Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure

Pierantonio Laveneziana,1,2 Denis E. O’Donnell,2 Dror Ofir,2 PierGiuseppe Agostoni,3 Luigi Padeletti,4 Giuseppe Ricciardi,4 Paolo Palange,5 Roberto Duranti,1 and Giorgio Scano1,6
1Department of Internal Medicine, Section of Immunology and Respiratory Medicine, University of Florence, Florence, Italy; 2Respiratory Investigation Unit, Department of Medicine, Queen’s University, Kingston, Ontario, Canada; 3Centro Cardiologico Monzino, Istituto di Ricovero e Cura a Carattere Scientifico, Istituto di Cardiologia, University of Milan, Milan, Italy; 4Division of Cardiology, Clinica Medica Careggi, University of Florence, Florence, Italy; 5Department of Clinical Medicine, University “La Sapienza”, Rome, Italy; and 6Department of Pulmonary Rehabilitation, Fondazione Don C. Gnocchi, Florence, Italy

Submitted 10 June 2008; accepted in final form 24 February 2009

Laveneziana P, O’Donnell DE, Ofir D, Agostoni P, Padeletti L, Ricciardi G, Palange P, Duranti R, Scano G. Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure. J Appl Physiol 106: 1574–1583, 2009. First published February 26, 2009; doi:10.1152/japplphysiol.90744.2008.—Despite the growing evidence supporting the use of biventricular cardiac resynchronization therapy (CRT) in patients with chronic heart failure (CHF), the mechanisms whereby acute hemodynamic improvements lead to improved exertional dyspnea are not precisely known. We hypothesized that improved cardiac function and ventilation-perfusion relations following CRT would reduce ventilatory demand, thereby improving dynamic operating lung volumes and enhancing tidal volume expansion during exercise. This, in turn, would be expected to reduce perceived exertional dyspnea and contribute to improved exercise performance. In a randomized, double-blind, crossover study, we compared cardiovascular, metabolic, ventilatory responses (breathing pattern, operating lung volumes, pulmonary gas exchange) and exertional symptoms in seven stable CHF patients who undertook incremental cardiopulmonary exercise test with CRT switched to the “on” (CRTon) or “off” (CRToff) modality. Following CRTon, peak oxygen uptake was significantly increased by 15%, and dyspnea ratings were lower for a given work rate (at work rate of 40 W, dyspnea = 1 ± 0.4 vs. 2.5 ± 0.9 Borg units, P < 0.05) and ventilation (at ventilation of 31 l/min, dyspnea = 2 ± 0.7 vs. 3.5 ± 1.1 Borg units, P < 0.05). CRTon was associated with improvements in ventilatory threshold, oxygen uptake, and oxygen uptake/work rate relationships (10.2 ± 1 vs. 7.9 ± 1.3 ml·min⁻¹·W⁻¹, P < 0.05). CRTon reduced the ventilatory requirement during exercise as well as the steepness of ventilation–CO₂ production slope (35 ± 4 vs. 45 ± 7, P < 0.05). Changes in end-expiratory lung volume during exercise were less with CRTon than with CRToff (0.12 vs. 0.37 liter, P < 0.05), and breathing pattern was correspondingly slower and deeper. Biventricular pacing improved all noninvasive indexes of cardiac function and oxygen delivery during exercise. The decreased ventilatory demand, improved dynamic operating lung volumes, and the increased ability to expand tidal volume during exercise are potential factors in the reduction of exertional dyspnea.

heart failure; dyspnea; dynamic lung hyperinflation; ventilation; resynchronization

CHRONIC HEART FAILURE (CHF) is a common and disabling syndrome, affecting 2.5% of the North American population (45). Despite optimal modern pharmacological treatment, many CHF patients experience severe and persistent symptoms, and their prognosis remains poor (12, 28). In selected patients who present with severe left ventricular systolic dysfunction with intra- and interventricular conduction delays, biventricular cardiac resynchronization therapy (CRT) has been found to improve symptoms, exercise tolerance, and quality of life (1, 10, 23, 44, 57).

Despite the growing evidence supporting the use of CRT, the potential mechanisms by which acute hemodynamic improvements lead to improved exertional dyspnea and exercise performance remain uncertain. Previous studies lasting up to 6 mo have found that long-term CRT was associated with improvements in indirect indexes of cardiovascular function and ventilatory efficiency during exercise (51, 54). However, these studies did not examine the impact of CRT on detailed dynamic respiratory function during exercise or on the intensity of the exertional symptoms.

Comparison of physiological responses to CRT with patients randomized acutely to the “on” and “off” modality (CRTon and CRToff, respectively) provides a unique opportunity to elucidate the downstream effects of acutely improving cardiac output on respiratory function and dyspnea intensity during exercise. The present study is the first to explore this approach.

