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Long-term evolution of N-terminal pro-brain natriuretic peptide levels and exercise capacity in 132 left ventricular assist device recipients

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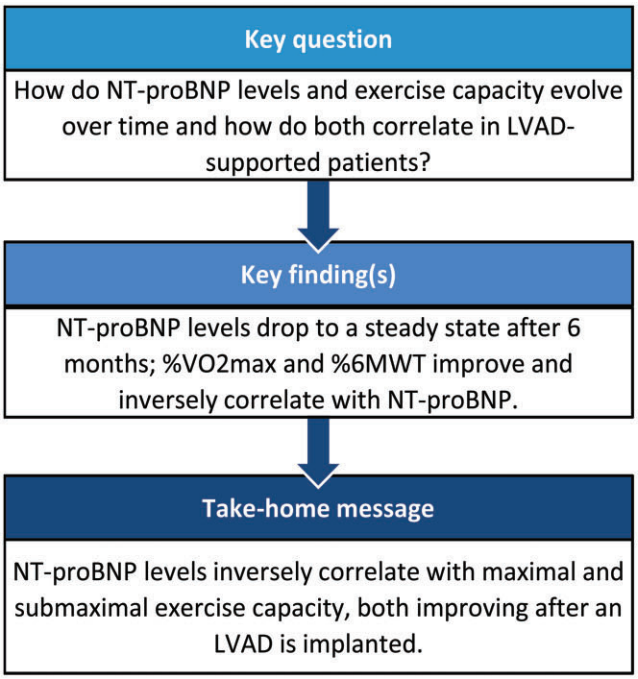

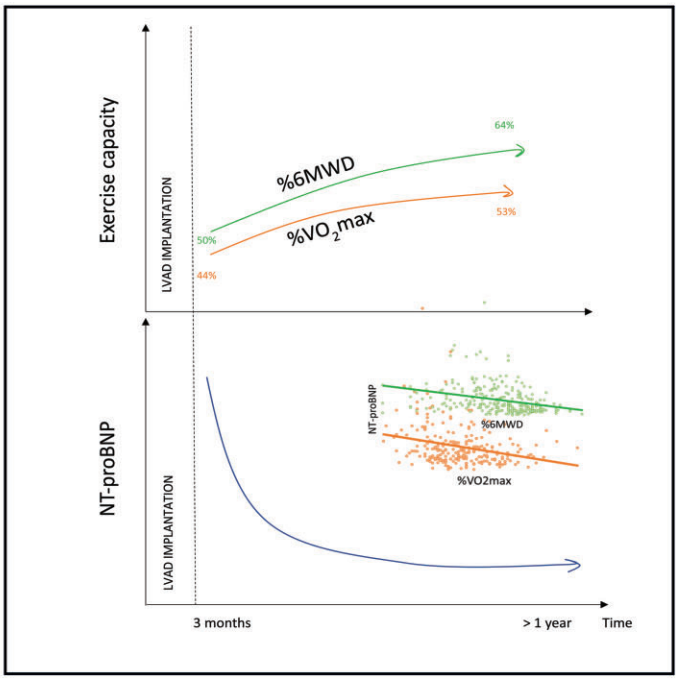

Abstract

OBJECTIVES: N-terminal pro-brain natriuretic peptide (NT-proBNP) is a widely used biomarker in clinical practice in the context of heart failure. Little is known about the long-term evolution of NT-proBNP levels in left ventricular assist device (LVAD) recipients. Besides this, the potential correlation of NT-proBNP with exercise capacity on the long term after LVAD implantation has not been previously studied.

METHODS: We retrospectively analysed 132 single-centre LVAD recipient records (HeartMate II/III; HeartWare; between March 2007 and January 2018; mean follow-up 559 days). Blood samples, 6-min walking test (6MWT) and maximal cardiopulmonary exercise test were performed in a standardized way.

