 h post-implantation: $P = 0.002$, OR 1.023, CI 1.008–1.038]. Regarding longer-term outcome, there was no difference in 5-year survival between both groups (66.7% vs 69.0% after 1 year, 56.6% vs 52.4% after 5 years, $P = 0.78$; Levo vs control, respectively) (Supplementary Material, Fig. S1a).

Clinical outcomes in propensity score-matched patients

To minimize the bias due to some covariates, e.g. operative approach and device choice, we performed 1:1 PSM in the study cohort, allocating 74 patients in each group (Table 3). Statistical analysis of the PSM patients confirmed above results. Patients in the Levo group had significantly less prevalence of postoperative RV-F (Levo vs control; 21.6% vs 40.5%, $P = 0.01$; respectively) as well as higher VIS and VS at 24 h post-implantation (VIS, 31.2 ± 21.1 vs 24.0 ± 21.4; VS, 22.8 ± 17.0 vs 15.3 ± 16.4, $P = 0.002$), as compared to those in the control group (Table 4 and Fig. 2b). Again, multivariate analysis showed a significantly reduced incidence of postoperative RV-F ($P = 0.006$, OR 2.982, CI 1.364–6.518; respectively) and increased VIS at 24 h post-implantation ($P = 0.022$, OR 1.021, CI 1.003–1.039; respectively) in the Levosimendan group as compared to the control group. Also, 5-year survival in the PSM patients showed no significant differences between the Levo and control groups, respectively (62.4% vs 62.7% at 1 post-year, 55.6% vs 46.3% at 5 post-year, $P = 0.52$; Supplementary Material, Fig. S1b).

Subgroup analyses in patients with/without preoperative RV-impairment

Further subgroup analysis was performed in patients with or without preoperatively impaired RV function ($n = 82$ vs $n = 142$; respectively). Interestingly, preoperative Levosimendan therapy made no significant difference regarding peri- and postoperative outcomes in patients with impaired RV function (Supplementary Material, Tables S1 and S2 and Fig. 2c). However, in patients with preserved RV function preoperative Levosimendan therapy significantly reduced the incidence of peri- and postoperative RV-F (Levo vs control; 17.8% vs 33.3%, $P < 0.05$) (Table 5 and Fig. 2d). Nonetheless, long-term clinical outcome, in terms of 1- and 5-year survival—did not differ in both groups (Levo vs control group; 70.8% vs 73.2% 1-year survival, 59.5% vs 65.7% 5-year survival, $P = 0.97$) (Fig. 3).

Table 2: Postoperative outcomes in consecutive 224 patients undergoing left ventricular assist device implantation

	All patients (*n* = 224)	Levo group (*n* = 117)	Control group (*n* = 107)	*P*-Value
RV-F, *n* (%)	66 (29.5)	27 (23.1)	39 (36.4)	0.03
Dialysis, *n* (%)	121 (54.0)	62 (53.0)	59 (55.1)	0.75
CVA, *n* (%)	26 (11.6)	13 (11.1)	13 (12.1)	0.81
Sepsis, *n* (%)	38 (17.0)	21 (17.9)	17 (15.9)	0.68
ARDS, *n* (%)	24 (10.7)	11 (9.4)	13 (12.1)	0.51
Pump malfunction, *n* (%)	11 (4.9)	5 (4.3)	6 (5.6)	0.64
Tracheotomy, *n* (%)	48 (21.4)	29 (24.8)	19 (17.8)	0.20
ICU stay (days)	28.1 ± 29.0	27.7 ± 28.0	28.5 ± 30.2	0.85
Hospital stay (days)	49.6 ± 38.2	51.0 ± 38.5	48.0 ± 37.9	0.56
VIS at 24 h	27.1 ± 21.0	31.0 ± 20.9	22.7 ± 20.3	0.004
VIS at 48 h	19.8 ± 17.1	21.4 ± 17.8	16.7 ± 15.9	<0.05
VIS at 72 h	13.3 ± 15.1	13.6 ± 14.6	13.0 ± 15.6	0.78
VS at 24 h	18.3 ± 16.9	21.8 ± 16.9	14.2 ± 16.0	<0.001
VS at 48 h	13.0 ± 13.1	15.1 ± 14.1	10.6 ± 11.5	0.01
VS at 72 h	8.70 ± 11.9	9.08 ± 11.1	8.28 ± 12.8	0.34
30-Day mortality, *n* (%)	29 (12.9)	14 (12.0)	15 (14.0)	0.65
In-hospital mortality, *n* (%)	47 (21.0)	22 (18.8)	25 (23.4)	0.40
Transition to HTX, *n* (%)	83 (37.1)	37 (31.6)	46 (43.0)	0.08
Recovery from LVAD, *n* (%)	8 (3.6)	3 (2.6)	5 (4.7)	0.40

Data are documented as *n* (%) or mean ± standard deviation.