The mechanisms of exertional dyspnea in CHF are multifactorial, but we have previously postulated that a combination of increased ventilatory demand [secondary to increased ventilation (V̇E)-perfusion mismatching, and to chemo- and metaboreflexes] and abnormal dynamic ventilatory mechanics/muscle function may be important contributory factors (37). Previous studies have demonstrated expiratory flow limitation (EFL), dynamic lung hyperinflation (DH), and “restrictive” ventilatory mechanics during exercise, even in nonsmoking patients with CHF (3, 37). In other words, in the presence of EFL, progressive reduction in dynamic inspiratory capacity (IC) may precipitate an early plateau of tidal volume (VT) and of inspiratory reserve volume (IRV) at a relatively low V̇E and oxygen uptake (V̇O₂) compared with health. We have proposed that this inability to expand VT appropriately in the face of increasing inspiratory muscle contractile effort can lead to perceived respiratory difficulty earlier in exercise in patients with CHF (37). However, no study to date has established whether partial reversal of these mechanical abnormalities (i.e., decreased dynamic IC, VT, and IRV) leads to alleviation of exertional
dyspnea in CHF, a result that would support the role of such mechanical factors in dyspnea causation.

The main objective of this study was, therefore, to determine the acute effects of CRT on cardioventilatory and subjective responses to incremental cycle exercise in patients with stable CHF. Our hypothesis was, first, that improved cardiac function following CRT would reduce ventilatory demand (by improving ventilatory efficiency and delaying metabolic acidosis). Thus reduced reflexic central ventilatory drive (and central corollary discharge) would be associated with improved respiratory sensation. Second, the reduced \( \dot{V}e \) in the setting of EFL should increase dynamic IC, thereby enhancing the ability to expand \( Vr \) during exercise. Collectively, reduced ventilatory drive with improved thoracic volume displacement should improve neuromechanical coupling of the respiratory system and, therefore, improve perceived respiratory difficulty during exercise.

**MATERIALS AND METHODS**

**Subjects.** Seven consecutive, normoxemic CHF patients in regular sinus rhythm, meeting strict inclusion criteria (below), with a cardiac-resynchronization device implanted since at least 6 mo, completed the study. Eligible patients were in stable New York Heart Association functional class III–IV, have received individually optimized medical therapy for \( \geq 6 \) mo after implantation of the cardiac-resynchronization device (including angiotensin-converting enzyme inhibitors, \( \beta \)-blockers, and diuretics), and have presented with a left ventricular ejection fraction of no more than 35%, dilated cardiomyopathy of any etiology, sinus rhythm, and QRS interval of at least \( \geq 120 \) ms on the electrocardiogram. All of the patients were included in the study without knowing a priori whether they were responders or nonresponders to CRT in terms of exercise performance. Patients were excluded if they had showed: 1) a major cardiovascular event in the previous 6 wk; 2) a heart failure requiring continuous intravenous therapy; 3) resting oxygen saturation (\( Sp_o2 \)) < 90% or a sustained decrease of > 4% during exercise; 4) other medical conditions, i.e., respiratory diseases and primary pulmonary hypertension, which could cause or contribute to breathlessness and exercise intolerance; or 5) other problems that could interfere with carrying out of exercise testing, i.e., neuromuscular diseases, orthopedic diseases, etc. Also excluded were patients with atrial fibrillation or severe cardiac arrhythmias, since, in such patients, CRT benefits are less clear (9, 14, 13).

The biventricular CRT device was programmed with the lower heart rate (HR) limit set at 30 beats/min, to limit the amount of continuous atrial pacing that might compromise mechanical function of the left heart in patients with CHF. All implanted devices were programmed to the active mode with the upper rate limit at 85% of the maximal predicted HR, according to the age and sex of the patient. Each patient underwent Doppler echocardiography to determine the optimal atrioventricular delay (electrical delay between atrial and ventricular excitation) during atrioventricular pacing (10).

**Study design.** This was a randomized, double-blind, crossover study. The research was carried out in accordance with the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee, and all subjects signed written, informed consent at the time of their first assessment. Subjects were tested on 3 consecutive days. The first visit was considered as a “learning session” to let patients familiarize with symptom scales; afterwards, each subject underwent careful clinical evaluation, assessment of resting pulmonary function, and a symptom-limited incremental exercise to make them feel comfortable with all of the testing procedures. During the subsequent two visits (visits 2 and 3), participants completed baseline pulmonary function tests, followed by an incremental cycle exercise testing under different pacing modalities, in a random order. It means that, at the end of each visit, the CRT device was programmed, in a random order, to allow a different pacing modality for the subsequent visit (the day after) (see Supplemental Fig. 1). (The online version of this article contains supplemental data.) The pacing modalities were as follows: biventricular pacing modality “off” (CRT,a), i.e., with no stimulation of both right and left heart catheters), and biventricular pacing modality “on” (CRT,a). In this way, all of the patients underwent the first visit while they had their biventricular pacing active. At the end of visit 3, we ensured that all participants had their biventricular pacing modality back to “on”. Subjects were asked to avoid caffeine or heavy meals at least 4 h before testing and avoid major physical exertion entirely on each visit day. Visits were conducted at the same time of day for each subject.

**Procedures.** Baseline spirometry and lung volumes were assessed in accordance with recommended techniques (34, 35, 52) using an automated pulmonary function testing system (Vmax29c, SensorMedics, Yorba Linda, CA). Measurements were standardized as percentages of predicted normal values; predicted normal values for IC were calculated as predicted total lung capacity (TLC) minus predicted functional residual capacity.

Symptom-limited incremental cardiopulmonary cycle exercise testing was conducted on an electronically braked cycle ergometer (Ergometrics 800, Sensors Medics, Yorba Linda, CA) using the Vmax29c: Cardiopulmonary Exercise Testing System (SensorMedics). The equipment was calibrated before each test. All exercise tests consisted of a steady-state resting period of 6 min and a 3-min warm-up of unloaded pedaling, followed by an incremental test in which the work rate (WR) was increased in 1-min intervals by increments of 10 W until the point of symptom limitation (peak exercise). Patients were instructed to maintain the pedaling rate between 50 and 70 revolutions/min.