RESULTS: Pre-LVAD NT-proBNP levels were increased (9736 ± 1072 ng/l) and dropped significantly after implantation [14 days: 4360 ± 545 ng/l ($P < 0.0001$), 6 months: 1485 ± 139 ng/l ($P < 0.0001$)]. Afterwards a steady state was reached during follow-up (after 1 year: 1592 ± 214 ng/l, after 5 years: 1679 ± 311 ng/l). Submaximal exercise capacity significantly improved postoperatively [percentage of the predicted distance walked during the 6MWT 50 ± 2% (0–3 months); 61 ± 2% (3–6 months, $P < 0.001$)], with a steady state afterwards [66 ± 2% (6–12 months, $P = 0.08$); 64 ± 3%, $P = 0.70$ later on]. We found a gradual increment of percentage of the expected peak oxygen consumption postoperatively [44 ± 2% (0–3 months); 49 ± 2% (3–6 months); 52 ± 2% (6–12 months); 53 ± 1% (after 12 months)] with a significant improvement between 0 and 3 months versus after the first year on LVAD. Furthermore, we showed a significant moderate correlation between NT-proBNP levels and results at both the 6MWT (correlation coefficient: -0.31, $P < 0.0001$) and cardiopulmonary exercise testing (correlation coefficient: -0.28, $P < 0.0001$).

CONCLUSIONS: NT-proBNP decreased on LVAD support. We showed that submaximal (6MWT) and maximal exercise capacity (cardiopulmonary exercise testing) improve after LVAD implantation and demonstrated an inverse correlation of both tests with NT-proBNP levels.

Keywords: Left ventricular assist devices • N-terminal pro-brain natriuretic peptide • Rehabilitation

ABBREVIATIONS

%6MWT	Percentage of the predicted distance walked during the 6MWT
%VO_2max	Percentage of the expected peak oxygen consumption
6MWT	6-Min walking test
BNP	Brain natriuretic peptide
CPET	Cardiopulmonary exercise testing
HFrEF	Heart failure with reduced ejection fraction
LVADs	Left ventricular assist devices
NT-proBNP	N-terminal pro-brain natriuretic peptide

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) remains a complex syndrome involving a multitude of interacting pathophysiologic mechanisms. The activation of various neurohormonal pathways is one of the major causes of rapid development and progression of HFrEF [1]. In case of pressure overload, the resulting increased wall stress induces the release of atrial natriuretic peptide and brain natriuretic peptide (BNP) by atrial and ventricular myocytes, respectively. This natriuretic peptide system works as a counter regulator for sodium and water retention and counteracts vasoconstriction caused by upregulation of the renin–angiotensin aldosterone system, arginine vasopressin and the autonomic nervous system [2]. Both plasma BNP and its amino-terminal fragment, N-terminal pro-BNP (NT-proBNP), correlate with ventricular dilatation and function as a diagnostic and prognostic biomarker in acute or chronic HFrEF [3].

When HFrEF becomes refractory to conventional medical therapy or residual cardiac function impairs tissue oxygen supply, left ventricular assist devices (LVADs) can provide mechanical support to the failing ventricle to normalize the cardiac output. LVADs can serve either as a bridge to transplantation, bridge to destination or a definitive treatment (destination therapy) [4]. Because LVADs directly drain the left ventricle (LV), they reduce LV diastolic pressure and wall stress and most importantly myocardial oxygen consumption. This unloading effect is supposed to reduce NT-proBNP release and improve functionality.

In this study, we analysed 132 continuous-flow LVAD patient records during a mean follow-up of 559 days (min. 37 days, max. 2752 days). First, we describe the evolution over time of NT-proBNP levels until up to 5 years after surgery. Second, we investigate the evolution of submaximal and maximal exercise capacity after LVAD implantation, by studying results of repetitive 6-min walking tests (6MWTs) and cardiopulmonary exercise testing respectively, in the same patient population. Finally, we search for a possible correlation between NT-proBNP levels versus percentage of the predicted distance walked during the 6MWT (%6MWT) and percentage of the expected peak oxygen consumption (%VO_2max).

MATERIALS AND METHODS

Ethical statement

This study was approved by The Research Ethics Committee UZ/KU Leuven (reference number MP005143) on 04 April 2018. Written informed consent was waived.