ARDS: acute respiratory distress syndrome; CVA: cerebrovascular accident; HTX: heart transplantation; ICU: intensive care unit; Levo: Levosimendan; LVAD: left ventricular assist device; RV-F: right ventricular failure; VIS: vasoactive inotropic score; VS: vasoactive score.

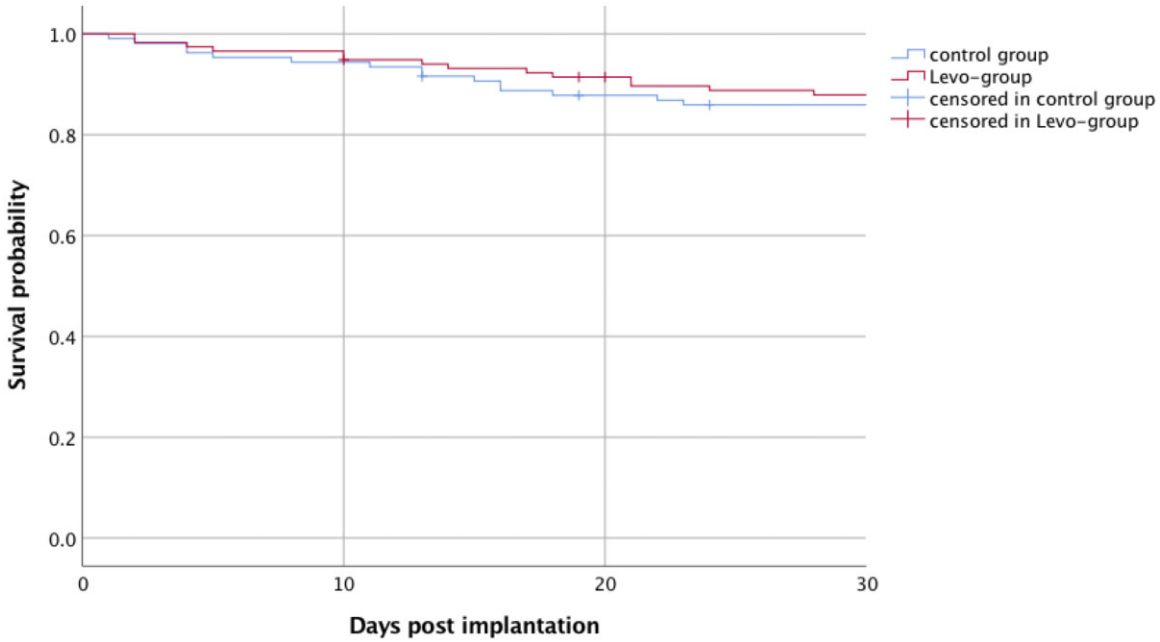


Figure 1: Comparative 30-day survival after left ventricular assist device implantation.

DISCUSSION

With recent advancements in LVAD technology survival after LVAD implantation has significantly improved during the last years [19]. However, patient outcome after LVAD implantation is still predominantly conditioned by the preoperative patient status and perioperative complications, such as RV-F. Hence, optimization of perioperative therapy strategies is crucial to further reduce morbidity and mortality after LVAD implantation. In our study cohort, preoperative Levosimendan therapy before LVAD implantation was associated with reduced risk of postoperative RV-F, especially in patients with normal preoperative RV function.

