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Highlights

- LVAD speed can be modified according to patients' activity
- Increasing LVAD speed improves exercise performance, cardiac output, O_2 kinetics.
- Lung diffusion deteriorates, and obstructive apneas increase
- Self-adjusting LVAD speed is possible but requires monitoring of intrathoracic fluids

Comprehensive effects of LVAD speed changes on alveolar gas exchange, sleep ventilatory pattern, and exercise performance

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Short title: LVAD speed changes and hemodynamics

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Abstract

Background. Increasing left ventricular assist device (LVAD) pump speed according to patients' activity is a fascinating hypothesis. This paper is an analysis of the short-term effects of LVAD speed increase on cardiopulmonary exercise performance, muscle oxygenation (NIRS), lung diffusion capacity (DLCO and DLNO), and sleep quality.

Methods. We analyzed CPET, DLCO and DLNO, and sleep in 33 Jarvik 2000 LVAD patients. After a maximal cardiopulmonary exercise test (CPET, n=28), patients underwent two maximal CPETs with LVAD speed randomly set at 3 or increased from 3 to 5 during effort (n=15). Then, at LVAD speed randomly set at 2 or 4, we performed: a) constant workload CPETs assessing O_2 kinetics, cardiac output (CO), and muscle oxygenation (n=15); b) resting DLCO and DLNO (n=18); c) nocturnal cardiorespiratory monitoring (n=29).

Results. The progressive pump speed increase raised peak VO_2 (12.5±2.5 ml/min/kg vs. 11.7±2.8 at speed 3; p=0.001). During constant workload, from speed 2 to 4, CO increased (3.18±0.76 L/min vs. 3.69±0.75, p=0.015, at rest; 5.91±1.31 L/min vs. 6.69±0.99, p=0.014, during exercise), and system efficiency (τ= 65.8±15.1 sec vs. 49.9±14.8, p=0.002) and muscle oxygenation improved. At speed 4, DLCO decreased, and obstructive apneas increased despite a significant apnea/hypopnea index and a reduction of central apneas.

Conclusion. Short-term LVAD speed increase improves exercise performance, CO, O_2 kinetics, and muscle oxygenation. However, it deteriorates lung diffusion, and it increases obstructive apneas, likely due to an increase of intrathoracic fluids. Self-adjusting LVAD speed is a fascinating but possibly unsafe option, probably requiring a monitoring of intrathoracic fluids.

Keywords:

LVAD; exercise; CPET; cardiac output; lung diffusion

Introduction

Nowadays, a number of heart failure (HF) patients live with left ventricular assist devices (LVADs) implanted either as a destination therapy or as a bridge to heart transplant or to heart transplant candidacy (1,2). In all these cases, LVAD usually remains for a prolonged time after post-surgical stabilization, during which patients' daily quality of life must be improved as much as possible. LVADs are usually set at a fixed number of revolutions per minute (rpm), so that LVAD output changes during daily activities are only preload- and afterload-dependent, with limited variability. Despite a demonstrated better hemodynamics, exercise capacity is inconsistently improved in LVAD recipients (3). However, LVAD output can be changed by increasing LVAD rpm (4). The usual rpm value is a compromise between the highest possible LVAD output and the risk of left ventricle (LV) sucking, which is a possibly dangerous, life-threatening event when LVAD speed is increased. Indeed, a few reports showed that an increase in rpm is associated with an increase in total cardiac output (CO), i.e. the sum of LVAD and primary heart outputs, both at rest and during exercise, but the net effects on exercise performance, as inferable from peak oxygen uptake (VO_2), are still unclear, with discrepancy in published results (1,5-10). Similarly, it is unknown whether an increase in LVAD rpm allows a better exercise onset with a faster way to a steady-state condition. Moreover, no data are available as regards muscle oxygenation, which is the final aim of CO increase, with different LVAD rpm, both at rest and during exercise. Finally, it is unknown whether and how rpm increase affects alveolar-capillary gas diffusion, which is, at least in part, dependent on pulmonary hemodynamics (11-13).

In severe HF patients, derangement of sleep has been reported and considered as a negative prognostic indicator and responsible for a poor quality of life, since a poor sleep is associated with daily hypersomnia and reduced mental concentration and working capacity (14,15). Notably,

central sleep apneas (CSAs) have been linked with a reduced CO. Indeed, we recently reported, in a pilot study, that CSAs can be reduced by increasing LVAD rpm (16).

This study was designed to give a comprehensive overview of the effects of LVAD rpm changes as regards exercise onset, exercise at constant workload, maximal performance and muscle oxygenation, and finally as regards alveolar-capillary membrane diffusion and ventilatory pattern during sleep, since all these are, at least in part, hemodynamic-dependent. Some of the patients whose data are reported in the present paper participated in previous studies published by our group (5,16).

Methods

This study is part of a project assessing the change of several physiological variables in patients with severe chronic HF who underwent Jarvik 2000 (Jarvik Heart Inc., New York, NY, USA) LVAD implantation. In the present analysis, we included 33 LVAD patients, implanted for at least 4 months, in stable clinical conditions and on optimized medical treatment, willing to perform a cardiopulmonary exercise test (CPET) and to tolerate nocturnal cardiorespiratory monitoring. Twelve patients were implanted at Centro Cardiologico Monzino (Milano), 15 at Padua Univeristy Hospital, 2 at Chieti University Hospital, 3 at Catanzaro Hospital and 1 at Legnano Hospital.

The study was approved by the Ethical Committee of Centro Cardiologico Monzino and registered as R272/15-CCM 288.

