

Prolonged mechanical ventilation after left ventricular assist device implantation: risk factors and clinical implications

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Abstract

Aims Unsuccessful weaning from ventilator after major cardiovascular procedures has been shown to be associated with increased post-operative morbidity and mortality. Our study aimed to identify predictors and clinical implications of prolonged mechanical ventilation (PMV) after left ventricular assist device (LVAD) implantation.

Methods and results We analysed the data of patients receiving a continuous-flow LVAD in our centre from December 2010 to September 2017. PMV was defined by a duration of invasive ventilation of >7 days after LVAD implantation. Multivariable logistic regression analysis was performed for predictors of PMV. Survival was estimated by the Kaplan–Meier method. During the study period, 156 patients received a continuous-flow LVAD in our centre. Seventeen patients were excluded due to early death (<7 days), and 139 patients were enrolled in the study (mean age: 58 years; male: 84%). The median duration of mechanical ventilation post-operatively was 94 h (range: 5 to 4192 h). PMV was observed in 43% of patients. Patients on PMV were characterized by a more severe disease state at baseline, compared with the group of early extubation, as reflected by their Inter-agency Registry for Mechanically Assisted Circulatory Support level (Level 1–3: 72 vs. 49%, $P = 0.008$). Patients on PMV exhibited higher pulmonary wedge pressures (25 vs. 21 mmHg, $P = 0.04$), lower estimated glomerular filtration rate (53 vs. 60 mL/min/1.73 m², $P = 0.02$), lower haemoglobin (10.6 vs. 11.6 g/dL, $P = 0.02$), and lower platelet counts (189 vs. 240/nL, $P = 0.02$). Previous sternotomy was more frequent in the PMV group (32 vs. 13%, $P = 0.006$). Higher rates of preoperative circulatory support (30 vs. 11.4%, $P = 0.006$), dialysis (31.7 vs. 10.1%, $P = 0.001$), and invasive ventilation (35 vs. 7.6%, $P < 0.001$) were reported for the PMV group. Logistic regression analysis revealed that estimated glomerular filtration rate [odds ratio (OR) 0.977, confidence interval (CI) 0.955–0.999, $P = 0.038$], platelet count (OR 0.994, CI 0.989–0.998, $P = 0.008$), and previous sternotomy (OR 5.079, CI 1.672–15.427, $P = 0.004$) were independent predictors of PMV. PMV was accompanied by longer intensive care unit (24 vs. 4 days, $P < 0.001$) and hospital stay (47 vs. 32 days, $P = 0.003$). Survival analysis revealed a profound increase in mortality at 180-day post-implantation in the PMV group (62 vs. 10%, log-rank: $P < 0.001$).

Conclusions Prolonged mechanical ventilation affects nearly half of patients after LVAD implantation. Previous sternotomy, renal function, and platelet counts are associated with increased risk for PMV. PMV is accompanied by decreased survival at 180-day post-implantation and longer hospitalizations.

Keywords Prolonged ventilation; Ventricular assist devices; Weaning

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Introduction

Prolonged mechanical ventilation (PMV) after major cardiovascular procedures has been shown to adversely affect

post-operative outcome and survival and is accompanied by incremental health costs.^{1–9} Previous studies in patients undergoing general cardiac surgery have reported an incidence of 2–10%, with in-hospital mortality rates exceeding

40%.^{2,5,6,9} In the setting of advanced heart failure refractory to conventional therapy, the implantation of a left ventricular assist device (LVAD) is nowadays an established treatment option with rapidly expanding indications and availability. Beyond the severity of the heart failure syndrome itself, the significant burden of co-morbidities poses these patients at high risk for post-operative complications such as respiratory failure, right ventricular insufficiency, systemic infections, and multi-organ failure. The condition of PMV after LVAD implantation has not been reported in the literature so far. We aimed to investigate the predictive potential of preoperative and intraoperative variables for the assessment of PMV probability as well as the clinical relevance of PMV in this patient cohort, in terms of the duration of post-operative hospitalization and short-term survival.

