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MAIN TEXT

Incidence and risk factors of late right heart failure in chronic mechanical circulatory support

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Abstract

Background: Late right heart failure (LRHF) is a common complication during long-term left ventricular assist device (LVAD) support. We aimed to identify risk factors for LRHF after LVAD implantation.

Methods: Patients undergoing primary LVAD implantation between 2006 and 2019 and surviving the perioperative period were included for this study ($n = 261$). Univariate Cox proportional hazards analysis was used to assess the association of clinical covariates and LRHF, stratified for device type. Variables with $p < 0.10$ entered the multivariable model. In a subset of patients with complete echocardiography or right catheterization data, this multivariable model was extended. Postoperative cardiopulmonary exercise test data were compared in patients with and without LRHF.

Results: Nineteen percentage of patients suffered from LRHF after a median of 12 months, of which 67% required hospitalization. A history of atrial fibrillation (AF) (HR: 2.06 [1.08–3.93], $p = 0.029$), a higher preoperative body mass index (BMI) (HR: 1.07 [1.01–1.13], $p = 0.023$), and intensive care unit (ICU) duration (HR: 1.03 [1.00–1.06], $p = 0.025$) were independent predictors of LHRF in the multivariable model. A significant relation between the severity of tricuspid regurgitation (TR) and LRHF (HR: 1.91 [1.13–3.21], $p = 0.016$) was found in patients with echocardiographic data. Patients with LRHF demonstrated a lower maximal workload and peak VO2 at 6 months postoperatively.

Conclusion: A history of AF, BMI, and longer ICU stay may help identify patients at high risk for LRHF. Severity of TR was significantly related to LRHF in a subset of patients

KEYWORDS

late right heart failure, left ventricular assist device, mechanical circulatory support, risk factor

Susanne E. A. Felix and Lieke Numan contributed equally to this work.

1 | INTRODUCTION

Mechanical circulatory support (MCS) has been established as a valuable treatment option for patients with advanced heart failure.[1] Left ventricular assist device (LVAD) therapy is characterized by a good survival (58% at 5 years),[2–4] improved quality of life, and exercise capacity.[5] Despite this favorable outcome, adverse events in patients on LVAD support, including infection, bleeding, thrombosis, arrhythmias, and right heart failure (RHF), each may occur in up to 40% of patients.[6,7]

As a result of the increased use of MCS and the longer duration of support per patient, more information on adverse events and long-term management is obtained. Right heart failure after LVAD implantation is a major clinical problem, which may occur early after implantation, but also later in the course. Early perioperative RHF is encountered in approximately 10% of the patients and is associated with impaired survival and major adverse events.[6,8] Several risk scores were developed for the prediction of early RHF, including the EUROMACS-RHF score, which is based on the data derived from the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) database.[9–11] Despite these risk scores, early RHF remains difficult to predict in daily clinical practice.[6,9,11]

Late RHF after MCS, however, was studied to a lesser extent. Apart from the need for hospitalization, late RHF has been associated with a decreased functional capacity (6-minute walk distance) and a reduced quality of life.[12] In addition, the occurrence of late RHF might increase the need for urgent heart transplantation. Furthermore, the definition of late RHF used in current literature is not uniform.[11,13,14]

Recently, the MCS academic research consortium updated the definition of all adverse events related to MCS.[15] Late RHF was defined as the need for implantation of an RVAD > 30 days following LVAD implantation or the need for hospitalization > 30 days postimplant with the requirement of intravenous diuretics or inotropes for at least 72 hours in association with clinical signs of right sided congestion or hemodynamic compromise (e.g., renal failure, elevated lactate).[15] Two studies on this subject defined late RHF as the need for hospitalization after indexed LVAD implant hospitalization and either the need for inotropes or the need for intensified diuretic therapy, inotropic support, and right ventricular assist device (RVAD) implantation.[12,14,16]

The abovementioned definitions of RHF are heavily based on hospitalization of the patient, while an important argument for LVAD therapy actually is to keep the patient with severe HF out of hospital. Furthermore, the initial treatment of late RHF consists mainly of increasing oral dosages of diuretics. So relying only on hospitalization for the definition of late RHF negates those patients who do show signs of RHF but can be treated by higher doses of diuretics. Therefore, we aimed to identify risk factors for the development of late RHF in all patients on MCS, including patients without the need for hospitalization.