Levosimendan has an inotropic effect without increasing myocardial oxygen consumption and is therefore increasingly applied in HF patients as well as patients undergoing cardiac surgery [6, 9]. In a large multicentre randomized study (LEVO-CTS), Levosimendan administration before coronary artery bypass grafting and/or heart valve surgery significantly reduced the incidence of postoperative low cardiac output syndrome; however,

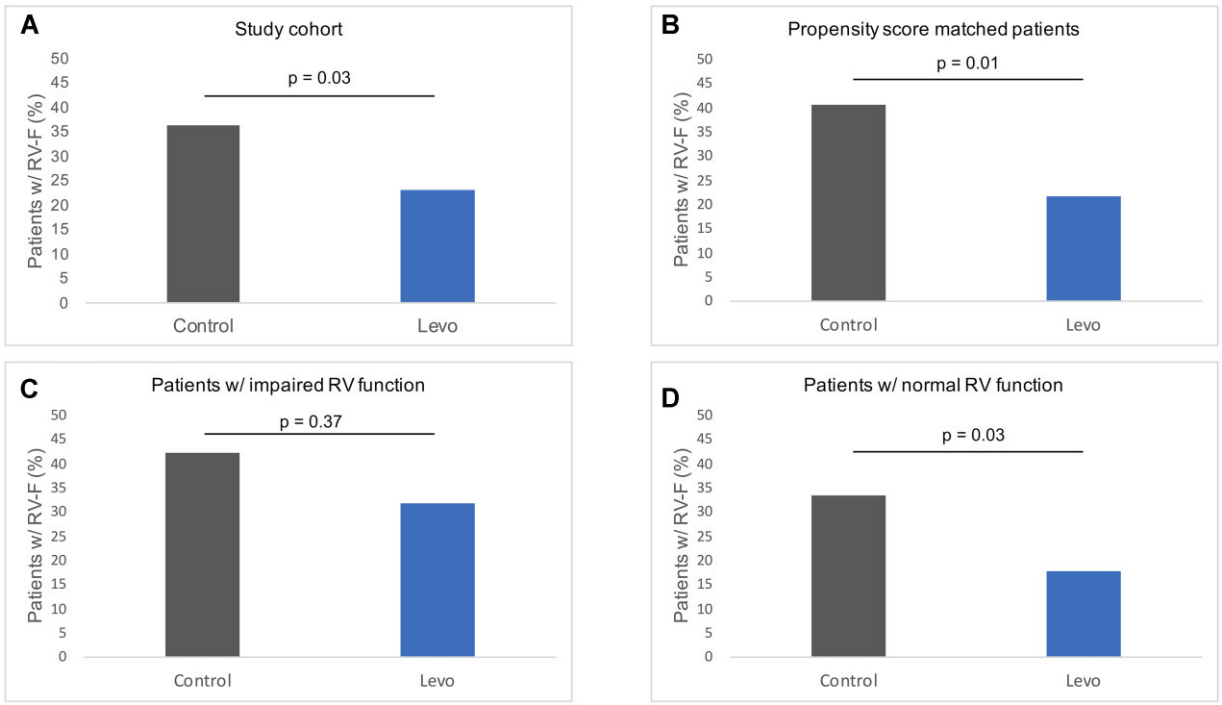


Figure 2: The difference regarding the prevalence of peri- and postoperative RV-F after LVAD implantation in (**a**) all cohorts ($n = 224$), (**b**) propensity score matched patients ($n = 148$), (**c**) patients with impaired preoperative RV function ($n = 82$) and (**d**) in patients with preserved preoperative RV function ($n = 142$). Levo: Levosimendan; LVAD: left ventricular assist device; RV (-F): right ventricular (failure); w/: with.

Table 3: Clinical characteristics in propensity score matched patients undergoing left ventricular assist device implantation

	Levo group ($n = 74$)	Control group ($n = 74$)	*P*-Value
Age (years)	58.1 ± 12.2	56.5 ± 10.5	0.42
Male, *n* (%)	63 (85.1)	67 (90.5)	0.31
Bridge to transplant, *n* (%)	49 (66.2)	57 (77.0)	0.20
INTERMACS profile 1, *n* (%)	26 (35.1)	29 (39.2)	0.84
INTERMACS profile 2, *n* (%)	12 (16.2)	11 (14.9)	0.84
ICM, *n* (%)	44 (59.5)	45 (60.8)	1.00
DCM, *n* (%)	28 (37.8)	28 (37.8)	1.00
Myocarditis, *n* (%)	1 (1.4)	1 (1.4)	1.00
Pre. mech. support, *n* (%)	24 (32.4)	30 (40.5)	0.78
impaired RV function, *n* (%)	29 (39.2)	28 (37.8)	0.87
Dialysis, *n* (%)	58 (78.4)	55 (74.3)	0.56
LIS, *n* (%)	24 (32.4)	23 (31.1)	0.86
Sternotomy, *n* (%)	50 (67.6)	51 (68.9)	0.86
Combined operation, *n* (%)	10 (13.5)	7 (9.5)	0.44
HVAD, *n* (%)	48 (64.9)	52 (70.3)	0.48
HM2, *n* (%)	22 (29.7)	19 (25.7)	0.58
HM3, *n* (%)	4 (5.4)	3 (4.1)	0.70

Data are documented as *n* (%) or mean ± standard deviation.