Methods

Study design

We retrospectively reviewed the database of our interdisciplinary heart failure unit to identify consecutive adult patients who received a durable, continuous-flow LVAD at our institution from December 2010 through September 2017. Clinical data regarding patients' medical history and disease status in the recent preoperative period, as well as operative variables, were prospectively collected in a digitalized database dedicated to clinical surveys. Post-operative complications and follow-up data were extracted retrospectively from the surgical reports and the patients' electronic health records. The follow-up visits in the outpatient clinic were prospectively scheduled at 3 and 6 months after implantation according to a standardized internal protocol. Patients were excluded from analysis if they were already on LVAD support and received exchange for pump failure or in case of early death before the seventh post-operative day. All study participants provided written consent to anonymized data analysis for scientific purposes at admission but no individual informed consent. The study received approval by the ethics committee of our institution (18-8174-BO) and was conducted in accordance with the Declaration of Helsinki on ethical principles for medical research.

Ventilation and weaning protocol

Ventilation was initiated intraoperatively unless a deprived clinical status resulting in respiratory insufficiency had previously rendered intubation and mechanical ventilation inevitable. All LVAD implantations were performed by the same surgical team at the West-German Heart and Vascular Centre, University Hospital Essen, Germany. After the implant procedure, patients were transferred immediately from the

operating room to the intensive care unit (ICU) of the transplant department. The first spontaneous breathing trial was performed within a minimum of 5 h after arriving at the ICU. Patients were considered eligible for extubation, if they achieved adequate oxygenation and ventilation indices in the blood gas analysis, sustained haemodynamic stability with no need for or low dose of vasoactive drugs, exhibited normal neurologic findings, and had a drainage volume loss of less than 100 mL/h after reduction of post-operative anaesthesia. The final decision to extubate, re-intubate, or perform a percutaneous tracheostomy was left to the independent discretion of the attending intensivist. Post-operative PMV was defined as the inability to wean from the ventilator for more than 7 days after surgery or reintubation before the Day 7, with ongoing mechanical ventilation on Post-operative Day 7 and a cumulative time on ventilation longer than 7 days. The cut-off at 7 days was chosen in accordance with the definition proposed by the European Respiratory Society Task Force.¹⁰ Preoperative PMV was defined by ventilation for >7 consecutive days up to the implantation day. Patients were discharged from the ICU to the intermediate care unit after being successfully weaned from mechanical ventilation and cardiorespiratory stable or on minimal support by non-invasive ventilation for more than 24 h.

Statistical analysis

Continuous variables are summarized as means (standard deviations), unless indicated otherwise, and categorical variables as counts (percentages). Continuous data were evaluated for normality of distribution with the Shapiro–Wilk test. The two-sided *t*-test was used for comparison of continuous, normally distributed data, otherwise the non-parametric Mann–Whitney *U*-test. The χ^2 test was used for testing the association between two categorical variables. Binomial logistic regression analysis was performed to ascertain the effects of preoperative variables on the likelihood of PMV. Variables were selected on the basis of clinical relevance and were introduced in the model with the one-step enter method. Kaplan–Meier analysis was conducted to estimate survival. Patients were censored at the time of transplant, explantation for recovery or by the end of the study period. The log-rank test was utilized to determine differences in survival between groups. The level of significance was set at 0.05. All analyses were performed using SPSS (IBM Corp., SPSS Statistics, version 23.0. Armonk, NY).

Results

During the study period, 156 patients received a durable, continuous-flow LVAD at our centre. Seventeen patients

were excluded due to early death before the end of the seventh post-operative day, and 139 patients were enrolled in the study. The mean age was 58 years, and 84% were male. The treatment goal was destination therapy in 62% of patients and 59% of patients were on INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) Level 1–3 at the time of implantation. Overall, the median duration of mechanical ventilation post-operatively was 94 h, ranging from 5 to 4192 h, whereas 27 patients were already on mechanical ventilation at the time of the procedure.

PMV was observed in 43% of the study patients. *Table 1* displays the preoperative and intraoperative data of patients

with PMV in comparison with patients who achieved early extubation (EE) after device implantation, according to the aforementioned definition.¹⁰ There was a higher proportion of patients with critical or declining clinical condition in the PMV group, as shown by the higher proportion of patients with INTERMACS Level 1 ($P < 0.001$) or INTERMACS Level 1–3 in this group ($P = 0.008$). Concerning age, demographics, and somatometrics, no significant differences were noted. Although left ventricular ejection fraction and cardiac index were similar, patients with PMV had higher pulmonary wedge pressure (24.8 vs. 21.5 mmHg, $P = 0.04$). Furthermore, they had worse renal function at baseline [estimated glomerular