2 | MATERIALS AND METHODS

2.1 | Study sample and data collection

Between 2006 and 2019, 262 out of 296 patients were successfully discharged after LVAD implantation using the HeartMate II (HM-II, Abbott, St. Paul, MN, USA), the HeartMate 3 (HM3, Abbott, St. Paul, MN, USA), or the HeartWare (HVAD, Medtronic, Framingham, MA, USA) at the University Medical Centre of Utrecht, all initially implanted as a bridge to transplantation or bridge to decision (BTT or BTD). The standard surgery technique was a full median sternotomy using cardiopulmonary bypass. Cardiopulmonary exercise test (CPET) was prospectively planned at 6 months postoperatively together with laboratory test including hemoglobin and B-type natriuretic peptide (BNP). CPET was performed on a bicycle ergometer using previously published methods.[5]

Baseline data, including preimplant demographics, medical history, and clinical status, were collected in a central database and are further addressed as "baseline dataset." This dataset was enriched with the data obtained from the postoperative CPET results and adverse events defined according to the Inter-agency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria (except for late RHF, which is defined below).[15] Preoperative right ventricular function was evaluated using echocardiogram and hemodynamic measurements, maximally 90 days before LVAD implantation. Echocardiographic parameters included the tricuspid annular plane systolic excursion (TAPSE, in mm), peak systolic velocity on tissue Doppler imaging (TDI-RV, in cm/s), and severity of tricuspid regurgitation (TR, categorized as no/mild or moderate/severe TR). Invasively measured hemodynamic parameters included central venous pressure (CVP, in mm Hg), mean pulmonary artery pressure (mPAP, in mm Hg), cardiac index (CI, in l/min/m^2), and RVSWI (in mL × mm Hg/m^2). An overall assessment of right ventricular function (categorized as poor, intermediate, or good) was made by two independent cardiologists using previously published methods.[17]

Retrospectively, the occurrence of late RHF during MCS, in both outpatients and hospitalized patients, was extracted from the electronic health records. Follow-up was completed for all patients until death, heart

transplantation, explantation, or the end of the study (March 2019). This study was approved by our institutional ethical board and the need for informed consent was waived.

2.2 | Definitions of RHF and end points

Early (perioperative) RHF was defined as right ventricular dysfunction, requiring right ventricular assist device (RVAD)-implantation, inhaled nitric oxide, or inotropic therapy for more than 1 week during the index hospitalization for LVAD implantation <30 days post implantation.

Late RHF was defined as the occurrence of right ventricular dysfunction associated with symptoms of right heart failure (i.e., jugular venous distension, hepatic congestion, and peripheral edema), if diagnosed by a cardiologist after the index hospitalization for LVAD implantation >30 days post implantation. The primary end point of this study was the diagnosis of late RHF in combination with the need for intensification of diuretics (either with or without hospitalization) and/or the need for inotropes and/or RVAD. Secondary outcomes include the requirement for hospitalization due to late RHF and functional capacity, examined by CPET at 6 months postoperatively.

2.3 | Statistical analysis

Categorical variables are reported in percentages. Comparison of dichotomous variables between patients with and without late RHF was performed with Fisher's exact test. Continuous variables are reported as median (interquartile range). Differences in continuous variables between patients with and without late RHF were analyzed with the Mann–Whitney U test. Kaplan–Meier analysis was used to evaluate the LRHF free survival, censoring for explantation, and heart transplantation. The relationship between the occurrence of early and late RHF was tested using a chi-squared test.

Univariate stratified cause-specific Cox proportional hazards models were used to assess the association between each of the demographic, pre- and peri-operative covariates, and the occurrence of late RHF. Patients were censored for heart transplantation, death, explantation, or ongoing support at the end of the follow-up. Univariate variables with $p < 0.10$ entered the multivariable Cox model.

In addition, we separately assessed an extension of this multivariate Cox model in a subset of patients who had a complete assessment of right ventricular function by echocardiography or right catheterization prior to the LVAD implantation. We stratified by device type, as the hazards were not proportional for the different devices. All covariates with $p < 0.05$ were defined significant in the multivariable analysis.

3 | RESULTS

Between 2006 and 2019, 296 LVAD implants were performed at our center. Thirty-four (11%) patients died during the index hospitalization, leaving 262 for inclusion of this study with complete baseline data in 261 (99.6%) (66% male, median age 53 (interquartile range (IQR): 17) years at implantation). The median duration of MCS was 779 (IQR: 881) days, resulting in 647 patient-years MCS experience.