DCM: dilated cardiomyopathy; HM: Heartmate; HVAD: HeartWare HVAD; ICM: ischaemic cardiomyopathy; INTERMACS: interagency registry for mechanically assisted circulatory support; Levo: Levosimendan; LIS: less invasive surgery; LVAD: left ventricular assist device; mech.: mechanical; pre.: preoperative; RV: right ventricle.

Table 4: Postoperative outcomes in propensity score matched patients undergoing left ventricular assist device implantation

	Levo group ($n = 74$)	Control group ($n = 74$)	*P*-Value
RV-F, *n* (%)	16 (21.6)	30 (40.5)	0.01
Dialysis, *n* (%)	39 (52.7)	40 (54.1)	0.87
CVA, *n* (%)	8 (10.8)	12 (16.2)	0.34
Sepsis, *n* (%)	11 (14.9)	15 (20.3)	0.39
ARDS, *n* (%)	6 (8.1)	10 (13.5)	0.29
Pump malfunction, *n* (%)	4 (5.4)	5 (6.8)	1.00
Tracheotomy, *n* (%)	19 (25.7)	16 (21.6)	0.56
ICU stay (days)	29.5 ± 31.4	29.2 ± 31.8	0.95
Hospital stay (days)	52.5 ± 43.7	48.1 ± 37.7	0.51
VIS at 24 h	31.2 ± 21.1	24.0 ± 21.4	<0.05
VIS at 48 h	21.3 ± 19.0	17.6 ± 15.4	0.21
VIS at 72 h	13.9 ± 14.9	13.9 ± 16.7	1.00
VS at 24 h	22.8 ± 17.0	15.3 ± 16.4	0.002
VS at 48 h	14.8 ± 13.9	11.0 ± 10.7	0.12
VS at 72 h	8.83 ± 10.2	9.13 ± 14.1	0.46
30-Day mortality, *n* (%)	10 (13.5)	12 (16.2)	0.64
In-hospital mortality, *n* (%)	15 (20.3)	19 (25.7)	0.43
Transition to HTX, *n* (%)	20 (27.0)	28 (37.8)	0.16
Recovery from LVAD, *n* (%)	3 (4.1)	3 (4.1)	1.00

Data are documented as *n* (%) or mean ± standard deviation.

ARDS: acute respiratory distress syndrome; CVA: cerebrovascular accident; HTX: heart transplantation; ICU: intensive care unit; Levo: Levosimendan; LVAD: left ventricular assist device; RV-F: right ventricular failure; VIS: vasoactive inotropic score; VS: vasoactive score.

early mortality and need for postoperative mechanical circulatory support did not differ statistically [13]. Therefore, prophylactic use of Levosimendan in cardiac surgery patients remains a matter of debate.

Until today, literature on preconditioning LVAD candidates with Levosimendan before surgery remains scarce [20]. Sponga *et al.* reported a cases series of 21 patients demonstrating that

preoperative Levosimendan therapy might be profitable for improving preoperative patient condition by reducing pulmonary artery pressure and central venous pressure, although it had no impact on postoperative RV-F [21]. Another case series of Theiss *et al.* [22] reported a favourable first-year outcome in 9 patients pretreated with Levosimendan as compared to the fifth INTERMACS annual report. In addition, Kocabeyoglu *et al.* [15] compared the outcomes of 85 LVAD patients with or without preoperative Levosimendan therapy in a retrospective study, demonstrating improvement end-organ function at the time of surgery but no impact on postoperative RV-F and short-/long-term mortality.

