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Pump speed modulations and sub-maximal exercise tolerance in left ventricular assist device recipients: A double-blind, randomized trial

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BACKGROUND: The effect of pump speed increase on sub-maximal exercise tolerance, corresponding to activities of daily living (ADLs), is unknown. The aim of this study was to determine the effects of increasing pump speed during exercise at a sub-maximal level below anaerobic threshold (AT).
METHODS: Patients each completed 3 exercise sessions on an ergometer cycle. On Day 1 workload at AT was defined. On Day 2 of the study, 2 sub-maximal tests at a workload below AT were undertaken: one at fixed baseline pump speed ($Speed^{base}$) and the other with baseline pump speed + 800 rpm ($Speed^{inc}$). The sequence of the 2 sub-maximal tests was determined by randomization. Both patient and physician were blinded to the sequence. Exercise duration, oxygen consumption (VO2) and rate of perceived exertion (RPE), using the Borg scale (score 6 to 20), were recorded.
RESULTS: Nineteen patients (all with a HeartMate II ventricular assist device) completed 57 exercise tests. Baseline pump speed was 9,326 ± 378 rpm. At AT, workload was 63 ± 26 W (25 to 115 W) and VO_2 was 79 ± 14% of maximum. Exercise duration improved by 106 ± 217 seconds (~13%) in $Speed^{inc}$ compared with $Speed^{base}$ (837 ± 358 vs 942 ± 359 seconds; $p = 0.048$). The RPE was 13.2 ± 2.5 in $Speed^{base}$ vs 12.7 ± 2.4 in $Speed^{inc}$ ($p = 0.2$).
CONCLUSION: Increasing pump speed by 800 rpm during sustained, low-intensity physical activity is safe and prolongs exercise duration in patients supported with a HeartMate II device. Automated pump speed increase during light exercise may contribute to improved quality of life by facilitating ADLs.
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Due to the shortage of donor organs and the contra-indications to cardiac transplantation, an increasing number of end-stage heart failure (HF) patients are supported long term with continuous-flow left ventricular assist devices (CF-LVADs).[1] The focus has predominantly been on survival and avoiding complications, but quality of life (QOL) and exercise tolerance during support are also important to patients. Functional capacity, in terms of New York Heart Association (NYHA) class, generally improves after implantation of a CF-LVAD, but maximal exercise capacity remains greatly reduced.[2–4] In patients with CF-LVADs, complex central and peripheral pathophysiologic mechanisms have been attributed to the continued exercise intolerance, as has fixed pump speed, which prevents adequate circulatory support during strenuous exercise.[2,5] Manually increasing pump speed during maximal exercise improves peak oxygen uptake (peak VO2) and can be done safely.[6–9] The effect of pump speed increase on *sub-maximal* exercise tolerance, namely corresponding to activities of daily living (ADLs), is

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unknown. Our aim in this study was, using a double-blind, randomized approach, to examine the clinical relevance of increased pump speed during exercise at a sub-maximal level below anaerobic threshold (AT).

Methods

Study cohort

Subjects studied were HF patients supported with a CF-LVAD (HeartMate II [HMII], Thoratec Corporation, Pleasanton, CA). All were ambulatory outpatients recruited from 2 centers, the University Hospital Rigshospitalet (Copenhagen, Denmark) and the Johns Hopkins Hospital (Baltimore, Maryland), from December 2013 to February 2015. The trial was approved to be in accordance with the Helsinki Declaration by the Ethics Committee of Copenhagen (H-1-2013-103) and the institutional review board of Johns Hopkins Hospital (NA_00092081). The trial was registered at ClinicalTrials.gov (Identifier NCT02335684). All patients provided written informed consent.

Study design

The study was designed to test the hypothesis that exercise tolerability during low to moderate workloads in CF-LVAD patients is improved when pump speed is increased soon after the onset of exercise. To test this hypothesis, each patient completed 3 exercise sessions on 2 study days.