During follow-up, 49 (19%) patients developed late RHF. Figure 1 depicts LRHF free survival after LVAD implantation. In all patients, medical therapy was intensified, 2/3 ($n = 33$, 67%) required hospitalization, of which one patient underwent RVAD implantation. This patient suffered from recurrence of giant cell myocarditis. Late RHF occurred after a median of 363 (IQR: 837) days after LVAD implantation. Nineteen patients (7%) who suffered from late RHF died after a median of 120 (IQR: 292) days after diagnosis and twelve were transplanted after a median of 200 (176) days after the first diagnosis of late RHF.

In comparison to patients without late RHF ($n = 212$), patients with late RHF had a significantly higher preoperative body mass index (BMI), more often received preoperative temporary support and were less frequently classified as INTERMACS 3–7 at the time of LVAD implantation. In addition, the duration of index hospitalization (including stay on the intensive care unit (ICU)) was longer, as shown in Table 1. Baseline laboratory results

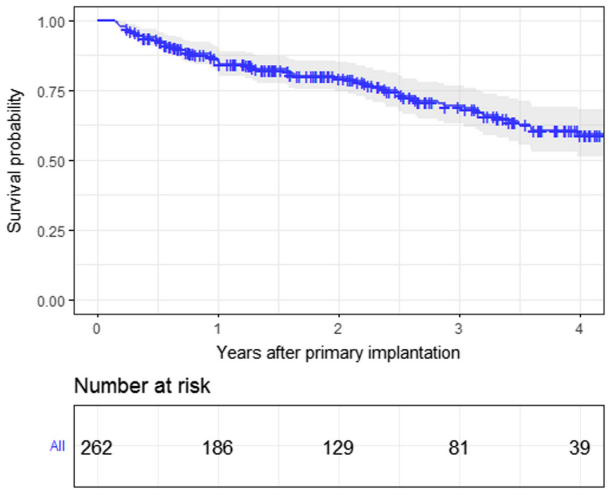

FIGURE 1 Late right heart failure free survival after primary left ventricular assist device implantation, censoring for explantation and heart transplantation. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline data in patients with and without late right heart failure (LRHF).

Patient characteristics	No LRHF ($n=212$) n (%) or median [IQR]	LRHF ($n=49$) n (%) or median [IQR]	p value
Gender – male	70 (33.0)	18 (36.7)	0.743
Age at implant	53.1 [44–60]	53.2 [44–61]	0.744
Body mass index (kg/m^2)	23.4 [22–26]	25.3 [23–28]	0.006
Etiology – dilated cardiomyopathy	135 (63.7)	27 (55.1)	0.341
INTERMACS 0 (Preoperative temporary support)	31 (14.6)	17 (34.7)	0.002
Preoperative support: ECMO	20 (9.4)	15 (30.6)	<0.001
Preoperative support: IABP	8 (3.8)	0 (0)	0.357
Preoperative support: Impella	1 (0.5)	0 (0)	1.000
Preoperative support: Other	2 (0.9)	2 (4.1)	0.334
INTERMACS 1	10 (4.7)	2 (4.1)	1.000
INTERMACS 2	86 (40.6)	18 (38.8)	0.945
INTERMACS 3–7	90 (42.5)	11 (22.4)	0.016
Details primary LVAD implantation			
TV concomitant	32 (15.1)	8 (16.3)	1.000
Previous (CABG)	14 (6.6)	4 (8.2)	0.940
Previous major cardiac surgery	34 (16.0)	13 (26.5)	0.129
CPB time (min)	112 [92–135]	115 [103–132]	0.201
Device type			
HeartMate II	119 (56.1)	22 (44.9)	0.005
HeartWare	48 (22.6)	22 (44.9)	
HeartMate 3	45 (21.2)	5 (10.2)	
Total duration hospitalization (days)	42 [31–54]	47 [36–70]	0.036
ICU stay (days)	6.0 [4–9]	7.0 [5–19]	0.005
Medical history			
History of hypertension	22 (10.4)	3 (6.1)	0.520
Diabetes mellitus	23 (10.8)	9 (18.4)	0.228
COPD	10 (4.7)	3 (6.1)	0.965
TIA/CVA	18 (8.5)	2 (4.1)	0.455
Atrial fibrillation	47 (22.2)	17 (34.7)	0.098
Preoperative laboratory results			
Blood urea nitrogen (mg/dL)	29.0 [22–38]	32.0 [24–41]	0.354
Kreatinin (mg/dL)	1.27 [1.0–1.6]	1.22 [1.0–1.6]	0.784
eGFR <60 mL/min/m^2	89 (42)	25 (51)	0.322
Bilirubin total (mg/dL)	1.29 [0.9–2.1]	1.17 [0.9–1.8]	0.730
AST (U/L)	41.5 [26–68]	41.0 [33–64]	0.562
ALT (U/L)	55.0 [27–132]	44.0 [24–95]	0.383
Right heart function – echo ($n=159$)			
TAPSE (mm)	14.0 [12–17]	14.0 [12–17]	0.984
TDI-RV (cm/s)	8.1 [7–10]	8.4 [7–10]	0.641
No/mild tricuspid regurgitation	96 (49.5)	18 (43.9)	0.633
Moderate tricuspid regurgitation	58 (29.9)	7 (17.1)	0.140
Severe tricuspid regurgitation	40 (20.6)	16 (39.0)	0.021