The Jarvik 2000 LVAD is a continuous blood flow pump withdrawing blood from the left ventricle and pumping it into the ascending or descending thoracic aorta (17). It has 5 different settings for rotational speeds (1 to 5, corresponding to 8000 to 12000 rpm in steps of 1000 rpm), allowing, in a bench experimental setting, a progressively greater pump flow (17). Once per minute, pump speed decreases for 8 seconds, thus allowing the opening of the aortic valve. Consequently, during

these 8 seconds, the flow becomes pulsatile, allowing the measurement of blood pressure and arterial hemoglobin O_2 saturation.

In all the patients included in our study population, as clinical stability was reached, Jarvik 2000 LVAD pump speed was set at 3 by referring physicians, and it was maintained so during follow-up.

Study Protocol

The analysis was divided into three experimental phases, since it includes the evaluation of exercise, alveolar-capillary membrane diffusion, and ventilatory parameters during sleep (Figure 1).

Study Phase 1. The exercise assessment protocol was carried out in 3 steps. In the first step, we measured the exercise capacity from a maximal CPET performed at LVAD pump speed 3 (baseline CPET, cycle ergometer, personalized ramp protocol, breath-by-breath respiratory gas collection and analysis, V-max 2900 metabolic cart, Sensor Medics, Yorba Linda, CA) to assess patients' ability to perform the exercise, to define the appropriate exercise workload, and to obtain baseline exercise data. Then, on two separate days, two maximal CPETs, using the same equipment and protocol of step-1 CPET, were randomly performed (Step 2), with either LVAD speed set at 3 or changing the LVAD pump speed from 3 to 5 (progressively incremental LVAD-speed CPET). To do so, the exercise workload achieved at the baseline CPET (step 1) was divided into three equal parts that were used, in the progressively incremental LVAD speed CPET, to set LVAD speed at 3, 4, and 5 in the first, second and third part of the exercise, respectively.

In the third step of the exercise protocol (Figure 1), patients underwent two constant workload CPETs, on two different days, at LVAD pump speed randomly set at 2 or 4. The constant workload CPETs were performed (cycle ergometer, breath-by-breath respiratory gas collection and analysis, Quark PFT Cosmed, Roma, Italy) after changing pump speed and monitoring the clinical condition

for a few hours to make sure that hemodynamic stability was reached at that speed. The constant workload CPETs were performed at 60% of the workload reached at the maximal baseline CPET, and they lasted for 6 minutes, allowing to assess VO_2 onset kinetics, expressed through the time constant τ (tau) (18,19) (Figure 2). During constant workload exercise, we also non-invasively measured CO through the inert gas rebreathing method (IGR, Innocor rebreathing system, Innovision A/S, Odense, Denmark), at rest and at the end of the active workload exercise. Finally, we measured peripheral muscle oxygenation throughout the test by means of near-infrared spectroscopy (NIRS, NIMO, Near Infrared Muscle Oximeter, Nirox Optoelectronics, Brescia, Italy).

Study Phase 2. After standard spirometry, alveolar-capillary membrane function (Figure 1, Phase 2) was analyzed at rest by means of DLCO and DLNO at LVAD speed 3. Furthermore, DLCO and DLNO were measured with LVAD speed randomly set at 2 or 4 shortly before the constant workload CPETs were performed.

Study Phase 3. Regarding the sleep breathing assessment (Figure 1, Phase 3), patients underwent two nocturnal cardiorespiratory monitoring studies at LVAD pump speed randomly set at 2 or 4.

Study Procedures

Cardiopulmonary exercise test

Maximal ramp CPET. Maximal CPETs were performed using a ramp protocol on an electronically braked cycle ergometer (Erg 800S, Sensor Medics, Yorba Linda, CA). The CPET protocol was set to reach peak exercise in eight to twelve minutes, but tests were stopped as patients reported maximal effort, regardless of the respiratory quotient (RQ) reached (20). CPET data were analyzed by CPET experts using a standard methodology. Specifically, peak VO_2 was calculated as the 20-second average of the highest recorded VO_2, while the ventilation/carbon dioxide (VE/VCO_2) slope was calculated as the slope of the linear relationship between VE and VCO_2 from one minute after

the beginning of loaded exercise to the end of the isocapnic buffering period(21). The VO_2/work rate relationship was evaluated throughout the exercise. The percentage of predicted peak VO_2 was calculated according to Hansen et al. (22). The anaerobic threshold (AT) was measured by V-slope analysis from the plot of VCO_2 vs. VO_2 on equal scales. The AT value was confirmed by ventilatory equivalents and end-tidal pressures of CO_2 and O_2 (23).

Constant workload CPET. Constant workload CPETs were performed on an electronically braked cycle ergometer (Lode Medical B. V. Technology, Groningen, The Netherlands) at 60% of the workload achieved during the maximal baseline CPET. The researchers who performed the tests were blinded vs. the pump speed selected.

Non-invasive cardiac output assessment

Non-invasive CO measurement was made by IGR, as previously described in detail (24). In brief, IGR uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide, N_2O) and an inert insoluble gas (0.1% sulfur hexafluoride, SF6). SF6 is insoluble in blood, and it is used to determine lung volume. N_2O is soluble in blood, and its concentration decreases during rebreathing with a rate proportional to pulmonary blood flow, which is the blood flow that perfuses the alveoli participating in gas exchange, i.e. ventilated and perfused. CO is equal to pulmonary blood flow in the absence of pulmonary shunt flow. The researchers who analyzed IGR data were blinded vs. the pump speed selected.

Near-infrared spectroscopy

NIRS is a non-invasive technique allowing the real-time measurement of the oxygenation status of human tissues. In particular, it allows to directly quantify the changes in muscular concentrations of oxygenated hemoglobin (O_2Hb), deoxygenated hemoglobin (HHb), and total hemoglobin (tHb).

These changes can be interpreted as changes in blood volume in the tissues and of muscular oxygen uptake During the test, a probe positioned above the left quadriceps muscle was connected to the patient and fixed with an elastic strip, avoiding external light interference. For the analysis of NIRS parameters, O_2Hb, HHb, and tHb, three specific timings were considered for each variable, specifically the resting value, the value at the beginning of the exercise, and the value at the end of the loaded exercise, identified as 1, 2, and 3 in Figure 3, respectively.

