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### Effects of left ventricular assist device implantation on respiratory drive

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## RESEARCH ARTICLE

## EFFECTS OF LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION ON RESPIRATORY DRIVE

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## Abstract

**Background:** Patients with heart failure (HF) suffer from ventilatory abnormalities that are related to poor prognosis.

**Aim:** The aim of the study was to investigate the respiratory drive in HF patients early after left ventricular assist device (LVAD) implantation.

**Methods:** We enrolled eight HF patients after LVAD (HeartMate II) implantation and 8 patients with advanced HF (control group). Patients were evaluated with cardiopulmonary exercise testing, respiratory function tests and transthoracic echocardiographic examination at 1, 3 and 6 months. Respiratory drive was estimated by the mouth occlusion pressure- $P_{0.1}$  and the  $P_{0.1}/P_{imax}$  ratio.

**Results:** LVAD patients at 1, 3 and 6 months after implantation had significantly improved  $P_{0.1}/P_{imax}$ % ratio ( $4.17 \pm 0.43$  vs  $3.29 \pm 1.0$  vs  $2.56 \pm 0.35$  respectively,  $p < 0.01$ ) as well as significantly increased in  $P_{imax}$ . No changes were observed in the HF control group. A significant decrease in LVEDD, LVESD and an improvement in LVEF is also observed during follow up.

**Conclusions:** Our results imply LVAD implantation induces a progressive and significant improvement of respiratory drive and Left ventricle reverse remodeling during a 6 month follow-up period.

**Key words:** Heart failure, left ventricular assist device, LVAD, respiratory drive, reverse remodeling.

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## INTRODUCTION

Despite modern optimal pharmacological management, patients with advanced heart failure (HF) experience severe exercise intolerance mainly manifested by marked dyspnea and fatigue.

HF patients present several respiratory derangements, including restrictive and obstructive breathing pattern<sup>1</sup> decreased lung compliance and hyperventilation.<sup>2</sup> Respiratory muscle weakness<sup>3,4</sup> and decreased inspiratory capacity<sup>5</sup> have also been observed in these group of patients and are associated with exercise intolerance. Respiratory drive is significantly attenuated, indicating the exertion of a greater respiratory effort and is closely associated with dyspnoea,<sup>6</sup> autonomic nervous system impairment, microcirculation dysfunction, exercise intolerance and disease severity,<sup>7,8</sup> while it improves after interventions such as exercise training.<sup>9</sup>

Long term mechanical support of the advanced failing heart utilizing left ventricular assist devices (LVAD) has become a standard bridge to transplantation and a destination therapy for selected patients with end-stage heart failure. Interestingly severe heart failure can be reversed in selected patients with the combination of LVAD and pharmacologic therapy (bridge to recovery).<sup>10</sup>

We hypothesized that LVAD unloading, reversing the chronic stressor state, would induce beneficial effects in terms of myocardial remodeling process and in the increased respiratory drive.

We demonstrated previously a beneficial effect of LVAD implementation on adversely affected parameters of respiratory function, in patients with advanced HF.<sup>11</sup> In the present study we aimed to evaluate the effects of a continuous-flow LVAD on respiratory drive during a 6 month follow-up period after implantation.

## MATERIAL AND METHODS

### Study population

Our study design was a prospective observational study and the study population consisted of 8 consecutive patients with end-stage HF (6 males and 2 females, 44±19yrs, 22.9±2.4 kg/m<sup>2</sup>, Left ventricular ejection fraction (LVEF): 21±3%, Left

ventricular end-diastolic diameter (LVEDD): 68±7mm, Left ventricular end-systolic diameter (LVESD): 59±6mm, Pulmonary Capillary Wedge Pressure (PCWP): 27±5 mmHg, Cardiac Index (CI): 1.7±0.4 liters/min/m<sup>2</sup>) who received LVAD. Four patients, suffering from end-stage ischemic cardiomyopathy underwent LVAD implantation as "destination therapy" and 4 patients with non-ischemic cardiomyopathy as bridge to transplantation or to "recovery" ("Harefield Athens Recovery Program"). All patients received an implantable axial flow, non-pulsatile Heart Mate II LVAS (Thoratec Corp; Pleasanton, CA).

### Clinical protocol

All patients underwent serial evaluation with cardiopulmonary exercise test (CPET) and respiratory function tests after LVAD implantation.