(Continues)

TABLE 1 (Continued)

Patient characteristics	No LRHF ($n=212$) n (%) or median [IQR]	LRHF ($n=49$) n (%) or median [IQR]	p value
Poor RV function	31 (14.9)	8 (17.0)	0.889
Intermediate RV function	151 (72.2)	36 (76.6)	0.706
Good RV function	26 (12.5)	3 (6.4)	0.348
Right heart catheterization ($n=165$)			
Central venous pressure (mm Hg)	9.0 [5–13]	11.0 [8–15]	0.016
Mean pulmonary artery pressure (mm Hg)	32.0 [25–37]	30.0 [24–42]	0.793
Cardiac index (l/min/m^2)	1.77 [1.4–2.1]	1.75 [1.5–2.0]	0.954
Right ventricular stroke work index (mL × mm Hg/m^2)	411 [278–582]	288 [241–486]	0.079
Postoperative adverse events			
Early right heart failure	49 (23.1)	16 (32.7)	0.227
Dialysis	21 (9.9)	7 (14.3)	0.524
Hypertension	11 (5.2)	1 (2.0)	0.569
Atrial fibrillation	64 (30.2)	27 (55.1)	0.002

representing renal and liver function did not differ between patients with or without late RHF. In the postoperative course, significantly more patients with late RHF suffered from atrial fibrillation (AF: paroxysmal, persistent, or permanent).

Using the chi-squared test, no relation was found between the occurrence of early RHF and late RHF ($p=0.220$), although one-third of the patients who developed late RHF also suffered from early RHF and a quarter of patients showing early RHF later-on developed late RHF.

3.1 | Cox proportional hazard analysis

Univariate factors significantly associated with late RHF were: a higher BMI (hazard ratio (HR) 1.06 [95% confidence interval (CI) 1.01 to 1.11], $p=0.018$), preoperative temporary support (HR: 2.41 [95% CI: 1.34–4.35], $p=0.003$), and a history of AF prior to implantation (1.79 [95% CI: 0.99–3.23], $p=0.054$). In addition, a longer duration on the intensive care unit (ICU) (1.03 [95% CI: 1.01–1.04], $p=0.003$) and duration of hospitalization (1.01 [95%CI: 1.00–1.02], $p=0.042$) after primary implantation were significant univariate factors. Renal and liver function before MCS implantation was not associated with the occurrence of late RHF. Table 2 shows the results of all univariate regression results.

Multivariable stratified Cox proportional hazard analysis showed a history of AF (HR 2.06; 95% CI 1.08–3.93, $p=0.029$), a higher preoperative BMI (in kg/m^2, HR 1.07; 95% CI 1.01–1.13, $p=0.023$), and longer duration on the ICU after primary implantation (in days, HR 1.03; 95% CI 1.00–1.06, $p=0.025$) to be independent predictors of late RHF.