Standard spirometry and alveolar-capillary membrane diffusion

Standard spirometry and alveolar-capillary diffusion by means of DLCO and DLNO (25-27) were measured at rest with LVAD speed set at 3 and at least 16 hours after setting LVAD speed at 2 or 4 in the morning following the polysomnographic evaluation. Specifically, we measured DLCO and DLNO with the single-breath technique, according to the American Thoracic Society 1995 update and to the ATS-ERS 2005 guidelines (25-27), using a dedicated cart (Jaeger Masterscreen, D-97204 Hoechberg, Germany). The breath-holding time we used was 4 s, since a short breath hold was needed due to the fast NO kinetics (28). Gas mixtures were: 400ppm NO balanced with N_2 for DLNO, and CO 0.28%, O_2 21%, helium 9% balanced with N_2 for DLCO. The two gas mixtures were administered simultaneously. The inspired NO concentration used was 40 ppm, a dose free of hemodynamic effects. We calculated membrane diffusion, capillary volume, and their ratio over alveolar volume.

Nocturnal cardiorespiratory monitoring and complete polysomnography

Nocturnal respiratory behavior was recorded by a simple nocturnal cardiorespiratory monitoring or by a complete polysomnography. The former was performed with a portable system (EmblettaX100, Embla Systems, Colorado, USA) with simultaneous and continuous recording of

ECG, body position, respiratory flow, and snoring by a nasal cannula thermistor, of thoracic and abdominal respiratory effort by strain gauges, and of O_2 saturation by a finger digital oximeter. Due to limited availability, a complete polysomnographic recording (Embletta MPR, Embla Systems, Colorado, USA) was performed only in a group of patients. Complete polysomnography included two EEG leads (C4-M2; C3-M2), left and right electrooculogram, and chin electromyography, allowing the detection of wake and sleep periods and the determination of REM and non-REM sleep phases by standard diagnostic criteria (29).

In both cases, apnea was identified as a reduction in the amplitude of the respiratory flow signal, defined as a respiratory flow amplitude <10% of the preceding baseline value for at least 10 seconds, while hypopnea was defined as a reduction of respiratory flow to <50% of the baseline for at least 10 seconds. Guidelines also recommend to use oxygen desaturation >3% as criterion to detect hypopnea (29). However, this additional criterion was not used, because the saturation signal is difficult to evaluate during continuous flow. Differently, in patients with EEG recording, the additional criterion of micro-arousal was used. Apneas were considered of central origin (CSA) when the interruption in respiratory flow was associated with the absence of thoracic and abdominal respiratory effort; obstructive (obstructive sleep apnea, OSA) if respiratory thoracic activity or abdominal activity were present during a cessation in respiratory flow, and mixed when an initially central apnea turned into obstructive in its final phase (29). Apnea and hypopnea indexes were calculated as the number of apneas and hypopneas per hour of estimated or measured sleep time, respectively. In patients in whom sleep was not identified by EEG scoring, time in bed, defined as the time spent by the subject lying down with no or minor trunk movements during light-off period, allowed the estimation of sleep time. The apnea/hypopnea index (AHI) is the sum of apneas and hypopneas per hour of sleep.

In the subgroup of patients who underwent complete polysomnography, circulation time was measured with patients awake at rest in sitting position. Circulation time, an index of the delay from the alveoli to carotid chemoreceptors, was measured as the time between the end of a voluntary apnea able to induce a desaturation of at least 3% and the nadir of SaO_2 detected at the earlobe, and it was calculated as the mean of 5 tests.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or as median and interquartile range, as appropriate. CPET variables are reported as a 20-second average or as relationship slopes, as appropriate. A sample size of 15 patients provided a power of 80% to deem as significant a within group difference of about 7% (=0.85 mL/min/Lg) for peak VO_2 or of about 19% (=12.5 s) for τVO_2. Differences between speed 2 and speed 4 or between speed 3 and incremental speed were analyzed by paired t-test or Wilcoxon signed-rank test for non-parametric variables. Statistical significance was accepted at $p < 0.05$. All tests were performed using Microsoft EXCEL or IBM SPSS Statistics 23.0.

Results

We included in the analysis 33 HF patients bearing Jarvik 2000 LVADs (32 males and 1 female, mean age 62.4±8.2 years). LVAD was a destination therapy in 21 cases, bridge to heart transplant in 9 cases, and bridge to candidacy in 3 cases. The mean time from implantation was 15±3 months. At the time of study enrolment, all patients were on optimized medical treatment for HF and in stable clinical conditions. Out of the 33 patients, 28 completed the step-1 exercise protocol; the 5 patients unable to complete the step-1 exercise protocol did not participate in any of the exercise studies. Fifteen subjects completed the ramp exercise (step 2) and the constant workload (step 3)

protocols, 31 underwent DLCO and DLNO measurements at LVAD speed 3 and 18 at LVAD speed 2 and 4. Twenty-nine patients underwent nocturnal cardiorespiratory monitoring; fifteen of them underwent a complete polysomnographic study. Thirteen patients performed all the study tests. During the study, patients were hospitalized for safety reasons.

Exercise Protocol (Study Phase 1)

- **Ramp CPET with LVAD speed set at 3 (Figure 1, step 1)**

Twenty-eight subjects safely performed the test, which showed a reduced exercise performance (peak VO_2=11.4±2.6 ml/min/kg, peak workload 53±19 Watts, VE/VCO_2 slope=37.3±13.6). Average exercise Watt increase was 5.7±1.6 Watts/min.