Breath-by-breath data were collected while subjects breathed through a facemask (dead space, 70 ml) with attached low-resistance flow transducer: \( \dot{V}e \), \( \dot{V}O2 \), carbon dioxide production (\( \dot{V}CO2 \)), end-tidal carbon dioxide partial pressure (\( \dot{V}PCO2 \)), \( Vt \), respiratory frequency (f), inspiratory and expiratory time (Ti and Te, respectively), duty cycle (Ti/total breath time), and mean inspiratory (Vr/Ti) and expiratory flow (Vr/Ti) were calculated. Electrophysiographic monitoring of HR, rhythm, ST-segment changes, blood pressure (by indirect sphygmomanometry), and \( Sp_o2 \) by ear lobe sensor pulse oximetry (RAD-9, Masimo, Irvine, CA) were carried out continuously at rest and throughout exercise testing. The patients were strongly encouraged to perform a maximal test, but they determined when their symptoms were so severe that it was necessary to stop cycling. Exercise variables were measured continuously and averaged over the last 30 s of each minute and at peak exercise. When the IC maneuver was performed during exercise, all variables were averaged over the first 30 s of that minute-step to avoid the possible influence that the performance of an IC maneuver might have on exercise variables measurements. Peak WR, peak \( \dot{V}O2 \) (\( \dot{V}O2peak \)), and peak \( \dot{V}e \) were defined, respectively, as the highest level of exercise and the highest \( \dot{V}O2 \) and \( \dot{V}e \) that could be sustained for at least 30 s during the last stage of exercise. Metabolic and cardioventilatory variables were reported in absolute units, after correction of body weight, and as a percentage of predicted normal values, accounting for age, weight, and sex (27). \( \dot{V}e \) was compared with the maximal ventilatory capacity that was estimated by multiplying the maximal respiratory flow rate transducer: \( \dot{V}e,V\dot{O2}, \) carbon dioxide production (\( \dot{V}CO2 \)), end-tidal carbon dioxide partial pressure (\( \dot{V}PCO2 \)) by 10.220.32.247 on September 9, 2017 http://jap.physiology.org/ Downloaded from
subject. Exercise capacity was assessed by measuring the VO2 at VTh and peak, and by calculating the VO2/WR relationship as an index of cardiovascular performance. The VO2/WR relationship was evaluated throughout the entire incremental cycle exercise, after elimination of the increase in WR during the first 45–60 s to account for the time constant for the VO2 response to the WR increase (20). Mismatching of the heart and lungs was evaluated via the ventilatory efficiency measure Ve/VCO2 slope, i.e., the slope of the linear relationship between Ve and VCO2 from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period. The dead space volume of the facemask was subtracted from the total Ve before calculating Ve/VCO2 slopes and ratios. Two experts independently read each test, and the results were averaged.

Exertional symptoms evaluation. Dyspnea, or breathlessness, was defined as “the unpleasant sensation of laboured or difficult breathing” and leg discomfort as “the level of leg discomfort experienced during exercise.” Before exercise testing, subjects were familiarized with the Borg scale (5), and its end points were anchored such that “0” represented “no breathlessness (and leg discomfort)” and “10” represented “the most severe breathlessness (and leg discomfort) that they had ever experienced or could imagine experiencing.” By pointing to the Borg scale, subjects rated the magnitude of their perceived breathlessness and leg discomfort at rest, every minute, and at peak exercise. Symptom ratings predicted IC maneuvers by at least five breaths to avoid interference with pre-IC breathing patterns, and to avoid the possible influence that the performance of an IC maneuver might have on dyspnea intensity.

Immediately after exercise cessation, subjects were also asked to verbalize their main reason(s) for stopping exercise (i.e., breathlessness, leg discomfort, both, or others).

Operating lung volumes and ventilatory constraints. Since TLC does not change significantly during the exercise (3), the change (decrease) in IC reflects the change (increase) in dynamic end-expiratory lung volume (EELV), or the extent of DH. Therefore, IC was gathered at rest, every 2 min during exercise, and at peak exercise to estimate changes in EELV. The IRV was calculated as IC minus Vr; likewise, changes in IRV (IRV = IC – Vr) reflect changes in end-inspiratory lung volume (EILV) (EILV = TLC – IRV). Technical difficulties for performing and accepting IC measurements have been previously described (40). At each visit, the correct conduct of IC maneuvers was explained to the patient and then practiced at rest until consistently reproducible efforts were made (i.e., within ±5% or ±100 ml, whichever was larger). Subjects were given a few breaths of warning before an IC maneuver, a prompt for the maneuver (i.e., “At the end of the next normal breath out, take a deep breath all the way IN”), and then strong verbal encouragement to make a maximal effort (i.e., “in. . ., in. . ., in. . .”) before returning to their regular breathing. The resting IC was recorded as the mean of the two best reproducible efforts. Satisfactory technique and repeatability of maneuvers was ensured before proceeding with exercise testing. During the incremental cycle exercise tests, IC maneuvers were performed at 2-min intervals during the last 30-s period of each interval. When subjects indicated the desire to terminate exercise, an “end-exercise” IC maneuver was performed within 15 s, and the subjects were permitted to cool down, or, if an acceptable IC had been performed within the preceding 30 s and the breathing pattern had not restabilized, then the value for that IC was used as the end-exercise value. If an exercise IC maneuver was found to be unacceptable (i.e., submaximal effort or anticipatory changes in breathing pattern immediately preceding the IC maneuver), it was not repeated and was excluded from the analysis.