All patients after LVAD implantation were under optimal medical treatment. In patients with non-ischemic cardiomyopathy, clenbuterol ( $\beta_2$ -agonist) was added to standard treatment when maximal regression of the LVEDD had plateaued.

In the study we also included a control group of 8 patients (6 males, 4 with ischemic and 4 with dilated cardiomyopathy, 53±11years, BMI: 28±5kg/m<sup>2</sup>, EF: 28.5±5.8%) with advanced systolic HF, and a peak oxygen uptake  $\leq$  19ml/kg/min non-treated with LVAD. These patients were randomly chosen from the population followed in our long-term heart failure program. Informed consent was obtained from all patients, and the study was approved by the Human Studies Ethics Committee of our Institution.

### Respiratory function tests

After familiarization of the patient with the laboratory environment, measurements of forced vital capacity (FVC) and forced expiratory volume at 1 sec (FEV<sub>1</sub>) were performed in the sitting position with a closed-circuit spirometer (SensorMedics, Yorba Linda, CA). In all patients the maximal inspiratory pressure (P<sub>imax</sub>) was measured at rest, using a system for pulmonary tests as previously described.<sup>4</sup> All tests were performed 1, 3 and 6 months after LVAD implantation.

Measurements of the mouth occlusion pressure (P<sub>0.1</sub>) were made 100ms after the onset of inspiration at rest. P<sub>0.1</sub> is the

inspiratory pressure that develops in the first 100ms of an inspiratory effort against a closed valve, at the level of functional residual capacity, at rest. After 4 calm breaths with stable functional residual capacity (FRC) the level of FRC was detected. Then the valve was randomly closed, to minimize the likelihood of a deliberate respiratory effort exerted by the patient against the valve. The measurement was repeated 6-8 times, and  $P_{0.1}$  was calculated as the average of 4 measurements that differed by <5%.<sup>9</sup>  $P_{0.1}$  was expressed as an absolute value (cmH<sub>2</sub>O), and as a percentage of  $P_{imax}$  ( $P_{0.1}/P_{imax}$ ) to normalize its measurement for individual differences in inspiratory muscle strength.

### Exercise test

Each subject performed a symptom-limited ramp-incremental exercise test, so as to aim for a test of 8-12 min duration (work increments calculated as previously described<sup>9</sup>). The subjects breathed through a mouthpiece allowing pulmonary gas exchange and ventilatory variables to be obtained from gas analyzers and a mass flow sensor (Vmax 229; Sormedics; Yorba Linda, CA). Mean inspiratory flow ( $V_T/T_I$ ) and end-tidal carbon dioxide ( $P_{ETCO_2}$ ), minute ventilation ( $V_E$ ), tidal volume ( $V_T$ ), breathing frequency (fb), inspiratory time ( $T_I$ ), total respiratory time ( $T_{Tot}$ ), and respiratory cycle ( $T_I/T_{Tot}$ ), were also calculated.

### Echocardiography

Conventional transthoracic echocardiographic examination was performed in all patients in order to assess Left Ventricle (LV) internal dimensions and LVEF.

### Statistical analysis

Continuous variables are presented as mean±Standard Deviation. Group means of continuous variables were compared by unpaired Student's t-test. Repeated measures of analysis of variance (ANOVA) and Bonferroni post hoc test of significance were used for the statistical evaluation of the within and between group differences during the follow-up period. Normality of distribution was assessed with the Shapiro-Wilk test. Correlations between variables were obtained and tested by Pearson's correlation coefficient after tested for normality curves.

## RESULTS

All LVAD patients had impaired respiratory drive at initial evaluation which presented a trend towards normalization during the 6 month follow-up period. Specifically a decrease in  $P_{0.1}$  and  $P_{0.1}/P_{imax}\%$  (Figure 1) as well as an increase in  $P_{imax}$  and  $V_T$  at peak exercise was observed (Table 1). The patients in the control group had a statistically insignificant trend for a decrease in  $P_{0.1}$ .

A significant increase in exercise capacity was noted in all LVAD patients, expressed by  $VO_{2p}$  and  $VO_{2AT}$ , as previously described.<sup>11</sup> The  $P_{imax}$  increase after 6 months of follow-up was inversely correlated with the  $VO_{2p}$  increase ( $r=-0.88$ ;  $p<0.05$ ). No deference in exercise capacity was observed in the control group.