Table 1 Preoperative and intraoperative parameters in patients with prolonged mechanical ventilation vs. early extubation

Variable	PMV <i>n</i> = 60	EE <i>n</i> = 79	<i>P</i> value
Age (years)	58.5 ± 10.5	57.5 ± 10.5	0.88
Male gender	50 (83.3)	67 (84.8)	0.81
INTERMACS level			0.01
1	23 (38.3)	10 (12.7)	<0.001
2	8 (13.3)	10 (12.7)	0.91
3	12 (20.0)	19 (24.1)	0.57
4	12 (20.0)	32 (40.5)	0.01
5	5 (8.3)	8 (10.1)	0.72
1–3	43 (71.7)	39 (49.4)	0.008
Ischaemic heart disease	34 (56.7)	41 (51.9)	0.58
Destination therapy	40 (66.7)	46 (58.2)	0.31
Body mass index (kg/m ²)	26.5 ± 5.3	26.7 ± 5.5	0.84
BSA (m ²)	1.94 ± 0.23	1.99 ± 0.22	0.23
Mean PAP (mmHg)	36.2 ± 9.8	30.8 ± 11.3	0.18
PCWP (mmHg)	24.8 ± 7.0	21.5 ± 8.9	0.04
Cardiac index (L/min/m ²)	1.75 ± 0.4	1.86 ± 3.6	0.31
LVEF (%)	17.9 ± 6.7	16.6 ± 6.5	0.26
Creatinine (mg/dL)	1.58 ± 0.65	1.47 ± 0.91	0.04
eGFR (mL/min/1.73 m ²)	53.2 ± 22.3	60.1 ± 22.1	0.02
BNP (pg/mL) ^a	943 (4794)	862 (4973)	0.38
Haemoglobin (g/dL)	10.6 ± 2.1	11.6 ± 2.0	0.002
Platelets (/nL)	189 ± 99	240 ± 115	0.02
Anaemia	52 (86.7)	60 (75.9)	0.10
CKD	27 (45)	33 (42)	0.46
Hypertension	43 (72)	52 (66)	0.46
Diabetes mellitus	15 (25.0)	32 (40.5)	0.056
Atrial fibrillation	33 (55)	29 (36.7)	0.03
Chronic lung disease	15 (25.0)	19 (24.1)	0.90
Peripheral arterial disease	4 (6.7)	8 (10.1)	0.47
Smoking history	35 (60.8)	48 (58.3)	0.77
Previous sternotomy	19 (31.7)	10 (12.7)	0.006
IABP	6 (10.0)	5 (6.3)	0.43
ECLS/temporary VAD	18 (30.0)	9 (11.4)	0.006
Invasive ventilation preop.	21 (35.0)	6 (7.6)	<0.001
Duration of preoperative ventilation (h) ^a	107.82 (1328)	17.54 (548)	<0.001
PMV preop.	16 (26.7)	4 (5.1)	<0.001
Tracheostomy preop.	11 (18.3)	3 (3.8)	0.005
Dialysis preop.	19 (31.7)	8 (10.1)	0.001
Inotropes preop.	38 (63.3)	54 (68.4)	0.54
CPB duration (min)	92.2 (31.8)	85.2 (27.4)	0.33
Concomitant procedure	10 (16.7)	14 (17.7)	0.87
Concomitant valve procedure	2 (3.3)	5 (6.3)	0.49

Note. BNP, B-type natriuretic peptide; BSA, body surface area; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; ECLS, extracorporeal life support; EE, early extubation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PMV, prolonged mechanical ventilation; VAD, ventricular assist device.

^aVariables are presented as median (range).

filtration rate (eGFR) 53 vs. 60 mL/min/1.73 m², $P = 0.02$], whereas a similarly high prevalence of chronic kidney disease (CKD) was observed in the two groups (45 vs. 42%, $P = 0.46$). The prevalence of anaemia (haemoglobin < 12 g/dL for women and < 13 g/dL for men) was very high for both groups (>70%), but in the PMV group, lower haemoglobin (10.6 vs. 11.6 g/dL, $P = 0.002$) and platelet counts (189 vs. 240 cells/nL, $P = 0.02$) were measured. Among all reported co-morbidities, only atrial fibrillation was more frequently observed in the PMV group (55 vs. 37%, $P = 0.03$).

