VAFRACT

The effects of echo-optimization of left Ventricular Assist devices on Functional capacity: a RAndomized Controlled Trial.

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BACKGROUND

The evolution, not only in technologies but also in the selection of patients, and the development of competences in peri-operative and post-operative management have led to a constant improvement in the survival of left ventricular assist device (LVAD) carriers.

However, after LVAD implantation, patient's functional capacity is still reduced with peak oxygen uptake (VO_2 peak) values calculated by cardiopulmonary exercise testing (CPET) ranging from 11 to 20 mL/kg/min.[1]

Various determinants have an influence on functional capacity. Only few previous reports have analysed the effects of pump speed increase on exercise performance in LVAD patients with contradictory results: an upgrade was observed in some,[2,3] but not in all reports.[4]

Moreover, the role of right ventricle (RV) is often underestimated: Murninkas et al. found a decrease in VO2 peak of 0.97 mL/kg/min for each ejection fraction reduction of the RV by 10%.[5] A more favourable haemodynamic profile for the RV and a probable better response in terms of functional capacity can therefore be expected from LVAD echo-optimization (EO).

Uriel et al. demonstrated that EO can help patient management: in particular, the haemodynamic improvement was evident with an increase in cardiac output and a decrease in pulmonary capillary wedge pressure, confirmed by right heart catheterization.[6]

We conduct a prospective randomized trial [The Effects of Echo-optimization of Left Ventricular Assist Devices on Functional Capacity, a RAndomized Controlled Trial (VAFRACT)] to evaluate the additional benefit of an EO approach on functional capacity measured by CPET and on quality of life in LVAD carriers.

MATERIALS AND METHODS

STUDY POPULATION

Subjects studied are patients supported with a continuous-flow LVAD: HeartMate II (Thoratec Inc., Pleasanton, CA) and HeartMate 3TM (Abbott, North Chicago, IL). All are ambulatory patients recruited by our Day Hospital of the Division of Cardiovascular Surgery at the University Hospital of Verona.

Inclusion criteria are as follows:

- enrolment at least 3 months after LVAD implantation;
- compliance to the required follow-up schedule;
- age ≥ 18.

Exclusion criteria are as follows:

- distance of less than 150 m on the 6 min walking test or impossibility to perform CPET;
- poor acoustic window for echocardiographic imaging acquisition;
- recent finding of any major device-related complication (sepsis, thrombosis ...).

Patients are randomized with a 1:1 allocation (using random block sizes of 4 and 6) to EO (EO group) vs. standard settings (CONTROL group) after at least 3 months from the LVAD implantation. Randomization is performed using a web-based service with secured password and protected login, managed by a doctor not involved in the trial. The ordering of blocks and their respective size is unknown to the investigators.

Patients randomized to EO treatment performed echo-guided device programming[7] at randomization. In CONTROL group, patients performed LVAD EO, but the optimal device speed is not confirmed at the end of procedure. The flow chart is specified in **Figure 1**.

The primary endpoint of our study is VO_2 peak change at 3 months after the EO.

The secondary endpoints are as follows: right ventricular function (assessed by echocardiography and evaluated by fractional area change); device-related hospital admissions (complications are defined according to the Interagency Registry for Mechanically Assisted Circulatory Support[8]); N-terminal pro-brain natriuretic peptide (NT-proBNP) levels; CPET exercise time and changes in quality of life perceived by the EuroQol Five Dimensions 3L questionnaire (EuroQol Group, Rotterdam, the Netherlands) and the Kansas City Cardiomyopathy Questionnaire.

SAMPLE SIZE DETERMINATION

Kerrigan et al.[9] proposed a design similar to our protocol, with the intention, however, of verifying the contribution of another tool (rehabilitation) to improve the functional capacity of LVAD patients. It has been hypothesized that the EO group undergoes a variation equal to the rehabilitated group reported by Kerrigan, while the non-optimized group behaves like the control group of that study. Because the study did not report the standard deviation of the differences, it is estimated taking into account the correlation between the two measurements, according to the value of r = 0.50, as suggested by the Cochrane Heart Group. Therefore, a variation is obtained for the control group of 0.8 ± 2.8 and for the 'active' group of 3.1 ± 1.87. Assuming an alpha value of 0.05 and a power of 80%, an estimated sample size of 18 patients for each group is obtained.