A significant decrease in LVEDD, LVESD and an improvement in LVEF is observed at 1, 3 and 6 months after LVAD implantation (Table 2).

## DISCUSSION

The main findings of the study were that implantation of a continuous-flow LVAD in advanced HF patients progressively induced a significant improvement in respiratory drive with parallel improvement in exercise capacity and LV systolic function and dimensions in the non-ischemic group.

Previous studies have demonstrated a higher respiratory drive, reflected by resting  $P_{0.1}$  and  $P_{0.1}/P_{imax}$  in patients with HF in comparison to healthy controls<sup>6,12</sup> and that is associated with HF severity<sup>8</sup>. An excessive activation of the ergoreceptors has been reported in these patients, along with cachexia, autonomic abnormalities and elevated plasma catecholamines concentrations.<sup>13</sup> The heightened sympathetic activation, vasoconstrictor response and ventilatory drive might be partially explained by the exaggerated ergoreflexes during exercise.

It is possible that LVAD implantation, reversing the chronic stressor state and the ensuing neurohormonal activation, can induce similar changes in skeletal muscles. We have previously shown that LVAD induces a progressive improvement in respiratory skeletal muscle dysfunction.<sup>11</sup> Though, the enhanced ergoreflex of HF patients could be brought to levels closer to normalization after LVAD, possibly inducing changes to res-

piratory drive similar to those observed after exercise rehabilitation.<sup>9</sup>

Autonomous nervous system is severely deranged immediately after LVAD implantation and these abnormalities persist 3 months after LVAD implantation with a tendency to improve.<sup>14</sup> The autonomic derangement being restored after LVAD implantation through unloading of the failing heart, may contribute to respiratory drive restoration up to a point<sup>15,16</sup> improving the adrenergic pathways and the sympathetic innervation.

Previous studies have shown a significant reverse remodeling of the failing myocardium, as well as, a hemodynamic improvement after LVAD implantation.<sup>17-19</sup> Our study results are consistent with those of previous studies in patients with non-ischemic HF.

Interestingly, in our study a significant inverse correlation of the percentage changes of  $P_{\text{imax}}$  and  $\text{VO}_{2\text{p}}$  was evident after six months of LVAD support mainly evidenced in non-ischemic LVAD patients. An explanation of these findings may be the additional effect of clenbuterol in these patients comparing to ischemic LVAD patients and its greater effect on the peripheral muscles strength, with 'less positive' effects to muscle oxidative capacity.

#### Limitations

The small number of patients and the short follow up period are the main limitations of our study. We also included patients with ischemic and non-ischemic HF patients, although the sample size was small for separate analysis according to HF etiology. Finally the use of clenbuterol might interpret alongside with LVAD implantation.

#### CONCLUSIONS

Concluding, with this study we demonstrate that a continuous-flow LVAD induces a progressive and significant improvement of respiratory drive and Left ventricle reverse remodeling during a 6 month follow-up period.

#### FINANCIAL DISCLOSURE

Authors of the present manuscript have nothing to disclose.

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## ANNEX

TABLE 1. Respiratory drive, respiratory function and CPET parameters in LVAD patients