3.2 | Additional preoperative diagnostic results to predict late right heart failure

Complete echocardiographic data, including TAPSE, TDI-RV, severity of tricuspid regurgitation, and overall right ventricular function, were available in 145 (55%) patients. Right heart catheterization (RHC) before LVAD implantation was available in 155 (59%) patients. The incidence of late RHF in this subgroup with complete echocardiographic data (18%) and hemodynamic data (19%) was similar to the incidence in the whole group in the "baseline dataset" (19%). Noteworthy, patients in the group with complete ECHO differed from patients without complete ECHO data, especially in INTERMACS score. Patients with complete RHC data differed from patients without RHC data, especially in age, etiology, INTERMACS score, and cardio pulmonary bypass (CPB) time. Baseline difference for both groups is displayed in supplementary Table S2 and S3.

Out of all echocardiographic variables, preoperative TR severity was a significant univariate predictor (HR 1.95 [95% CI 1.23–3.08, $p=0.004$]). For the RHC variables, RVSWI (HR 0.99 [95% CI 1.00–1.00, $p=0.05$]), CVP (HR 1.11 [95% CI 1.05–1.17, $p<0.001$]), and PAPi (HR 0.68 [95% CI 0.53–0.89, $p=0.005$]) were selected for the multivariate model.

To analyze the contribution of echocardiography and/or right heart catheterization at baseline to the prediction of late RHF, these parameters were included in the multivariable Cox regression model in subsets of patients with complete echocardiographic and/or invasive hemodynamic assessment of right ventricular function (Supplementary Table S4 and S5). TR-severity remained

TABLE 2 Univariate and significant multivariable demographic and perioperative risk factors for late RHF ($n = 261$).

	Univariate risk factors		Multivariable risk factors	
Parameters	**HR [95% CI]**	**p-value**	**HR [95% CI]**	***p* value**
Gender – male	1.05 [0.59–1.88]	0.865		
Age at implantation (years)	1.01 [0.98–1.03]	0.556		
Body mass index (kg/m^2)	1.06 [1.01–1.11]	0.018	1.07 [1.01–1.13]	0.023
Etiology – dilated cardiomyopathy	0.72 [0.41–1.27]	0.261		
Preoperative temporary support	2.38 [1.32–4.29]	0.004	1.45 [0.71–2.96]	0.305
INTERMACS 1	1.21 [0.29–4.98]	0.796		
INTERMACS 2	0.92 [0.52–1.64]	0.775		
Details primary LVAD implantation				
TV concomitant	1.12 [0.53–2.40]	0.761		
Previous CABG	1.10]0.39–3.07]	0.861		
Previous major cardiac surgery	1.64 [0.87–3.10]	0.126		
Cardiopulmonary bypass time	1.00 [1.00–1.01]	0.429		
Duration on ICU (days)	1.03 [1.01–1.04]	0.003	1.03 [1.00–1.06]	0.025
Duration of hospitalization (days)	1.01 [1.00–1.02]	0.042	0.99 [0.98–1.01]	0.402
Medical history				
History of hypertension	0.84 [0.26–2.71]	0.771		
Diabetes mellitus	1.55 [0.75–3.20]	0.235		
History of COPD	1.80 [0.56–5.82]	0.326		
History of TIA/CVA	0.59 [0.14–2.42]	0.462		
History of atrial fibrillation	1.79 [0.99–3.23]	0.054	2.06 [1.08–3.93]	0.029
Preoperative laboratory results				
Blood urea nitrogen (mg/dL)	1.01 [0.99–1.02]	0.307		
Kreatinin (mg/dL)	1.07 [0.64–1.81]	0.781		
eGFR <60 mL/min/m^2	1.36 [0.77–2.38]	0.288		
Bilirubin (mg/dL)	0.91 [0.66–1.27]	0.597		
Aspartate aminotransferase (U/L)	1.00 [1.00–1.00]	0.290		
Alanine transaminase (U/L)	1.00 [1.00–1.00]	0.111		

significant in the multivariable Cox regression analysis in the ECHO dataset, with HR 1.91 [95% CI 1.13–3.21, $p = 0.016$]. For the hemodynamic parameters, none of the selected covariates remained significant in the multivariable model.

3.3 | Functional capacity

As it is known that patients with late RHF have an impaired exercise tolerance, we analyzed the results of routinely planned CPET at 6 months after implantation. Results of the CPET were compared between patients who developed late RHF (after a median of approximately 1 year after implantation) and patients who did not develop late RHF. CPET data at 6 months after LVAD implantation were available in 146 patients. Those patients who developed late RHF ($n = 23$) demonstrated already a significant lower maximal work load and peak VO2 (both $p < 0.001$) 6 months after LVAD implantation in comparison with patients without late RHF ($n = 123$), while respiratory quotient did not differ significantly ($p = 0.185$)

(Table 3). In addition, patients with late RHF had a significantly lower peak heart rate during the test ($p = 0.011$).