Regarding the preoperative treatment measures, we noted a disproportionate increase in therapeutic interventions in the PMV group. In particular, patients received more frequently dialysis (32 vs. 10%, $P = 0.001$), temporary circulatory support devices, that is, extracorporeal life support (ECLS) or a temporary LVAD (30 vs. 11%, $P = 0.006$), and were more often placed on mechanical ventilation (35 vs. 8%, $P < 0.001$) prior to implantation of the durable assist device. Regarding the latter, the duration of mechanical ventilation prior to LVAD implantation was much longer (108 vs. 18, $P < 0.001$) and was accompanied by higher rates of preoperative PMV (27 vs. 5%, $P < 0.001$) and preoperative tracheostomy (18 vs. 4%, $P = 0.005$). The need for a concurrent cardiac procedure, such as valve replacement or repair, was similar between groups, as well as the duration of cardiopulmonary bypass. Binomial logistic regression analysis revealed that the eGFR value, the platelet count, and prior sternotomy significantly predicted the occurrence of PMV, whereas diabetes mellitus was associated with decreased risk in our study group, as shown in *Table 2*.

Table 3 summarizes the outcome measures of the study. As expected, patients in the PMV group exhibited much longer ventilation duration post-operatively (566 vs. 164 h, $P < 0.001$). The need for post-operative tracheostomy was extremely high (63 vs. 1%, $P < 0.001$), and patients were

Table 2 Binomial logistic regression for predictors of prolonged mechanical ventilation

Variable	Odds ratio	95% confidence interval	<i>P</i> value
INTERMACS Level 1–3	2.070	0.829–5.165	0.12
eGFR (mL/min/1.73 m ²)	0.977	0.955–0.999	0.038
Haemoglobin (g/dL)	0.910	0.727–1.141	0.42
Platelet count (/nL)	0.994	0.989–0.998	0.008
Diabetes mellitus	0.378	0.154–0.926	0.033
Previous sternotomy	5.079	1.672–15.427	0.004
ECLS/temporary VAD	0.322	0.061–1.692	0.181
Preoperative ventilation	6.594	0.974–44.652	0.053
Preoperative dialysis	1.145	0.324–4.050	0.834
Duration of preoperative ventilation (h)	1.001	0.997–1.006	0.571
Constant	16.044		0.130

ECLS, extracorporeal life support; eGFR, estimated glomerular filtration rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; VAD, ventricular assist device.

Table 3 Outcome measures

Variable	PMV <i>n</i> = 60	EE <i>n</i> = 79	<i>P</i> value
Duration of post-operative ventilation (h)	565.5 (4064)	18 (164)	<0.001
Post-operative tracheostomy	38 (63.3)	1 (1.3)	<0.001
Severe intrathoracic bleeding	21 (35.0)	6 (7.6)	<0.001
ICU stay (days)	24 (192)	4 (34)	<0.001
Hospital stay (days)	47 (186)	32 (266)	0.003
In-hospital death	36 (60.0)	2 (2.5)	<0.001
180-day death	37 (61.7)	8 (10.1)	<0.001

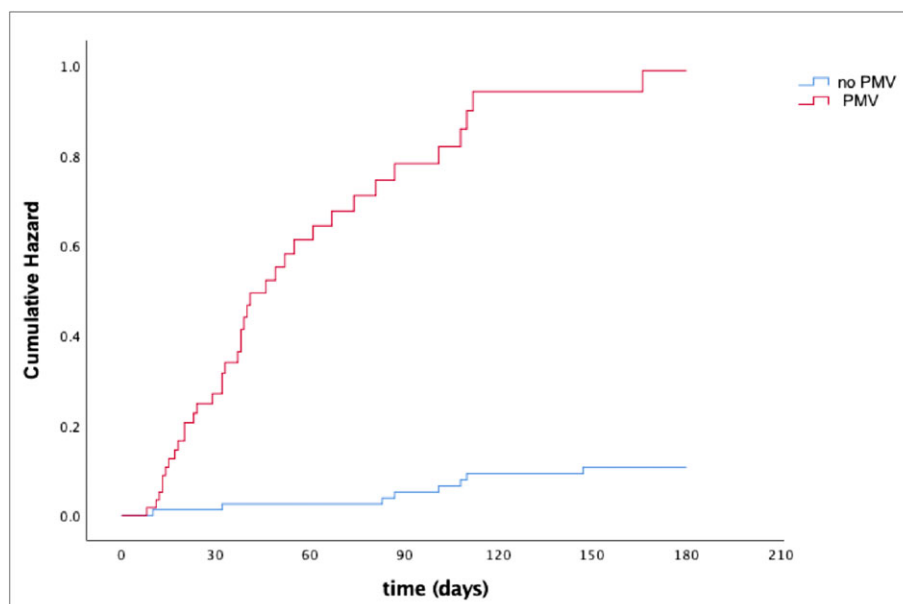
EE, early extubation; PMV, prolonged mechanical ventilation. Continuous variables are presented as median (range).