- **Comparison between maximal CPET at LVAD speed fixed at 3 and progressively incremental LVAD speed CPET (Figure 1, step 2)**

Exercise performance, as analyzed in step 1, was similar between patients who participated in step 2 of phase 1 vs. those who did not participate in this part of the study. The comparison between the CPET at LVAD speed set at 3 for the entire duration of exercise and the incremental LVAD speed CPET (n=15) showed that the change in LVAD speed during exercise was responsible for an improvement of functional capacity expressed by an increased value of peak VO_2 (11.7±2.8 vs. 12.5±2.5 ml/min/kg, respectively; p=0.001), despite a similar workload achieved at peak exercise (Table 1). Peak VO_2 increase was associated with higher values of the VO_2/work relationship and of O_2 pulse and with an improvement of the ventilatory efficiency during effort, expressed by a reduction in the VE/VCO_2 relationship slope (Table 1).

- **Comparison between constant workload CPETs at LVAD speed 2 and 4: CO and VO_2 kinetics**

Constant workload CPETs (n=15) were performed at an average workload of 35.1±9.8 Watts/min. IGR CO analysis showed a significant improvement of CO from LVAD speed 2 to LVAD speed 4, both at rest (3.18±0.76 L/min vs. 3.69±0.75, respectively; p=0.015) and at the end of constant workload exercise (5.91±1.31 L/min vs. 6.69±0.99, respectively; p=0.014) (Table 2). In parallel, we observed a significant improvement of VO_2 kinetics, expressed by a reduction of the τ value from LVAD speed 2 to LVAD speed 4 (65.8±15.1 s vs. 49.9±14.8, respectively; p=0.002), as an expression of system efficiency recovery (Table 2, Figure 2).

- **Oxygen extraction: NIRS analysis at LVAD speed 2 and 4**

An analysis of muscular oxygen delivery and uptake through NIRS methodology was performed. Quality of NIRS data was constantly reliable during both exercise tests in 11 of the 15 patients. NIRS data showed significant differences at each analyzed point between LVAD speed 2 and 4. Specifically, O_2Hb and tHb showed significantly increased values at rest, at the beginning of exercise, and at the end of exercise at LVAD speed 4 compared to LVAD speed 2 (Table 3). Inversely, HHb showed no differences between LVAD speeds 2 and 4, indicating an increased peripheral O_2 extraction at increased LVAD speed at each exercise phase analyzed.

Standard spirometry and alveolar-capillary membrane diffusion (Study Phase 2)

Standard spirometry, measured in 31 cases, showed a moderate restrictive lung disease: forced expiratory volume (FEV_1) 2.25±0.62 l, corresponding to 73±21% of the predicted value, forced vital capacity (FVC) 2.95±0.80 l, corresponding to 77±22% of the predicted value, and FEV1/FVC 0.76±0.09. Alveolar-capillary gas diffusion was reduced: DLCO 13.7±6.0 ml/min/mmHg (53±16% of the predicted value), DLNO 55.3±18.5 ml/min/mmHg. In 18 subjects, DLCO and DLNO were also evaluated at rest after a prolonged period of time with LVAD speed set at 2 and at 4. DLCO and

DLNO were both very low, regardless of LVAD pump speed. Increasing pump speed from 2 to 4 was associated with a further reduction of DLCO, suggesting fluid accumulation (Table 4).

Sleep protocol (Study Phase 3)

The sleep studies (n=29) showed that the change in pump speed from to 2 to 4 was associated with a significant decrease of AHI (from 12 [IQR 5.05-30.5] to 7.35 [IQR 2.95-21.55], respectively; p=0.007), CSAs, and hypopnea index, but not of obstructive apnea index, which inversely showed an increase from speed 2 to 4 (Table 5). Mixed apneas were not significantly reduced by the transition from speed 2 to speed 4. In patients with significant CSA (index >10; n=8), the CSA index decreased from 19.4 [IQR 15.3-23.1] to 7.0 [IQR 0.38-17.7] (p=0.023).

Complete polysomnographic recording was performed in 15 patients, but, because of poor EEG quality in 2 cases, sleep scoring was reliable in 13 patients. The analysis of the complete polysomnographic studies showed a non-significant sleep time increase (from 298±95 to 323±72 min p = 0.317) when increasing LVAD speed from 2 to 4. Pooling data with estimated sleep time gave an average sleep time of 385±120 min at speed 2 and 411±107 min (p=0.089) at speed 4. Circulation time was correctly estimable in 13 patients, and it decreased from 39.6±8.6 at LVAD speed 2 to 33.0±6.6 s at LVAD speed 4 (p=0.0021).

O_2 saturation signal was not reliable in some patients and in some nocturnal recordings, in particular at speed 4, probably as a consequence of the continuous flow generated by the LVAD pump. Accordingly, O_2 saturation data were excluded from the analysis.

Discussion

This report is the sum of a number of experiments aimed at understanding the effects of pump speed increase in LVAD-bearing HF patients. We showed that an increase in LVAD rpm is

associated with an improvement in CO, which translates into a faster VO_2 kinetics at the onset of exercise and a greater O_2 delivery to the working muscles. Moreover, a progressive increase in LVAD speed allows a better exercise performance in terms of peak VO_2 and efficiency of ventilation during exercise. However, an rpm increase of a few hours translates into a reduction in alveolar-capillary membrane gas diffusion, likely as a consequence of an increased lung fluid (8,13,30,31). Finally, during sleep, LVAD rpm increase reduces AHI by reducing CSAs, which are CO-dependent, but it also increases, albeit numerically in a smaller amount, OSAs, which are likely related to an increase in right atrial pressure and to the consequent upper airway fluid content.