4 | DISCUSSION

We presented the prevalence and risk factors for late right heart failure after LVAD implantation including patients presented at the outpatient clinic in addition to patients in need of hospitalization (graphical abstract). In a cohort of 261 patients, successfully discharged after LVAD implantation, 19% of patients suffered from late RHF, indicated by the need for intensification of diuretics with/without inotropes, of which two-third required hospitalization. The incidence of late RHF is higher in comparison with previous studies,[12,16] as patients treated at the outpatient clinic were included as well. Using the stricter criteria, one-third of the cases in our study (16 patients) would have been missed. We prefer to include those cases as early recognition and treatment of late RHF might even prevent re-hospitalization. Readmission for late RHF was necessary in 33 patients (13% of the total population), which is in line with current literature (8–17%).[12,16]

In contrast to Alkhunaizi et al., we found no association between early RHF and LRHF.[14] One-third of the patients who suffered from late RHF also had early RHF, though only a quarter of the patients with early RHF developed late RHF. Probably late RHF is caused by other mechanisms than RHF in the early postoperative phase. Wagner et al. demonstrated that preoperative right heart failure increases the risk of early RHF and persistent RHF, but not for new onset LRHF.[18] Early RHF can be caused by acute volume overload and septal shift of the RV at the start of left ventricular unloading by the pump (LVAD) in combination with a rise in pulmonary vascular resistance due to excessive blood loss.[19,20]

Late RHF in our study was significantly associated with a postoperative duration on the ICU, likely related to the severity of disease in the perioperative phase. This could be explained by different mechanisms. First, in the severely hemodynamically compromised patients, volume overload of the right ventricle might result in increased cardiomyocyte apoptosis, compromising the remaining cardiomyocytes in the RV with dire consequences in the long run.[21]

On univariate analysis, INTERMACS 0 was significantly related to late RHF. However, it was not significant in the multivariable model. Patients with a worse INTERMACS classification are probably reflected by patients with a longer hospitalization and ICU-duration, which was a significant predictor in the multivariable model. Cotts et al. demonstrated a significant relation between INTERMACS classification and the hospital duration after primary LVAD implantation.[22]

Furthermore, progression of the underlying disease, such as dilating cardiomyopathy, might enhance further deterioration of right ventricular function.[23–26] In addition, pump speed of the LVAD is important to the pre- and afterload of the right ventricle, also affecting the position of the interventricular septum. Too much unloading of the LVAD will shift the interventricular septum leftward

TABLE 3 Results of cardiopulmonary exercise test at 6 months postoperatively in patients with and without late RHF ($n = 146$).

Parameter	No late RHF ($n = 123$)	Late RHF ($n = 23$)	p value
Gender – male (no, %)	89 (72%)	13 (57%)	0.129
Age (years, mean ± SD)	49.4 ± 12.8	50.6 ± 11.4	0.910
Body mass index (kg/m^2)	24.4 ± 3.4	23.7 ± 3.6	0.277
Max load (Watt, mean ± SD)	106 ± 33	76 ± 18	< 0.001
VO2 (L/min, mean ± SD)	1.28 ± 0.40	0.96 ± 0.24	< 0.001
VO2% predicted (mean ± SD)	53 ± 12	42 ± 9	< 0.001
VO2/kg (mean ± SD)	16.7 ± 4.8	13.2 ± 3.5	< 0.001
VO2/kg % predicted (mean ± SD)	52 ± 12	43 ± 12	0.001
Anaerobic threshold (mean ± SD)	11.1 ± 3.0	9.1 ± 2.6	0.004
Respiratory exchange ratio (mean ± SD)	1.21 ± 0.11	1.21 ± 0.12	0.737
EqCO2 (mean ± SD)	36.4 ± 6.5	38.2 ± 5.5	0.185
Max heart rate (bpm, mean ± SD)	140 ± 28	122 ± 30	0.011
Hemoglobin (g/dL, mean ± SD)	12.9 ± 1.5	12.6 ± 1.4	0.474
B-type natriuretic peptide (pg/mL, mean ± SD)	180 ± 146	312 ± 330	0.060

together with an increased preload of the right ventricle resulting in RV overload.[27] Initially this volume overload is well tolerated by the RV, but in the end it will result in RV failure.[20] This could well explain the timing of clinical appearance of right heart failure in MCS patients. Therefore, echocardiographic follow-up is very important to identify alterations in right ventricular dimensions, function, and the position of the interventricular septum.[28]