Study population

We retrospectively analysed the records of 163 patients with end-stage HFrEF who had undergone continuous-flow LVAD implantation between March 2007 and January 2018 at the University Hospital Leuven, Belgium. Patients should at least have 2 postoperative NT-proBNP levels obtained, leaving 132 patients for analysis. Intent of LVAD implantation was bridge to transplantation in 85 patients (64%), bridge to destination in 32 patients (24%) and destination therapy in 15 patients (11%).

Left ventricular assist device implantation

Our population received one of the following continuous-flow LVAD devices: HeartMate II (Abbott, IL, USA) ($n = 96$, axial flow device), HeartWare (Medtronic, MN, US) ($n = 23$, centrifugal flow device) and HeartMate III (Abbott) ($n = 13$, centrifugal flow device). All HeartMate II and III implantations were performed through median sternotomy on cardiopulmonary bypass. Four HeartWare patients underwent a minimally invasive, off pump approach.

Data collection

Preoperative blood samples were obtained not >12 h before surgery. Postoperative blood samples were prospectively collected at fixed timepoints after implantation (at day 14, at 3 months,

Table 1: Patient characteristics

Total number of patients	132
Gender (M/F), *n* (%)	108 (82)/24 (18)
Age (years)	49 ± 15
BMI (kg/m^2)	25 ± 4
BSA (m^2)	2 ± 0.3
Diabetes (%)	9.1
Intent of LVAD implantation: BTT/BTD/DT, *n* (%)	85 (64)/32 (24)/15 (11)
INTERMACS class at LVAD implantation (%)	
I	21
II	29
III	21
IV–VII	29
Heart failure aetiology (%)	
Ischaemic	46
Non-ischaemic	54
Status before LVAD implantation	
Wedge pressure (mmHg)	28 ± 8
CVP (mmHg)	15 ± 7
PAP mean (mmHg)	37 ± 11
MAP (mmHg)	72 ± 11
Cardiac index (l/min/m^2)	1.9 ± 0.5
EF (%)	18 ± 7
LVEDD (mm)	64 ± 10
Inotropic support (yes/no)	51/134
NT-proBNP (ng/l)	9736 ± 12 452
CRP (mg/l)	67 ± 92
Creatinine (mg/dl)	1.6 ± 0.8
GFR (ml/min)	62 ± 32
BUN (mg/dl)	76 ± 40

Variables are expressed as mean ± standard deviation.
BMI: body mass index; BSA: body surface area; BTD: bridge to destination; BTT: bridge to transplantation; BUN: blood urea nitrogen; CRP: C-reactive protein; CVP: central venous pressure; DT: destination therapy; EF: ejection fraction; F: female; GFR: glomerular filtration rate; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; LVAD: left ventricular assist device; LVEDD: left ventricular end diastolic diameter; M: male; MAP: mean arterial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAP: pulmonary artery pressure.

followed by every 3 months) and in case of hospitalization for adverse events (e.g. in case of pump thrombosis, right HF, arrhythmia, device failure, stroke, bleeding or infectious complications). Furthermore, we assembled data regarding submaximal exercise capacity, evaluated by a 6MWT and maximal exercise capacity, evaluated by cardiopulmonary exercise testing (CPET). 6MWT was performed in a standardized way according to the guidelines of the American Thoracic Society [5]. The covered distance was expressed as percentage (%6MWT) compared to age, weight, height and gender-specific reference standards calculated according to Troosters *et al.* [6]. The CPET was performed as reported in Fresiello *et al.* [7].

Peak oxygen consumption was determined as the highest mean value of the last 30-s interval and was expressed as percentage of the expected value (%VO_2max) according to Wasserman's equation using the age and weight data collected on the day of the test [8].

We correlated NT-proBNP levels with the corrected results of 6MWT and VO_2max, represented as a percentage of the expected value.

Statistical analysis

The statistical analysis was executed using the IBM SPSS statistics software (version 23; SPSS Inc., Chicago, IL, USA). Data were checked for normality using the Shapiro–Wilk test. Data were reported as means and standard error of the mean for normally distributed numerical variables and as percentage of occurrence for categorical and dichotomous variables. Student's *t*-test was used to analyse normally distributed continuous variables. A Spearman's rho or a Pearson univariable correlation analysis was performed between both %VO_2max and %6MWT versus NT-proBNP. Statistical significance was considered for $P < 0.05$.