Contrary to the previous reports, in our study cohort preoperative Levosimendan therapy was associated with reduced peri- and postoperative RV-F. As certain patient and procedural characteristics may strongly influence the incidence of RV-F after LVAD implantation, such as a LIS implantation approach [23–25], we additionally performed a PSM in the study cohort. Here, PSM confirmed the association between preoperative Levosimendan therapy and reduced peri- and postoperative RV-F in patients undergoing LVAD implantation. As postoperative RV-F after LVAD implantation is also highly dependent on preoperative RV function [2], we further performed a subgroup analysis stratifying patients depending on their preoperative echocardiographic assessment. Interestingly, we observed that particularly patients without preoperative RV impairment might benefit from preoperative Levosimendan therapy in terms of preventing from peri- and postoperative RV-F. It seems that Levosimendan preconditioning contributes to preserve RV function after LVAD implantation mainly in patients without preoperative RV impairment, while in patients with already reduced RV function Levosimendan preconditioning fails to reduce the risk of postoperative RV-F. The reason for this remains unclear and may be related to structural changes in the RV with less contractile reserve after chronic RV impairment. However, further investigations are strongly warranted to elucidate differences in those patient subgroups.

Despite lower incidence of peri- and postoperative RV-F in patients with preoperative Levosimendan therapy before LVAD implantation, short- and long-term survival remained comparable to those patients who did not receive preoperative Levosimendan treatment in our study cohort. This observation is quite congruent to the available literature [15]. Although the reasons for this remain unclear, improved clinical management of peri- and postoperative RV-F in LVAD patients and the relatively low incidence of RV-F in our patient cohort may account for the lacking differences in survival. However, survival should not be the only outcome marker as RV-F is associated with higher morbidity and reduced quality of life [2].

In our patient cohort, Levosimendan therapy could be administrated safely in all patients without relevant adverse events. Due to the longstanding vasodilatation effects of Levosimendan, patients with preoperative Levosimendan therapy required higher doses of catecholamines postoperatively, which however did not affect postoperative outcomes, as beneficial effects of Levosimendan on RV-F seem to outweigh the potentially deteriorating effects of higher postoperative catecholamines with regard to outcome in our patient cohort. Hence, as preoperative Levosimendan therapy can be safely employed in patients undergoing LVAD implantation [20] and it seems to be associated with lower incidence of peri- and postoperative RV-F, it should be discussed to include it in the preoperative management of LVAD candidates.

Table 5: The prevalence of postoperative right ventricular failure in patients with preoperative normal right ventricular function

	Levo group ($n = 73$)	Control group ($n = 69$)	*P*-Value
RV-F, *n* (%)	13 (17.6)	23 (31.1)	0.03

Data are documented as *n* (%).
Levo: Levosimendan; RV-F: right ventricular failure.

Limitations

There are some limitations to this study. First, it is a single-centre, retrospective analysis with a limited cohort size of non-randomized patients, within a very heterogenous patient population. Second, the patients undergoing LVAD implantation were heterogeneous in their characteristics, whereas we analysed all patients as a homogenous cohort in this study. Third, due to developing institutional standards the use of preoperative

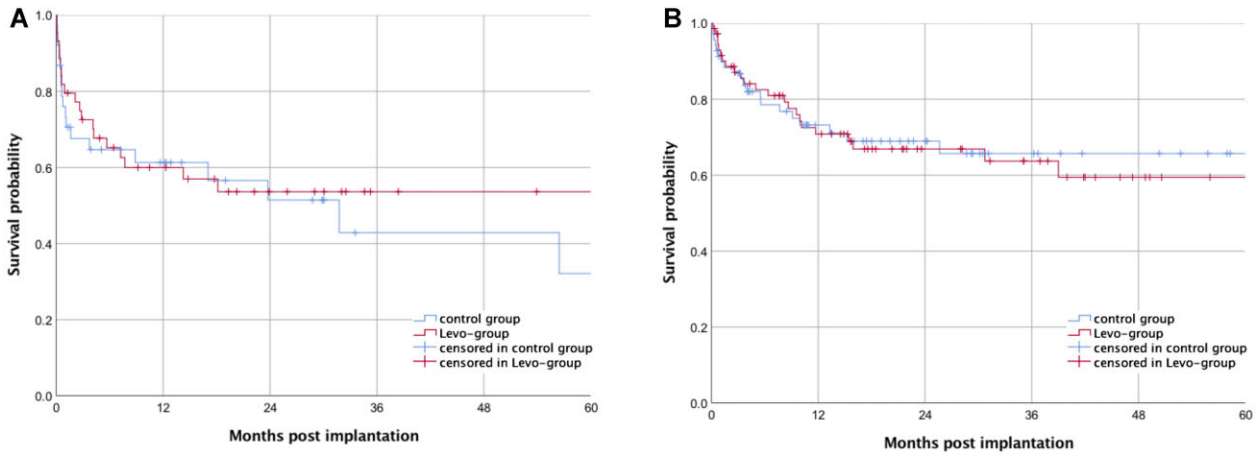


Figure 3: Kaplan–Meier survival curve for 5 post-implant years between Levo group and control group in the setting of (**a**) with or (**b**) without preoperative impaired RV function. Levo: Levosimendan; RV: right ventricular.

