Hemodynamic Effects of Exercise Training in Heart Failure

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ABSTRACT

Background: Exercise performance improvement after training in heart failure (HF) can be due to central or peripheral changes.

Methods and Results: In 70 HF stable patients we measured peak VO_2 and cardiac output (CO, inert gas rebreathing technique) and calculated arteriovenous O_2 differences (a-v O_2diff) before and after an 8-week training program. Peak VO_2 changed from 1111 ± 403 mL/minute to 1191 ± 441 ($P < .001$), peak workload from 68 ± 29 watts to 76 ± 32 ($P < .0001$), peakCO from 6.6 ± 2.2 L/minute to 7.3 ± 2.5 ($P < .0001$), and peak a-v O_2diff from 17.5 ± 5.1 mL/100 mL to 16.6 ± 4.1 ($P = .081$). Changes in peak CO and a-v O_2diff allowed to identify 4 behaviors: group 1: (n = 15) reduction in peak CO and increase in a-v O_2diff (peak VO_2 unchanged, peak workload +9.5%); group 2: (n = 16) both peak CO and a-v O_2diff increased as well as peak VO_2 (23%) and workload (18%); group 3: (n = 4) peak CO and a-v O_2diff reduced as well as peak VO_2 (-18%) and workload (-5%); group 4: (n = 35) peak CO increased with a-v O_2diff reduced (increase in peak VO_2 by 5.5 and workload by 8.4%).

Conclusions: Exercise training improves peakVO_2 by increasing CO with unchanged a-v O_2diff. A reduction after training of a-v O_2diff with an increase in CO is frequent (50% of cases), is suggestive of blood flow redistribution and, per se, not a sign of reduced muscle performance been associated with improved exercise capacity. (*J Cardiac Fail 2011;17:916−922*)

Key Words: Training, heart failure, cardiac output.

The effects of exercise training on functional capacity and quality of life in heart failure (HF) patients are well recognized. Exercise prescription is recommended in the most recent European and American guidelines on comprehensive HF management.[1,2] Several studies analyzed the effects of physical training on peak oxygen consumption (VO_2), and they found at the end of training a peak VO_2 increase between 12% and 31%.[3]

Peak VO_2, following the Fick principle, corresponds to cardiac output (CO) × the arteriovenous oxygen difference (a-v O_2diff). It is generally accepted that measurements of VO_2 and CO during exercise should allow to discriminate between exercise limitation because of altered left ventricular pump function or other causes including muscle deconditioning. Indeed, a low peak exercise a-v O_2diff is considered a sign of low O_2 uptake by the muscles suggestive of muscles inefficiency or inadequate muscle perfusion.

Muscle deconditioning in HF has been assumed to be the major target of exercise training.[4−6] Indeed, identification of CO response and peripheral muscle deconditioning before rehabilitation is of major importance because it would allow selection of patients who would benefit most from a rehabilitation program.[7,8] Up to now, however, limited data have been available as regards of the differential effect of an exercise training program on central hemodynamic parameters or peripheral muscle improvement[6] because of the invasive nature of the most widely used methods of CO measurement during exercise. Consequently, almost no experience exists for exercise CO and a-v O_2diff response as guides or targets for an exercise training program.

Recently, an inert gas rebreathing (IGR) method was proposed for the measurement of CO at rest and during exercise in HF patients,[9] which offers a new noninvasive tool for the assessment of exercise parameters in HF patients.

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The present study was performed to evaluate the hemodynamic effects of exercise training in HF patients, measuring simultaneously CO and VO_2. Moreover we aimed to discern predictors that would enable us to select patients who would benefit most from an exercise training program.

Methods

Study Population

We studied HF patients who belonged to a cohort of HF patients regularly followed at the Heart Failure Unit of the Centro Cardiologico Monzino, Milan, Italy, and the unit of Cardiovascular Prevention and Rehabilitation of the Bern University Hospital, Switzerland. All patients had been previously familiarized with cardiopulmonary exercise testing (CPET). Study inclusion criteria were: presence of HF with an age range between 18 and 80 years, left ventricle ejection fraction (LVEF) $<40\%$ (assessed by transthoracic echocardiography), clinical stable condition for at least 3 months before study enrollment, capability and willingness to participate in a training program, optimized and individually tailored drug treatment, and capability of performing CPET with CO determination by IGR. Study exclusion criteria were: comorbidity or other limitations that interfere with performing exercise training and measurements, major cardiovascular event (6 weeks) or cardiovascular procedure (including ICD or CRT implantation) within the previous 6 months, planned cardiovascular procedure or expectation of receiving a cardiac transplant within the next 6 months, HF secondary to significant uncorrected primary valvular disease (except for mitral regurgitation secondary to LV dysfunction) or congenital heart disease, obstructive cardiomyopathy, use of fixed-rate pacemakers, pacemakers or ICD devices with an inability to or with heart rate limits set lower than 80% of the peak exercise predicted heart rate, and exercise testing results that would preclude safe exercise training. Subjects' characteristics are reported in Table 1. The study complies with the Declaration of Helsinki, the locally appointed ethics committee approved the research protocol and informed consent was obtained from all patients.