We studied a sizable population of LVAD-bearing patients who, regardless of stable clinical conditions and optimized treatment, showed a relevant exercise limitation. All our patients' LVADs had been set at speed 3 by the referring physicians. However, except for the maximal CPET and as in our previous studies (5,16), we compared speed 2 and 4 in order to have the greatest pump speed difference but avoiding the lowest and highest speeds for patients' safety. The idea of an LVAD with gears that can be turned up when an increase in CO is needed is fascinating. Indeed, the possibility of a self-regulating LVAD has been explored, and a model was proposed. However, some reports suggested caution before following this approach because of the potential of LV sucking, which might abruptly reduce or even stop LVAD output, and because of the documentation of a further right and left atrial pressure increase during exercise with high rpm compared to low rpm (6,10). Accordingly, a comprehensive analysis of cardiorespiratory performance and fluid balance during exercise is mandatory.

A progressive increase of LVAD speed from 3 to 5 is associated with a better exercise performance compared to fixed LVAD speed set at 3, as shown by higher peak VO_2 and lower VE/VCO_2 slope and

a trend toward a postponed anaerobic threshold (Table 1) (6). Accordingly, we confirmed data previously reported from our laboratory, where a higher peak VO_2 was observed during exercise in patients bearing Jarvik 2000 at a fixed speed of 4 vs. 2 (5). A comparison between the present and the previous results is not possible, although the differences seem minimal. In our opinion, the progressively incremental LVAD speed seems to be a more physiological approach to the exercise-induced hemodynamic needs. It should be remarked that both peak VO_2 and VE/VCO_2 slope are among the cornerstone CPET parameters in the assessment of HF severity and prognosis, although we do not know whether this applies to LVAD patients, and even more to LVAD rpm changes.

Several variables, all integrated with each other, influence CO in LVAD patients, so that rpm changes cannot be translated directly into CO changes (4,8,32-34). Indeed, LVAD patients' CO is strictly preload- and afterload-dependent, and direct measurements of CO are recommended to precisely assess LVAD output, particularly when a change in the hemodynamic setting is likely, such as during exercise or sleep. In the present study, we measured CO by IGR technique – a consolidated technique to measure CO both at rest and during exercise (35,36). We showed that CO was higher with increased rpm both at rest and during constant workload exercise (37). However, the increase was smaller than the bench-predicted one(17). In the present study, we measured CO by IGR during constant workload exercise for two main reasons: a) to have a steady-state condition avoiding the rapid CO changes of a ramp protocol, and b) because the rebreathing maneuver requires 10 to 20 seconds and a full collaboration by the patients. However, although it was not proven in the present study, it is likely that CO was higher with high rpm at maximal effort (5) and during sleep.

A higher CO allows to reach a VO_2 steady-state condition faster, and therefore it reduces the amount of the so-called O_2 deficit. This was shown by the time constant τ of VO_2 changes, which was lower with high rpm, at least at the constant workload exercise test performed at 60% of the maximal workload. Notably, no side effects or unexpected events were reported by the patients who participated in this part of the study, so that it may be suggested that an rpm increase is feasible for short-lasting submaximal efforts.

The increase in CO during exercise is associated with an improvement of oxygen delivery to the exercising muscles (38,39). Indeed, NIRS analysis showed that both tHb and O_2Hb were higher at each step of exercise, but HHb was unaffected by rpm changes. We analyzed 3 phases of exercise, precisely resting condition, exercise beginning with squeezing of the muscles, and abrupt hemoglobin reduction followed by a CO-dependent progressive hemoglobin increase. We speculate that the differences in tHb and O_2Hb observed in all examined exercise phases are likely to depend on muscular blood flow.

Lung diffusion was significantly impaired at rest in LVAD patients, as is expected in chronic HF patients. Indeed, a long-term DLCO derangement, albeit not directly associated with hemodynamic conditions, is associated with HF severity and prognosis (11,12,40,41). Moreover, in severe HF, short-term hemodynamic deterioration, as happens during exercise, is associated with a further DLCO reduction and BNP increase (30,42). In this study, we showed that DLCO is lower with high rpm as a likely consequence of higher left atrial pressure and lung fluid content. In parallel, DLNO, membrane diffusing capacity (DM), and capillary volume (VCap) as absolute values or normalized for alveolar volume showed a non-significant trend toward reduction. All these observations, performed after an overnight period with changed LVAD speed, suggest a possible

risk in letting patients autonomously adjust LVAD speed without medical control. It should be noticed that repeated DLCO measurements were not performed, so that the kinetic behavior of DLCO/DLNO changes with LVAD speed changes remains unknown. In conclusion, as regards exercise, an increase in rpm allows a faster VO_2 kinetics at the beginning of exercise, a higher O_2 delivery to the muscles, and a higher peak VO_2, paralleled by a lower VE/VCO_2 slope. However, caution is needed in suggesting a free application of this approach, because alveolar gas diffusion decreases with high rpm, suggesting an increase in lung fluid, so that a prolonged rpm increase is possibly unsafe.

Sleep alterations are frequently reported in severe HF, with an increase in both CSAs and OSAs. Sleep apnea is associated with a deterioration of life quality and with poor prognosis in HF (14,15). The patients of our cohort showed a high AHI at low rpm that was significantly reduced at higher rpm, mainly due to a reduction of central apneas and hypopneas. We previously reported, in a pilot study (16), that the reduction of central apneas was associated with a reduction in blood transit time from the alveoli to the carotid bodies, a likely consequence of CO increase. The present observation, obtained in a much larger group of patients, confirms the original findings. However, we also demonstrated an increase in obstructive apneas, albeit numerically small. This finding may be the consequence of an increase of intrathoracic fluids related to a right heart preload increase (43), which justifies the obstruction of the upper airways and the consequent increase in OSAs during night rest (44,45). Notably, both DLCO reduction and obstructive sleep apnea increase match with the concept that, with prolonged LVAD speed increase, thoracic fluids also increase.