	Post LVAD 1 month	Post LVAD 3 months	Post LVAD 6 months
<b>Respiratory drive parameters</b>			
P <sub>0.1</sub> , cmH <sub>2</sub> O	2.61±0.58	2.44±0.42	2.34±0.44
P <sub>0.1</sub> /P <sub>imax</sub> %	4.17±0.43	3.29±1.0	2.56±0.35†
P <sub>imax</sub> , cmH <sub>2</sub> O	63±16	78±17	93±20†
V <sub>Tbase</sub> , L	0.5±0.07	0.5±0.1	0.6±0.1
V <sub>Tpeak</sub> , L	1.18±0.21	1.29±0.29	1.51±0.33†
V <sub>T</sub> /T <sub>Ibase</sub> , L/min	26.8±9.6	22.5±6.8	30.1±8
V <sub>T</sub> /T <sub>Ipeak</sub> , L/min	116.2±30.4	103.8±21.4	129.3±23.2*
P <sub>ETCO<sub>2</sub>base</sub> , mmHg	32.7±6.3	36.7±4.8	30.7±2.6*
P <sub>ETCO<sub>2</sub>peak</sub> , mmHg	26.7±6.8	31.6±6.7	26.1±3.9*
f <sub>bbase</sub> , bpm	23.8±3.8	22.2±2.1	22.5±3.7
f <sub>bpeak</sub> , bpm	48.8±10.6	40.2±5.9	43.3±6*
<b>Respiratory function parameters</b>			
FEV <sub>1</sub> (L)	1.97±0.29	2.22±0.45	2.4±0.49*
FEV <sub>1</sub> (%predicted)	59±7	66±12	71±13*
FVC(L)	2.33±0.45	2.8±0.66	3.1±0.75*
FVC(%predicted)	53±11	67±13	74±15*
FEV <sub>1</sub> /FVC(%)	86±11	80±7	79±9*
<b>CPET parameters</b>			
VO <sub>2p</sub> , L/min	0.78±0.08	0.87±0.17	1.1±0.14†
VO <sub>2p</sub> , ml/kg/min	12.5±1.3	13±1.5	14.9±1.6*
VO <sub>2AT</sub> , ml/kg/min	7.7±0.75	9±0.8	10.9±1.7*
VO <sub>2</sub> (% predicted)	39.28±1.88	42.0±7.07	48.14±4.22†
V <sub>E</sub> /VCO <sub>2</sub> slope	41.8±13.3	33.7±6.3	37.6±3.5
ExerciseTime(min)	5±1.7	6.5±1.7	8.5±1.1*
RER	1.4±0.18	1.3±0.21	1.2±0.07
V <sub>D</sub> /V <sub>T</sub> at peak	0,3±0,04	0.28±0,05	0.25±0.05*
HR rest	91±8	75±21	76±14
HR peak	131±15	120±41	124±25
HR recovery	22±14	14±15	20±10

Data are expressed as mean±standard deviation. Baseline for the LVAD group was 1 month after implantation.

P<sub>0.1</sub>=mouth occlusion pressure 100 ms after the onset of inspiration, P<sub>0.1</sub>/P<sub>imax</sub>=mouth occlusion pressure/max inspiratory pressure, P<sub>imax</sub>=Maximum inspiratory pressure, V<sub>Tbase</sub>=Tidal volume at baseline, V<sub>Tpeak</sub>= Tidal volume at peak exercise, V<sub>T</sub>/T<sub>Ibase</sub>=mean inspiratory flow at baseline, V<sub>T</sub>/T<sub>Ipeak</sub>= mean inspiratory flow at peak exercise, P<sub>ETCO<sub>2</sub>base</sub>=end-expiratory CO<sub>2</sub> at baseline, P<sub>ETCO<sub>2</sub>peak</sub>=end-expiratory CO<sub>2</sub> at peak exercise, f<sub>bbase</sub>=breathing frequency at baseline, f<sub>bpeak</sub>=breathing frequency at peak exercise, FEV<sub>1</sub>=Forced expired volume in 1 sec, FVC=forced vital capacity, VO<sub>2p</sub>=Peak oxygen uptake, VO<sub>2AT</sub>=Anaerobic threshold, V<sub>E</sub>=Minute ventilation. V<sub>E</sub>/VCO<sub>2</sub> slope=the slope of ventilatory equivalent for carbon dioxide output, RER=Respiratory exchange ratio, V<sub>D</sub>/V<sub>T</sub> at peak =the ratio of physiologic [dead space](#) over [tidal volume](#)

†p<0.01 vs baseline, \*p<0.05 vs baseline.

TABLE 2. Echocardiographic measurements at rest, before and after LVAD implantation

	pre LVAD (n=8)	Post LVAD 1 month (n=8)	Post LVAD 3 months (n=7)	Post LVAD 6 months (n=5)
LVEDD, mm	68±6	60±6	58±6*	56±11*
LVESD, mm	59±6	49±9*	46±9*	41±11†
LVEF, %	20±3	25±5	34±16	40±15†

Data expressed as mean±standard deviation. LVEDD=Left ventricular end-diastolic diameter, LVESD=Left ventricular end-systolic diameter, LVEF=Left ventricular ejection fraction

\*p<0.05 vs baseline, †p<0.01 vs baseline

**FIGURE 1.** Error bar of  $P_{0.1}/P_{i_{max}}$  % at 1, 3 and 6 months post LVAD implantation

