New Developments: Recent Trials and Investigations

Relationship Between Reverse Remodeling and Cardiopulmonary Exercise Capacity in Heart Failure Patients Undergoing Cardiac Resynchronization Therapy

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ABSTRACT

Background: Studies on the relationship between left ventricular reverse remodeling and cardiopulmonary exercise capacity in heart failure patients undergoing cardiac resynchronization therapy (CRT) are scarce and inconclusive.

Methods and Results: Eighty-four patients with a 1st-time CRT-defibrillator (mean age 65 ± 11; 73% male) underwent echocardiography and cardiopulmonary exercise testing (CPX) before implantation (baseline) and 6 months after implantation. At baseline, patients also completed a set of questionnaires measuring mental and physical health. The association between echocardiographic response (left ventricular end-systolic volume decrease ≥15%) and a comprehensive set of CPX results was examined. Echocardiographic responders (54%) demonstrated higher peak oxygen consumption and better exercise performance than nonresponders at baseline and at 6-month follow-up. Furthermore, only echocardiographic responders showed improvements in ventilatory efficiency during follow-up. Multivariable repeated measures analyses revealed that, besides reverse remodeling, New York Heart Association functional class II and good patient-reported health status before implantation were the most important correlates of higher average oxygen consumption during exercise, and that nonischemic etiology and smaller pre-implantation QRS width were associated with better ventilatory efficiency over time.

Conclusions: During the first 6 months of CRT there was a significant positive association between reverse remodeling and cardiopulmonary exercise capacity. (*J Cardiac Fail 2016;22:385–394*)

Key Words: Cardiac resynchronization therapy, reverse remodeling, heart failure, exercise capacity.

Cardiac resynchronization therapy (CRT), with or without an implantable cardioverter defibrillator, is a well established treatment in selected patients with drug-refractory heart failure (HF) and an electrical conduction delay.[1] Several large-scale randomized controlled trials have demonstrated that CRT enhances functional status, exercise capacity, and quality of life and reduces HF-related hospitalizations and mortality in these patients.[2–8]

Echocardiographic measures of left ventricular (LV) reverse remodeling, including a reduction in left ventricular end-systolic volume (LVESV), are most frequently used to determine response to CRT.[9,10] In addition, several large-scale randomized trials of CRT have prospectively assessed exercise capacity to evaluate treatment effects,[2,11–15] although the majority of those studies were limited to measurements of peak oxygen consumption (VO_2) and

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6-minute walk distance. There is a need to know whether reverse remodeling translates into improved exercise capacity, because exercise capacity determines to a large extent the health status of HF patients.[16] So far, the paucity of studies examining this relationship found that echocardiographic responders showed enhanced exercise capacity after CRT and nonresponders did not.[17–19] Surprisingly, however, the baseline exercise capacity of these responders differed considerably across studies, with one study showing that responders had lower peak VO_2 levels and cardiorespiratory reserve at the time of implantation and another study showing no baseline differences in exercise capacity between echocardiographic responders and nonresponders.[17,19] Thus, the current evidence on the relationship between echocardiographic CRT response and cardiopulmonary exercise capacity is inconclusive and limited by the fact that 2 of the 3 studies performed so far had small sample sizes, including, respectively, 28 and 50 patients.[17,18] Also, analyses are missing to compare the change in exercise capacity over time between echocardiographic responders and nonresponders while controlling for potential confounders. Importantly, none of the earlier studies controlled for patient-perceived physical and mental health status and psychologic functioning, although studies have shown that this may have a strong influence on exercise capacity test outcomes.[13,20–22]

Therefore, the aim of the present study was to elucidate the relationship between left ventricular reverse remodeling and cardiopulmonary exercise capacity in patients undergoing CRT treatment, by comparing echocardiographic responders (decrease in LVESV $\geq$15%) with nonresponders on a comprehensive set of exercise capacity variables assessed at baseline and 6 months after implantation with the use of univariable and multivariable repeated measures analyses adjusting for clinical and patient-reported health factors.