Tidal flow-volume curves at rest, every 2 min during exercise, and at peak exercise were constructed for each patient and placed within their respective maximal flow-volume envelopes, according to coinciding IC measurements. Maximal flow-volume loops were performed only at rest for this analysis. The presence or absence of flow limitation was then determined by comparing tidal expiratory flows with those of the maximal envelope at isovolume: we looked at the shape and limits of the maximal flow-volume curve in the tidal operating range [forced expiratory flow at 50% and 75% of the forced vital capacity (FEF50% and FEF75%, respectively)], as well as the extent of EFL by evaluating the percentage of Vr that encroached on the maximal flow-volume envelope (26).

Statistical analysis. Results are expressed as means ± SE. Metabolic, cardioventilatory, and perceptual responses at iso-Ve and iso-VO2 were calculated by linear interpolation between adjacent measurement points for each subject. All group responses (CRTon vs. CRToff) were compared at rest, iso-WR, iso-Ve, iso-VO2, and peak exercise by using paired t-tests with appropriate Bonferroni adjustments for multiple comparisons. Repeated-measures ANOVA (with treatment, times/points, and interaction as fixed effects, and subject as a random effect) was applied to compare the overall treatment effects over the course of the exercise test (i.e., rest vs. iso-WR vs. peak). A P < 0.05 level of statistical significance was used for all analyses. All statistical procedures were carried out using Intercooled Stata 6.0 for Windows (Stata, College Station, TX) and Statgraphics Plus 5.1 for Windows (Manugistics, Rockville, MD).

RESULTS

Comparisons are shown by only applying paired t-tests with appropriate Bonferroni adjustments for multiple comparisons (see Tables 2 and 3).

By repeated-measures ANOVA, there were significant interactions between treatment and time points during exercise (rest vs. iso-WR vs. peak for both conditions) for exertional symptom ratings, Ve (except for peak), f (except for peak), Vr (in absolute value and as percentage of either VC predicted or IC predicted), Ti and Te (except for resting Ti), IC (either in absolute value or as percent predicted), EELV (except for iso-WR vs. peak), HR, VO2, and O2 pulse (i.e., the treatment effect did vary at different time points).

Repeated-measures ANOVA showed a significant treatment effect for Vr/VO2 and Vr/VCO2 ratios, with no significant interactions between treatment and exercise time points.

Pulmonary function and baseline characteristics. Subject characteristics and resting pulmonary function at visit 1 (familiarization visit) are summarized in Table 1. There were

Table 1. Subjects characteristics and resting pulmonary function testing during the first visit

<table>
<thead>
<tr>
<th>Metric</th>
<th>Mean(SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>71±2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171±3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78±3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26±5±0.7</td>
</tr>
<tr>
<td>Cigarette smoking history (smoker/nonsmoker)</td>
<td>4/5</td>
</tr>
<tr>
<td>FVC, %predicted</td>
<td>91±8</td>
</tr>
<tr>
<td>FEV1, %predicted</td>
<td>97±9</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>73±5</td>
</tr>
<tr>
<td>FEV1/SVC, %</td>
<td>70±4</td>
</tr>
<tr>
<td>TLC, %predicted</td>
<td>100±6</td>
</tr>
<tr>
<td>SVC, %predicted</td>
<td>90±6</td>
</tr>
<tr>
<td>IC, %predicted</td>
<td>90±8</td>
</tr>
<tr>
<td>FRC, %predicted</td>
<td>104±8</td>
</tr>
<tr>
<td>RV, %predicted</td>
<td>115±8</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>44±3</td>
</tr>
</tbody>
</table>

Values are means ± SE. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; TLC, total lung capacity; SVC, slow vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; FEV1/FVC, FEV1/SVC, and RV/TLC are ratios.
Improvement in the VO2peak was seen in five of seven patients. At V˙E/V˙CO2, the MVC, and f, there were no changes between resting pulmonary function at visit 1 and those obtained in the two subsequent visits. See the online data supplements for more detail.

**Cardiovascular response to exercise.** The highest equivalent standardized exercise WR (iso-WR) achieved by all participants during all the tests corresponded to 40 W. Measurements at rest, at iso-WR, and at peak exercise are shown in Table 2. Measurements at iso-Vo2 are shown in Table 3. CRToff patients stopped exercise at lower VO2peak, WR, and O2 pulse, but at higher HR compared with CRTon patients (Fig. 1). An improvement in the VO2peak was seen in five of seven patients with CRTon compared with CRToff in line with the existent literature (51). The change (Δ) in VO2/DWR relationship was upwards shifted and increased from the value of 7.9 ± 1.3 ml·min⁻¹·W⁻¹ during CRToff session to normal value of 10.2 ± 1 ml·min⁻¹·W⁻¹ during CRTon session (by ~24%, P < 0.05). See the online data supplements for more detail.

**Ventilatory response to exercise.** Compared with the CRTon session, VE was significantly increased at rest and at any submaximal VO2 and exercise intensity during CRToff session (Fig. 2 and Table 2).