more likely to suffer a refractory intrathoracic bleeding requiring explorative thoracotomy in order to achieve haemostasis (35 vs. 8%, $P < 0.001$). The median ICU stay was longer than that of the EE group (24 vs. 4 days, $P < 0.001$), as well as the cumulative hospital stay (47 vs. 32 days, $P = 0.003$). In-hospital mortality rates exceeded 50% in the PMV group, in comparison with as low as 2.5% in the EE group ($P < 0.001$). Interestingly, 36 out of the 37 deaths observed in the PMV group during the 180-day follow-up period were in-hospital deaths and were observed post-operatively during the index hospitalization. The 180-day mortality rate of 62% was by far higher than those observed in the EE group (62 vs. 10%, $P < 0.001$). Survival analysis by the Kaplan–Meier method revealed a profound and continuous difference in the reported death rates up to 180-day post-implantation (log-rank test: $P < 0.001$), as depicted in *Figure 1*.

Discussion

Patients should be extubated and resume spontaneous breathing as soon as they have recovered from general anaesthesia during the first 24 h after leaving the operating room. The condition of PMV after cardiac surgery has long been the focus of clinical research, as it was early shown to be associated with an adverse clinical outcome and increased mortality. Despite the technical advances and the ongoing evolution of the modern intensive care, PMV rates still remain high. Several studies aimed to decipher the aetiology and clinical implications of PMV in this setting.^{1–9} One recent large-scale study reported a 7% rate of post-operative ventilation for more than 48 h after cardiac surgery with an in-hospital death rate of 22.3%.⁹ Circulatory assist devices were though excluded from these studies. Our analysis revealed a 43% rate of PMV among LVAD recipients, which is higher than the rates reported in the general cardiac surgery population. This reflects the elevated risk profile of this patient cohort at baseline and may be attributed to the chronically deprived cardiorespiratory function, the vulnerability for

Figure 1 Hazard curves depicting mortality rates up to 180-day post-implantation among patients with vs. without prolonged mechanical ventilation (PMV). Log-rank test: $P < 0.001$.



bacterial infections, and the increased burden co-morbidities accompanying the heart failure syndrome.¹¹ Chronic lung congestion, valve disease, and right ventricular dysfunction are highly prevalent in advanced heart failure and are considered common culprits of an adverse post-operative outcome.

Our study patients requiring PMV exhibited a higher burden of co-morbidities and were more severely ill at baseline. This is reflected by the lower eGFR, the higher pulmonary wedge pressure, and the lower haemoglobin and platelet count. Although not different among the groups, conditions such as chronic lung disease, anaemia, CKD, and hypertension exhibited high prevalence in our study population (*Table 1*). Atrial fibrillation was diagnosed more frequently in the PMV group. A obvious conclusion derived from our analysis is that patients who had to remain long on ventilation after device placement were frequently those who were in a critical disease state preoperatively, ICU dependent, and ‘crashing and burning’ hospitalized patients with advanced multi-organ failure. Approximately one-third were on ECLS or on temporary LVAD, ventilated invasively and on renal replacement treatment prior to LVAD implantation. These rates were three-fold higher than those of the EE group. Furthermore, approximately one-third of the PMV group had previously undergone median sternotomy. In an attempt to identify predictors of PMV, logistic regression analysis was performed. After adjusting for co-variables, previous sternotomy was associated with a five-fold increased risk for PMV, whereas decreasing eGFR and platelet counts were associated with higher probability of PMV. Although literature data regarding predictors of PMV are missing, there is a known relationship of