Levosimendan therapy gradually increased over the study period (Supplementary Material, Fig. S2), with evolving criteria for administration at the discretion of the surgical team. While at the beginning it was only administered to patients with perceived RV dysfunction, as experience grew usage became more liberal. Forth, this retrospective study covers a large period of time in which strategies in the treatment of LVAD patients evolved concomitant to the increased use of Levosimendan in our institution. Due to the limitations of this study inherent to its single centre and retrospective nature, more studies are warranted to evaluate the effects of preoperative Levosimendan therapy before LVAD implantation on clinical outcomes.

CONCLUSION

Preoperative use of Levosimendan did not reduce 30-day, in-hospital and 5-year post-implant mortality. However, it significantly reduced the risk of postoperative RV-F, especially in patients with normal preoperative RV function.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

ACKNOWLEDGEMENTS

The authors thank the whole medical staff of the Department of Cardiac Surgery at Heinrich-Heine-University Medical School for their contribution to this study.

Funding

This study was funded by institutional grants of the Dept. of Cardiac Surgery, Medical Faculty and University Hospital, Heinrich Heine University Düsseldorf, Germany.

Conflict of interest: Payam Akhyari receives speaker honoraria from Medtronic, Abbott, Edwards, Ascyrus Medical, and Abiomed. Artur Lichtenberg and Payam Akhyari have received research grants from Abbott and Edwards outside the submitted work. Other authors declare no conflicts of interest.

Data availability

All relevant data are within the article and its supporting information files. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Yukiharu Sugimura: Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing—original draft. **Nikolaos Kalampokas:** Data curation; Formal analysis; Investigation; Software; Validation; Writing—review & editing. **Metin Arikan:** Data curation; Investigation; Methodology. **Phillip Rellecke:** Investigation; Methodology; Writing—review & editing. **Hannan Dalyanoglu:** Writing—review & editing. **Igor Tudorache:** Writing—review & editing. **Ralf Westenfeld:** Writing—review & editing. **Udo Boeken:** Writing—review & editing. **Artur Lichtenberg:** Supervision; Writing—review & editing. **Payam Akhyari:** Funding acquisition; Project administration; Resources; Supervision; Writing—review & editing. **Hug Aubin:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing—review & editing.

Reviewer information

Interdisciplinary CardioVascular and Thoracic Surgery thanks Suresh Keshavamurthy and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