During CRTon session, f was significantly lower at rest and throughout the entire exercise, with the exception of peak (Fig. 3). Rest-to-peak changes in Vr ranged from 0.54 liter during CRToff session to 0.72 liter during CRTon session (P < 0.05).

Upon evaluation of individual Hey plots (22), the average VE at the Vr inflection point was similar at 32 and 29 l/min in CRTon and CRToff patients, respectively; however, this inflection occurred at a significantly (P < 0.05) lower VO2 and WR in CRToff patients.

Differences were also noted in the timing components of the breathing pattern. Both Ti and Te were higher during CRTon session throughout the exercise (Fig. 3) compared with CRToff session, excepted for the value of resting Ti, which did not

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**Table 2. Metabolic and cardiorespiratory responses to cardiopulmonary cycle exercise testing in patients with chronic heart failure**

<table>
<thead>
<tr>
<th>Variables</th>
<th>CRToff</th>
<th>CRTon</th>
<th>CRToff</th>
<th>CRTon</th>
<th>CRToff</th>
<th>CRTon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work rate, W (%pred)</td>
<td>0.266 ± 0.02 (15.1 ± 1)</td>
<td>0.274 ± 0.02 (16.1 ± 1)</td>
<td>0.606 ± 0.06 (35.5 ± 5)</td>
<td>0.684 ± 0.05 (40.5 ± 5)</td>
<td>0.766 ± 0.06 (45.4 ± 5)</td>
<td>0.987 ± 0.07 (58.7 ± 5)</td>
</tr>
<tr>
<td>VO2/kg</td>
<td>3.4 ± 0.2</td>
<td>3.5 ± 0.2</td>
<td>7.7 ± 0.8</td>
<td>8.9 ± 0.6*</td>
<td>9.9 ± 0.9</td>
<td>13.1 ± 4*</td>
</tr>
<tr>
<td>HR, beats/min (%pred)</td>
<td>75 ± 6 (46 ± 3)</td>
<td>69 ± 6* (42 ± 3)*</td>
<td>93 ± 10 (57 ± 6)</td>
<td>83 ± 8* (51 ± 5)*</td>
<td>110 ± 11 (68 ± 7)</td>
<td>102 ± 9* (63 ± 5)*</td>
</tr>
<tr>
<td>O2 pulse, ml/breath</td>
<td>3.6 ± 0.3</td>
<td>4.1 ± 0.3*</td>
<td>6.6 ± 0.6</td>
<td>8.5 ± 0.6*</td>
<td>7.7 ± 1.4</td>
<td>10.2 ± 1.2*</td>
</tr>
<tr>
<td>Ve, l/min (%MVC)</td>
<td>12.3 ± 1.2 (15 ± 2)</td>
<td>9.7 ± 1.5* (12.2 ± 2)*</td>
<td>27.3 ± 3.4 (36 ± 8)</td>
<td>25.2 ± 2.8* (32 ± 7)*</td>
<td>36.3 ± 4 (35 ± 7)</td>
<td>39 ± 2 (49 ± 7)</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>17 ± 1</td>
<td>14 ± 2*</td>
<td>26 ± 4</td>
<td>21 ± 3*</td>
<td>30 ± 4</td>
<td>28 ± 2</td>
</tr>
<tr>
<td>Vr, liters (%VC pred)</td>
<td>0.718 ± 0.05 (19 ± 2)</td>
<td>0.709 ± 0.04 (18 ± 1)</td>
<td>1.07 ± 0.07 (27 ± 1)</td>
<td>1.19 ± 0.05* (31 ± 1)*</td>
<td>1.26 ± 0.11 (32 ± 1)</td>
<td>1.43 ± 0.10* (37 ± 2)*</td>
</tr>
<tr>
<td>Vr, %IC pred</td>
<td>25 ± 1</td>
<td>25 ± 2</td>
<td>37 ± 1</td>
<td>42 ± 1*</td>
<td>43 ± 2</td>
<td>50 ± 2*</td>
</tr>
<tr>
<td>IC, liters (%pred)</td>
<td>2.24 ± 0.3 (78 ± 5)</td>
<td>2.34 ± 0.3 (82 ± 10)</td>
<td>4.3 ± 0.4 (68 ± 6)</td>
<td>4.0 ± 0.4* (63 ± 6)*</td>
<td>4.37 ± 0.4 (70 ± 6)</td>
<td>4.01 ± 0.4* (64 ± 6)*</td>
</tr>
<tr>
<td>EELV, liters (%TLC pred)</td>
<td>4 ± 0.4 (63 ± 6)</td>
<td>3.9 ± 0.4 (62 ± 6)</td>
<td>46 ± 4</td>
<td>36 ± 2*</td>
<td>47 ± 3</td>
<td>40 ± 3*</td>
</tr>
<tr>
<td>Ve/O2</td>
<td>46 ± 2</td>
<td>35 ± 3*</td>
<td>52 ± 4</td>
<td>43 ± 3*</td>
<td>49 ± 3</td>
<td>42 ± 3*</td>
</tr>
<tr>
<td>Ve/VCO2</td>
<td>52 ± 3</td>
<td>40 ± 4*</td>
<td>2.5 ± 0.9</td>
<td>1 ± 0.4*</td>
<td>4.6 ± 1.2</td>
<td>2.7 ± 0.9*</td>
</tr>
<tr>
<td>Dyspnea (Borg units)</td>
<td>0</td>
<td>0</td>
<td>3.1 ± 0.9</td>
<td>0.7 ± 0.4*</td>
<td>6.7 ± 0.7</td>
<td>4.7 ± 1.1*</td>
</tr>
<tr>
<td>Leg discomfort (Borg units)</td>
<td>0</td>
<td>0</td>
<td>0.05</td>
<td>0.05*</td>
<td>0.05</td>
<td>0.05*</td>
</tr>
</tbody>
</table>

Values are means ± SE. IRV, inspiratory reserve volume. *P < 0.05.