We showed for the first time that a history of AF increases the risk of developing late RHF. Alkunaizi et al. found a trend towards increased postoperative (6 months) AF in LRHF patients, but no significant association between preoperative AF and LRHF.[14] In general, atrial fibrillation is known to affect prognosis in heart failure patients in a negative way, both in heart failure with a reduced ejection fraction and heart failure with a preserved ejection fraction.[29,30] A recent study identified an association between atrial fibrillation and the development of right ventricular dysfunction in patients with a preserved left ventricular systolic function during 4-year follow-up.[31] This is an interesting observation and seems analogous to the situation in long-term MCS. In addition, we showed that a higher BMI, probably a surrogate for other risk factors, is associated with late RHF. This relationship was previously published in a meta-analysis.[32] In contrast to previous studies, we did not find an association between preoperative renal function and late RHF. Significantly higher pre- and postoperative BUN levels were correlated with LRHF.[12,14,16] Generally, BUN levels in these studies were higher in comparison with our study, probably reflecting an older population with a higher prevalence of ischemic heart disease.

As expected, we showed that a preoperative TR severity was an independent predictor for late RHF, as it is a surrogate marker for RV dysfunction. Consistent with our study, Schlöglhofer et al. found no significant relation between preoperative CVP and right heart failure. However, they showed that early postoperative CVP is an independent predictor of right heart failure.[13] Wagner et al. demonstrated no predictive value of echocardiographic of hemodynamic parameters for new onset LRHF.[18]

An important finding in our study is that physical impairment in patients developing late RHF is already apparent at an exercise test 6 months postoperatively, long before the RHF is clinically discernable in most patients. This reduced exercise may result from subclinical right heart failure, as the right ventricular ejection fraction is related to peak VO2 in patients with advanced heart failure.[33] Thus, setting standards for expected peak VO2 after LVAD implantation will help identify patients with a reduced exercise capacity during follow-up, in whom closer monitoring and early treatment are indicated to prevent LRHF. In addition to our between group comparison of VO2, it is of interest whether VO2 is predictive at the individual level.

4.1 | Limitations

There are some inherent limitations to this study. First, this study was conducted in patients initially implanted as a BTT or BTD. Although many patients were supported for a longer time as a result of the shortage of donor hearts, results might not be extrapolated directly to patients with MCS as destination therapy which generally is an older population with more comorbidities.

Additionally, analysis was done including patients on HMII, HVAD, or HM3 support. This is a limitation, as HMII and HVAD are withdrawn from the market. Hence, larger studies including HM3 patients only are warranted to confirm current findings.

As the data were not complete for all patients, we performed the multivariate stratified Cox model with the addition of echocardiography and right heart catheterization parameters in a subpopulation with available data, which may not account for the whole population as these patients differed in baseline characteristics.

Late RHF warranting increased medical therapy with or without admission to the hospital is a dreaded complication of chronic MCS and affects 19% of the patients, after a median postoperative duration of one year. We demonstrated that a history of atrial fibrillation, a higher preoperative BMI, and a longer duration of stay on the ICU after implantation were significantly related to late RHF. In a subanalysis, we showed that a TR-severity preoperatively is an independent predictor for late RHF. Furthermore, patients with late RHF demonstrated a reduced exercise capacity already at 6 months after implantation in comparison to patients without late RHF. Patients at higher risk of development of late RHF should be followed-up more closely and treated more intensively to prevent hospitalization.

AUTHOR CONTRIBUTIONS

Concept/design: Susanne E. A. Felix, L.W.L, N.J., Marish I. F. Oerlemans. *Data analysis/interpretation*: Susanne E. A. Felix, Lieke Numan, E. Aarts, Linda W. van Laake. *Drafting article*: Susanne E. A. Felix, Lieke Numan. *Critical revision of article*: All. *Approval of article*: All. *Statistics*: Susanne E. A. Felix, E.A., Lieke Numan. *Data collection*: Susanne E. A. Felix, Lieke Numan.

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CONFLICT OF INTEREST STATEMENT

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