STUDY PROCEDURES

MEASUREMENT OF BLOOD CHEMISTRY AND HAEMATOLOGIC VARIABLES

Fasting blood samples are collected at baseline and at 3 months to assess parameters of haemolysis (lactate dehydrogenase and haptoglobin) or infection (complete blood count and high sensitivity C-reactive protein) and to investigate kidney (creatinine and blood urea) and liver function (bilirubin and alanine and aspartate aminotransferase). Lipid profile (low-density lipoprotein, high-density lipoprotein, and total cholesterol, triglycerides), blood glucose, and serum electrolytes (sodium and potassium) were also measured. Dosage of NT-proBNP, as secondary endpoint of our study, are included in the evaluation. Lastly, measurement of prothrombin time–international normalized ratio are fundamental to allow our procedure of EO in safe conditions (a value at least >1.8 was requested).

CARDIOPULMONARY EXERCISE TEST

For the exercise test, a bicycle ergometer is used (Quark CPET, COSMED, Rome, Italy). Respiratory gas exchange measurements are obtained breath-by-breath (Omnia 1.6.5, COSMED, Rome, Italy) using a face-mask as patient/metabolic cart interface.

The aim of the exercise duration is 10 ± 2 min. In all patients, the initial workload is 10 W, and it was gradually increased by a 10 W/min ramp until patients reached exhaustion. The protocol is not changed between baseline and 3 months CPET. Patients are motivated to put their maximal effort

thus allowing a reliable measurement of VO_2 peak, calculated in mL/kg/min. We considered the highest 30 s average VO_2 value over the last minute of the exercise phase. Minute ventilation/CO_2 production slope is calculated as the slope of the linear relationship between minute ventilation and CO_2 production form excluding the initial part of the test (potentially influenced by hyperventilation) and the final part (from the end of the isocapnic tamponade to the end of the exercise).[10] The anaerobic threshold is measured with the V-slope analysis from the plot of CO_2 output vs. O_2 uptake on equal scales. This value is confirmed analysing ventilatory equivalents and end-tidal pressures of CO_2 and O_2.[11] A respiratory exchange ratio >1.05 is used as an indicator of an adequate performed test.

ECHO-OPTIMIZATION PROCEDURE

Complete transthoracic echocardiographic exams are performed in accordance with current American Society of Echocardiography guidelines,[12] using a CX-50 xMatrix Philips cardiac ultrasound system (Philips S.p.A, Milan, Italy).

Before starting the procedure, blood pressure is recorded. The patient's device speed is lowered to the minimum speed clinically recommended. After 2 min, the following parameters are documented: left ventricular (LV) end-diastolic dimension, LV end-systolic diameter, frequency of aortic valve (AV) opening, degree of aortic regurgitation, degree of mitral regurgitation, right ventricular systolic pressure, blood pressure, and heart rate. Also, the other pump parameters are recorded (power, pulsatility index, and flow).

Left ventricular end-diastolic and end-systolic dimensions are measured from the parasternal long-axis view; AV opening is assessed using M-mode over the AV in the parasternal long-axis view. Visual estimation of the severity of aortic and mitral regurgitation is performed in the parasternal long-axis view using the colour Doppler imaging technique. For the assessment of aortic and mitral regurgitation, the degree is graded from 0 to 3 (0, none; 1, mild; 2, moderate; and 3, severe). Right ventricular systolic pressure is estimated from peak tricuspid regurgitation velocity using the modified Bernoulli's equation.

The recommended speed range varies according to the indications given in the data sheet for each specific device: for the HeartMate II, the clinical recommended range is between 8800 and 10 000, and the speed can be changed by an increment or reduction of 200 rpm; for the HeartMate 3TM, the

allowed speed is between 4800 and 6200 rpm with possible modifications of 100.

Therefore, the device speed is increased, at 2 min intervals with repeated acquisition of all echocardiographic and device parameters at each speed step, up to the maximum clinically recommended speed.

The optimal velocity is defined as the one that allows an intermittent AV opening and a neutral position of the interventricular septum without increasing aortic and/or tricuspid regurgitation, associated or not to a dilatation of the RV.[12]

The test is stopped in case of a decrease in LV end-diastolic diameter ≤ 3 cm, suction events, ventricular arrhythmias, symptoms (palpitations, dizziness, dyspnoea, chest pain, or headache), hypertension (mean artery pressure > 100 mmHg), and hypotension (mean artery pressure < 60 mmHg). At the end of the exam, a new assessment of blood pressure is performed, and the images recorded are reviewed.

STATISTICAL ANALYSIS

The Student's t-test and the χ^2 test are used to compare groups at baseline for continuous and nominal data, respectively.

A paired t-test is used to assess within-group changes from baseline to 3 months. Analysis of covariance is used to compare the differences in change from baseline to follow-up between the two groups. Statistical significance is defined as $P < 0.05$ (two-tailed).

Data are presented as mean ± standard deviation unless otherwise stated. All statistical analyses are performed with IBM SPSS Version 22.0 (Armonk, New York).

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FIGURE 1 – FLOW CHART