Methods

Study Design and Participants

The study sample comprised a consecutive cohort of patients receiving a 1st-time CRT with defibrillator (CRT-D) in accordance with guidelines[1] and evidence-based medicine from January 2009 to August 2011 at the University Medical Center Utrecht (UMCU), the Netherlands. Patients participated in the influence of PSYchological factors on health outcomes in HEART failure patients treated with Cardiac Resynchronization Therapy (PSY HEART-CRT) study, a prospective single-center observational study.[23] One day before implantation (baseline) and 6 months after implantation, patients were asked to complete a set of standardized and validated questionnaires to assess patient-reported physical and mental health and psychologic functioning. Before and 6 months after implantation, echocardiographic studies and exercise tests also were performed. Only those patients with LVESV and peak VO_2 values at both time points were included in the present analysis. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Medical Ethics Committee of the UMCU. All patients received oral and written information about the study and signed written informed consent forms.

Demographic and Clinical Variables

Information on demographic variables, including age, sex, educational level, and working and marital statuses, was obtained by means of purpose-designed questions at baseline. Information on clinical variables, including etiology (ischemic vs nonischemic), years since diagnosis, New York Heart Association (NYHA) functional class, heart rhythm, QRS duration, left bundle branch block, diabetes mellitus, chronic obstructive pulmonary disease, renal insufficiency (creatinine $>$120 μmol/L), smoking, and cardiac medication, were extracted from patients' medical records.

Echocardiographic Variables

Before implantation and 6 months after implantation, patients underwent echocardiographic evaluation to assess LVESV, left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), and diastolic function. Patients were in the left lateral decubitus position during imaging. LVESV and LVEDV were defined as the smallest and largest, respectively, ventricular volume within 1 RR cycle with both the mitral valve and aortic valve being closed. Subsequently, volume traces were set along the endocardial border. Papillary muscles were included in the LV cavity. Volumes were assessed according to the Simpson biplane method. Echocardiographic response to CRT was defined as a decrease in LVESV of $\geq$15% measured at the 6-month follow-up. Diastolic function was measured in accordance with the guidelines of the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE).[24] The grading scheme of diastolic dysfunction is mild/grade I (impaired relaxation pattern), moderate/grade II (pseudonormal LV filling), and severe/grade III (restrictive filling).

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPX) was performed with the use of a bicycle ergometer until symptom limitation. Patients started with unloaded cycling for 2 minutes after which a protocol of stepwise incremental exercise was applied, starting at 25 W with increments of 5, 10, or 15 W every minute depending on estimated maximum workload. Rotation speed was kept at $\sim$60 per minute. Before testing, gas and flow sensors were calibrated with the use of gases having established concentrations of O_2 and CO_2. For each patient, VO_2 (L/min and mL kg^{-1} min^{-1}), rate of carbon dioxide elimination (VCO_2; L/min), and minute ventilation (VE; L/min) were measured throughout the exercise on a breath-to-breath basis. Peak VO_2, percent-predicted peak VO_2, VE/VCO_2 slope, peak workload, peak heart rate (HR), peak O_2 pulse, respiratory rate (RR) at rest/peak, HR reserve, HR at 1-minute recovery, respiratory exchange ratio (RER), and oxygen uptake efficiency slope (OUES) were assessed. Peak VO_2 is the level of oxygen consumption during peak effort and averaged over a 30-second period.[25] Percent-predicted peak VO_2 was calculated as follows: (peak VO_2/Wasserman-predicted peak VO_2) $\times$ 100.[26] The VE/VCO_2 slope provides a measure of CO_2 exchange efficiency by assessing required ventilation (VE) for CO_2 elimination.[25] Data for the VE/VCO_2 slope were collected throughout the exercise, excluding the unloaded cycling and recovery periods. Calculation of the VE/VCO_2 slope was executed with the use of the slope calculation option of Excel software.