re-sternotomy during LVAD surgery with the risk of post-operative mortality. Data from the large LVAD registries point out to a higher mortality risk after redo sternotomy^{12,13} However, this was not confirmed in recent single-centre studies on selected LVAD populations receiving third generation, continuous-flow devices.^{14,15} Similarly, creatinine as a marker of renal function and platelet count have both been integrated in a validated risk score model for prediction of post-operative mortality after LVAD, the HeartMate II risk score.¹⁶ Renal function indices (blood urea nitrogen and creatinine) have been unequivocally linked to short-term and long-term mortality in all recent large registry reports.^{12,13} Surprisingly, diabetes mellitus was shown to be much more prevalent in the EE group and was inversely associated with PMV. We consider this as a finding that needs further confirmation in future studies.

Prolonged mechanical ventilation was related to an increased mortality reflecting the severity of disease in this group of patients at baseline. A death rate of 62% was observed at 180-day post-implant, which was at least six-fold higher, compared with uncomplicated weaning. This rate is exceeding the highest observed in-hospital death rates of the published studies in cardiac surgery to date, in which an in-hospital mortality of 20–45% was observed after PMV. The LVAD patient cohort, however, represents a severely ill population, and a direct comparison with recipients of cardiac surgery for other indications is at least oversimplified. Overall survival at 180 days in our study was 68%, which is lower than the rates reported by the published literature to date for LVAD therapy (80% survival at 1 year). However, our sample

consists of a high-risk population. A significant proportion of patients were on critical or rapidly declining clinical state (overall 59% in INTERMACS Level 1–3) and non-eligible for bridging therapies. As a result, 62% were allocated to destination therapy, which is slightly higher than the 45–50% reported rate in the relevant literature.^{12,13} Destination therapy is repeatedly shown to be an independent predictor of death, and this may have led to an increase in the reported PMV rates and mortality.^{12–14} In addition, the higher risk profile is reflected by the fact that many patients were on ECLS or temporary assist devices prior to durable LVAD placement, as our centre serves as a supra-regional ECLS referral unit with a 24/7 out-of-hospital mobile ECLS retrieval service. Accordingly, a bridge-to-bridge strategy has been implemented as a salvage option for selected high-risk patients, in an attempt to stabilize end-organ function and improve outcomes, as it was recently shown.^{17–19}

As expected, the duration of ICU and hospital stay exceeded those of patients with uncomplicated weaning. Tracheostomy was performed in 63% of patients on PMV, according to existing evidence for improved outcomes. Surgical re-exploration for intrathoracic bleeding was seven-fold more frequent in the PMV group. However, it is difficult to unravel the cause and effect relationship between the two conditions. Despite not being part of the current analysis, it is readily recognizable that PMV is associated with an immense rise in resource consumption and health costs.

This is the first study to investigate the condition of PMV in LVAD recipients. Our analysis demonstrated a high prevalence of PMV in this patient population, which is probably attributed to the increased severity of disease at baseline and is accompanied by decreased survival. Consequently, a better identification of the pathological substrate and the factors predisposing to PMV is of paramount importance. Precise assessment of the individual patient risk preoperatively may allow treatment of modifiable factors, better scheduling and allocation of resources, and prediction of costs. Furthermore, it may support clinicians with family counselling, consent process, and clinical decision making (tracheostomy, early physiotherapy, etc.).

Our study is primarily limited by the small number of patients and the retrospective design. It reflects a single-centre experience with a high-risk population. As a result, overestimation of outcomes is possible. The specific cause of PMV

was not consistently recorded. Baseline lung function data and echocardiographic data regarding right ventricular function at baseline were not available and may have an impact on the weaning outcome. The risk factor analysis included only preoperative and intraoperative variables and is not exhaustive, while early post-implantation indices and critical illness severity scores may have a crucial role on PMV prediction. However, with certain post-operative measures, it would be difficult to support causality, as ventilation and the LVAD therapy itself are both accompanied by profound physiologic alterations. Furthermore, the derivation of a predictive model would require a validation cohort in the context of a large-scale prospective study.

Our study sheds light on the condition of PMV as an important outcome measure and essential prognostic factor in the LVAD setting. A high proportion of LVAD recipients remains ventilator dependent for a prolonged period after implantation, has poor survival, and requires long hospitalization. Predicting PMV should be of high priority in an attempt to improve patient outcomes and minimize health care costs and resource consumption.

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Conflict of interest

None declared.

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