**Table 3. Significant change in metabolic and cardiorespiratory variables at iso-Vo2 and iso-VE during cardiopulmonary cycle exercise testing in patients with chronic heart failure**

<table>
<thead>
<tr>
<th>Variables</th>
<th>iso-Vo2</th>
<th>iso-VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work rate, W (%pred)</td>
<td>47 ± 6 (34 ± 5)</td>
<td>53 ± 7 (37 ± 4)</td>
</tr>
<tr>
<td>VO2, l/min (%pred)</td>
<td>0.694 ± 0.06 (41 ± 4)</td>
<td>0.692 ± 0.05 (40 ± 4)</td>
</tr>
<tr>
<td>Vo2/kg</td>
<td>9.0 ± 0.8</td>
<td>9.0 ± 0.8</td>
</tr>
<tr>
<td>HR, beats/min (%pred)</td>
<td>97 ± 9 (60 ± 5)</td>
<td>84 ± 7* (51 ± 5)*</td>
</tr>
<tr>
<td>O2 pulse, ml/breath</td>
<td>7.6 ± 1.2</td>
<td>8.6 ± 1.1*</td>
</tr>
<tr>
<td>Ve, l/min (%MVC)</td>
<td>30 ± 3 (38 ± 6)</td>
<td>25 ± 3* (32 ± 5)*</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>27 ± 3</td>
<td>22 ± 2*</td>
</tr>
<tr>
<td>Vr, liters (%VC pred)</td>
<td>1.16 ± 0.09 (30 ± 1)</td>
<td>1.19 ± 0.08 (30 ± 1)</td>
</tr>
<tr>
<td>Vr, %IC pred</td>
<td>40 ± 2</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>IC, liters (%pred)</td>
<td>2.3 ± 0.8 (69 ± 2)*</td>
<td>1.94 ± 0.2 (68 ± 7)</td>
</tr>
<tr>
<td>EELV, liters (%TLC pred)</td>
<td>4.24 ± 0.4 (68 ± 6)</td>
<td>4.3 ± 0.4 (68 ± 6)</td>
</tr>
<tr>
<td>IRV, liters (%TLC pred)</td>
<td>0.84 ± 0.2 (13 ± 3)</td>
<td>0.73 ± 0.2 (12 ± 3)</td>
</tr>
<tr>
<td>Ve/Vo2</td>
<td>44 ± 3</td>
<td>46 ± 3</td>
</tr>
<tr>
<td>Ve/Vco2</td>
<td>48 ± 3</td>
<td>49 ± 3</td>
</tr>
<tr>
<td>Dyspnea (Borg score)</td>
<td>2.7 ± 0.9</td>
<td>3.3 ± 1.1</td>
</tr>
<tr>
<td>Leg discomfort (Borg score)</td>
<td>3.3 ± 0.8</td>
<td>4.1 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE. IRV, inspiratory reserve volume. *P < 0.05.

Downloaded from [http://jap.physiology.org](http://jap.physiology.org) by 10.220.32.27 on September 9, 2017.
reach statistical significance ($P = 0.08$). Consequently, the total time allowed to breathe ($T_t$) was greater in CRT$_{on}$ patients throughout the exercise.

The $V_{E}/V_{O_2}$ and $V_{E}/V_{CO_2}$ ratios were significantly lower ($P < 0.05$) during CRT$_{on}$ sessions compared with CRT$_{off}$ sessions at rest and throughout the entire exercise (Tables 2 and 3). The $V_{E}/V_{CO_2}$ slope, a strong CHF prognostic indicator independent of $V_{O_2peak}$ (11, 29, 43), was significantly elevated during CRT$_{off}$ session (45 ± 7) and improved significantly by ~20% during CRT$_{on}$ session (35 ± 4, $P < 0.05$). See the online data supplements for more detail.

Operating lung volume response to exercise. In the present study, all of the CHF subjects presented with resting EFL, which was not abolished by CRT$_{on}$.

EELV was significantly higher ($P < 0.05$) in CRT$_{off}$ patients at any submaximal exercise intensity (Tables 2 and 3). Rest-to-peak changes in EELV ranged from 0.12 liter during CRT$_{on}$ session to 0.37 liter during CRT$_{off}$ session (Fig. 4, $P < 0.05$). Of note, six out of seven CHF patients improved their dynamic IC in response to active cardiac pacing. See the online data supplements for more detail.

Dyspnea and leg discomfort. Dyspnea intensity was higher in CRT$_{off}$ patients during exercise at a given WR, as well as at iso-$V_{O_2}$ and iso-$V_{E}$ and at peak (Fig. 5, Tables 2 and 3). Dyspnea/$V_{E}$ and dyspnea/$V_{O_2}$ slopes were also greater in CRT$_{off}$ patients than CRT$_{on}$ patients by 50 and 47%, respectively ($P < 0.05$).