This study has several limitations that should be acknowledged. Firstly, due to the complexity of the study protocol and to the severity of the patients, it was impossible to perform all tests in all patients, except for 13 cases. Secondly, we did not measure natriuretic peptide changes in the various phases of the study, which could have helped us better define the hemodynamic profile in the various experimental settings. However, we did not analyze natriuretic peptides because we could not be sure that they had returned to baseline conditions between each study period. Indeed, time-dependent BNP variability in patients with severe HF after effort or hemodynamic changes is presently undefined and likely not homogeneous among patients. Thirdly, hemodynamic data were not directly measured, but prolonged invasive hemodynamic monitoring during sleep and during upright cycle ergometer exercise was considered too demanding for the patients and possibly unsafe. However, it would have helped the interpretation of our data. Fourthly, we limited our observation to the effect of rpm increase on exercise performance after short-term LVAD speed changes, so that we do not know the effects of a more prolonged rpm increase. Fifthly, the definition of hypopnea is a reduction of flow >50% with at least 3% desaturation. However, in a few circumstances, oxygen saturation cannot be recorded with continuous flow. In these cases, hypopneas were defined by the simple reduction of nasal flow during nocturnal cardiorespiratory monitoring or by nasal flow reduction combined with micro-arousal at complete polysomnography. Finally, we only evaluated patients with Jarvik 2000 LVADs. In Jarvik 2000, pump speed can be easily changed, but the same can be done in all LVADs available. It is likely, but unproven, that the present observation can be extended to all LVADs.

In conclusion, we showed that a short-term increase in LVAD speed in patients bearing Jarvik 2000 is associated with an increase in CO both at rest and during exercise, and that this increase improves exercise performance in terms of VO_2 kinetics at the onset of exercise, peak VO_2,

efficiency of ventilation and muscle oxygenation, and that it improves breathing pattern during sleep by significantly reducing AHI. However, it deteriorates alveolar-capillary gas diffusion, and it increases obstructive apneas, likely due to an increase of intrathoracic fluids. Accordingly, allowing patients to self-adjust LVAD speed may be useful but possibly unsafe. Self-adjusting LVAD speed with intrathoracic fluid monitoring is possibly the right answer.

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Disclosure

None.

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Figure legend

Figure 1: Flowchart of the study phases with the number of patients who successfully ended each step.

*Complete polysomnographic recording was performed in 15 patients, but, because of poor EEG quality in 2 cases, sleep scoring was reliable in 13 patients. The 2 patients were added to the nocturnal cardiorespiratory monitoring group.

Figure 2: Example of VO_2 changes during constant workload exercise at LVAD speed 2 (red line) and 4 (black line). Blue and green curves represent τ calculation at speed 2 and 4, respectively.

Figure 3: Example of total hemoglobin changes, detected by NIRS technique, during constant workload exercise.

- 1: Rest
- 2: Beginning of exercise
- 3: End of exercise

Table 1 Comparison between maximal CPET at LVAD speed 3 vs. incremental speed (n=15).

	Speed 3	Speed 3-4-5	Delta	p
Workload (Watt)	57 ± 17	59 ± 17	1.3 ± 5.3	0.349
HR rest (bpm)	73 ± 14	72 ± 10	-0.4 ± 6.7	0.820
HR peak (bpm)	100 ± 22	99 ± 19	-1.4 ± 7.9	0.501
VO_2 peak (mL/min)	948 ± 238	1014 ± 219	65.3 ± 85.3	0.001
VO_2 peak (mL/min/Kg)	11.7 ± 2.8	12.5 ± 2.5	0.8 ± 1.1	0.001
VO_2 peak (% of predicted)	45.1 ± 12.0	48.4 ± 11.4	3.3 ± 4.1	0.008
VO_2/work slope	9.3 ± 1.7	10.4 ± 1.8	1.1 ± 1.3	0.006
VE/VCO_2 slope	34 ± 6	32 ± 6	-1.9 ± 3.1	0.031
O_2 pulse (L/beat)	9.7 ± 2.7	10.3 ± 2.1	0.6 ± 1.0	0.030
VO_2 AT (mL/min)	643 ± 171	693 ± 161	50.6 ± 97.3	0.064
VO_2 AT (mL/min/Kg)	7.9 ± 1.9	8.5 ± 1.6	0.6 ± 1.1	0.061
VE peak (L/min)	49.3 ± 13.4	48.1 ± 11.5	-1.2 ± 7.7	0.564
RR peak (breath/min)	33.2 ± 5.4	32.1 ± 5.6	-1.1 ± 3.7	0.253

Data are presented as mean ± standard deviation.
HR= Heart Rate; VO_2= Oxygen uptake; VE= Ventilation; VCO_2= carbon dioxide production; AT= Anaerobic threshold; RR= Respiratory Rate.

Table 2 Comparison between constant workload CPET at LVAD speed 2 vs. speed 4 (n=15).

	Speed 2	Speed 4	Delta	p
HR rest (bpm)	71 ± 11	67 ± 11	-3.7 ± 11.5	0.238
HR exercise (bpm)	88 ± 17	86 ± 17	-1.9 ± 8.1	0.384
τ VO_2 (s)	65.8 ± 15.1	49.9 ± 14.8	-15.9 ± 16.1	0.002
VO_2 rest (mL/min)	189 ± 77	201 ± 54	11.7 ± 57.9	0.445
VO_2 exercise (mL/min)	666 ± 218	711 ± 139	44.5 ± 141.0	0.241
CO rest (L/min)	3.18 ± 0.76	3.69 ± 0.75	0.5 ± 0.7	0.015
CO exercise (L/min)	5.91 ± 1.31	6.69 ± 0.99	0.8 ± 1.1	0.014
PBF rest (L/min)	3.08 ± 0.67	3.42 ± 0.56	0.3 ± 0.6	0.058
PBF exercise (L/min)	5.83 ± 1.26	6.35 ± 0.83	0.5 ± 0.8	0.033
CI rest (L/min/m^2)	1.63 ± 0.35	1.89 ± 0.38	0.3 ± 0.4	0.012
CI exercise (L/min/m^2)	3.05 ± 0.61	3.47 ± 0.50	0.4 ± 0.6	0.012

Data are presented as mean ± standard deviation.
HR= Heart Rate; τ= Kinetic constant; VO_2= Oxygen uptake; CO= Cardiac output; PBF= Pulmonary Blood Flow;
CI= Cardiac index.