RESULTS

We retrospectively analysed records of 132 LVAD recipients. Preoperative patient characteristics are summarized in Table 1. During a mean follow-up time of 559 days (min. 37—max. 2752), 15 patients (11%) had died, 76 patients (58%) underwent heart transplantation, 5 patients (4%) could be weaned of the LVAD and 36 patients (27%) were still supported by the LVAD. One patient had been switched from HeartMate II to HeartMate III device because of pump thrombosis.

Evolution of N-terminal pro-brain natriuretic peptide levels after left ventricular assist device implantation

NT-proBNP trends after LVAD implantation are shown in Fig. 1. The preoperative NT-proBNP levels were markedly increased in this population with a mean value of 9736 ± 1072 ng/l. This level decreased significantly during the first 14 days after LVAD implantation [4360 ± 545 ng/l ($P < 0.0001$)] and continued to decrease [3231 ± 277 ng/l at 1 month ($P < 0.0001$), 2589 ± 239 at 2 months ($P < 0.0001$), 1979 ± 168 ng/l at 3 months ($P < 0.0001$)] until 6 months after surgery [1485 ± 139 ng/l ($P < 0.0001$)]. Afterwards, a steady state was reached during follow-up (1592 ± 214 ng/l at 1 year; 1421 ± 241 ng/l at 2 years; 2038 ± 661 ng/l at 3 years; 2427 ± 1005 ng/l at 4 years) until 5 years after device implantation (1679 ± 311 ng/l). No differences in NT-proBNP trends were noted between axial and centrifugal flow devices.

N-terminal pro-brain natriuretic peptide and exercise capacity

To examine the relationship between NT-proBNP and submaximal and maximal exercise capacity, we analysed the patient records for 6MWT and CPET, respectively. The mean %6MWT increased significantly during postoperative measurements from 50 ± 2% (383 ± 12 m, $N = 105$) during the first 3 months to 61 ± 2% (471 ± 14 m, $N = 74$) between 3 and 6 months ($P < 0.001$). After 6 months, the mean percentage of the predicted 6MWT distance remained stable, with a mean of 66 ± 2% (502 ± 18 m, $N = 53$) at 6–12 months ($P = 0.08$) and a mean of 64 ± 3% (454 ± 20 m, $N = 41$) afterwards ($P = 0.70$).

To investigate the relationship between NT-proBNP levels and percentage of the predicted walking distance during the 6MWT, we performed a Pearson's correlation test between both. We found a significant moderate negative correlation (Pearson's correlation coefficient of -0.31, $P < 0.0001$) (Fig. 2a). No differences in %6MWT trends were noted between axial and centrifugal flow devices.