Leg discomfort intensity was higher in CRT$_{off}$ patients during exercise at a given WR, as well as at iso-$V_{O_2}$ and at peak (Fig. 5, Tables 2 and 3). Leg discomfort/WR and leg discomfort/$V_{O_2}$ slopes were also greater in CRT$_{off}$ patients...
DISCUSSION

The main findings of this study are that biventricular pacing was associated with the following: 1) improved indirect indexes of cardiovascular function; 2) reduced ventilatory requirements, increased dynamic IC, and a deeper, slower breathing pattern; and 3) significant reduction in exertional symptoms and increased symptom-limited $V_O^2_{peak}$.

The present is the first study to evaluate, in a crossover fashion, the acute effects of CRT on cardiovascular and respiratory function in patients with severe CHF with an average $V_O^2_{peak}$ of only 9.9 ml $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$. Accordingly, these results may not apply to patients with CRT, but less severe CHF. Exercise tolerance was clearly compromised in our patients with CHF: peak symptom-limited $V_O^2$ was reduced to 55% of the predicted normal value (Table 2). CRT on was associated with consistent increases in $V_O^2_{peak}$ by 15% predicted. Previous hemodynamic studies (24, 48, 50) have confirmed acute and chronically maintained improvements in cardiac output following biventricular pacing in selected patients. Wasserman et al. (54) also reported improvements in cardiovascular indexes in a large series of patients who underwent CRT. In the present study, improvements in cardiovascular function and oxygen delivery are suggested by the following: 1) the increased $V_O^2$ at VTh and at peak of exercise; 2) the greater $O_2$ pulse at rest and on exertion; 3) improved HR responses; 4) the increase in the $V_O^2$/WR relationship; and 5) delay in the VTh.

In accordance with the results of previous studies (54), CRT on was associated with consistent reductions in $V_E$ at a given $V_O^2$ (by $\sim$17%) or power output (by $\sim$10%) throughout exercise in the absence of any measurable deterioration in pulmonary gas exchange (both $S_{PO_2}$ and $P_{ETCO_2}$ were pre-
This reduced ventilatory requirement, in turn, likely reflected improved V˙E/perfusion relations as a result of improved ability to reduce a higher physiological dead-space during exercise due to improved pulmonary perfusion. Greater expansion of VT during CRTon could also have contributed to this (Fig. 2, Tables 2 and 3). Ventilatory efficiency improved, as indicated by reduced steepness of V˙E/V˙CO2 slope (by ∼20%) and the lower V˙E/V˙CO2 and V˙E/V˙O2 ratios throughout exercise (Fig. 2, Tables 2 and 3). Additionally, a consistent increase in the VTh during CRTon condition suggests delayed onset of metabolic acidosis secondary to improved oxygen delivery, or utilization, or both.

**Improvement of dynamic ventilatory mechanics.** This study extends the results of previous studies and is the first to examine the impact of improved cardiac function on the ventilatory mechanical parameters relevant to symptom perception. Resting pulmonary function was largely preserved in our CHF patients and was not altered by activation of biventricular pacing. Small airway dysfunction and EFL during exercise have previously been described in CHF (3, 37). The nature of the airway dysfunction in CHF is poorly understood and may reflect bronchial mucosal edema, airway hyperresponsiveness, or the attendant effects of aging or tobacco smoking or various combinations of these factors (8, 15, 16, 18, 30). The reduced resting ERV and the shape and limits of the maximal flow-volume curves in the tidal operating range (showing a reduction of FEF50% and FEF75% by 76 and 55%, respectively), as well as the encroachment of VT upon the maximal flow-volume envelope in our CHF patients, mean that operating VT was positioned closer to residual volume, thus increasing the propensity for EFL (15) (Table 1). During the accelerated ventilatory response to exercise, IC decreased by an average of 0.37 liter from rest to peak exercise, in keeping with previous reports (37). If we accept that TLC remains stable throughout exercise, and there is good evidence for this from the study of Agostoni and colleagues (3), we can assume that the decreases in dynamic IC reflect increase in the rate of change in EELV (DH). This suggests that the mechanical time constants for lung emptying were delayed in CHF patients to a degree that air trapping was precipitated during the tachypnea of exercise. Of interest, DH in CHF patients was associated with a more rapid, shallow breathing at each stage of exercise, as well as at iso-V˙E (Fig. 3).

When randomized to CRTon, there were consistent increases in dynamic IC and IRV with corresponding improvements in the volume and timing components of breathing: VT increased by an average of 0.72 liter (50% of predicted IC), and f was reduced due to prolongation of both TI and TE (Fig. 3). The mechanisms of reduced DH were not fully elucidated: we were unable to demonstrate improved mean expiratory flow rates or reduced EFL during exercise. It is reasonable to assume that the reduced V˙E (by 10 –12%) and reduced f seen in this study would reduce the extent of air trapping in patients with EFL, as it has been demonstrated in COPD patients (38, 47). It is also conceivable that improvement in the time constant for lung emptying of heterogeneous alveolar units may occur in response to improved cardiopulmonary interactions during active cardiac pacing and not be reflected in our estimation of EFL by the flow-volume overlap method.