Table 3 NIRS - Near infrared spectroscopy results during constant workload exercise (n=11).

		Speed 2	Speed 4	Delta	p
O_2Hb (mmol/L)	rest	64.5 ± 24.2	81.4 ± 24.8	16.8 ± 16.4	0.007
	beginning exercise	45.3 ± 20.2	58.6 ± 28.0	13.4 ± 17.5	0.030
	end exercise	58.1 ± 22.7	76.5 ± 32.1	18.5 ± 19.0	0.009
HHb (mmol/L)	rest	18.5 ± 5.0	19.0 ± 7.4	0.5 ± 5.9	0.804
	beginning exercise	16.5 ± 4.2	16.5 ± 5.4	0.2 ± 4.9	0.686
	end exercise	18.8 ± 5.9	19.5 ± 7.2	0.5 ± 3.9	0.891
tHb (mmol/L)	rest	82.2 ± 24.1	98.7 ± 26.7	16.5 ± 20.7	0.025
	beginning exercise	64.3 ± 19.4	76.0 ± 29.8	11.7 ± 19.4	0.073
	end exercise	76.1 ± 19.5	77.0 ± 13.4	14.9 ± 21.5	0.045

Data are presented as mean ± standard deviation.
O_2Hb= oxygenated hemoglobin; HHb= deoxygenated hemoglobin; tHb= total hemoglobin.

Table 4 Standard spirometry and alveolar capillary membrane diffusion at LVAD speed 2 and 4 (n=18).

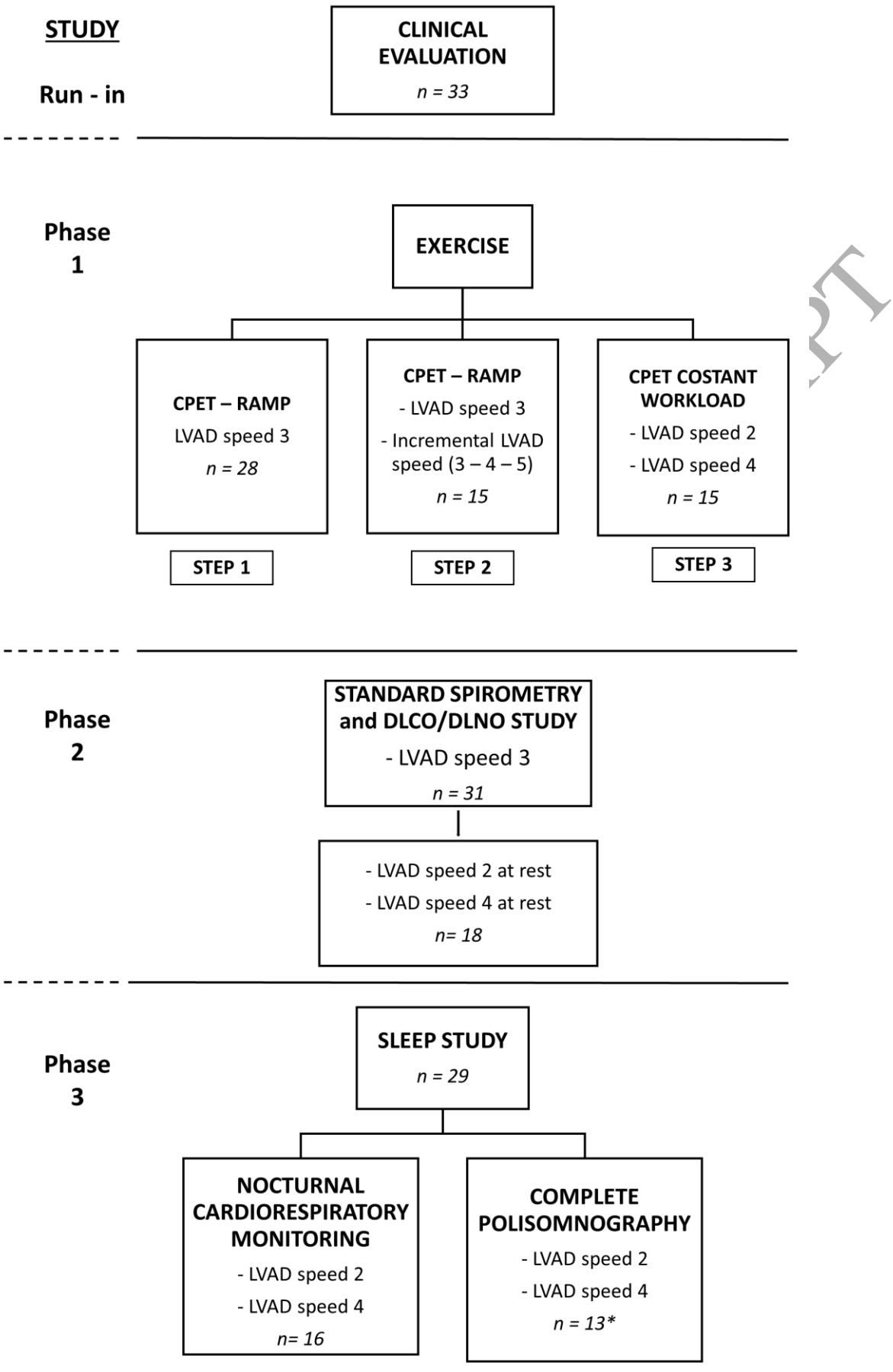
	Speed 2	Speed 4	Delta	p
FVC (L)	2.68 ± 0.75	2.70 ± 0.66	0.29 ± 0.79	0.412
FEV_1 (L)	2.07 ± 0.61	2.07 ± 0.58	0.21 ± 0.64	0.835
DLCO (mL/min/mmHg)	12.50 ± 3.62	11.34 ± 3.00	0.10 ± 3.47	0.010
DLNO (mL/min/mmHg)	58.92 ± 16.02	54.40 ± 11.85	1.37 ± 14.63	0.188
DM (mL/min/mmHg)	30.04 ± 8.21	27.70 ± 6.09	0.66 ± 7.46	0.182
VCap (mL)	33.11 ± 10.32	30.66 ± 11.10	0.86 ± 12.84	0.083
VA (L)	3.91 ± 0.82	4.00 ± 0.71	0.48 ± 1.23	0.358
DLCO/VA (mL/min/mmHg/L)	3.25 ± 0.83	2.85 ± 0.60	-0.08 ± 1.02	0.009
DLNO/VA (mL/min/mmHg/L)	15.33 ± 3.80	13.70 ± 2.42	-0.10 ± 4.39	0.085
DM/VA (mL/min/mmHg/L)	7.81 ± 1.92	6.98 ± 1.24	-0.05 ± 2.23	0.082
VCap/VA (mL/L)	8.60 ± 2.33	7.65 ± 2.30	-0.09 ± 3.59	0.034