Table 1. Descriptive Characteristics of Patients

Age (y)	61.6 ± 9.6
Sex (M/F)	54/16
HF etiology	
Idiopathic dilated cardiomyopathy	26
Coronary artery disease	37
Valvular heart disease	7
LVeSV (mL)	135 ± 71
LVeDV (mL)	193 ± 77
LVEF (%)	31.8 ± 10.4
Concomitant therapy	
β-blockers	96%
ACE inhibitors	64%
AT1 blockers	29%
Diuretics	80%
Antialdosterone	57%
Amiodarone	29%
Anticoagulant	40%
Digitalis	7%
ASA	57%

F, female; HF, heart failure; LVeDV, end-diastolic left ventricular volume; LVEF, left ventricular ejection fraction; LVeSV, end-systolic left ventricular volume; M, male; NYHA, New York Heart Association.

Carvedilol equivalent β-blockers dose was calculated on a 1 to 5 ratio between carvedilol and bisoprolol or nebivolol and on a 4 to 1 ratio between metoprolol.

Study Design

Baseline Evaluation. All patients underwent clinical evaluation associated with collection of history and recent instrumental data. All subjects underwent 1 CPET with CO determination for familiarization purposes and to confirm the appropriateness of the rate of the workload increase of the personalized ramp protocol. Afterward, each patient carried out a CPET consisting of a personalized ramp protocol to maximum tolerance associated with CO measurement by IGR at rest and at peak exercise. This test was done in the week preceding the beginning of the training program. Normal CO response to exercise was defined according to the Higginbotham formula lower limit of CO at peak exercise $= 5 \times (VO_2\text{pred mL/minute} + 3000 \text{ mL/minute})$.[10]

Training Program. We studied the effects of the exercise training program after 8 weeks. Patients performed an aerobic training 3 to 5 times a week, either on a bike or on a treadmill combined with standard callisthenic exercises. The training was performed in a gymnasium with medical/nurses surveillance. Each session consisted of a 10- to 15-minute warm-up followed by a 20- to 30-minute period of exercise at the target workload, considered as the workload at 70% to 80% of peak VO_2, and a 5-minute cool down.

Final Evaluation. At the end of the training program, all patients underwent a clinical e-evaluation and performed a CPET equal to the one at baseline with CO measurement at rest and at peak exercise. This evaluation was done within 1 week from the end of the training program.

Ramp Protocol CPET

CPET was performed on a cycle-ergometer with progressive work-rate increase in a ramp pattern, after 3 minutes of rest and 3 minutes of unloaded cycling. All tests were done in the morning with the patients receiving their usual treatment. Expiratory O_2, CO_2, and ventilation were measured breath by breath (Innocor® rebreathing system, Innovision A/S, Odense, Denmark). A 12-lead electrocardiogram was recorded (Marquette, Case800, Milwaukee, WI). The patients were strongly encouraged to perform a maximal test but the maximum was self-determined when they approached near maximal exercise, allowing the final 30 seconds for the rebreathing maneuver. The rate of work-rate increase during testing was decided to achieve peak exercise in 8 to 10 minutes during the increasing work-rate period. Peak VO_2 is reported as a mean over the last 20 seconds of the increasing work-rate period.

CO Measurement. Noninvasive CO measurements were performed during CPET at baseline and at peak exercise using the Innocor rebreathing system (Innovision A/S, Odense, Denmark).[11–16] IGR technique uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulphur-hexafluoride). Details of the Innocor rebreathing system have been described elsewhere.[11–16] The IGR measurements of CO at peak exercise has been validated in a small sample of patients with chronic HF, showing a coefficient of variation for repeated measures of 10.8% and a good correlation with thermodilution and Fick methods. Notably, IGR measurements of CO do not require steady state conditions.

Two experts independently read each test, evaluated the linearity of end-expiratory gas pressure decay, and the results were