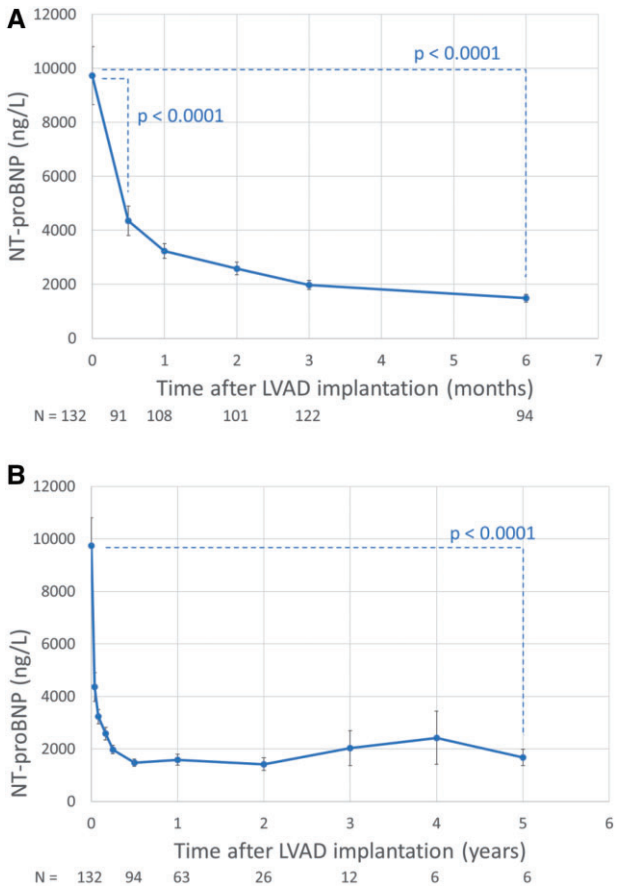

Figure 1: Evolution of N-terminal pro-brain natriuretic peptide levels over time after left ventricular assist device implantation. (**A**) The markedly increased N-terminal pro-brain natriuretic peptide levels preoperatively (at time point zero, 9736 ± 1072 ng/l) and the significant drop after left ventricular assist device implantation over the first weeks and months (at 14 days postoperatively, 4360 ± 545 ng/l; $P < 0.0001$; at 6 months: 1485 ± 139 ng/l; $P < 0.0001$). (**B**) The N-terminal pro-brain natriuretic peptide levels over 5 years after implantation (after 1 year: 1592 ± 214 ng/l, after 5 years: 1679 ± 311 ng/l; $P < 0.0001$). Results are shown as mean ± standard error of mean. Student's *t*-test was used. *N*: number of patients analysed at each timepoint.

The percentage of predicted VO_2max did not increase significantly after LVAD implantation. %VO_2max was 44 ± 2% (13 ± 1 ml/kg/min, $N = 16$) during the first 3 months and 49 ± 2% (15 ± 1 ml/kg/min, $N = 70$) between 3–6 months postoperatively ($P = 0.13$). This mean percentage of predicted VO_2max increased gradually from 52 ± 2% (15 ± 1 ml/kg/min, $N = 72$, $P = 0.20$) up to 6–12 months postoperatively, further rising to 53 ± 1% (14 ± 0 ml/kg/min, $N = 94$, $P = 0.72$) on tests performed after the first year on LVAD. When we compared %VO_2max values between 0 and 3 months postoperatively to the values on tests performed after the first year on LVAD support, we found a significant increase ($P = 0.007$). Seventy-five percentage of the patients achieved a respiratory exchange ratio of >1.05.

Again, we found a significant moderate negative correlation (Pearson's correlation coefficient of -0.28: $P < 0.0001$) between NT-proBNP levels and maximal exercise capacity (Fig. 2b). No differences in %VO_2max trends were noted between axial and centrifugal flow devices.

DISCUSSION

In this study, we described the evolution of NT-proBNP levels in a population of 132 patients with end-stage HF after continuous-flow LVAD implantation during a mean follow-up of 551 days. Preoperative NT-proBNP levels were markedly elevated and decreased significantly until 6 months after device implantation. Afterwards, steady state was seen during a 5-year postoperative follow-up. However, NT-proBNP levels during this steady state were higher as compared to previously reported levels in non-LVAD patients with HFrEF in large trails. For example, patients from the PARADIGM-HF trail had levels of 859 and 1102 ng/l 8 months after randomization to sacubitril/valsartan ($N = 885$) and enalapril ($N = 874$), respectively [9]. This initial decrease and persisting steady state can be explained by the prolonged reduction in LV diastolic pressure and wall stress due to the LVAD support and was in accordance with several previous studies; Ahmad *et al.* [10] showed a decrease in NT-proBNP levels in 37 patients pre- versus postimplantation of a continuous-flow LVAD (median timing 136 days postoperatively). Several other studies found similar findings in smaller study populations during short-term follow-up (103 patients during 3 months follow-up at most) [11–13]. This decrease in NT-proBNP levels after implantation was also discussed in older reports, studying patients on pulsatile LVADs [14–16]. The study of Hasin *et al.* contrasted these findings [17]. They included 72 patients with a follow-up of '1–4 months (mean 3 months)' after implantation of a continuous-flow LVAD and could only detect a preoperative decrease in NT-proBNP levels, explained by the preoperative optimalization and stabilization of the patient's haemodynamic state. However, their postoperative samples were obtained based on 'clinical judgement' and not routinely measured. We included 1 preoperative baseline value of NT-proBNP from a sample taken immediately before device implantation and collected our samples at fixed timepoints after implantation, as previously described. Therefore, the initial drop in NT-proBNP levels could not be attributed to preoperative optimalization and the postoperative values could not be affected by detection bias.