REFERENCES

[1] Hanff TC, Birati EY. Left ventricular assist device as destination therapy: a state of the science and art of long-term mechanical circulatory support. Curr Heart Fail Rep 2019;16:168–79.
[2] Lampert BC, Teuteberg JJ. Right ventricular failure after left ventricular assist devices. J Heart Lung Transplant 2015;34:1123–30.
[3] Conte SM, Florisson D.S, De Bono JA, Davies RA, Newcomb AE. Levosimendan following cardiac surgery. Heart Lung Circ 2019;28: e19–e20.
[4] Wang B, He X, Gong Y, Cheng B. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery: an update meta-analysis and trial sequential analysis. Biomed Res Int 2018;2018: 7563083.
[5] Putzu A, Clivio S, Belletti A, Cassina T. Perioperative levosimendan in cardiac surgery: a systematic review with meta-analysis and trial sequential analysis. Int J Cardiol 2018;251:22–31.
[6] Guarracino F, Heringlake M, Cholley B, Bettex D, Bouchez S, Lomivorotov VV *et al.* Use of levosimendan in cardiac surgery: an update after the LEVO-CTS, CHEETAH, and LICORN trials in the light of clinical practice. J Cardiovasc Pharmacol 2018;71:1–9.
[7] Pathak A, Lebrin M, Vaccaro A, Senard JM, Despas F. Pharmacology of levosimendan: inotropic, vasodilatory and cardioprotective effects. J Clin Pharm Ther 2013;38:341–9.
[8] Sorsa T, Pollesello P, Solaro RJ. The contractile apparatus as a target for drugs against heart failure: interaction of levosimendan, a calcium sensitiser, with cardiac troponin c. Mol Cell Biochem 2004;266:87–107.
[9] Pollesello P, Ovaska M, Kaivola J, Tilgmann C, Lundstrom K, Kalkkinen N *et al.* Binding of a new Ca2+ sensitizer, levosimendan, to recombinant human cardiac troponin c. A molecular modelling, fluorescence probe, and proton nuclear magnetic resonance study. J Biol Chem 1994;269: 28584–90.
[10] Papp Z, Agostoni P, Alvarez J, Bettex D, Bouchez S, Brito D *et al.* Levosimendan efficacy and safety: 20 years of simdax in clinical use. Card Fail Rev 2020;6:e19.
[11] Qiu J, Jia L, Hao Y, Huang S, Ma Y, Li X *et al.* Efficacy and safety of levosimendan in patients with acute right heart failure: a meta-analysis. Life Sci 2017;184:30–6.
[12] Immohr MB, Akhyari P, Boettger C, Erbel S, Westenfeld R, Scheiber D *et al.* Levosimendan for treatment of primary graft dysfunction after heart transplantation: optimal timing of application. Exp Clin Transplant 2021; 19:473–80.
[13] Mehta RH, Leimberger JD, van Diepen S, Meza J, Wang A, Jankowich R *et al.*; LEVO-CTS Investigators. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. N Engl J Med 2017;376: 2032–42.
[14] Landoni G, Lomivorotov VV, Alvaro G, Lobreglio R, Pisano A, Guarracino F *et al.*; CHEETAH Study Group. Levosimendan for hemodynamic support after cardiac surgery. N Engl J Med 2017;376:2021–31.
[15] Kocabeyoglu SS, Kervan U, Sert D. E, Karahan M, Aygun E, Beyazal OF *et al.* Optimization with levosimendan improves outcomes after left ventricular assist device implantation. Eur J Cardiothorac Surg 2020;57: 176–82.

[16] Belletti A, Lerose CC, Zangrillo A, Landoni G. Vasoactive-Inotropic Score: Evolution, Clinical Utility, and Pitfalls. J Cardiothorac Vasc Anesth 2021; 35:3067–77. https://doi.org/10.1053/j.jvca.2020.09.117.

[17] Kormos RL, Antonides CFJ, Goldstein D. J, Cowger JA, Starling RC, Kirklin JK *et al.* Updated definitions of adverse events for trials and registries of mechanical circulatory support: a consensus statement of the mechanical circulatory support academic research consortium. J Heart Lung Transplant 2020;39:735–50.

[18] Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and monte carlo simulations. Biom J 2009;51:171–84.

[19] Mehra MR, Uriel N, Naka Y, Cleveland JC Jr, Yuzefpolskaya M, Salerno CT *et al.*; MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device–final report. N Engl J Med 2019;380: 1618–27.

[20] Abdelshafy M, Elsherbini H, Elkoumy A, Simpkin AJ, Elzomor H, Caliskan K *et al.* Perioperative levosimendan infusion in patients with end-stage heart failure undergoing left ventricular assist device implantation. Front Cardiovasc Med 2022;9:888136.

[21] Sponga S, Ivanitskaia E, Potapov E, Krabatsch T, Hetzer R, Lehmkuhl H. Preoperative treatment with levosimendan in candidates for mechanical circulatory support. ASAIO J 2012;58:6–11.

[22] Theiss HD, Grabmaier U, Kreissl N, Hagl C, Steinbeck G, Sodian R *et al.* Preconditioning with levosimendan before implantation of left ventricular assist devices. Artif Organs 2014;38:231–4.

[23] Wachter K, Franke UFW, Rustenbach CJ, Baumbach H. Minimally invasive versus conventional lvad-implantation—an analysis of the literature. Thorac Cardiovasc Surg 2019;67:156–63.

[24] Reichart D, Brand CF, Bernhardt AM, Schmidt S, Schaefer A, Blankenberg S *et al.* Analysis of minimally invasive left thoracotomy hvad implantation—a single-center experience. Thorac Cardiovasc Surg 2019;67:170–5.

[25] Mohite PN, Sabashnikov A, Raj B, Hards R, Edwards G, Garcia-Saez D *et al.* Minimally invasive left ventricular assist device implantation: a comparative study. Artif Organs 2018;42:1125–31.