An alternative explanation for the increase in IC during exercise when patients were randomized to the active cardiac pacing modality is improved inspiratory muscle performance, secondary to improved blood perfusion to muscle (due to the increased cardiac output) (42). Thus, if this is the case, increases in dynamic IC might reflect an increased ability to reach TLC during the IC maneuvers. It is possible that improved cardiac function with CRTon, by improving oxygen delivery and inspiratory muscle regional blood flow, may have reduced respiratory muscle fatigue and/or decrease the competition for blood flow with locomotor muscles (6). Given this scenario, the alterations in breathing pattern following active...
cardiac pacing may reflect increased functional strength of the inspiratory muscles. However, the behavior of the inspiratory muscles in CHF during exercise is still debated (32, 42). Mancini et al. (32) showed no fatigue of the diaphragm after incremental exercise using phrenic nerve stimulation in CHF population. Interestingly, there is evidence that rats may protect diaphragm blood flow during exercise, despite severe left ventricle dysfunction (36). Johnson et al. (25) showed that both CHF and healthy subjects achieved inspiratory tidal flows that approached a similar percentage of the maximal available inspiratory flows, suggesting that the inspiratory flow-generating reserve of the inspiratory muscles at peak exercise was similar (but occurred at lower lung volumes in the CHF patients). In the absence of esophageal pressure measurements in this study, we must concede that both mechanisms of dynamic IC recruitment (either singly or in combination) are possible. However, regardless of the underlying mechanisms, improved dynamic IC during exercise is likely to have salutary sensory and mechanical consequences for patients with CHF.

Improved exertional symptoms with biventricular pacing. Although intolerable leg discomfort is usually the primary limiting symptom in patients with CHF, as seen in this study, patients also report severe dyspnea (19, 37). Potential mechanisms include the following: 1) increased vascular congestion/distension and interstitial edema (41); 2) DH (37); 3) excessive loading (due to decreased lung compliance from pulmonary edema or increased airways resistance) of inspiratory muscles (3, 33); 4) ventilatory muscle weakness (33); and 5) increased ventilatory demand (secondary to increased ventilation/perfusion mismatching and to chemo- and metaboreflexes) (31, 49). Dyspnea/VE slopes were consistently reduced by ~50% during exercise in response to active cardiac pacing. The attendant reduction in central respiratory drive is likely to ameliorate dyspnea intensity. Improved dynamic IC (either due to reduced DH, or increased inspiratory muscle strength, or both) should reduce the central motor command output (and central corollary discharge to the somatosensory cortex) required to drive the ventilatory muscles, thereby improving dyspnea (39). Reduced f would also reduce the velocity of shortening of the inspiratory muscles and reduce dynamic functional weakness in this manner. Improved cardiopulmonary interaction during active cardiac pacing in patients with CHF may favorably alter activation patterns in mechanosensors in the lung, airways, heart, and pulmonary vasculature and reduce unpleasant respiratory sensation in a manner that is not fully understood (7, 37, 46, 56). The net effect of these changes in ventilatory control, dynamic respiratory mechanics, and ventilatory muscle function is enhanced neuromechanical coupling of the respiratory system.

Perceived leg discomfort was significantly reduced during CRT$_{on}$ (Fig. 5), suggesting that active cardiac pacing improved $\dot{O}_2$ transport and the metabolic milieu at the active locomotor muscle level. We previously demonstrated that inspiratory muscle unloading (using pressure support $\dot{V}_E$) during exercise in patients with CHF similarly relieved leg discomfort (37). We postulated that improved cardiopulmonary interactions with reduced ventilatory/locomotor muscle competition were the most plausible mechanism (6, 21). Further mechanical studies are needed to determine whether the reduced leg discomfort, in association with CRT$_{on}$, is explained by similar mechanical improvements.

LIMITATIONS

In the absence of esophageal pressure measurements, we must concede that improvement in dynamic IC in response to active cardiac pacing may be due either to reduced DH, increased inspiratory muscle contractile strength, or both in combination. Regardless of the mechanism, the consistent increase in dynamic IC in six of the seven patients following CRT is likely to be physiologically and clinically meaningful. Given the small sample size and the heterogeneous pathophysiology that is normally characteristic of patients with CHF (many of whom have respiratory comorbidities), we must be careful to avoid any generalization of our findings to the larger CHF population. Although we did not preselect our CHF patients, the majority (5 out of 7) improved their $\dot{V}O_2$peak when randomized to active pacing. Similar high response rates have been reported elsewhere (51). However, further studies that contain a larger sample size (which includes nonresponders to CRT) will be required to definitively elucidate the physiological mechanisms of benefit of this intervention.

In summary, CRT$_{on}$ was associated with consistent improvements of all noninvasive indexes of cardiac function and oxygen delivery during exercise. We suggest that, collectively, the decrease in ventilatory demand, improved dynamic operating lung volumes (due to either reduced DH, improved muscle function, or both), and an increased ability to expand VT during exercise could have contributed to the impressive reduction in exertional dyspnea. Future controlled studies that utilize CRT in this manner have the potential to offer unprecedented insights into the nature of cardiopulmonary interaction and the origin of intolerable exertional symptoms in patients with CHF.

ACKNOWLEDGMENTS

Some of the results of this study have been previously reported in the form of an abstract presented at European Respiratory Society Annual Congress 2007 (Eur Respir J Suppl 51: 19s, 2007).

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