The persistent higher levels of NT-proBNP years after surgery could have several explanations, like the persisting release of NT-proBNP by the right ventricle which is not unloaded by the LVAD. Besides this also patient-related factors such as valvular disease could attribute to the higher values. The correlation between the presence of aortic regurgitation and NT-proBNP levels in our study population was significant (Fig. 3). Another reason for the persistent higher levels of NT-proBNP could be the fact that continuous-flow devices are associated with less effective mechanical unloading compared to pulsatile devices [18]. In our study, we found no differences between NT-proBNP trends between axial versus centrifugal flow devices. This is in accordance with the study of Al-Sarie *et al.*; they prospectively studied 133 patients with end-stage heart failure implanted with CF-LVADs, including 107 patients supported by axial flow devices (HeartMate II) and 26 patients supported by centrifugal flow devices (HeartWare), and found comparable effects on mechanical unloading induced by axial and centrifugal flow devices regarding myocardial structural and functional parameters during 12 months follow-up [19].

Figure 2: Correlations between N-terminal pro-brain natriuretic peptide and submaximal and maximal exercise capacity, evaluated by 6-min walking test (**A**) and cardiopulmonary exercise testing (**B**), respectively. N-terminal pro-brain natriuretic peptide and percentage of the predicted distance walked during the 6MWT correlated negatively with a Pearson's correlation coefficient of -0.31 ($P < 0.0001$). N-terminal pro-brain natriuretic peptide and percentage of the expected peak oxygen consumption also correlated negatively with Pearson's correlation coefficient of -0.28: ($P < 0.0001$).

This study is, to the best of our knowledge, the most comprehensive report on the long term systematically followed evolution of NT-proBNP levels after continuous-flow LVAD implantation.

Second, we studied exercise capacity and its correlation with NT-proBNP values during long-term follow-up. Our study found a significant increase in percentage of predicted distance walked during the 6MWT from 50 ± 2% during the first 3 months to 61 ± 2% between 3 and 6 months postoperatively, reaching a steady state afterwards. Furthermore, we showed a moderate inverse correlation between NT-proBNP and %6MWT. An increase in time performing moderate intensity physical activity in an LVAD population has already been described by Moreno-Suarez *et al.* In this study, the levels of moderate intensity physical activity, monitored with an Actiheart monitor, in LVAD recipients were compared to patients with advanced CHF and higher levels were found in the former group [20]. The importance of a submaximal exercise capacity test in an LVAD population is showed by the study of Hasin *et al.*, including 65 LVAD patients who also performed a 6MWT [21]. This study demonstrated that the distance walked in metres in a postoperative 6MWT was the strongest predictor of late post-LVAD mortality, with a 21% increased risk for overall mortality for every 10-m short of 300 metres. The observation of a steady state after the initial improvement in distance walked during the 6MWT was also found in a paediatric population of 27 patients during a follow-up of 1 year in the study of Goldberg *et al.* [22]. However, in this study, the steady state was reached after 3 months with no significant improvement afterwards.