Determining individually defined workload at anaerobic threshold (Day 1)

At study Day 1 patients completed a maximal cardiopulmonary exercise test (CPET) according to guidelines[10] during which workload, expressed in watts (W), was measured at AT. Anaerobic threshold was defined as the time at which respiratory exchange ratio (RER) exceeded 1 without going below 1 again during the remaining exercise time. The aim of the exercise duration was 8 to 10 minutes and, based on previous experience, the protocol started at 25 W and was followed by an increase of 10 W/min. After reaching AT, patients were encouraged to keep exercising until exhaustion, thus enabling a measure of peak VO_2, calculated as milliliters per kilogram per minute (ml/kg/min). Exercise testing was done using upright cycle ergometers. Breath-by-breath respiratory gas[11] was analyzed by 1 of 2 similar systems at the 2 centers; CS-200, Ergospiro (Schiller,Switzerland) or Vmax, Sensormedics (Bilthoven, the Netherlands). Oxygen consumption (VO_2), carbon dioxide excretion (VCO_2) and expiratory minute ventilation(VE) were adjusted with standard temperature pressure dry (STPD). Calibration before each test for gas, ambient conditions and volume, according to manufacturer instructions, was performed to address changes in room temperature, humidity and air oxygen content.

Sub-maximal exercise protocol (Day 2)

On Day 2 of the study, each patient performed 2 sub-maximal exercise tests using the same CPET equipment as for Day 1. The exercise protocol was individually formulated depending on workload at AT found at Day 1. To ensure workload did not exceed conditions corresponding to a sub-maximal level, the protocol was set to increase resistance by 10 W/min until reaching the pre-defined, patient-specific workload at AT − 10 W (~10 W below AT load), followed by no further changes in workload. Rates of perceived exertion (RPEs) according to the Borg scale (6 to 20) were recorded at the end of each exercise minute and total exercise time was noted for each test.

Pump speed protocol and randomization

One of the sub-maximal tests at Day 2 was performed with pump speed remaining at the fixed baseline setting ($Speed^{base}$), that is, the "usual" speed setting for the patient. The other test was performed with increased pump speed corresponding to baseline rpm + 800 rpm ($Speed^{inc}$). Pump speed was increased by 400 rpm pump speed being increased by 400 rpm after 1 minute and a further 400 rpm after 2 minutes of exercise. The order of $Speed^{base}$ and $Speed^{inc}$ in each patient was determined by randomization and tests were separated by ≥2 hours to allow for restitution. Patient and physician were blinded to the sequence and an additional observer was present to perform the pump speed changes. For the $Speed^{base}$ test, the observer would mimic changes on the controller so the controller noises were made, but did not finalize those changes.

Statistical analysis

Statistical analysis was carried out using SAS version 9.4 statistical software (SAS, Inc., Cary, NC). Comparison between groups was performed using 2-sided paired or unpaired Student's *t*-test or analysis of variance as appropriate. With studies involving small samples, a statistical analysis of data distribution (i.e., differences in exercise time between tests) is often subject to uncertainty. Therefore, the change in exercise duration from $Speed^{base}$ to $Speed^{inc}$ was analyzed with both paired *t*-test and Wilcoxon's matched-pairs signed rank sum test. The association between continuous variables was described using Spearman's rank or Pearson's correlation coefficient, as appropriate. Statistical significance was defined as $p < 0.05$ (2-tailed). Data are presented as mean ± standard deviation unless otherwise stated. Due to the lack of published data on bicycle exercise time at workloads below AT in CF-LVAD patients, a statistical power calculation was not performed.

Results

Cohort characteristics

Nineteen of the 23 patients recruited were enrolled in the study. Four were excluded due to: (1) ventricular tachycardia before exercise testing; (2) multiple cancellations of appointments; (3) upper tract respiratory infection causing inability to wear face mask; and (4) technical equipment failure. The cohort, aged 33 to 75 years, consisted predominantly of male patients (79%) with non-ischemic cardiomyopathy (74%). Most patients were bridge-to-transplant candidates (58%) but overall support duration was 1,017 ± 828 days. Average pump speed (HMII) was 9,326 ± 378 rpm. At rest, average heart rate and mean arterial pressure (MAP) were 84 ± 12 bpm and 89 ± 10 mm Hg, respectively. Approximately 90% of patients received β-blocking therapy. Detailed characteristics are presented in Table 1.

Peak exercise capacity

Average peak VO_2 was 12.6 ± 4.3 ml/kg/min with RER of 1.2 ± 0.09. Patients in a lower NYHA class