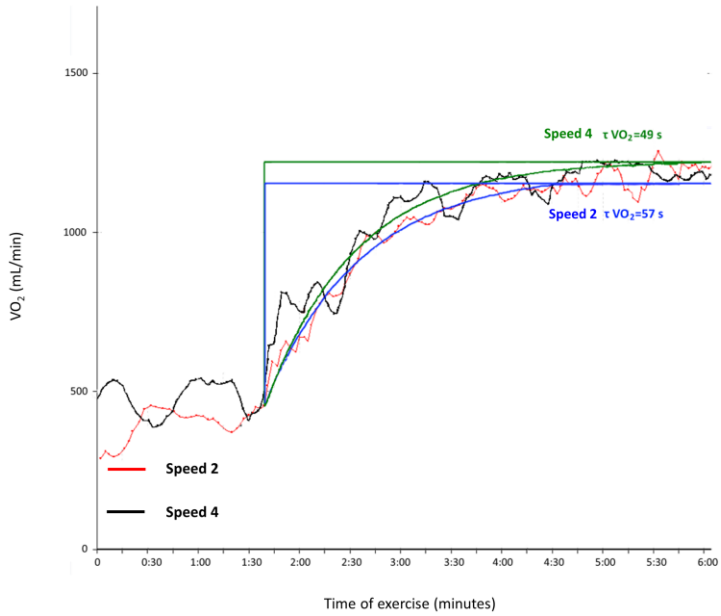
Data are presented as mean ± standard deviation.
FVC= Forced vital capacity; FEV_1= Forced expiratory volume in 1 second; DLCO= Diffusing lung capacity for carbon monoxide; DLNO= Diffusing lung capacity for nitric oxide; DM= Membrane diffusion; VCap= Capillary volume; VA= Alveolar volume.

Table 5 Sleep-disordered breathing at LVAD speed 2 vs. 4 (n=29).

	Speed 2	Speed 4	delta	p
AHI	12 [5.05-26.5]	7.35 [2.95-21.55]	-4.0 [0.4- -8.8]	0.007
OSA index (events/h)*	1.4 [0.05-4]	2.65 [0.225-10.15]	0.2 [3.8- -1.5]	0.015
CSA index (events/h)*	0.8 [0.0-13.75]	0.2 [0-2.675]	0.0 [1.1- -3.3]	0.047
Mixed index (events/h)*	0.2 [0.0-1.9]	0.05 [0.0-0.1]	0.0 [0.2- -1.7]	0.615
Hypopnea index (events/h)*	4.6 [3.05-10.65]	1.95 [0.625-4.225]	-2.7 [1.1- -9.5]	0.001
CSA duration (s)	20.5 [15.5-24.6]	19.1 [16.3-23.2]	-0.5 [0.9- -5.5]	0.201
OSA duration (s)	20.5 [17.2-24.0]	18.9 [15.3-26.8]	0.0 [2.9- -3.2]	0.411
Mixed duration (s)	25.2 [21.5-31.0]	21.5 [15.7-26.7]	0.0 [0.0- -3.4]	0.102
Hypopnea duration (s)	25.5 [21.9-30.7]	22.6 [18.8-26.1]	-4.6 [-1.5- -9.9]	0.008

* Index calculated in 16 patients using time in bed and in 13 using EEG measurements.
Data are presented as median [25°-75° percentile].
AHI= Apnea/Hypopnea index; OSA= Obstructive Sleep Apnea; CSA= Central Sleep Apnea.


STUDY
Run - in
CLINICAL EVALUATION
n = 33
Phase 1
EXERCISE
CPET – RAMP
LVAD speed 3
n = 28
CPET – RAMP
- LVAD speed 3
- Incremental LVAD speed (3 – 4 – 5)
n = 15
CPET COSTANT WORKLOAD
- LVAD speed 2
- LVAD speed 4
n = 15
STEP 1
STEP 2
STEP 3
Phase 2
STANDARD SPIROMETRY and DLCO/DLNO STUDY
- LVAD speed 3
n = 31
- LVAD speed 2 at rest
- LVAD speed 4 at rest
n= 18
Phase 3
SLEEP STUDY
n = 29
NOCTURNAL CARDIORESPIRATORY MONITORING
- LVAD speed 2
- LVAD speed 4
n= 16
COMPLETE POLISOMNOGRAPHY
- LVAD speed 2
- LVAD speed 4
n = 13*



Total hemoglobin (tHb)