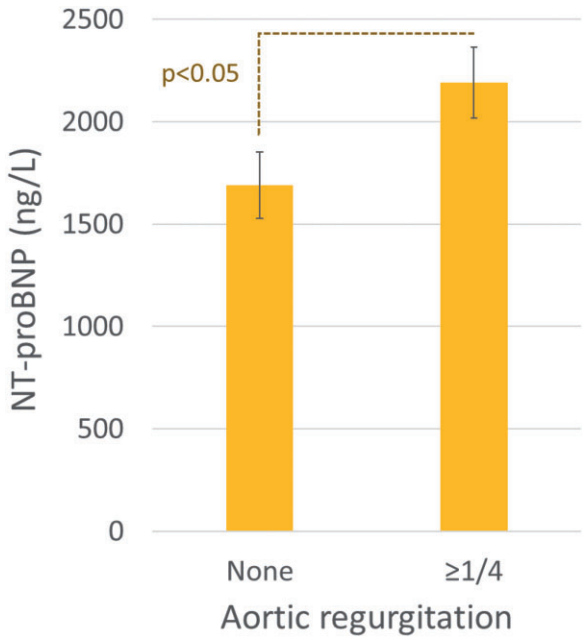

Figure 3: N-terminal pro-brain natriuretic peptide levels in the presence or absence of aortic regurgitation. Aortic regurgitation in ultrasounds performed from 2 weeks until 2 years postoperatively was linked to N-terminal pro-brain natriuretic peptide values that day (or at most 1 day sooner or later). There is a significant difference between N-terminal pro-brain natriuretic peptide values in the presence or absence of aortic regurgitation. N-terminal pro-brain natriuretic peptide is expressed as mean ± standard error of the mean.

VO_2max represents peak exercise capacity as it includes total cardiac output, oxygen delivery and oxygen utilization by skeletal muscles. Exercise haemodynamics during CPET in LVAD recipients have been described thoroughly by Martina *et al.* [23]. In our study, the exercise capacity increased gradually after implantation with a significant difference in %VO_2max between 0 and 3 months after LVAD implantation versus tests performed after 1 year on LVAD support, but no significant differences between values 3–6 versus 6–12 months and 6–12 months versus values of tests performed after 1 year on LVAD support. Furthermore, these values remained far below the age- and sex-predicted normal values as well as below values of patients who have received a heart transplant, a finding already previously described by Dunlay *et al.* [24] and Jung and Gustafsson [25]. Martina *et al.* also found a consistent maximal exercise capacity 6 and 12 months after LVAD implantation (%VO_2max values were 51% and 52%, respectively; values comparable to ours) [23]. They describe that decreased systemic vascular resistance during exercise was the strongest determinant of increased total cardiac output, while increased pump flow contributes only partially.

Another study that investigated the evolution over time of VO_2max was performed by Benton *et al.* They compared the results on VO_2max in a population of 10 patients before versus 6 months after device implantation and found a significant improvement. Their mean percentage predicted of VO_2max 6 months after device implantation (in a total population of 37 patients) was again comparable to our results (51%).

However, no other study followed the evolution of maximal exercise capacity exceeding more than 1 year after device implantation.

Submaximal exercise capacity (steady state around 65% percentage predicted of the distance walked during 6MWT) recovers better than maximal exercise capacity (steady state around 51% percentage predicted of VO_2max value) after LVAD implantation in patients with end-stage chronic HF. This result is in agreement with previous studies on LVAD patients. The relatively better submaximal exercise capacity can possibly indicate a limited LVAD flow increase during physical exercise that can sustain light physical activity but too modest to sustain maximal exertion [26–28]. In this work, we demonstrated a moderate inverse correlation between NT-proBNP and maximal exercise capacity, expressed as percentage of predicted VO_2max uptake, in LVAD patients. This result is in agreement with previous data from our group collected on a smaller LVAD patients' cohort [26]. Previous studies came to the same conclusion in non-LVAD supported HFrEF patients [29, 30].

CONCLUSIONS

We showed that NT-proBNP levels rapidly decrease after LVAD implantation and that submaximal and maximal exercise capacities improve postoperatively. We identified NT-proBNP as a marker to cardiopulmonary exercise testing in the follow-up of LVAD patients as its levels are inversely correlated to both submaximal and maximal exercise capacities.

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Conflict of interest: none declared.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Charlotte Van Edom: Writing—original draft. **Steven Jacobs:** Conceptualization; Writing—original draft. **Libera Fresiello:** Writing—review & editing. **Katrien Vandersmissen:** Data curation. **Christophe Vandenbriele:** Writing—review & editing. **Bart Meyns:** Methodology; Supervision; Writing—review & editing. **Walter Droogné:** Writing—review & editing.

Reviewer information

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